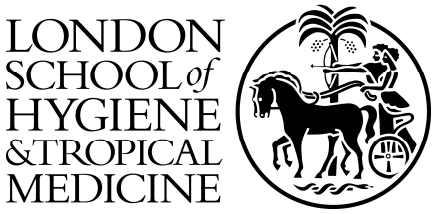

Long-term mental health and quality of life in women with a history of breast cancer

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Thesis submitted in accordance with the requirements for the degree of

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of the
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Research group affiliation: Electronic Health Records Group

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Statement of own work

I, Helena Isabel Morim Carreira, confirm that the work presented in this thesis is my own. Where information was derived from other sources, I confirm that this has been indicated in this thesis.

Student Signature [redacted]

Date 10 January 2020

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Funding and role of funding sources

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MRC had no role in study design; in the collection, analysis, and interpretation of data; and in the writing of the articles, and thesis.

The study presented in Chapter 7 was conducted in collaboration with CPRD. CPRD participated in study design; in the collection, analysis, and interpretation of data; and in the writing of the articles. More specifically, members of the CPRD Observational and Interventional Research Teams provided comments on the study protocol. The CPRD Interventional Research Team was pivotal in the acquisition of data for the study. Dr Rachael Williams, who is employed by CPRD and was the associate supervisor of this PhD, was involved in all studies in this thesis.

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‘No man is an island, entire of itself’

(John Donne)

This thesis exists thanks to a number of extraordinary people. The following paragraphs attempt to give credit where credit is due.

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'Every man is a piece of the continent, a part of the main'

(John Donne)

No human being thrives in isolation, and I am no exception. LSHTM has been my home away from home for nearly seven years. During this time, I had the privilege of meeting and working with many brilliant and talented minds, from all continents and backgrounds. I am humbled that some of them became close friends.

To Rhea Harewood, (soon to be Dr) Manuela Quaresma and Dr Renata Abrahão, no words can express how grateful I am to have you in my life. Thank you for

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'Eles não sabem nem sonham
que o sonho comanda a vida
e que sempre que o homem sonha
o mundo pula e avança
como bola colorida
entre as mãos duma criança'
(António Gedeão)

To my family, for being the steady and safe harbour that allows me to roam free and mingle far and beyond my childhood dreams. None of this would have been possible without you. This PhD is as much mine as it is yours.

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À minha avó, Maria Fernandes Eusébio,
que me ensinou as mais importantes lições na vida
sem saber ler ou escrever.

Saudades.

To my grandmother, Maria Fernandes Eusébio,
who taught me the most important lessons of my life
without knowing how to write or read.

I will always miss you.

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Abstract

This thesis focused on the long-term mental health and quality of life of breast cancer survivors, compared to women with no prior cancer.

The first study was a systematic review of studies that assessed adverse mental health outcomes in women who had breast cancer and non-cancer controls. This found evidence suggestive of an increased risk of anxiety, depression, suicide, and neurocognitive and sexual dysfunctions in breast cancer survivors.

The second study systematically summarised the lists of Read codes and clinical definitions used in previous studies of mental health-related outcomes in primary care databases of electronic health records in the UK. The results showed substantial heterogeneity across studies and informed the definition of the outcomes in this thesis.

The third study used data from the UK Clinical Practice Research Datalink (CPRD) GOLD primary care database to quantify the risk of adverse mental health-related outcomes in 57,571 breast cancer survivors and 230,067 women with no previous cancer. Breast cancer survivorship was positively associated with anxiety, depression, fatigue, pain, sexual dysfunction, sleep disorder and being prescribed opioid analgesics, but there was no evidence of association with cognitive dysfunction or fatal and non-fatal self-harm.

The fourth study included 353 breast cancer survivors and 252 women with no prior cancer who replied to questionnaires assessing quality of life and mental health. Compared to women with no prior cancer, breast cancer survivors had poorer quality of life in the domains of cognitive problems, sexual function, and fatigue, but no evidence of difference in negative feelings, positive feelings, pain, or social avoidance. Women with advanced-stage cancer at diagnosis, and/or prior receipt of chemotherapy, had poorer quality of life and mental health.

In conclusion, breast cancer survivorship is associated with impaired quality of life and raised risk of adverse mental health-related outcomes, persisting well into the survivorship period.

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List of abbreviations & acronyms

95%CI	95% confidence interval
AI	Aromatase Inhibitors
BNF	British National Formulary
CCGs	Clinical Commissioning Groups
CIS-R	Clinical Interview Schedule Revised
CPRD	Clinical Practice Research Datalink
DALYs	Disability Adjusted Life Years
DNA	Deoxyribonucleic acid
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3th Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3th Edition Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EGFR	Epidermal Growth Factor Receptor
EHR	Electronic Health Records
ER	Oestrogen Receptor
ESMO	European Society for Medical Oncology
G-CSF	Granulocyte colony stimulating factor
GCSEs	General Certificate of Secondary Education
GOLD	General Practitioner Online Database
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale – Depression subscale
HER2	Human Epidermal growth factor Receptor 2
HES-APC	Hospital Episode Statistics, Admitted Patient Care
HRQoL	Health-Related Quality of Life
HR	Hazard Ratio
ICD-9	International Statistical Classification of Diseases and Related Health Problems, 9th revision
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
IMD	Index of Multiple Deprivation
ISAC	The Independent Scientific Advisory Committee for MHRA Database Research
LSOA	Lower-layer Super Output Areas
MDD	Major Depressive Disorder
MHDS	Mental Health Data Set

MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute for Health Research
NICE	National Institute for Health and Care Excellence
ONS	Office of National Statistics
OR	Odds Ratio
PTSD	Post-traumatic Stress Disorder
QLACS	Quality of life in Adult Cancer Survivors
SDI	Socio-economic Development Index
UK	United Kingdom
YLD	Years Lived with Disability

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1 Background

1.1 Introduction

This thesis focuses on the mental health and quality of life of breast cancer survivors in the UK, compared to women with no history of cancer. This opening chapter provides background information on the current knowledge of the aetiology and epidemiology of mental health conditions and breast cancer, the potential intersection between the two, and plausible implications for health-related quality of life (HRQoL). This motivated the aims and objectives of this thesis, which are provided in Chapter 2.

1.2 Mental disorders

Mental disorders are very common conditions. A meta-analysis of 155 studies from 55 countries, estimated a one-year prevalence of all mental disorders of 17.6% (95% confidence interval (95%CI): 16.3% to 18.9%) [1]. Anxiety and mood disorders represented 88% of all diagnosis [1], therefore the following sections focus in detail on these two groups of disorders, and briefly on other mental disorders.

1.2.1 Depressive disorders

Definition

Depressive disorders are characterised by cardinal feelings of sadness, anhedonia, lack of interest, feelings of helplessness, irritability, and tearfulness, among others [2]. These negative feelings are amongst the panoply that occur normally in mammals, and short periods of sadness are part of everyday life [2, 3]. Depression in the pathological sense occurs when the severity and duration of these symptoms are exaggerated, so much so that they disrupt daily life. Major depressive disorder (MDD) is the terminology used to refer to the most severe cases, and is defined by the following criteria in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V): the presence of 1) an abnormal depressed mood most of the day, nearly every day, for at least two weeks; or an abnormal loss of all interest and pleasure most of the day, nearly every day, for at least two weeks; and 2) at least two of the following symptoms during those same two weeks: depressed mood, loss of all pleasure, appetite or weight disturbance, sleep disturbance, agitation or

slowing, fatigue or loss of energy, abnormal inappropriate guilt, poor concentration, thoughts of death or suicide [4].

Historically, the terms ‘depressive disorders’, ‘mood disorders’ and ‘affective disorders’ have all been used to describe a group of disorders that are characterised by depressive episodes. These groups included unipolar depressive disorder and bipolar disorder (sometimes referred to as manic depression), among other less common disorders. In DSM-V, published in 2013, the category of ‘Mood disorders’ was replaced by two categories: ‘Bipolar and related disorders’ and ‘Depressive disorders’. This split was motivated by the similarities in symptomatology, family history and genetics between psychotic disorders and bipolar disorders. Unipolar depressive disorder has always represented the vast majority of the cases in any group of ‘mood disorders’, and it is the focus of the following section on aetiology. For simplicity, unipolar depressive disorder is hereafter referred to as depression.

Aetiology

The aetiology of depression is complex. Early studies showed that depression tended to occur in those with a family history of the disorder, suggesting that genetic components could be involved [5]. Adoption studies explored the role of environmental exposures, as families tend to share both genetics and habits. The higher frequency of major depression in adoptees with biological family history of depression, compared to adoptees without, further lent support to the theory of genetic susceptibility [5]. Heritability for depression has now been estimated at around 30-40% (at population level), based on studies with monozygotic and dizygotic twins [5]. Studies on the specific genes involved revealed a multifaceted picture of polygenic inheritance, where several genes contribute a small or modest effect independently [5, 6].

Stress plays a central role in the aetiology of depression [7]. The Oxford dictionary defines stress as ‘a state of mental or emotional strain or tension resulting from adverse or demanding circumstances’ [8]. Adverse psychological exposures during childhood appear to affect one’s predisposition to subsequently develop depression [9]. In addition, there is vast empirical evidence that recent stressful events, measured in several forms, may precipitate episodes of depression [10-12]. Increasing odds of depression were also found for more long-lasting forms of stress, such as lower socio-economic status [13], distressed partnered relationships [14], singlehood at older ages [15], motherhood with low social support [16], and work-

related factors, such as job strain, workplace bullying, lack of autonomy and decision capacity [17].

Stress is often induced by change [7]. Whilst some changes may be avoided, those arising from one's life course trajectories are less so. The life course social field model (Figure 1.1) puts forward a number of life span events that may act as stressors during an individual's lifetime and trigger episodes of depression; these events are thought to be closely related to the higher incidence of depression in certain age groups (*vide* section 1.2.1.4) [7].

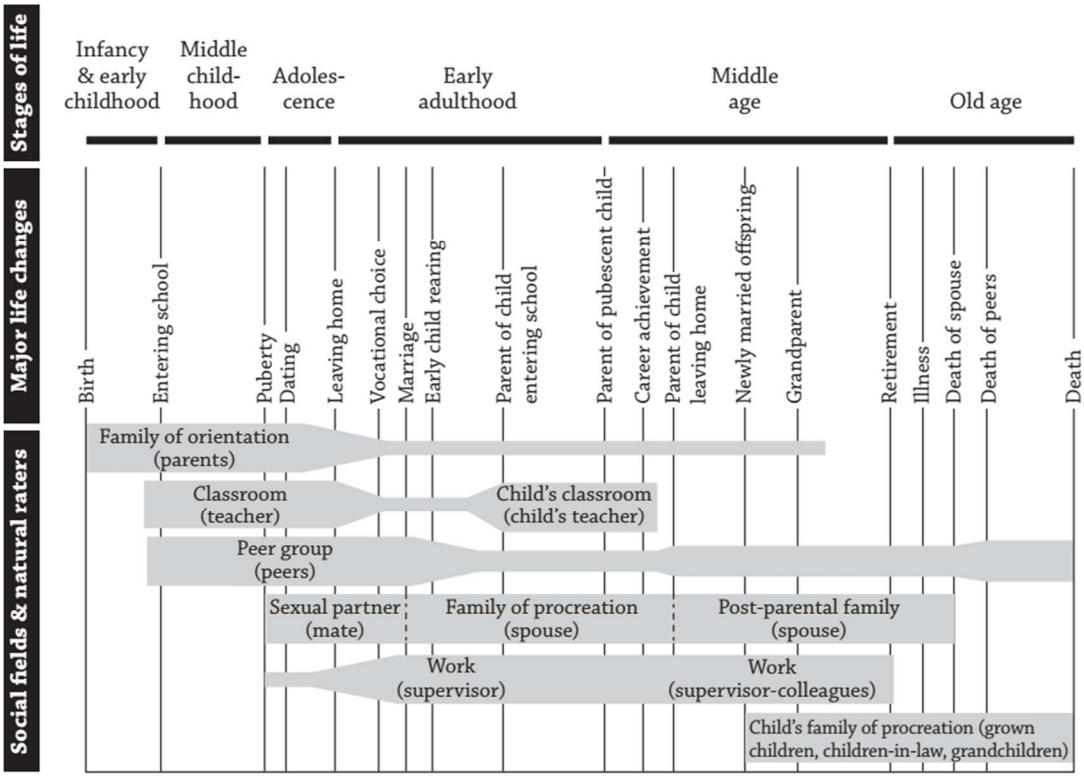

Figure 1.1 Life course social field model. Figure adapted from [7]; reproduced with permission from Oxford Publishing Limited.

The diathesis stress model (Figure 1.2) explains the interaction between genes and stress in the aetiology of depression. The model postulates that neither genes nor stress alone invoke most pathological events, but instead it is the combination of sufficient components of the two that are implicated [18, 19].

Several factors, at individual and societal levels, have been described as modifiers of the association between stress and depression in susceptible individuals. For example, personality traits, such as higher levels of neuroticism, have been shown to interact with stress and potentiate the risk of depression [20]. Increased social support, measured as higher perceived social support, higher number of social relationships, working outside home, or having someone to confide in, have been

shown to buffer some of the negative effects of stress, particularly among women, and protect against depression [21, 22].

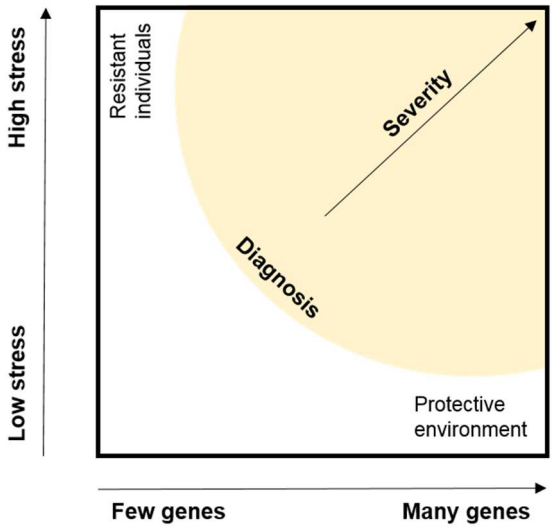

Figure 1.2 The diathesis stress model. Figure from [7]; reproduced with permission from Oxford Publishing Limited.

Physical activity appears to also protect against the onset of depression [23], and part of this effect may be due to increased social interaction.

Natural course of depression

Diagnosed episodes of depression usually last for months, and are on average for four weeks longer in women compared to men [24]. A 12-year longitudinal study on the prognosis of depression reported that 50% of the patients did not observe any further episode, 35% achieved remission but later relapsed, and 15% had unremitting disease during the 12-year period [24]. Depression has also a lengthy prodromal period, often longer than the depressive episode itself [24].

Epidemiology

The risk of depression varies by age and sex, typically following the distribution shown in Figure 1.3 in high-income settings. The higher risk of depression in females starts around puberty, and rates increase rapidly in both sexes, peaking around the mid-twenties and early thirties [25]. Incidence rates tend to decline in both sexes until the mid to late 50s, when small increases have been noted [24, 25]. One may observe that these peaks coincide with life stages when major changes occur (Figure 1.1). In young adulthood, the societal expectations are for one to start a career, be financially independent, have a partner, start a family, etc., which may be a reasonable source of emotional strain for many [7]. In the late 50s, many experience angst over their own children's independence, illnesses, loss of loved

ones, retirement and defining a meaning for the fewer years ahead [7]. Social interactions often change around these stages in life, possibly adding further strain through reduced social support.

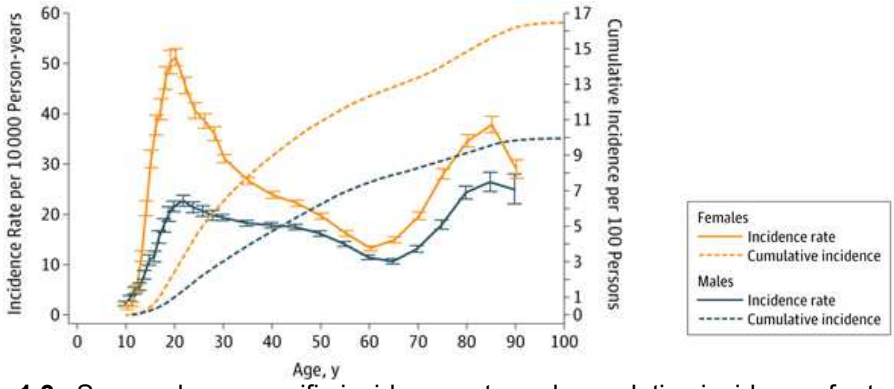

Figure 1.3 Sex- and age-specific incidence rate and cumulative incidence, for treated mood disorders in Denmark. Limit lines show the 95% confidence intervals. Figure adapted from [25]; reproduced with permission from the American Medical Association.

In 2000, unipolar depressive disorder accounted for 4% of all disability adjusted life years (DALYs) in the world, ranking only below infections of the lower respiratory tract and human immunodeficiency virus [26, 27]. In the most affluent regions, it accounted for nearly 8% of the DALYs, ranking only after ischaemic heart disease [26, 27]. Years of life lost due to depression are few (usually attributed to suicide) but the number of years lived with disability (YLDs) is phenomenally high. Women have the largest share of this burden, due to higher prevalence and duration of the disease. In women, YLDs increased 32.2% from 1990 to 2007 and 14.1% from 2007 to 2017 (Figure 1.4). Depressive disorders rank third in the global rank of YLDs in women since 2007 [28].

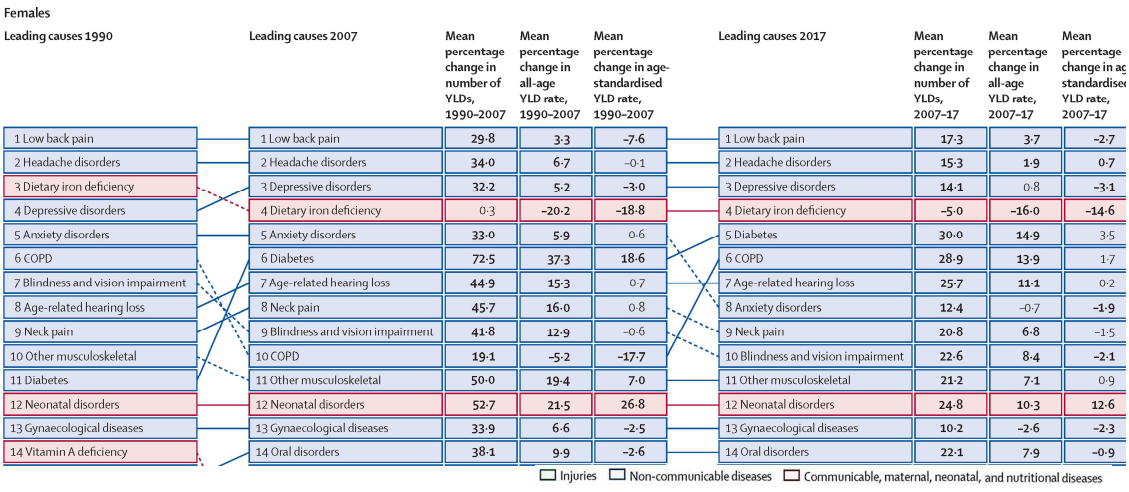

Figure 1.4 Leading causes of global years lived with disability (YLDs) for women in 2017, and percentage change in the number of YLDs and all-age and age-standardised rates. Figure adapted from [28]; reproduced under the terms of a Creative Commons (CC) By Attribution (BY) license.

The global variation in burden of disease may be partially explained by differences in the prevalence of depression across settings. For example, the one-year prevalence of depression was found to vary in a systematic review from <1% in Taipei, Taiwan, to 15.4% in the Republic of Udmurtia, Russia [29]. Several factors may contribute to this disparity, including true heterogeneity in the risk and course of the disease, differential reporting of negative feelings in settings where mental health conditions are stigmatised, and differences in the criteria used to establish 'caseness' (e.g. inclusion/exclusion of dysthymia and bipolar disorders in 'depression').

In the UK, the 2014 Adult Psychiatric Morbidity Survey estimated that 4% of women and 3% of men aged 16-64 met the criteria for a depressive episode in the past week, and a further 11% and 6%, respectively, had symptoms of mixed anxiety and depression [30]. This represented an increase of 2% in the frequency of depressive episodes in both sexes since 1993 (Figure 1.5).

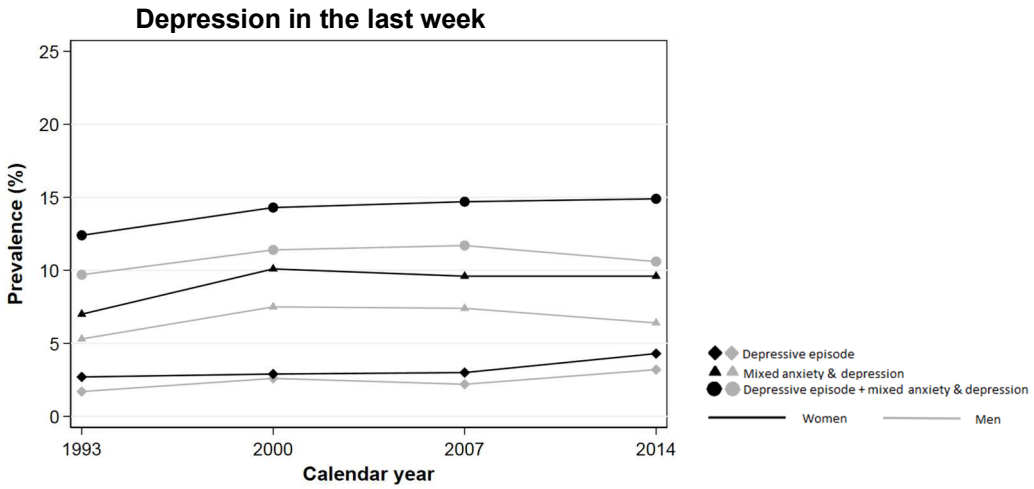

Figure 1.5 Results from the Adult Psychiatric Morbidity Surveys[1] [30] for the prevalence of depressive episodes and mixed depression and anxiety in the week before interview by calendar year of data collection and sex.

In summary, depression affects approximately a fifth of women and a tenth of men during their lifetime. Episodes of depression, even when of mild severity, are debilitating, affecting the individual and their social groups. The high prevalence, duration and impairments generated by the disorder are translated into large numbers of years lived with disability, and demand for public health strategies that mitigate these effects.

[1] The Adult Psychiatric Morbidity Survey includes a large probability sample of the adult general population (aged ≥16 years) living in private households [15] and evaluated the presence of common mental health conditions in the previous week using the revised Clinical Interview Schedule (CIS-R) [16]. Participants were aged 16-64; data for subjects aged over 64 were collected in the two most recent waves, but were not included in the graph to retain comparability over time. The three first waves include data for the whole UK, while only England has been included in 2014.

1.2.2 Anxiety disorders

Definition

Anxiety is the physiological response to situations perceived as dangerous, an ancient biological programming to survive [2]. Low to moderate levels of anxiety are normally associated with enhanced performance but high levels are counter-productive [31]. Anxiety disorders are characterised by exaggerated mental symptoms of fears and anxiousness, physical symptoms, and respective behavioural reactions [4]. Fear is defined in DSM-V as 'the emotional response to a real or perceived immediate threat', while anxiety is 'the anticipation of future threat' [4]. Anxiety disorders have several components, including psychological (feelings of dread, restlessness, narrowed attention, increased alertness and irritability), somatic (hyperventilation and muscle tension), autonomic (increased heart rate and sweating) and avoidance (phobia) [2].

DSM-V includes five anxiety disorders common in adults: specific phobias, social anxiety disorder (social phobia), panic disorder, agoraphobia, and generalised anxiety disorder [4]. Whilst all have symptoms of fear and anxiety at their core, they are differentiated by different patterns in cognition, behaviour, physiology and temporal aspects [7].

Phobias, including specific phobias, social phobia, and agoraphobia, are marked by sporadic anxiety that occurs when one is exposed to a particular object, place or situation, and it causes anxious anticipation and avoidance. Specific phobias refer to fear of specific objects or situations (e.g. heights, blood, flying), while social phobia refers to the fear and anxiety caused by social situations (e.g. meeting strangers). Agoraphobia is characterised by fears related to places and/or situations from which escaping might be, or is perceived as, difficult, and these situations are intensely avoided (e.g. public transportation, crowed spaces, going outside home). Even though the individual recognises these fears as irrational, anticipation or exposure to the object/situation inevitably triggers intense anxiety, causing one to markedly avoid the situation [4].

Anxiety in panic disorder is also intermittent, but unrelated to a particular exposure [2]. Panic disorder is defined by spontaneous and recurrent panic attacks, and at least one month of concerns about additional attacks and their consequences, or changes in behaviour because of the panic attacks [4]. A panic attack, in turn, is defined by fear, with four or more of the following symptoms developing and peaking within 10 minutes: palpitations, sweating, shaking or trembling, shortness of

breath, feeling of chocking, chest pain, nausea, feeling dizzy or faint, de-realization, numbing or tingling sensation, chills or hot flushes [4].

Generalised anxiety disorder is defined by a continuum of excessive and uncontrollable anxiety and worry, in more days than not, for at least six months. Anxiety in generalised anxiety disorder is linked to three or more of the following: restlessness, fatigue, concentration problems, irritability, muscle tension and sleep disturbance [4].

Traditionally, anxiety disorders also included obsessive-compulsive, acute stress-related disorders, and post-traumatic stress disorder (PTSD) [32]. In DSM-V, obsessive-compulsive and stress-related disorders were separated from anxiety disorders. In their new categories, diagnostic criteria remained similar, with obsessive-compulsive disorders having as central features compulsions guided by obsessions (e.g. hoarding) and stress-related disorders originating from a well-defined traumatic situation [4].

Aetiology

The aetiology of anxiety is also complex, and has several similarities to the aetiology of depression. Anxiety disorders are thought to also have a genetic component [33], with studies with twins estimating heritability at ~10-15% at population level [5]. The individual susceptibility to anxiety disorders, however, is thought to be the product of several gene-environment interactions (Figure 1.6) [34].

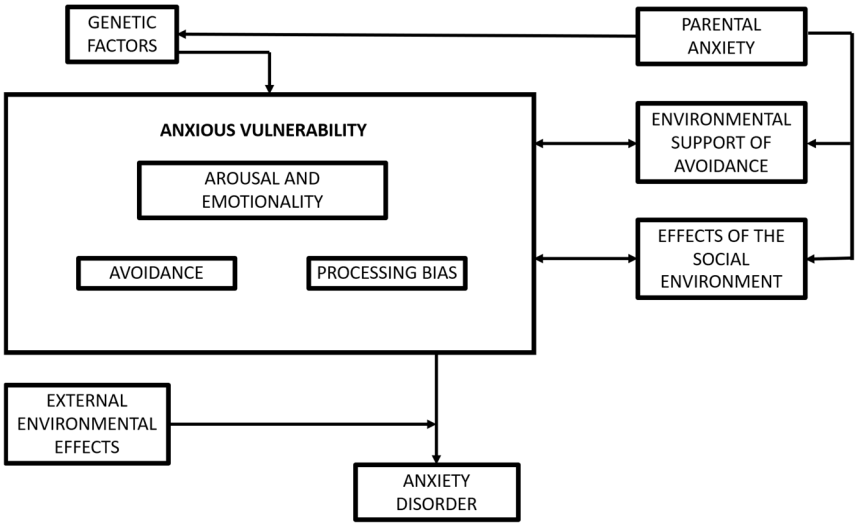

Figure 1.6 Model of anxiety aetiology. Figure from [35]; reproduced with permission from Oxford Publishing Limited.

Environmental factors that appear to contribute to increased susceptibility to anxiety disorders include some that negatively affect personality development during childhood, including parental indifference, physical or sexual abuse, parenting styles dominated by overprotection and lack of emotional warmth [36-39]. Individual personality traits, such as neuroticism may also be implicated [2].

In individuals with increased susceptibility, stress also plays a major role in the incidence of anxiety disorders [2, 35]. Compared to depression, evidence on the stressors for anxiety disorders is scarcer. Lower socio-economic status (measured through levels of income and years of education) was a strong predictor of panic attacks (odds ratio (OR) for <12 years vs. >15 years of schooling: 4.9), panic disorder (OR: 10.4) and panic disorder with agoraphobia (OR: 7.6) [40-42]. Social support has been associated with better outcomes in the treatment of anxiety disorders [43]. Higher levels of physical activity also protect against the onset of anxiety [44].

Epidemiology

Steel et al. estimated the lifetime prevalence of anxiety disorders was 18.2% in women and 10.1% in men based on comprehensive systematic review of studies conducted between 1980 and 2013 [1]. However, there has been considerable variation in the prevalence estimates of anxiety disorders available in the literature, and results from studies using stricter, diagnostic manual, definitions of anxiety disorders tend to show lower estimates. For example, the World Health Organization (WHO) reported that the prevalence of anxiety disorders worldwide in 2015 was 3.6% [45].

Considering specific anxiety disorders, Eaton et al. found that 4% of patients met the criteria for a lifetime DSM-III-R diagnosis of panic disorder, and 16% met the criteria for lifetime fearful spell (i.e. met some but not all DSM-III-R criteria for panic disorder) [40]. Phobias, including agoraphobia, social phobia and specific phobias, are quite common in the population. In the United States, the lifetime prevalence of agoraphobia has been estimated at 9.0% in women and 4.1% in men, while social phobia affected 15.5% of women and 11.1% of men during their life time [42].

Incidence of anxiety disorders registered in EHRs of patients attending primary care practices in 1998-2008 in the UK was estimated at 7.4 per 1000 person-years in women (95%CI: 7.4 to 7.5), and 3.9 per 1000 in men (95%CI: 3.9 to 4.0) [46]. A declining trend in recording of diagnosis of anxiety, accompanied by an increasing

recording of symptoms for anxiety, was observed during the 10-year period [46]. The risk of having an anxiety diagnosis recorded was 58% (95%CI: 37% to 82%) higher in patients in the most deprived areas, compared to those least deprived ones [46]. Incidence of anxiety disorders was lowest in the age group 16 to 24 years and highest among those aged 45-64 years [46]. Figure 1.7 describes the prevalence of each anxiety disorder in the UK Adult Psychiatric Morbidity Surveys. In 2014, 24.6% of the women and 15.9% of the men met the criteria for an anxiety disorder in the week before [30]. Although these figures are not directly comparable to those from EHRs, it is still interesting to observe the increasing trends in patient-reported anxiety.

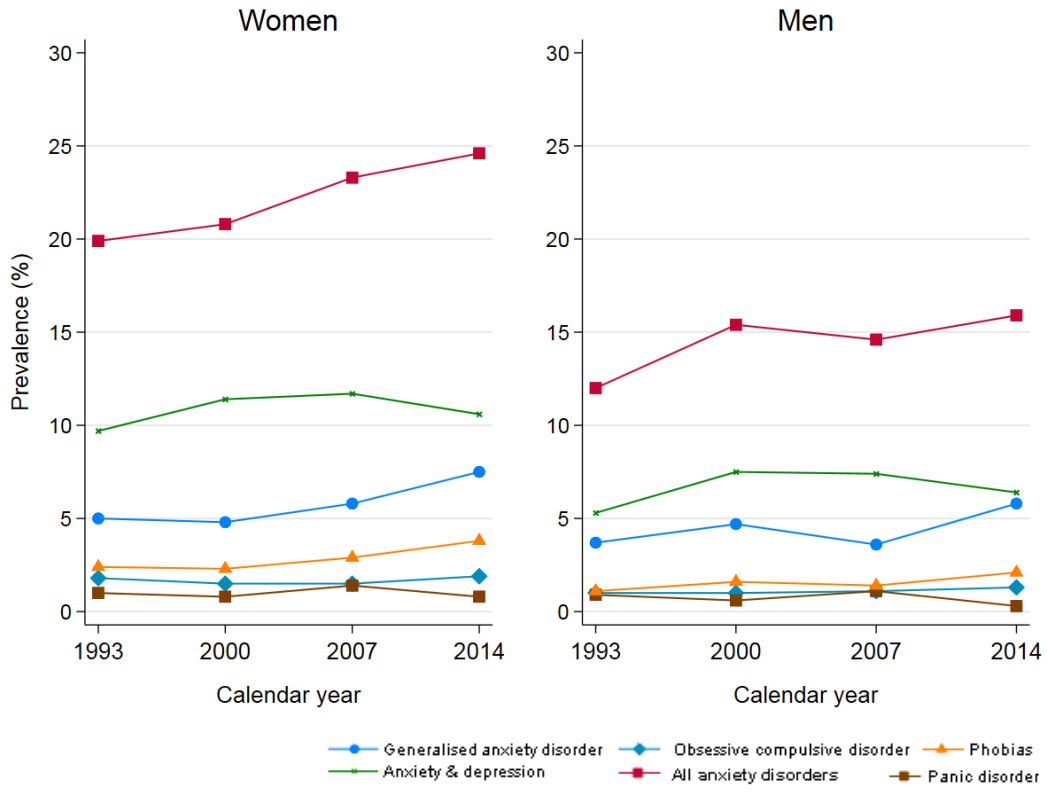

Figure 1.7 Results from the Adult Psychiatric Morbidity Surveys [30] for the prevalence of anxiety disorders in the week before interview by calendar year of data collection and sex.

Anxiety disorders rank eight in the global rank of YLDs (Figure 1.3). The burden of anxiety is particularly high in countries with high socio-demographic index (Figure 1.8). This might be partially explained by the higher lifetime prevalence of anxiety disorders diagnosed in high-income countries (19.4%), compared to low- and middle-income countries (16.0%) [1].

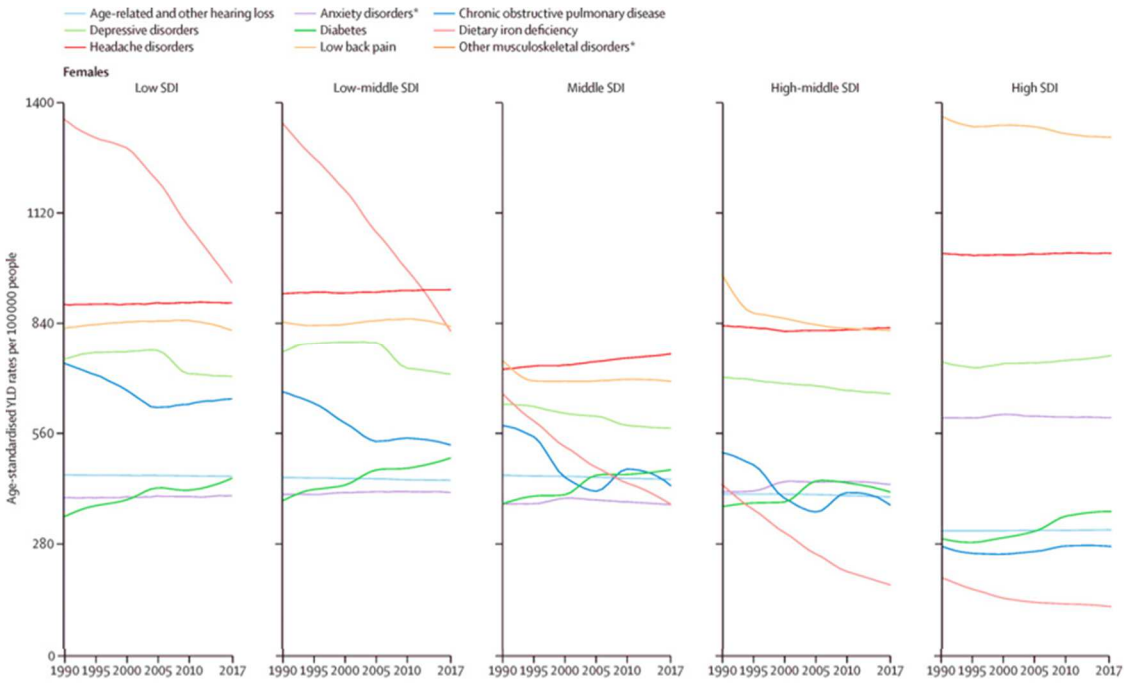

Figure 1.8 Trends of age-standardised YLD rates per 100,000 for the top eight causes of non-fatal burden in 2017 for each sex by socio-economic development index (SDI) quintile, 1990-2017. Figure adapted from [28]; reproduced under the terms of a CC BY license.

In summary, anxiety disorders arise from stressful situations in anxiety personality-prone individuals. The burden generated by anxiety disorders is high, particularly in high-income countries. Women and those with lower socio-economic status are more likely to have an anxiety disorder during their lifetime.

1.2.3 Relationship between anxiety & depression

Descriptive data on anxiety and depressive disorders show considerable similarities [7]. It was postulated that anxiety disorders themselves may also include depressive symptoms [47], with increased stress causing dysthymia, and if these persist, symptoms of panic and agoraphobia may also appear (Figure 1.9). This explains the high co-morbidity of anxiety and depression at individual level.

Data from prospective studies have shown that anxiety and depression are positively correlated both at baseline and at follow-up, in addition to being correlated with the incidence of the other between baseline and follow-up [48]; this means that these conditions predict one another, and share syndrome (i.e. anxiety symptoms may be present in depressive disorders, anxiety disorders may include depressive symptoms). So, while these conditions may be considered as two broad entities, part of the symptomatology will overlap, and many patients present with mixed symptomatology of anxiety and depression.

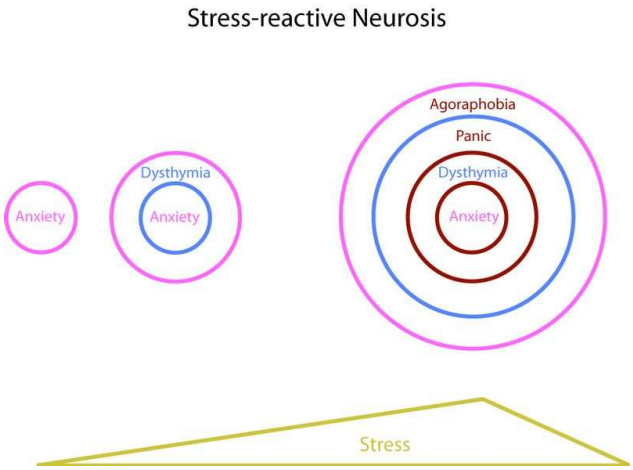

Figure 1.9 Model of stress-reactive neurosis. As the levels of stress increase, dysthymia is present. This explains the high comorbidity of depressive and anxiety symptoms. Figure from [49]; reproduced under the terms of a CC BY Non-Commercial (NC) license.

In addition, for both conditions, lower socio-economic status is associated with raised risks, while social support exerts protective effects [50]. Further evidence for the overlap between these two conditions is provided by genetic studies where, for example, a family history of depression has been shown to increase the odds of having been diagnosed with panic disorder [51]. The natural course of anxiety and depression is also somehow similar, varying from patients who recover fully, patients who keep relapsing over time, and who have unremitting course [52]. Both conditions are more frequent in women, are precipitated by similar stressors, and respond to treatment with similar pharmacological agents [53]. History of depressive disorder appears to increase the risk of panic disorder [41], and both disorders are strong predictors of suicide [54].

1.2.4 Other mental health conditions

Mental disorders other than depressive and anxiety disorders listed in DSM-V are provided in Table 1.1.

Table 1.1 DSM-V categories for mental disorders other than anxiety and depression.

Neurodevelopmental disorders
Schizophrenia spectrum and other psychotic disorders
Bipolar and related disorders
Obsessive compulsive and related disorders
Somatic symptoms and related disorders
Feeding and eating disorders
Elimination disorders
Trauma and stressor related disorders

(continued)

Table 1.1 (continued)

Dissociative disorders
Sleep-wake disorders
Sexual dysfunctions
Gender dysphoria
Disruptive, impulse-control, and conduct disorders
Substance-related and addictive disorders
Neurocognitive disorders
Personality disorders
Paraphilic disorders

The aetiology of these disorders is varied. Some disorders have typical onset during childhood (e.g. neurodevelopmental disorders), and thus are unlikely to be associated with exposures characteristic of adult life. A few disorders are known to be associated with biological changes in the central nervous system due to a specific medical condition (e.g. dementia in multiple sclerosis, or after stroke). Other disorders can have both physical and psychological origin (e.g. sexual dysfunction). And several disorders are defined by similar symptoms (e.g. anxiety as symptom in sleep disorders).

The following paragraphs briefly describe sleep-wake disorders, sexual dysfunctions, neurocognitive disorders, and self-harm. There were chosen due to their onset in adult life, and potential association with stress. Self-harm is also described because it is the manifestation of mental distress, even though it is not a mental disorder per se.

Sleep disorders

Sleep disorders are related to impairments in sleep quantity, quality or timing [4]. Insomnia and hypersomnia are the most common conditions. Insomnia is characterised by difficulties in initiating or maintaining sleep, causing sleep deprivation that can cause substantial distress to the patient [4]. Hypersomnia refers to prolonged sleep (>9 hours or recurrent episodes sleep) that is not restorative [4].

Sleep disorders are relatively common [55]. A review showed prevalences in the general population that varied from 8% to 33%, depending on the definitions used [56]. In the UK, a survey of the general population in 1994 described a prevalence of insomnia of 6.8% in men and 10.6% in women [57].

Risk factors for sleep disorders include female gender, depression, chronic physical illnesses, and possibly lower socio-economic status, widowhood, and loneliness and

perceived stress [58-60]. Insomnia becomes chronic in nearly 50% of the patients [61] and is often comorbid with other distressing conditions (most often anxiety, pain and dementia) or excess use of substances such as caffeine or ethanol [2].

Female sexual dysfunction

Sexual dysfunctions refer to impaired or unsatisfied sexual experiences [2]. In females, the most common sexual dysfunctions are orgasmic disorders, arousal disorders, and genito-pelvic pain [4]. Orgasmic disorder is defined by the absence or substantial delay in reaching orgasm in most (75-100%) of the sexual activity events, which can cause distress to the individual [4]. Arousal disorder occurs when the woman has persistent (>6 months) lack of, or importantly reduced, sexual interest that causes clinically significant distress [4]. Genito-pain disorders (including vaginismus and dyspaneuria) include difficulties with vaginal penetration or pain during vaginal penetration, with or without constriction of the pelvic floor muscle that prevent penetration, that last for six or more months and causes distress [4].

The advances in the understanding of sexual dysfunctions are great challenges for the definition of objective criteria to establish a diagnosis and, consequently, for research in this area. All revisions of the DSM have included changes related to sexual dysfunctions [62]. DSM-V reduced the categories of sexual dysfunctions compared to DSM-IV, and included stricter criteria for diagnoses of sexual dysfunction (e.g. present in 75-100% of the time, for ≥6 months, and causing significant distress), aiming at reducing the over-diagnoses of sexual dysfunctions with DSM-IV criteria and better represent the most recent model of female sexual function [63, 64].

In 2003, a survey of women aged 15-44 in Britain reported that 10% had a lack of sexual interest, 14% were unable to reach orgasm, and 12% had painful intercourse [65]. In a more recent survey (2010-2012), lack of sexual activity in the previous year was associated with problems in sexual function, and 10.9% of women who had had sex during the previous year were distressed about their sex life [66].

Decreased sexual activity in post-menopausal women may be explained by a wide range of factors, including lack of partner available (e.g. widowhood, separation), presence of medical conditions more common older ages (back pain, dementia, erectile dysfunction), bereavement for loved ones, relationship difficulties, fatigue, among others [58]. Psychiatric disorders, such as depression and/or anxiety, and some psychotropic drugs, such as selective serotonin receptors inhibitors (SSRI) or tricyclic antidepressants, may also impair the female sexual function [2].

Neurocognitive dysfunction

Neurocognitive dysfunctions have impairments of the intellect, memory and personality as central features; 95% of cases are irreversible [2]. The main conditions in this category are Alzheimer's disease, vascular dementia, frontotemporal dementia, Lewy bodies disease, and dementia in Parkinson's disease [4]. Neurodegenerative alterations in the central nervous system, usually visible through brain atrophy, are often observed in patients with these conditions, and explain the pathophysiology. In cases where impairments to the domains of cognitive function are not sufficient for a specific diagnosis, the term mild cognitive dysfunction is used [4]. Between 10% and 20% of the cases mild cognitive impairment are expected to progress to dementia [67].

Incidence of dementia was estimated at 14.3 per 1000 person years in men and 17.0/1000 person years in women aged 50 or more in England in 2010 [68]. In those aged ≥60 years, prevalence was estimated to vary between 5 and 7% [69]. Alzheimer's disease usually accounts for 50-60% of all dementia cases, followed by vascular dementia (20-25%) and dementia with Lewy bodies (15-20%) [2].

Several factors have been pointed out to increase the risk of dementia, such as hypertension, diabetes, obesity, and alcohol use [70-73]. Trends in the incidence of Alzheimer's disease appear to be stable in western countries, but the burden has almost doubled between 1990 and 2013 due to the increased survival [74].

Fatal and non-fatal self-harm

Intentional self-harm is commonly associated with an underlying mental condition, and it may occur for several reasons, including a desire to punishing oneself, to express distress to others, to escape or avoid situations, to release feelings of anger, tension, anxiety or depression, among others [75-77]. The severity of self-harm ranges from injuring behaviour with no suicidal intent, to suicide.

Figure 1.10 shows some of the most relevant risk factors for self-harm and suicide in adolescents and young adults, and the mechanisms that may be involved [78]; the model for adults is likely to be similar. Alcohol consumption, previous psychiatric disorder, previous self-harm attempts that led to health-service contact, among others, appear to be strong predictors of self-harm [77, 79]. Risk factors for suicide are in all similar to those for self-harm. There is also a considerable body of research on chronic diseases as a risk factor for suicide, including heart failure [80],

chronic obstructive pulmonary disease [81], atopic dermatitis [82], multiple sclerosis [83], chronic pain [84], among others.

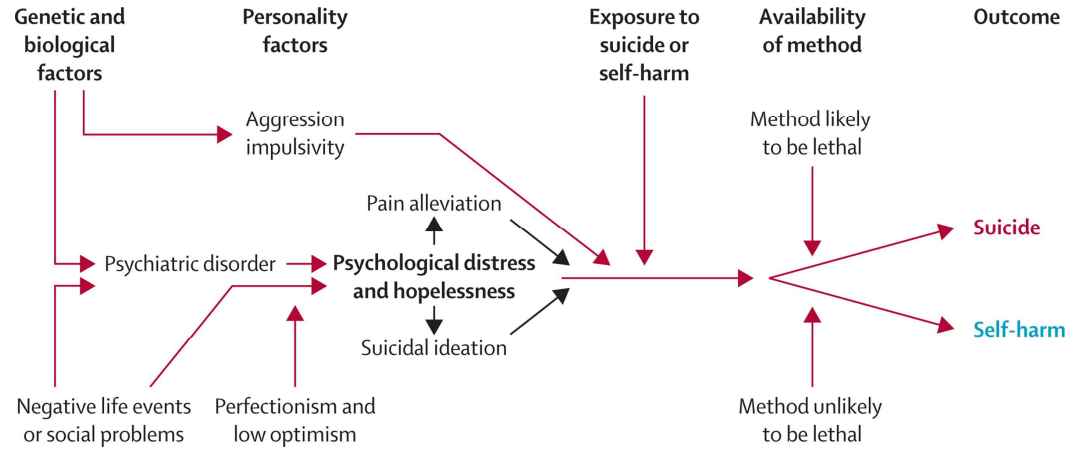

Figure 1.10 Risk factors for self-harm and suicide. Figure from reference [78]; reproduced with permission from Elsevier.

Self-harm is most common in adolescents and young adults, but the proportion of subjects who self-harm around midlife in England is not negligible [77] (Figure 1.11). In addition, the prevalence of intentional self-harm without suicidal ideation in England increased from 2.4% in 2000 to 6.4% in 2014 [77].

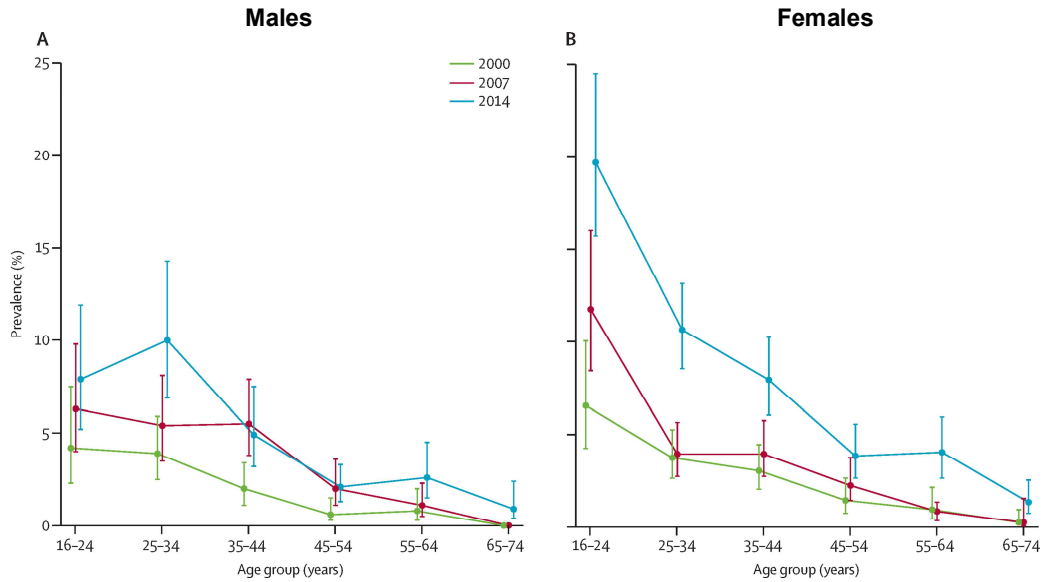

Figure 1.11 Prevalence of self-harm without suicidal intention in males (panel A) and females (panel B) in England. Figure from [77]; reproduced under the terms of a CC BY license.

Self-poisoning, commonly with paracetamol or anti-depressants, accounted for 78.6% of the men, and 86.8% of the women, aged 40-59 years old that presented to hospital with self-harm; the remaining were cases of self-injury and/or self-poisoning [85].

Self-harm is a strong risk factor for suicide [86] but only a small proportion of the self-harm cases result in death (Figure 1.12) [87].

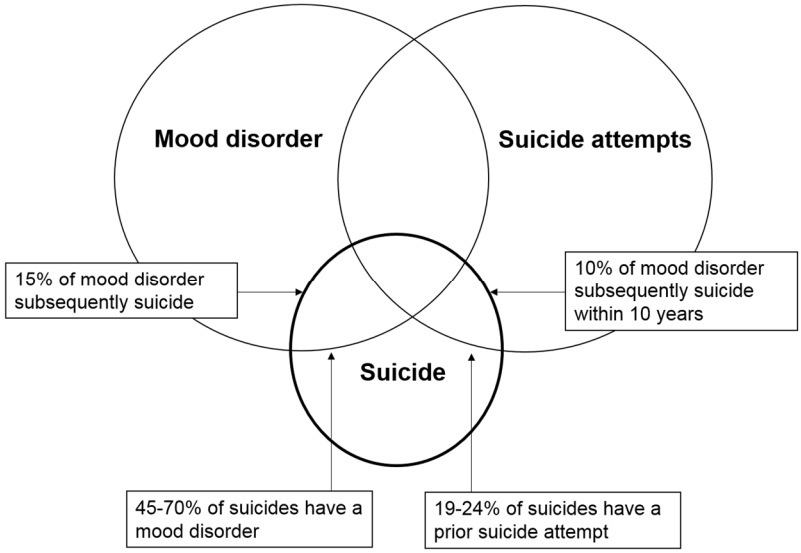

Figure 1.12 Venn diagram showing the relation between suicide attempts, suicides and mood disorders. Adapted from [88]; reproduced with permission from Wolters Kluwer Health.

Following the global trends, the rate of suicide has increased in the UK since 1950 [2]. Even though self-harm is more common among women, completed suicide is more common in men. The highest risk of suicide in the UK in 2014 was observed for men aged 45-59 years (23.9 deaths per 100,000 population). The corresponding highest risk estimate for women was also in the age group of 45-59 years, with 7.3 deaths per 100,000 population [89].

1.3 Breast cancer

1.3.1 Incidence

Breast cancer incidence markedly increased during the last decades (Figure 1.13) and it is currently the most frequently diagnosed malignancy in women in the UK, excluding non-melanoma skin cancer [90, 91].

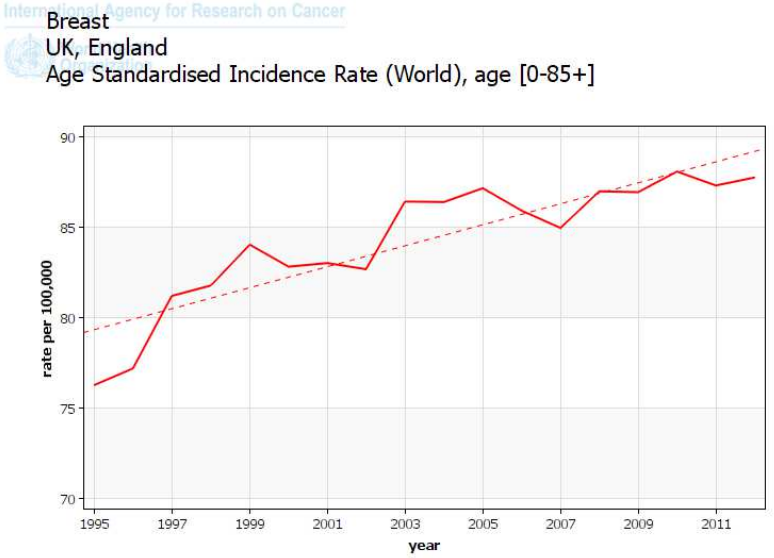

Figure 1.13 Trends (full line) and linear trend (dashed line) of the age-standardised incidence rates of breast cancer in England (1995-2011). Figure from [92]. reproduced 'as is' for research and education purposes.

Breast cancer is currently understood as being a disease closely related to exposure to hormones. The female breast is composed of glandular tissue whose primary function is milk production after parturition [93]. The development of the breast tissue during adolescence relates to the effects of oestrogen and progesterone, two hormones that start to be produced with the onset of the luteal phase of the ovary [94]. During the subsequent menstrual cycles, if no pregnancy occurs, the breast develops and then regresses [95]. However, if a pregnancy occurs, the placenta produces hormones that stimulate the development of the breast tissue (e.g. oestrogen, progesterone and placental lactogen [94]) causing the expansion of the ducts and lobules [95]. Women exposed to a higher number of menstrual cycles during their lifetime, through menarche at younger age [96], late menopause [96], or no pregnancy- or lactation-related amenorrhea [97, 98], have an increased risk of breast cancer [96]. Use of exogenous hormones, such as oral

contraceptives and hormone replacement therapy, are also associated with an increased risk of breast cancer [99].

It is estimated that around 10% of the breast cancer cases occurring the western world are due to genetic predisposition [100], even though not much is known about how many and which genes increase the risk of breast cancer. Identified genes have been shown to have autosomal dominance with limited penetrance, passing to the next generations through either parent, and not leading to cancer development in all carriers. BRCA1 and BRCA2 are two notable oncogenes in this area, located on chromosomes 17 and 13, respectively [100]. BRCA1 and BRCA2 are tumour suppressor genes, involved in the regulation of transcription and reparation of DNA. Alterations in these genes are rare in the general population, at about 0.1% [95]. However, approximately 60-80% of the women who carry these mutations develop breast cancer, usually around the age of 50 years [95].

Several lifestyle risk factors for breast cancer have been identified and some of these vary by women's menopausal status [101]. The World Cancer Research Fund International and the American Institute for Cancer Research have produced robust evidence on the effect of food, nutrition and physical activity in the development of breast cancer [101-103]. According to the latest revision of the evidence, based on comprehensive systematic reviews and meta-analyses, there is strong evidence that lactation, physical activity and body fatness in young adulthood are associated with a decreased risk of breast cancer in both pre- and post-menopausal women (Table 1.2) [103].

Table 1.2 Lifestyle risk factors for breast cancer: levels of evidence.

	Protective factors (level of evidence)		**Risk factors (level of evidence)**	
Pre-menopause	Lactation	(P)	Alcoholic drinks	(P)
	Body fatness	(P)	Adult attained height	(C)
	Vigorous physical activity	(P)	Greater birth weight	(P)
	Non-starchy vegetables (ER- only)	(S)		
	Dairy products	(S)		
	Carotenoid rich foods	(S)		
	Diets high in calcium	(S)		
	Physical activity	(S)		
Post-menopause	Lactation	(P)	Alcoholic drinks	(C)
	Physical activity of all types	(P)	Body fatness	(C)
	Body fatness in young adulthood	(P)	Adult attained height	(C)
	Non-starchy vegetables (ER- only)	(S)	Adult weight gain	(C)
	Carotenoid rich foods	(S)		
	Diets high in calcium	(S)		

C = convincing; P = probable; S = suggestive.
Convincing and probable levels of evidence are supported by strong evidence from the literature; suggestive is supported by limited evidence.
Table adapted from [103].

Of the established risk factors for breast cancer, only a few are amenable to change: exogenous hormone use, post-menopausal excess of body weight and alcohol intake. Reproductive factors are less likely to be changed for cancer prevention purposes in modern societies. Therefore, breast cancer will continue to have high incidence globally in the foreseeable future. With the gains in life expectancy observed in the last century [104], the aging of the population alone will result in increased numbers of breast cancer patients.

1.3.2 Control

Breast cancer control strategies have mainly focused on early detection and treatment. A mass-screening programme targeting women aged 50-64 years old has been operating since 1988 [105]; in 2000, screening was extended up to the age of 70 years [106]. Tumours detected through mammography tend to have a lower stage at diagnosis, and consequent better survival, than tumours detected when the disease is symptomatic [107]. Even for late-stage tumours, the (neo-)adjuvant hormonal and immune therapies, introduced in the last decades, resulted in notable improvements in survival. In England and Wales, for example, 5-year age-adjusted net survival from breast cancer increased from 53% in 1971-72 to 87% in 2010-11 (Figure 1.14) [108].

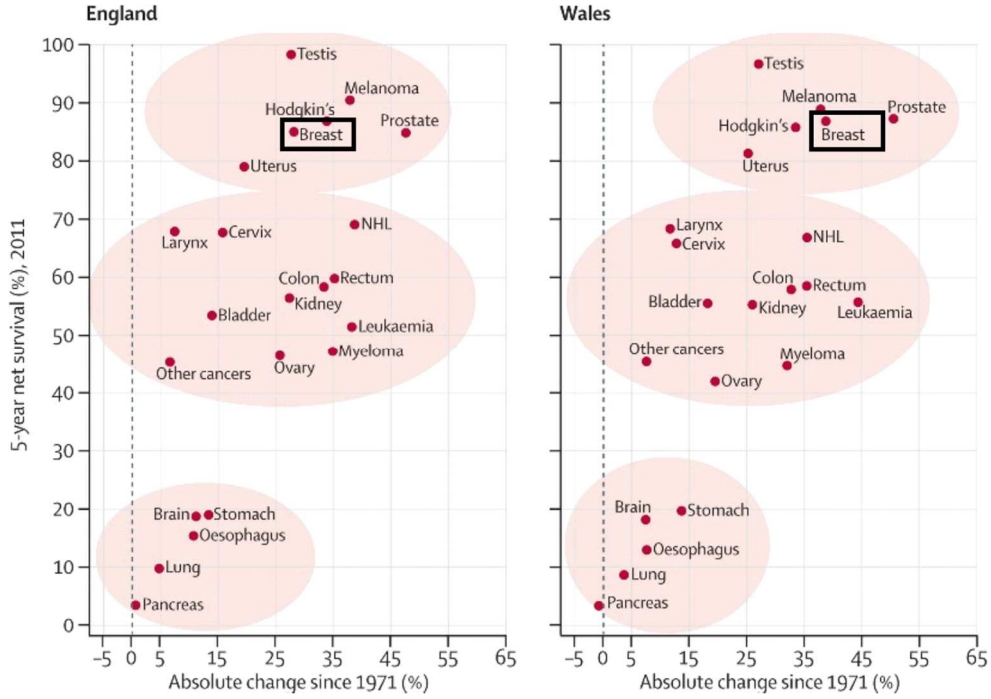

Figure 1.14 Five-year net survival, adjusted for age, for patients diagnosed in 2010-2011, and absolute change since 1971 in England and Wales. Figure adapted from [108]; reproduced under the terms of a CC BY license.

This is translated into unprecedented numbers of breast cancer survivors in the general population. Approximately 570,000 women in the UK were estimated to have a history of breast cancer in 2010 [109].

A comparison of the survival estimates estimated for the UK with those from three Nordic countries (Figure 1.15), which have similar national health systems, shows that there is still margin for improvements, and therefore the number of breast cancer survivors is still expected to increase in the decades to come.

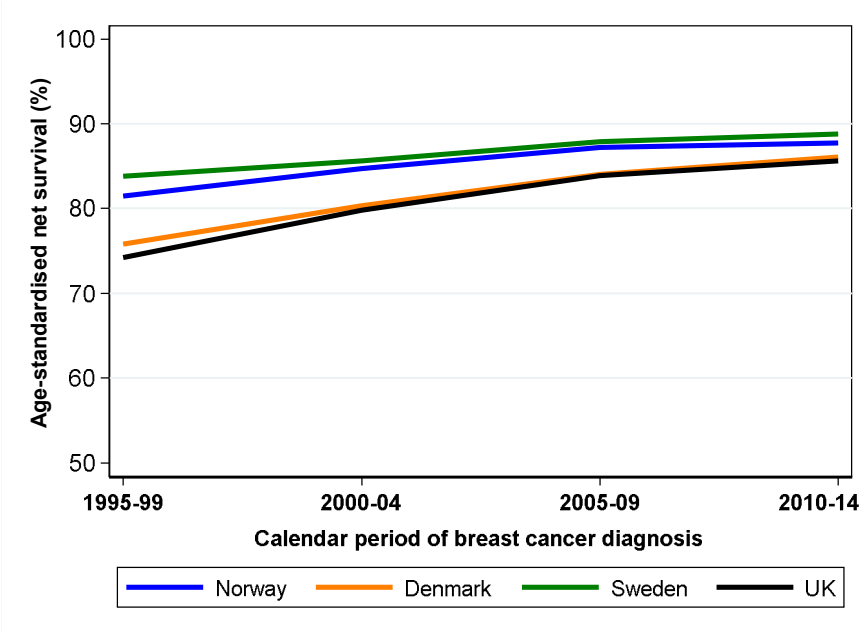

Figure 1.15 Trends in five-year age-standardised net survival (%) from breast cancer in the United Kingdom (UK) and in three Nordic countries from 1995-99 to 2010-14.
Figure created using data publicly available from [110, 111].

By 2040, projections indicate that there will be 1.5 million women with history of breast cancer living in the UK [109].

1.3.3 Treatment

Current treatment modalities with curative intent include combinations of surgery (mastectomy or breast conserving surgery, with sentinel lymph node biopsy or axillary dissection), radiotherapy, chemotherapy (e.g. antracyclines and/or taxanes), endocrine therapy (tamoxifen or aromatase inhibitors) for oestrogen receptor (ER) positive tumours, and monoclonal antibody therapy (trastuzumab) for Human Epidermal growth factor Receptor 2 (HER2) positive tumours [112]. An example of the combinations recommended by the European Society for Medical Oncology (ESMO) for treatment of early breast cancer is given in Figure 1.16.

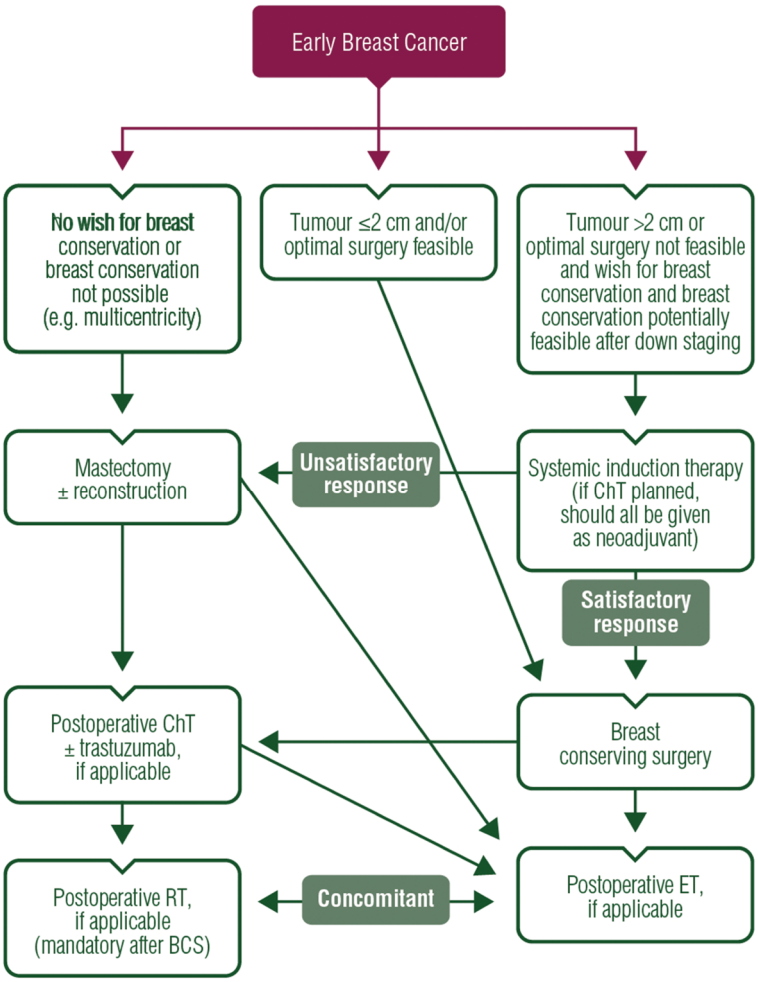

Figure 1.16 Early breast cancer treatment algorithm [16].

Reproduced with permission from Oxford University Press. Cht = chemotherapy; BCS = breast-conserving surgery; ET = endocrine therapy; RT = radiotherapy.

Surgery is an essential treatment offered to all patients treated with curative intent. Currently, 60-80% of the breast cancer patients are eligible for breast-conserving surgery and mastectomy is only recommended for a subset of patients with specific characteristics or who prefer it [112]. Assessment of the lymph nodes status is mandatory for the determination of the stage of the disease and is generally carried out by axillary lymph node dissection or sentinel lymph node biopsy during surgery.

Treatment pathways after surgery largely depend on the biological characteristics of the tumour, stage of the disease and patient's physical condition [112]. For early-stage breast cancer, adjuvant radiotherapy is effective in reducing breast cancer related mortality [113], and thus almost always offered to women who have breast-conserving surgery. Six months of chemotherapy regimens have been shown to decrease the annual breast cancer death rate by 20-38% [114].

Adjuvant systemic treatments for breast cancer, other than chemotherapy, include hormone and immune therapies. Endocrine therapy is currently recommended for patients with tumours whose cells express high proportions of ER (70% of breast cancers) to reduce the risk of recurrence [112]. Tamoxifen, a selective oestrogen receptor modulator, given for 5-10 years is usually the primary choice for pre-menopausal women [112]. Five years of tamoxifen decreased breast cancer death rates by 31%, independently of the use of chemotherapy [114] and improved survival of women with metastatic breast cancer [115]. For post-menopausal women both tamoxifen (5-10 years) and aromatase inhibitors (AI) (5 years) have been used [112], but AIs have become the preferred choice, as meta-analyses indicated lower risk of recurrence compared to tamoxifen [116, 117]. Approximately 10-20% of breast cancer patients have tumours that overexpress proteins encoded by the HER2 [118], an oncogene that belongs to the epidermal growth factor receptor (EGFR) family, which is involved in the cell growth and differentiation [119]. Trastuzumab is a monoclonal antibody therapy effective in treating HER2+ tumours [120].

1.4 Common physical consequences of breast cancer treatments

All breast cancer treatments carry the risk of long-term iatrogenic effects.

Surgery inevitably results in a life-long scar and may change women's body image. Women who had mastectomy have reported more body image concerns compared to women who had breast-conserving surgery [121, 122].

The axillary lymph node dissection, conducted for the purposes of breast cancer staging, carries the risk of intercostobrachial nerve damage [123], which is located close to the lymph nodes and has many anatomical variants [124, 125]. Persistent pain after breast cancer treatment has been estimated to affect 25-60% of women [126], depending on patients' selection and methodology of pain assessment. Pain usually affects the axilla, medial upper arm, breast and/or chest wall [126]. Women who had axillary lymph node dissection reported more frequently persistent pain than women who had sentinel lymph node biopsy [127-129].

Axillary surgery and/or radiotherapy may lead to lymphoedema [130], a chronic condition characterised by the accumulation of fluids in the interstitial tissues due to incapacity of the lymphatic system to effectively distribute lymph [131]. The most common symptoms include shoulder, arm and hand swelling, heaviness, tightness, firmness, pain, numbness, and impaired upper member mobility [132]. The

incidence of lymphoedema in patients who had axillary lymph node dissection is estimated at around 19.9% (95%CI: 13.5-28.2%), while the corresponding figure for women who had sentinel lymph node biopsy is 5.6% (95%CI: 6.1-7.9%) [133].

Other important side effects of radiotherapy include skin reactions (e.g. dermatitis, skin thickening, hyperpigmentation, ulceration), oedema, pain, stunning or burning bothers, and fatigue [134]. Radiotherapy may also result in irradiation to the heart and blood vessels [135], oesophagus and lungs. Radiotherapy administered in the 1970s was shown to increase mortality from heart disease [136, 137] and lung cancer 10-20 years after irradiation [136]. Radiotherapy technologies and techniques have changed since then, and it is unclear whether increased cardiovascular risk persists [138, 139]. Women also often experience fatigue during the chemotherapy and radiotherapy; around 30% of women continue experiencing fatigue after treatment [140]. The aetiology of fatigue is unclear, but most likely includes psychological and biological factors, such as depression and increased pro-inflammatory cytokines [140].

The side effects of chemotherapy highly depend on the regimen used [141]. Common acute side effects of chemotherapy and their adjuvant treatments, such as granulocyte colony stimulating factor (G-CSF), include nausea, gum bleeding, diarrhoea, constipation, increased risk of infection, anaemia, insomnia, alopecia, bone pain and fatigue [142, 143]. Alopecia in some cases becomes permanent [144, 145]. Chemotherapy induced amenorrhea has long been described in premenopausal women [146-148]. The proportion of women aged 50 year or younger at diagnosis who become post-menopausal after adjuvant chemotherapy varied between 33% and 77% [149]. In addition, neurocognitive changes affect 13-70% of the cancer patients within two years of treatment [150] and may be long-lasting [151, 152]. These neurocognitive changes, also known as “chemo fog”, are a form of cognitive impairment that usually involving memory deficits, reduced concentration and executive function [151, 153]. The pathophysiology of cognitive dysfunction in these patients is unknown, but chemotherapy may have direct toxic effect to neurons and other non-neuronal structures of the central nervous system [154, 155]. Chemotherapy may also induce damages to the pelvic nerves, causing neuropathy, which may lessen body sensations and impair the ability to reach orgasm [156]. Another adverse effect of the chemotherapy is loss of bone mineral density [157-159], through direct toxic effect and indirect effects related to ovarian failure in pre-menopausal women. Use of anthracyclines regimens has also been also linked to cardiomyopathy and congestive heart failure, especially if

concomitantly used with trastuzumab [160]. Most cases of cardiac dysfunction are detected after one year of treatment completion and are often irreversible [142].

Hormonal treatments, including both tamoxifen and aromatase inhibitors, have been associated with increased risk of uterine and endometrial cancers (tamoxifen), arthralgias/myalgias, fatigue, deep venous thrombosis (tamoxifen) besides climacteric symptoms induced by oestrogen deprivation [161]. It is unclear whether aromatase inhibitors are associated with higher risk of cardiovascular events, but tamoxifen has been suggested to have cardioprotective effects by reducing levels of total cholesterol and low-density lipoproteins [161, 162]. The reductions of oestrogen levels, which can be caused either by endocrine treatments or chemotherapy-induced ovarian failure, have physical implications similar to those experienced in menopause – vaginal atrophy and dryness – and make sexual intercourse painful [163].

Adverse effects of trastuzumab include a non-negligible cardio-toxic effect, as noted by significantly decreases in left ventricular ejection fraction and increased risk of congestive heart failure [164, 165]. Presently trastuzumab is administered with taxanes, for which cardiotoxicity is thought to be much lower [112].

1.5 Mental health and quality of life beyond breast cancer

The period of breast cancer survivorship starts at diagnosis, which is often a major cause of emotional distress for a patient [166]. The general population perceives breast cancer as life threatening and many women report traumatic experiences with the diagnosis [167, 168]. Common reactions to this ominous diagnosis include anxiety, fear of death, hopelessness, anger, suicidal thoughts, among others [169, 170].

The main treatments for breast cancer have also been associated with substantial emotional and physical distress, and there are many stressors for this. During the treatment period women are forced to adjust to a new reality that includes a new body image with alterations that may go beyond the breast disfiguration or amputation. Alopecia due to chemotherapy treatments, for example, has been often reported as is highly distressing [171], not only due to the altered body appearance also because it allows other people to become aware of the patient's cancer diagnosis and treatment. Lymphoedema is also perceptible to others, and often associated pain, numbness, tightness, increased risk of infections, among others, and all of these are distressing for the patients [152, 172, 173]. Breast cancer

survivors sometimes find social relationships challenging, as they have to adapt to the uncertainty brought by their diagnosis, which affects themselves and their significant others, including their offspring and spouse [174-176]. Neurocognitive changes, even of the milder severity, are also reported as distressing by the patients, as they interfere with important aspects of everyday life, including work performance [177]. Fatigue and persistent pain have been shown to be associated with low health-related quality of life and functional impairments [178-181]. Early menopause brings fertility concerns for women who want more children, and force women to take life-long reproductive decisions, which affect their partners as well [149, 182]. With the panoply of life-changing events, the possible presence of acute and long-term symptoms resulting from the cancer treatments, and the need to deal with the fear of cancer recurrence and death [183], it is not surprising that clinically relevant symptoms of anxiety and/or depression are common during the treatment period [184, 185]. Virtually all domains of HRQoL, including mental health, have been described as impaired in women who had recently been diagnosed with breast cancer [186, 187].

Longitudinal studies on the HRQoL of breast cancer survivors showed that mean scores for the mental health domain tend to improve over time, reaching similar levels to those of the general population around the first anniversary of diagnosis [188, 189]. This is consistent with women psychologically adjusting to a life beyond the traumatic event of breast cancer. In addition, not all changes induced by the cancer are negative. Studies have described that up to 60% of women experience post-traumatic growth, a phenomenon of heightened well-being with one-self after a stressful event, where life is seen through different lenses [190]. Women have described feeling improved empathy, closer relationships, healthy lifestyle changes, greater appreciation for life and oneself, among others. This is likely to have a positive impact in the women's quality of life and mental health [191]. However, carrying on a life after breast cancer implies coping with the negative effects of cancer as well, and positive and negative aspects most likely interact in and with time, and offset some of the negative effects [191].

Some particular groups of breast cancer survivors, however, have been described to have poorer long-term HRQoL. Examples reported in the literature include those with younger age at diagnosis [192, 193], lower socio-economic status [194], having persistent fatigue [195], lymphedema or arm symptoms [196, 197], or having had chemotherapy [198, 199]. In addition, previous research on the trajectories of

depressive symptoms after a breast cancer diagnosis showed that the symptoms persisted for at least two years in one out of every five women [200].

The long-term mental health and quality of life implications of having been diagnosed and treated for a breast cancer have not been extensively studied, partially because only relatively recently the number of women living beyond breast cancer has reached considerable numbers at population level. This increase in the prevalence of breast cancer survivors in the general population raises questions on the specific long-term health care needs of this group, and whether they might benefit from increased opportunistic screening for mental disorders. Even though depression and anxiety are the most commonly studied outcomes in the literature, it was still unclear whether breast cancer survivors had an increased risk compared to women with no history of cancer. This was because most studies involved breast cancer survivors only, without comparing the results with a group without cancer, making it difficult to ascertain whether the reported changes in the mental health of the breast cancer survivors can be attributed to the previous cancer diagnosis or are only characteristic of the aging process. In addition, little is known about the frequency of sleep disturbances, sexual disorders and post-traumatic stress disorder in breast cancer survivors, compared to women with no history of cancer. Research on the HRQoL of breast cancer survivors is scarce in the UK, and mostly has focused on establishing the feasibility of widespread collection of patient-reported outcomes [201, 202].

With the increasing numbers of breast cancer survivors, the potential for mental health impact of their medical history, and the burden generated by mental disorders, it is imperative to generate evidence on the absolute and relative risk of mental disorders in this key patient group. This may in turn be used to underpin public health strategies that aim to mitigate the burden of mental disorders in these patients, and ultimately provide breast cancer patients with evidence-based care that meets their specific needs.

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1.6 Summary

- The lifetime risk of a depressive or anxiety disorder is one in five for women, and one in 10 for men. Stress acts as the precipitating factor for the onset of mental disorders in susceptible individuals.
- Episodes of the mental disorders are highly incapacitating. Only half of the patients achieve lifetime remission, with the remaining having unremitting or recurrent episodes.
- Women in the UK currently have a one in seven risk of being diagnosed with breast cancer during their lifetime. This is the most common cancer diagnosed in the UK, except for non-melanoma skin cancer, and 5-year net survival is now approaching 90%, resulting in a record number of women carrying on post-breast cancer.
- Women with history of breast cancer may have long-term physical consequences of their cancer and treatments, some of which are debilitating and may affect patients' mental health and health-related quality of life (Table 1.3).

Table 1.3 Possible physical and psychological consequences of breast cancer treatments.

Treatment *	Consequences (definitive or possible)	
	Physical	**Psychological**
Surgery[1] [121, 123, 125, 133]	Breast shape alteration (BCS) Breast amputation (mastectomy) Life-long scar Intercostobrachial nerve damage (ALND) Lymphoedema	Body image concerns Low self-esteem Persistent pain Psychological distress
Radiotherapy [134, 136]	Skin reactions (e.g. hyperpigmentation) Oedema Fatigue Heart disease Lung cancer	Pain Psychological distress
Chemotherapy[2] [143, 144, 147, 153, 157, 171]	Alopecia Amenorrhea (if premenopausal) Cardiac dysfunction (anthracyclines) Fatigue Loss of bone mineral density Vasomotor symptoms	Body image concerns Cognitive impairment Psychological distress
Endocrine therapy[3] [161, 162]	Deep venous thrombosis Vasomotor symptoms Arthralgias Fatigue Uterine cancer (tamoxifen and AI) Endometrial cancer (tamoxifen)	Psychological distress Sexual dysfunction
Immune therapy[4] [164, 165]	Left ventricular dysfunction Congestive heart failure	Psychological distress

BCS – breast conserving surgery; ALND – axillary lymph node dissection; AI – aromatase inhibitors.
* Most women receive more than one treatment.
[1] Refers to the procedures for tumour removal (breast-conserving surgery or mastectomy) and evaluation of the presence of metastasis in the lymph nodes (axillary lymph node dissection or sentinel lymph node biopsy). [2] Regimens with taxanes or anthracyclines. [3] Includes selective oestrogen receptors modulators and aromatase inhibitors. [4] Trastuzumab.

- Even though depression and anxiety are the most commonly studied outcomes in the literature, it is still unclear whether there is an increased risk in breast cancer survivors. Most studies involved breast cancer survivors only, without comparing the results with a group without cancer, and it is not possible to ascertain if the reported changes in the mental health of the breast cancer survivors can be attributed to the previous cancer.
- Little is known about the frequency of sleep disturbances, sexual disorders and post-traumatic stress disorder in breast cancer survivors, compared to women with no history of cancer.
- With the increasing numbers of breast cancer survivors, the potential impact of their medical history on their mental health, and the burden generated by mental disorders, it is imperative to generate evidence on the absolute and relative risk of mental disorders in this key patient group, to inform prevention and mitigation strategies.

2 Aims and objectives

Progress in breast cancer control has resulted in large and growing numbers of women living with and beyond breast cancer. The long-term mental health and quality of life impact of having a history of breast cancer is largely unknown.

The research in this thesis addresses these gaps in knowledge, and had two aims:

Aim 1 To quantify the relative risk of adverse mental health outcomes in women with a history of breast cancer, compared to women who have never had cancer, using routinely collected primary and secondary care data from the UK.

Aim 2 To investigate the health-related quality of life and the severity of symptoms of anxiety and depression in women with a history of breast cancer (>1 year), compared to women with no history of cancer.

The specific objectives were:

Objective 1: To systematically review and summarise the studies that quantified the frequency or severity of adverse mental health outcomes in women with a history of breast cancer, compared with women with no history of cancer (Chapter 3);

Objective 2: To systematically review the strategies used to identify adverse mental health outcome in studies that used electronic health records (EHRs) from primary care databases in the UK (Chapter 5);

Objective 3: To quantify the risk of adverse mental health outcomes in women who had breast cancer, compared to women with no history of cancer, using primary care EHRs data (Chapter 6);

Objective 4: To compare patient-reported measures of HRQoL, anxiety, and depressive symptoms, between breast cancer survivors and women with no prior cancer, and to explore the impact of demographic and clinical factors (Chapter 7);

Objective 5: To describe cancer-specific measures of HRQoL in breast cancer survivors and explore the effect of demographic and clinical factors (Chapter 7);

Objective 6: To compare patient-reported HRQoL, and anxiety and depressive symptoms, with the information in the EHRs for similar constructs (Chapter 8).

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3 Review of the associations between breast cancer survivorship and adverse mental health outcomes

3.1 Introduction

The first objective of this thesis was to systematically review the studies that quantified the frequency and/or severity of adverse mental health outcomes in women with a history of breast cancer, compared with women with no history of cancer. The research in this chapter directly addresses this objective. The results of this review informed the selection of the specific adverse mental health outcomes to be studied in this thesis.

3.2 Systematic review protocol

A study protocol was created prior to carrying out the systematic review, following best practice recommendations in systematic review studies. The protocol was published in a peer-reviewed scientific journal. The article is provided in the following pages.

3.3 Article

The results of the systematic review were reported in an article that has been published in a peer-reviewed scientific journal. This article is also provided in the following pages. The lengthy supplementary appendix referred to in this systematic review is provided in Appendix 1 of this thesis.

Dr Hulliard et al. inquired whether there were data available on the incidence of mental health outcomes by history of the condition prior to the cancer diagnosis, as their data suggested that a 'the diagnosis of cancer itself may not be a sufficient psychological and physical burden to trigger a mental disorder according to the DSM-V' [203]. The response to this letter is included after the systematic review.

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Student ID Number	1513226	**Title**	Ms
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Surname/Family Name	Morim Carreira		
Thesis Title	Long-term mental health and quality of life in women with history of breast cancer		
Primary Supervisor	Professor Krishnan Bhaskaran		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMC Systematic Reviews		
When was the work published?	August 2017		
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Where is the work intended to be published?	n/a
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	HC, RW and KB designed the study. HC drafted the protocol. RW, RH, MM, and KB, provided comments on the draft and revised the paper for important intellectual content.

SECTION E

Student Signature	[redacted]
Date	09 December 2019

Supervisor Signature	[redacted]
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Systematic Reviews

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Adverse mental health outcomes in breast cancer survivors compared to women who did not have cancer: systematic review protocol

Helena Carreira[1*], Rachael Williams[2], Martin Müller[3], Rhea Harewood[1] and Krishnan Bhaskaran[1]

Abstract

Background: Recent increasing trends in breast cancer incidence and survival have resulted in unprecedented numbers of cancer survivors in the general population. A cancer diagnosis may have a profound psychological impact, and breast cancer treatments often cause long-term physical sequelae, potentially affecting women's mental health. The aim of this systematic review is to identify and summarise all studies that have compared mental health outcomes in breast cancer survivors, versus women who did not have cancer.

Methods: This study will be a systematic review of the literature. Four databases, including MEDLINE and PsycINFO, will be searched to identify potentially relevant studies. The search expressions will use a Boolean logic, including terms for the target population (women who have had breast cancer), outcomes (psychiatric disorders) and comparators (e.g. risk, hazard). All mental disorders will be eligible, except those with onset normally occurring during childhood or strong genetic basis (e.g. Huntington disease). The eligibility of the studies will be assessed in two phases: (1) considering the information provided in the title and abstract; (2) evaluating the full text. Studies including women diagnosed with breast cancer 1 year or more ago and that provide original data on mental health outcomes will be eligible. Studies in which all women were undergoing surgery, chemotherapy or radiotherapy, or hospitalised or institutionalised, will be excluded, as well as studies that include patients selected on the basis of symptomatology. Two investigators will do the screening of the references and the data extraction independently, with results compared and discrepancies resolved by involving a third investigator when necessary. Study quality and risk of bias will be assessed across six broad domains. Results will be summarised by outcome, and summary measures of frequency and/or association will be computed if possible.

Discussion: This review will summarise the evidence on the mental health outcomes of women who have been diagnosed with breast cancer. This information can be used to motivate further research and increase understanding of the most common mental health conditions affecting this growing population of women.

Systematic review registration: PROSPERO CRD42017056946

Keywords: Breast neoplasms, Survivors, Mental health, Mental disorders, Systematic review, Protocol

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Background

Survival from breast cancer increased markedly during the last decades [1]. In 2005–2009, 5-year age-standardised net survival was higher than 85% in North America and between 71 and 87% in 29 European countries [1]. Considering that breast cancer is the most frequent malignancy diagnosed in women worldwide, after non-melanoma skin cancer [2], this has already translated into an unprecedentedly large number of breast cancer survivors in the general population. Many women find the diagnosis a traumatic experience [3], and the usual reactions include anxiety, hopelessness, anger and negative and suicidal thoughts [4, 5]. Some of the treatments can also cause severe long-term suffering. For example, surgery usually results in a lifelong scar and may cause breast shape alteration, persistent pain and/or lymphoedema [6–8]. The diagnosis and treatment of the breast cancer might also affect the woman's family, including intimacy with their partners [9] and relationships with their offspring [10]. Women who return to work may also face new challenges, not only in the relationship with their work colleagues [11] but also in their cognitive functioning [12, 13]. Women must also deal with the fear of cancer recurrence and death [14]. All of these factors may have a long-term negative impact on the mental health of breast cancer survivors.

Several systematic reviews summarised the frequency of selected mental health outcomes in oncological patients under and post-treatment [15–22]. Two reviews focused on breast cancer survivors [16, 22]. Howard-Anderson et al. [22] focused on younger breast cancer survivors (<50 years at diagnosis), an important group but who represent a small proportion of all breast cancer survivors. The systematic review by Maass et al. [16] reported prevalences of anxiety between 18 and 33% and of depression between 9 and 66%; however, most of the studies included in this review did not involve a comparison group, and therefore, it is unclear how the figures compare to those of women who did not have cancer. The range of adverse mental health outcomes in breast cancer survivors is also unlikely to be limited to anxiety and depressive disorders alone. Other outcomes, such as sleep disturbances, have been reported as frequent during the treatment period and afterwards [23, 24], and very little is known about the long-term impact of these in breast cancer patients.

The overall aim of this study is to identify and summarise studies that have quantitatively compared mental health outcomes in breast cancer survivors of at least 1 year since diagnosis, versus women who did not have cancer. Specifically, through summarising such studies, this systematic review will:

- Identify mental disorders that may be associated with a history of breast cancer
- Summarise and, where possible, synthesise quantitative estimates of associations between breast cancer history and a range of specific psychiatric outcomes
- Summarise the instruments used to evaluate mental disorders or their severity in breast cancer survivors

Methods

This systematic review protocol follows the guidance outlined by the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) [25]. Additional file 1 provides information for each item of the PRISMA-P checklist. This review has been registered in the International prospective register of systematic reviews (PROSPERO 2017:CRD42017056946).

Eligibility

Inclusion criteria

Manuscripts reporting studies satisfying the following criteria will be eligible for inclusion:

- Based on original data.
- Uses any observational study design (i.e. cohort, case-control, cross-sectional designs).
- Includes adult women (≥18 years) diagnosed with breast cancer and who survived the first year after the diagnosis.
- Includes a population-based adult female comparison group with no prior cancer.
- Provides data on at least one of our pre-specified mental health outcomes of interest, namely the following: anxiety disorders; bipolar and related disorders; disruptive, impulse control and conduct disorders; feeding and eating disorders; mood disorders; neurocognitive disorders; neurotic disorders; personality disorders; schizophrenia spectrum and other psychotic disorders; sexual dysfunctions of a psychological nature; sleep-wake disorders; somatoform disorders; substance-related disorders (including alcoholism); and trauma- and stressor-related disorders. Studies providing data on self-injurious behaviour (including self-harm, suicide and suicidal ideation) will also be included. These outcomes were selected by reviewing the list of mental disorders available in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* [26] and the *ICD-10 Classification of Mental and Behavioural Disorders* [27].

Exclusions

Articles will be excluded according to the following criteria:

- Review articles, editorials, commentaries, conference abstracts, case reports and studies involving animals.

- Studies in which the selection of the breast cancer survivors depended on symptoms (e.g. *only* patients with persistent pain or fatigued) or on a mental health outcome (e.g. *only* women with depression).
- Studies which *only* presented data for the first year after the breast cancer diagnosis; however, studies following women from diagnosis may still be eligible if outcomes at ≥ 1 year or more since diagnosis are reported separately.
- Studies in which all breast cancer patients remain under treatment for cancer (except for long-term endocrine therapy) at the time of outcome ascertainment.
- Studies in which all women are institutionalised (e.g. hospitalised or in hospices).

Search strategy

We will consider as potentially eligible all studies published in the journals indexed in MEDLINE, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Social Sciences Citation Index, since the inception of each database up to when the database was last updated at the time of the search. A search expression will be defined with a Boolean logic, including terms for the target population (breast cancer patients), outcome (psychiatric disorder) and comparators (risk, hazard, etc.). The search expression used in MEDLINE includes terms for Medical Subject Headings (MeSH) as well as key text words with truncation to allow for variations in terminology (Table 1). The search expression will be adapted to each database, to take into account the specificities of the search algorithms.

We will restrict the search to studies including humans. We will not apply any time, geographic or language restriction. If a study is published in a language not sufficiently understood by the authors, we will seek assistance to translate/understand the content.

Backwards and forward citation tracking will also be used to identify additional potential eligible studies that were not captured by the database searches.

Table 1 MEDLINE search expression, via OVID®

1	exp Breast Neoplasms/
2	(breast and (cancer* or carcinoma* or tumo?r* or neoplas*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3	1 or 2
4	exp catatonia/ or exp depression/ or exp self-injurious behavior/ or exp anxiety/
5	mental disorders/ or exp anxiety disorders/ or exp "bipolar and related disorders"/ or exp "disruptive, impulse control, and conduct disorders"/ or exp dissociative disorders/ or "feeding and eating disorders"/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or pica/ or exp mood disorders/ or exp motor disorders/ or neurocognitive disorders/ or amnesia/ or cognition disorders/ or auditory perceptual disorders/ or mild cognitive impairment/ or consciousness disorders/ or delirium/ or dementia/ or exp neurotic disorders/ or exp personality disorders/ or exp "schizophrenia spectrum and other psychotic disorders"/ or sexual dysfunctions, psychological/ or exp sleep wake disorders/ or exp somatoform disorders/ or exp substance-related disorders/ or exp "trauma and stressor related disorders"/
6	(depressi* or dysthymia or catatonia or self-injur* or self-injury or self-injurious or self-mutilation or "self mutilation" or suicid* or self-harm or "self harm" or "self injury" or anxious* or anxiety or (panic adj1 (disorder# or attack#)) or catastrophi* or (mental adj1 (disorder or disorders)) or phobia or phobic or neurotic or (compulsive adj1 disorder) or bipolar or neurotic or (personality adj1 disorder) or psychotic or psychosis or paranoid or delusional or (sexual adj1 (disorder or dysfunction or problem#)) or insomnias or (sleep adj1 (disorder or dysfunction or problem#)) or somatoform or (substance adj3 (disorder or problem#)) or stress ajd3 disorder or (adjustment adj3 disorder)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7	4 or 5 or 6
8	(prevalence# or frequenc* or incidence# or risk or rate* or ratio or odds or epidemiolog* or percent* or outcomes or hazard).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9	3 and 7 and 8
10	Humans/
11	Animals/
12	10 and 11
13	11 not 12
14	9 not 13

Data management and selection process

All records will be imported into EndNote X7 (EndNote X7, Thomson Reuters, NY, USA), and studies identified as duplicates by the software will be removed. A backup of the search expression and the records obtained from each database, as well as the date of last update and run, will be saved.

The references will be screened in two consecutive phases by two authors (HC and MM, or HC and RH). In the first phase, the title and the abstract of each study will be read to determine their eligibility for the study by applying the pre-defined inclusion and exclusion criteria (see the "Eligibility" section above). If the information provided in the title and abstract does not allow the unequivocal exclusion of the study, the full text will be considered. In the second phase, the full text of each study considered eligible in the first phase will be obtained and read in order to determine the eligibility considering all the information in the paper. The studies will be reassessed for data extraction.

The decisions taken independently by each of the investigators will be compared, and discrepancies will be

resolved, involving a third investigator when necessary (RW or KB). The agreement between the two investigators will be calculated (kappa statistics).

If more than one study reports data on the same study population, we will include only the study providing data for the largest sample; if the sample size is the same, we will consider the study providing more detailed information on outcomes (e.g. results stratified for age or type of treatment received) and consider both studies for abstraction of information on the participants' characteristics (e.g. age, menopausal status, stage at diagnosis).

A record of excluded/included studies, with the respective exclusion criterion, will be kept, and the selection process including numbers excluded at each stage for different criteria will be summarised in a flow chart.

Data extraction

Two authors (HC and MM, or HC and RH) will extract data from each included study into a pre-defined form in Microsoft Office Excel (2013). The form will be piloted using four studies and adapted if necessary. Information will be collected on (1) study characteristics (e.g. authors, year of publication, country where the sample was obtained or duration of follow-up if applicable); (2) characteristics of the breast cancer survivors (details on participant recruitment, sample size, demographics, distribution of stage at diagnosis, time since diagnosis and type of treatments); (3) characteristics of the women who did not have cancer (recruitment of the participants, sample size, demographics); (4) information on the mental health outcomes (name of the mental condition, diagnostic criteria, instruments applied); and (5) quantitative information on the mental health outcome (e.g. prevalence or mean/median score in each group and/or relative risk comparing groups) and variables considered as potential confounders.

If a prospective study provides data for more than one point in time, we will abstract all available information.

The data extracted by each author will be compared and discrepancies resolved by consensus or involving a third researcher (KB or RW) if necessary.

Risk of bias in individual studies

We will evaluate study quality and risk of bias in the original studies by assessing the main domains identified by Sanderson et al. as important for observational study quality and bias assessment [28], informed by the "STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)" guidelines [29]. These domains are: methods for selecting study participants, methods for measuring the exposure and the outcome variables, design-specific sources of bias (excluding confounding), methods to control for confounding, statistical methods (excluding confounding) and conflict of interest [28]. Within each of the above domains, individual studies will be rated as at high risk of bias, low risk of bias or unclear risk of bias, following the Cochrane Collaboration approach formulated for clinical trials [30].

Data analysis and synthesis

The results will be reported according to the PRISMA guidelines [31]. Tables and descriptive text will be used to summarise study characteristics and results, stratified by outcome and likely sources of heterogeneity (e.g. study design, type of population).

Quantitative synthesis of results (meta-analysis) will only be attempted for selected outcomes where deemed appropriate, taking into account the number of studies available, study designs and methods and equivalence of outcome measures and effect estimates used. Where quantitative synthesis is attempted, the DerSimonian and Laird method [32] will be used to compute summary estimates of the association between breast cancer and the discrete psychiatric outcome in question, along with 95% confidence intervals. Sub-group analyses by time since diagnosis will be conducted if possible. Prospective studies providing data for two or more time points after the first anniversary of diagnosis will be included once in meta-analysis; the relative risk estimate for the first eligible time point will be chosen. Heterogeneity will be quantified using Higgins and Thompson's I-squared statistic [33]. The meta-analysis will be repeated excluding any studies identified as at high risk of bias in the quality assessment. For outcomes deemed suitable for meta-analysis as described above, funnel plots and Egger's regression asymmetry test [34] will be used to assess publication bias and small study effects if more than ten studies are available [35].

Discussion

The number of women who have had breast cancer is higher than ever before. These women may face many challenges when trying to assimilate back into life following their cancer diagnosis and treatment, and it is imperative to understand the long-term psychological consequences. This systematic review aims to provide a comprehensive overview of the associations between breast cancer history and mental health conditions.

Most reviews on the topic have been restricted to studying the prevalence of depression among cancer patients [15, 20]. We opted for considering a much broader list of mental disorders that have their onset during adulthood as outcomes, to give a more comprehensive picture of the spectrum of mental disorders that may affect breast cancer survivors. We also chose to include only studies in which a comparison group was available, so that the relative frequency or severity of these conditions compared to the general population could be studied.

We will include studies in which women were diagnosed with breast cancer at least one year prior to outcome measurement. Women who completed breast cancer treatments with curative intent (i.e. surgery, chemotherapy and/or radiotherapy) are often considered as survivors; however, the precise point in time when the treatments end is frequently unknown and a widely accepted definition of cancer survivor does not exist [36]. Researchers commonly use a fixed point in time to capture, in a pragmatic way, the moment at which the main course of treatment is likely to have been completed. At 1 year after the diagnosis, the vast majority of women are expected to have completed the main treatments and many have returned to their pre-cancer routines. The effect of having been diagnosed and treated for breast cancer may also vary over time [37], and thus, an adequate characterisation of the risk of mental disorders requires a known time since diagnosis.

Studies involving mental health outcomes are prone to selection bias. We will report the characteristics of the samples involved in the original studies, including the details on the recruitment of the participants. We will also evaluate and report the risk of bias and use this information to help interpret the results.

Mental disorders largely interfere with the functioning of the patients and are leading causes of disability worldwide [38]. The mean prevalence of depression among women who had breast cancer has been described in the range between 10 and 20%, depending on the methods used to evaluate it [15]. This indicates that the burden of at least depressive disorders in this population is far from negligible. The impairments caused by depression are likely to be higher in these women than in women with depression alone [39].

Even though there are several pharmacological and non-pharmacological treatments available, mental disorders are often undiagnosed and untreated. The results of this review can be used to inform health professionals about the range, frequency and severity of mental disorders among breast cancer survivors.

Additional file

Additional file 1: PRISMA-P 2015 checklist. Checklist of the compliance of the systematic review protocol with the guidance established by the "Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P)" statement. (DOCX 38 kb)

Abbreviations

MeSH: Medical Subject Headings; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols; PROSPERO: International prospective register of systematic reviews

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Availability of data and materials

Not applicable.

Role of the funding source

The funding source had no role in developing the protocol for the study.

Authors' contributions

HC, RW and KB designed the study. HC wrote the first draft of the protocol. MM, RH, RW and KB made substantial contributions to the manuscript, revised it critically for important intellectual content and read and approved the final version. HC is the guarantor of the review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	JNCI – Journal of the National Cancer Institute		
When was the work published?	December 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Where is the work intended to be published?	n/a
Please list the paper's authors in the intended authorship order:	n/a
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	HC, RW, and KB designed the study. HC defined the search expression, screened all references, and extracted the data from the original studies. RH and MM duplicated the screening of the references and data extraction. HC did the analysis and wrote the first draft of the manuscript. All authors provided comments and revised the paper for important intellectual content.

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Review

REVIEW

Associations Between Breast Cancer Survivorship and Adverse Mental Health Outcomes: A Systematic Review

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Abstract

Background: We aimed to systematically review the evidence on adverse mental health outcomes in breast cancer survivors (≥1 year) compared with women with no history of cancer.
Methods: Studies were identified by searching MEDLINE, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature, and the Social Sciences Citation Index, and through backward citation tracking. Two researchers selected the studies, extracted data, and assessed the risk of bias.
Results: Sixty studies were included. Of 38 studies of depression, 33 observed more depression in breast cancer survivors; this was statistically significant in 19 studies overall, including six of seven where depression was ascertained clinically, three of four studies of antidepressants, and 13 of 31 that quantified depressive symptoms. Of 21 studies of anxiety, 17 observed more anxiety in breast cancer survivors, statistically significant in 11 studies overall, including two of four with clinical/prescription-based outcomes, and in eight of 17 of anxiety symptoms. Breast cancer survivors also had statistically significantly increased symptoms/frequency of neurocognitive dysfunction (18 of 24 studies), sexual dysfunctions (5 of 6 studies), sleep disturbance (5 of 5 studies), stress-related disorders/PTSD (2 of 3 studies), suicide (2 of 2 studies), somatisation (2 of 2 studies), and bipolar and obsessive-compulsive disorders (1 of 1 study each). Studies were heterogeneous in terms of participants' characteristics, time since diagnosis, ascertainment of outcomes, and measures reported. Approximately one-half of the studies were at high risk of selection bias and confounding by socio-economic status.
Conclusions: There is compelling evidence of an increased risk of anxiety, depression and suicide, and neurocognitive and sexual dysfunctions in breast cancer survivors compared with women with no prior cancer. This information can be used to support evidence-based prevention and management strategies. Further population-based and longitudinal research would help to better characterize these associations.

Women with a history of breast cancer are the largest group of cancer survivors in high-income countries (1). In the United States alone, more than 2.9 million women were estimated in 2012 to be living with a previous diagnosis of breast cancer (2). By 2022, this number is estimated to approach 4 million (2). Similarly, in the United Kingdom, the number of women living beyond breast cancer is expected to surpass 1.5 million during the next 20 years (3).

A diagnosis of breast cancer is often overwhelmingly distressing (4). Women frequently experience some combination of anger, anxiety, despair, helplessness, fear of death, and suicidal thoughts (5,6). Clinically relevant symptoms of anxiety and/or depression are common during the treatment period (7,8), when acute treatment side effects may restrict daily activities (9). High prevalence of depressive symptoms and anxiety have also been observed during survivorship (10,11), with one

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study finding depressive symptoms persisting for at least two years after diagnosis in one in five women (12). Other adverse mental health outcomes, such as sleep disturbance, have also been reported both during cancer treatment and afterwards (13). A substantial proportion of the breast cancer survivors experience long-term iatrogenic effects of treatment, including fatigue, persistent pain, lymphedema, vasomotor symptoms, and infertility, all of which may negatively affect quality of life and mental health (14). Other important psychological challenges in the long term can include difficulties in re-adapting to professional, social, and intimate relationships and coping with the uncertainty about the future (15).

To our knowledge, no systematic review to date has summarized the evidence from studies comparing breast cancer survivors with a noncancer control group for a broad spectrum of adverse mental health outcomes. Therefore, the aim of this study was to identify and summarize the studies that have quantitatively compared mental health outcomes in breast cancer survivors (≥1 year) vs women who did not have cancer; we also assessed the quality of the evidence on this topic by applying objective quality assessment criteria.

Methods

This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO 2017: CRD42017056946) and followed the a priori methods outlined in the protocol (published elsewhere [16]). Results were reported in accordance with the guidance of the Preferred Reporting Items for Systematic review and Meta-Analysis (17).

Outcomes

The predefined outcomes of interest were anxiety disorders; bipolar and related disorders; disruptive, impulse control, and conduct disorders; feeding and eating disorders; mood disorders; neurocognitive disorders; neurotic disorders; personality disorders; schizophrenia spectrum and other psychotic disorders; sexual dysfunctions of psychological nature; sleep wake disorders; somatoform disorders; substance-related disorders (including alcoholism); and trauma- and stressor-related disorders. We also considered eligible the studies providing data on self-injurious behavior (including self-harm, suicide, and suicidal ideation). These categories were selected after systematically reviewing those listed in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (18) and in the ICD-10 Classification of Mental and Behavioural Disorder (19) to exclude conditions with usual onset during childhood or with strong genetic component (eg Huntington's disease). The comprehensive list of outcomes was aimed at exploring what evidence was available on the topic without making strong assumptions as to whether the stress induced by the breast cancer diagnosis and treatment could trigger the condition. The outcomes of interest were disorders clinically diagnosed, but we also considered symptomatology evaluated with psychometric instruments.

Data Sources and Identification

Potentially eligible studies were identified in four databases: MEDLINE, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature, and the Social Sciences Citation Index. A search expression tailored for each database was created including terms for the exposure (breast cancer), outcomes (the predefined mental disorders), and comparators (eg, risk) (full MEDLINE search string provided in the Appendix [Supplementary Table 1, available online]). Results retrieved from the inception of the databases up to November 1, 2017 were considered for this study. Two authors screened the list of references by applying the same inclusion and exclusion criteria to determine each study's eligibility. The bibliographic references of eligible studies were manually screened to detect additional studies.

Study Eligibility

We considered as eligible observational studies that provided original data comparing the prevalence, incidence, or odds/hazard of at least one of the predefined lists of mental health outcomes (see above), clinically diagnosed or their symptomatology assessed through validated instruments, between adult female breast cancer survivors and a comparison group of women with no prior cancer. Female breast cancer survivors were defined as women with a history of breast cancer or in situ tumor for one year or longer. Studies with patients diagnosed with breast carcinomas in situ were included because despite of their excellent prognosis (20), they receive similar treatment to invasive breast cancers (21), and patients often experience substantial psychological distress both during and after the treatment period (22,23). Studies with no control group but reporting standardized incidence ratios were also eligible if the standardization was against a general female population. Studies that used psychometric instruments that had been altered from the standard/validated version were excluded, except where the alteration was limited to omission of questions that would not apply to the population under study. Studies including women who were institutionalized, under active treatment for breast cancer (excluding endocrine therapy), or who were specifically selected based on distressing psychological and/or physical symptoms were excluded. Studies evaluating the effect of further screening or diagnostic tests for cancer on the mental health of breast cancer survivors were excluded. There was no restriction in the language of study publication.

The eligibility of individual studies was assessed by two reviewers (HC and MM, or HC and RH) who independently applied the predefined inclusion/exclusion criteria. Initial agreement between reviewers in the assessment of abstracts was 92.5% for HC/MM and 81.3% for HC/RH (Cohen's kappa [κ] = 0.51 and 0.32, respectively), and initial agreement in the full-text assessment was 95.9% ($\kappa = 0.69$) and 90.6% ($\kappa = 0.54$), respectively. All discordant assessments were discussed and successfully resolved.

Data Extraction

We systematically abstracted data on the characteristics of the study and study samples. We extracted quantitative data on the frequency (incidence or prevalence) or severity (mean scores) of adverse mental health outcomes for each participant's group or for the comparison between groups (eg, relative risk, hazard ratio, odds ratio), as available, and the results of any hypothesis testing reported in the original studies. Prevalences from studies involving psychometric instruments were based on the cutoffs defined by the authors of the original studies. When two or more studies reported data on the same study population, we extracted data from the study with largest sample size, or if equal, the one providing more detailed outcome information. Data were extracted independently by two investigators (HC and MM, or HC and RH) and discrepancies were resolved.

Risk of Bias in Individual Studies

The risk of bias in the included studies was assessed by two reviewers who independently evaluated domains previously identified as important in observational studies (24). The domains were: participants' selection, outcome assessment, temporality (breast cancer diagnosed prior to the onset of the mental health outcome), control for confounding by age and socio-economic status, statistical methods, handling of missing data, and disclosure of conflicts of interest. Within each domain, the studies were rated as having a high, low, or unclear risk of bias; some criteria were not applicable to all studies. Supplementary Table 2 (available online) provides the criteria used for each category and domain.

Statistical Methods

Tables, graphs, and descriptive text were used to summarize study characteristics and results stratified by mental health outcome and method used to define outcomes (ie, clinical diagnosis, drug prescription, or symptoms). When sufficient information was provided in the original studies, we calculated the prevalence ratio for each outcome (25) if this was not directly reported in the paper. If prevalence data were provided by severity categories, we computed prevalence ratios for the comparison of mild to severe symptoms of the outcome between the two groups; this was the most common dichotomization in the studies that did not provide results by severity. The 95% confidence intervals (CIs) for derived prevalence ratios were estimated using the delta method (25). *P* values for the comparison of mean scores from psychometric instruments between breast cancer survivors and women who did not have cancer were estimated with the independent samples *t* test; all tests were two-sided. To ensure comparability of the results across studies, we applied a type-1 error rate (α) of .05 when summarizing statistical significance even if studies themselves had provided results using a different statistical significance level. A quantitative synthesis of the results (ie, meta-analysis), as planned in the study protocol (16), was not possible due to the heterogeneity of the eligible studies in the clinical characteristics of the cancer survivors, time elapsed since breast cancer diagnosis, and instruments used to evaluate symptoms of mental health disorders.

Results

Characteristics of Included Studies

Of the 7517 individual publications identified, 729 studies were eligible for full-text evaluation, and 60 (26–85) were ultimately included (Figure 1). The most commonly evaluated outcomes were anxiety (n = 21 studies), depression (n = 38), neurocognitive dysfunction (n = 24), and sexual dysfunction (n = 6) (Table 1). Schairer et al. (41) estimated the risk of suicide in more than 720 000 women diagnosed with breast cancer in 1953 to 2001, using data from 16 population-based cancer registries in Scandinavia and the United States; thus, only two studies were eligible for suicide, because smaller studies with overlapping data were excluded. The studies were heterogeneous in study design, participants' characteristics, and methods involved to assess outcomes. A total 38 of 60 studies (63.3%) included small, nonprobabilistic samples of breast cancer survivors. Mental health outcomes were most commonly evaluated with psychometric instruments (50/60 studies = 83.3%), followed by clinical diagnoses registered in electronic healthcare databases (10/60 = 16.7%).

Findings for Specific Mental Health Outcomes

Table 2 provides an overview of the directions of association reported for all studies/outcomes and statistical significance of the between-group comparisons. Figure 2 summarizes the relative measures of effect for the most commonly studied outcomes in the studies where these were available. Figure 3 shows the prevalence (for cross-sectional analyses) or cumulative incidence (for follow-up analyses) of outcomes in the samples of breast cancer survivors included in the original studies.

Anxiety

Twenty-one eligible studies reported data for anxiety (Table 1; Supplementary Table 3, available online). Of 21 studies, 17 (81.0%) observed increased anxiety in the breast cancer survivor group compared with the noncancer group; the difference was statistically significant in 11 of 21 (52.4%) studies (Table 2).

Four longitudinal, population-based studies evaluated anxiety with clinical diagnoses (n = 2) or clinical diagnoses and anxiolytics prescription (n = 2); all used electronic health records data and pointed towards an increased risk in breast cancer survivors, but this was supported by strong statistical evidence in two studies only (Figure 2). The relative risk estimates in the four studies of clinically assessed anxiety varied between 1.06 (95% CI = 0.97 to 1.16) and 2.00 (95% CI = 1.69 to 2.37). The two studies that reported on anxiolytics prescription reported an 8% (95% CI = 1% to 15%) and 47% (95% CI = 35% to 61%) increase in breast cancer survivors compared with women who did not have cancer (Figure 2).

Seventeen studies investigated symptoms of anxiety using scales (Table 2). There was strong statistical evidence of increased symptoms of anxiety in eight of 17 studies, including in the six of 12 studies that focused on comparing mean scores between groups, and in two of five studies that reported prevalence of scoring above a clinically relevant threshold. For all of the latter, observed prevalence was higher in cancer survivors but confidence intervals were generally wide (Figure 2).

Prevalences of anxiety were generally less than 20% when electronic health records or anxiolytics were studied and in the range of 20% to 50% when scales were used (Figure 3). Determinants of clinically assessed anxiety were provided in one study. Clinically diagnosed anxiety in breast cancer survivors tended to decrease over time since diagnosis (58) and was independently associated with younger age and presence of comorbidities at diagnosis, having less favorable tumor characteristics, and receiving chemotherapy (58).

Depression and Suicide

Thirty-eight studies provided data on depression (Table 1; Supplementary Table 4, available online), and 33 of 38 (86.8%) described more depression in the breast cancer survivor group compared with women who did not have cancer, with 19 fo 38 (50.0%) reporting statistical evidence of increased depression (Table 2).

Of seven studies that analyzed depression based on clinical diagnoses, six found strong evidence of an elevated risk among breast cancer survivors, with relative risk estimates ranging

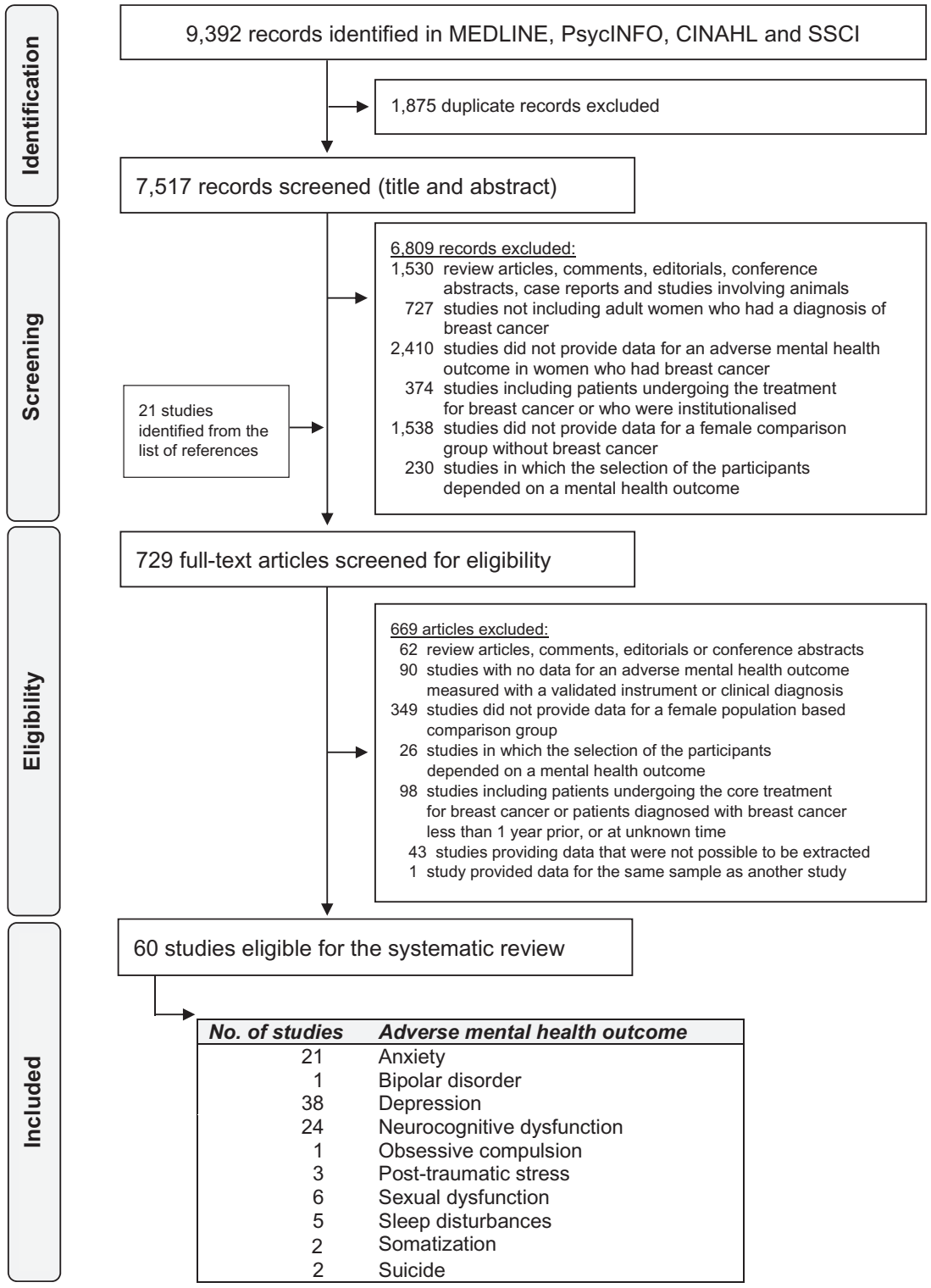

Figure 1. Systematic review flowchart. CINAHL = Cumulative Index to Nursing and Allied Health Literature; SSCI = Social Sciences Citation Index.

from 1.06 (95% CI = 1.00 to 1.12) to 2.04 (95% CI = 1.76 to 2.36) (Figure 2). All four studies defining depression by antidepressant use found higher use in breast cancer survivors, though for one smaller study the confidence interval was wide and overlapped the null; relative risk estimates ranged between 1.16 (95% CI = 1.11 to 1.22) and 2.06 (95% CI = 1.94 to 2.18).

Of 31 studies that evaluated depressive symptoms with scales, 13 reported strong statistical evidence of higher severity of depressive symptoms among women who had breast cancer (Table 2); among these, eight of nine studies that focused on the prevalence of scoring above a clinically relevant threshold found higher prevalence in breast cancer survivors, but this was

Table 1. Summary of the main characteristics of the eligible studies (N = 60)

Study characteristic	Studies, n (%)
Type of study	
Cohort	22 (36.7)
Cross-sectional	38 (63.3)
Type of population	
Population-based	10 (16.7)
Convenience samples recruited at health institutions	43 (71.7)
Randomly selected	3 (5.0)
Convenience samples recruited from the community	7 (11.7)
Randomly selected	0 (0.0)
Characteristics of the women with history of breast cancer	
Mean/median age	
≤49 y	16 (26.7)
50–69 y	41 (68.3)
≥70 y	3 (5.0)
Mean/median time since diagnosis*	
~1 y	12 (20.0)
>1 and ≤5 y	26 (43.3)
>5 and ≤10 y	17 (28.3)
>10 y	5 (8.3)
Sample size†	
<50	18 (30.0)
50–100	20 (33.3)
101–1000	14 (23.3)
>1000	8 (13.3)
Stage at diagnosis inclusion criteria	
In situ only	1 (1.7)
In situ and nonmetastatic invasive	6 (10.0)
In situ and invasive all stages	3 (5.0)
Invasive, nonmetastatic	30 (50.0)
Invasive, all stages	20 (33.3)
Treatment-related inclusion criteria	
Breast-conserving surgery	1 (1.7)
Mastectomy	5 (8.3)
Breast reconstruction	2 (3.3)
Chemotherapy	13 (21.7)
No chemotherapy	1 (1.7)
Hormone therapy	3 (5.0)
Radiotherapy	2 (3.3)
Immunotherapy	0 (0.0)
All treatments	33 (55.0)
Disease progression related inclusion criteria	
Only patients who did not have recurrence or relapse	15 (25.0)
Only patients who were tumor free at recruitment	12 (20.0)
Patients with disease recurrence included‡	19 (31.7)
Unclear	14 (23.3)
Adverse mental health outcome§	
Anxiety	21 (35.0)
Bipolar disorder	1 (1.7)
Depression	38 (63.3)
Neurocognitive dysfunction	24 (40.0)
Obsessive compulsion	1 (1.7)
Sexual dysfunction	6 (10.0)
Sleep disturbances	5 (8.3)
Stress-related / posttraumatic stress	3 (5.0)
Somatization	2 (3.3)
Suicide	2 (3.3)
Adverse mental health outcome assessment§	
Clinical diagnosis	10 (16.7)
Pharmacological treatment‖	5 (8.3)
Psychometric instruments	50 (83.3)

*Or mean/median time since treatment completion, as reported in the original studies.
†Refers to patients included in analysis.
‡Includes studies that explicitly stated the inclusion of patients with recurrence, and longitudinal studies including newly diagnosed patients and that did not report exclusions related to recurrence/relapse during follow-up.
§Studies may have provided data for more than one outcome and may have assessed one outcome by more than one method.
‖Includes self-reported medication intake.

statistically significant in only three studies and most estimates again had wide confidence intervals (Figure 2).

The prevalence of depression in breast cancer survivors was highest when evaluated with self-reported instruments (with most estimates >30%) and lower for clinically diagnosed depression (most estimates <10%; Figure 3). Determinants of depression clinically assessed in breast cancer survivors were seldom reported. Independent predictors of clinically diagnosed depression included younger age, having comorbidities at diagnosis and less favorable tumor characteristics (42,58), living alone, and having lower levels of education (42).

Two studies of suicide found breast cancer survivors to have 37% (95% CI = 28% to 47%) to 60% (95% CI = 21% and 112%) higher risk than women in the comparison group (Figure 2).

Neurocognitive Dysfunction

Twenty-four studies evaluated domains of neurocognitive function (Table 1; Supplementary Table 5, available online). All studies described that breast cancer survivors performed worse than noncancer controls for one or more domains of neurocognitive function (Table 2); this was supported by strong statistical evidence in 18 of 24 (75.0%) studies. When prevalence estimates were provided, all seven studies showed point estimates tending towards an increased neurocognitive dysfunction in breast cancer survivors compared with control subjects, even though this was supported by strong statistical evidence in only three instances; prevalence ratio estimates varied between 1.54 (95% CI = 0.95 to 2.49) and 5.51 (95% CI = 1.86 to 16.30) (Figure 2).

Of the 24 studies of neurocognitive dysfunction, 21 investigated the effect of being exposed to chemotherapy vs no chemotherapy; these studies consistently showed increased risk of neurocognitive impairments in breast cancer survivors exposed to chemotherapy. Three studies evaluated the effect of being exposed to hormone therapy in chemotherapy-naïve patients (29,82,85); two found strong evidence of increased neurocognitive dysfunction among breast cancer survivors exposed to hormone therapy. In most studies, neurocognitive impairments were described to affect 20% to 40% of women one year post-diagnosis (Figure 3).

Table 2. Summary of the results of the studies included in the systematic review and studies' quality assessment*

Study	Sample size (BCS/ controls)	Anxiety			Bipolar	Depression			Neuro-cognitive dysfunction†	Obsessive compulsion	Sexual dysfunction†	Sleep disturbance†	Somatization	Stress-related disorders /PTSD	Suicide	Studies risk of bias assessment‡						
		Diag	Drug	Symp		Diag	Drug	Symp								Sel	Inf	Temp	Conf	Stat	Miss	COI
Aerts, 2014 (45)	114/149	—	—	—	—	—	—	H§	—	—	—	—	—	—	—	Y	?	Y	Y	N	?	N
Ahles, 2010 (77)	110/39	—	—	—	—	—	—	—	H§	—	—	—	—	—	—	Y	N	N	N	N	?	N
Amir, 2002 (26)	39/39	—	—	H§	—	—	—	H§	—	H§	—	—	H§	—	—	?	?	Y	N	N	?	Y
Ancoli-Israel, 2014 (27)	44/35	—	—	—	—	—	—	H§	—	—	—	H§	—	—	—	?	?	N	N	N	?	N
Bailey, 2010 (46)	515/496	—	—	—	—	—	—	L	—	—	—	—	—	—	—	?	?	Y	Y	N	?	N
Bizetti Pelai, 2012 (60)	89/43	—	—	—	—	—	—	H	—	—	—	—	—	—	—	?	?	Y	Y	—	?	Y
Boehmer, 2015 (28)	85/85	—	H	H	—	—	H	H	—	—	—	—	—	—	—	Y	?‖/Y¶	Y	Y	N	?	N
Boehmer, 2014 (47)	85/85	—	—	—	—	—	—	—	—	—	H§	—	—	—	—	Y	?	Y	Y	N	?	N
Boele, 2015 (29)	63/44	—	—	H	—	—	—	H	H§	—	—	—	—	—	—	Y	?	N	N	N	?	N
Brezden, 2000 (70)	40/36	—	—	—	—	—	—	—	H§	—	—	—	—	—	—	Y	?	Y	N	N	?	Y
Broeckel, 2002 (30)	58/61	—	—	—	—	—	—	H§	—	—	H§	—	—	—	—	Y	?	Y	Y	N	?	Y
Calvio, 2010 (31)	122/113	—	—	H§	—	—	—	H§	H§	—	—	—	—	—	—	Y	?	Y	N	N	?	N
Castellon, 2004 (74)	53/19	—	—	L§, #	—	—	—	L	H§	—	—	—	—	—	—	Y	?	Y	?	N	?	N
Claus, 2006 (48) (in situ)	795/702	—	—	—	—	—	—	H§	—	—	H§	—	—	—	—	Y	?	Y	N	N	?	N
Cohen, 2011 (32)	56/66	—	—	H§	—	—	—	H	—	—	—	—	H§	—	—	Y	?	Y	N	N	?	Y
Collins, 2014 (67)	54/54	—	—	—	—	—	—	—	H§	—	—	—	—	—	—	Y	N	N	N	N	?	N
Conroy, 2013 (83)	24/23	—	—	L	—	—	—	L	H§	—	—	—	—	—	—	?	?	Y	N	N	?	N
Dahl, 2011 (33)	337/1685	—	—	H§	—	—	—	L§	—	—	—	H§	—	—	—	?	?	Y	N	N	?	N
Earle, 2007 (34)	463/3108	—	—	—	—	H§	—	—	—	—	—	—	—	—	—	N	N	Y	N	—	—	Y

(continued)

Table 2. (continued)

Study	Sample size (BCS/ controls)	Anxiety				Depression			Neuro-cognitive dysfunction†	Obsessive compulsion	Sexual dysfunction†	Sleep disturbance†	Somatization	Stress-related disorders /PTSD	Suicide	Studies risk of bias assessment‡						
		Diag	Drug	Symp	Bipolar	Diag	Drug	Symp								Sel	Inf	Temp	Conf	Stat	Miss	COI
El Rafihi-Ferreira, 2011 (63)	50/50	—	—	—	—	—	—	—	—	—	—	H§	—	—	—	?	?	Y	Y	—	?	Y
Ernst, 2002 (85)	16/33	—	—	—	—	—	—	—	H	—	—	—	—	—	—	Y	?	Y	Y	N	?	N
Fan, 2005 (68)	91/83	—	—	—	—	—	—	—	H§	—	—	—	—	—	—	?	N	N	N	N	?	N
Fang, 2012 (64)	74 977/ND	—	—	—	—	—	—	—	—	—	—	—	—	—	H§	N	N	N	N	N	—	N
Frazzetto, 2012 (49) (R)	32/35	—	—	—	—	—	—	H§,**	—	—	—	—	—	—	—	?	?	Y	Y	—	?	N
Garcia-Torres, 2013 (35)	22/22	—	—	L	—	—	—	H	—	—	—	—	—	—	—	Y	?	Y	Y	N	?	Y
Gurevich, 2004 (50)	66/69	—	—	—	—	—	—	—	—	—	—	—	—	H§	—	Y	?	Y	Y	N	?	Y
Hermelink, 2017 (59)	56/150	—	—	—	—	—	—	H§	H††	—	—	—	—	—	—	?	?‖/N	Y	?	N	N	Y
Hjerl, 2002 (51)	60 431‡‡/ ND	H	—	—	—	H§	—	—	—	—	—	—	—	—	—	N	N	N	Y	N	—	Y
Hung, 2013 (52)	26 629‡‡/ 26 629‡‡	H§	—	—	H§	H§	—	—	—	—	—	—	—	—	—	N	N	N	Y	N	—	N
Inagaki, 2007 (84)	105/55	—	—	—	—	—	—	—	H	—	—	—	—	—	—	Y	N	Y	Y	N	?	N
Jenkins, 2006 (75)	128/49	—	—	—	—	—	—	—	H	—	—	—	—	—	—	Y	N	N	N	N	N	N
Khan, 2010 (36)	16 938/ 67 649	H	H§	—	—	H	H§	—	—	—	—	—	—	—	—	N	N	N	N	N	—	N
Kim, 2017 (62)	2130/8520	—	—	—	—	H§	—	—	—	—	—	—	—	—	—	N	N	N	N	—	—	N
Klein, 2011 (53)	652/1188	—	—	H§	—	—	—	—	—	—	—	—	—	—	—	Y	?	Y	N	N	?	N
Koppelmans, 2012 (71)	196/1509	—	—	—	—	—	—	L§	H§	—	—	—	—	—	—	N	?	Y	N	N	?	N
Kreukels, 2008 (72)	63/60	—	—	H§	—	—	—	H§	H§	—	—	—	—	—	—	?	?‖/N	Y	Y	N	?	N
Kesler, 2013 (80)	42/35	—	—	—	—	—	—	H	H§	—	—	—	—	—	—	Y	?	Y	?	N	?	N
Lejbak, 2010 (82)	28/37	—	—	—	—	—	—	—	H§	—	—	—	—	—	—	Y	?	Y	?	N	N	Y

(continued)

Table 2. (continued)

Study	Sample size (BCS/ controls)	Anxiety			Bipolar	Depression			Neuro-cognitive dysfunction†	Obsessive compulsion	Sexual dysfunction†	Sleep disturbance†	Somatization	Stress-related disorders /PTSD	Suicide	Studies risk of bias assessment‡						
		Diag	Drug	Symp		Diag	Drug	Symp								Sel	Inf	Temp	Conf	Stat	Miss	COI
Lee, 2011 (61)	206/496	—	—	—	—	—	—	H	—	—	—	—	—	—	—	N	?	Y	N	N	?	N
McDonald, 2010 (78)	29/18	—	—	H	—	—	—	H	—	—	—	—	—	—	—	?	?	N	Y	N	?	N
Miao, 2016 (79)	23/26	—	—	H	—	—	—	H	H§	—	—	—	—	—	—	?	?	Y	Y	N	?	N
Min, 2010 (54)	52/104	—	—	—	—	—	—	H§	—	—	—	—	—	—	—	Y	?	Y	Y	—	?	Y
Myers, 2015 (66)	156/46	—	—	—	—	—	—	—	H§	—	—	—	—	—	—	Y	?	Y	?	N	N	N
Nguyen, 2013 (86)	57/30	—	—	—	—	—	—	H	H§	—	—	—	—	—	—	Y	?	Y	N	N	?	N
Otte, 2010 (37)	246/246	—	—	—	—	—	—	H§	—	—	—	H§	—	—	—	Y	?	Y	?	N	?	N
Phillips, 2012 (81)	129/184	—	—	—	—	—	—	—	H§	—	—	—	—		—	?	N	Y	N	N	?	N
Root, 2015 (65)	113/37	—	—	L	—	—	—	H	H§	—	—	—	—	—	—	?	?	Y	N	N	?	N
Rubino, 2007 (38)	33/33	—	—	H§	—	—	—	H§	—	—	H	—	—	—	—	?	N	Y	Y	N	?	Y
Safarinejad, 2013 (39)	186/204	—	—	—	—	—	—	—	—	—	H§	—	—	—	—	?	?	Y	N	N	?	N
Saleeba, 1996 (40)	52/88	—	—	H§	—	—	—	—	—	—	—	—	—	—	—	Y	?	Y	N	N	?	Y
Schairer, 2006 (41)	723 810/ND	—	—	—	—	—	—	—	—	—	—	—	—	—	H§	N	N	N	Y	N	—	N
Schagen, 2006 (69)	57/60	—	—	—	—	—	—	—	H	—	—	—	—	—	—	Y	N	N	Y	N	?	N
Silverman, 2007 (73)	24/10	—	—	—	—	—	—	—	H	—	—	—	—	—	—	?	?	Y	Y	N	?	N
Suppli, 2014 (42)	44 494‡‡/ 2M‡‡	—	—	—	—	H§	H§	—	—	—	—	—	—	—	—	N	N	N	Y	N	—	N
Vazquez-Ortiz, 2010 (55)	30/30	—	—	—	—	—	—	—	—	—	H§	—	—	—	—	?	?	Y	Y	N	?	Y
Voigt, 2016 (76)	150/56	—	—	—	—	—	—	—	—	—	—	—	—	H§§	—	?	?	N	N	N	N	N
Von Ah, 2012 (57)	62/78	—	—	—	—	—	—	H	—	—	—	H§	—	—	—	Y	?	Y	N	N	?	N

(continued)

Table 2. (continued)

Study	Sample size (BCS/ controls)	Anxiety			Bipolar	Depression			Neuro-cognitive dysfunction†	Obsessive compulsion	Sexual dysfunction†	Sleep disturbance†	Somatization	Stress-related disorders /PTSD	Suicide	Studies risk of bias assessment‡						
		Diag	Drug	Symp		Diag	Drug	Symp								Sel	Inf	Temp	Conf	Stat	Miss	COI
Von Ah, 2009 (56)	52/52	—	—	—	—	—	—	H	H§	—	—	—	—	—	—	Y	?	Y	N	N	?	N
Weitzner, 1997 (43)	60/93	—	—	H	—	—	—	H§	—	—	—	—	—	—	—	Y	?	Y	N	N	?	Y
Yang, 2017 (58) (Inv)	40 849/ 452 507	H§	H§	—	—	H§	H§	—	—	—	—	—	—	H§	—	N	N	N	Y	N	—	Y

*When a cohort study provided estimates for more than one point in time, we presented all data in the supplementary tables but described the estimate for only the first time point after the first anniversary of cancer diagnosis. When a study provided data for invasive and in situ tumors, we presented the results for the invasive tumors only. When a study provided data on the prevalence of subjects considered impaired as well as the mean scores of the psychometric instrument, we showed the result of the hypothesis test for the comparison of the prevalences. BCS = breast cancer survivors; COI = conflict of interest; Conf = confounding (by age and SES); Diag = clinical diagnoses; Drug = based on relevant drug prescriptions; H = study observed higher prevalence, risk, or severity of outcomes in breast cancer survivors compared with women who did not have cancer; Inf = information bias; Inv = invasive tumors; L = study observed lower prevalence, risk, or severity of outcomes in breast cancer survivors compared with women who did not have cancer; M = million; Miss = missing data; N = low risk of bias; R = recurrence; Sel = selection bias; Stat = statistical methods; Symp = based on symptoms; Temp = temporality of events; Y = high risk of bias; ? = unclear risk of bias.

†The risk of neurocognitive impairment, sexual dysfunction, and sleep disturbance was considered increased when the study reported statistically significant impairments in one or more domains of neurocognitive or sexual function, or sleep, respectively. When subjective and objective measures of neurocognitive function were provided, we considered the results of the objective measures.

‡Risk of bias assessment was not applicable for the domain of statistical methods for studies where no results for formal statistical comparisons between the two groups were provided; risk of bias assessment was also not applicable for the missing data domain if the study was based on electronic health records.

§Statistically significant ($P < .05$).

‖For anxiety or depression outcomes.

¶Self-reported anxiolytics and antidepressants intake.

#Breast cancer survivors reported lower symptoms for state anxiety compared with controls ($P = .01$). No statistically significant between-group differences were observed for trait anxiety ($P = .08$).

**Severe depression and mild to severe depression were increased in breast cancer survivors ($P < .05$). Mild depression did not differ between groups ($P \geq .05$).

††There was no strong statistical evidence of increased risk of cognitive dysfunction in women who had breast cancer compared with the healthy control group. However, strong statistical evidence for an increased frequency of cognitive dysfunction among breast cancer patients was found when considering the mean composite scores at one year ($P < .05$); the comparison remained statistically significant after correcting for multiple testing.

‡‡Number of women at baseline; number of women at 1 year after diagnosis not reported. Suppli et al: 44 494 breast cancer survivors and 1 997 669 for depression analysis; the corresponding figures for the antidepressant analysis were 35 286 (exposed to breast cancer) and 1 860 552 (background population).

§§There was no strong statistical evidence of an increased risk of PTSD in breast cancer survivors compared with women without cancer. However, the mean number of PTSD symptoms in breast cancer survivors was statistically significantly higher from the mean number of symptoms in the control group ($P < .001$).

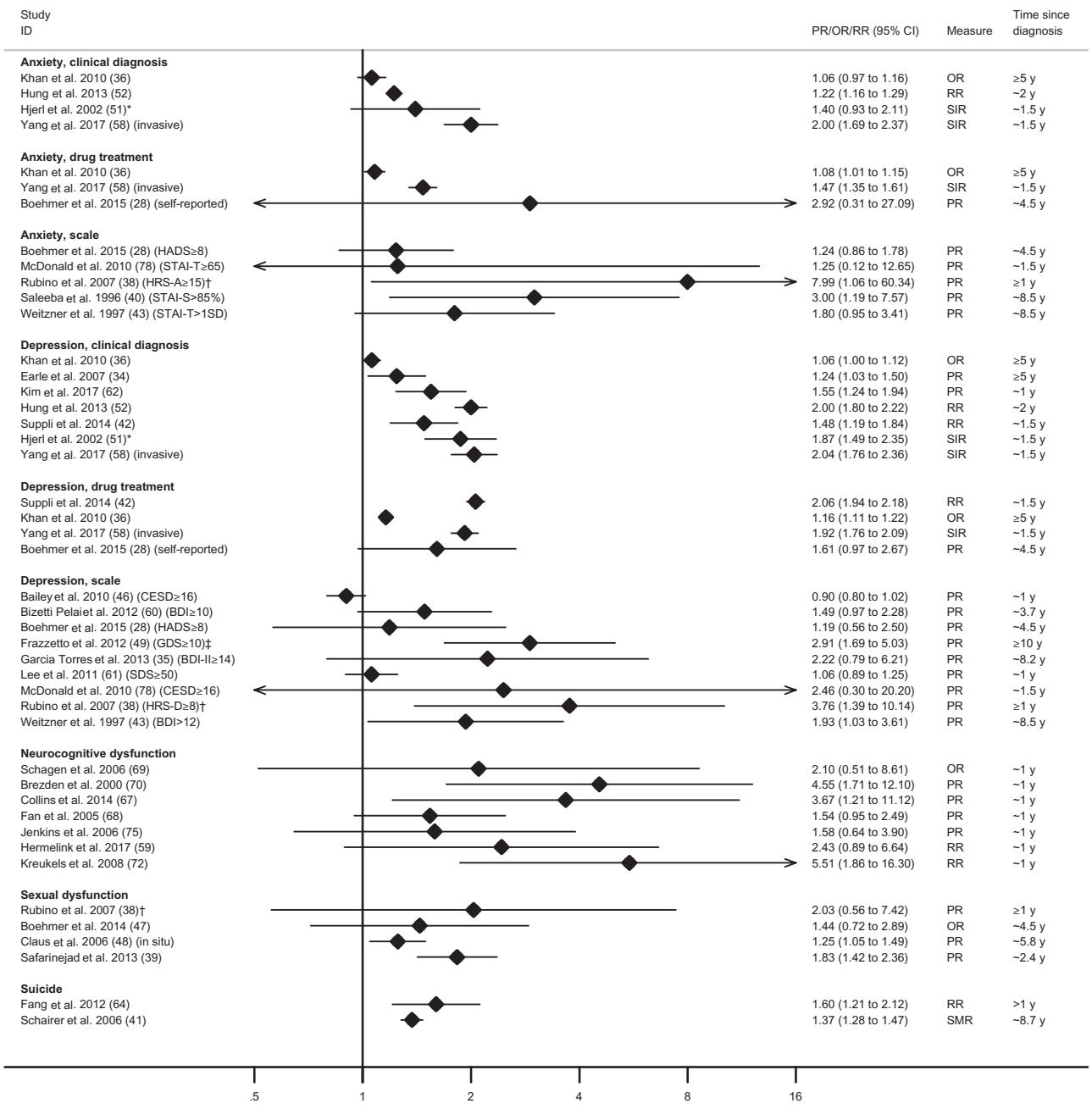

Figure 2. Associations between breast cancer history and anxiety, depression, neurocognitive and sexual dysfunctions, and suicide. We considered that anxiolytics were being taken to treat anxiety and antidepressants to treat depression. Time since diagnosis refers to the mean/median time elapsed since the breast cancer diagnosis or completion of initial course of treatment, as reported in the original studies, for the sample of cancer survivors. When this information was not reported in the original studies, we presented the lower limit of survivorship time reported in the inclusion criteria of the study. The minimum, mean/median, and maximum follow-up of longitudinal studies are reported in the Supplementary Appendix (available online). *The original study provided relative risk estimates stratified by area of residence (urban/rural). The combined estimate presented in the forest plot was computed with inverse-variance-weighted meta-analysis methods using the command "metan" in Stata v14. BDI(-II) = Beck Depression Inventory(-II); CESD = The Center for Epidemiologic Studies, Depression Scale; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; HRS-A = Hamilton Rating Scale for Anxiety; HRS-D = Hamilton Rating Scale for Depression; OR = odds ratio; PR = prevalence ratio; RR = relative risk; SD = standard deviation; SDS = Self-rating Depression Scale; SIR = standardized incidence ratio; SMR = standardized mortality ratio; STAI-S = State-Trait Anxiety Inventory (state anxiety subscale); STAI-T = State-Trait Anxiety Inventory (trait anxiety subscale). †Women who have had breast reconstruction after mastectomy. ‡Refers to a group of women who had breast cancer recurrence 10 years after the first diagnosis.

Sexual Dysfunction

Six studies, all involving convenience samples, reported data for sexual dysfunction (Table 1). Five of these reported impairments in one or more domains of sexual function (Table 2). All studies for which prevalence ratios were available showed increased dysfunction in breast cancer survivors, with relative risk estimates between 1.25 (95% CI = 1.05 to 1.49) and 2.03 (95% CI = 0.56 to 7.42) (Figure 2), but the width of the confidence intervals did not exclude the probability of this being due to

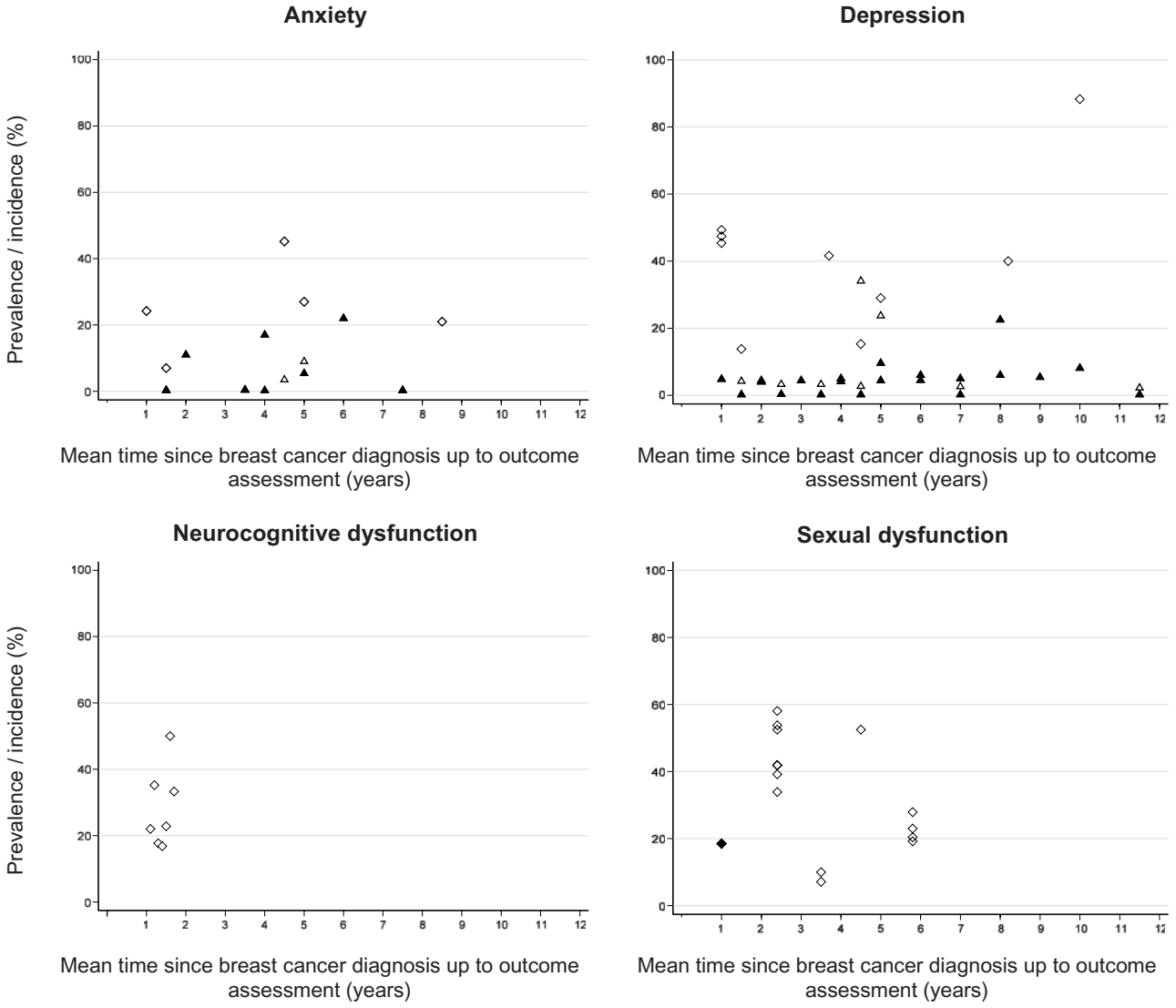

Figure 3. Absolute frequency of anxiety, depression, and neurocognitive and sexual dysfunctions reported in the original studies for breast cancer survivors. Estimates for cognitive and sexual dysfunctions refer to the prevalence of women impaired for the condition or specific domains, as reported in the original studies. EHR = electronic health records. **Black triangle** = cumulative incidence, diagnoses in EHR; **white triangle** = cumulative incidence, drug treatment; **white diamond** = prevalence, psychometric instruments; **black diamond** = prevalence, psychiatric interview.

chance in two studies. The prevalence of reported impaired sexual function overall or for specific domains was generally in the range of 20% to 60% (Figure 3). Safarinejad et al. (39) reported that women who had radiotherapy, chemotherapy, and hormone therapy had four to six times higher odds of disorder for all domains, compared with women who did not have cancer (39) (Supplementary Table 6, available online).

Other Outcomes: Bipolar Disorder, Obsessive-Compulsive Problems, Stress-Related and Posttraumatic Stress, Sleep Disturbance, and Somatization

Other outcomes were infrequently studied, but five of five studies of sleep disturbance found a statistically significantly higher prevalence in breast cancer survivors, as did two of three studies of stress-related disorders, two of two studies of somatization, and the single studies identified with bipolar disorder and obsessive-compulsive outcomes (Table 2).

Quality of the Studies

Approximately 50% of the studies were rated at high risk of selection bias, mostly because of the nonprobabilistic recruitment of participants (eg, fliers and advertisements [28,31,44,47,56,57]) and the low proportion of women who accepted to participate in the studies (30,45,50,53,54) (Figure 4). In most studies (>70%), the risk of information bias was unclear, and the cross-sectional design precluded the unequivocal assertion that the onset of the mental disorder was posterior to the breast cancer diagnosis. Approximately 40% of studies reported results likely to have been affected by confounding by age and socio-economic status,

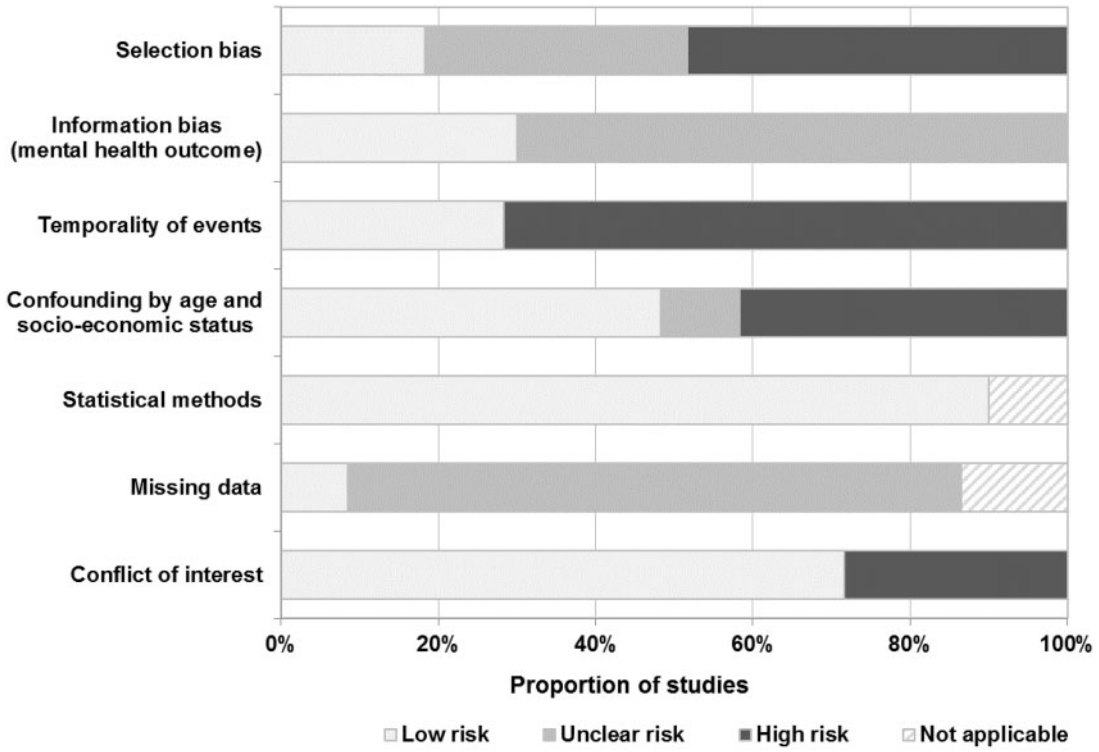

Figure 4. Summary of the risk of bias in the studies included in the systematic review. The risk of bias in statistical methods was considered not applicable when formal statistical comparisons between the two groups were not presented in the original study. Missing data criteria were not applicable for studies involving electronic health records.

and strategies to handle missing data were seldom reported. Individual study ratings are provided in Table 2.

Discussion

Anxiety, depression, neurocognitive dysfunction, sexual dysfunction, and suicide appear to be more common in breast cancer survivors compared with noncancer groups. Scarcer data were available for other adverse mental health outcomes, but they were also reported as increased among breast cancer survivors. Common limitations of the current available evidence include use of nonprobabilistic samples, cross-sectional study designs making temporality of events difficult to assess, lack of power, and lack of consideration for important confounders such as socio-economic status.

Strengths of this review include the extensive search of multiple databases, the duplicated screening of the references and data extraction, and the systematic evaluation of the quality of the studies. The restriction to studies involving nonhospitalized samples and the inclusion of studies with in situ tumors allowed for a more generalizable characterization of the long-term burden of mental disorders in women in the community who have had breast cancer. We aimed to reduce the potential for information bias in the outcomes by considering only studies in which outcomes were assessed clinically or with validated instruments. However, this review also has limitations. Studies that reported mood assessments as secondary outcomes may not have been identified in the searches of electronic publication databases if the mental health outcome was not mentioned in the title, abstract, keywords, or indexing terms. This problem should have been minimized by our use of the four largest and most relevant databases in this field, supplemented by manual searches of all reference lists to further reduce the chances of major studies being missed. The comparability of clinically diagnosed outcomes over time may be limited by the changes in the diagnostic criteria, especially in cases such as sexual dysfunction where the criteria became narrower over time (87). We defined explicit criteria to evaluate the risk of bias in the studies, but our assessment may have been affected by the quality of the reporting of the original studies. We considered that confounding by age and socio-economic status had been accounted for when the studies matched participants for these factors, even though we acknowledge that matching per se may not completely remove the confounding effect (88).

The population-based studies included in this review consistently described more depression and anxiety in breast cancer survivors compared with the general population when these outcomes were clinically assessed. The group of breast cancer patients who receive a psychiatric diagnosis or who contact clinical services in relation to their mental health are likely to represent the most severe cases only; these patients are likely to benefit from medical treatment. Studies using receipt of antidepressants and anxiolytics prescriptions to define depression and anxiety, respectively, are likely to capture the specific group of patients who were thought to benefit from pharmacological intervention, which is only a subset of all patients with anxiety and depression. The indication of these drugs was not explored in any of the original studies, and misclassification of the outcome may have occurred because some of these drugs have other indications and are routinely used to manage vasomotor symptoms secondary to breast cancer treatments (89,90). In addition, we cannot rule out that patients with breast cancer

history may have been more likely to be diagnosed with a mental health outcome due to increased contact with the health services compared with participants who did not have cancer.

The results from the original studies involving self-assessment scales, especially to assess symptoms of anxiety and depression, need to be interpreted with caution. These were often small, low-powered, cross-sectional studies using nonprobabilistic samples. Several of the original studies excluded women with psychiatric conditions and relied on voluntary participation. This may have resulted in an overrepresentation of psychologically healthier women, because diseased people are less likely to volunteer to participate in epidemiological studies (91,92); it is unclear if this would be differential between breast cancer survivors and control groups. The clinical profile of the patents included in these studies may also have been more favorable, because 45% of the studies included only patients with no recurrence and who were disease free at recruitment. In addition, misclassification of the outcome may have occurred, because these scales are screening tools and not suitable to establish definitive diagnoses. For example, the Hospital Anxiety and Depression Scale had only 50% sensitivity as a screening test for major depressive disorder in breast cancer survivors compared with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (93). Despite these limitations, scales are widely used in psychiatric epidemiology and in psycho-oncology research, and their results in this review are helpful to show the consistency of the results across methods of assessment.

For all methods of outcome definition, selective reporting in the original studies cannot be ruled out. Information on missing data was rarely well reported, and there was limited adjustment for potentially important confounders such as age and socioeconomic status; residual confounding is still likely to be present in the studies that adjusted for education only.

Clinically relevant symptoms of anxiety and stress-related/adjustment disorders are common shortly after diagnosis (94), which is an expected response to a stressor that may be perceived as life-threatening and considering the uncertainty about the future that women may feel at this point (95). Declining trajectories of anxiety suggest that most women adjust to the diagnosis over time (96), but clinically relevant symptoms may persist in subgroups of women. Evidence on long-term trajectories of outcomes is scarce and needs to be further explored. Reported determinants of anxiety included younger age at diagnosis and having comorbidities; this is consistent with literature reporting that young breast cancer survivors have specific concerns, for example, fertility issues for women who want more children or weight gain during and after treatments (10). The increased symptoms of posttraumatic stress is consistent with a meta-analysis reporting that 10% of breast cancer survivors have posttraumatic stress disorder (97). Results for somatic and obsessive-compulsive symptoms must be interpreted with caution because they come from a small number of studies.

The increased frequency of depression in breast cancer survivors is plausible considering that many report unmet needs in several domains that affect quality of life (98), including impact on relationships, lifestyle changes induced by the cancer, lack of psychological support, and difficulties obtaining understandable information about the physical long-term effects of the treatments (99–101). Risk factors for depression in breast cancer patients appear to be similar to those for the general female population, including less social support and lower socio-economic status (46). Suicide almost always occurs among people suffering from a mental health disorder, most often depression (102,103). The increased risk of suicide in breast cancer survivors is likely to be underestimated, because suicide is often classified under other causes of death, and this may happen more often in women who have had cancer.

Neurocognitive dysfunction, also known as chemo-fog, has been linked to the neurotoxic effects of chemotherapy (104). Other determinants of neurocognitive dysfunction recently postulated include posttraumatic stress disorder (59) and exposure to hormone therapy due the effects of estrogen deprivation in the neuronal structures (82). Impairments for one or more domains of neurocognitive function (eg, memory [65,83] and processing speed [77,81]) were often described, but the methodological heterogeneity of the studies (105) as well as the challenge to measure neurocognitive function (106) hamper comparisons, and it is currently debatable which specific domains are impaired.

The narrow inclusion/exclusion criteria in some eligible studies of sexual dysfunction preclude generalizability to the general population of breast cancer survivors. For example, Safarinejad et al. (39) excluded women who did not attempt sexual intercourse weekly and Boehmer et al. (47) included only in lesbian or bisexual women. The aetiology of sexual dysfunction in women with a history of breast cancer is thought to be multifactorial. Vaginal dryness is a common iatrogenic effect of hormone therapy or chemotherapy-induced ovarian failure and may lead to dyspareunia (14). However, impaired sexual function, compared with healthy women, has also been reported in women treated with surgery only (48), indicating that factors other than the physical ones may be involved. Indeed, the distress in partnered relationships (107–110), body image concerns (111,112), depressive feelings (113), younger age at diagnosis (113), and presence of comorbidities (114) have all been reported amongst the most important determinants of female sexual dysfunction.

Mitchell et al. (115) systematically reviewed studies providing data for depression and anxiety in survivors from several types of cancer (>2 years since diagnosis) and in healthy subjects. The results indicated that anxiety, but not depression, may be increased among cancer survivors (115). This conclusion arose from the meta-analysis of nine studies that provided data for anxiety and included patients diagnosed with breast, colorectal, prostate, testicular, and cervical cancers or Hodgkin's lymphomas as well as patients diagnosed with cancers during adolescence and young adulthood. It is currently unknown if, and how, the risk of anxiety and depression varies by cancer type, and thus we cannot directly compare our results. Other systematic reviews on the topic assessed the prevalence of anxiety and depressive symptoms in cancer survivors (11,116–118), including studies without a comparison group. Maass et al. (11) described a higher frequency of depressive symptoms among breast cancer survivors (>1 year since diagnosis) compared with normative data found in the literature. The results for cognitive dysfunction are in accordance with those reported by Jim et al. (119), who found small but increased cognitive deficits in breast cancer survivors treated with chemotherapy compared with noncancer and cancer controls.

Several studies have reported no differences in most domains of health-related quality of life (HRQoL) between long-term breast cancer survivors and women in the general population (120–122). The interpretation of our results in the context of the literature for HRQoL is not straightforward, and the apparent difference is likely to be explained by the combination of several factors, including the differential participation of

psychologically healthier women in HRQoL surveys and positive effects of surviving breast cancer. Patients with adverse mental health outcomes, especially those with the most severe categories, may be less likely to participate in HRQoL surveys. This contrasts with the studies in this review that included women with a clinical diagnosis and/or treated for a mental health disorder and were thus likely to capture the most severe cases. In addition, long-term breast cancer survivors report changes in several aspects of their lives, but not all of them are negative. Women in the survivorship period have described feeling improved empathy, closer relationships, and a greater appreciation for life (123). This phenomenon of heightened well-being after a stressful event—known as posttraumatic stress growth—has been described to affect up to 60% of breast cancer survivors (124). Quality of life reflects how women perceive their current status, and the occurrence of posttraumatic growth may offset some of the negative feelings associated with breast cancer (125). In addition, studies of HRQoL often reported mean scores of overall and domain-specific measures of HRQoL; subgroups that have a different trajectory of symptoms can be hard to disentangle based on standard analyses.

This study has several implications for clinical practice. It is important to raise awareness amongst health care professionals acting at various levels of the health care system of the increased risk of mental health symptoms among breast cancer survivors, in particular anxiety, depression, and neurocognitive and sexual dysfunctions. Screening for mental health disorders in some or all of the breast cancer survivor population may be warranted. Predictors of distress among breast cancer survivors include having perceived functioning limitations, fatigue, younger age, lower socioeconomic status, and psychiatric history, and modifiable factors such as vasomotor symptoms, pain, less social support, physical activity, and cigarette smoking (126). As such, screening for anxiety and depression may be especially relevant for younger patients, and all those within the first few years of survivorship, with co-morbidities, living alone, or diagnosed with more advanced disease; patients with depression should be assessed for suicidal ideation. Patients who experienced treatment-induced menopause are likely to benefit from being asked about their sexual function, because they may avoid this topic with their clinicians; patients who received chemotherapy may also benefit from assessment for clinically significant cognitive impairments. Psychosocial support and routine monitoring of patient-reported outcomes during survivorship care are likely to help reduce the burden of these conditions. Differentiated psychological services are becoming the norm in specialized breast cancer clinics; however, only a fraction of the breast cancer survivors are followed-up in these settings (127). The holistic approach to the patients' unmet needs also requires equipping health care professionals with evidence-based information on the optimal management strategies. For example, treatment for sexual dysfunction may require not only management of anxiety and depressive symptoms, but also vaginal dryness, which may be undertreated in women with history of estrogen-receptor positive breast cancer due to concerns over the effect of hormonal vaginal treatments (128) and unawareness of the recommendations for lubricants and moisturizers (129). Patients' education on common changes post breast cancer, and the strategies available to manage these, may help women to better understand and cope with their disease, increase patients' awareness of common symptomatology, and help to decrease the stigma associated with mental health disorders.

Our review also identified areas for further research. There is a pressing need for studies evaluating clinically diagnosed adverse mental health outcomes in samples of women likely to represent the cohort of survivors in the general population and with sufficient numbers to allow effects to be detected. Further research is particularly needed to better characterize the trajectories of mental health outcomes over time, particularly of anxiety, depression, and neurocognitive dysfunction. The long-term risk of sleep disorders needs clarification, because breast cancer treatments such as chemotherapy and steroids have been suggested to be associated with impaired sleep (130,131), possibly due to increased risk of vasomotor symptoms that affect the sleep quality and quantity (132). Evidence on the long-term effect of being diagnosed in situ vs invasive tumors and on having undergone breast reconstructive surgery is scarce despite the increasing numbers of ductal carcinoma in situ diagnoses and aesthetics surgeries performed. The role of systemic treatments other than chemotherapy on neurocognitive function also needs clarification, including the role of the different types of hormonal treatments (selective oestrogen receptors modulators vs aromatase inhibitors). Efforts should be made to employ standardized definitions of the outcomes, because the heterogeneity of diagnostic codes and psychometric instruments hampers comparability of results across studies. Further research is also needed on the performance of commonly used scales for anxiety and depression as screening tools for these conditions in breast cancer survivors. Studies should also consider that the incidence of mental health disorders after a breast cancer diagnosis may vary with age, socio-economic status, time, stage of disease, recurrence, type of treatment, and sequelae from cancer among other factors. The inclusion of a comparison group is essential to estimate the excess risk of the breast cancer survivorship.

In conclusion, women with a history of breast cancer appear to be at higher risk of a wide range of adverse mental health outcomes up to several years post diagnosis and treatment compared with women who did not have cancer. The evidence was particularly compelling for anxiety, depression and neurocognitive and sexual dysfunctions, and suicide, which were most often studied. However, there is a pressing need for more population-based research to better characterize the association between breast cancer history and mental health. Our results can be used to inform prevention and management strategies directed at tackling the burden of adverse mental health outcomes in breast cancer survivors.

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SECTION A – Student Details

Student ID Number	1513226	**Title**	Ms
First Name(s)	Helena Isabel		
Surname/Family Name	Morim Carreira		
Thesis Title	Long-term mental health and quality of life in women with history of breast cancer		
Primary Supervisor	Professor Krishnan Bhaskaran		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	JNCI – Journal of the National Cancer Institute		
When was the work published?	December 2018		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	HC wrote the first draft. All authors provided comments.

SECTION E

Student Signature	[redacted]
Date	09 December 2019

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Response

Response to Hulliard, Le Strat, Dubertre, et al.

Helena Carreira, Rachael Williams, Martin Müller, Rhea Harewood, Susannah Stanway, Krishnan Bhaskaran

See the Notes section for the full list of authors' affiliations.
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Dr Huillard et al. suggested that we report on mental health outcomes in breast cancer survivors with and without history of mental disorders. Twenty-two of the 60 studies excluded participants with history of mental disorders. Of the 38 studies that did not mention psychiatric history in their exclusion criteria, three accounted for it either through matching or adjustment in multivariable analyses; only one study explored the role of psychiatric history (it showed no correlation between psychiatric history and symptoms of posttraumatic stress).

Dr Huillard et al. noted that in a previous study, an increased risk of mental disorders was only observed among cancer patients who had a history of mental disorder (1). As noted above, results stratified by psychiatric history were seldom available in studies that we reviewed. However, we believe that the results of the studies that included only participants with no history of mental disorders are informative. Four population-based studies included in our review, in which outcomes were clinically ascertained, showed an increased risk of anxiety and/or depression in breast cancer survivors with no history of mental disorders, relative to comparable women without cancer (2–5). This shows that for breast cancer survivors (>1 year), the risk of first-ever disorders is increased relative to women who never had cancer. If the hypothesis of Dr Huillard et al. is correct, the burden of mental disorders is likely to be underestimated in the studies restricted to women with no history of mental disorders. We should also note that our study focused solely on female breast cancer survivors at least 1 year after diagnosis, whereas the Huillard et al. study included patients with a wide range of cancers (16% were of the breast). It is plausible that the effect of a cancer diagnosis on the patients' mental health varies by cancer site. We thank Dr Huillard et al. for their interest in our study.

Notes

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3.4 Systematic review update

The research described in the systematic review was based on search expressions that had been last run on the 1st of November 2017. The search was updated on the 2nd of October 2019, with a total of 2,041 new records identified. Using the same inclusion/exclusion criteria, 126 studies were eligible for full text assessment and ultimately six studies were eligible for the systematic review update (Table 3.1). In total, 66 studies, covering nine mental health outcomes, were eligible (60 from the original search, six from the update).

The most commonly evaluated outcomes were anxiety (n=23 studies) and depression (n=41). Of 23 studies of anxiety, 12 observed more anxiety in breast cancer survivors, including two of four studies with clinical/ prescription-based outcomes, and in 10 of 19 of anxiety symptoms. Of 41 studies of depression, 22 reported some statistical evidence of more depression in breast cancer survivors, compared to the non-cancer group; this included seven of eight studies where depression was ascertained clinically, and 15 of 33 studies that quantified depressive symptoms. Breast cancer survivors also had statistically significantly increased symptoms/frequency of neurocognitive dysfunction (21 of 28 studies), sexual dysfunctions (6 of 7 studies), sleep disturbance (5 of 5 studies), stress-related disorders (2 of 3 studies), suicide (2 of 2 studies), somatisation (2 of 2 studies), and bipolar and obsessive-compulsive disorders (1 of one study each).

Studies were heterogeneous in terms of participants' characteristics, time since diagnosis, ascertainment of outcomes, and measures reported. This precluded a quantitative summary of the data. A total 44 of 66 studies (66.7%) included small, non-probabilistic samples of breast cancer survivors. Mental health outcomes were most commonly evaluated with psychometric instruments (55/66 studies=83.3%), followed by clinical diagnoses registered in electronic healthcare databases (11/66=16.7%). Approximately one-half of the studies were at high risk of selection bias due to non-probabilistic recruitment of participants or low participation rates. In most studies (>70%), the risk of information bias was unclear and the cross-sectional design precluded the unequivocal assertion that the onset of the mental disorder was posterior to the breast cancer diagnosis. Approximately 40% of studies reported results likely to have been affected by confounding by age and socio-economic status.

Table 3.1 Results of the studies eligible in the update of the systematic review.

First author, year of publication Country	Breast cancer survivors Type of population and main characteristics	Stage at diagnosis (%)	Breast cancer treatments (%)	Time since diagnosis† in years: mean/median (SD), range	Comparison group Type of population and main characteristics	Outcome assessment	Quantitative measure of the outcome Breast cancer survivors	Comparison group	Relative risk estimate (RR, OR, SIR, PR)	P-value* or 95% confidence interval	Notes
Anxiety											
Cheng, 2018 [204] China	Convenience sample Patients aged 20-60 years, with non-metastatic disease, working at least 20h per week recruited from hospitals in four regions of China	I (47.2%) II (46.8%) III (6.0%)	Srg only (13.5%) RT only (6.7%) Srg + RT (34.5%) Srg + CT (7.1%) Srg + RT + CT (38.2%)	3.2 (ND), 2-ND	Convenience sample Women with no history of cancer, aged 20 to 60 years, working >20h per week and in the current job for >1yr	HADS	Mean score (SD): 5.43 (3.51)	Mean score (SD): 2.89 (1.37)	-	P<0.0001	Higher scores represent more anxiety.
Wirkner, 2017 [205] Germany	Convenience sample 20 breast cancer survivors recruited from one center	ND (ND)	Srg (ND%) RT (85%) CT (100% HT (75%)	3.43 (1.9), ND-7	Convenience sample 31 healthy controls recruited via bulletin boards	STAI (trait anxiety only)	Mean score (SD): 48.40 (2.09)	Mean score (SD): 31.67 (1.70)		P<0.001	Cases and controls matched for age, education and handedness
Depression											
Cheng, 2018 [204] China	Convenience sample Patients aged 20-60 years, with non-metastatic disease, working at least 20h per week recruited from hospitals in four regions of China	I (47.2%) II (46.8%) III (6.0%)	Srg only (13.5%) RT only (6.7%) Srg + RT (34.5%) Srg + CT (7.1%) Srg + RT + CT (38.2%)	3.2 (ND), 2-ND	Convenience sample Women with no history of cancer, aged 20 to 60 years, working >20h per week and in the current job for >1yr	HADS	Mean score (SD): 6.71 (3.56)	Mean score (SD): 2.30 (1.26)	-	P<0.0001	Higher scores represent more depression.
Wirkner, 2017 [205] Germany	Convenience sample 20 breast cancer survivors recruited from one center	ND (ND)	Srg (ND%) RT (85%) CT (100% HT (75%)	3.43 (1.9), ND-7	Convenience sample 31 healthy controls recruited via bulletin boards	BDI-II	Mean score (SD): 16.20 (1.64)	Mean score (SD): 4.57 (1.34)		P<0.001	Cases and controls matched for age, education and handedness

(Continued)

Table 3.1 Continued

First author, year of publication Country	Breast cancer survivors Type of population and main characteristics	Stage at diagnosis (%)	Breast cancer treatments (%)	Time since diagnosis† in years: mean/median (SD), range	Comparison group Type of population and main characteristics	Outcome assessment	Quantitative measure of the outcome		Relative risk estimate (RR, OR, SIR, PR)	P-value* or 95% confidence interval	Notes
Depression											
Ng, 2019 [206] Canada	Convenience sample 12,127 women aged >18, diagnosed with breast cancer between 2005-2009, from the cancer registry. Women who did not have health insurance were excluded.	I (40.8%) II (30.9%) III (12.4%) IV (3.9%) Unknown (12.0%)	ND (ND)	ND (ND), 4-9	Convenience sample Women with no cancer history or history of prescription of chemotherapy agents, selected at random from primary care databases.	Primary care diagnosis of depression, ICD codes or antidepressant prescription	Incidence rate: 5.57 (5.34-5.82)	Incidence rate: 3.05 (2.94-3.17)	HR=1.68	95%CI: 1.60-1.76	Adjusted for neighborhood quintile of deprivation, presence of comorbidity at baseline.
Neurocognitive dysfunction											
Cheng, 2018 [204] China	Convenience sample Patients aged 20-60 years, with non-metastatic disease, working at least 20h per week recruited from hospitals in four regions of China	I (47.2%) II (46.8%) III (6.0%)	Srg only (13.5%) RT only (6.7%) Srg + RT (34.5%) Srg + CT (7.1%) Srg + RT + CT (38.2%)	3.2 (ND), 2-ND	Convenience sample Women with no history of cancer, aged 20 to 60 years, working >20h per week and in the current job for >1yr	CSC-W21	Mean score (SD): 6.43 (18.32)	Mean score (SD): 0.32 (0.71)	-	P<0.0001	Higher scores represent more problems.
Jung, 2016[207] United States	Convenience sample 62 right-handed women recruited from one breast cancer center	I (18%) II (57%) IIIa (25%)	Srg, M (54%) Srg, BC (46%) RT (90.3%) CT (45.2% HT (80.6%)	~1 year	Convenience sample 30 healthy women with no cancer	VWMT	Overall deficit score, CT group: +0.4 Overall deficit score, non-CT group: 0.0	Overall deficit score: -0.6	-	P=0.007	The group exposed to CT had significantly worse performance at 1 year evaluation compared to women in the control group.

(Continued)

Table 3.1 Continued

First author, year of publication Country	Breast cancer survivors Type of population and main characteristics	Stage at diagnosis (%)	Breast cancer treatments (%)	Time since diagnosis† in years: mean/median (SD), range	Comparison group Type of population and main characteristics	Outcome assessment	Quantitative measure of the outcome		Relative risk estimate (RR, OR, SIR, PR)	P-value* or 95% confidence interval	Notes
Neurocognitive dysfunction											
Wirkner, 2017 [205] Germany	Convenience sample 20 breast cancer survivors recruited from one center	ND (ND)	Srg (ND%) RT (85%) CT (100% HT (75%)	3.43 (1.9), ND-7	Convenience sample 31 healthy controls recruited via bulletin boards	WMS-R	Mean score (SD): Digit span forward: 33.90 (6.22) Digit span backward: 60.84 (6.69) Logical memory I: 67.12 (6.39) Logical memory II: 61.40 (6.26)	Mean score (SD): Digit span forward: 53.32 (5.26) Digit span backward: 61.61 (5.51) Logical memory I: 84.66 (5.40) Logical memory II: 89.02 (5.29)	-	Digit span forward: P=0.021 Digit span backward: P=0.930 Logical memory I: P=0.042 Logical memory II: P=0.002	Cases and controls matched for age, education and handedness
Kesler, 2017 [208] China	Convenience sample 31 newly diagnosed breast cancer patients aged 34-65 years recruited from one center	I (16%) II (65%) III (19%)	Srg (ND%) RT (65%) CT (100% HT (71%)	~1 year	Convenience sample 43 frequency matched healthy controls	RAVLT A1	Mean score (SD): 54 (8.3)	Mean score (SD): 57 (8.8)	-	P>0.193	-
						RAVLT A6	Mean score (SD): 10 (3.0)	Mean score (SD): 11 (2.8)	-	P>0.193	
						CTMT 1	Mean score (SD): 53 (9.7)	Mean score (SD): 58 (9.6)	-	P>0.193	
						CTMT 5	Mean score (SD): 53 (9.5)	Mean score (SD): 57 (8.9)	-	P>0.193	
						COWA	Mean score (SD): 47 (9.0)	Mean score (SD): 52 (13)	-	P>0.193	
						MCAB Adjustment Index	Mean score (SD): 1.7 (1.9)	Mean score (SD): 0.73 (1.2)	-	P>0.193	

(Continued)

Table 3.1 Continued

First author, year of publication Country	Breast cancer survivors Type of population and main characteristics	Stage at diagnosis (%)	Breast cancer treatments (%)	Time since diagnosis† in years: mean/median (SD), range	Comparison group Type of population and main characteristics	Outcome assessment	Quantitative measure of the outcome		Relative risk estimate (RR, OR, SIR, PR)	P-value* or 95% confidence interval	Notes
Sexual dysfunction											
Soldera, 2018 [209] Canada	Convenience sample 248 women who had been newly diagnosed with breast cancer at one of three metropolitan hospitals, who didn't not have neo adjuvant chemotherapy and lived within 1 hour distance of the hospital. :	I-III (100%)	Srg, M (25%) Srg, BC (75%) RT (28%) CT (29% HT (27%)	12.5 (ND), 9.4-17.6	Convenience sample 159 Women undergoing screening mammography at the same hospitals, age-matched to the breast cancer group. Abnormalities in the mammography were excluded as well as women with previous cancer diagnosis.	SAQ: Pleasure	Mean score (SD): 12 (4.25)	Mean score (SD): 12 (4.41)	-	P=0.56	Adjusted for age. There was a significant interaction between menopausal status and type of population, with pre- and peri-menopausal women being less likely to be sexually active compared to controls (Odds ratio=0.12, P=0.012).
						SAQ: Discomfort	Mean score (SD): 2 (2)	Mean score (SD): 2 (2.02)	-	P=0.14	
						SAQ: Habit	Mean score (SD): 1 (0.46)	Mean score (SD): 1 (0.54)	-	P=0.49	

* Underlined text is used to denote that the differences between the two groups were supported by some statistical evidence (P<0.05).

BDI-II = Beck Depression Inventory-II; COWA = Controlled Oral Word Association; CT = chemotherapy; CTMT = Comprehensive Trail Making Test; CSC-W21 = Chinese version of the Cognitive symptoms Checklist; HADS = Hospital Anxiety and Depression Scale; HR = hazard ratio; HT = hormone therapy; MCAB = Mobile Cognitive Assessment Battery; ND = not defined; RAVLT = Rey Auditory Verbal Learning Test; RT = radiotherapy; SAQ = Sexual Activity Questionnaire; STAI = State-Trait Anxiety Inventory; Srg, M = mastectomy; Srg, BC = breast conserving surgery; SD = Standard deviation; TAP = Test battery for Assessment of Attention; VWMT = Verbal Working Memory Test; 95%CI = 95% confidence interval.

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3.5 Summary

- This systematic review summarised the evidence of the studies that quantified differences in the frequency and/or severity of adverse mental health outcomes between women with a history of breast cancer (>1 year) and women who never had cancer.
- 66 studies were included after updating the searches in October 2019. These studies provided data for 9 mental health outcomes. Depression (n=41 studies), neurocognitive dysfunction (n=28) and anxiety (n=23) were the most commonly studied outcomes. Fewer studies provided data for sexual dysfunction (n=7), sleep disturbances (n=5), post-traumatic stress (n=3), obsessive compulsion (n=1), somatization (n=2), bipolar disorder (n=1), and suicide (n=2).
- Overall, the studies provided some evidence of a raised risk of anxiety, depression and suicide, and neurocognitive and sexual dysfunctions, in breast cancer survivors compared with women with no prior cancer, persisting for several years post-treatment. Sleep disturbances, sexual disorders and post-traumatic stress disorder, also appear to be increased in breast cancer survivors, but the smaller number of studies precludes firm conclusions.
- However, the quality of most studies investigating mental health outcomes in breast cancer survivors, compared to women with no prior cancer, was suboptimal. Studies often relied on small convenience samples that are likely to lack statistical power. There was a large potential for misclassification of the outcomes in several studies and outcomes were rarely based on clinical assessments. Confounding by age and socio-economic status is also likely to have affected 40% of the studies.
- The current body of research lacks-well powered studies involving samples of breast cancer survivors broadly representative of those in the general population, and with clinically assessed outcomes.

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4 Description of the data sources

4.1 Introduction

The research in this thesis is based on electronic health records (EHRs) of patients attending primary care practices that contributed with data to the Clinical Practice Research Datalink (CPRD) General Practitioner Online Database (GOLD) (hereafter referred to as CPRD GOLD primary care database). For Aim 1 (i.e. quantifying the risk of adverse mental health outcomes in breast cancer survivors compared to women with no history of cancer), the data in the CPRD GOLD primary care database were linked to EHRs from secondary care, official death registration data, and area- and patient-level deprivation data. The research to address Aim 2 (i.e. investigating the HRQoL and presence/severity of anxiety and depressive symptoms breast cancer survivors compared to non-cancer controls) involved using the CPRD primary care database to select both women with a history of breast cancer and women who never had cancer, and invite them to respond to questionnaires on their HRQoL, anxiety and depressive symptoms. This chapter provides the description of the data.

4.2 Clinical Practice Research Datalink General Practitioner Online Database

CPRD is a UK government research service supported by the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR). CPRD has been collecting, processing, and releasing anonymised EHRs from patients attending primary and secondary care in the UK since 1987 [210].

4.2.1 Data and database version

The CPRD GOLD primary care database is one of the largest and longest-established databases of EHRs in the world. Data come from primary care practices that use the general practitioner (GP) software system InPS Vision, which is one of the four main systems in use in the NHS GP practices (TPP SystmOne, EMIS Web, and Microtest Evolution are the others) [211]. The number of practices using InPS Vision has decreased during the recent years, with several practices opting to move to EMIS Web or TPP SystmOne. Figure 4.1 shows the spatial distribution of the percentage of the population share and number of practices using the InPS Vision software system in 2016 at both Clinical Commissioning Group and NHS region levels.

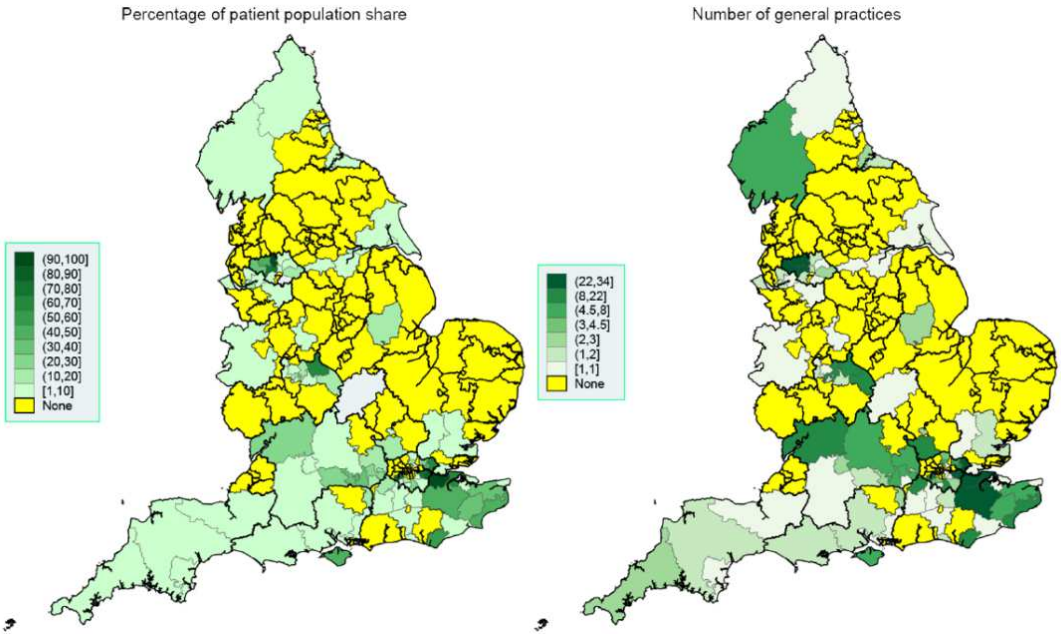

Figure 4.1 Spatial distribution of the 7526 general practices in the UK by number of general practices using InPS Vision, and percentage of the population share, at both Clinical Commissioning Group (thinner borders) and NHS region (thicker border) levels. Figure from [212]; reproduced under the terms of a CC BY license.

The data in the InPS Vision system are routinely entered by the patient's GP or the health care team, at the point of providing care, for consultations occurring at the participating practices [213]. The resulting clinical record includes information collected prospectively on demographics, lifestyles, biochemical analysis results, diagnoses, prescriptions, and referrals to secondary and tertiary care. When a patient is referred for secondary care, information from inpatient and outpatient care is usually sent back to the GP to be added to their clinical record. It should be noted that the availability of this information may differ from the information that is collected during primary care appointments (e.g. conditions added to the free text section of the clinical record would not be included in CPRD GOLD data; nor would discharge letters scanned and kept as attachments to the patient record).

Much of the information (but not all) recorded in the InPS Vision system uses version 2 Read codes [214]. The Read code classification includes approximately 250,000 codes that allow for the recording of a wide range of information, such as diagnoses and symptoms, biochemistry laboratory results, tests, family history of diseases, therapeutic and surgical procedures and surgeries carried out, ethnicity, religion, occupation, social circumstances, and administrative details related to patient care. To enter data in the patient record during consultations, the GP searches for relevant codes using keywords, which prompts a list of potential codes with the keyword in their description

to come up. The GP then selects the preferred code from the list; the consultation manager interface also includes a section for comments where free text can be added. If no suitable code is found, a new code may be added. Data can also be added retrospectively, with a past event date, which in this case will be different from the system date. Prescription data are recorded at the point of issue using product codes, which are based on the drugs listed in the British National Formulary (BNF).

The CPRD periodically retrieves data and processes and releases data for wider use in public health research. Procedures are in place to ensure the confidentiality of the data. Identifiable information in the patients' EHR, such as name, address, telephone number, or day and month of birth in adults, is sent to a trusted third party (NHS Digital, the statutory body in England that is allowed to receive identifiable patient information), where a set of anonymised patient identifiers are generated. CPRD automatically retrieves from the system InPS Vision anonymised clinical data, to which the anonymised patient identifiers are added. The information in the free text notes added by the GP is not sent to CPRD, as this may contain identifiable information. This process ensures that there is total separation, with the trusted third party never seeing the patient medical information, and CPRD never receiving information that allows for patients to be identified.

4.2.2 Quality control

At CPRD, the quality of the data is checked both at patient- and practice-level. Data quality controls at patient-level include internal consistency checks such as having a date of registration with the practice that is later than the date of birth, among others (Table 4.1). At the end of the checks, a flag is added to the data indicating whether the patient record failed one or more of the checks; patients who pass all checks are considered to have medical records of acceptable data quality for research purposes.

Table 4.1 Example of internal consistency checks performed by CPRD on the data collected from the InPS Vision software.

Valid gender and birth date
First registration posterior to birth date
Current registration date:
Valid
After the first registration date
After date of birth
Permanent registration with the practice
Transferred out of the practice & reason: either both missing or both completed
If transferred out of the practice, dates consistent with registration and birth dates.
Valid event date recording (e.g. not a future date, or <1st Jan 1980).

The data are also checked at practice-level for completeness, internal consistency and external validity. Examples of these checks at practice-level include assessing whether there are temporal gaps in the data provided by the practice to CPRD, and whether the mortality rates observed for patients registered with the practice lie within reasonable expected limits. A field is also added to the data indicating the date after which the data in that practice is considered of sufficient quality to be used for research (termed by CPRD as the "up to standard date").

4.2.3 Representativeness of the broad UK general population

The representativeness of the data included in the CPRD GOLD primary care database needs some consideration. In the UK, virtually all inhabitants are registered with a GP practice [215]. Access to NHS services is free of charge, following the principle that 'access to NHS services is based on clinical need, not an individual's ability to pay' [216]. The GP practices throughout the UK provide the first level of care to the population within the NHS, and are responsible for providing preventive care, treatment for suitable illnesses and act as gatekeepers to other levels of care. The data gathered by CPRD comes from computer software systems that are used in clinical practice to create, add and manage information in patients' EHR. As of January 2019, the CPRD GOLD primary care database included data from 18.4 million patients from 761 GP practices. Within each contributing GP practice, patients may opt out of having their data transferred to other entities or used for research purposes, which is a threat to the population-based nature of the data. In July of 2013, the CPRD GOLD primary care database included data for 11.3 million patients, of which 4.4 million were alive and registered (7% of the UK population). It is known that the distribution of the GP practices contributing data in the most recent years is not geographically representative of the UK as a whole (Figure 4.1); this may potentially lead to overrepresentation of wealthier areas in the UK. Nevertheless, patients in the database were shown to be broadly representative of the UK general population in terms of age, sex and ethnicity [210, 213].

4.2.4 Validity and completeness of the data

The completeness and validity of the information in CPRD GOLD primary care database is of major interest. The CPRD GOLD primary care database has been shown to capture more than 90% of the cancer diagnoses registered in the cancer registries (gold-standard) [217]. The completeness of the information on mental health

is more difficult to ascertain, as a gold standard for comparisons has not been available until recently (the CPRD Mental Health Dataset). The absence of a Read code for a mental health condition is typically interpreted as evidence of the patient not having the condition, but one has to acknowledge the potential for low sensitivity [213]. For other types of information, such as weight or smoking habits, absence of the information may be related to the information itself; for example, it is plausible that obese patients are more likely to have their weight recorded compared to those who have healthy weight [213].

Several studies employed strategies to validate outcomes defined in CPRD primary care data [218, 219]. These most often ascertained positive predictive values (i.e. the proportion of cases who are confirmed to have the disease), using as gold-standard information requested from the patient's GP (e.g. GP questionnaires) [219]. The proportion of cases confirmed varies by disease type; for infectious disease, neoplasms, skin diseases, genitourinary conditions, congenital disorders and external causes of morbidity and mortality the median proportion of cases confirmed was >90% [219]. For mental and behavioural disorders, the median proportion of cases confirmed in 20 validation studies was 83.0% (95%CI: 52-100) [219].

4.2.5 Linkage to other sources of data

The data in the CPRD GOLD primary care dataset are linked to other databases containing health care data at individual patient level [220]. Examples of established linkages include the Hospital Episode Statistics Admitted Patient Care (HES-APC), the National Cancer Registration and Analysis Service data from Public Health England, and Office of National Statistics (ONS) death registration data.

The data flow from the other data sources is similar to the one described for the CPRD GOLD primary care database. Data from the external sources is sent to CPRD, alongside a link identifier, at the same time that identifiable patient data (NHS number, date of birth, postcode, gender and link identifier) is sent to a trusted third party (NHS Digital). The trusted third party then links the data of the two datasets, and generates the IDs that allow the sources of data to be linked. Once the process is completed, the identifiers are provided to CPRD, allowing for in-house linkage of the data [220].

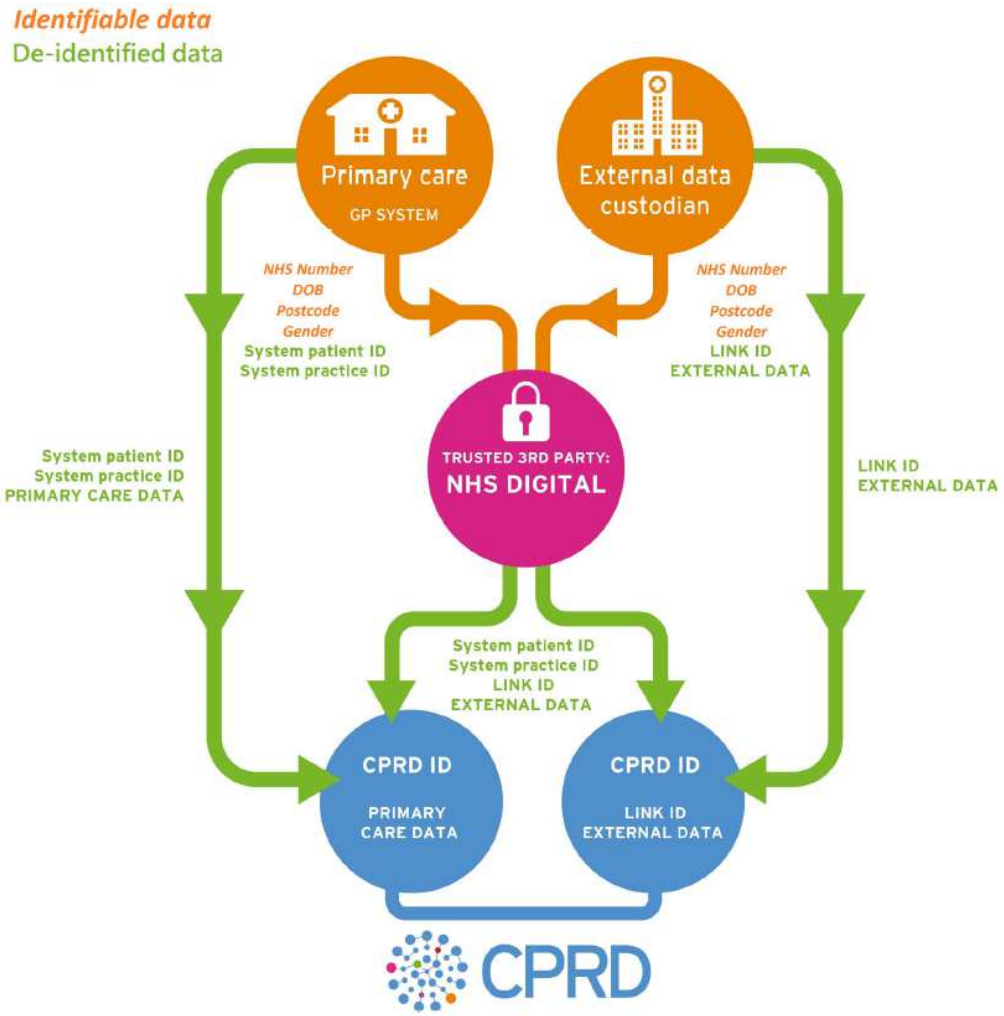

Figure 4.2 Data flow for primary care data linkage. Figure from [220]; reproduced under the terms of a CC BY license.

The linkage of the data is done using deterministic methods, involving eight steps with decreasing specificity [220]. The first step involving matching on exact NHS number, gender, date of birth and postcode; patients who do not match on all of these characteristics between the two databases are considered for the subsequent steps. In the second step, the criterion for post code match is dropped, and during the following five steps the linkage is attempted after removing one or more variables. The last step involves searching for the same exact NHS number only [220]. Linkage between the CPRD GOLD June 2018 version and HES showed that over 95% of the patients eligible for linkage are linked within the first two steps (67.6% in the first, and 28.7% in the second).

It should be noted that linkage is only available for GP practices geographically located in England and that consented to take part in the linkage scheme (80% of the practices in England, 60% of those in the UK). In the practices participating in the linkage scheme, patients can opt out of having their data linked to other sources of data.

4.3 Hospital Episodes Statistics, Admitted Patient Care

The HES database includes information on all contacts with NHS hospitals in England, including outpatients appointments, hospitalizations and emergency visits [221]. All patients receiving care in NHS Clinical Commissioning Groups (CCGs) in England are present in HES, including private patients treated in the NHS, residents outside of England treated in England, and care outside of the NHS but funded by the NHS [221].

This database is maintained by NHS Digital, and extraction from the main database occurs on a monthly basis [221]. There are different versions of the database, which differ on the type of contact with the hospital: accident and emergency attendance, outpatient appointments and attendances, critical care, and admitted patient care (APC); the latter includes inpatients and day case admissions to the hospital [221].

The research in this thesis used data from the HES-APC database. Data on APC have been collected since 1989, and are available for linkage with CPRD GOLD primary care data from 1997 onwards. In this thesis, HES-APC set 16 data were used linked to the CPRD GOLD primary care database, covering the period between April 1997 and December 2017 [222]. The linkage process has been described before (see section 4.2.5). Patients in the HES-APC database may not be eligible for linkage with CPRD primary care data, as they may live outside England and attended care in England, or have invalid identifiers for linkage. Source files were available identifying each patients' eligibility for linkage.

The data in the HES-APC are organized by hospitalisations and episodes. Hospitalisations are defined by the period between admission and discharge from the hospital [222]. Episodes are defined by the period during which a patient is under continuous care of one consultant in one health care institution [222]. Patients may be transferred to the care of another consultant during the same hospital stay, generating another episode within the same hospitalisation [222]. Each episode may be recorded with up to 20 diagnosis, which are coded using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [223].

The data from this database were used to identify outcomes of self-harm, which have been described as imperfectly recorded in the CPRD GOLD primary care database [224].

4.4 Index of Multiple Deprivation

The Index of Multiple Deprivation (IMD) is a widely used measure of relative deprivation in England, and similar measures are available for Wales [225], Scotland [226] and Northern Ireland [227]. This measure was used to account for the potential confounding effect of socio-economic status (*vide* Chapters 6 and 7).

The IMD is an ecological measure based on the premise that deprivation can be measured by different dimensions at small area level, and that individuals living in these areas share these dimensions of deprivation [228].

The IMD is calculated for small geographical areas including approximately 1,500 residents, which are known as Lower-layer Super Output Areas (LSOA). Based on the 2011 Census, there were 32,844 LSOA in England. Mathematically, the IMD is calculated by using a set of indicators (at LSOA level) to produce information for seven domain indices that are related to material deprivation (income deprivation; employment deprivation; education, skills and training deprivation; health deprivation and disability; crime; barriers to housing and services; and living environment deprivation) [228]. The data from these seven domains are combined using specified weights to produce a single measure for each LSOA. The 32,844 LSOA are then sorted by measure of deprivation, and assigned a rank from one to 32,844, creating a relative measure of deprivation. For research purposes, IMD is typically categorised in percentile-based groups (e.g. quintiles) [228]. The IMD has been estimated periodically, and the most recent version (2015) has been used for this thesis.

All GP practices contributing with data to the CPRD GOLD primary care database can be assigned IMD rank based on the GP practice post-code. This has been used in several studies as a proxy measure for socio-economic status at individual level because it is available for all patients, even though the ecological fallacy might apply (i.e. the individual experience may be different that the group). IMD based on the LSOA of the individual patient's residential address allows for a finer adjustment for confounding by socio-economic status, even though it is still based on area and therefore may not correspond to the patient's true socio-economic status. IMD for patient postcode has the disadvantage of only being available for patients in England and whose data are eligible for linkage.

Data from the IMD at practice level were used in the analyses presented in Chapters 6 and 7, to adjust for the potential confounding effect of deprivation on the associations between breast cancer survivorship and adverse mental health outcomes and quality of

life. Patient level IMD were limited to patients eligible for linkage and used in sensitivity analyses only.

4.5 Office for National Statistics mortality data

The Office for National Statistics (ONS) mortality data include all deaths occurring in the UK, and are the basis of the official mortality statistics issued on behalf of the UK government [229]. In the UK, by law, all deaths must be registered with the General Register Office within five days (8 in Scotland), and to do so, one needs to provide either a Medical Certificate of Cause of Death issued by the attending doctor (most cases), or permission from the coroner to report the death, if that has been reported to a coroner [230]. Cremation or burial are not allowed before death registration [230].

The ONS mortality data include information entered in the death certificate by the doctor attending the deceased. This includes the primary cause of death, which is defined by the World Health Organization as 'the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury' [231], and space for up to 15 contributory causes of death.

Some deaths are referred to a coroner for investigation. Reasons for this include an unknown cause of death, suspicious or violent causes of death, possible suicide, among others [229]. The rules specify that the certifying doctor must have seen the deceased during the last two weeks of life to complete a certificate, otherwise it has to be referred to a coroner [229]. Deaths referred to the coroner are subsequently investigated, and assigned a primary cause of death, using post-mortem examinations to ascertain whether it was a natural death if needed [229]. In cases where a natural death cannot be unequivocally ascertained, there is a coroner's inquest and the primary cause of death, if ascertained, is registered later [229].

To assign a primary cause of death, the text of the death certificate is converted to ICD codes, using computerised algorithms [229]. Since 2010, the data have been coded using ICD-10 codes, with ICD-9 codes being used prior to that [223, 232].

Data on cause-specific deaths were used in this thesis to define suicide (one of the outcomes of interest, vide Chapter 6), which is poorly captured in the CPRD GOLD primary care database [224].

4.6 Patient-reported outcomes

HRQoL refers to how a patient *perceives* their overall health status, and is a multidimensional construct that encompasses physical, psychological, social and spiritual dimensions of well-being [233, 234]. Standard methods for HRQoL assessment involve collecting information directly from the patients using validated questionnaires [235]. A similar approach was used in this thesis. The following paragraphs described the scales that were used the study of patient-reported outcomes that assessed quality of life and symptoms of anxiety and depression.

4.6.1 Quality of Life

Ideally, a tool to measure HRQoL would include items for several dimensions of quality of life (e.g. physical, emotional, social, role performance, pain and other symptoms relevant to the patient population). In addition, the tools should produce the same results on repeated use of the instrument (reliability), measure the concept they intend to measure (validity), provide different results when circumstances change (sensitivity to change), be appropriate to the question being assessed (appropriateness to the question) and have the potential for clinical interpretability (practicality) [236, 237].

Several tools have been used to assess HRQoL in breast cancer survivors [238]. Some tools were developed to assess HRQoL during the main treatments for cancer, and include items that may not apply to long-term survivors (e.g. nausea secondary to cytotoxic drugs), besides lacking items that are specific to cancer survivors' long-term concerns such as fear of cancer recurrence. Recognising the need for tools that address concerns beyond the treatment phase of the disease, researchers have developed disease-specific tools specifically for long-term cancer survivors [239].

Chopra *et al* conducted a systematic review of validated quality of life instruments that have been used in studies of breast cancer survivors [239]. 10 instruments were identified; their properties are listed in Table 4.2 [239]. Most scales have been shown to have good reliability and validity, but few were ever tested for sensitivity to changes (responsiveness). This is an important disadvantage because breast cancer survivorship is a journey, and it is important that tools are able to detect changes in HRQoL [239].

Table 4.2 Instruments identified by Chopra et al. as having been used to assess HRQoL in samples of breast cancer survivors, with respective domains and psychometric properties. Table adapted from [237]; reproduced under the terms of a CC BY license.

Instrument	HRQoL domain				Properties		
	Physical	Mental	Social	Spiritual	Reliability	Validity†	Responsiveness
BIRS	☑	☑	☑	☒	Internal consistency: 0.94	Convergent & divergent	Not Reported
CARES-SF	☑	☑	☑	☒	Internal consistency: 0.85-0.61	Concurrent	Not Reported
EORTC QLQ-30	☑	☑	☑	☒	Internal consistency >0.70	Content, concurrent, discriminant	Not Reported
EORTC QLQ-BR23	☑	☒	☒	☒	Internal consistency: 0.46-0.94	Content, construct, criterion-relate	Responsiveness in side effects & body image
QLI-CV	☑	☑	☑	☑	Internal consistency: 0.95	Concurrent (criterion related, r=0.80 construct.	Not Reported
FACT-B	☑	☑	☑	☒	Internal consistency: 0.90 Test-retest=0.85	Content, construct, concurrent (r=0.87), divergent, known group	Sensitive to 2-month changes
FACT-G	☑	☑	☑	☒	Internal consistency: 0.89 Test-retest=0.92	Content, construct, divergent, known group.	Not Reported
FACIT-SP	☒	☒	☒	☑	Internal consistency: 0.81-0.88	Discriminant, convergent	Not Reported
QOL-CS	☑	☑	☑	☑	Internal consistency: 0.93 Test-retest: 0.89	Content, concurrent (r=0.78), predictive, construct, discriminant	Not Reported
QLACS	☑	☑	☑	☑	Internal consistency: generic=0.95; cancer-specific=0.98	Concurrent, retrospective	Change in health status

BIRS = Body Image and Relationship Scale; CARES-SF = Cancer Rehabilitation Evaluation System Cancer -Short Form; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer - Breast module; QLI-CV = Ferrans and Powers's Quality of Life Index -Cancer Version; FACT-B = Functional Assessment of Cancer Therapy-Breast; FACT-G = Functional Assessment of Cancer Therapy-General; FACIT-SP = Functional Assessment of Chronic Illness Therapy-Spiritual Well Being Scale; QOL-CS = Quality of life-Cancer Survivor; QLACS = Quality of Life-Cancer Survivors.

† Construct validity assesses if a test measures what it aims to measure; it is composed of convergent and discriminant validity. Convergent validity refers to how well a scale is related to other measures of the same construct. Discriminant validity aims to assess that variables that should not be associated with a given factor, are found to not be associated in the study. Divergent validity aims to establish how one concept is different from the others included in the scale. Concurrent validity refers to the performance of a test against another test that has been previously validated.

Of the scales that addressed HRQoL specifically in cancer survivors beyond the treatment phase, the Quality of Life in Adult Cancer Survivors Scale (QLACS) [240] showed good validity, reliability and responsiveness compared to the other scales. In addition, it was one of the only three instruments that included items for physical, mental, social and spiritual domains of HRQoL [239]. Further investigation showed that the QLACS scale was developed to take into account the specific needs of long-term cancer survivors (≥5 years), including issues that continue after treatment, new issues

that arise during the period post-cancer, late physical effects of the cancer treatments and positive aspects of surviving to cancer [240]. The QLACS scale has also been used to evaluate HRQoL in a sample of early post-treatment (18-24 months) breast cancer survivors [241]. This scale was therefore chosen to assess HRQoL in this thesis.

The QLACS scale includes 47 items, divided between seven generic and five cancer-specific domains (specific domains shown in Table 4.3) [240]. Answers to the QLACS scale are provided on an ordinal Likert-type of scale, with values for individual items ranging from 1 to 7. Breast cancer survivors were asked to reply to all 47 items. Women who never had cancer replied to the 28 items of the generic domains only.

Table 4.3 Items of the Quality of Life in Adult Cancer Survivors scale grouped by domain.

Generic domains
Negative feelings
19 Bothered by mood swings
7 Felt blue or depressed
9 Worried about little things
24 Felt anxious
Positive feelings
8 Enjoyed life
28 Content with life
6 Felt happy
22 Had a positive outlook on life
Cognitive problems
3 Bothered by having a short attention span
4 Had trouble remembering things
2 Difficulty doing things requiring concentration
23 Bothered by forgetting what started to do
Pain
13 Bothered by pain preventing activities
17 Mood disrupted by pain or its treatment
27 Pain interfered with social activities
21 Had aches or pains
Sexual interest/ function
16 Lacked interest in sex
26 Avoided sexual activity
12 Dissatisfied with sex life
10 Bothered by inability to function sexually
Energy/fatigue
11 Lacked energy to do things wanted to
14 Felt tired a lot
1 Had energy to do things wanted to do
5 Felt fatigued
Social avoidance
18 Avoided social gatherings
20 Avoided friends
25 Reluctant to meet new people
15 Reluctant to start new relationships

(Continued)

Table 4.3 Items of the Quality of Life in Adult Cancer Survivors scale grouped by domain.

Cancer-specific domains
Financial problems
43 Had money problems from cancer
45 Financial problems from loss of income due to cancer
30 Financial problems from cost of cancer surgery or treatment
37 Problems with insurance because of cancer
Benefits of cancer
40 Cancer helped recognize what important in life
41 Better able to deal with stress because of cancer
32 Cancer helped cope better w/problems
29 Appreciated life more because of cancer
Distress-family
34 Worried whether family had cancer causing genes
31 Worried family members were at risk for cancer
42 Worried family should have genetic tests - cancer
Appearance
35 Felt unattractive because of cancer or its treatment
33 Self-conscious about appearance because of cancer
44 Felt treated differently because of changes in appearance
38 Bothered by hair loss from cancer treatments
Distress-recurrence
39 Worried about cancer coming back
46 When felt pain, worried it was cancer again
36 Worried about dying from cancer
47 Preoccupied with concerns about cancer

4.6.2 Symptoms of anxiety and depression

Symptoms of anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS) [242]. This scale has been widely used in samples of the general population as well as hospitalized patients, as it excludes somatic symptoms of anxiety/depression that may be disease manifestations. This scale has been validated for use in primary care [243] and was used in primary care studies in the UK [244-246].

HADS is a 14-item self-reported screening tool capturing anxiety and depressive symptoms in the past week. It contains two subscales, one for anxiety (HADS-A) and another for depression (HADS-D), with seven items each [242]. The scale then uses cut-off points to identify patients who are likely to have clinically relevant symptoms of depression and anxiety.

4.7 Demographic data

Information on education, ethnicity and living arrangements (as a proxy for social support) were collected directly from the patients alongside the patient-reported outcomes, as this information is known to be incompletely recorded in the patients' EHR. Education was evaluated by qualifications held (up to GCSEs, O levels, or equivalent; A levels or equivalent; undergraduate degree; post-graduate degree; trade, technical or vocational training). Ethnicity categories were based on the 2011 census categories, without sub-specification of the White and Asian categories (White; Asian/Asian British; Black/African/Caribbean/Black British; Mixed/Multiple ethnic groups; Other ethnic group). Living arrangements options were: living with partner/spouse; living with family/friends; living alone; in a long term care facility; other).

4.8 Clinical data

Information regarding treatments received for breast cancer, stage of the disease at diagnosis, current status of the disease and menopausal status are also sub optimally reported in the EHRs. A questionnaire was therefore used to collect information directly from the patients.

4.9 Data collection procedures

The operational aspects of my study on patient-reported outcomes were conducted in collaboration with CPRD, to enable active data collection from CPRD participants (study protocol in Appendix 4). The Interventional Research Team is able to liaise with primary care practices actively contributing with data to the CPRD GOLD primary care database, and holds both CPRD GOLD and InPS Vision patient identifiers.

At the beginning of the study, the Interventional Research Team at CPRD identified a list of 253 GP practices that were actively contributing with data to CPRD in December of 2018, and invited them to participate in the study by email and post. The Interventional Research Team sent a further reminder to all those that did not reply.

I generated lists of potentially eligible patients from each GP practice using data from the CPRD GOLD primary care database, and passed these on to the Interventional Research Team at CPRD.

Practices that agreed to participate in the study were sent the list of potentially eligible patients from their practice, and asked to confirm each patient's eligibility. A

compensatory payment of £40 per list checked was provided in line with common practice for other studies at CPRD.

Upon receiving a list of eligible patients back fro the GPs, the Interventional Research Team at CPRD prepared packs containing all materials to be sent to the patients, and sent these by post to the GP practice. Each questionnaire included an InPS Vision software identifier, referring to the patient to be sent.

At the GP practice, members of staff used the InPS Vision software identify the patient's name and address, added these to the respective envelope, and posted these out to the patients.

Women received in their home address the envelope sent by their primary care practice, which contained an invitation letter, study participant information sheet, anonymised questionnaires and a pre-paid envelope to return the questionnaires. The envelopes were pre-addressed to the Interventional Research Team at CPRD.

Once the completed questionnaires were received at CPRD, the Interventional Research Team replaced the InPS Vision software identifier with the CPRD GOLD patient identifier, ensured that no identifiable information had been included, and sent the scanned questionnaires to me for data entry and analysis.

The data in the questionnaire were entered, cleaned and analysed. A broad description of the methods, and the full results of this study are reported in Chapters 6, 7 and 8.

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4.10 Summary

- The research in this thesis is largely based on data stored in the CPRD GOLD primary care database. This is one of the largest databases of primary care electronic health records in the world, with data for >18.6 million patients from over 760 GP practices in the whole UK.
- Information in the CPRD GOLD primary care database comes directly from GP practices that use InPS Vision software to manage patient records. The data are recorded during consultations by the patients' GP using Read codes, a clinical terminology that captures a wide range of information including symptoms, diagnoses, social characteristics, among others.
- Major strengths of the UK CPRD GOLD primary care database are the prospective nature of the data routinely collected at the point of patient care, the representativeness of the data in terms of age, sex and ethnicity of the broad UK population.
- Weaknesses of this data source include the lack of geographical representativeness, the potential for missing data, and misclassification of exposures and outcomes due to the lack of validated definitions of several conditions. Even though the validity of outcomes defined in the CPRD GOLD primary care database has been generally high, the variation by group of diseases warrants consideration.
- The CPRD GOLD primary care database can be linked to other sources of data using deterministic methods. The research in Chapter 6 includes analyses of primary care data linked to HES-APC, practice- and patient-level linked IMD, and ONS mortality data.
- Data on patient-reported outcomes were collected with collaboration with the Interventional Studies Team at CPRD and the patients' primary care practices.
- HRQoL was evaluated with the QLACS, which has been developed to take into account the specific needs of long-term cancer survivors. It includes 47 items, divided between seven generic and five cancer-specific domains.
- Depressive and anxiety symptoms were assessed with HADS. This is a 14-item self-reported screening tool addressing symptoms in the past week.

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5 Review of the identification of mental health and quality of life-related outcomes in primary care databases in the UK

5.1 Introduction

Chapter 5 directly addresses Objective 2 of this thesis (i.e. to systematically review the strategies used to identify adverse mental health outcome in studies that used EHRs from primary care databases in the UK). This chapter arose from the necessity to better understand the definition of mental health conditions in CPRD using codelists. The CPRD GOLD primary care database contains a vast amount of information primarily collected to support patient care, and its use for research purposes needs careful consideration of the completeness and accuracy of the data. This systematic review aimed to summarise the lists of Read codes used in studies that looked at these outcomes before, as well as gather information on the results from validation studies carried out, and the range of clinical conditions that authors included in their definitions of the outcomes (e.g. bipolar disorder in depression studies). In addition to mental health outcomes selected from Chapter 3, I also reviewed studies of pain and fatigue, because these conditions affect a large proportion of breast cancer survivors (as described in Chapter 1) and are relevant to the HRQoL-related objectives in this thesis. The definition of the outcomes in the studies presented in Chapter 6, 7 and 8 were informed by this systematic review.

5.2 Systematic review protocol

The systematic review protocol is included in Appendix 2, as it was included in the supplementary materials to the paper (see below).

5.3 Article

The results of the systematic review were reported in an article that has been published in a peer-reviewed scientific journal. The article is provided in the following pages; the lengthy supplementary materials referred to in this systematic review paper are provided in Appendix 2 of this thesis.

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Student ID Number	1513226	**Title**	Ms
First Name(s)	Helena Isabel		
Surname/Family Name	Morim Carreira		
Thesis Title	Long-term mental health and quality of life in women with history of breast cancer		
Primary Supervisor	Professor Krishnan Bhaskaran		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Open		
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SECTION E

Student Signature	
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Identification of mental health and quality of life outcomes in primary care databases in the UK: a systematic review

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ABSTRACT

Objectives To summarise the definitions and combinations of codes used to identify outcomes of anxiety, depression, fatigue, cognitive dysfunction (including mild cognitive dysfunction and dementia), sexual dysfunction, pain, sleep disorders, and fatal and non-fatal self-harm in studies using electronic health records from primary care databases in the UK.

Design Systematic review.

Data sources Medline, Embase and lists of publications of the main primary care databases in the UK.

Eligibility criteria Included data from a UK primary care database and studied outcome(s) of interest.

Data extraction and synthesis We abstracted information on the outcomes definition and codelists. When necessary, authors were contacted to request codelists.

Results 120 studies were eligible. Codelists were available for 17/42 studies of depression; 21/41 studies of fatal and non-fatal self-harm; 17/27 studies of dementia/cognitive dysfunction; 5/12 studies of anxiety; 4/8 studies of pain; 3/6 studies of fatigue and sexual dysfunction; 1/2 studies of sleep disorders. Depression was most often defined using codes for diagnoses (37/42 studies) and/or antidepressants prescriptions (21/42 studies); six studies reported including symptoms in their definition. Anxiety was defined with codes for diagnoses (12/12 studies); four studies also reported including symptoms. Fatal self-harm was ascertained in primary care data linked to the Office for National Statistics mortality database in nine studies. Most studies of cognitive dysfunction included Alzheimer's disease, and vascular and frontotemporal dementia. Fatigue definitions varied little, including chronic fatigue syndrome, neurasthenia and postviral fatigue syndrome. All studies of sexual dysfunction focused on male conditions, principally erectile dysfunction. Sleep disorders included insomnia and hypersomnia. There was substantial variability in the codelists; validation was carried out i21/120 studies.

Conclusions There is a need for standardised definitions and validated list of codes to assess mental health and quality of life outcomes in primary care databases in the UK.

Strengths and limitations of this study

- ► Comprehensive systematic review of the literature aiming at describing the definitions and combination of codes used to identify outcomes of mental health and quality of life in electronic health records databases in the UK.
- ► Potential for error in the selection of the eligible studies minimised by duplication of the screening.
- ► The authors of the original studies were contacted to obtain the list of Read codes used when these were not publicly available.
- ► We only considered definitions of study outcomes, and did not consider studies where mental health or quality of life variables were covariates or exposure variables, limiting the generalisability of our results to these other contexts.

INTRODUCTION

Primary care databases of electronic health records (EHRs) in the UK such as The Clinical Practice Research Datalink (CPRD), QResearch or The Health Improvement Network (THIN) have been widely used to study mental health outcomes such as depression,[1 2] and other key aspects of quality of life (QoL), such as fatigue and pain,[3 4] even though the identification of patients with these conditions is not straightforward.

Strategies to identify patients with a given condition in the EHRs typically include generating lists of relevant codes, then searching the patients' record for these codes to identify symptoms, diagnoses, referrals, appointments for disease management and monitoring, and/or prescriptions of interest.[5] The process of developing a list of codes of interest, and deciding how to apply them, may be subjective. For example, a study on the selection of codes for stroke, a relatively well-defined clinical outcome, showed that researchers with clinical and epidemiological experience may have differing interpretations of the relevance of each code.[6] A systematic review on the identification of patients with cancer in UK primary care databases described several combinations of Read codes used across studies.[7] Estimates of validity of diagnoses in these databases have been generally high across disease types,[8 9] but the heterogeneity in the codelists raises issues of misclassification, and hampers

the comparability of studies using the same data to assess the same outcome.[10] The pattern of use of the codes by the general practitioners (GPs) also needs consideration. For example, in recording depression, it has been shown that GPs have switched from diagnostic to symptom codes in recent years[11]; this may have a large impact on outcome definitions based around diagnostic codes. In addition, outcome definitions using prescription data may lead to misclassification where drugs have multiple indications: for example, sertraline, paroxetine or escitalopram, among the most commonly used antidepressants, are also first-line treatments for generalised anxiety disorder[12]; and amitriptyline, a tricyclic antidepressant, is also a first-line treatment for neuropathic pain.[13]

Given the broad interest in mental health and QoL outcomes, and the strong potential for primary care data to contribute to studying these outcomes, our aim was to systematically review and summarise the strategies used to define such outcomes in previous studies, and the extent to which case definitions have been validated.

METHODS

This review followed the a priori defined methods specified in the systematic review protocol (online supplementary appendix 1).

Outcomes of interest

The outcomes of interest for this review were: anxiety, depression, fatigue, cognitive dysfunction, pain, sexual dysfunction, sleep disorder and fatal and non-fatal self-harm. We considered that a study provided data for cognitive dysfunction when dementia, mild cognitive impairment or single domains of cognitive function were studied (ie, attention, executive function, memory, language, motor and social). Composite outcomes of two or more of these outcomes (eg, psychological impairment defined by anxiety or depression) were also eligible.

Information sources and search strategy

We searched MEDLINE and Embase via Ovid, from inception up to 28 June 2018, to identify studies that involved EHRs from primary care databases and studied one of the outcomes of interest (see above). The search expressions are provided in online supplementary appendix 1, and combined terms to identify primary care databases, terms to identify mental health and QoL outcomes, and terms indicating UK-based research. The CPRD, THIN and QResearch list of publications, available in their websites, were manually revised to identify additional studies. The lists of bibliographical references of the studies considered eligible for the review were also screened by hand to identify additional studies.

Studies eligibility

We considered eligible the studies that used data from a primary care database that routinely gathers EHR data from primary care practices in the UK, and in which the outcome of interest was one of those of interest for this study (see list above). This included purely descriptive studies on the incidence/prevalence of the outcome and analytical studies where the condition of interest was one of the main outcomes of the study. Studies of primary care data linked to other sources of data, such as the Hospital Episode Statistics (HES) or the Office for National Statistics (ONS) mortality data, were also considered eligible.

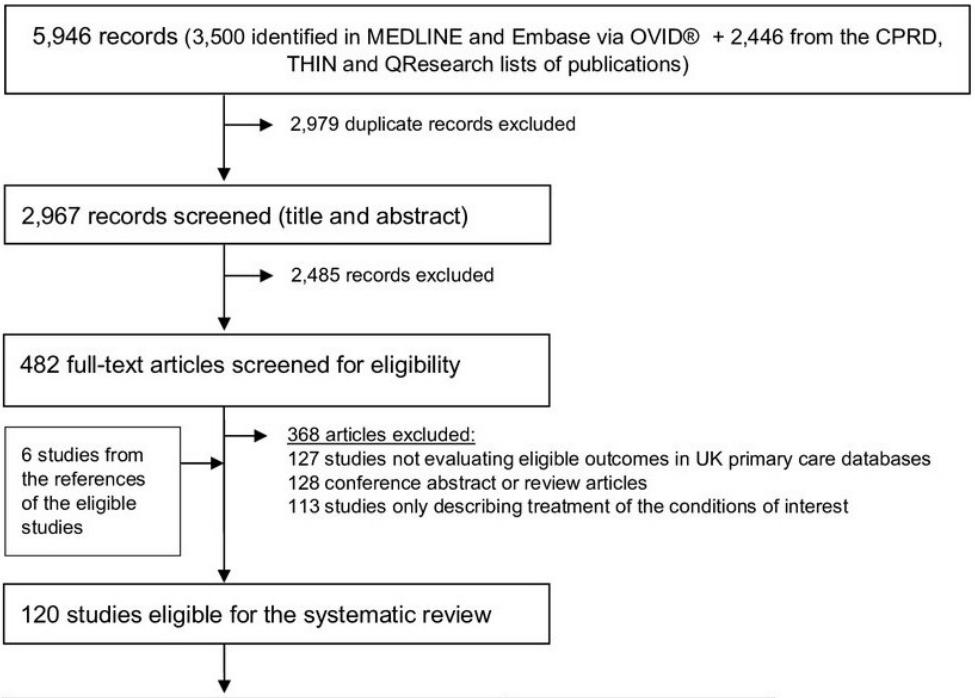
Abstracts from conferences were excluded, as it was unlikely that the methods section would provide sufficiently detailed information on the definition of the outcomes. Studies of pain caused by infectious agents (eg, herpes zoster) were excluded; similarly, studies of sleep apnoea and narcolepsy were excluded due to their unlikely psychological origin.[14 15] Studies reporting only on patterns of treatment of the conditions of interest were excluded, unless pharmacological treatment was clearly used as a proxy for the definition of the condition. Studies, where the outcome of interest was comorbidity, were also excluded. Where there were multiple studies from the same group of authors, we considered these separately, since the definition of the same outcomes could have been updated over time.

The eligibility of the studies was determined by two authors (HC and HS) reviewing all records retrieved from the publications databases. First, the title of each study was read to determine the eligibility for the review; when the information provided in the title was insufficient for a clear exclusion of the study, the study was considered for further assessment. Second, the full text of each study not previously excluded was read, in order to determine the eligibility. Disagreements over study eligibility between the two reviewers were resolved by discussion, including with a third researcher (KB or RW) where needed.

Data acquisition and extraction

We abstracted data on study characteristics (title, study design), the primary care database used, any database(s) linked to the primary care data, outcome(s) reported, definition of the outcome(s) (ie, Read codes, drug prescriptions, International Classification of Diseases (ICD) codes, etc) and any codelist available. When there were two or more definitions of the outcome (eg, used in sensitivity analyses), we abstracted all information but considered only the main outcome for data analysis in this review. We also abstracted data on whether the codelist had been validated, and any description related to the handling of past or prevalent (at baseline in cohort studies) episodes of these outcomes. We considered that the study had attempted to validate the list of codes when the results were compared with data from another source, or when outcomes were confirmed by enquiring the patients' GP or by reviewing the patients' medical record. The data extraction process was repeated by a second author (HS) for 10% of the papers included for each outcome, to check for reliability in the extraction process.

When a study did not provide the codelist for the definition of the outcome in the original publication or in a publicly available repository, we contacted the



	Number of studies
Anxiety	12
Depression	42
Anxiety and depression (composite outcome)	2
Dementia/ cognitive impairment	27
Fatigue	6
Pain	8
Sexual dysfunction	6
Sleep disorder	2
Fatal and non-fatal self-harm	41

Figure 1 Systematic review flow chart. CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network.

corresponding author of the study by email seeking this information (online supplementary appendix 2). In the case of emails that could not be delivered to the corresponding author, we searched the contact of another study author, usually the first or the last author, and addressed the email to her/him; if this failed to be delivered, no further attempt of contact was made. For all delivered emails, if no response was received within 2 weeks, a follow-up email was sent.

Data analysis

We produced descriptive tables showing the number and proportion of studies eligible for each outcome, by primary care database and codelist availability. We described, for each outcome, the types of codes used in the definition of the outcomes (eg, diagnosis codes, symptom codes, prescription codes). The lists of codes were also reviewed to assess the clinical characteristics of the disorders included (eg, whether mixed anxiety and depression was included in the definition of anxiety or depression); this was done by manually reviewing the list of codes to identify codes related to different clinical characteristics of the specific outcome. To describe the Read codes most commonly used to identify these outcomes in the data, we produced a list of Read codes sorted by number of studies that used the code. The results of the validation studies described in the original papers were reported descriptively.

Patient and public involvement

No patients or public were involved in the design and conduct of this study.

RESULTS

Of 5946 records initially identified in the bibliographical references search, 2979 were discarded as being duplicated, which left 2967 records to be assessed for eligibility (figure 1). The title assessment resulted in the exclusion of 2485 records, and 482 studies were considered for full-text assessment. Of these, 368 studies were excluded, mostly because they were abstracts from conferences or did not evaluate relevant outcomes. Six papers were identified from the screening of the references. A total of 120 studies were eligible for the systematic review; a list of codes were obtained for nearly half of the studies. The definitions and combinations of codes used to identify

Table 1 Characteristics of the studies included in the systematic review

	Anxiety		Depression		Anxiety and depression (composite outcome)		Dementia/ cognitive impairment		Fatigue		Pain		Sexual dysfunction (male)		Sleep disorders		Fatal and non-fatal self-harm	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total no of studies	12	100.0	42	100.0	2	100.0	27	100.0	6	100.0	8	100.0	6	100.0	2	100.0	41	100.0
Main primary care database																		
CPRD	7	58.3	24	57.1	0	0.0	21	77.8	5	83.3	5	62.5	4	66.7	1	50.0	31	75.6
PCCIU	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
THIN	5	41.7	10	23.8	1	50.0	5	18.5	1	16.7	0	0.0	2	33.3	0	0.0	6	14.6
Other	0	0.0	7	16.7	1	50.0	1	3.7	0	0.0	3	37.5	0	0.0	1	50.0	4	9.8
Outcome ascertained using linked data (HES or ONS)																		
Yes	1	8.3	2	4.8	0	0.0	2	7.4	0	0.0	0	0.0	0	0.0	0	0.0	9	22.0
No	11	91.7	40	95.2	2	100.0	25	92.6	6	100.0	8	100.0	6	100.0	2	100.0	32	78.0
Code list availability																		
Total no of studies with code lists available	5	41.7	17	40.5	2	100.0	17	63.0	3	50.0	4	50.0	3	50.0	1	50.0	21	51.2
Stated in publication	2	16.7	7	16.7	1	50.0	10	37.0	1	16.7	2	25.0	2	33.3	1	50.0	17	41.5
Cited another paper or web repository	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	12.5	0	0.0	0	0.0	0	0.0
Obtained from authors	3	25.0	10	23.8	1	50.0	7	25.9	2	33.3	1	12.5	1	16.7	0	0.0	4	9.8
Total no of studies with code lists not available	7	58.3	25	59.5	0	0.0	10	37.0	3	50.0	4	50.0	3	50.0	1	50.0	20	48.8
Cited another paper or web repository but couldn't obtain	1	8.3	1	2.4	0	0.0	1	3.7	1	16.7	0	0.0	0	0.0	0	0.0	3	7.3
Stated available on request but did not provide	2	16.7	4	9.5	0	0.0	3	11.1	2	33.3	0	0.0	1	16.7	1	50.0	0	0.0

Continued

Table 1 Continued

	Anxiety			Depression			Anxiety and depression (composite outcome)			Dementia/ cognitive impairment			Fatigue			Pain			Sexual dysfunction (male)			Sleep disorders			Fatal and non-fatal self-harm	
	N	%		N	%		N	%		N	%		N	%		N	%		N	%		N	%		N	%
Not mentioned in the paper and did not provide	4	33.3		19	45.2		0	0.0		6	22.2		0	0.0		4	50.0		2	33.3		0	0.0		17	41.5
Type of codes available*																										
Read/medical codes	5	100.0		14	82.4		2	100.0		17	100.0		3	100.0		4	100.0		3	100.0		1	100.0		8	42.1
OXMIS codes	0	0.0		3	17.6		0	0.0		0	0.0		0	0.0		2	50.0		0	0.0		0	0.0		8	42.1
ICD codes	1	20.0		2	4.8		0	0.0		2	11.7		0	0.0		0	0.0		0	0.0		0	0.0		9	47.4
Definition of the outcome†																										
Study described that codes for diagnosis were included																										
Yes [in isolation‡]	12	100.0	[5]	37	88.1	[14]	2	100.0	[0]	27	100.0	[19]	6	100.0	[1]	–	–		5	83.3	[2]	2	100.0	[2]	–	–
No	0	0.0		5	11.9		0	0.0		0	0.0		0	0.0		–	–		1	16.7		0	0.0		–	–
Unclear	0	0.0		0	0.0		0	0.0		0	0.0		0	0.0		–	–		0	0.0		0	0.0		–	–
Study described that codes for symptoms were included																										
Yes [in isolation‡]	4	33.3	(0)	6	14.3	[0]	2	100.0	[0]	6	22.2	[0]	5	83.3	[0]	8	100.0	[6]	0	0.0	[0]	0	0.0	[0]	-	-
No	6	50.0		33	78.6		0	0.0		20	74.1		1	16.7		0	0.0		4	66.7		2	100.0		-	-
Unclear	2	16.7		3	7.1		0	0.0		1	3.7		0	0.0		0	0.0		2	33.3		0	0.0		-	-
Study described that prescriptions were included																										
Yes [in isolation‡]	1	8.3	[0]	21	50.0	[6]	2	100.0	[0]	4	14.8	[0]	0	0.0	[0]	2	25.0	[0]	3	50.0	[1]	0	0.0	[0]	-	-
No	11	91.7		21	50.0		0	0.0		23	85.2		6	100.0		6	75.0		3	50.0		2	100.0		-	-
Unclear	0	0.0		0	0.0		0	0.0		0	0.0		0	0.0		0	0.0		0	0.0		0	0.0		-	-
Handling of outcomes occurring prior to study period																										
Excluded	5	41.7		15	35.7		0	0.0		21	77.8		3	50.0		3	37.5		1	16.7		1	50.0		7	17.1
Adjusted/matched for	2	16.7		8	19.0		0	0.0		1	3.7		1	16.7		0	0.0		3	50.0		0	0.0		10	24.4
Stratified results	1	8.3		3	7.1		2	100.0		0	0.0		1	16.7		0	0.0		3	50.0		0	0.0		4	9.8
Not stated	3	25.0		11	26.2		0	0.0		1	3.7		0	0.0		3	37.5		0	0.0		1	50.0		15	36.6
Not applicable §	2	16.7		8	19.0		0	0.0		4	14.8		2	33.3		2	25.0		0	0.0		0	0.0		9	22.0

Continued

Table 1 Continued

	Anxiety		Depression		Anxiety and depression (composite outcome)		Dementia/ cognitive impairment		Fatigue		Pain		Sexual dysfunction (male)		Sleep disorders		Fatal and non-fatal self-harm	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Validation of list of codes																		
Yes	2	16.7	5	11.9	1	50.0	5	18.5	0	0.0	3	37.5	0	0.0	0	0.0	9	22.0
None stated	10	83.3	37	88.1	1	50.0	22	81.5	6	100.0	5	62.5	6	100.0	2	100.0	32	78.0
Study aiming at validating the outcome	0	0.0	0	0.0	1	50.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	7.3

*Refers only to studies providing codelists. A study may include more than one type of codes.
†Defined based on the description of the outcome provided in the original studies. Studies were considered to have included symptoms in the definition of the outcomes when this information was explicitly stated by the authors. Pain was considered a symptomatic outcome, regardless of how it was described in the original publications.
‡The number of studies where the definition of the outcome included only this category of codes is provided in squared brackets.
§Depends on study design and outcome. For example, it includes studies describing the epidemiology of first ever diagnoses or focusing on completed suicide only.
CPRD, Clinical Practice Research Datalink; HES, Hospital Episodes Statistics; ICD, International Classification of Diseases; ONS, Office for National Statistics; OXMIS, Oxford Medical Information System; PCCIU, Primary Care Clinical Informatics Unit Research Data Set; THIN, The Health Improvement Network.

mental health and QoL outcomes from UK primary care databases were heterogeneous for all outcomes; there was particular variability in the inclusion/exclusion of codes for symptoms of the mental disorders. Prescriptions were not frequently used as proxy for mental disorders. Validation efforts were rarely employed. Detailed results for each outcome are provided below.

Anxiety

Twelve studies had anxiety as an outcome (table 1 and online supplementary appendix 3 table 1); of these, two studied panic only.[2 16] The list of codes used to identify outcomes of anxiety was available for 5 of the 12 studies (41.7%); in one study, the cases of anxiety were identified in CPRD data linked to HES. All 12 studies included codes for diagnosis of anxiety, and 4 (33.3%) included also codes for anxiety symptoms. Prescriptions were considered in the definition of the outcome in one study only (8.3%).

Of the five studies for which codelists were available, five included codes for generalised anxiety disorder (100%), four for phobia (80.0%), four for panic disorder/attacks (80.0%), three for mixed anxiety and depression (60.0%), and two for stress-related disorders (40.0%) (table 2). Codes for post-traumatic stress disorder and obsession-compulsion were less often included (one study each, 20.0%).

Only one study reported including drugs prescriptions in the definition of the outcome[17]; this considered diazepam and lorazepam only (table 3).

Two studies[2 18] assessed the validity of the codelists (table 4). The proportion of cases confirmed was reported in one study: 73.5% for cases treated with anxiolytics, antidepressants and hypnotics, and 89.6% in those not pharmacologically treated.[18]

Online supplementary appendix 4 table 1 provides the list of Read codes used to identify patients with anxiety in the eligible studies; online supplementary appendix 4 table 2 provides the list of ICD-10 codes.

Depression

Forty-two studies identified outcomes of depression (table 1 and online supplementary appendix 3 table 2). The list of codes used to identify outcomes of depression was available for 17 of the 42 studies (40.5%); 2 studies identified cases of depression in primary care data linked to HES data, using ICD-10 codes. Six studies defined depression by proxy of antidepressants intake only; the remaining 36 studies described to have included codes for diagnoses of depression and 6 (14.3%) studies also considered symptoms of depression in the definition of the outcome. Fifteen studies (35.7%) reported having excluded patients with history of depression.

Of the 17 studies for which the codelists were available, 10 included codes for mixed anxiety and depression (58.8%), 4 for bipolar disorder (23.5%) and 3 for depression in dementia (17.6%) (table 2).

Antidepressant prescriptions, in isolation or combination with diagnostic/symptoms Read codes, were considered in the identification of patients with depression in 21 studies (50.0%); in six studies, depression was solely

Table 2 Clinical characteristics of the outcomes of interest in the studies for which the list of codes was available

Study included codes for	N	% of total with code lists available
Anxiety	5	100.0
Generalised anxiety disorder	5	100.0
Panic disorder/attacks	4	80.0
Phobia	4	80.0
Mixed anxiety and depression	3	60.0
Stress-related disorders	2	40.0
Obsession-compulsion	1	20.0
Post-traumatic stress disorder	1	20.0
Depression	17	100.0
Unipolar depression	17	100.0
Depression with psychotic symptoms	14	82.4
Mixed anxiety and depression	10	58.8
Bipolar disorder	4	23.5
Depression in dementia	3	17.6
Dementia/cognitive impairment	17	100.0
Alzheimer's disease	13	81.3
Vascular dementia	13	81.3
Frontotemporal dementia	12	75.0
Lewy bodies disease	11	68.8
Mild cognitive impairment only	3	17.6
Fatigue	3	100.0
Chronic fatigue syndrome/myalgic encephalitis	3	100.0
Neurasthenia	3	100.0
Post viral fatigue syndrome	3	100.0
Fibromyalgia	2	66.7
Pain	4	100.0
Chest pain	1	25.0
Chronic widespread pain	1	25.0
Musculoskeletal pain	1	25.0
Unspecified abdominal pain	1	25.0
Sexual dysfunction (male)	3	100.0
Erectile dysfunction	3	100.0
Other male sexual dysfunctions	1	33.3
Sleep disorder	1	100.0
Insomnia	1	100.0
Hypersomnia	1	100.0
Fatal and non-fatal self-harm	21	100.0
Completed suicide	17	80.9
Completed suicide only	8	38.1
Completed and attempted suicide only	6	28.6
Completed and attempted suicide, and self-harm	4	19.1
Included deaths of undetermined intent	7	33.3
Attempted suicide/self-harm	4	19.1

defined by the prescription of antidepressants (table 3). The list of antidepressant categories was seldom provided; of the studies that reported this information, selective serotonin reuptake inhibitors were the group most often considered (six studies), followed by monoamine oxidase inhibitors and tricyclic and related antidepressants drugs (three studies each).

Five studies (11.9%) assessed the performance of the list of codes to identify patients with depression (table 4). The proportion of cases confirmed was reported by two studies only: 83.3%[19] and 89.6%.[20]

The list of Read codes used to identify patients with depression is provided in online supplementary appendix 4 tables 3 and 4 provides the list of ICD-10 codes.

Composite outcome of anxiety and depression

Two studies provided data for composite outcomes of anxiety and depression (table 1 and online supplementary appendix 3 table 3). The codelist was available for the two studies. The studies reported including codes for symptoms as well as diagnosis of anxiety and depression, and included prescriptions of antidepressants and anti-anxiety drugs in the definition of the outcome.

John *et al*[21] compared the performance of 12 different algorithms to identify patients with anxiety and depression in the Secure Anonymised Information Linkage Databank; the positive predictive value of the Read codes for anxiety and depression diagnoses, symptoms and treatments, against the five-item Mental Health Inventory (gold standard), varied between 61% and 76%[21] (table 4). The list of Read codes used to identify patients with composite outcomes of anxiety and depression is provided in online supplementary appendix 4 table 5.

Cognitive dysfunction (including mild cognitive dysfunction and dementia)

Twenty-seven studies reported outcomes of dementia or cognitive function (table 1 and online supplementary appendix 3 table 4). The codelists were available for 17 studies (63.0%); in two studies dementia was ascertained in primary care data linked to other sources of data. All studies included codes for diagnosis of dementia or cognitive impairment, and six studies (22.2%) reported to have included also codes for symptoms of dementia. Twenty-one studies (77.8%) referred to have excluded

Table 3 Pharmacological categories used in the studies that used drug prescriptions to identify patients with the outcome of interest

Outcome	No of studies	%
Anxiety	12	100.0
Studies of anxiety that used drugs prescriptions only	0	0.0
Studies of anxiety that used drugs prescriptions	1	8.3
Diazepam and lorazepam	1	8.3
Depression	42	100.0
Studies of depression that used drugs prescriptions only	6	14.3
Studies of depression that used drugs prescriptions	21	50.0
Antidepressants, categories not further specified	15	35.7
Antidepressants, categories further specified	6	14.3
Tricyclic and related antidepressant drugs	3	7.1
Monoamine oxidase inhibitors	3	7.1
Selective serotonin reuptake inhibitors	6	14.3
Other antidepressant drugs	3	7.1
Dementia	27	100.0
Studies of dementia that used drugs prescriptions only	0	0.0
Studies of dementia that used drugs prescriptions	4	14.8
Anticholinesterases	4	14.8
Dopaminergic drugs	4	14.8
Pain	8	100.0
Studies of pain that used drugs prescriptions only	2	25.0
Studies of pain that used drugs prescriptions	2	25.0
Analgesics, not otherwise specified	2	25.0
Antidepressants	2	25.0
Antiepileptics	2	25.0
Anaesthetics	2	25.0
Sexual dysfunction (male)	6	100.0
Studies of sexual dysfunction that used drugs prescriptions only	1	16.7
Studies of sexual dysfunction that used drugs prescriptions	3	50.0
Phosphodiesterase type-5 inhibitors	2	33.3
Prostaglandin analogues and prostamides	1	16.7

patients with prior diagnoses of dementia from longitudinal analyses.

Of the 17 studies for which the codelists were available, 13 reported codes for Alzheimer's disease (81.3%), 13 for vascular dementia (81.3%), 12 for frontotemporal dementia (75.0%) and 11 for Lewy bodies disease (68.8%) (table 2). Three studies reported data for cognitive impairment without dementia (17.6%).

Four studies (14.8%) used prescriptions in the identification of patients with dementia; all four included anticholinesterases and dopaminergic agents (table 3).

Five studies[22–26] involved validation of the list of codes; the proportion of cases confirmed varied between 74% and 100% (table 4).

The list of Read codes used in the studies is provided in online supplementary appendix 4 table 6; the list of ICD-10 codes is provided in online supplementary appendix 4 table 7.

Fatigue

Six studies had fatigue as the outcome (table 1 and online supplementary appendix 3 table 5). All studies considered codes for diagnoses of fatigue, and five studies also described including codes for symptoms of fatigue. The list of codes use to identify patients with fatigue was provided in three studies (50.0%).

The three studies for which the codelist was available included codes for chronic fatigue syndrome, neurasthenia and postviral fatigue syndrome (table 2). Fibromyalgia was included in two studies (66.7%). None of the

Table 4 Methods and results of the validation of the outcomes reported in the original studies

Outcome and study authors	Validation method	# case validations completed/# case validations attempted	% of cases confirmed
Anxiety			
Martín-Merino *et al,* 2010[18]	GP questionnaire	135/140	Among pharmacologically treated: 73.5%; Among not pharmacologically treated: 89.6%.
Meier *et al,* 2004[2]	Record review	nr/nr	nr
Depression			
Becker, 2011	Sensitivity analysis with different definitions	nr/nr	nr
Hagberg, 2016	Record review	nr/nr	nr
Martín-Merino *et al,* 2010[18]	GP questionnaire	135/140	89.6%
Meier *et al*, 2004[2]	Record review	nr/nr	nr
Yang *et al*, 2003[19]	Record review	30/nr	83.3%
Anxiety and depression (composite outcome)			
John, 2016	Compared 12 EHR algorithms to results of the Mental Health Inventory , a subscale of SF-36	2799*	Between 61% and 76%, depending on the algorithm.
Dementia/cognitive impairment			
Imfeld *et al*, 2013 and Imfeld *et al*, 2015[22 23]	GP questionnaire	nr/120	Alzheimer's disease: 79%; Vascular dementia: 74%.
Dunn *et al*, 2005[24]	GP asked to confirm diagnosis	50/200	100%
Dunn *et al,* 2005[26]	GP questionnaire	95/~100	83%
Strom *et al*, 2015[25]	GP questionnaire	86/100	88.4%
Strom *et al*, 2015[25]	Review of free text	1047/1048	1.5% patients excluded as not having the diagnosis; 42.4% confirmed as having definite memory loss, 36.8% possible memory loss, 3.2% undetermined and 16.0% unknown.
Pain			
Hall *et al,* 2013[4]	GP questionnaire	48/54	56%
Mansfield *et al,* 2017[27]	EHR data linked to self-reported pain status collected by postal questionnaire	1780*	97%
Becker, 2008	GP questionnaire	176/200	86.4%
Self-harm			
Thomas *et al* 2013[29]	Comparison of cases of suicide and self-harm identified in CPRD with Read codes, with the cases identified in CPRD data linked to HES data, and published self-harm incidence data.	74236*	68.4%
Suicide (attempted and completed)			
Hagberg, 2016	Record review	nr/nr	nr
Haste, 1998	GP asked to confirm suicides	77% of uncertain deaths/nr	82%
Jick, 1995	Record review	nr/nr	nr
Meier *et al*, 2004[2]	Record review	nr/nr	nr

Continued

Table 4 Continued

Outcome and study authors	Validation method	# case validations completed/# case validations attempted	% of cases confirmed
Schuerch, 2016	Outcomes identified in CPRD were compared with those identified in CPRD linked to HES and ONS data.	nr/nr	Compared with CPRD data, the frequency of the outcomes in linked data was approximately three times higher.
Yang *et al*, 2003[19]	Record review	30/nr	83.3%
Suicide (completed)			
Arana, 2010	GP questionnaire and record review	nr/132	97%
Arana, 2010	GP questionnaire and record review	nr/86	87%
Hall, 2009[28]	GP questionnaire and record review	33/33	21.2%
Thomas *et al*, 2013[29]	Comparison of cases of suicide and self-harm identified in CPRD with Read codes, with the cases identified in CPRD data linked to ONS mortality data, and national suicide rates.	1767*	59.7% for men; 46.0% for women.

*Validation attempted and completed for all patients identified in electronic health records database.
CPRD, Clinical Practice Research Datalink; EHR, electronic health record; GP, general practitioner; HES, Hospital Episode Statistics; nr, not reported; ONS, Office for National Statistics; SF-36, 36-item Short Form Health Survey.

studies assessed the validity of the list of the codes. The list of Read codes used in the studies of fatigue is available in online supplementary appendix 4 table 8.

Pain

Pain was the outcome in eight studies (table 1 and online supplementary appendix 3 table 6). The list of codes was available for four of the eight studies. Of these four studies, three looked at pain by body site (ie, chest, abdominal, musculoskeletal pain), one study studied widespread body pain (table 2). Two studies included drugs in the identification of patients with pain; all considered antiepileptics (in the absence of codes for an epilepsy diagnosis), anaesthetics, antidepressants and analgesics (table 3).

Three studies validated the list of patients selected with the codelist (table 4). The proportion of cases confirmed varied between 56% and 86.4%. One study compared pain recorded in the EHR with pain reported in a survey; in 97% of the self-reported cases of pain, there was an entry in the EHR.[27]

Online supplementary appendix 4 table 9 provides the list of codes used in the original studies.

Sexual dysfunction

Six studies had sexual dysfunction as an outcome, all of which focused on male sexual dysfunction (table 1, online supplementary appendix 3 table 7). Three studies provided codelists (50.0%). Of these, all included codes for erectile dysfunction and one study included codes for other male sexual dysfunctions (table 2). Three studies included considered the prescription of drugs sufficient to ascertain the outcome; two studies considered phosphodiesterase type-5 inhibitors (table 3). No study validated the list of codes used. The list of Read codes used in the original studies is available in online supplementary appendix 4 table 10.

Sleep disorders

Two studies were eligible for sleep disorders (table 1, online supplementary appendix 3 table 8); the two studies included diagnoses of insomnia, and one included hypersomnia as well (50%) (table 2). The list of codes was available for one study. No validation was reported. Online supplementary appendix 4 table 11 provides the list of Read codes used in the original study.

Fatal and non-fatal self-harm

Forty-one studies had outcomes related to fatal and non-fatal self-harm (table 1 and online supplementary appendix 3 table 9). The list of codes used to define the outcomes was available for 21 studies (51.2%); 9 studies reported using ICD-10 codes.

Of the 21 studies for which the codelist was available, 17 studies (80.9%) included completed suicide, while 4 studies focused on attempted suicide only (19.1%). Of the 17 studies including completed suicide as an outcome, eight reported only completed suicides, six considered completed and attempted suicides and four included complete and attempted suicide, as well as self-harm (table 2). All studies where outcomes were identified using primary care data linked to ONS mortality data (gold standard) considered deaths recorded as of undetermined intent in the definition of suicide.

Nine studies involved some method of validation of the list of cases identified via code search (table 4). Four studies referred to have revised the clinical record of the patient to determine the final outcome and two studies asked the GPs to confirm the events. The proportion of

cases confirmed varied between 21.2% and 97%. Hall[28] assessed the validity of cause of death recording in the THIN primary care database through search of the free text and death certificate review; the underlying cause of death registered in the death certificate was listed as the cause of death in the EHR in 70% of the cases. Thomas *et al*[29] compared the ascertainment of cases of suicide and self-harm using Read codes in CPRD, with those ascertained when data from HES and ONS mortality data were available. 26.1% of the cases of suicide identified in the ONS mortality data were registered in the CPRD primary care database. HES was considered the gold standard for self-harm; 68.4% of the cases of self-harm in HES were identified as such in CPRD.

Online supplementary appendix 4 table 12 provides the list of Read codes used to identify outcomes of fatal and non-fatal self-harm in primary care data; online supplementary appendix 4 table 13 includes the lists of ICD-10 codes using in studies of linked data.

DISCUSSION

Results overview

This review summarised the definitions and combinations of codes used to identify outcomes of anxiety, depression, dementia and cognitive impairment, fatigue, pain, male sexual dysfunction, sleep disorder and self-injurious behaviour in primary care databases of patients in the UK. The list of codes used in the original studies was obtained for approximately half of the papers; the lack of detailed information on the definition of the outcomes in most studies raises important questions as to whether studies can be replicated by others. In the studies where the codelist was available, for all outcomes, there was substantial heterogeneity in the type of codes included (eg, diagnoses and symptoms) and drugs selected to identify outcomes; for the remaining studies, the details provided in the original publications suggest a similar pattern. We also noted considerable variability in the clinical definition of some outcomes (eg, inclusion/exclusion of bipolar disorders in studies of depression). Validation of codes used to identify these outcomes was rarely carried out; where done, positive predictive values of case definitions were variable but mostly above 80%. To overcome these issues in the current context of limited number of studies with validation efforts, it is imperative that researchers develop, validate and make publicly available code lists for these outcomes.

Strengths and limitations

This review is based on an extensive search of the studies involving EHRs in the UK. Errors in study selection and data extraction were minimised by the independent assessment of the studies by two investigators. We contacted the authors of all original studies where the list of codes had not been provided in the original publication to seek this information; this largely increased the number of studies for which lists of codes were available, and contributed to a more detailed characterisation of the combination of codes used to define mental health outcomes in primary care databases of EHR in the UK.

However, this review has limitations. Some relevant studies may have been missed due to imperfect search terms, as there is no Medical Subject Headings (MeSH) term for the primary care databases, and studies could be potentially missed if the keywords did not appear in the title and abstract, or due to inaccurate indexing in the publications database. We attempted to minimise the risk of missing potential eligible studies by using broad search terms incorporating both indexing terms and keywords, two databases with different indexing systems, and an additional manual check of the eligible studies and list of bibliographical references from the main EHR databases. We only considered studies where mental health or QoL variables were the outcomes of interest, limiting generalisability to other contexts. For example, we excluded studies where these variables were covariates because we expected that detailed information about covariate definitions would rarely be available. We also excluded studies where the mental health or QoL variable was used to define the patient population (eg, a study of risk of stroke in depressed patients), on the basis that decisions about how to define cases may have had quite different motivations, compared with studies where the condition was the outcome of the study, making case definitions difficult to meaningfully compare. We included studies that explicitly referred to using prescription data as a proxy for the definition of the condition (eg, treated depression assessed by proxy of antidepressant intake), but we acknowledge that it was not always clear to decide whether treatment of the condition was being used to define the condition. This could have resulted in a few studies erroneously excluded, even though this should have been minimised by the duplication of the search and study selection process by two researchers working independently, with discussion of all discordant results. It is unclear if the list of codes that could not be obtained differ in any systematic way to the ones obtained. Some authors expressed concerns over intellectual property when sharing the list of codes, and this may have been a bigger concern among those who put a lot of time and thought into their codelists; on the other hand, authors who have concerns about the quality of their codelist may have been less willing to share them. Lastly, we summarised the types of codes used to define the outcome based on what was stated in original studies' methods sections (because code lists were not available for all studies), but this may have been inaccurate, for example, some studies that reported in their methods only including diagnosis codes then provided code lists that appeared to also contain symptom codes.

Availability of the list of codes

The list of codes was provided in the original publications for just over a quarter of the studies. Contacting the authors resulted in codelists being made available for approximately half of the studies. For the remaining

studies, the authors either could not be contacted (eg, moved institutions, retired) or could not locate the relevant codelist (including for some studies where the paper had stated that the codelist would be available on request). Provision of codelists within the publication or in a web repository would eliminate the difficulties of authors having to be contacted and archived codelists retrieved. Most journals currently accept codelists in online supplementary appendices. Codelists were hardly ever obtained for older studies, especially those published before 2000, when email addresses were not routinely included in the details of the corresponding authors. We searched for alternative contacts in these cases, but not always successfully.

Variability in the definition of cases and codelists

Anxiety and depression

Anxiety was often defined with diagnostic and symptoms codes, and in a few studies by the prescription of anxiolytics and hypnotics. Even though the sensitivity of symptoms codes for anxiety is expected to be high, the positive predictive value is unknown. Anxiolytics may also result in misclassification of the outcomes, as they are currently discouraged as first line of treatment for anxiety[12] and are often prescribed for management of other conditions such as insomnia. No study considered antidepressants in the definition of anxiety even though these are currently used to manage anxiety[12]; this may have resulted in cases of anxiety treated with antidepressants, and where no Read code was available, being missed.

The inclusion/exclusion of codes for symptoms may have a larger impact in the definition of depression, as it has been shown that GPs switched from diagnostic to symptoms codes after the introduction of performance indicators in the GP contract Quality and Outcomes Framework in 2006[11] and under claims that depression was being overdiagnosed.[30 31] Codelists solely relying on Read codes for diagnosis of depression are, therefore, likely to have low sensitivity, but the impact of including/excluding a specific code will be variable, depending on how often that code is used by GPs at the point of providing care. In a few studies, depression was defined by proxy of antidepressant prescribing, alone or in combination with Read codes for symptoms/diagnosis. Considering antidepressant prescribing in the definition of depression has several issues. Certain types of antidepressants are currently used as first line of treatment for other conditions, such as pain and anxiety, and the studies relying solely on this information will be affected by misclassification of the outcome; some studies took this into account by excluding low dose tricyclic antidepressants, usually prescribed for pain, from their list of codes used to define depression.[32–34] Among the studies that did include antidepressants in their definition, there was heterogeneity in the group of antidepressants included, with some studies selecting only a few specific drugs commonly used for the treatment of depression. Studies defining depression by proxy of antidepressant prescribing only are likely also to be affected by changes in the behaviour of antidepressant prescribing. In 2004, the National Institute for Health and Care Excellence (NICE) issued guidelines discouraging antidepressants for mild depression,[35] and in 2006 a performance indicator in the UK GP Quality and Outcomes Framework pay for performance was introduced for depression severity assessed with validated symptoms questionnaires.[36] Following this measure, the proportion of new cases of pharmacologically treated depression decreased (from 73% in 2003 to 61% in 2012[37]), but the proportion of recurrent episodes pharmacologically treated increased from 74.3% to 77.8%.[37] Treatment duration times with antidepressants also increased over time[38]; this may affect the number of new episodes of depression identified in the studies. In several studies, the authors chose to report separate results for antidepressant prescribing, without using this information to ascertain the outcome of depression[39 40]; this may partially be due to the difficulties of ascertaining the indications for which antidepressants were prescribed. John *et al* explored the indications of antidepressants; more than half of the new antidepressant prescriptions were for depression, with increasing but low incidence of prescriptions for pain and anxiety, but the authors could not identify the indication for antidepressants in 17% of the new prescriptions.[41]

Regardless of the type of codes included, authors will need to often choose the inclusion/exclusion of codes relating to the clinical profile of the patients. This may have a particular impact for conditions that are highly comorbid. For example, the code for 'mixed anxiety and depression' was sometimes used in the definition of anxiety and in the definition of depression; anxiety and depression are highly comorbid and the inclusion/exclusion of these patients may have an impact on the results. In addition, for depression, the inclusion of codes related to depression in the context of bipolar disease, dementia and schizophrenia may raise issues as to whether it represents a primary depressive episode.

Part of the heterogeneity in the list of codes used to identify these outcomes may be explained by the complexity of these conditions and by the purpose for which these data are collected. Electronic healthcare data are primarily collected to provide patients with treatment, and distinctions between diagnosis and symptoms may have less weight at the point of care than when researchers aim to define these conditions using data routinely collected.

Fatal and non-fatal self-harm

Routinely collected primary care data were shown to have low sensitivity to detect cases of suicide.[29] Thus, record linkage to ONS mortality data is of interest; this has the advantage of including causes of death other than suicide. Ascertainment of the cause of death is not always straightforward when the death is non-natural, and several studies have included cases of accidents and open verdicts in their case definition. Open verdicts have been shown to include many similarities with suicides, and several are

later registered as suicides; these are recommended to be included in studies of suicide.[42] Studies varied on whether cases of self-harm without suicidal ideation were included (eg, Rubino *et al* reviewed free text to exclude those who did not seem to have attempted suicide[43]). For self-harm, linkage to HES data will allow for more cases to be identified,[29] even though authors must consider the balance between reduction of sample size and ascertainment of the outcome, as linkage is only available for a subset of patients.

Pain

The aetiology and location of pain in the studies involved in this review varied due to our broad inclusion criteria. When pharmacological treatment was included in the definition of pain, this was most often done with prescriptions of antidepressants and antiepileptics. Antidepressants such as first-generation tricyclic antidepressants have been used for over 30 years to manage neuropathic pain (eg, amitriptyline, doxepin, clomipramine and dosulepin).[44] Antiepileptic drugs reduce neuronal excitability and alleviate pain through several mechanisms.[44]

Other outcomes

We considered cognitive dysfunction as a composite outcome including studies from mild to severe impairments such as those in dementia; between 10% and 20% of the patients with mild cognitive impairment are expected to convert to dementia.[45 46] Fewer studies had fatigue, sexual dysfunction and sleep disorders as the outcome, and no study was eligible for female sexual dysfunction. The definition of these outcomes varied little across the studies but the small numbers preclude firm conclusions. It has been reported that chronic fatigue increased prior to 2001,[3] but decreased between 2001 and 2013,[47] possibly due to the introduction of diagnostic criteria from NICE[48]; in the same period, increases were noted in the diagnoses of fibromyalgia.[47] This may reflect the complexity of diagnosing fatigue, which is done by exclusion of other causes only.[48]

Validation

Outcomes identified in EHRs may lack of validity: a person meeting the operational definition for the outcome based on specific codes may not have the diagnosis or vice versa. Only a small number of studies assessed validity in their studies, and this was almost always about assessing positive predictive value of the case definition, with sensitivity and specificity rarely explored. Of these, some studies only stated that validation had been carried out, but did not report the results, which makes the performance of the case definition unclear. However, the studies that reported results tended to show a high proportion of cases confirmed by their primary care physician or by further investigations (ie, a high positive predictive value). This is in accordance with the results of two systematic reviews that assessed the validity of the diagnostic coding within the CPRD primary care database.[8 9] Studies in which identified cases were validated by the GP did not usually specify how this validation was done—that is, whether the GPs confirmed cases by consulting the EHR, referring to additional information, relying on memory or using other methods. If GPs simply checked the same EHR used to identify the case in the first place, resulting estimates of positive predictive value would be expected to be high, but may be misleadingly optimistic.

Implications

Mental health and QoL-related outcomes are difficult to identify in EHR databases; and thus, extra care needs to be used when defining these outcomes. The use of a particular code can vary between GP practices; for example, a study on the interpractice use of Read codes for diabetes showed that the most generic code was used in 14%–98% of the patients with diabetes in the practices.[49] GPs can derive Read codes for their practice; this may raise issues with new codes being added over time,[50] and codelists that need to be updated. It is important that authors clearly document the process of selection of the codes, so that these are available with clear rationale if needed.[5] Repositories of lists of codes allow researchers to access codelists easily. However, these repositories also need funding to be maintained, which limits their stability and consequently their use. Some studies of depression and dementia referred to using the Read codes recommended by the Quality and Outcomes Framework[36]; these are likely to be highly specific. It is also important to better understand the patterns of recording of some of these conditions, as changes in the patterns of use of the codes may have impact in the list of codes chosen. The inclusion of codes for symptoms and prescriptions must consider what is known about the use of codes by GPs at the point of patient providing care, as data recording in this setting is primarily intended to support clinical care. Future works are needed to understand how GPs conceptualise mental health problems, as these are expected to have less stringent definitions than psychiatrists, and this could provide insights into more meaningful case definitions.

Validation of the outcomes appears to be essential to understand the validity of case definitions. A balance between sensitivity and specificity may be considered depending on the aim of the study[5]; for depression, for example, the inclusion of terms such as ‘low mood’ may increase sensitivity, at the expense of decreased specificity, as some individuals who would not fit more stringent criteria for a diagnosis will be incorrectly classified as depressed.[5] A particular challenge with validation of primary care-based mental health outcomes is quantifying false negatives, which requires linkage to a high-quality external source of information, to identify cases that may have been ‘missed’ in primary care records. The Mental Health Dataset, which includes individual patient records of adults seeking mental health services in secondary care and has recently been made available for linkage with CPRD primary care databases, represents an opportunity

to assess the proportion of false negatives identified with the code lists, at least for more severe outcomes. Until then, sensitivity analysis using different lists of codes should be done, so that results can be compared and the impact of using different code lists evaluated. The consequences of underascertaining mental health outcomes are likely to depend on study design; in a cohort design this will not generally result in biased relative risks, whereas in a case–control context, a bias towards the null is likely. Studies might consider to use internal validation strategies, by assessing the proportion of patients referred for treatment or prescribed a relevant pharmacological agent.

Primary care databases of EHRs have made important contributions to medicine worldwide, particularly in the fields of infectious, respiratory and cardiovascular diseases. The burden of mental disorders in high-income countries has increased substantially in the last decades,[51] and more research is needed to be better understand these conditions. Primary care databases of EHRs have potential to make huge contributions to this area but, for this to happen, we need coordinated efforts across funding and research organisations to improve data quality. For example, if scientific journals make a requirement of having publicly available lists of codes, this would likely encourage researchers to spend more time defining the outcomes and potentially seek funding for validation studies, which in turn could increase the awareness of funding institutions for the importance of assessing data quality in projects using these data. In the meantime, transparency in the list of codes used to define these outcomes and reporting of sensitivity analysis with different lists of codes are key.

Despite the difficulties of assessing each separate outcome, we must take into account that mental health disorder symptoms often overlap, and is difficult to disentangle what is attributable to each condition. Lastly, these conditions have a long period of exposure to medication after symptoms have disappeared, besides a high probability of relapse and recurrence,[52] which may raise issues on whether the condition is incident or prevalent.

CONCLUSIONS

Detailed information about codes used to identify outcomes of anxiety, depression, fatigue, cognitive dysfunction, sexual dysfunction, pain, sleep disorders, and fatal and non-fatal self-harm in studies using EHRs from primary care databases in the UK was unavailable for around half of studies of these outcomes. Where available, there was substantial heterogeneity in the list of codes used to ascertain cases. Most studies did not validate case definitions, though when this was done, positive predictive values were generally high. This review focused on common mental health disorders and QoL outcomes, but our conclusions are likely to be generalisable to other mental health outcomes. Caution is needed when interpreting and comparing results between studies, as heterogeneity in case definitions may be large. Future studies should fully report outcomes definitions, use sensitivity analysis to mitigate uncertainties about the impact of the case definition on studies' reported outcomes, and seek to validate the list of codes used to identify these outcomes.

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5.4 Summary

- EHRs have been extensively used to study mental health and HRQoL-related outcomes in the UK, despite difficulties in defining these outcomes in the data.
- Codelists were available for 17/42 studies of depression; 21/41 studies of fatal and non-fatal self-harm; 17/27 studies of dementia/cognitive dysfunction; 5/12 studies of anxiety; 4/8 studies of pain; 3/6 studies of fatigue and sexual dysfunction; 1/2 studies of sleep disorders.
- Outcome definitions and codelists were heterogeneous. 21 of the 120 studies validated their methods; these show positive predictive values above 80%.
- Anxiety definitions included symptoms in 33% of the studies; one study also considered drug prescriptions. Where codelists were available, these most often (80-100%) included terms for generalised anxiety disorder, panic and phobias; 60% included terms for mixed anxiety and depression.
- Depression definitions included prescriptions in 50% of the studies, and symptoms in 14%. Terms for bipolar disorder and depression in dementia were present in 25% and 18% of the codelists available, respectively, while terms for mixed anxiety and depression were present in 60%.
- Definitions of cognitive dysfunction were often tailored to the diagnosis of specific types of dementia. 15% of the studies considered diagnoses and prescriptions of anticholinesterase and dopaminergic drugs, and one study reported having included symptoms of dementia in their definition.
- Fatigue definitions included symptoms in all but one study, and varied little, except in the inclusion of fibromyalgia, which was done in two of the six studies only.
- Fatal and non-fatal self-harm definitions included completed suicide only, completed and attempted suicide, and completed and attempted suicide plus self-harm. Completed suicide was often ascertained in primary care data linked to the ONS mortality data; a validated codelist was available for self-harm.
- For the other outcomes, only two studies reported on sleep disorders, and pain definitions varied by the anatomical location; these were too heterogeneous to be meaningfully compared. No study of female sexual dysfunction was identified.

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6 Quantification of the associations between breast cancer survivorship and adverse mental health-related outcomes: a population-based matched cohort study

6.1 Introduction

In this chapter, I used data from the UK CPRD GOLD primary care database to estimate the risk of adverse mental outcomes in breast cancer survivors, compared to women with no history of cancer. This directly responds to Objective 3 of this thesis. A matched cohort study design was chosen; the exposed cohort included all eligible women with a record of breast cancer in the database, and a random sample of women with no prior history of cancer formed the unexposed cohort. The outcomes of this study were selected among conditions identified in Chapters 1 and 3, and their definition was informed by the systematic review in Chapter 5.

6.2 Study protocol and ethical approvals

The study protocol (in Appendix 3) outlined the *a priori* defined methods and rationale for this study. This study received approval from The Independent Scientific Advisory Committee for MHRA Database Research (ISAC) (protocol 18_253; Ethics1 in Appendix 3) and the London School of Hygiene & Tropical Medicine Ethics Committee for Observational Research (ref. 16225; Ethics2 in Appendix 3).

6.3 Article

The research article produced to disseminate results is provided in the following pages. Appendix 3 of this thesis includes the supplementary materials to the article. This is currently under review.

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SECTION A – Student Details

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First Name(s)	Helena Isabel		
Surname/Family Name	Morim Carreira		
Thesis Title	Long-term mental health and quality of life in women with history of breast cancer		
Primary Supervisor	Professor Krishnan Bhaskaran		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	n/a		
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Where is the work intended to be published?	JAMA Oncology
Please list the paper's authors in the intended authorship order:	Helena Carreira, Rachael Williams, Garth Funston, Susannah Stanway, Krishnan Bhaskaran
Stage of publication	**Undergoing revision**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	HC, RW and KB designed the study. HC and KB obtained approvals to access the data. HC did data management and analysis, and wrote the first draft of the manuscript. GF provided clinical input in defining the list of Read codes used to identify outcomes. All authors provided comments on the manuscript and revised the paper for important intellectual content.

SECTION E

Student Signature	[redacted]
Date	09 December 2019

Supervisor Signature	[redacted]
Date	09 December 2019

Risk of adverse mental health outcomes in women with history of breast cancer: a matched population-based cohort study in the United Kingdom (1988-2018)

Subtitle: Adverse mental health outcomes in breast cancer survivors in the UK

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Abstract

Importance: Increasing numbers of women survive breast cancer but the long-term mental health impact of having been diagnosed and treated for the disease is unclear.

Objective: To estimate the risk of anxiety and depression (primary outcomes), and seven secondary mental health-related outcomes, in breast cancer survivors compared to women with no prior cancer.

Design: Matched population based cohort study. Median follow-up was 4.5 years in the exposed group (inter-quartile range (IQR): 1.9-8.5) and 5.2 years in the comparison group (IQR: 2.2-9.3).

Setting: Primary care practices in the United Kingdom.

Participants: All adult women diagnosed with an incident breast cancer between 1988 and 2018 in the Clinical Practice Research Datalink (CPRD) GOLD primary care database; women with a prior history of other cancers were excluded. The unexposed cohort comprised a random selection of women with no history of cancer, matched to exposed women on age and primary care practice.

Exposure: Breast cancer.

Main outcome measures: Relative risk of the primary and secondary outcomes.

Results: 57,571 women diagnosed with breast cancer (mean age 62.3 ± 13.9 years) and 230,067 women with no previous cancer were included. Breast cancer survivorship was positively associated with the primary outcomes of anxiety (adjusted hazards ratio=1.33; 95%CI: 1.29-1.36), and depression (1.35; 1.32-1.38), and the secondary outcomes of fatigue (1.28; 1.25-1.31), pain (1.22; 1.20-1.24), sexual dysfunction (1.27; 1.17-1.38), sleep disorder (1.68; 1.63-1.73) and being prescribed opioid analgesics (1.86; 1.83-1.90), but there was no evidence of an association with cognitive dysfunction (1.00; 0.97-1.04) or fatal and non-fatal self-harm (1.15; 0.97-1.36). Hazard ratios for anxiety and depression reduced over time ($p<0.001$) but raised risks persisted for two and four years, respectively, after cancer diagnosis. For the secondary outcomes, increased levels of pain and sleep disorder persisted for at least 10 years. Younger age was associated with larger increases in the risks of depression, cognitive dysfunction, pain, opioid analgesic use and sleep disorders (p-interaction<0.001 in each case).

Conclusion: Breast cancer survivorship is associated with raised risks of anxiety and depression, as well as other adverse mental health-related outcomes, persisting well into the survivorship period.

Introduction

Breast cancer is the most common cancer to occur in women, with over two million new cases diagnosed annually worldwide.[1] In countries with the highest incidences, five-year age-standardized net survival is generally >80%.[2] This is resulting in a large population of women living beyond a breast cancer diagnosis, including 2.9 million in the United States and over 570,000 in the United Kingdom (UK), with numbers projected to rise further.[3,4] Given this, it is important to understand the long-term consequences of breast cancer diagnosis and treatment. Breast cancer survivorship has been associated with a wide range of iatrogenic effects including myocardial infarction, stroke and cancer.[5,6] Evidence on long-term mental health outcomes is less clear.

In a recent systematic review, anxiety, depression, sexual and cognitive dysfunctions, and suicide, were found to be more common in breast cancer survivors than in women with no history of cancer.[7] However, evidence was often drawn from studies at high-risk of selection and information bias, likely to be confounded by age and socio-economic status, and lacking generalisability to the broader group of women with a history of breast cancer.[7] Evidence on other outcomes, such as sleep disturbance, was insufficient to draw conclusions.[7]

The burden of depressive and anxiety disorders is remarkably high, particularly in high-income settings.[8] The efficient planning and delivery of mental health services that suit the needs of the largest group of cancer survivors requires timely and robust estimates on the risk of clinically assessed outcomes at the population level. We aimed to quantify the risk of several adverse mental health-related outcomes in women with a history of breast cancer followed in primary care in the UK National Health Service, compared to similar women who never had cancer. The primary outcomes were anxiety and depression, two common mental disorders primarily managed in primary care settings in the UK. Secondary outcomes were cognitive impairment (including dementia), fatigue, pain, sleep disorder, sexual dysfunction, and fatal and non-fatal self-harm.

Methods

Study design and data sources

This was a matched cohort study including data from the UK Clinical Practice Research Datalink (CPRD) GOLD primary care database (July 2018 version). This database includes anonymised electronic health records (EHRs) from 18.4 million patients registered with 761 primary care practices across the UK. The data are routinely recorded by general practitioners (GP) in the InPS Vision software system, using version 2 Read codes,[9] and were shown to be broadly representative of the UK population in terms of age, sex and ethnicity.[10] A subset of CPRD patients in England were linked at patient-level, using deterministic methods,[11] to the Office for National Statistics (ONS) mortality data (containing dates and causes of death),[12] patient-postcode linked Index of Multiple Deprivation (IMD, an area-based measure of socioeconomic status),[13] and the Hospital Episodes Statistics – Admitted Patient Care (HES-APC) database (containing coded diagnostic information from hospital admissions).[14]

Study populations

The exposed cohort included all women (≥18 years) with an incident diagnosis of breast cancer (list of codes available at https://datacompass.lshtm.ac.uk/1429/) recorded between the database inception (1987) and July 2018, and who had ≥12 months of uninterrupted prior registration meeting CPRD quality control criteria (to ensure the exclusion of prevalent breast cancer cases). We excluded women with severe mental or neurological disorders (i.e. schizophrenia and other psychotic disorders, bipolar disorders, neurocognitive disorders and substance-related disorders), or a cancer diagnosis (except non-melanoma skin cancer) prior to breast cancer. As treatment for some mental health outcomes might last for several months, we excluded from each outcome-specific analysis patients who had that outcome in the year before the breast cancer diagnosis (index date). Patients with an outcome last recorded >1 year before the index date were not excluded, and the mental disorder was assumed to be in remission.

The comparison group included women with no history of cancer at the index date (defined as the date of the breast cancer diagnosis for the matched breast cancer patient), except for non-melanoma skin cancer. For each breast cancer survivor, we randomly selected four control women with no history of cancer, matched to the cancer survivor on age (within a 3-year range), primary care practice, and eligibility of the data

for linkage (to enable a sensitivity analyses among patients with linked data). Women in the exposed cohort were eligible for selection as controls up to the date of breast cancer diagnosis. Similar to the exposed group, women in the unexposed cohort had ≥12 months of uninterrupted prior registration. Exclusion criteria were the same as those applied to the exposed group.

Primary outcomes definition: anxiety and depression

The primary outcomes of anxiety and depression were identified by either a diagnostic Read code for conditions where anxiety/depression is the cardinal symptom (e.g. generalised anxiety disorder, major depressive disorder), or a Read code for a symptom (e.g. low mood) accompanied by a prescription of an antidepressant, for depression, or an anxiolytic or a relevant antidepressant, for anxiety, within 90 days (Methods1 in Appendix 3). The outcome definitions were informed by a systematic review on the topic.[15] The Read codelists (available at https://datacompass.lshtm.ac.uk/1429/) were created using a systematic approach by a practicing GP (author GF).

Secondary outcomes definition: cognitive dysfunction, fatigue, pain, opioid analgesics, sleep disorder, sexual dysfunction, fatal and non-fatal self-harm

The definitions of the outcomes are provided in the Methods1 in Appendix 3; lists of codes are available at https://datacompass.lshtm.ac.uk/1429/. Briefly, fatigue, pain and sexual dysfunction were defined with Read codes only. Sleep disorder was identified using Read codes and combinations of Read codes and prescriptions of anxiolytics/hypnotics. Cognitive dysfunction was defined by Read codes, or a dementia-specific drug prescription.[16] For self-harm, we updated a validated list of codes.[17] Suicide was defined by International Classification of Diseases, tenth revision (ICD-10) codes X60-X84 and Y10-34, excluding Y33.9 where the verdict is pending.[18]

Statistical analysis

Incidence rates were calculated for each outcome in each cohort. Follow-up started at the index date (date of breast cancer diagnosis in the exposed cohort; controls took the same index date as their matched cases) and terminated at the earliest date of: outcome observed, cancer diagnosis other than breast in the exposed cohort, any cancer diagnosis in the comparison cohort, death, transference out of the practice, and last data collection for the practice.

Associations between breast cancer survivorship and each outcome were quantified using Cox regression models, with time since index as the underlying time scale, and stratifying on matched set to account for matching by age, primary care practice and data eligibility for linkage. Robust estimates of the standard errors were used to calculate 95% confidence intervals (95%CI). For the subset of patients for which data were available, we estimated hazard ratios (HR) adjusted for diabetes mellitus at baseline (yes/no), body mass index (BMI) category (<18.50; 18.5-24.9; 25.0-29.9; 30.0-34.9; 35.0-39.9; ≥40.0 kg/m^2), smoking status (non-smoker, current smoker, former smoker) and drinking status (never drinker; current drinker; former drinker). The directed, acyclic graph is provided in Figure 6.1; covariates definitions are provided in Methods2 in Appendix 3. Missing data were not imputed, as the missingness for these variables is likely to dependent on the values themselves, a violation of the missing at random assumption.[19]

We assessed the potential for effect modification by age group at index date (18-34; 35-44; 45-54; 55-64; 65-74; 75-84; ≥85 years), practice postcode-linked quintile of IMD, calendar period of index date (1988-94; 1995-99; 2000-04; 2005-09; 2010-14; 2015-18), follow-up time (1 year interval up to 5 years, and 5-10 years, an implicit test of proportional hazards), cardiovascular comorbidity (yes/no), and history of the outcome <1 year before index date (yes/no), by fitting interaction terms between the exposure and these variables.

All analyses were conducted in Stata version 15.[20]

Sensitivity analysis

We repeated the analyses including only patients with no history of the outcome before the index date. For the subset of patients for whom linked data were available, we ran analyses using linked HES-APC data to improve outcome ascertainment, and adjusted for deprivation based on the patient postcode (rather than practice postcode). We ran analyses with alternative outcome definitions that are expected to have higher specificity, to assess the impact of choice of outcome codes on our results. For opioid analgesics, we ran the analysis excluding codeine, which can be prescribed for its antitussive or antidiarrheal properties. We re-ran the analyses of fatal and non-fatal self-harm considering these as two separate outcomes (self-harm and completed suicide).

Ethical approvals

The study protocol (Protocol in Appendix 3) was approved by The Independent Scientific Advisory Committee for MHRA Database Research (ISAC) (protocol 18_253; Ethics1 in Appendix 3) and the London School of Hygiene & Tropical Medicine Ethics Committee for Observational Research (ref. 16225; Ethics2 in Appendix 3). Informed consent was not required as the data were anonymised.

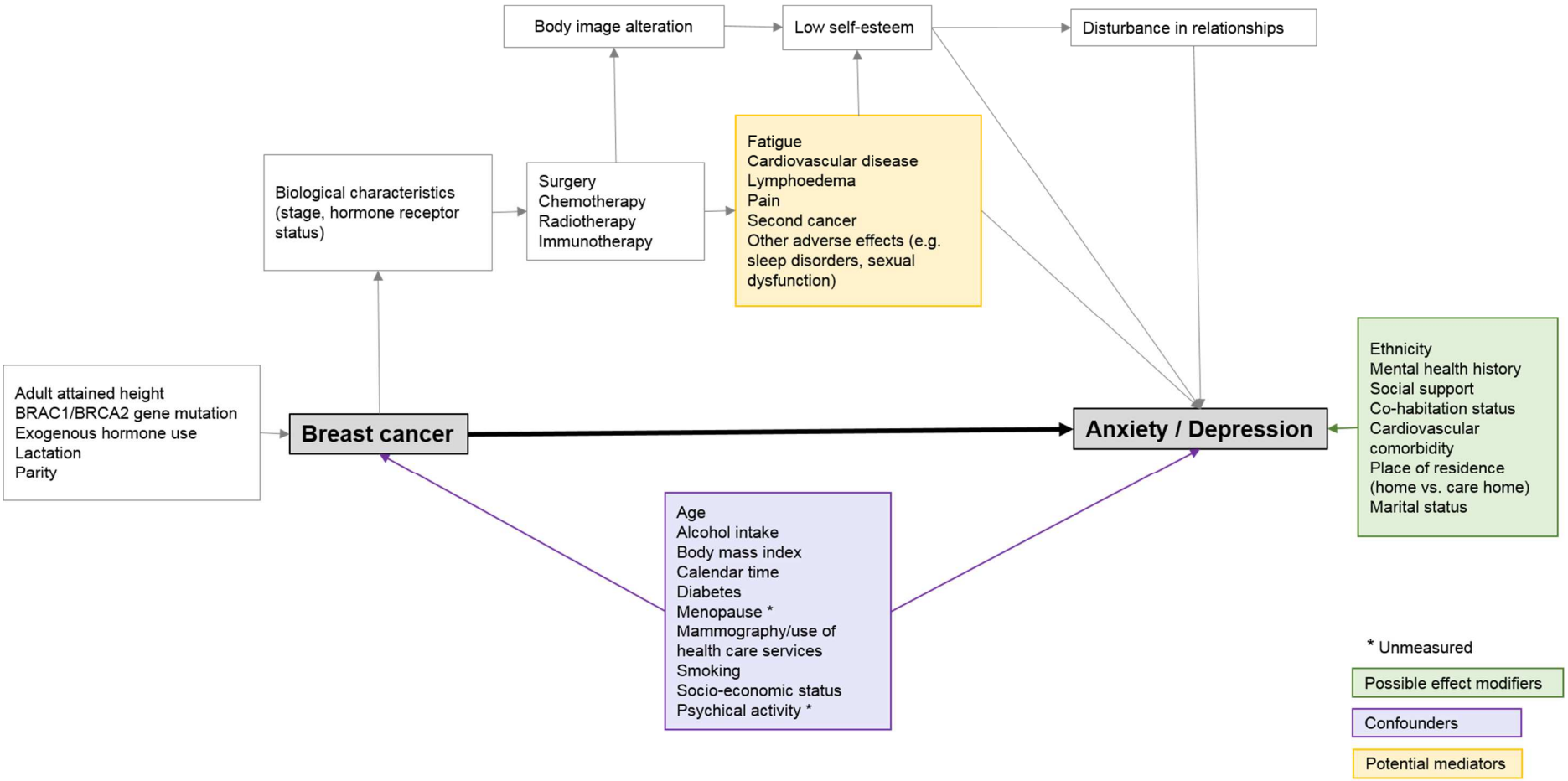


Figure 6.1 Direct acyclic graph.

Results

57,571 women with history of breast cancer and 230,067 women with no history of cancer were included in the study (Figure 6.2). Overall median follow-up time was 4.5 years in the exposed group (inter-quartile range (IQR): 1.9-8.5 years) and 5.2 years in the comparison group (IQR: 2.2-9.3 years). Outcome specific follow-up time and person-time at risk are included in Tables 1A to 1C in Appendix 3. 11,790 breast cancer survivors (24%) and 55,609 women in the comparison group (20%) had ≥10 years of follow-up. Approximately 20% of all participants had anxiety recorded >1 year before the index date, and 29% had history of depression (Table 6.1).

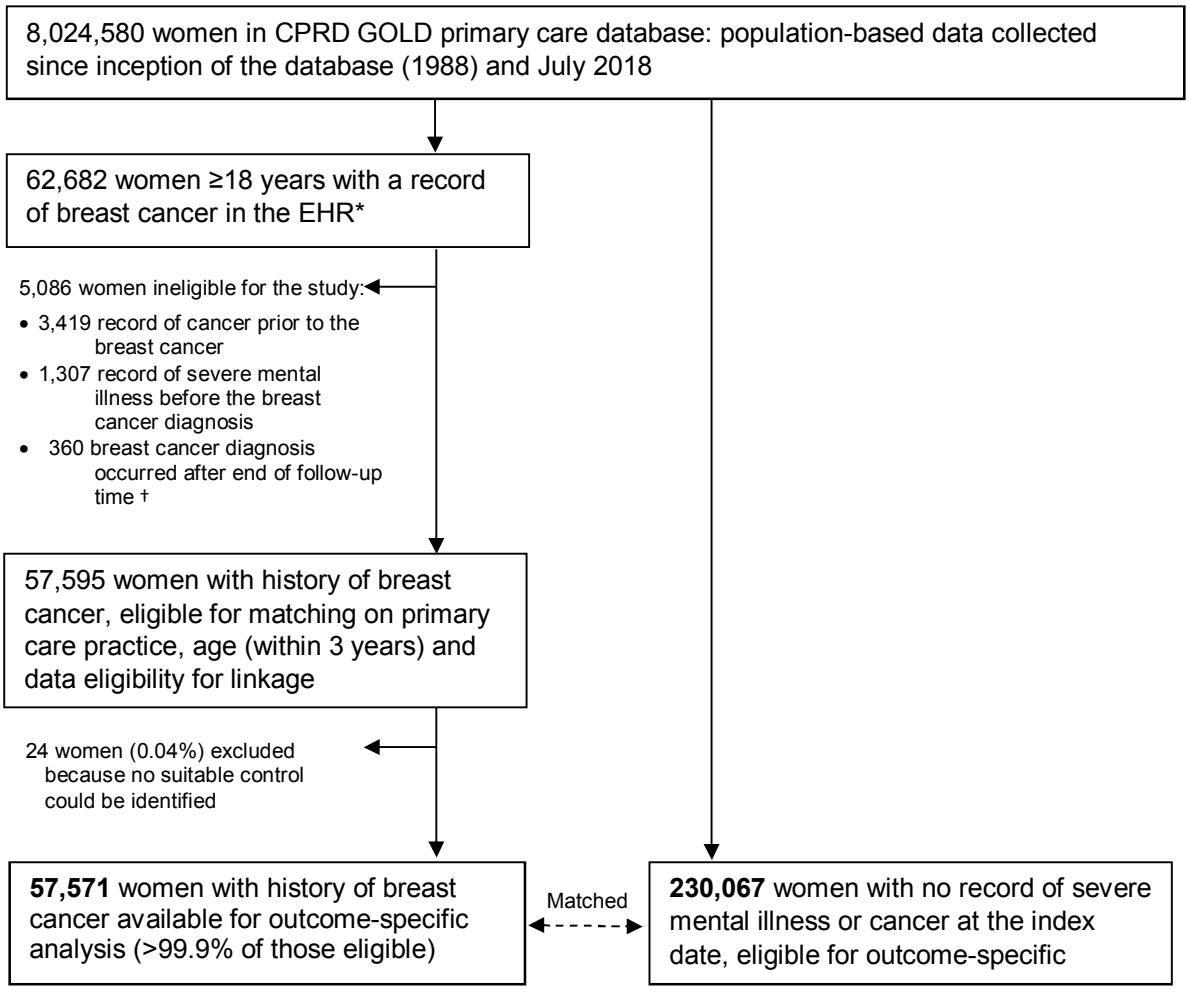


Figure 6.2 Flowchart of the selection of the study cohorts.

EHR = electronic health records; CPRD =Clinical Practice Research Datalink.
* Women with research quality follow-up, as defined by CPRD based on systematic checks for data quality at both patient and practice level.
† Almost all had a first record of breast cancer a few days after the recorded date of death.

Table 6.1 Characteristics of the study participants.*

	Women with history of breast cancer		Women with no history of cancer	
	No.	%	No.	%
All participants	**57,571**	100.0	**230,067**	100.0
Socio-demographic				
Age group at index date (years) †				
18-34	781	1.4	3,125	1.4
35-44	4,768	8.3	19,059	8.3
45-54	13,039	22.6	52,114	22.7
55-64	14,436	25.1	57,707	25.1
65-74	12,361	21.5	49,395	21.5
75-84	8,386	14.6	33,524	14.6
85+	3,800	6.6	15,143	6.6
Calendar period of diagnosis				
1988-1994	2,656	4.6	-	-
1995-1999	4,796	8.3	-	-
2000-2004	11,590	20.1	-	-
2005-2009	16,381	28.5	-	-
2010-2014	15,733	27.3	-	-
2015-2018	6,415	11.1	-	-
Ethnicity				
White	21,187	36.8	86,187	37.5
South Asian	411	0.7	2,247	1.0
Black	271	0.5	1,384	0.6
Other & mixed	221	0.4	1,228	0.5
Unknown	35,481	61.6	139,021	60.4
Practice deprivation (quintiles of IMD)				
1 (least deprived)	11,381	19.8	45,502	19.8
2	9,913	17.2	39,618	17.2
3	11,820	20.5	47,239	20.5
4	11,736	20.4	46,899	20.4
5 (most deprived)	12,721	22.1	50,809	22.1
Lifestyle				
Body mass index (kg/m^2) at index date ‡				
<18.50	908	1.6	4,561	2.0
18.50-24.99	20,958	36.4	85,030	37.0
25.00-29.99	17,565	30.5	69,052	30.0
30.00-34.99	8,666	15.1	32,401	14.1
35.00-39.99	3,302	5.7	12,549	5.5
≥40.00	1,490	2.6	6,350	2.8
Unknown	4,682	8.1	20,124	8.7
Alcohol intake at index date				
Never drinker	7,780	13.5	35,065	15.2
Current drinker	40,438	70.2	156,604	68.1
Former drinker	4,436	7.7	17,181	7.5
Unknown	4,917	8.5	21,217	9.2

(Continued)

Table 6.1 Continued

Smoking status at index date				
Non-smoker	30,452	52.9	122,985	53.5
Current smoker	9,565	16.6	39,986	17.4
Former smoker	16,343	28.4	60,604	26.3
Unknown	1,211	2.1	6,492	2.8
Comorbidity				
History of diabetes at index date	3,844	6.7	14,030	6.1
History of coronary heart disease or stroke	4,648	8.1	18,523	8.1
Mental health history (>1 year before index date) §				
Anxiety	11,986	20.8	45,482	19.8
Depression	16,771	29.1	65,628	28.5
Cognitive dysfunction ¥	-	-	-	-
Fatigue	11,200	19.5	42,578	18.5
Sleep disorder	7,221	12.5	27,528	12.0
Pain	44,829	77.9	173,536	75.4
Sexual dysfunction	1,670	2.9	6,479	2.8
Self-harm	1,652	2.9	6,847	3.0

IMD - Index of multiple deprivation.* Refers to all patients potentially eligible for analyses. The number of patients included in the analyses varied by outcome because we excluded women who had that particular outcome in the year before the index date, as we assumed that these were likely to still be under treatment at the index date.

† Women with no history of cancer were individually matched by age (within a 3-year age range) to women in the exposed group.

‡ Body mass index was calculated from weight and height records, when available. Missing information was supplemented with data from Read codes when possible. Patients with a Read code of obesity without indication of the category (e.g. 66C.00 - obesity monitoring) were categorised in the BMI 30.00-34.99 category; Read codes referent to morbid obesity were included in the BMI≥40 category.

§ Refers to women who had the outcome recorded at >1 year before the index date. Women who had the outcome in the year before the index date were excluded from the cohort.

¶ After the first record of breast cancer in the exposed group, it was not possible to differentiate between this cancer and what could be a recurrence or second breast cancer; therefore only cancers other than breast and non-melanoma skin cancer were considered. In the comparison group, all cancers, except non-melanoma skin ones, were considered.

¥ Patients with a record of cognitive dysfunction at any point prior to the index date were excluded, as changes in cognitive function are often non-reversible.

Relative and absolute risks of mental health outcomes in breast cancer survivors compared with cancer-free controls

Breast cancer survivors had an increased risk of anxiety (adjusted HR 1.33, 95%CI 1.29-1.36) and depression (HR=1.35, 95%CI 1.32-1.38) compared with cancer-free controls, with adjustment for potential confounders having little influence on effect estimates (Table 6.2). The cumulative incidence of anxiety 10 years after diagnosis was 16.4% (95%CI 15.9-16.8%); for depression, this figure was 28.5% (95%CI 28.0-29.1%) (Figure 6.3; Table 2 in Appendix 3).

Raised risks were also observed for the secondary outcomes of fatigue, pain, sexual dysfunction, sleep disorder, and being prescribed an opioid analgesic. The most common secondary outcomes after 10 years of follow-up were pain (85.6%), opioid analgesics (45.5%), and fatigue (23.9%) (Figure 6.3).

Table 6.2 Associations between breast cancer survivorship and adverse mental health outcomes.

			Unadjusted associations *					Adjusted for diabetes, BMI category, smoking and drinking status *				
	No. exposed	**No. unexposed**	**No.**	**PY at risk**	**No. events**	**HR**	**95%CI**	**No.**	**PY at risk**	**No. events**	**HR**	**95%CI**
Primary outcomes												
Anxiety	55,616	224,138	279,754	1,594,899	26,112	**1.35**	1.31-1.38	244,766	1,431,613	24,038	**1.33**	1.29-1.36
Depression	54,073	216,355	270,428	1,463,728	44,733	**1.37**	1.35-1.40	236,146	1,308,004	41,173	**1.35**	1.32-1.38
Secondary outcomes												
Cognitive dysfunction	56,052	224,444	280,496	1,700,632	24,213	**1.03**	1.00-1.60	245,595	1,532,084	21,956	**1.00**	0.97-1.04
Fatigue	55,911	223,506	279,417	1,547,957	37,245	**1.31**	1.28-1.34	244,381	1,386,056	34,610	**1.28**	1.25-1.31
Pain	38,771	162,037	200,808	605,762	118,693	**1.28**	1.26-1.30	172,779	514,616	107,132	**1.22**	1.20-1.24
Sexual dysfunction	57,444	229,577	287,021	1,761,230	2,836	**1.34**	1.24-1.44	251,340	1,586,969	2,703	**1.27**	1.17-1.38
Sleep disorder	56,210	225,583	281,793	1,628,851	22,800	**1.71**	1.66-1.76	246,717	1,463,804	20,806	**1.68**	1.63-1.73
Opioid analgesics	52,672	213,190	265,862	1,429,809	62,165	**1.95**	1.92-1.98	232,154	1,277,168	56,190	**1.86**	1.83-1.90
Fatal and non-fatal self-harm	57,508	229,752	162,971	1,015,108	752	**1.16**	0.99-1.36	144,083	918,441	672	**1.15**	0.97-1.36

95%CI = 95% confidence interval; BMI = body mass index; HR = hazard ratio; PY = person-years.

* Women with a breast cancer diagnosis were matched with women without cancer on age (within a 3-year range), primary care practice (proxy of socio-economic status), and eligibility for data linkage (to avoid loss of precision in subset analyses).

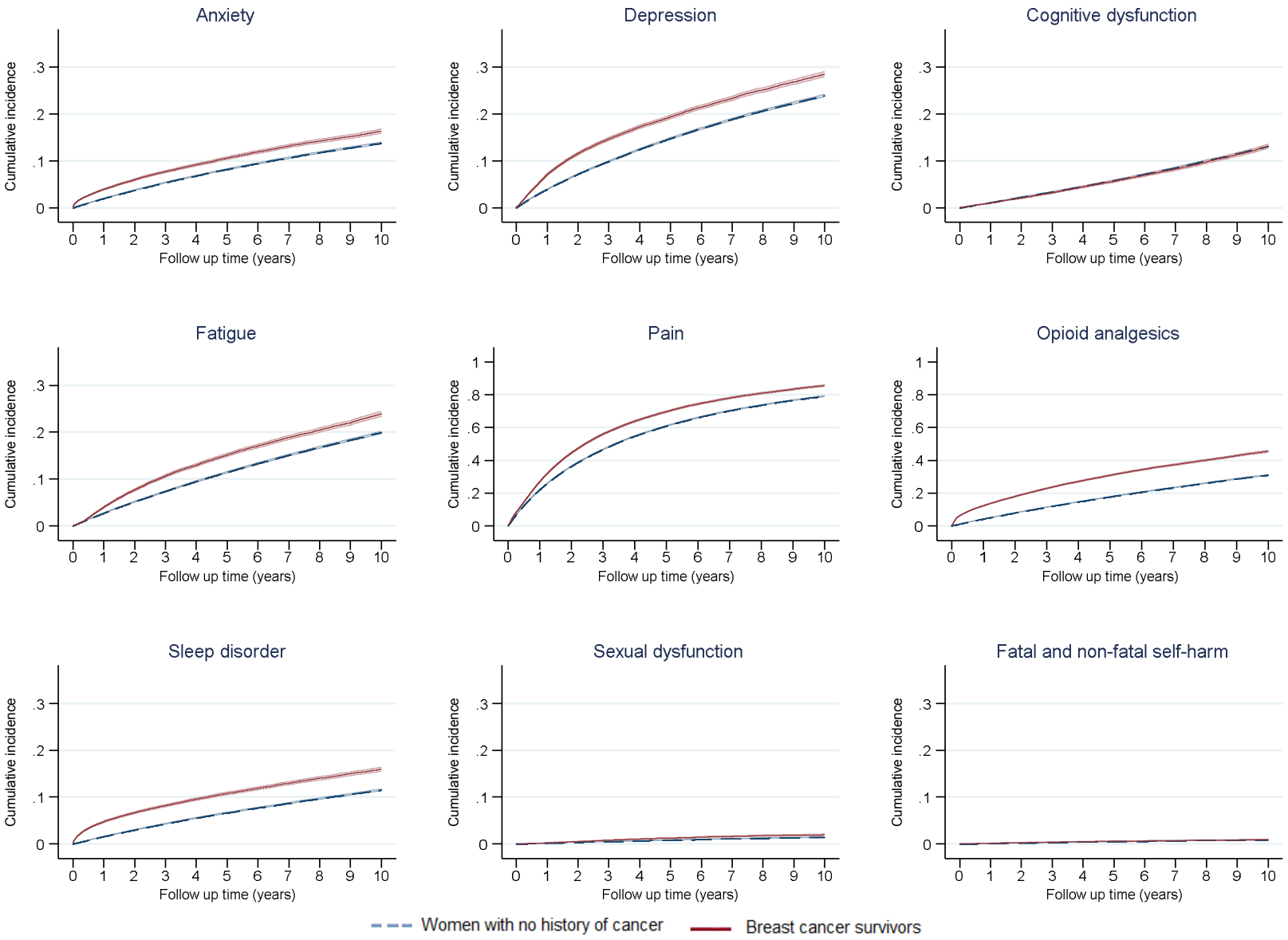


Figure 6.3 Risk of anxiety and depression in breast cancer survivors and women with no prior cancer.

Effect of age, deprivation, calendar period, follow-up time, cardiovascular comorbidity and history of the outcomes on the association between breast cancer survivorship and adverse mental health outcomes

Figure 6.4 shows the association between breast cancer survivorship and anxiety, and depression, stratified by potential effect modifiers. HRs for anxiety tended to be larger for younger women, in more deprived areas, and in later calendar years; HRs for depression were also larger in younger women. For both outcomes, HRs tended to decline over time since diagnosis ($p \leq 0.001$), and risks were no longer significantly elevated after two years for anxiety and four years for depression.

Effect modification for the secondary outcomes is shown in Figures 6.5A and 6.55B. Similar variation by age was found for cognitive dysfunction, pain, opioid analgesics prescribing and sleep disorder ($p<0.001$). HRs for most secondary outcomes also tended to diminish in magnitude over time, though statistically raised risks of fatigue, pain, opioid analgesic use, and sleep disorder persisted for at least 5-10 years.

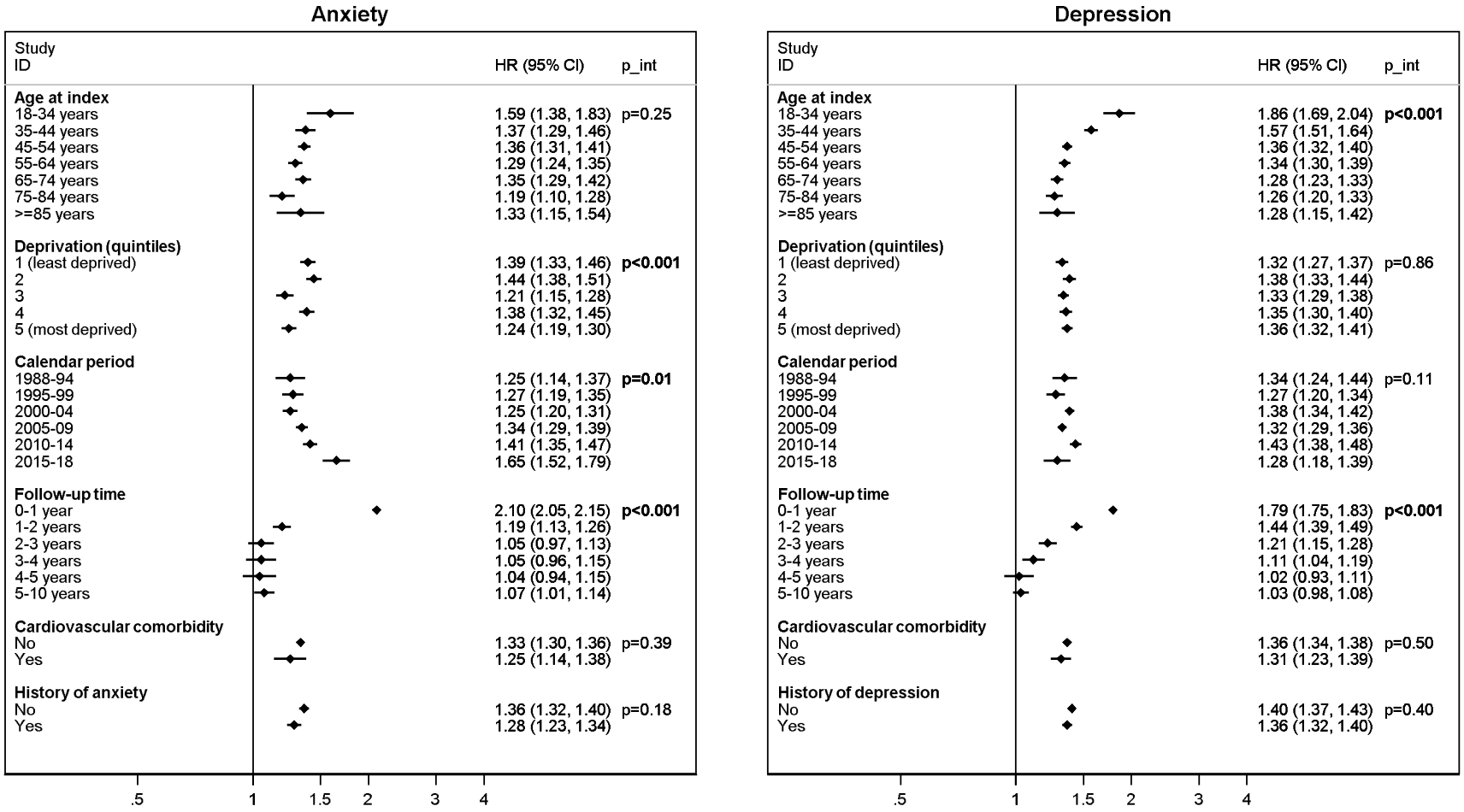


Figure 6.4 Associations between breast cancer survivorship and anxiety, and depression, by potential effect modifiers.

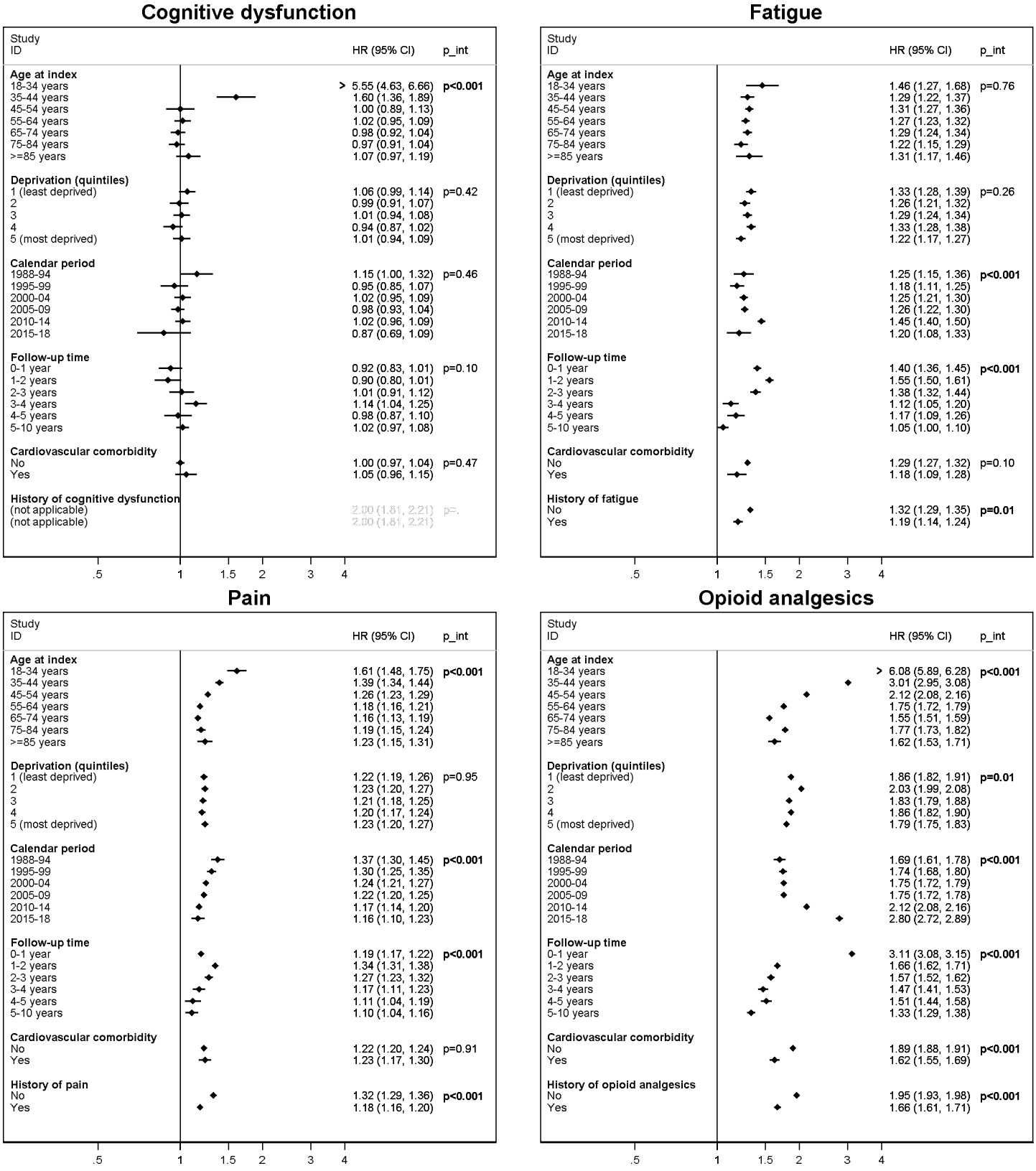
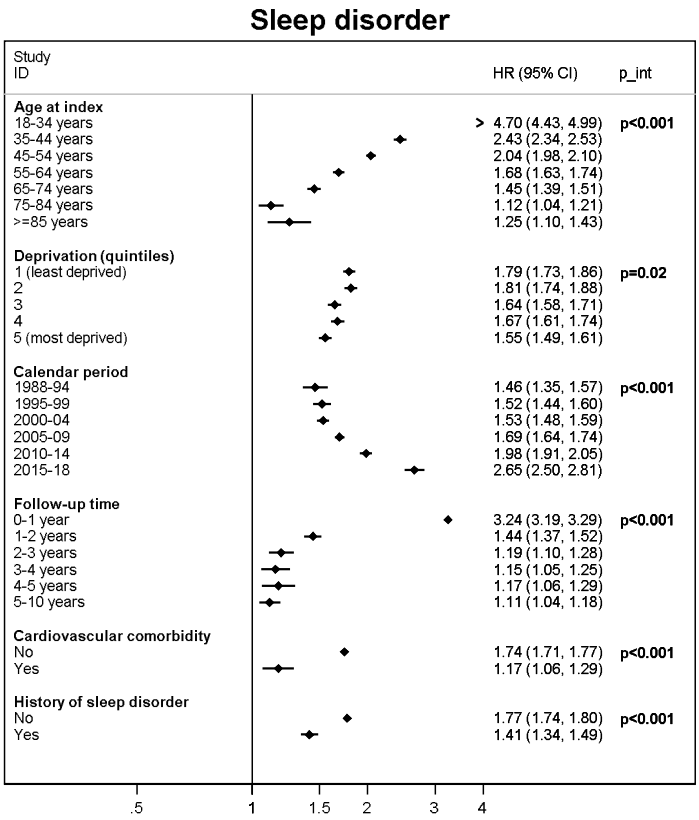
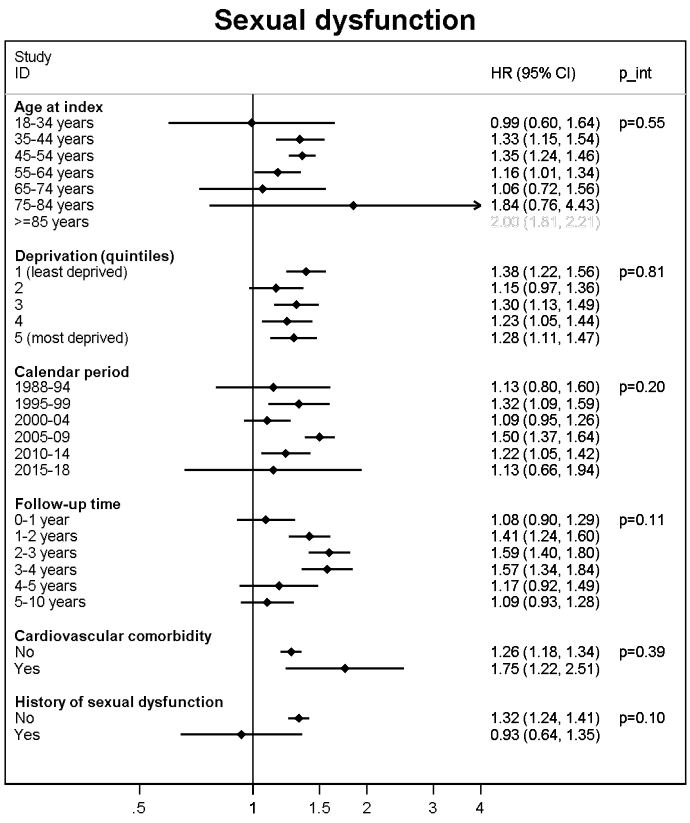


Figure 6.5A Associations between breast cancer survivorship and cognitive dysfunction, fatigue, pain and opioid analgesics, by potential effect modifiers.





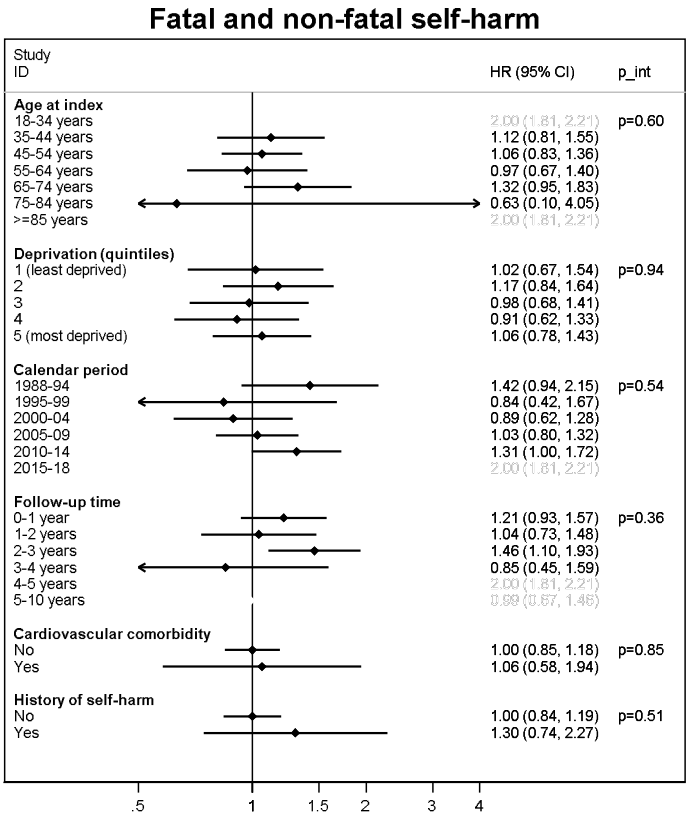


Figure 6.5B Associations between breast cancer survivorship and sleep disorder, sexual dysfunction and fatal and non-fatal self-harm, by potential effect modifiers.

Sensitivity analyses

Sensitivity analyses yielded generally similar results to the main analyses, with the exception of an analysis using a more specific definition for anxiety, which moved the association close to the null (Figure 6.6).

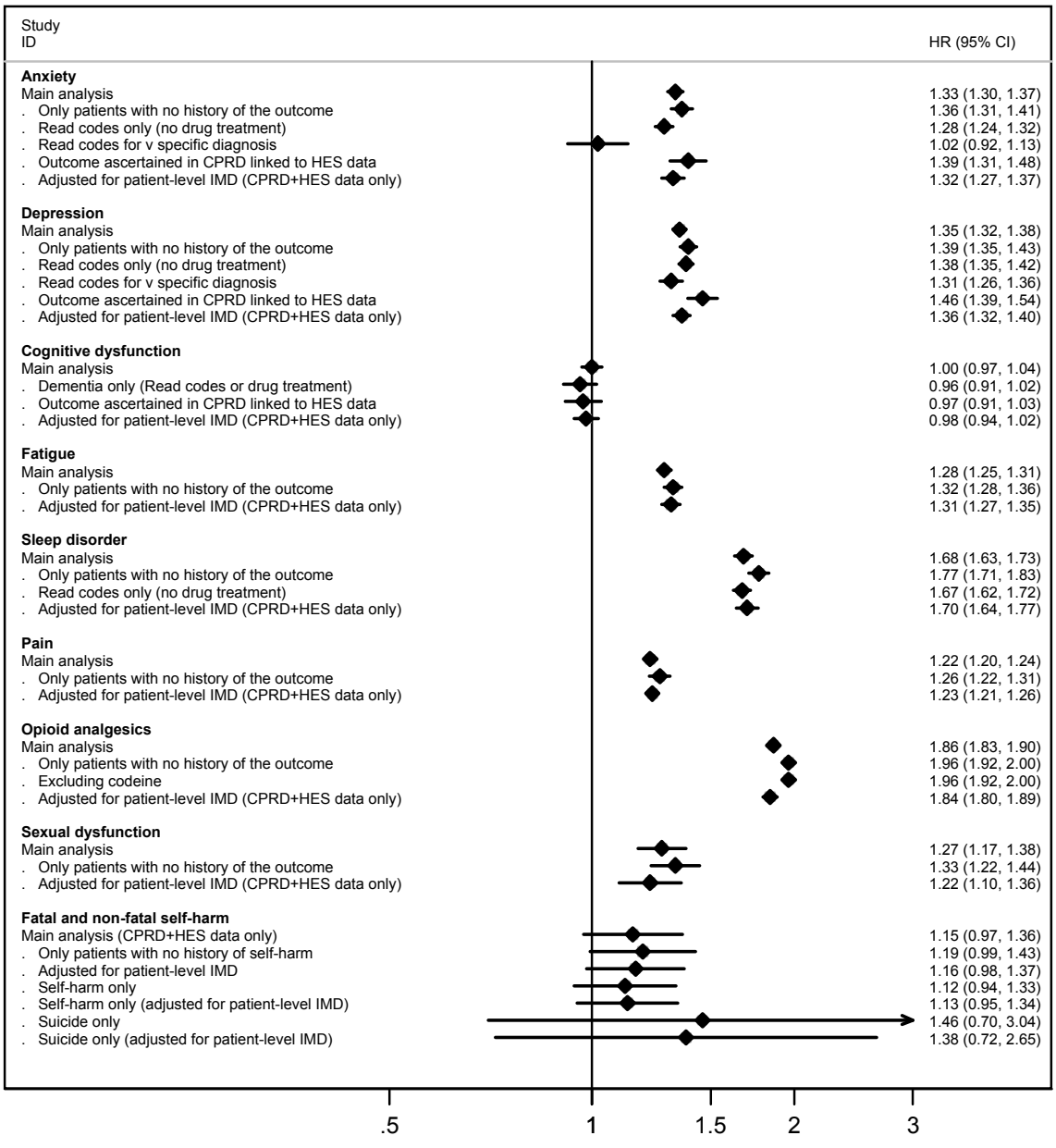


Figure 6.6 Results of sensitivity analysis.

Discussion

Compared to women with no history of cancer, breast cancer survivors had higher risks of anxiety and depression compared to women with no history of cancer. We also found evidence of raised risks of several secondary mental-health related outcomes, namely fatigue, pain, sexual dysfunction, sleep disorder, and being prescribed opioid analgesics. Younger age at diagnosis and more recent diagnosis were strong determinants of increased risk for most outcomes. The excess risks tended to decline over time since diagnosis, but risks of depression and anxiety remained significantly elevated for at least two and four years. Raised risks of fatigue, pain, opioid use and sleep disorders persisted for at least 5-10 years.

Our findings are consistent with results from previous studies.[7] Results remained virtually unchanged in sensitivity analyses, except for an analysis using a highly specific outcome definition for anxiety; it is plausible that GPs do not use specific codes for these disorders in cases where there is another medical condition such as breast cancer. The frequency of anxiety and depression in our sample was higher than other studies involving EHRs, which have reported incidences below 10%,[7] but these studies often used data from psychiatric registries, which usually include patients with more severe or persistent symptomatology. Our estimates for secondary outcomes were consistent with previous literature (e.g. pain and fatigue[21,22]) but sexual dysfunction was much lower compared to the 20-50% reported both in breast cancer survivors and in the general female population.[7,23] Only 21% of the British women with sexual problems seek help for their condition, which may explain the discrepancy.[24]

A major strength of this study is the population-based nature of the data, which make our results representative of the broad population of breast cancer survivors in the UK. Selection bias is unlikely, as registration with a primary care practice is nearly universal. The large study size and the wealth of data in the CPRD GOLD primary care database permitted the study of several outcomes with sufficient power to detect small effects. We accounted for major confounders such as age and socio-economic status; matching for GP practice also accounted for practice-level characteristics that are difficult to measure (e.g. shared environment). We carried out extensive sensitivity analyses exploring different definitions of outcomes, as well as the impact of the data sources, to assess the robustness of our results.

However, this study has limitations. The CPRD GOLD primary care database captures >90% of the cancers compared to the cancer registries,[25] which may have resulted in a

small proportion of women being incorrectly classified as unexposed and biased our results towards the null. The alternative of obtaining a list of patients from linked cancer registry data would have restricted our study to the roughly 50% of patients in England who are eligible for linkage, reducing sample size, power, and generalisability. There is a potential for misclassification of the outcomes due to the incompleteness of the information registered in EHRs (e.g. diagnoses in secondary care not fed back to the GP), or lack of validity of the definitions, even though outcomes defined in our data source generally showed high positive predictive values (median 83% of cases confirmed for mental and behavioral disorders).[26] We sought to maximize completeness and validity by conducting a systematic review of outcome definitions used in previous studies to inform decisions.[15] Unmeasured and residual confounding might also affect our results. We were unable to account for menopausal status, physical activity and mammography screening, as this information is often not registered, though age-matching should to some extent have taken account of menopausal status. Data on smoking and alcohol drinking habits relied on patients self-reporting accurately to their GP. We censored patients diagnosed with cancer during follow-up, but we were unable to distinguish between a second primary of the breast and recurrence in the exposed group. Lastly, breast cancer survivors may have more regular contact with health services making it more likely for conditions to be recorded in their records, due to a detection bias.

Symptoms of anxiety and depression are considered a normal response to the diagnosis, but some patients have traumatic reactions, and symptoms of post-traumatic stress disorder are not uncommon.[27] An increased risk of depression was observed for longer, possibly because some women struggle to cope in the long-term. Breast cancer is an ominous diagnosis that brings several changes to the woman's life, including concerns over the impact of their disease on significant others, for example their children and spouses (e.g. carer roles, financial constrains), and for herself, who has to cope with many physical consequences of the cancer treatments. The drivers of raised risks of fatigue, sleep disorders, pain and sexual dysfunction cannot be discerned from this study, but may include physical consequences of breast cancer treatments (e.g. chemotherapy-induced fatigue,[28] arthralgias as a side effect of hormone therapy)[29] and psychological factors, such as body image concerns for sexual dysfunction,[30] or anxiety for sleep disorders.[31]

Effective treatments are available for anxiety and depression, and it is important that these women are diagnosed early, and receive appropriate support and treatment. The risks were particularly increased during the main treatment period, and screening all

women at this point could help identify patients struggling to cope. Mental disorders still carry considerable stigma and not all patients will self-present. It is important that clinicians at all levels of care are aware of the increased risk of these conditions in breast cancer survivors, so that they can provide the necessary support if needed. Breast cancer survivors in the UK had low levels of self-efficacy to manage the complications of their disease, particularly fatigue and distress.[32] Cancer rehabilitation interventions with focus on potential physical and mental health consequences of breast cancer might reduce the disease burden by empowering women to better understand their disease.[33] Reducing waiting time for mental health services in general will also benefit breast cancer survivors.

Future studies should explore the possible modifying effect of social support, as increased social support may buffer some of the negative effects of stress.[34,35] Consequences of breast cancer treatments, such as lymphoedema, may mediate the association between breast cancer survivorship and mental health outcomes, and should be the subject of further work.

In conclusion, breast cancer survivorship was associated with raised risks of anxiety and depression, and several other mental health-related outcomes, persisting for several years after the cancer diagnosis.

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6.4 Summary

- This population-based matched cohort study aimed to estimate the risk of a range of anxiety and depression (primary outcomes), and seven secondary mental health-related outcomes, in breast cancer survivors compared to women with no prior cancer.
- The exposed cohort included all 57,571 women diagnosed with an incident breast cancer registered in the CPRD GOLD primary care database between 1988 and 2018. The comparison cohort was comprised of 230,067 women with no previous cancer, randomly selected from the same data source, matched to exposed women on age and primary care practice. Median follow-up was 4.5 years in the exposed group (inter-quartile range (IQR): 1.9-8.5) and 5.2 years in the comparison group (IQR: 2.2-9.3).
- Five years after diagnosis, the most common outcomes in breast cancer survivors were pain (70%), depression (19%) and fatigue (15.2%). Recorded sexual dysfunction (1%) and fatal and non-fatal self-harm (<1%) were rare.
- Breast cancer survivorship was positively associated with anxiety (adjusted HR=1.33; 95%CI: 1.29 to 1.36), depression (1.35; 1.32 to 1.38), fatigue (1.28; 1.25 to 1.31), pain (1.22; 1.20 to 1.24), sexual dysfunction (1.27; 1.17 to 1.38), sleep disorder (1.68; 1.63 to 1.73) and being prescribed opioid analgesics (1.86; 1.83 to 1.90), but there was no evidence of an association with cognitive dysfunction (1.00; 0.97 to 1.04) or fatal/non-fatal self-harm (1.15; 0.97 to 1.36).
- Hazard ratios for anxiety and depression reduced over time ($p<0.001$) but raised risks persisted for two and four years, respectively, after cancer diagnosis, while increased levels of pain and sleep disorder persisted for at least 10 years. Younger age was associated with larger increases in the risks of depression, cognitive dysfunction, pain, opioid analgesic use and sleep disorders (p-interaction<0.001 in each case).

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7 Quantification of the associations between breast cancer survivorship and quality of life and mental health: a study of patient-reported outcomes

7.1 Introduction

This chapter describes the research conducted to answer Aim 2 (i.e. to investigate quality of life and mental health in women with a history of breast cancer, compared to women with no history of cancer). A cross-sectional study was designed, in which two groups of women (one group of breast cancer survivors and one group of women with no prior cancer) were asked to complete validated questionnaires that assess HRQoL, and anxiety and depressive symptoms. Patient recruitment and the rationale for opting for each scale are described in detail in Chapter 4.

7.2 Study protocol and ethical approvals

The study protocol is provided in Appendix 4. Favourable ethical opinions for this study were obtained from the NHS East of England - Cambridge South Research Ethics Committee (Ref: 17/EE/0403; Ethics1 in Appendix 4); the London School of Hygiene & Tropical Medicine Observation Research Ethics Committee (Ref: 14417; Ethics2 in Appendix 4); the Health Research Authority and the Health and Care Research Wales (IRAS Project ID224561: Ethics3 in Appendix 4).

7.3 Article

The manuscript that describes the results of this study is provided in the following pages. The supplementary tables are provided in Appendix 4.

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SECTION A – Student Details

Student ID Number	1513226	**Title**	Ms
First Name(s)	Helena Isabel		
Surname/Family Name	Morim Carreira		
Thesis Title	Long-term mental health and quality of life in women with history of breast cancer		
Primary Supervisor	Professor Krishnan Bhaskaran		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	n/a		
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Where is the work intended to be published?	JNCI – Journal of the National Cancer Institute
Please list the paper's authors in the intended authorship order:	Helena Carreira, Rachael Williams, Harley Dampsey, Susannah Stanway, Liam Smeeth,Krishnan Bhaskaran
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	HC, RW, SS, LS, and KB designed the study. HC, RW, and KB got the approvals to collect the data. HD liaised with primary care practices in the UK, and provided logistical assistance with the questionnaire packages. HC did the data entry and analyses. HC drafted the manuscript, and RW and KB provided comments.

SECTION E

Student Signature	[redacted]
Date	09 December 2019

Supervisor Signature	[redacted]
Date	09 December 2019

Mental health and quality of life of breast cancer survivors compared to women with no prior cancer: a study of patient-reported outcomes in the United Kingdom

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Keywords: breast cancer; anxiety; depression; quality of life; United Kingdom.

Abstract

Background: Breast cancer and its treatment may affect long-term health-related quality of life (HRQoL) and mental health of survivors, but few studies have quantified this. We aimed to assess HRQoL, anxiety, and depressive symptoms in breast cancer survivors (>1 year), compared to women with no prior cancer.

Methods: A matched cross-sectional study of patient-reported outcomes was carried out among women included in the UK Clinical Practice Research Datalink GOLD primary care database. Breast cancer survivors and women with no prior cancer, frequency matched by age and primary care practice, were invited to participate. Outcomes were measured via postal questionnaire using the Quality of Life in Adult Cancer Survivors Scale (QLACS) and Hospital and Anxiety Depression Scale (HADS). Linear and logistic regression models were fitted to estimate adjusted associations between breast cancer survivorship and HRQoL domains, and anxiety and depressive symptoms.

Results: 353 BCS (mean time since diagnosis 8.1 years) and 252 women with no prior cancer were included. Compared to women with no prior cancer, BCS had poorer HRQoL (higher mean QLACS score) in the domains of cognitive problems (adjusted β (aβ)=1.4, p=0.01), sexual function (aβ=1.7, p=0.02) and fatigue (aβ=1.3, p=0.01), but no evidence of difference in negative feelings, positive feelings, pain, or social avoidance. BCS had non-significantly higher odds of probable anxiety (HADS-anxiety score ≥11) than controls (adjusted OR (aOR)=1.40, 0.93-2.10), however there was strong evidence of a difference when a more sensitive threshold (score ≥8, "borderline/probable anxiety") was used (aOR=1.47, 1.15-1.87). There were no differences in odds of probable depression (aOR=1.18, 0.52-2.68). Poorer quality of life and mental health outcomes were more pronounced among women with advanced-stage cancer at diagnosis, and/or treated with chemotherapy.

Conclusion: BCS had raised risks of problems with cognition, sexual function, fatigue and borderline/probable anxiety, particularly where their cancer was advanced and/or treated with chemotherapy.

Introduction

Breast cancer is the most common malignancy diagnosed in women in most countries, and incidence is still on the rise [1]. Trends in survival from the disease also markedly increased in the last decades and five-year age-standardised net survival is now close to 90% in the United States, Canada, and several European countries [2]. This is resulting in millions of women worldwide living for several years beyond their disease, including over 2.7 million in the United States and 500,000 in the United Kingdom (UK) [3, 4]. In spite of the increasing prevalence of breast cancer survivors, little is known about the long-term impact of breast cancer on the patients' mental health and health-related quality of life (HRQoL).

The National Cancer Research Institute identified several areas related to psychological wellbeing and quality of life in the top 20 priorities for patients living with and beyond cancer [5]. A large proportion of breast cancer survivors in England have been reported to experience issues that may negatively affect HRQoL, such as worries of family members getting the disease (73%), weight changes (60%), and stress (58%) [6]. These numbers suggest that breast cancer survivors may have poor HRQoL, but quantitative data on HRQoL, and its determinants, in this patient population are scarce. Furthermore, it is unclear whether differences in HRQoL exist between breast cancer survivors and women with no history of cancer. A recent study using primary care EHRs showed that breast cancer survivors in the UK were more likely to have anxiety and depression, as well as sexual dysfunction, sleep disturbance, fatigue, and pain recorded in their clinical record, compared to women with no cancer (unpublished data; please refer to Chapter 6 of this thesis). However, recording of some of these outcomes in routinely collected health records is likely to be incomplete and susceptible to ascertainment bias if cancer survivors are more likely to have problems recorded due to more healthcare contact. Collecting data on anxiety and depressive symptoms directly from cancer survivors and cancer-free controls may overcome these limitations.

This study aimed to quantify HRQoL, and anxiety and depressive symptoms, in breast cancer survivors (>1 year), compared to women with no prior history of cancer. We also investigated socio-demographic and clinical determinants of HRQoL among breast cancer survivors.

Methods

Study design and sampling frame

We designed a matched cross-sectional study including breast cancer survivors and a comparison group of women with no prior cancer. Between October 2018 and August 2019, we invited all primary care practices that were actively contributing with data to the Clinical Practice Research Datalink (CPRD) GOLD primary care database in August 2018 to participate in the study. CPRD is a UK government research service that collects, processes, and releases anonymised electronic health records (EHR) from patients attending the UK National Health Service. Patients registered with primary care practices that accepted to participate were potentially eligible for the study (see details below).

Patient eligibility criteria

Inclusion criteria for the breast cancer survivors group were: 1) a prior diagnosis of invasive breast cancer at least one year before; 2) aged 18-80 years; 3) alive and registered with the practice. To ensure that the recorded breast cancer was incident, we required one year of follow-up in CPRD prior to the diagnosis. For the comparison group, inclusion criteria were: 1) no history of cancer (except non-melanoma skin cancer); 2) alive and registered with the practice; and 3) at least two years of follow-up data in CPRD (since we required one year of follow-up before and after cancer to be included in the breast cancer group). Exclusion criteria for both groups were: 1) inability to complete a self-reported questionnaire (e.g. due to dementia); 2) having had another (non-breast) cancer or having been treated for a non-invasive breast tumour.

Patient selection and recruitment

The CPRD GOLD primary care database was used to identify all breast cancer survivors from the participating practices, as well as a random sample of women with no prior cancer from the same practice. Women in the comparison group were frequency-matched on age to breast cancer survivors in the same practice. Initially controls were matched to exposed women (breast cancer survivors) with a ratio of 1:1, but this was revised early in recruitment to 2:1 due to ~50% lower response among controls. The authors had full access to the CPRD GOLD primary care database to create the list of potentially eligible patients. General practitioners then reviewed the records of potentially eligible patients, applied the inclusion and exclusion criteria (*vide* above), and sent the study materials to the eligible patients' addresses with a pre-paid

envelope to return the questionnaires. Patients were recruited between January and October 2019.

Patient-reported outcomes

Anxiety and depressive symptoms were measured with the Hospital Anxiety and Depression Scale (HADS) [7]. This is a 14-item self-reported screening tool for anxiety and depressive symptoms in the past week [7]. The recommended cut-offs were used to categorise patients as non-case (scores 0-7), borderline (scores 8-10) and probable case (scores 11-21) [7].

HRQoL was assessed with the Quality of Life in Adult Cancer Survivors Scale (QLACS) [8]. This tool includes 47 items, divided in seven generic domains (i.e. negative feelings; positive feelings; cognitive problems; pain; sexual function/interest; energy/fatigue; and avoidance) and five cancer-specific domains (i.e. financial problems; benefits of cancer; distress-family; appearance; distress-recurrence). Women with no history of cancer replied to the generic domains only. Items refer to the previous four weeks, and responses range between 1 (never) and 7 (always); higher scores indicate poorer HRQoL, except for positive feelings and benefits of cancer.

Demographic and clinical information

All women were asked to complete a questionnaire with information on education, ethnicity, and social support by proxy of living arrangements (alone/not alone). Breast cancer survivors provided information about treatments for their cancer, stage of the disease at diagnosis, time since last treatment (excluding long-term hormonal therapy), menopausal status, and status of the disease (active/remission). The patient-reported outcomes were also linked to the patient's EHR and to the practice-postcode Index of Multiple Deprivation (IMD) quintile, via a patient identifier generated by CPRD. The research team had no access to patient identifiable information.

Statistical analysis

Descriptive HRQoL and anxiety and depressive symptoms

We calculated domain scores for each patient. When a participant had one missing response for an item within a domain, we imputed the mean of the responses to the other items within that same domain; if ≥2 responses were missing, the domain score was not calculated [9]. The summary score for generic domains of HRQoL was calculated by the sum of the domain scores, with reverse scoring for the positive feelings domain. For the cancer specific domains, we added all domain scores,

excluding the score for 'benefits of cancer'. Scores were summarised for each group using means and measures of dispersion.

We also calculated mean and median scores for each subscale of HADS. When there were three or fewer items missing per subscale, we imputed these as the average of the responses in that subscale following proposed methods [10].

Comparison of outcomes between breast cancer survivors and controls

We fitted domain-specific multiple linear regression models, using the domain scores as the dependent variable and the following independent variables: patient group (exposed vs. control), age group (<60, 60-69, 70-81 years); higher education degree (yes/no), and practice postcode-linked quintile of IMD. Interactions between the exposure and socio-demographic variables were tested, but not included in the final models as these were not significant.

Outcome-specific logistic regression models were used to estimate the association between breast cancer survivorship and abnormal levels of anxiety (HADS-A≥11) and depression (HADS-D≥11). Models were further adjusted for age (<60, 60-69, 70-81 years), higher education degree (yes/no), and quintile of IMD. In an *a priori* defined sensitivity analysis (see protocol, Appendix 4 of this thesis), we used a lower cut-off (HADS-A≥8; HADS-D≥8) for caseness, as the standard cut-off ≥11 was found to have low sensitivity (50%, 95%CI: 27% to 73%) to detect cases of depression in this patient population [11].

In a post-hoc analysis, we estimated the effect of stage at diagnosis and chemotherapy treatment on the HRQoL and HADS scores of the breast cancer survivors compared to women in the comparison group. For this, we fitted domain-specific multivariate linear regression models using the scores as the dependent variable, and a three-level exposure variable as the independent variable (e.g. for chemotherapy: cancer survivors with prior chemotherapy, cancer survivors without prior chemotherapy, controls), adjusting for age, education and IMD quintile.

For all models, robust standard errors were computed to account for patient clustering by primary care practice, and regression coefficients (β) and 95% confidence intervals (95%CI) were reported.

Socio-demographic and clinical determinants of HRQoL, and anxiety and depressive symptoms in breast cancer survivors

We used linear regression models to assess the impact of socio-demographic, clinical and treatment factors on the generic and cancer-specific domains of HRQoL, and

HADS-subscales. Socio-demographic variables were age (<60, 60-69 and 70-81), practice postcode-linked IMD quintile, higher education degree (yes/no), and living arrangements (alone/not alone). Clinical variables were type of surgery (breast conserving/mastectomy), breast reconstruction (yes/no), stage at diagnosis (localised/regional or distant metastases), remission status (yes/no), menopausal status (pre/postmenopausal), time since diagnosis (<10/≥10 years), and treatment with chemotherapy (yes/no), radiotherapy (yes/no), hormone therapy (yes/no) and immunotherapy (yes/no). For age at diagnosis, education, stage at diagnosis, and exposure to chemotherapy, we fitted models adjusted for socio-demographic factors only (age, education, deprivation and country), as well as models adjusted for chemotherapy (yes/no) and stage at diagnosis (early/advanced). The regression coefficients (β) and respective 95%CIs were reported.

Ethical approvals

The study protocol was approved by the East of England - Cambridge South Research Ethics Committee (Ref: 17/EE/0403; Ethics1 in Appendix 4), the London School of Hygiene and Tropical Medicine Interventions Research Ethics Committee (Ref: 14417; Ethics2 in Appendix 4) and the Health Research Authority and Health and Care Research Wales (IRAS Project ID: 224561; Ethics3 in Appendix 4). Implicit patient consent was obtained when the patient posted the completed questionnaires.

Results

353 women with a history of breast cancer and 252 women with no history of cancer, from 40 primary care practices, participated in the study (Figure 7.1). Participants and non-participants were similarly distributed by country (England, Wales, Scotland, Northern Ireland) and deprivation, but participants in the control group tended to be older than those in the breast cancer survivor group (Supplementary Table 1 in Appendix 4). Mean age was 64.8 years among breast cancer survivors (standard deviation (SD) 9.0, range 34-81) and 65.5 years in the non-cancer comparison group (SD=9.4; range 36-81 years) (Table 7.1). Breast cancer survivors were on average 8.1 years post-diagnosis. In both groups, a quarter of the women had a higher education degree. 99% of the breast cancer survivors had surgery (35% mastectomy), 80% radiotherapy, 49% hormone therapy, and 41% chemotherapy. Most women had been diagnosed with localised (54.4%), or locally invasive disease (43.3%).

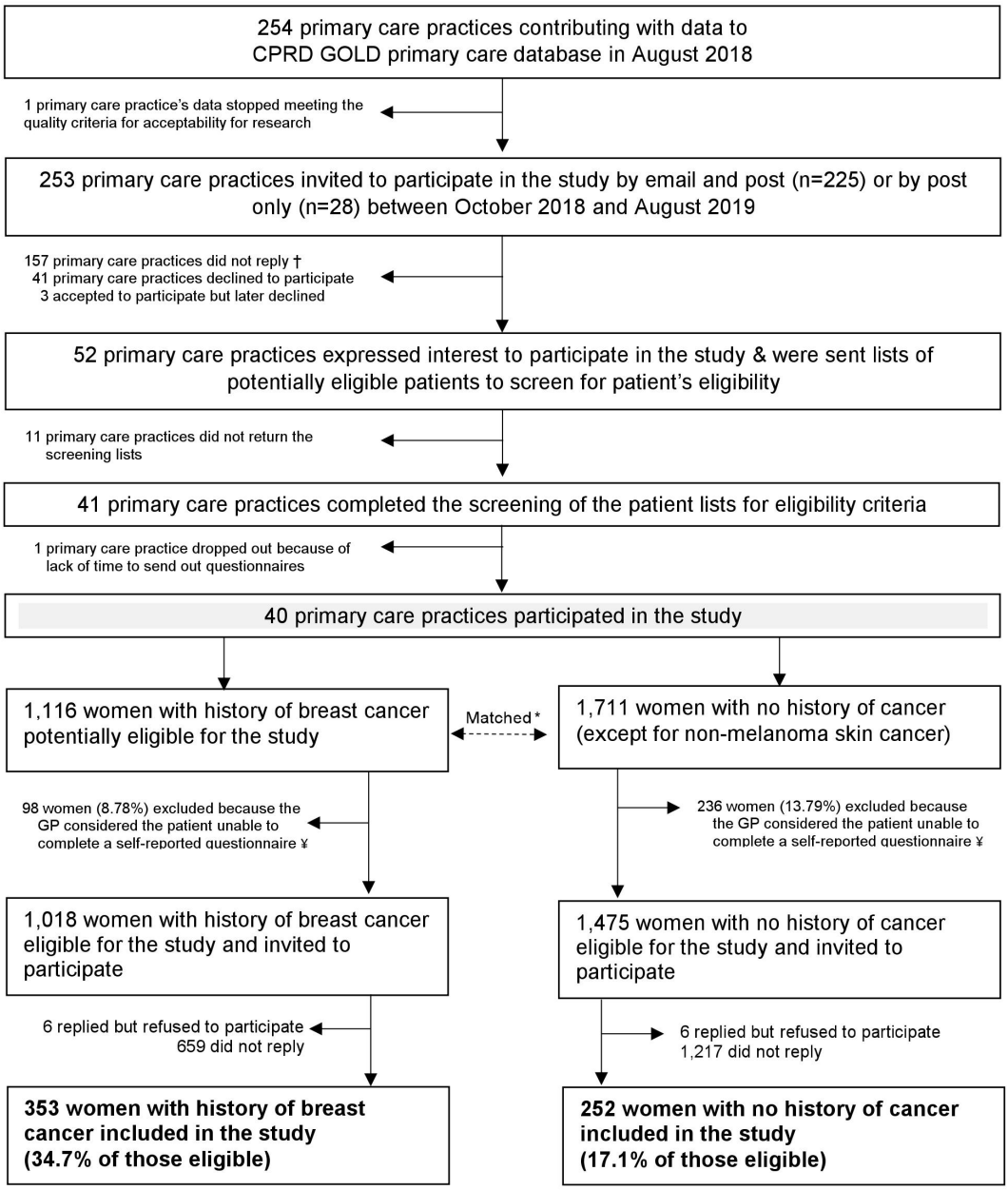

Figure 7.1 Flowchart of patient recruitment.

CPRD – Clinical Practice Research Datalink.

† 292 reminders were sent; all primary care practices that did not reply to the first invitation were sent at least one reminder.

* Women in the comparison group included a random sample of women with no history of cancer that had the same age distribution as the breast cancer survivors in the primary care practice (frequency matching). Initially matching occurred on a ratio of one case to one control. We later revised this to one case to two controls, to account for lower participation rate in the control group.

¥ Exclusion criteria included patients with dementia, terminally ill, or with another cancer diagnosis. GPs also excluded patients who were not able to complete questionnaires in English, or who had died or transferred out of their practice recently.

Table 7.1 Characteristics of the study participants.*

	No history of cancer (N=252)		Breast cancer survivors (N=353)	
	N	(%)	N	(%)
Age at completion of questionnaire				
34-59 years	71	28.2	100	28.3
60-69 years	80	31.7	130	36.8
70-81 years	101	40.1	123	34.8
Highest education level				
Up to GCSEs, O levels, or equivalent	78	31.0	127	36.0
A levels or equivalent	29	11.5	35	9.9
Trade or technical training	52	20.6	54	15.3
Undergraduate or post-graduate degree	66	26.2	92	26.1
Did not want to disclose	27	10.7	45	12.7
Ethnicity				
White	242	96.0	344	97.5
Asian / Asian British	6	2.4	1	0.3
Did not want to disclose	4	1.6	8	2.3
IMD deprivation quintile				
1 (most deprived)	53	21.0	71	20.1
2	36	14.3	54	15.3
3	26	10.3	53	15.0
4	98	38.9	140	39.7
5 (least deprived)	39	15.5	35	9.9
Living arrangements				
Not alone	185	73.4	270	76.5
Alone	63	25.0	76	21.5
Did not want to disclose	4	1.6	7	2.0
Country				
England	64	25.4	50	14.1
Northern Ireland	16	6.3	33	9.3
Scotland	74	29.4	114	32.3
Wales	98	38.9	156	44.2
Time since breast cancer diagnosis				
1-5 years	-	-	133	37.7
5-10 years	-	-	111	31.4
10-15 years	-	-	88	24.9
15-20 years	-	-	16	4.5
>20 years	-	-	5	1.4
Breast cancer treatments				
Surgery	-	-	348	98.6
Lumpectomy	-	-	225	63.7
Mastectomy	-	-	122	34.6
Reconstruction	-	-	42	11.9
Radiotherapy	-	-	282	79.9
Chemotherapy	-	-	143	40.5
Hormone therapy	-	-	174	49.3
Immunotherapy	-	-	6	1.7

(Continued)

Table 7.1 Continued

Stage at diagnosis				
Localised to the breast	-	-	192	54.4
Regional metastasis	-	-	153	43.3
Distant metastasis	-	-	2	0.6
Unknown	-	-	6	1.7
Time since last treatment for breast cancer				
Undergoing treatment	-	-	3	0.8
<12 months	-	-	2	0.6
Between 1 and 5 years	-	-	123	34.8
More than 5 years	-	-	217	61.5
Doesn't know	-	-	8	2.3
Disease status at questionnaire response				
In remission	-	-	319	90.4
Active disease	-	-	7	2.0
Doesn't know			27	7.6
Menopausal status				
Menopausal at breast cancer diagnosis	-	-	244	69.1
Became menopausal during treatments for breast cancer	-	-	71	20.1
Not menopausal	-	-	31	8.8
Unknown	-	-	7	2.0

* Information on age at questionnaire completion, time since breast cancer diagnosis, practice postcode level of deprivation and country were obtained from the EHRs of the participating patients. Information on education, ethnicity, living arrangements, treatments for breast cancer, stage at diagnosis, time since last treatment for breast cancer, and disease and menopausal status, were collected directly from the patients using a self-reported questionnaire.

HRQoL, anxiety and depressive symptoms in breast cancer survivors and women with no history of cancer

Table 7.2 shows the mean scores for all HRQoL domains. Fatigue and sexual dysfunction were the domains for which women in both groups reported poorer HRQoL (i.e. higher scores); breast cancer survivors also had cognitive dysfunction amongst the highest scoring domains. The correlation coefficients among HRQoL domains are shown in Supplementary Table 2 in Appendix 4.

Compared to women with no history of cancer, breast cancer survivors had poorer HRQoL for cognitive problems ($p<0.01$), sexual function ($p=0.02$) and fatigue ($p<0.01$) (Table 7.3); the differences for the other domains were compatible with chance variation. Breast cancer survivors had non-significantly higher odds of probable anxiety (HADS-anxiety score ≥11) than controls (adjusted OR (aOR)=1.40, 0.93-2.10), however there was strong evidence of a difference when a more sensitive threshold (score ≥8, "borderline/probable anxiety") was used, (aOR=1.47, 1.15-1.87). There were no differences in odds of probable depression (aOR=1.08, 0.78-1.50) (Table 7.4).

The worse HRQoL and mental health outcomes among breast cancer survivors appeared to be driven by higher risk in those treated with chemotherapy and/or diagnosed with more advanced disease (Table 7.3). Breast cancer survivors treated with chemotherapy reported significantly more negative feelings, cognitive problems, sexual dysfunction, fatigue, and anxiety than women with no history of cancer; in contrast, differences between breast cancer survivors with no chemotherapy exposure and cancer-free controls were smaller and (except for fatigue) non-significant. Similarly, breast cancer survivors diagnosed with more advanced disease had significantly more negative feelings, cognitive problems, sexual dysfunction, and fatigue than women with no history of cancer, while no significant differences were seen between survivors of localised cancers and cancer-free controls.

Table 7.2 Mean scores for HRQoL domains, anxiety and depressive symptoms, in each group of women.

	No history of cancer (N=252)						Breast cancer survivors (N=353)					
	No. (Imputed*)	Mean score	SD	Range	% Floor	% Ceiling	No. (Imputed*)	Mean score	SD	Range	% Floor	% Ceiling
Quality of Life in Adult Cancer Survivors Scale§												
Generic domains												
Negative feelings	251 (7)	11.0	4.9	4 - 26	3.7	0.0	343 (22)	11.6	5.3	4 - 28	4.4	0.3
Positive feelings§	250 (5)	21.1	5.4	7 - 28	0.0	9.9	344 (18)	20.8	5.7	7 - 28	0.0	10.8
Cognitive problems	251 (4)	10.5	4.7	4 - 28	6.2	0.8	347 (19)	11.7	5.3	4 - 27	4.9	0.0
Physical pain	249 (4)	11.1	6.5	4 - 28	12.0	0.8	344 (19)	11.2	6.2	4 - 28	9.6	1.5
Sexual interest/function	227 (8)	12.0	6.4	4 - 28	13.2	2.7	327 (27)	13.7	7.2	4 - 28	13.2	4.9
Energy/Fatigue	251 (1)	12.3	4.8	4 - 24	4.1	0.0	347 (11)	13.3	5.0	4 - 25	3.8	0.0
Social avoidance	251 (21)	9.8	5.6	4 - 28	17.3	0.4	344 (45)	9.9	5.9	4 - 28	25.0	0.6
Summary ‡	226 (0)	75.7	27.7	28 - 157	-	-	315 (0)	80.4	29.1	29 - 162	-	-
Cancer-specific domains												
Financial problems	-	-	-	-	-	-	348 (9)	7.2	5.1	4 - 28	46.6	0.6
Distress related to family	-	-	-	-	-	-	349 (4)	12.3	7.5	4 - 28	2.6	7.8
Appearance concerns	-	-	-	-	-	-	347 (12)	9.3	5.8	4 - 28	20.1	4.9
Distress over recurrence	-	-	-	-	-	-	348 (8)	13.9	6.8	4 - 28	27.7	0.9
Summary	-	-	-	-	-	-	347 (0)	42.5	19.5	4 - 28	7.2	2.9
Benefits of cancer§	-	-	-	-	-	-	345 (7)	17.0	6.6	4 - 28	-	-
Hospital Anxiety and Depression Scale												
Anxiety	248 (7)	6.4	4.1	0 - 20	5.0	0.4	348 (14)	6.8	4.6	0 - 20	8.1	0.3
Depression	249 (4)	3.6	3.3	0 - 17	14.5	0.0	349 (3)	3.6	3.6	0 - 19	17.8	0.0

SD: standard deviation.

* Number of patient with score imputed. When one item was missing out of the four items in the domain, we imputed this item with the arithmetic mean of the values in the other three items. Mean domain score was not calculated for patients that did not reply to two or more items in a domain.

§ Higher scores represent poorer HRQoL, except for the domains 'positive feelings' and 'benefits of cancer'.

‡ Calculated as the sum of all domain scores except for positive feelings.

Table 7.3 Comparison of patient-reported outcomes between breast cancer survivors and controls, by chemotherapy and stage at diagnosis.

					Breast cancer survivors by chemotherapy						**Breast cancer survivors by stage at diagnosis**						
	Controls	**All breast cancer survivors**			**No chemotherapy**			**Chemotherapy**			**Localised**			**Advanced**			
		β*	**lb**	**ub**	**β***	**lb**	**ub**	**β***	**lb**	**ub**	**β***	**lb**	**ub**	**β***	**lb**	**ub**
Generic domains																	
Negative feelings	Ref.	0.7	-0.1 -	1.4	0.2	-0.7 -	1.0	**1.5**	**0.2 -**	**2.7**	0.2	-0.6 -	1.1	**1.3**	**0.2 -**	**2.5**
Positive feelings	Ref.	-0.4	-1.3 -	0.5	-0.2	-1.2 -	0.8	-0.7	-1.9 -	0.6	-0.3	-1.3 -	0.6	-0.5	-1.8 -	0.8
Cognitive problems	Ref.	**1.4**	**0.4 -**	**2.3**	0.6	-0.3 -	1.5	**2.6**	**1.3 -**	**3.8**	0.9	-0.1 -	1.9	**2.0**	**0.9 -**	**3.2**
Pain	Ref.	0.0	-1.1 -	1.5	-0.2	-1.6 -	1.2	0.9	-0.8 -	2.6	-0.6	-2.0 -	0.8	1.2	-0.4 -	2.8
Sexual function	Ref.	**1.7**	**0.4 -**	**3.1**	1.2	0.0 -	2.4	**2.5**	**0.7 -**	**4.4**	0.9	-0.5 -	2.2	**2.9**	**1.3 -**	**4.6**
Energy/Fatigue	Ref.	**1.3**	**0.4 -**	**2.2**	**1.2**	**0.2 -**	**2.1**	**1.5**	**0.3 -**	**2.7**	1.0	0.0 -	2.0	**1.7**	**0.6 -**	**2.9**
Avoidance	Ref.	0.1	-1.0 -	1.2	-0.3	-1.5 -	0.8	0.8	-0.6 -	2.2	-0.2	-1.2 -	0.8	0.6	-0.9 -	2.2
Summary	Ref.	5.9	0.0 -	11.9	2.2	-3.7 -	8.2	**11.2**	**3.8 -**	**18.6**	1.8	-4.1 -	7.7	**11.1**	**3.8 -**	**18.3**
HADS																	
Anxiety	Ref.	0.5	-0.1 -	1.0	0.1	-0.6 -	0.8	**1.1**	**0.2 -**	**2.0**	0.4	-0.3 -	1.0	0.8	-0.2 -	1.7
Depression	Ref.	0.1	-0.5 -	0.7	0.1	-0.6 -	0.7	0.2	-0.7 -	1.0	0.0	-0.7 -	0.7	0.3	-0.5 -	1.0

* Adjusted for age, education and deprivation.
HADS: Hospital Anxiety and Depression Scale; lb – lower bound of the 95% confidence interval; ub – upper bound of the 95% confidence interval.
Bold is used to denote statistical significance.

Table 7.4 Unadjusted and adjusted associations between breast cancer survivorship and anxiety and depression.

	Anxiety						Depression					
	Cut-off ≥11 for caseness			Cut-off ≥8 for caseness			Cut-off ≥11 for caseness			Cut-off ≥8 for caseness		
	No. of cases (%)	Odds ratio	95% CI	No. of cases (%)	Odds ratio	95% CI	No. of cases (%)	Odds ratio	95% CI	No. of cases (%)	Odds ratio	95% CI
Univariate analysis												
No cancer	43 (17.3)	Ref		87 (35.1)	Ref		9 (3.6)	Ref		38 (15.3)	Ref	
Breast cancer	79 (22.7)	1.36	0.95 - 1.96	153 (44.0)	**1.45**	**1.14 - 1.86**	17 (4.87)	1.37	0.69 - 2.70	54 (15.5)	1.02	0.72 - 1.42
Multivariate analysis*												
No cancer	39 (17.7)	Ref		79 (35.8)	Ref		8 (3.6)	Ref		33 (14.9)	Ref	
Breast cancer	69 (22.6)	1.40	0.93 - 2.10	137 (44.9)	**1.47**	**1.15 - 1.87**	12 (3.9)	1.18	0.52 - 2.68	46 (15.0)	1.08	0.78 - 1.50

* Adjusted for age at questionnaire completion (<60 years; 60-69 years; 70+ years), education (university degree vs. no university degree) and quintile of practice-level postcode linked deprivation. Bold is used to denote statistical significance.

Determinants of HRQoL, anxiety and depressive symptoms in breast cancer survivors

Younger age, more advanced disease at diagnosis, receipt of chemotherapy, not being menopausal were all strongly associated with poorer HRQoL for both generic and cancer-specific domains (Table 7.5). In addition, women with no higher education, and who did not live alone had poorer HRQoL for the cancer-specific domains. Symptoms of anxiety were associated with younger age, receipt of chemotherapy, and not being menopausal (Table 7.6). For depression, only living in a more affluent area was associated with more symptoms.

Figures 7.1 and 7.2 show the variation of the summary scores, as well as individual HRQoL domain scores, by age, education, chemotherapy and stage at diagnosis. After adjusting for socio-demographic and clinical variables, older women reported significantly better HRQoL than women in the youngest age group (34-60 years) for all domains except positive feelings, pain, fatigue, benefits of cancer, and family-related distress (Table 7.7). Women with higher education had better HRQoL for several domains, but only pain, family-related distress and distress with recurrence were significantly lower after adjusting for confounders (Table 7.8). Women treated with chemotherapy had poorer HRQoL for a number of domains, but significant differences were only observed for cognitive problems, appearance concerns, and distress with recurrence after adjusting for confounders (Table 7.9). For stage, in adjusted models, significantly worse HRQoL in women with more advanced disease, compared to those diagnosed with localised tumours, was found for cognitive problems, pain, sexual function, financial problems, distress with appearance and recurrence (Table 7.10). Anxiety and depression scores did not vary by exposure to chemotherapy, stage at diagnosis, or education in adjusted models. However, women aged 70-81 years had significantly less anxiety and depressive symptoms, compared to women aged 34-59.

Table 7.5 HRQoL in breast cancer survivors by socio-demographic, clinical and treatment characteristics (N=353).

	Generic domains: summary score					Cancer-specific domains: summary score				
	No.	**Mean**	**SD**	**β**	**95%CI**	**No.**	**Mean**	**SD**	**β**	**95%CI**
Age group										
34-59 years	92	86.4	30.7	Ref.		99	47.4	21.3	Ref.	
60-69 years	118	81.7	28.7	-4.7	-13.4 to 4.0	129	43.1	18.2	-4.3	-10.3 to 1.7
70-81 years	105	73.6	27.0	**-12.8**	**-22.9 to -2.6**	119	37.9	18.3	**-9.5**	**-14.8 to -4.1**
IMD quintile										
1 (most deprived)	66	73.6	26.0	Ref.		70	41.3	18.2	Ref.	
2	50	81.5	30.7	7.9	-0.3 to 16.2	54	42.1	18.8	0.8	-5.8 to 7.4
3	48	79.9	23.5	6.3	-2.8 to 15.4	52	42.8	19.5	1.5	-4.1 to 7.1
4	120	82.6	30.1	9.0	-0.2 to 18.2	137	42.1	19.3	0.8	-3.6 to 5.3
5 (least deprived)	31	85.1	35.4	11.6	-1.9 to 25.0	34	47.2	23.9	5.9	-2.9 to 14.8
Higher education										
No	198	82.9	30.3	Ref.		214	44.4	20.6	Ref.	
Yes	85	76.4	26.2	-6.5	-14.8 to 1.7	91	38.5	16.5	**-5.9**	**-10.5 to -1.3**
Living arrangements										
Not alone	250	81.6	29.1	Ref.		267	44.0	19.4	Ref.	
Alone	59	75.1	28.3	-6.5	-15.5 to 2.5	73	38.6	19.5	**-5.4**	**-9.7 to -1.0**
Type of surgery										
Lumpectomy	188	80.6	28.1	Ref.		207	41.5	18.1	Ref.	
Mastectomy	112	81.5	31.6	0.94	-6.4 to 8.2	121	45.4	21.3	3.9	-1.1 to 8.9
Reconstruction										
No	277	79.3	28.8	Ref.		305	41.8	18.9	Ref.	
Yes	38	87.9	30.6	8.6	-1.0 to 18.3	42	47.8	22.8	6.0	-0.02 to 12.1
Radiotherapy										
No	59	74.8	31.3	Ref.		68	40.0	17.1	Ref.	
Yes	256	81.6	28.5	6.8	-0.4 to 14.0	279	43.1	20.0	3.1	-0.7 to 7.0
Chemotherapy										
No	183	76.6	28.4	Ref.		206	38.1	17.1	Ref.	
Yes	132	85.5	29.4	**8.9**	**3.9 to 13.9**	141	49.0	20.9	**11.0**	**7.4 to 14.5**
Hormone therapy										
No	160	79.3	28.5	Ref.		177	41.4	17.8	Ref.	
Yes	155	81.5	29.8	2.1	-4.1 to 8.4	170	43.7	21.0	2.3	-1.6 to 6.3
Immune therapy										
No	309	80.3	29.1	Ref.		341	42.3	19.3	Ref.	
Yes	6	82.2	33.8	1.8	-22.4 to 26.0	6	54.5	26.2	12.2	-7.8 to 32.2
Stage at diagnosis										
Early	169	76.7	27.8	Ref.		187	39.8	17.5	Ref.	
Advanced	142	85.3	30.1	**8.6**	**2.4 to 14.9**	154	46.5	21.2	**6.7**	**2.0 to 11.4**
Status of disease										
Remission	287	78.8	28.7	Ref.		314	41.1	18.9	Ref.	
Active disease	3	79.3	34.3	0.5	-34.1 to 35.1	6	52.2	21.5	11.0	-8.3 to 30.3
Menopausal status										
Menopausal	216	77.7	29.1	Ref.		239	40.8	18.6	Ref.	
Not menopausal	99	86.2	28.4	**8.5**	**2.1 to 14.9**	108	46.4	20.8	**5.6**	**1.2 to 10.0**
Time since diagnosis										
≤10 years	215	80.0	28.9	Ref.		242	42.0	19.9	Ref.	
>10 years	100	81.1	29.8	1.1	-6.1 to 8.2	105	43.7	18.5	1.6	-3.6 to 6.9

No.: number; SD: standard deviation.
Bold text is used to denote that the differences between the two groups were supported by some statistical evidence.

Table 7.6 Anxiety and depressive symptoms in breast cancer survivors by socio-demographic, clinical and treatment characteristics (N=353).

	Hospital Anxiety and Depression Scale									
	Anxiety					Depression				
	No.	Mean	SD	β	95%CI	No.	Mean	SD	β	95%CI
Age group										
34-59 years	100	7.9	4.4	Ref.		100	4.1	3.8	Ref.	
60-69 years	129	6.7	4.7	-1.1	-2.5 to 0.18	129	3.6	3.4	-0.5	-1.5 to 0.4
70-81 years	119	6.0	4.5	**-1.8**	**-3.1 to -0.5**	120	3.3	3.6	-0.8	-2.1 to 0.4
IMD quintile										
1 (more deprived)	71	7.2	4.6	Ref.		71	2.9	3.4	Ref.	
2	52	6.3	4.3	-0.8	-2.5 to 0.8	52	3.3	3.1	0.3	-0.4 to 1.0
3	52	5.7	4.0	**-1.5**	**-2.7 to -0.3**	52	3.3	2.5	0.4	-0.3 to 1.0
4	138	7.1	4.7	-0.02	-1.2 to 1.2	139	4.1	3.8	**1.2**	**0.3 to 2.1**
5 (least deprived)	35	7.2	5.0	0.06	-1.6 to 1.8	35	4.3	4.8	**1.4**	**0.1 to 2.6**
Education										
No graduate degree	214	6.8	4.7	Ref.		214	3.9	3.7	Ref.	
Graduate degree	91	7.2	4.0	0.4	-1.0 to 1.8	92	3.0	3.0	-0.8	-1.7 to 0.02
Living arrangements										
Not alone	268	7.0	4.6	Ref.		268	3.7	3.6	Ref.	
Alone	73	6.2	4.6	-0.8	-2.0 to 0.4	74	3.4	3.5	-0.3	-1.3 to 0.8
Type of surgery										
Lumpectomy	209	6.6	4.4	Ref.		210	3.5	3.4	Ref.	
Mastectomy	119	7.3	4.7	0.7	-0.4 to 1.8	119	3.9	3.8	0.4	-0.6 to 1.3
Breast reconstruction										
No	306	6.7	4.5	Ref.		307	3.6	3.6	Ref.	
Yes	41	7.8	4.8	1.1	-0.2 to 2.4	42	3.6	3.5	0.01	-1.1 to 1.1
Radiotherapy										
No	67	6.8	4.6	Ref.		68	3.7	3.6	Ref.	
Yes	281	6.8	4.6	0.0	-1.1 to 1.1	281	3.6	3.6	-0.1	-1.0 to 0.8
Chemotherapy										
No	205	6.4	4.7	Ref.		206	3.6	3.6	Ref.	
Yes	143	7.5	4.3	**1.1**	**0.2 to 2.0**	143	3.7	3.5	0.2	-0.6 to 0.9
Hormone therapy										
No	175	6.8	4.7	Ref.		176	3.6	3.6	Ref.	
Yes	173	6.8	4.4	0.0	-1.3 to 1.2	173	3.7	3.6	0.04	-0.8 to 0.9
Immune therapy										
No	342	6.8	4.6	Ref.		343	3.6	3.6	Ref.	
Yes	6	7.8	5.2	1.0	-2.9 to 5.0	6	3.5	4.0	-0.1	-3.1 to 2.9
Stage at diagnosis										
Early	187	6.6	4.5	Ref.		188	3.4	3.3	Ref.	
Advanced	155	7.2	4.7	0.5	-0.7 to 1.8	155	3.9	3.8	0.5	-0.4 to 1.4
Current status of disease										
Remission	315	6.5	4.5	Ref.		315	3.3	3.3	Ref.	
Active disease	7	10.7	7.0	4.2	-2.3 to 10.7	7	6.1	4.8	2.9	-1.2 to 6.9
Menopausal status										
Menopausal	241	6.3	4.5	Ref.		242	3.5	3.5	Ref.	
Not menopausal	107	8.0	4.5	**1.7**	**0.5 to 2.8**	107	3.9	3.7	0.4	-0.6 to 1.5
Time since diagnosis										
<10 years	242	6.7	4.6	Ref.		243	3.6	3.6	Ref.	
≥10 years	106	7.1	4.5	0.4	-0.8 to 1.6	106	3.8	3.5	0.2	-0.7 to 1.1

No.: number; SD: standard deviation. Bold text is used to denote that the differences between the two groups were supported by some statistical evidence.

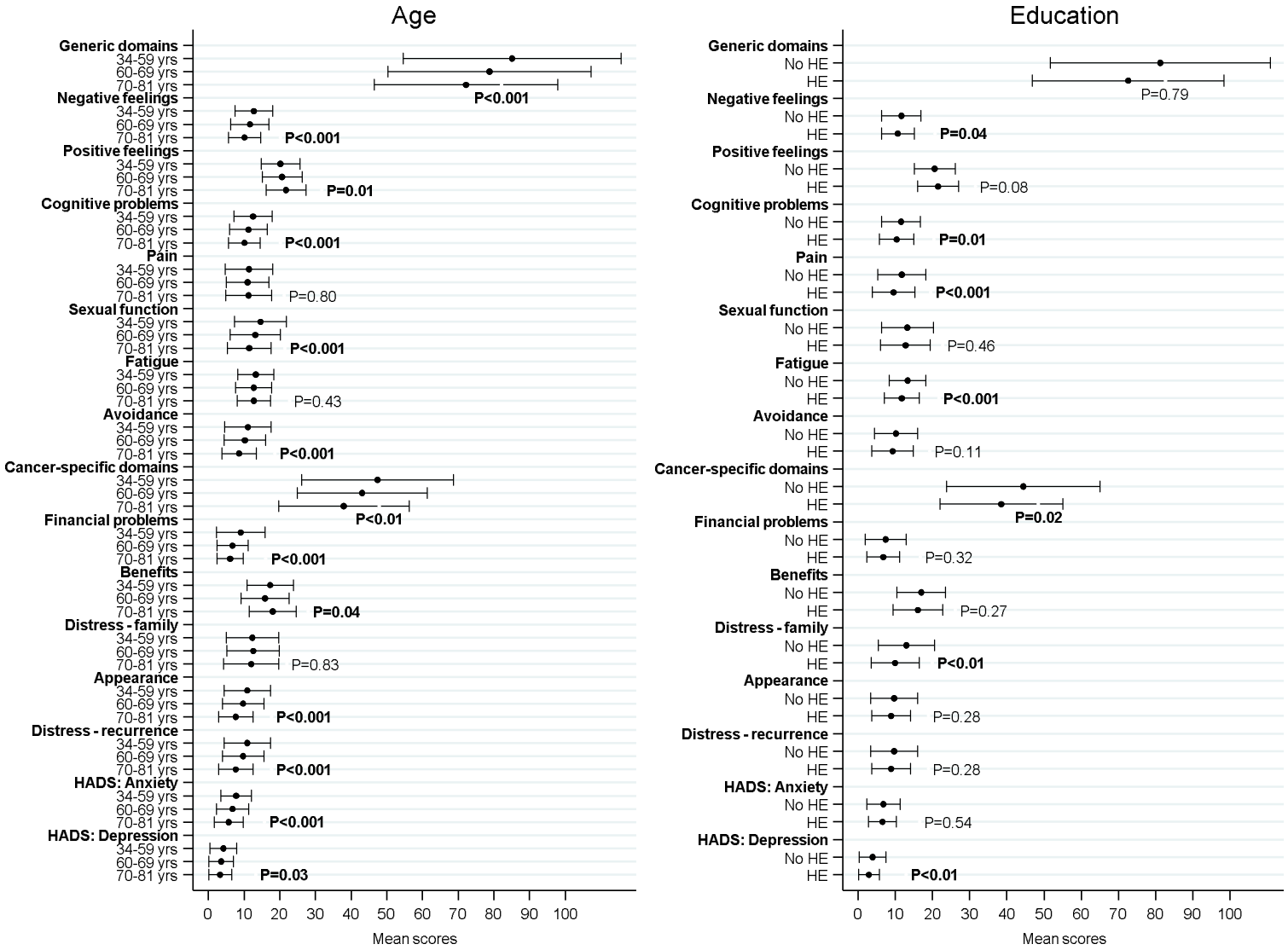

Figure 7.2 Mean scores of HRQoL and anxiety and depression, by age at questionnaire response and education (N=353).

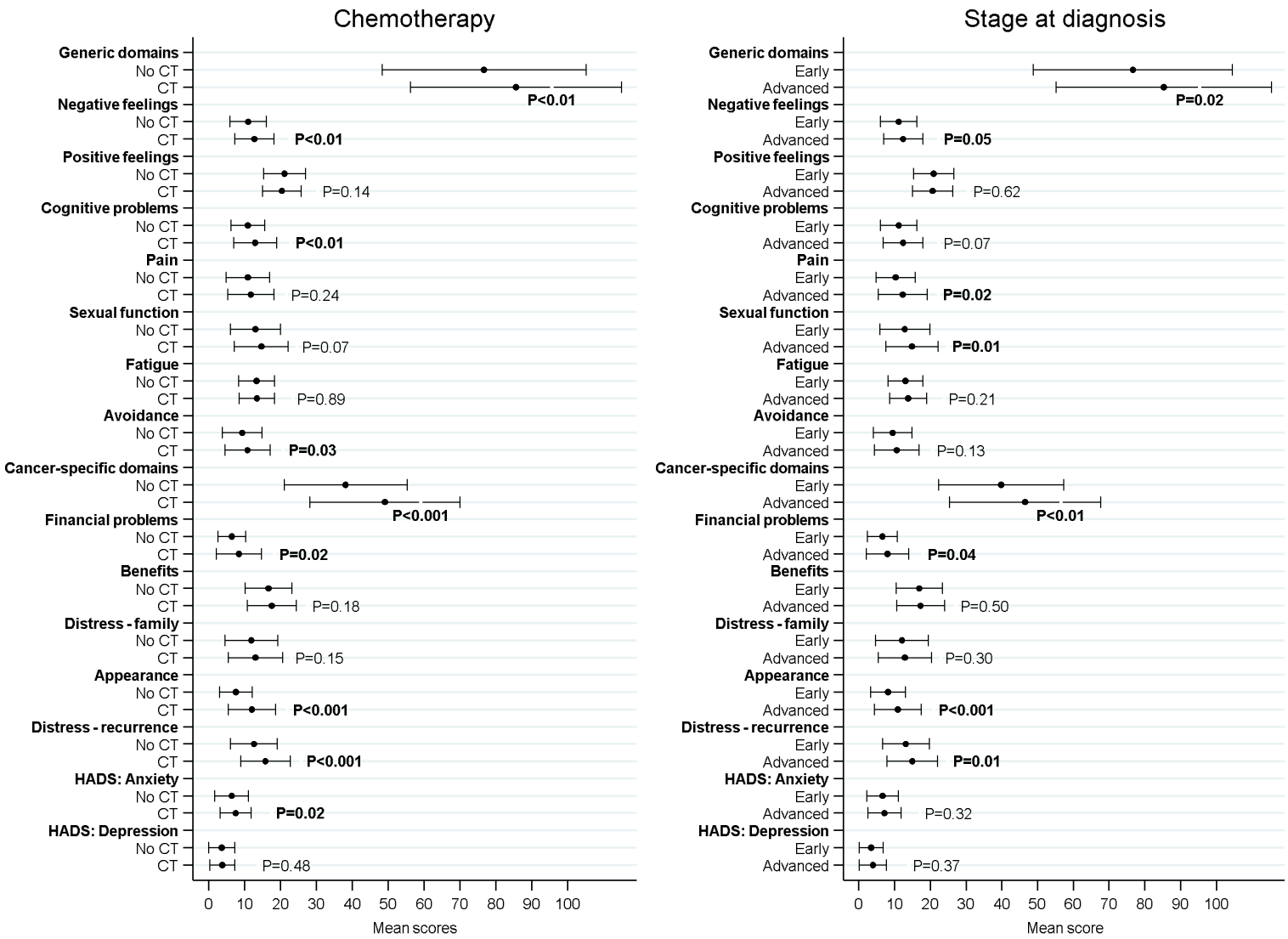

Figure 7.3 Mean scores of HRQoL and anxiety and depression, by exposure to chemotherapy and stage at diagnosis in breast cancer survivors (N=353).

Table 7.7 Associations between age and quality of life, anxiety and depression in breast cancer survivors (N=353).

	Age														
	Unadjusted association					Model 1: adjusted for socio-demographic variables[1]					Model 2: model 1 + stage and chemotherapy				
	<60 years	60-69 years		70-81 years		<60 years	60-69 years		70-81 years		<60 years	60-69 years		70-81 years	
		β	P	β	P		β	P	β	P		β	P	β	P
Quality of Life in Adult Cancer Survivors Scale															
Generic domains															
Negative feelings	Ref.	-1.0	0.16	-2.1	**0.03**	Ref.	-1.4	0.07	-2.4	**0.01**	Ref.	-1.3	0.10	-2.2	**0.03**
Positive feelings	Ref.	0.3	0.57	1.3	0.12	Ref.	0.6	0.36	1.8	**0.04**	Ref.	0.4	0.51	1.6	0.08
Cognitive problems	Ref.	-1.1	0.13	-2.7	**<0.001**	Ref.	-1.6	**0.04**	-2.7	**0.001**	Ref.	-1.3	0.11	-2.2	**0.01**
Pain	Ref.	0.1	0.87	-0.5	0.62	Ref.	-0.1	0.93	-0.7	0.47	Ref.	0.1	0.87	-0.6	0.58
Sexual function	Ref.	-2.1	0.08	-3.3	**0.002**	Ref.	-3.5	**0.01**	-4.5	**<0.001**	Ref.	-3.3	**0.01**	-4.5	**<0.001**
Energy/Fatigue	Ref.	-0.3	0.61	-0.3	0.66	Ref.	-0.8	0.28	-0.7	0.38	Ref.	-0.7	0.32	-0.8	0.35
Avoidance	Ref.	-0.6	0.47	-2.3	**0.02**	Ref.	-1.1	0.21	-2.4	**0.02**	Ref.	-1.0	0.27	-2.3	**0.04**
Summary score	Ref.	-4.7	0.28	-12.8	**0.01**	Ref.	-9.2	**0.05**	-15.8	**0.002**	Ref.	-8.2	0.08	-14.8	**0.01**
Cancer specific domains															
Financial problems	Ref.	-2.3	**0.01**	-3.0	**<0.001**	Ref.	-2.2	**0.03**	-2.8	**<0.001**	Ref.	-2.1	**0.04**	-2.6	**<0.001**
Benefits of cancer	Ref.	-1.5	0.15	0.7	0.52	Ref.	-0.9	0.37	0.5	0.63	Ref.	-0.8	0.41	0.5	0.68
Distress-family	Ref.	0.3	0.80	-0.3	0.73	Ref.	0.5	0.57	-1.2	0.11	Ref.	0.5	0.57	-1.0	0.21
Appearance	Ref.	-1.2	0.14	-3.2	**<0.001**	Ref.	-1.6	0.06	-4.1	**<0.001**	Ref.	-1.0	0.26	-3.0	**0.001**
Distress-recurrence	Ref.	-1.3	0.22	-3.0	**0.002**	Ref.	-1.5	0.15	-3.4	**0.002**	Ref.	-1.1	0.32	-2.5	**0.02**
Summary score	Ref.	-4.3	0.15	-9.5	**<0.001**	Ref.	-4.8	0.12	-11.4	**<0.001**	Ref.	-3.6	0.26	-9.1	**0.001**
Hospital Anxiety and Depression Scale															
Anxiety	Ref.	-1.1	0.09	-1.8	**0.01**	Ref.	-1.0	0.14	-1.8	**0.01**	Ref.	-0.9	0.20	-1.7	**0.03**
Depression	Ref.	-0.5	0.27	-0.8	0.19	Ref.	-0.6	0.21	-1.3	**0.04**	Ref.	-0.6	0.28	-1.3	**0.04**

[1] Adjusted for education (university degree vs. no degree), practice postcode quintile level of the index of multiple deprivation (IMD), and country (Scotland, Wales, Northern Ireland, England).

Table 7.8 Associations between education and quality of life, anxiety and depression in breast cancer survivors (N=353).

	Education								
	Unadjusted association			Model 1: adjusted for socio-demographic variables[1]			Model 2: model 1 + stage and chemotherapy		
	No higher education	Higher education		No higher education	Higher education		No higher education	Higher education	
		β	P-value		β	P-value		β	P-value
Quality of Life in Adult Cancer Survivors Scale									
Generic domains									
Negative feelings	Ref.	-0.7	0.32	Ref.	-0.8	0.25	Ref.	-0.7	0.27
Positive feelings	Ref.	0.4	0.62	Ref.	0.4	0.63	Ref.	0.3	0.73
Cognitive problems	Ref.	-0.7	0.22	Ref.	-0.9	0.18	Ref.	-1.0	0.13
Pain	Ref.	-1.8	**0.01**	Ref.	-1.9	**0.01**	Ref.	-2.0	**0.01**
Sexual function	Ref.	-1.2	0.25	Ref.	-1.4	0.16	Ref.	-1.4	0.16
Energy/Fatigue	Ref.	-1.2	0.08	Ref.	-1.3	0.07	Ref.	-1.3	0.06
Avoidance	Ref.	-0.4	0.53	Ref.	-0.5	0.47	Ref.	-0.4	0.52
Summary score	Ref.	-6.5	0.12	Ref.	-7.3	0.08	Ref.	-7.4	0.08
Cancer-specific domains									
Financial problems	Ref.	-0.6	0.32	Ref.	-0.7	0.26	Ref.	-0.8	0.23
Benefits of cancer	Ref.	-0.9	0.27	Ref.	-1.1	0.20	Ref.	-1.5	0.10
Distress-family	Ref.	-3.0	**<0.001**	Ref.	-3.0	**<0.001**	Ref.	-3.0	**<0.001**
Appearance	Ref.	-0.8	0.32	Ref.	-1.1	0.18	Ref.	-1.2	0.12
Distress-recurrence	Ref.	-1.4	0.07	Ref.	-1.7	**0.04**	Ref.	-1.9	**0.02**
Summary score	Ref.	-5.9	**0.01**	Ref.	-6.5	**0.01**	Ref.	-7.0	**0.004**
Hospital Anxiety and Depression Scale									
Anxiety	Ref.	0.4	0.57	Ref.	0.3	0.69	Ref.	0.3	0.68
Depression	Ref.	-0.8	0.06	Ref.	-0.8	0.10	Ref.	-0.7	0.15

[1] Adjusted for age (<60, 60-69, 70-81 years), practice postcode quintile level of the index of multiple deprivation (IMD), and country (Scotland, Wales, Northern Ireland, England).

Table 7.9 Associations between exposure to chemotherapy and quality of life, anxiety and depression in breast cancer survivors (N=353).

	Chemotherapy exposure								
	Unadjusted association			Model 1: adjusted for socio-demographic variables[1]			Model 2: model 1 + stage at diagnosis		
	No ChT	ChT		No ChT	ChT		No ChT	ChT	
		β	P-value		β	P-value		β	P-value
Quality of Life in Adult Cancer Survivors Scale									
Generic domains									
Negative feelings	Ref.	1.7	**0.004**	Ref.	1.3	**0.05**	Ref.	1.0	0.15
Positive feelings	Ref.	-0.7	0.21	Ref.	-0.4	0.49	Ref.	-0.6	0.39
Cognitive problems	Ref.	2.0	**<0.001**	Ref.	1.9	**0.003**	Ref.	1.6	**0.03**
Pain	Ref.	0.8	0.22	Ref.	0.9	0.29	Ref.	-0.1	0.90
Sexual function	Ref.	1.6	**0.01**	Ref.	1.1	0.18	Ref.	0.1	0.91
Energy/Fatigue	Ref.	0.1	0.77	Ref.	0.3	0.53	Ref.	-0.2	0.66
Avoidance	Ref.	1.5	**0.01**	Ref.	1.0	0.09	Ref.	0.8	0.24
Summary score	Ref.	8.9	**<0.001**	Ref.	8.0	**0.02**	Ref.	4.4	0.25
Cancer specific domains									
Financial problems	Ref.	2.0	**0.003**	Ref.	1.4	0.06	Ref.	1.1	0.20
Benefits of cancer	Ref.	0.9	0.24	Ref.	0.5	0.58	Ref.	0.0	0.98
Distress-family	Ref.	1.2	**0.05**	Ref.	1.4	0.06	Ref.	1.0	0.20
Appearance	Ref.	4.5	**<0.001**	Ref.	4.2	**<0.001**	Ref.	3.6	**<0.001**
Distress-recurrence	Ref.	3.2	**<0.001**	Ref.	3.2	**<0.001**	Ref.	2.9	**<0.001**
Summary score	Ref.	11.0	**<0.001**	Ref.	10.1	**<0.001**	Ref.	8.5	**<0.001**
Hospital Anxiety and Depression Scale									
Anxiety	Ref.	1.1	**0.02**	Ref.	0.9	0.10	Ref.	0.8	0.14
Depression	Ref.	0.2	0.66	Ref.	0.0	0.92	Ref.	-0.2	0.63

[1] Adjusted for age (34-59, 60-69, 70-81 years), education (graduate degree: yes/no), practice postcode quintile level of the index of multiple deprivation (IMD), and country (Scotland, Wales, Northern Ireland, England). ChT = Chemotherapy.

Table 7.10 Associations between stage of at diagnosis and quality of life, anxiety and depression in breast cancer survivors (N=353).

	Stage at diagnosis								
	Unadjusted association			Model 1: adjusted for socio-demographic variables[1]			Model 2: model 1 + chemotherapy		
	Early stage	Regional or distant metastases		Early stage	Regional or distant metastases		Early stage	Regional or distant metastases	
		β	P-value		β	P-value		β	P-value
Quality of Life in Adult Cancer Survivors Scale									
Generic domains									
Negative feelings	Ref.	1.2	0.08	Ref.	1.2	0.07	Ref.	1.2	0.07
Positive feelings	Ref.	-0.3	0.70	Ref.	-0.1	0.85	Ref.	-0.1	0.85
Cognitive problems	Ref.	1.2	**0.01**	Ref.	1.2	**0.02**	Ref.	1.2	**0.02**
Pain	Ref.	2.0	**0.003**	Ref.	1.9	**0.01**	Ref.	1.9	**0.01**
Sexual function	Ref.	2.0	**0.01**	Ref.	2.0	**0.01**	Ref.	2.0	**0.01**
Energy/Fatigue	Ref.	0.8	0.16	Ref.	0.9	0.13	Ref.	0.9	0.13
Avoidance	Ref.	1.1	0.09	Ref.	1.0	0.12	Ref.	1.0	0.12
Summary score	Ref.	8.6	**0.01**	Ref.	9.7	**0.002**	Ref.	9.7	**0.002**
Cancer specific domains									
Financial problems	Ref.	1.4	**0.01**	Ref.	1.0	**0.04**	Ref.	1.0	**0.04**
Benefits of cancer	Ref.	0.4	0.56	Ref.	0.4	0.48	Ref.	0.4	0.48
Distress-family	Ref.	0.8	0.38	Ref.	1.2	0.24	Ref.	1.2	0.24
Appearance	Ref.	2.7	**<0.001**	Ref.	2.9	**<0.001**	Ref.	2.9	**<0.001**
Distress-recurrence	Ref.	1.8	**0.04**	Ref.	1.7	**0.05**	Ref.	1.7	**0.05**
Summary score	Ref.	6.7	**0.01**	Ref.	6.7	**0.004**	Ref.	6.7	**0.004**
Hospital Anxiety and Depression Scale									
Anxiety	Ref.	0.5	0.40	Ref.	0.5	0.38	Ref.	0.5	0.38
Depression	Ref.	0.5	0.25	Ref.	0.4	0.36	Ref.	0.4	0.36

[1] Adjusted for age (34-59, 60-69, 70-81 years), practice postcode quintile level of the index of multiple deprivation (IMD), and country (Scotland, Wales, Northern Ireland, England).

Discussion

Breast cancer survivors had more cognitive problems, sexual dysfunction, fatigue, and borderline to abnormal anxiety symptoms compared to women with no history of cancer. The poorer quality of life in breast cancer survivors compared to controls appeared to be driven by treatment with chemotherapy, and more advanced disease at diagnosis. Among breast cancer survivors, younger age, lower education, more advanced disease at diagnosis, and treatment with chemotherapy, were all independently associated with poorer HRQoL.

The increased cognitive problems, sexual dysfunction and fatigue in breast cancer survivors might be partially explained by the distress caused by the diagnosis and treatment, as well as physical and often permanent side effects of the breast cancer treatments. The direct toxic effect of chemotherapy regimens to the central nervous system may be involved in the pathophysiology of cognitive dysfunction [12, 13]. This is consistent with our results, where chemotherapy was independently associated with more cognitive problems, compared to both controls and breast cancer survivors not exposed to chemotherapy. Cognitive problems were also raised in women diagnosed with more advanced disease, independently of treatment with chemotherapy; this is also consistent with results from studies showing that post-traumatic stress may also be involved in the causation of cognitive dysfunction [14]. Fatigue is common during chemotherapy and radiotherapy, and is probably due to psychological and biological factors, such as depression and increased pro-inflammatory cytokines [15]. Sexual problems are often related to breast cancer treatments that lower circulating levels of oestrogen, and body imagine concerns after a surgery that inevitably changes breast appearance.

Our results on HRQoL varying by age, education, stage at diagnosis and treatment are consistent with the previous literature [16-20]. Post-traumatic growth, a phenomenon in which women appreciate life more after a traumatic event [21], is likely explain the better HRQoL of older women as they also had the highest scores for positive feelings and benefits of cancer.

This study has several strengths. We selected patients from the CPRD GOLD primary care database, which is representative of the UK population in terms of age, sex, and ethnicity [22]. Matching the groups by primary care practice and age is likely to have accounted for measurable and some unmeasurable confounding; we further collected data for education, ethnicity, and proxy of social support, which are known to be

imperfectly recorded in the patients' clinical records, and this allowed us to account for these variables in the analyses. The validity of the tools used to assess outcomes has been established. QLACS was specifically developed to assess HRQoL in long-term cancer survivors, and it has high validity and reliability, both in cancer patients early post-treatment [23] and in long-term survivors [24, 25]. HADS has also been validated for use in primary care [26]. Finally, our study was sufficiently powered for the main comparison of HRQoL between breast cancer survivors and controls, as we exceeded the target sample size.

However, this study also has limitations. The major threat to the validity of our results comes from the low participation rate (35% in the breast cancer survivors group and 17% in the control group). Even though this participation rate overall surpassed our estimate at study design of 20%, and is similar to participation rates in HRQoL studies among other cancer survivors in the UK [27], we cannot rule out selection bias where psychologically healthier women were more likely to participate. The broad demographic determinants of participation were similar between breast cancer survivors and controls, but we cannot rule out differential participation associated with the outcomes. Another limitation is that clinical information was self-reported, which may have led to some information bias, but we expect this to have a minor impact on our results. The QLACS was well accepted but some missing responses were observed, most often for items related to sexual interest and function, and social avoidance; our proportion of missing data was similar to another study assessing HRQoL with QLACS among cancer survivors in the UK [23]. It is unclear whether the missing responses were related to values themselves, but it is plausible that older women may not feel comfortable reporting their sexual function. In addition, older women may have fewer opportunities to engage in partnered sexual activity (e.g. widowed, erectile dysfunction in partners, etc.), and therefore consider these items not applicable to them. For the social avoidance domain, one item was left unanswered particularly often – it related to being 'reluctant to start new relationships'. We think this item might have been interpreted by the patients as starting new romantic relationships, and thus left blank due to no applicability.

The results of this study suggest that selected groups of breast cancer survivors in the UK may benefit from increased surveillance for mental health and consequences of treatment that negatively affect HRQoL, such as cognitive problems, sexual problems and fatigue. Early identification and management of problems related to these domains is likely to reduce the burden of the disease. In the most recent years, patient rehabilitation programs have been made available to help patients better understand

their disease and what can be expected from the cancer treatments. This is likely to help women to better cope with their disease, as well as raise awareness that help is available for these issues, and reduce the stigma associated with sensitive topics such as mental health and sexual function. It is also important to raise awareness among health care professionals that long-term breast cancer survivors may still experience important distress related to their history of cancer.

Future research on the HRQoL of breast cancer survivors in the UK should focus on interventions aimed at preventing declines in HRQoL in the long term after breast cancer, interventions aimed at improving HRQoL in patients currently reporting low levels of HRQoL, and assessing trends in HRQoL, as it is unclear whether modern treatments yield better HRQoL. Studies are also needed to assess whether women diagnosed with breast carcinomas *in situ* differ in terms of HRQoL from both breast cancer survivors and women with no history of cancer, as these tumours are treated similarly to early stage breast cancer.

In conclusion, breast cancer survivors in the UK reported raised risk of problems with cognition, sexual function, fatigue and borderline/probable anxiety, particularly where their cancer was advanced and/or treated with chemotherapy. This information can be used to tailor increased surveillance for mental health and HRQoL issues in these groups.

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7.4 Summary

- This cross-sectional study aimed to assess HRQoL, anxiety, and depressive symptoms in long-term breast cancer survivors (>1 year), compared to women with no prior cancer.

- The CPRD GOLD primary care database was used to identify all women with history of breast in the participating practices, and a random sample of women who have never had cancer. The patient's GP confirmed their eligibility and posted the questionnaires. Outcomes were measured using QLACS and HADS.

- 353 women with a history of breast cancer (mean time since diagnosis 8.1 years) and 252 women with no prior cancer, from all four UK countries, participated in the study. These were 35% of the breast cancer survivors and 17% of the women with no history of cancer that were invited to participate.

- Breast cancer survivors had poorer HRQoL (higher mean QLACS score) in the domains of cognitive problems (adjusted β (aβ)=1.4, p=0.01), sexual function (aβ=1.7, p=0.02) and fatigue (aβ=1.3, p=0.01), compared to women with no history of cancer, but we found no evidence of difference in negative feelings, positive feelings, pain, or social avoidance. Breast cancer survivors treated with chemotherapy or diagnosed with more advanced disease, also had poorer HRQoL for the domain of negative feelings (chemotherapy: aβ=1.5, 95%CI: 0.2-2.7; stage: aβ=1.3, 95%CI: 0.2-1.5).

- Breast cancer survivors also had non-significantly higher odds of probable anxiety (HADS-anxiety score ≥11) than controls (adjusted OR (aOR)=1.40, 0.93-2.10), however there was strong evidence of a difference when a more sensitive threshold (score ≥8, "borderline/probable anxiety") was used, (aOR=1.47, 1.15-1.87). There were no differences in the odds of probable depression (aOR=1.18, 0.52-2.68).

- Poorer HRQoL and mental health outcomes were more pronounced among women with advanced-stage cancer at diagnosis, and/or prior treatment with chemotherapy.

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8 Comparison between patient-reported outcomes and data recorded in the patients' electronic health record

8.1 Introduction

Objective 6 of this thesis, and s secondary aim of the cross-sectional study described in Chapter 7, was to assess the feasibility of using EHRs to study aspects of mental health and quality of life that are more typically captured directly from patients. If such outcomes could be adequately captured using routinely collected health records data, this would allow for much larger and lower-cost studies compared to when direct patient involvement is required. This chapter focuses on the comparison between information on certain domains of HRQoL that were directly reported by the patients participating in the study (N=602), and the data registered in their EHRs in the CPRD GOLD primary care database.

8.2 Methods

8.3 Identifying patients with poor quality of life (patient-reported outcome)

The QLACS includes seven generic domains of HRQoL (i.e. negative feelings, positive feelings, fatigue, cognitive problems, sexual function, physical pain and avoidance). Of these, five are particularly suitable for comparison with the data recorded in the EHR because women with distressing levels for these domains may have visited their GP to seek help: 'negative feelings', 'cognitive problems', 'physical pain', 'sexual problems' and 'fatigue'. Read codes for the 'social avoidance' domain are also available, and therefore this domain was also included. Data on 'positive feelings' were not expected to be captured in GP records so are not considered further here.

The domains of negative feelings, cognitive problems, physical pain, sexual problems, fatigue and social avoidance have four items each. Responses to each item are given on a Likert-type of scale that varies between 1 (never) and 7 (always). To identify women who had high levels of distress for each domain, I calculated the arithmetic mean of their responses (i.e. the sum of the individual item scores divided by four; mean values range between one and seven). I considered as reporting important levels of distress all women with a mean of ≥5 (corresponding to average replies of frequently, very often or always) in the domain. As this is an arbitrary cut-off, two

sensitivity analyses were conducted: 1) using a lower cut-off of ≥3 (corresponding to replies of sometimes and as often as not, in addition to replies of frequently, very often or always to most questions); 2) considering as exposed to important levels of distress all women who replied ≥5 to at least one item in the domain.

8.4 Identifying conditions closely related to specific domains of HRQoL in electronic health records

The EHRs data from the 602 patients that participated in the cross-sectional study were extracted from the CPRD GOLD primary care database. As patient-reported outcomes were collected between January and November 2019, I extracted data from the January 2019 version of CPRD, which included data from 1987 up to December 2018. In a sensitivity analysis, I used data from the CPRD GOLD primary care database version of July 2019, which included data collected from primary care practices up to June 2019.

For each domain of HRQoL being assessed, I produced lists of Read codes closely related to the QLACS items in the domain (please see Table 8.1 for concepts; lists of Read codes are provided in Chapter 6).

Table 8.1 Matching between HRQoL domain and information in the EHRs.

HRQoL domain	QLACS Items	Search in the EHR for Read codes* related to:
Negative feelings	19 Bothered by mood swings 7 Felt blue or depressed 9 Worried about little things 24 Felt anxious	Depression and/or anxiety (disorders and symptoms), antidepressants, or anxiolytic prescription
Cognitive problems	3 Bothered by having a short attention span 4 Had trouble remembering things 2 Difficulty doing things requiring concentration 23 Bothered by forgetting what started to do	Cognitive impairment; cognitive dysfunction symptoms; dementia*; dementia-specific drug*.
Physical pain	13 Bothered by pain preventing activities 17 Mood disrupted by pain or its treatment 27 Pain interfered with social activities 21 Had aches or pains	Pain; painful conditions; prescriptions of analgesics.
Sexual problems	16 Lacked interest in sex 26 Avoided sexual activity 12 Dissatisfied with sex life 10 Bothered by inability to function sexually	Low libido; anorgasmia; vaginismus.
Fatigue	11 Lacked energy to do things wanted to 14 Felt tired a lot 1 Had energy to do things wanted to do 5 Felt fatigued	Low energy; tiredness.
Social avoidance	18 Avoided social gatherings 20 Avoided friends 25 Reluctant to meet new people 15 Reluctant to start new relationships	Social isolation, or social avoidance.

* definitions were based on the systematic review provided in Chapter 5 when possible. QLACS – Quality of Life in Adult Cancer Survivors Scale; EHR – electronic health records.

The lists of Read codes were used to identify women with these codes registered in their EHR in the 3, 6, 12 and 24 months prior to the date of last data collection from the practice. The last collection date varied from practice to practice, but was generally within three weeks of the database version (e.g. in the January 2019 version, the date of last data collection from the practices was in median 20 days (inter-quartile range: 19-20) prior to 31 December 2018).

8.5 Comparison between patient-reported outcomes and information recorded in the electronic health records

To compare the two sources of data, I quantified for each domain:

1) of the women who reported high levels of distress in the questionnaires, how many had similar information in their EHR (sensitivity);
2) of the women who had information about the domain in the EHR, how many reported distressing levels in the questionnaires (positive predictive value).

Results are shown in tables.

8.6 Results

8.7 Sensitivity of electronic health data in capturing patient-reported distress

Of the 605 women that participated in the study, 100 (17%) reported high levels of distress (mean score ≥5) for negative feelings (Table 8.2). 36% of these had information related to anxiety and/or depression recorded in their EHR in the three months prior to the date of last data collection for the practice, and 50% had a record in the previous two years. Distress with pain was reported in the questionnaires by 122 (21%) of the women, and 52% and 75% of these had symptoms of pain or an analgesic prescription recorded the EHR in the previous three and 24 months, respectively. 93 women reported high levels of distress related to cognitive problems, 155 to sexual dysfunction, 157 to fatigue/energy, and 82 to social avoidance. No codes relevant to these domains were found in the patients' EHR up to 24 months prior to the date of last data collection for the practice. The results of the sensitivity analysis using data of the July 2019 version of CPRD were not meaningfully different (Table 8.3).

8.8 Positive predictive value of electronic health data for capturing patient-reported distress

Of the patients that had information about negative feelings recorded in their EHR (20-30% of all patients, depending on the length of the time-window used to identify codes), only a minority (20-30%) reported distressing levels of negative feelings in the questionnaires (Table 8.4). For pain, approximately one-half of the 134 patients who had pain recorded in their EHR also reported distressing levels for pain in the questionnaires. The positive predictive value tended to decline when older information was included in the ascertainment of negative feelings in the EHRs (i.e. when a longer time-window/look back period was used). For the other four domains, no codes were identified in the EHRs for in the observation period.

Table 8.2 Sensitivity analysis using a more recent CPRD data cut: patients scoring above a given threshold in the PRO study that had domain-related information in the EHRs by time prior to the last data collection for the practice in the CPRD version January 2019 (N=605 §)

				PROs		Patients scoring above a given threshold in the PRO study that had domain-related information in EHRs, by time prior to the last data collection for the practice							
						3mo		6mo		12mo		24mo	
Domain	**Items in the QLACS**	**Read codes for**	**Mean domain cut-off**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Negative feelings	19 Bothered by mood swings 7 Felt blue or depressed 9 Worried about little things 24 Felt anxious	Depression and/or anxiety, antidepressants, or anxiolytic prescription.	≥5 ≥3 1 item ≥5	100 383 226	16.8 64.5 37.4	36 89 65	36.0 23.2 28.8	37 90 66	37.0 23.5 29.2	47 109 82	47.0 28.5 36.3	51 129 95	51.0 33.7 42.0
Cognitive problems	3 Bothered by having a short attention span 4 Had trouble remembering things 2 Difficulty doing things requiring concentration 23 Bothered by forgetting what started to do	Cognitive impairment; cognitive dysfunction symptoms; dementia; dementia-specific drug.*	≥5 ≥3 1 item ≥5	93 391 192	15.6 64.6 31.7	0 0 0		0 0 0		0 0 0		0 0 0	
Physical pain	13 Bothered by pain preventing activities 17 Mood disrupted by pain or its treatment 27 Pain interfered w/social activities 21 Had aches or pains	Pain; painful conditions; prescriptions of analgesics.	≥5 ≥3 1 item ≥5	122 327 229	20.6 55.1 37.9	64 105 85	52.5 32.1 37.1	69 115 93	56.6 35.2 40.6	81 151 119	66.4 46.2 52.0	91 184 140	74.6 56.3 61.1
Sexual dysfunction	16 Lacked interest in sex 26 Avoided sexual activity 12 Dissatisfied w/sex life 10 Bothered by inability to function sexually	Low libido; anorgasmia; vaginismus.	≥5 ≥3 1 item ≥5	155 375 302	28.0 62.0 49.9	0 0 0		0 0 0		0 0 0		0 0 0	
Fatigue	11 Lacked energy to do things wanted to 14 Felt tired a lot 1 Had energy to do things wanted to do 5 Felt fatigued	Low energy; tiredness.	≥5 ≥3 1 item ≥5	157 469 533	26.3 77.5 88.1	0 0 0		0 0 0		0 0 0		0 0 0	
Social avoidance	18 Avoided social gatherings 20 Avoided friends 25 Reluctant to meet new people 15 Reluctant to start new relationships	Social isolation; social avoidance.	≥5 ≥3 1 item ≥5	82 292 194	13.8 48.6 32.1	0 0 0		0 0 0		0 0 0		0 0 0	

EHRs = electronic health records; HRQoL = Health-Related Quality of Life; mo. = month. PRO = Patient-reported outcomes.* Severe cognitive dysfunction was an exclusion criterion for the study.
§ 605 women participated in the study; due to missing data for some items, the number of women included in the denominator varies slightly by domain.

Table 8.3 Patients scoring above a given threshold in the PRO study that had domain-related information in the EHRS by time prior to the last data collection for the practice in the CPRD July 2019 version (N=605 §).

				PROs		Patients scoring above a given threshold in the PRO study that had domain-related information in EHRs, by time prior to the last data collection for the practice							
						3mo		6mo		12mo		24mo	
Domain	**Items in the QLACS**	**Read codes for**	**Mean domain cut-off**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Negative feelings	19 Bothered by mood swings	Depression and/or anxiety (disorders and symptoms), antidepressants, or anxiolytic prescription	≥5	100	16.8	37	37.0	37	37.0	48	48.0	55	55.0
	7 Felt blue or depressed		≥3	383	64.5	89	23.2	89	23.2	113	29.1	130	33.9
	9 Worried about little things		1 item ≥5	226	37.4	68	30.1	68	30.1	84	37.2	98	43.4
	24 Felt anxious												
Cognitive problems	3 Bothered by having a short attention span	Cognitive impairment; cognitive dysfunction symptoms; dementia; dementia-specific drug.*	≥5	93	15.6	0		0		0		0	
	4 Had trouble remembering things		≥3	391	64.6	0		0		0		0	
	2 Difficulty doing things requiring concentration		1 item ≥5	192	31.7	0		0		0		0	
	23 Bothered by forgetting what started to do												
Physical pain	13 Bothered by pain preventing activities	Pain; painful conditions; prescriptions of analgesics.	≥5	122	20.6	64	52.5	69	56.6	81	66.4	91	74.6
	17 Mood disrupted by pain or its treatment		≥3	327	55.1	106	32.4	116	35.5	152	46.5	185	56.6
	27 Pain interfered w/social activities		1 item ≥5	229	37.9	86	37.6	94	41.1	120	52.4	141	61.6
	21 Had aches or pains												
Sexual dysfunction	16 Lacked interest in sex	Low libido; anorgasm; vaginismus.	≥5	155	28.0	0		0		0		0	
	26 Avoided sexual activity		≥3	375	62.0	0		0		0		0	
	12 Dissatisfied w/sex life		1 item ≥5	302	49.9	0		0		0		0	
	10 Bothered by inability to function sexually												
Fatigue	11 Lacked energy to do things wanted to	Low energy; tiredness.	≥5	157	26.3	0		0		0		0	
	14 Felt tired a lot		≥3	469	77.5	0		0		0		0	
	1 Had energy to do things wanted to do		1 item ≥5	533	88.1	0		0		0		0	
	5 Felt fatigued												
Social avoidance	18 Avoided social gatherings	Social isolation; social avoidance.	≥5	82	13.8	0		0		0		0	
	20 Avoided friends		≥3	292	48.6	0		0		0		0	
	25 Reluctant to meet new people		1 item ≥5	194	32.1	0		0		0		0	
	15 Reluctant to start new relationships												

EHR = electronic health records; HRQoL = Health-Related Quality of Life; mo. = month. * Severe cognitive dysfunction was an exclusion criterion for the study. § 605 women participated in the study; due to missing data for some items, the number of women included in the denominator varies slightly by domain.

Table 8.4 Proportion of women who had information in the EHR who reported distressing levels when inquired about their HRQoL (N=605).

				Patients with info for the domain in EHR		Patients scoring as distressed, according to patient-reported data					
						≥5		≥3		At least one item 5	
Domain	**Items in the QLACS**	**Read codes related to:**	**Time prior to LDC**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Negative feelings	19 Bothered by mood swings	Depression and/or anxiety (disorders and symptoms), antidepressants, or anxiolytic prescription.	3 mo.	115	19.4	36	31.3	88	77.4	65	55.1
	7 Felt blue or depressed		6 mo.	117	19.7	37	31.6	90	76.9	66	55.0
	9 Worried about little things		12 mo.	142	23.9	47	33.1	109	76.8	82	56.2
	24 Felt anxious		24 mo.	170	28.6	51	30.0	129	75.9	95	54.3
Cognitive problems	3 Bothered by having a short attention span	Cognitive impairment; cognitive dysfunction symptoms; dementia; dementia-specific drug.*	3 mo.	0		-		-		-	
	4 Had trouble remembering things		6 mo.	0		-		-		-	
	2 Difficulty doing things requiring concentration		12 mo.	0		-		-		-	
	23 Bothered by forgetting what started to do		24 mo.	0		-		-		-	
Physical pain	13 Bothered by pain preventing activities	Pain; painful conditions; prescriptions of analgesics.	3 mo.	134	22.6	64	47.8	105	78.4	85	62.0
	17 Mood disrupted by pain or its treatment		6 mo.	146	24.6	69	47.3	115	78.8	93	62.4
	27 Pain interfered w/social activities		12 mo.	202	34.1	81	40.1	151	74.8	119	57.8
	21 Had aches or pains		24 mo.	257	43.3	91	35.4	184	71.6	140	53.4
Sexual dysfunction	16 Lacked interest in sex	Low libido; anorgasm; vaginismus.	3 mo.	0		-		-		-	
	26 Avoided sexual activity		6 mo.	0		-		-		-	
	12 Dissatisfied w/sex life		12 mo.	0		-		-		-	
	10 Bothered by inability to function sexually		24 mo.	0		-		-		-	
Fatigue	11 Lacked energy to do things wanted to	Low energy; tiredness.	3 mo.	0		-		-		-	
	14 Felt tired a lot		6 mo.	0		-		-		-	
	1 Had energy to do things wanted to do		12 mo.	0		-		-		-	
	5 Felt fatigued		24 mo.	0		-		-		-	
Social avoidance	18 Avoided social gatherings	Social isolation; social avoidance.	3 mo.	0		-		-		-	
	20 Avoided friends		6 mo.	0		-		-		-	
	25 Reluctant to meet new people		12 mo.	0		-		-		-	
	15 Reluctant to start new relationships		24 mo.	0		-		-		-	

EHR = electronic health records; HRQoL = Health-Related Quality of Life; mo. = month. * Severe cognitive dysfunction was an exclusion criterion for the study. § 605 women participated in the study; due to missing data for some items, the number of women included in the denominator varies slightly by domain.

8.9 Discussion and Conclusions

The results of this study suggest that EHRs have low sensitivity to detect patients experiencing poor HRQoL at a particular point in time, particularly for the domains of sexual function, fatigue, cognitive problems and social avoidance; none of the patients self-reporting distress in these domains in the questionnaires had corresponding codes present in their electronic data. For pain and negative feelings, some relevant codes were present in the EHRs, but both sensitivity and positive predictive values were <50%, which is likely to be too low to justify the use of EHRs data alone as a proxy for patient-reported outcomes in these domains.

Several factors might have affected the identification of the information in the EHRs, and are limitations of this study. First, no data were collected on the date of questionnaire response. This means that one cannot identify precisely, for each patient, the data from consultations that would have corresponded to when the patient-reported outcomes were evaluated. Since the results of the analyses using the January 2018 and July 2019 were very similar, this probably had little impact in the results. However, the July 2019 version may not capture distress recently acquired by patients that replied later in the year. In future follow-up work, I will conduct analyses using the January 2020 version, allowing me to consider EHRs across the full period of questionnaire data collection. The validity of the approach used to identify patients at probably distressed from QLACS scores has been untested. This limitation was addressed by using different cut-offs, which showed generally the same patterns. Another limitation of this study is that the database only captures drugs prescribed to the patients, and widely used drugs for pain and fatigue are sold over the counter. The comparison for cognitive problems was also limited by the need to exclude patients unable to reply to a self-reported questionnaire, which included patients with dementia, and we cannot rule out that general practitioners applying the exclusion criteria may have been overly strict in applying this criterion and also excluded those with codes for milder cognitive impairment (see below).

The results showed that one in three patients that reported distressing levels of negative feelings had similar information recorded in their EHR in the previous three months. This is consistent with patients often not seeking primary care for anxiety and depressive symptoms, possibly due to stigma associated with mental disorders and unawareness of the amenability of mental health symptoms to treatment [247].

Women may have felt more comfortable in disclosing these symptoms in an anonymous questionnaire.

Approximately one-half of the patients that reported poor HRQoL related to pain also had information related to pain in the EHR in the previous three months. This may be partly explained by patients self-treating pain with widely used over-the-counter treatments such as paracetamol and non-steroidal anti-inflammatory drugs (e.g. ibuprofen). On the other hand, the higher recording of pain compared to negative feelings may potentially be explained by patients seeking more often primary care for distressing concern that they perceive as being amenable to treatment.

I did not find any records of cognitive dysfunction, social avoidance, sexual dysfunction or fatigue entered in the EHRs of the participating patients in the last 24 months to the data cut-off. A complete absence of entries for social avoidance and sexual dysfunction are plausible. Read codes for social avoidance have seldom been used in the entire CPRD database, so lack of data on this in a relatively small patient group was expected. The absence of sexual problems in the EHRs was surprising, but may be explained, at least in part, by the rarity of the outcome (estimated in Chapter 6) and by the low proportion of subjects who ever contact their GPs for issues related to sexual function [65].

The lack of recording of cognitive problems and symptoms of fatigue in the EHRs was also unexpected. Severe cognitive dysfunction was an exclusion criterion for the study; a review of the motives provided by the GPs to exclude patients showed a non-negligible frequency of cognitive-related reasons, including cases of dementia as well as reasons such as ‘memory problems’. It is possible that cases of mild cognitive dysfunction that had sought primary care with these complains were excluded, leaving an overrepresentation of women who did not seek primary care for their concerns. For fatigue, a manual review of all entries in the EHR of a random sample of patients that reported distressing levels of fatigue in the questionnaires, revealed a common pattern of multi and complex morbidity, almost always with diagnoses where fatigue is implicit (e.g. heart failure, chronic obstructive pulmonary disease), but no explicit codes for fatigue. Fatigue is rarely seen as an isolated condition, as is more often associated with other diagnoses, which may explain the absence of codes in the data for this. This warrants further investigation, however, and follow-up work will be carried out on this topic.

The comparison of these results to other literature was not possible as, to my knowledge, no other study has attempted this comparison.

In conclusion, even though EHRs contain substantial data related to general domains of HRQoL, these do not appear to have good sensitivity and positive predictive value to capture outcomes that represent subjective experiences and are traditionally ascertained directly from patients.

8.10 Summary

- This chapter compares patient-reported outcomes for HRQoL domains, and information capturing similar constructs in patients' EHRs.
- Data were compared for six domains ('negative feelings', 'cognitive problems', 'physical pain', 'sexual problems', 'fatigue' and 'social avoidance'), as patients with high levels of distress for issues related to these domains may be likely to seek primary care.
- Patients were considered to report high levels of distress for a domain when they reported an average response of 'often' to 'always' to items in the domain (e.g. items for negative feelings shown in Table 8.5, mid-column).
- Read codes lists were defined for concepts closely related to items in each domain (e.g. last column of Table 8.5).

Table 8.5 Example of the HRQoL domain, its items and information searched in the EHR.

HRQoL domain	QLACS Items	Search in the EHR for Read codes* related to:
Negative feelings	19 Bothered by mood swings 7 Felt blue or depressed 9 Worried about little things 24 Felt anxious	Depression and/or anxiety (disorders and symptoms), antidepressants, or anxiolytic prescription

- Of the 100 patients that reported distressing levels of negative feelings, 17% had Read codes for similar constructs registered in their EHR in the previous three months.
- Of the 122 patients that reported distress with pain, 50% had Read codes for similar constructs registered in their EHR in the previous three months.
- Of the 605 women that participated in the study, 16% had high levels of distress related to cognitive problems, 28% to sexual dysfunction, 26% to fatigue/energy, and 14% to social avoidance. However, none had a Read codes related to these domains in their EHRs in the last two years.
- Approximately 30% of the patients with information for anxiety and/or depression the EHR reported distress with negative feelings. For pain, approximately 50% of the patients that had symptoms of pain or had been prescribed analgesics reported distressing levels of pain.
- Further work will include exploring different outcome definitions for EHR-based outcomes, and more recent versions of the CPRD GOLD primary care database.
- In conclusion, patient-reported HRQoL outcomes do not appear to be captured with adequate sensitivity in EHR data.

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9 Discussion

9.1 Introduction

This closing chapter aims to summarise the main discussion issues, focusing on overarching points that cut across the different chapters. Detailed study-specific discussion points were previously covered in the relevant individual chapters.

9.2 Summary of key findings

9.2.1 Aim 1: to quantify relative risk of adverse mental health outcomes in breast cancer survivors, compared to women who never had cancer

Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review

This systematic review included 66 studies that compared mental health conditions among breast cancer survivors and women with no history of cancer (Chapter 3). The most commonly evaluated outcomes were anxiety (n=23 studies) and depression (n=41). Of the 23 studies of anxiety, 12 observed more anxiety in breast cancer survivors, including 2/4 studies where ascertainment of anxiety was clinical/ prescription-based, and in 10/19 studies where ascertainment of anxiety was based on symptoms. Among 41 studies of depression, 22 reported significantly more depression in breast cancer survivors, compared to controls; this included seven of eight studies where depression was ascertained clinically, and 15/33 studies that quantified depressive symptoms. Breast cancer survivors also had statistically significantly increased symptoms/frequency of neurocognitive dysfunction (21/28 studies), sexual dysfunctions (6/7 studies), sleep disturbance (5/5 studies), stress-related disorders (2/3 studies), suicide (2/2 studies), somatisation (2/2 studies), and bipolar and obsessive-compulsive disorders (1/1 study each).

Identification of mental health and quality of life outcomes in primary care databases in the UK: a systematic review

This study summarised the definitions and combinations of Read and/or ICD codes used to identify outcomes of anxiety, depression, fatigue, cognitive and sexual

dysfunction, pain, sleep disorders, and fatal and non-fatal self-harm, in studies of EHRs from primary care databases in the UK (Chapter 4). 120 studies were eligible. Depression was most often defined using codes for diagnoses (37/42 studies) and/or antidepressants prescriptions (21/42 studies); six studies included symptoms in their definition. Anxiety was defined with codes for diagnoses (12/12 studies); four studies also included symptoms. Fatal/non-fatal self-harm was ascertained in primary care data linked to the ONS mortality database in nine studies. Three studies evaluated domains of cognitive function. Fatigue definitions varied little. No studies of female sexual dysfunction were found. Sleep disorders included insomnia and hypersomnia. Lists of Read codes were available for approximately one-half of the studies, and showed substantial variability; validation of codelists was carried out for 21/120 studies.

Risk of adverse mental health outcomes in women who had breast cancer compared to women with no history of cancer in the UK: a population based study

In this matched-cohort study, the aim was to estimate the risk of anxiety and depression, as primary outcomes, and fatigue, pain, sexual dysfunction, sleep disorder, cognitive dysfunction, and fatal and non-fatal self-harm, as secondary outcomes, in breast cancer survivors compared to women with no prior cancer, using EHR data routinely collected in primary care (Chapter 6). All women with history of incident breast cancer in the CPRD GOLD primary care database were included (n=57,571), and individually matched to women with no prior history of cancer (n=230,067), on age and primary care practice. Median follow-up time was approximately five years in both groups. After controlling for diabetes, body mass index, smoking and drinking status, breast cancer survivorship was found to be associated with a 33% raised risk of anxiety (HR 1.33 95%CI 1.29-1.36), and a 35% raised risk of depression (HR 1.35, 95% CI 1.32-1.38), as well as significantly raised risks of the secondary outcomes of fatigue, pain, sexual dysfunction, sleep disorder and opioid analgesics. However, there was no evidence of an association with cognitive dysfunction or fatal and non-fatal self-harm. The strength of the associations reduced over time but raised risks for anxiety and depression persisted for two and four years after cancer diagnosis, respectively. Increased levels of pain and sleep disorder persisted for at least 10 years. Younger age was associated with larger increases in the risks of depression, pain, opioid analgesic use, sleep disorders, and cognitive dysfunction (for which there was no association when considering all ages together).

9.2.2 *Aim 2: to investigate quality of life, anxiety, and depressive symptoms in breast cancer survivors, compared to women with no history of cancer*

Quality of life of women who had breast cancer compared to women with no history of cancer

A total of 353 breast cancer survivors and 252 women without history of cancer participated in the study (Chapter 7). Mean time since diagnosis was 8.1 years. Breast cancer survivorship was significantly associated with poorer HRQoL in the domains of cognitive problems, sexual function and fatigue, but no evidence of difference in negative feelings, positive feelings, pain, or social avoidance. Breast cancer survivors had a non-statistically significant 30% higher odds of probable anxiety (HADS-anxiety score>10), however there was a statistically significant 46% increase in breast cancer survivors when a more sensitive threshold (score≥8, "borderline/probable anxiety") was used. The odds of depression were similar in the two groups. Quality of life and mental health was poorer among women with more advanced disease and/or treated with chemotherapy. Similarly, among breast cancer survivors only, younger age, lower education, more advanced disease at diagnosis, and/or prior receipt of chemotherapy were associated with poorer HRQoL. Breast cancer survivors who had advanced disease reported more cognitive problems, pain, sexual function, financial problems, and distress with appearance and recurrence compared to localised disease. Cognitive problems, appearance concerns, and distress with recurrence were more common in younger women, and in women treated with chemotherapy.

Comparison between patient-reported outcomes and information in the patients' electronic health records.

Six hundred and five women participated in the study. One hundred women had answers consistent with high levels of negative feelings in the patient-reported outcomes. Of these, only 36% had information related to this in the EHRs in the last three months before the date of last data collection for the practice, and 50% had a record in the previous two years. One hundred and twenty two patients reported distress with pain; 52% and 75% of these had symptoms of pain or an analgesic prescriptions recorded in their EHR in the previous three and 24 months, respectively. A total of 93 women reported high levels of distress related to cognitive problems, 155 to sexual dysfunction, 157 to fatigue/energy, and 82 to social avoidance. No evidence of this was found in the patients' EHRs using Read codes up to 24 months prior to the date of last data collection for the practice. These

results suggest that electronic GP records did not have sufficient sensitivity to reasonably capture the subjective experience mental health and HRQoL outcomes that we obtained directly from patients in this study.

9.3 Explanation of results and comparison with the literature

9.3.1 Anxiety

Breast cancer survivors had increased risk of seeking primary care for anxiety in the two years after diagnosis (Chapter 6), and increased borderline/abnormal anxiety symptoms were also found in the study of patient-reported outcomes (Chapter 7). Similar results found in the studies included in the systematic review (Figure 9.1). Clinically relevant symptoms of anxiety and stress-related/adjustment disorders are common shortly after diagnosis [248], and are consistent with the stress induced by the diagnosis of a life-threatening condition. In Sweden, increased anxiety has been reported from the cancer diagnostic work-up [249]. This is in line with our findings, where more women were excluded from the exposed cohort in the study of EHRs because they had anxiety recorded in the year before the breast cancer diagnosis; most women went on to have the outcome registered after the index date.

The results of the patient-reported outcomes, which included breast cancer survivors on average 8.6 years from diagnosis, showed increased risk of anxiety only when considering a cut-off of borderline/abnormal. The raised anxiety symptomatology shortly after diagnosis is expected to decrease over time, with women psychologically adjusting to the new reality [250, 251]. In the long term, breast cancer survivors may experience distress with anxiety symptoms that do not meet criteria for formal diagnosis, similarly to what has been described in cancer patients [252]. Similarly to what has been described elsewhere [253], anxiety symptoms in breast cancer survivors were particularly raised in younger women. This may be because younger breast cancer survivors have specific concerns compared to older ones, such as the impact of their disease and possible death in their offspring upbringing, and infertility for women who want (more) children.

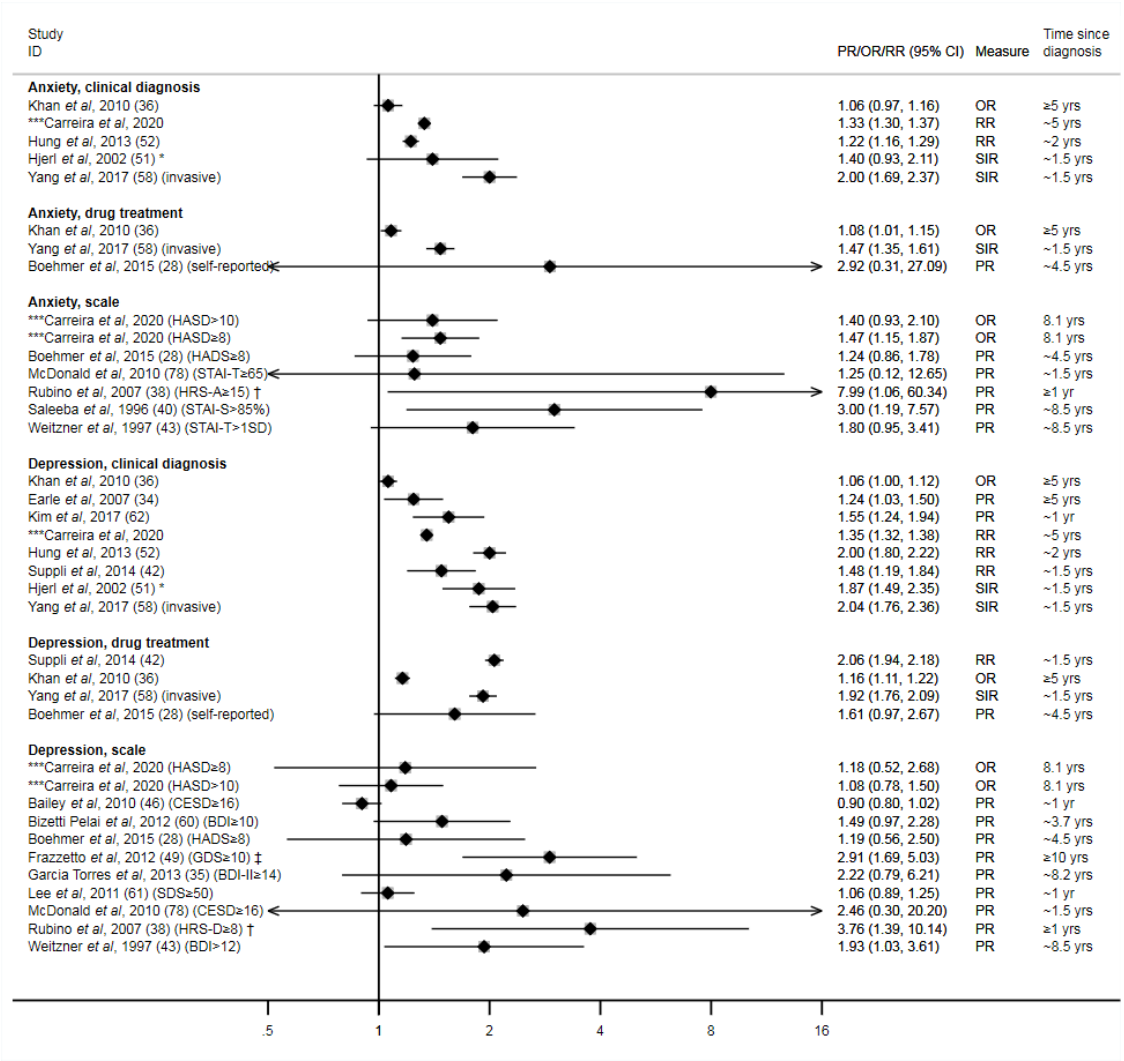

Figure 9.1 Results for anxiety and depression clinically assessed (Chapter 6), and symptoms of anxiety and depression (Chapter 7) (Study ID = ***Carreira *et al.* 2020) compared to the studies identified in the systematic review (Chapter 3).

Women treated with chemotherapy had exacerbated symptoms of anxiety possible due to fear of the side effects of chemotherapy and physical changes induced by the treatment [254]. HRQoL items for anxiety were included in the domain of negative feelings, alongside depression, which precludes a formal comparison of the results for anxiety with those for the domain of negative feelings.

9.3.2 Depression

Breast cancer survivors had increased risk of depression, compared to women with no prior cancer, for up to four years post-diagnosis in the study using primary care EHRs (Chapter 6). This is consistent with other studies of depression in breast cancer survivors using clinically assessed outcomes (Figure 9.1). One such study, by Khan et al [255], that included breast cancer survivors in the UK five or more

years post diagnosis, did not find higher odds of being diagnosed with anxiety or depression, compared to controls. The absence of evidence for a raised depression in the study of patient-reported outcomes (Chapter 7) may represent a lack of effect on the risk of depression among participants that were on average 8.1 years out of their breast cancer diagnosis, or could reflect a lack of power to detect small differences in this outcome. Breast cancer survivors that had a higher education degree reported fewer symptoms of depression, which is in line with previous studies suggesting that lower socio-economic status is a risk factor for depression, possibly due to higher baseline levels of distress and less access and utilization of mental health services [13, 256]. Similarly to anxiety, younger women had reported more depressive symptoms compared to older women, suggesting poorer adjustment amongst this group [253]. This younger group may be more sensitive to the negative consequences of breast cancer, such as the impact on loved ones, or the lifestyle changes induced by the cancer, among others [257-259].

9.3.3 Neurocognitive dysfunction

Neurocognitive dysfunction has been widely reported in breast cancer survivors [150, 268-271], and is thought to arise from the neurotoxic effects of chemotherapy [155], psychological symptoms such as post-traumatic stress [272], or exposure to hormone therapy [273]. Impairments are usually observed for domains of cognitive function such as memory, but these are generally mild and may not completely impede most daily activities, even though they may cause distress [274].

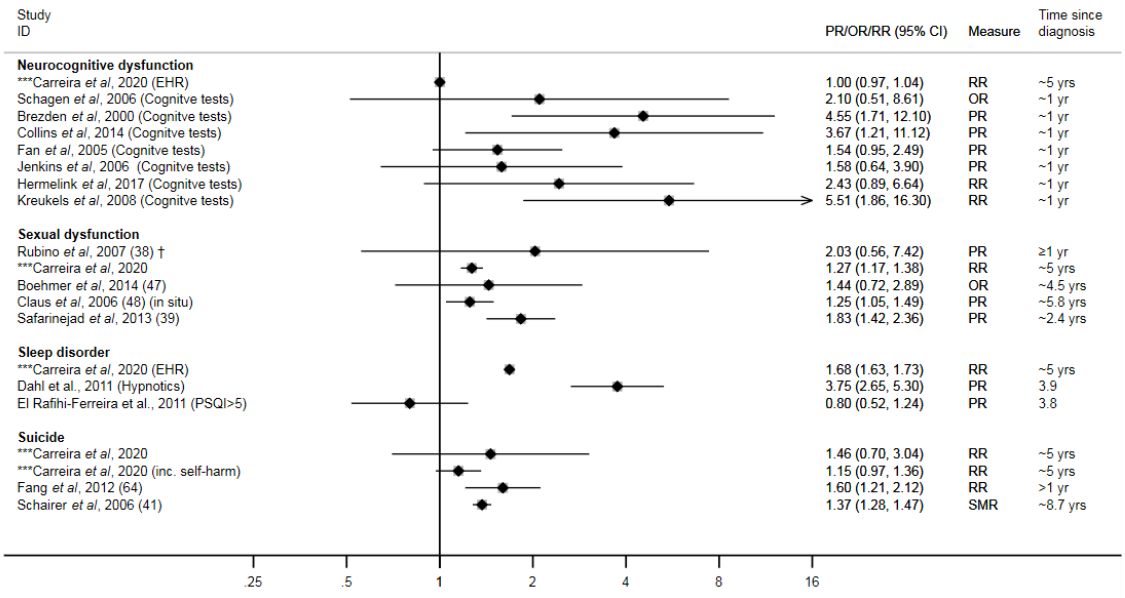

Figure 9.2 Results for cognitive dysfunction, sexual dysfunction, sleep disorder, suicide, and fatal and non-fatal self-harm reported in Chapter 6 (Study ID = ***Carreira *et al.* 2020), compared to the studies identified in the systematic review (Chapter 3).

The reasons for a lack of association between breast cancer survivorship and cognitive dysfunction in the study of EHRs (Chapter 6) require further exploration, but the results of Chapter 8 suggest that EHRs may sub optimally capture cases of mild cognitive dysfunction (see section 9.4.2 on the ascertainment of the outcomes). This might be because patients do not seek their GP with cognitive problems as their chief complaint, or that GPs do not record these symptoms using Read codes. In the systematic review (Chapter 3), all studies of cognitive dysfunction used batteries of cognitive tests to assess the outcomes (Figure 9.2). The results obtained by these very specific tools are unlikely to be comparable to assessments of cognitive function in everyday clinical practice. In contrast to the results of the EHR study, the analysis of patient-reported outcomes showed long-term breast cancer survivors reporting poorer HRQoL related to cognitive problems compared with controls (Chapter 7), similarly to other studies [275].

9.3.4 Fatigue

Symptoms of fatigue were more common in breast cancer survivors than in women who never had cancer, and the increased risk persisted for 5-10 years after diagnosis (Chapter 6). This is consistent with a vast body of research that describes fatigue as a common side effect of chemotherapy and radiotherapy [140]. Several biological mechanisms have been postulated, including inflammation, alterations in leucocytes, anaemia, five hydroxyl tryptophan (5-HT) dysregulation, among others [276]. Fatigue is highly debilitating and often interferes with normal daily functioning. This is likely to explain the poorer HRQoL related to this domain among breast cancer survivors found in Chapter 7, and in other studies [275].

9.3.5 Sexual dysfunction

Even though codes for sexual dysfunction were rarely used in the CPRD GOLD primary care database, breast cancer survivors had significantly increased risk compared to non-cancer controls (Chapter 6), similarly to studies included in the systematic review (Figure 9.2). The study of patient-reported outcomes also found poorer HRQoL related to this domain in breast cancer survivors (Chapter 7). Sexual dysfunction in breast cancer survivors has a complex aetiology, often including vaginal dryness and vaginal atrophy due to oestrogen deprivation, body image concerns, low self-esteem, depressive symptoms, among others [277, 278].

9.3.6 Pain

In CPRD, breast cancer survivors had higher frequency of pain compared to controls. It is possible that breast cancer survivors are more in contact with health care services, and thus have symptoms more often recorded (Chapter 6). However, these patients were also found to have increased prescriptions of analgesic opioids, which suggests that their pain may be more severe, as mild symptoms of pain are usually managed with paracetamol or nonsteroidal anti-inflammatory drugs. The increase in the prescriptions of opioid analgesics over calendar time was observed at the same time as symptoms of anxiety decreased; this may be due to improved pain management in these patients. No differences in the domain of physical pain were observed in the study of patient-reported outcomes (Chapter 7), which may be explained by patients having effective pharmacological management of their pain. This is also supported by the high proportion of patients reporting poor HRQoL related to pain and who had similar information recorded in the EHR, which suggests that patients do seek care for symptoms of pain (Chapter 8).

9.3.7 Sleep disorders

The increased risk of sleep disorders found in the study of EHRs (Chapter 7) is consistent with the few previous studies on this topic (*vide* Chapter 3). The trajectories of sleep disorders after breast cancer diagnosis have seldom been investigated, and the results in this thesis represent an important contribution to knowledge in this area. The aetiology of sleep disturbances is also largely unclear, but may involve comorbid anxiety, vasomotor symptoms may also interfere with sleep [279], as well as exposure to steroids [280] or chemotherapy [281]. Sleep is not a dimension captured in the QLACS scale, and no patient-reported information was available.

9.3.8 Fatal and non-fatal self-harm

Suicide and self-harm are relatively rare outcomes which require studies to include large samples to have sufficient power to study these associations. Even though we included all women with history of breast cancer in the CPRD GOLD primary care database, our study was underpowered to detect differences between the two groups, should these exist. Similar limitations have affected several locale-specific studies [260-265], although a statistically significant raised risk of suicide was demonstrated in a large international study of over 721,000 breast cancer survivors

[266]. The non-statistically significant raised risk of non-fatal self-harm follows the expected direction, as only a small proportion of the patients who attempt suicide actually complete it [2]. Self-harm almost always occurs with other mental health conditions, as the physical manifestation of the patient's psychological distress [267]. This was the first study, to my knowledge, to address non-fatal self-harm in breast cancer survivors compared to non-cancer controls.

9.4 Strengths and limitations

9.4.1 Selection of the samples

The systematic assessment of the literature (Chapter 3) showed that nearly one-half of studies had a high risk of selection bias due to recruitment of convenience samples and a high proportions of patients refusing to participate in the study. In addition, studies were heterogeneous in terms of participants' characteristics, clinical profile of the patients, and inclusion of patients at different times since diagnosis. This limited generalisability of results to the broad group of breast cancer survivors in the source population. In this thesis, population-based data were used to quantify the association between breast cancer survivorship and adverse mental health-related outcomes, and to identify patients for the study of quality of life; no restrictions were applied in terms of time since diagnosis, stage of the disease, disease progression, or comorbidity, and therefore the results in this thesis are more likely to apply to the broad population of breast cancer survivors. Selection bias is unlikely to have affected the results of the study of EHRs (Chapter 6). However, the participation rate in the study of patient-reported outcomes (Chapter 7) was low, and this might have introduced bias in the results. Even though participants and non-participants were similar in age and practice-postcode IMD quintile, they may have differed in terms of the outcome, as surveys tend to include healthier women. The results of this study may not be generalisable to the whole UK, as participation rate was very low in Northern Ireland.

9.4.2 Ascertainment of the exposure

All participants in the research presented in Chapters 6, 7 and 9 were identified from the CPRD GOLD primary care database, which includes more than 90% of the cancers registered in the cancer registry (gold standard, as notification is required by law) [217]. This was considered acceptable for the study using EHRs only

(Chapter 6), and preferable to the alternative of using primary care data linked to data from cancer registries, which is only possible for nearly 50% of the primary care practices in England, and would limit sample size and power, in addition to limit the generalisability of the results. In the study involving patient-reported outcomes (Chapter 7), the lists of potentially eligible patients were selected from the CPRD GOLD database using the same methods and GPs were asked to confirm each patient's eligibility, which largely reduced the potential for misclassification of the exposure in this study. The results of the exclusions in this study also showed a low potential for misclassification in the study of EHRs, especially among breast cancer survivors, as only one of the 98 patients excluded from this group was excluded because they did not have breast cancer.

9.4.3 Ascertainment of outcomes

The CPRD GOLD primary care database is expected to have good sensitivity to capture mental health-related clinical diagnoses because of the breadth of the data available that includes symptoms, diagnoses and drug prescriptions, among others. This is in contrast to the studies of EHRs identified in Chapter 3, which often used data from psychiatric registries in the Nordic countries, that are likely to have very high specificity, but they may lack sensitivity. For example, the Danish Psychiatric Central Research Register includes data on psychiatric admissions, emergency room contacts, and outpatient treatments for mental disorders, but does not include most of the mild and moderate cases diagnosed and treated in primary care [282]. It reassuring that all results point towards similar conclusions.

A limitation of this thesis is the lack of validation of the outcomes definitions using the lists of codes produced for this thesis. The protocol of the study in Chapter 6 (available in Appendix 3) included plans to externally validate the results of the codelists using as gold standard data from the Adult Psychiatric Morbidity Survey [283]. However, such comparison was deemed unwise upon further assessment because this survey contains data on the frequency of selected mental disorders (e.g. generalised anxiety disorder, depressive episodes) in the week before the interview, evaluated with the revised Clinical Interview Schedule [284], and classified with the ICD-10 diagnostic criteria [223]. This is by far more specific than what could be reasonably obtained with EHRs, and thus no comparison was done. However, I attempted to minimise this limitation by producing codelists using a systematic approach (described in Appendix 3), and the results of previous validation studies included in Chapter 5 showed high positive predictive values.

The study of patient-reported outcomes (Chapter 7) used questionnaires to collect data on HRQoL and symptoms of anxiety and depression. While questionnaires are the preferred method to quantify HRQoL [285], the results for anxiety and depression should be interpreted as patients being at risk of the disorders, as HADS is a screening and not diagnostic tool.

9.4.4 Study designs

The study that quantified the risk of adverse mental health outcomes in breast cancer survivors compared to controls (Chapter 6) had a longitudinal study design and excluded women with evidence of the disorder in the year prior to the breast cancer exposure, ensuring that all events were incident. This is an important advantage of the research in this thesis compared to the previous studies whose cross-sectional design precluded the unequivocal assertion that the onset of the mental disorder was posterior to the breast cancer diagnosis (see Chapter 3).

A cross-sectional study design was chosen to evaluate HRQoL and mental health outcomes in breast cancer survivors and women with no history of cancer (Chapter 7). Unfortunately, resources were not available for a longitudinal study on HRQoL to ensure temporality. Despite this, the results of the comparison are still of interest for clinical practice, and they showed that women with breast cancer survivors have poorer HRQoL for some domains compared to women with no history of cancer.

9.4.5 Control for confounding

The breadth of information available in the CPRD GOLD primary care database enabled me to estimate the risk of adverse mental health outcomes in breast cancer survivors (Chapter 6), while controlling for important confounders such as age and deprivation at study design, and other confounders that have rarely been taken into account. The confounding effects of body mass index, smoking, and alcohol drinking, were also adjusted for, which was seldom done in previous studies. One must acknowledge, however, that the quality of the adjustments depended on the quality of the data recorded in the EHRs. For some variables, such as smoking (current, former or never smokers), no detailed data on frequency or quantity were available for analysis. The broad levels of exposure used may not have been sufficient to completely remove the effect of smoking or alcohol drinking. In addition, missing data for these variables is likely to depend on the values (e.g. a patient with

obesity may be more likely to have this recorded in the EHR than a patient with normal weight), which precluded multi-imputation of the missing values.

9.4.6 Role of chance

The CPRD GOLD primary care database is one of the largest databases of EHRs of longitudinal data at patient level, including over 18 million patients, and the study of the risk of adverse mental health-related outcomes (Chapter 6) was well powered to detect differences in the risk between the two groups. The sample size calculations presented in the study protocol showed that the number of breast cancer survivors (the limiting factor, since controls would be easier to find) would provide sufficient power to estimate associations of similar magnitude of that reported in previous studies. The study of patient-reported outcomes (Chapter 7) was also well powered to compare HRQoL between the two groups, as well as mean scores of anxiety, but was underpowered to compare the mean scores of depression, and anxiety and depression categorised with the relevant cut-offs, between the two groups. Unfortunately, the sample size calculations showed that 26,340 women (13,170 in each group) would need to be invited to participate in the study to reduce the potential for an erroneous conclusion in all comparisons. This was not feasible for this PhD for reasons of time and cost. The study of patient-reported outcomes was still larger than most studies identified in the systematic review (Chapter 3), and confidence intervals were reported, when possible, to enable the reader to infer on the direction and precision of the estimates.

9.4.7 Multiple approaches

A strength of this thesis is the use of multiple approaches (e.g. data routinely collected as well as patient-reported outcomes) and study designs (i.e. systematic review, matched cohort study, cross-sectional study) to address the aims. Even though each approach has limitations, the use of multiple approaches helped to overcome those inherent to any single approach. For example, selection bias cannot be ruled out from the study of patient-reported outcomes (Chapter 7), but the results of the study that used only data from the CPRD GOLD primary care database (Chapter 6) are unlikely to have been importantly affected by selection bias. On the other hand, patient-reported outcomes allowed for the capture of subjective experiences that may negatively affect a patient's HRQoL, but are less likely to be captured in the EHRs.

Another strength of the study involving EHRs only (Chapter 6) was that the breadth of data in the CPRD GOLD primary care database allowed for multiple outcomes to be studied. This provided a comprehensive picture of the burden of mental health-related conditions in this patient population. The systematic review of the adverse mental health outcomes in breast cancer survivors (Chapter 3) included studies looking at any adverse mental health outcome, which allowed for the identification of outcomes for which not much is known (e.g. sleep disorders), and their subsequent study.

9.5 Contribution to knowledge

9.5.1 Summary of the evidence on the associations between breast cancer survivorship and mental health conditions

The main focus of studies of mental health in breast cancer survivors tend to be on outcomes of depression and anxiety and as a result systematic reviews on the topic also narrowly concentrated on these alone. Chapter 3 not only provides an up-to-date summary of the evidence available on depression and anxiety but included all mental health outcomes listed in DSM/ICD in the search where data were available. This added a level of comprehensiveness not previously seen and confirmed the paucity of evidence on a range of other outcomes including sleep disorders and sexual dysfunction.

9.5.2 Risk of mental health and quality of life-related outcomes in breast cancer survivors in the UK, compared to women who have not had cancer

Previously, of the 66 studies investigating mental health outcomes in female breast cancer survivors compared to those without cancer, only one was conducted in the UK [255], including data from three years on breast cancer survivors five or more years into the survivorship period, and focused on two outcomes, anxiety and depression. The research in this thesis built on this previous work, analysing 31 years of data, from 1988 to 2018, to evaluate the risk of not only anxiety and depression, but seven other mental health and HRQoL-related outcomes and investigated associations from as early as the first year after diagnosis. This generated evidence for outcomes where none existed (cognitive dysfunction,

fatigue, sexual dysfunction, pain, opioid prescriptions, sleep disorders, and fatal and non-fatal self-harm), and provided estimates of the risk of anxiety and depression in the early period of cancer survivorship. In doing this, it was also demonstrated the feasibility of using the CPRD primary care database to study these outcomes.

9.5.3 Quality of life of breast cancer survivors in the UK compared to women who did not have cancer

Very few studies are available for the HRQoL of breast cancer survivors in the UK. Where existing, these most often used tools that only comprised generic domains of quality of life, or that were created for the treatment period; both of which may not fully capture the experience of living beyond the acute phases of breast cancer treatment. In this thesis, HRQoL was measured with a validated tool developed for long-term cancer survivors, including domains for generic as well as cancer-specific quality of life. The novel research in this thesis provides robust results on the comparison of HRQoL in long-term breast cancer survivors in the UK, compared to women who never had cancer. The results not only highlighted that breast cancer survivors experienced impaired quality of life in the domains of cognitive function, fatigue and sexual dysfunction but also identified a high-risk group of the population (more advanced disease and/or treated with chemotherapy) with poorer quality of life compared to other breast cancer survivors and those without cancer.

9.5.4 Comparison of data in clinical records and patient-reported outcomes

EHRs hold information for several domains of HRQoL but its use as a proxy for the patients' HRQoL had never been assessed. The results of this thesis show that EHR are unlikely to be a good source of data to study HRQoL. This highlights the importance of patient reported outcomes, which even though costly or time consuming to collect, adds much needed insight into those quality of life outcomes not routinely captured in GP practices.

9.6 Implications for clinical practice

9.6.1 Patient education on the mental health consequences of their disease throughout the survivorship continuum

Patient education for prevention and early detection of treatment-related sequelae should start as early as possible (in the pre-operative period) [286], but current models focus on physical aspects and overlook mental health [286, 287]. Raising patient awareness on mental health conditions is needed, particularly as recent research showed that eight in 10 women with breast cancer were not told about the potential long-term impact of the cancer on their mental health [288]. Talking about mental health and common emotional challenges experienced by other patients may help women to understand better their own emotional journey, reduce stigma, and encourage patients to raise concerns about their mental health should they need. Educational interventions for fatigue, for example, have been shown to decrease anxiety and improve HRQoL [289].

9.6.2 Increased screening of mental disorders in breast cancer survivors followed in primary care may be needed

The raised risk of several mental disorders in breast cancer survivors calls for increased surveillance in primary care, especially among younger women (<60 years) and women treated with chemotherapy. For depression, a risk prediction algorithm is available and may help identify patients at increased risk [290]. NICE guidelines also recommend opportunistic screening for depression in adults with a chronic health problem [291]. The optimal screening method will depend on the specific mental health condition but, when possible, data should be collected using validated tools to enable progress monitoring [291]. It should be noted that patients may benefit from being asked about fatigue, cognitive and sexual dysfunction, as these were shown to negatively affected patients' HRQoL but were rarely recorded in the patients' EHRs.

9.6.3 Increased awareness of mental health-related conditions among health-care professionals is needed

Increased awareness among health care professionals, particularly primary care physicians, of the raised risks of anxiety, depression, fatigue, sexual dysfunction,

sleep disturbance and pain is needed to improve detection of the mental health conditions. Increased awareness may also help with communication between patients and clinicians, particularly about fatigue, cognitive problems, and sexual dysfunction, which negatively influence HRQoL. Communication about sex-related issues appears to be poor [292], highlighting the need for GPs to raise these issues [293].

9.6.4 Equipping health care professionals with evidence-based strategies to identify and manage mental health conditions in breast cancer survivors may be needed

Identification and management of mental health conditions in breast cancer survivors can be challenging due to the short consultation times with a panoply of somatic and psychological manifestations [294], and due to uncertainty about effectiveness and/or safety of the interventions. For sexual dysfunction, for example, clinicians tend to have little training on the topic [293, 295], and some may have concerns over the effect of hormonal vaginal treatments in patients with oestrogen-receptor positive breast cancer [296] and be unaware of the recommendations for lubricants and moisturisers [297]. Safety concerns have also been raised for the treatment of severe anxiety and depression with antidepressants, as per guidelines [53, 298], due to a possible interaction between antidepressants and tamoxifen. This is biologically plausible, as both substances are metabolised by cytochrome P450, and since antidepressants tend to have a better affinity for the enzyme, there is a potential for preferential binding of tamoxifen [299]. Studies have reported contradictory results about the increased risk of cancer recurrence in breast cancer patients taking antidepressants, with some studies finding no effect for any antidepressant [300], while others found increased risk of recurrence in patients prescribed paroxetine or trazodone [301]. Whether information is lacking or available, there is a need to equip health care professionals with clear guidance on what is safe and unsafe, effective and ineffective, as well as unclear interventions in these patients.

9.6.5 Encouraging utilization of cancer rehabilitation services, and other forms of social interaction

Of the variables that were found to be associated with poorer HRQoL (i.e. younger age, lower education, chemotherapy treatment), none are amenable to change.

However, there is evidence that factors such as social support and physical activity exert a protective effect on depression [21-23]. Recently, it has been reported that 75% of breast cancer survivors in the UK felt more socially isolated at the end of treatment than at diagnosis [288]. Raising awareness about the services available to patients, and how to access them, cannot be overlooked (e.g. support from Breast Cancer Care, or Mind, two UK based charities that provide support to breast cancer patients in need).

9.7 Implications for public health policy

9.7.1 Current provision of post-treatment support

Recognising the need for post-treatment support in cancer survivors, UK countries set out organised strategies for patients beyond cancer [302-304]. In England, the cancer strategy 'Achieving World-Class Cancer Outcomes: A Strategy for Cancer 2015-2020' includes access to a Recovery Package by 2020 among their goals [302]. Development of the cancer strategy included a Health and Wellbeing event, in which an overwhelming 96% of patients supported the idea of a breast cancer-specific health and wellbeing course at the end of treatment [305]. However, data to date show that 51% of NHS Hospital trusts do not provide breast cancer-specific support events. Breast cancer survivors seeking NHS support for mental health will be affected by the long waiting times currently observed. A survey commissioned by the Royal College of Psychiatrists revealed that one in four patients with a diagnosed mental health condition waited more than three months to access treatment in a NHS mental health service after referral [306].

9.7.2 Current needs and future planning

Public health interventions to tackle the burden of mental health conditions ought to be comprehensive, including risk reducing and reactive strategies. Preventive strategies such as improved patient support and patient education during the continuity of care cannot be overemphasized. Breast Cancer Now has created a course tailored to breast cancer survivors, which was found to improve patients' HRQoL, emotional wellbeing, and self-management measures [307]. Public health organisations should work towards every patient being able to access information

that meets their needs. Once significant distress is present, strategies are needed for early diagnosis and treatment of these conditions. As many as 41% of women in England reported not having received the professional support needed to cope with the long-term consequences of their disease [308]. This highlights the need for Cancer Alliances to provide or improve access to personalised support, as outlined in their priorities for 2019/2020 [308].

Mental health services are burdensome for publicly funded health care services, and the long-term provision of care that suits patients' needs is likely to require substantial investments, both in physical structures and in personnel. Waiting times for access to treatment for common mental health conditions needs to be shortened by increasing the supply of services, as current targets (75% of patients referred be treated within six weeks [309]) are not being met. Long term planning also needs to consider the need to build capacity in delivering psycho-oncology care.

9.8 Implications for further research

9.8.1 Drivers of the association between breast cancer survivorship and adverse mental health outcomes

One priority area for future research is to investigate the role of mediators of the association between breast cancer survivorship and adverse mental health outcomes, such as the type of surgery (lumpectomy vs. mastectomy, with and without reconstruction), receipt and type of systemic treatment (chemotherapy, endocrine and/or immunotherapy), tumour characteristics as well as presence of lymphedema. The role of having had disease progression, or another cancer diagnosis, also needs to be explored. The effect of age on the likelihood of cognitive dysfunction recorded in the EHRs also deserves further attention to ascertain whether this is a true increased risk, or differential recording of these codes by GPs. The aetiological components of the disorders also need to be explored further. The impact of chemotherapy, endocrine therapy and immunotherapy on depression, fatigue, sexual dysfunction and pain needs clarification, as these conditions negatively affect the patients' HRQoL and little is known about the exact mechanisms by which the risk is increased. Cognitive dysfunction has traditionally been linked to the cytotoxic effect of chemotherapy, but recent studies suggest that this might be mediated by post-traumatic stress symptoms [272]. A better

understanding of the drivers of adverse outcomes would help to identify opportunities for intervention, prevention and support.

9.8.2 Validation of the list of Read codes used to define mental health conditions

Recently, the Mental Health Data Set (MHDS) became available for linkage with the CPRD GOLD primary care database. This data set includes data from adult patients who accessed mental health services in secondary care and are thought to be suffering from a mental illness [310]. This could be used as the gold standard in a validation study aiming to assess the validity of Read codelists.

9.8.3 Longitudinal assessment of HRQoL in breast cancer survivors

Studies should focus on the longitudinal assessment of HRQoL in breast cancer survivors, as results are likely to change by domain across the survivorship period, and could help to identify critical periods for intervention (e.g. depression may arise on discharge from hospital follow-up, when women often feel isolated [288]).

9.8.4 Comparison of mental health outcomes in women who had breast cancer, women treated for in situ tumours, and women with no history of cancer.

The introduction of mass screening programs for breast cancer in the last decades resulted in many women being detected with *in situ* tumours, most often ductal carcinomas *in situ*. Patients diagnosed with non-invasive tumours have very good prognosis (10-year observed survival for patients surgically treated of 98.5% [311]), however, there is the potential for comparable adverse psychological effects as treatment modalities are similar to that of early-stage invasive breast cancer. This should be the subject of future studies. Also, the mental health impact of screening needs to be considered, particularly of false positive results.

9.8.5 Pressing need for evidence-based interventions for treatment of breast cancer survivors with mental health conditions

The benefit of most interventions for mental health conditions in breast cancer survivors needs to be established, including the optimal setting, method, and timing. There is an important gap in research about effective treatment strategies for

fatigue, sexual dysfunction and cognitive dysfunction, all of which negatively affected HRQoL. Trials are also needed to pilot and evaluate the feasibility and effect of interventions aiming at raising awareness and screening for mental health conditions. The acceptability of the interventions is likely to vary by age and physical condition of the patients (e.g. internet-based interventions may have less acceptability among senior patients).

9.9 Conclusions

In conclusion, breast cancer survivors in the United Kingdom have an increased risk of anxiety, depression, fatigue, pain, sexual dysfunction, sleep disorder and being prescribed opioid analgesics compared to women with no history of cancer. The risk of these disorders was particularly elevated in women within the first few years of breast cancer survivorship, and more pronounced in younger women. Increased risks of fatigue and pain were found to persist for 5-10 years post-diagnosis. In addition, breast cancer survivors had poorer HRQoL in the domains of cognitive problems, sexual function, and fatigue. Women with advanced-stage cancer at diagnosis, and/or treated with chemotherapy, had poorer HRQoL and mental health. It is imperative to raise awareness among patients, health-care professionals, and policy makers about the specific needs to the largest group of cancer survivors in the UK.

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11 Appendices

11.1 Appendix 1 Supplementary materials to the paper in Chapter 3

Carreira H, Williams R, Müller M, Harewood R, Stanway S, Bhaskaran K.

Associations Between Breast Cancer Survivorship and Adverse Mental Health Outcomes: A Systematic Review.

J Natl Cancer Inst. 2018 Dec 1;110(12):1311-1327

Contents

Supplementary Materials

Supplementary Table 1. MEDLINE search expression in OVID®.

#	Search
1	exp Breast Neoplasms/
2	(breast and (cancer* or carcinoma* or tumo?r* or neoplas*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3	1 or 2
4	exp catatonia/ or exp depression/ or exp self-injurious behavior/ or exp anxiety/
5	mental disorders/ or exp anxiety disorders/ or exp "bipolar and related disorders"/ or exp "disruptive, impulse control, and conduct disorders"/ or exp dissociative disorders/ or "feeding and eating disorders"/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or pica/ or exp mood disorders/ or exp motor disorders/ or neurocognitive disorders/ or amnesia/ or cognition disorders/ or auditory perceptual disorders/ or mild cognitive impairment/ or consciousness disorders/ or delirium/ or dementia/ or exp neurotic disorders/ or exp personality disorders/ or exp "schizophrenia spectrum and other psychotic disorders"/ or sexual dysfunctions, psychological/ or exp sleep wake disorders/ or exp somatoform disorders/ or exp substance-related disorders/ or exp "trauma and stressor related disorders"/
6	(depressi* or dysthymia or catatonia or self-injur* or self-injury or self-injurious or self-mutilation or "self mutilation" or suicid* or self-harm or "self harm" or "self injury" or anxious* or anxiety or (panic adj1 (disorder# or attack#)) or catastrophi* or (mental adj1 (disorder or disorders)) or phobia or phobic or neurotic or (compulsive adj1 disorder) or bipolar or neurotic or (personality adj1 disorder) or psychotic or psychosis or paranoid or delusional or (sexual adj1 (disorder or dysfunction or problem#)) or insomnias or (sleep adj1 (disorder or dysfunction or problem#)) or somatoform or (substance adj3 (disorder or problem#)) or stress ajd3 disorder or (adjustment adj3 disorder)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7	4 or 5 or 6
8	(prevalence# or frequenc* or incidence# or risk or rate* or ratio or odds or epidemiolog* or percent* or outcomes or hazard).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9	3 and 7 and 8
10	Humans/
11	Animals/
12	10 and 11
13	11 not 12
14	9 not 13

Supplementary Table 2. Criteria used to judge the risk of bias in the systematic review studies.

Judgment	Selection bias	Outcome variable: information bias	Design-specific source of bias (temporality)	Confounding by age and socio-economic status	Statistical methods	Missing data	Conflict of interest
Low risk of bias	Describes the source and methods of selection of the participants AND Eligibility criteria given AND (Participants selected at random OR population-based study) AND Proportion of participation >50% AND/OR ≤30% of attrition (for cohort studies with a pre-defined follow up time for the entire cohort)	Outcome assessed through one of the following: Psychiatric interviews OR Evidence of having been prescribed anxiolytics (for anxiety) and antidepressants (for depression) OR Record of a diagnostic code for mental health (for studies including electronic health records) OR Country's official mortality registry data (for completed suicide) OR Objective data on the trajectories of cognitive function over time (for neurocognitive dysfunction)	The breast cancer diagnosis preceded the onset of the mental health outcome OR Diagnosis of the relevant outcome prior to the BC diagnosis taken into account by restriction, matching or in multivariate analysis	The study attempts to minimise confounding using one or more of the following: Matching for age and for an indicator of socio-economic status (e.g. education, attending the same primary care practice, or small geographic area) AND/OR Multivariate analysis, reporting mean scores or association measures, adjusted for age and a socio-economic status indicator	Appropriate use of statistics for primary analysis of effect (specific to each study design and data)	≤15% of missing data (for studies with questionnaires), with or without multiple imputation methods for missing data OR >15% of missing data, with missing data imputed using multiple imputation methods	The study authors explicitly report the existence, or not, of conflicts of interests OR The study's funding source is acknowledged
High risk of bias	Participants not selected at random OR Proportion of participation ≤50% OR Women selected on the basis of a the relevant mental health outcome for this review OR >30% of attrition (for cohort studies with a pre-defined follow up time for the entire cohort)	Self-reported intake of anxiolytics (for anxiety) OR antidepressants (for depression)	Unclear whether the onset of the mental health outcome occurred before or after the breast cancer diagnosis OR Diagnoses of mental disorders before the onset of the BC not considered	The study only reports crude measures of frequency or association (e.g. univariate association, or mean scores of the instrument) OR (There are differences between the two the group of breast cancer survivors and the women in the comparison group for age OR for an indicator of socio-economic status)	Not appropriate use of statistics for primary analysis of effect	>15% of missing data (for studies using questionnaires), with missing data imputed with a measure of central tendency	The presence or absence of conflicts of interest is not reported and thus unknown AND No study's funding source is acknowledged
Unclear risk of bias	Unknown method of participants' recruitment OR Unknown exclusion criteria OR Unknown participation rate	Outcome assessed using self-reported scales	Not applicable	The study reports mean scores or measured of associations that were adjusted for an unclear or unknown list of potential confounders	Statistical methods not reported	Proportion of missing data not reported (for studies involving questionnaires) Not applicable if the study uses data from diagnoses ascertained via electronic records, or if formal statistical comparisons between breast cancer survivors and women who did not have cancer could not be done.	Not applicable

Supplementary Table 3. Anxiety: main characteristics and results of the studies that compared the risk, prevalence or severity of anxiety (disorders or symptoms) between breast cancer survivors (>1 year) and women who did not have cancer.

First author, year of publication Country	Breast cancer survivors				Comparison group	Outcome assessment	Quantitative measure of the outcome		Relative risk estimate (RR, OR, SIR, PR)	P-value or 95% confidence interval	Notes
	Type of population and main characteristics	Stage at diagnosis (%)	Breast cancer treatments (%)	Time since diagnosis/ treatment in years: mean/ median (SD), range	Type of population and main characteristics		Breast cancer survivors	Comparison group			
Electronic health records											
Hjerl et al., 2002 [1] Denmark (continues)	Population-based All 60,431 women aged >15 years with a first primary invasive breast cancer registered in the national Cancer Registry in 1970-1993.	All	ND	4 (ND), 0-15 (Median cohort follow up: 4 years since diagnosis; range: 0 to 15)	Population-based Danish female population aged >15 years.	EHR, first ever psychiatric admission, as registered in the Danish Psychiatric Central Registry ICD-8 codes: 300.81 and 300.00-300.99, except 300.49	Cumulative incidence: 0.25%	Cumulative incidence: 0.20%	SIR= 1.3 *	95%CI: 1.1-1.5	
									By age: 30-34: SIR= 1.93 35-39: SIR= 1.28 40-44: SIR= 0.91 45-49: SIR= 0.89 50-54: SIR= 1.24 55-59: SIR= 1.56 * 60-64: SIR= 1.18 65-69: SIR= 1.42 70-74: SIR= 1.98 * 75-79: SIR= 0.47 80-84: SIR= 1.27 85-89: SIR= 2.91 ≥90: SIR= 8.74	By age: 95%CI:0.69-4.15 95%CI:0.58-2.38 95%CI:0.48-1.52 95%CI:0.54-1.37 95%CI:0.84-1.76 95%CI:1.04-2.22 95%CI:0.69-1.86 95%CI:0.81-2.26 95%CI:1.12-3.21 95%CI:0.08-1.46 95%CI:0.21-3.91 95%CI:0.17-12.8 95%CI:0.50-38.5	Standardised incidence ratio estimated considering all follow up time since diagnosis.
									By calendar period: 1970-74: SIR=1.11 1975-79: SIR=1.15 1980-84: SIR=1.04 1985-89: SIR=1.80 * 1990-93: SIR=0.89	By calendar period: 95%CI:0.58-1.91 95%CI:0.78-1.61 95%CI:0.72-1.45 95%CI:1.37-2.31 95%CI:0.55-1.35	-
	Women aged >15 years with first invasive breast cancer registered in the national Cancer Registry in 1970-1993 and living outside Copenhagen city area (non-metropolitan).	All	ND	4 (ND), 0-15	Female population aged >15 years and living outside Copenhagen city area (non-metropolitan).	EHR, first ever psychiatric admission, as registered in the Danish Psychiatric Central Registry ICD-8 codes: 300.81 and 300.00-300.99, except 300.49	-	-	SIR= 1.3 *	95%CI: 1.1-1.5	Standardised incidence ratio estimated considering all follow up time since diagnosis.
				1.5			-	-	SIR= 1.4	95%CI: 0.8-2.1	Approximate SIR values estimated from the graphics provided in the original study.
				2.5			-	-	SIR= 1.1	95%CI: 0.6-1.8	
				3.5			-	-	SIR= 1.6	95%CI: 0.9-2.5	
				4.5			-	-	SIR= 1.5	95%CI: 0.6-2.4	
				5.5			-	-	SIR= 0.7	95%CI: 0.3-1.6	
				6.5			-	-	SIR= 1.3	95%CI: 0.5-2.6	
				7.5			-	-	SIR= 1.2	95%CI: 0.4-2.5	
				8.5			-	-	SIR= 0.8	95%CI: 0.3-2.2	
				9.5			-	-	SIR= 0.7	95%CI: 0.2-2.1	
				10.5			-	-	SIR= 0.4	95%CI: 0.1-1.9	
				11.5			-	-	SIR= 1.0	95%CI: 0.3-2.9	
				12.5			-	-	SIR= 2.6	95%CI: 0.8-6.0	
				13.5			-	-	SIR= 0.5	95%CI: 0.1-2.1	

Hjerl et al., 2002 [1] Denmark (continued)	Women aged >15 years with first invasive breast cancer registered in the national Cancer Registry in 1970-1993 and living in Copenhagen city area (metropolitan).	All	ND	4 (ND), 0-15	Female population aged >15 years and living in Copenhagen city area (metropolitan).	EHR, first ever psychiatric admission, as registered in the Danish Psychiatric Central Registry ICD-8 codes: 300.81 and 300.00-300.99, except 300.49	-	-	SIR= 1.1	95%CI: 0.8-1.6	Standardised incidence ratio estimated considering all follow up time since diagnosis.
				1.5			-	-	SIR= 1.4	95%CI: 0.5-2.5	Approximate values estimated from the graphics provided in the original study.
				2.5			-	-	SIR= 1.5	95%CI: 0.4-3.0	
				3.5			-	-	SIR= 0.7	95%CI: 0.2-2.2	
				5.0			-	-	SIR= 0.8	95%CI: 0.3-1.8	
				6.5			-	-	SIR= 1.3	95%CI: 0.4-4.0	
				7.5			-	-	SIR= 3.3	95%CI: 1.0-7.6	
				9.5			-	-	SIR= 0.5	95%CI: 0.1-1.8	
				13.0			-	-	SIR= 0.7	95%CI: 0.1-2.9	
Hung et al., 2013 [2] Taiwan	Population-based 26,629 women with no prior mood disorder and cancer, with breast cancer registered in the National Health Insurance Database in 2000-2005.	All	ND	2.7 (ND), ND-7 (median follow up years for breast cancer survivors: 2.7; for matched cohort: 3.2)	Population-based 26,629 women randomly selected from 1 million women who did not have breast cancer registered in the same database, individually matched for age and Charlson comorbidity score (categories of matching not reported).	EHR, recorded in the Registry for Catastrophic Illness with an ICD-9-CM code for anxiety (300-300.3, 300.5, 300.7-300.9)	Incidence rate: 49.64 per 1,000 person-years Cumulative incidence: 15%	Incidence rate: 40.82 per 1,000 person-years Cumulative incidence: 14%	RR= 1.22 *	95%CI: 1.16-1.27	Includes patients diagnosed with breast cancer at <1yr.
				2			Cumulative incidence: 11%	Cumulative incidence: 9%	RR= 1.22 * †	95%CI: 1.16-1.29	Approximate cumulative incidence values estimated from the graphics provided in the original study.
				4			17%	15%	RR= 1.13 * †	95%CI: 1.09-1.18	
				6			22%	20%	RR= 1.10 * †	95%CI: 1.06-1.14	
Khan et al., 2010 [3] United Kingdom	Population-based 16,938 women aged ≥30 with breast cancer registered in the UK General Practice Research Database.	All	ND	ND (ND), ≥5	Population-based 67,649 women who did not have breast or colorectal cancer at beginning of follow up; individually matched for age (± 1 year) and primary care practice (small area).	EHR, having primary care consultations for anxiety	Prevalence: 5.4%	Prevalence: 5.0%	OR= 1.06	95%CI: 0.97-1.16	Odds ratio adjusted for Charlson comorbidity score, previous history of anxiety and death.
						EHR, being prescribed an anxiolytic at least once	Prevalence: 9.0%	Prevalence: 7.7%	OR= 1.08 *	95%CI: 1.01-1.15	Odds ratio adjusted for Charlson comorbidity score, number of consultations, and death.
Yang et al., 2017 [4] Sweden (continues)	Population based All 4,402 women diagnosed with an in situ breast cancer at the age of 20-80 years between 2001-2009	0	ND	4.7 (4.4), 0-10 (median (IQR) duration of follow up: 4.7 (4.4))	Population based 452,507 women randomly selected from the respondents to the 1990 census	EHR, ICD-10 diagnostic codes for anxiety (F40-F41) at in patient or outpatient hospital visits	Cumulative incidence: 0.9%	Cumulative incidence: 0.9%	SIR= 0.99 By age group: 20-44: SIR= 1.18 45-54: SIR= 0.97 55-64: SIR= 0.95 65-80: SIR= 0.91	95%CI: 0.73-1.34 By age group: 95%CI: 0.59-2.36 95%CI: 0.57-1.64 95%CI: 0.53-1.72 95%CI: 0.45-1.81	Standardised incidence ratio estimated considering all follow up time since diagnosis.
				0-0.5			<0.1%	0.1%	SIR= 0.53	95%CI: 0.13-2.12	Standardised incidence ratios were standardised by calendar period (1-year categories), age (5-year categories), and region of residence (North, Stockholm-Gotland, South, Southeast, Uppsala-Orebro, West).
				0.5-1			0.0%	0.0%	-	-	
				1-2			0.3%	0.2%	SIR= 1.62	95%CI: 0.92-2.85	
				2-5			0.4%	0.4%	SIR= 1.09	95%CI: 0.68-1.73	
				5-10			0.2%	0.2%	SIR= 0.90	95%CI: 0.47-1.74	

Yang et al., 2017 [4] Sweden (continued)	Population based All 4,402 women diagnosed with an in situ breast cancer at the age of 20-80 years between 2001-2009	0	ND	4.7 (4.4), 0-10 (median (IQR) duration of follow up: 4.7 (4.4))	452,507 women randomly selected from the respondents to the 1990 census	EHR, being prescribed an anxiolytic (group N05B of the ATC classification system)	Cumulative incidence: 4.5%	Cumulative incidence: 2.8%	SIR= 1.64 *	95%CI: 1.43-1.88	Standardised incidence ratio estimated considering all follow up time since diagnosis. Standardised incidence ratios were standardised by calendar period (1-year categories), age (5-year categories), and region of residence (North, Stockholm-Gotland, South, Southeast, Uppsala-Orebro, West). The following were significant predictors of increased anxiety among breast cancer survivors: younger age at diagnosis, presence of co-morbidities, having moderate and high histological grade, and having had chemotherapy.
									By age group: 20-44: SIR= 1.52 45-54: SIR= 1.69 * 55-64: SIR= 1.57 * 65-80: SIR= 1.69 *	By age: 95%CI: 0.96-2.42 95%CI: 1.28-2.22 95%CI: 1.22-2.02 95%CI: 1.34-2.14	
				0-0.5			-	-	SIR= 3.86 *	95%CI: 3.17-4.71	
				0.5-1			-	-	SIR= 0.93	95%CI: 0.61-1.41	
				1-2			-	-	SIR= 1.28	95%CI: 0.97-1.70	
				2-4.5			-	-	SIR= 0.91	95%CI: 0.64-1.28	
	Population based All 40,849 women diagnosed with an invasive breast cancer at the age of 20-80 years between 2001-2009	I-IV	ND	4.5 (4.5), 0-10 (median (IQR) duration of follow up: 4.4 (4.5))	Population based 452,507 women randomly selected from the respondents to the 1990 census	EHR, ICD-10 diagnostic codes for anxiety (F40-F41) at in patient or outpatient hospital visits	Cumulative incidence: 1.4%	Cumulative incidence: 0.9%	SIR= 1.55 *	95%CI: 1.43-1.68	
									By age group: 20-44: SIR= 1.84 * 45-54: SIR= 1.56 * 55-64: SIR= 1.58 * 65-80: SIR= 1.31 *	By age group: 95%CI: 1.54-2.21 95%CI: 1.34-1.81 95%CI: 1.35-1.84 95%CI: 1.10-1.56	
				0-0.5			0.2%	0.1%	SIR= 2.53 *	95%CI: 2.05-3.13	
				0.5-1			0.2%	0.1%	SIR= 2.30 *	95%CI: 1.85-2.87	
				1-2			0.3%	0.2%	SIR= 2.00 *	95%CI: 1.69-2.38	
				2-5			0.4%	0.4%	SIR= 1.17 *	95%CI: 1.01-1.36	
				5-10			0.3%	0.2%	SIR= 1.18	95%CI: 0.97-1.42	
	Population based All 40,849 women diagnosed with an invasive breast cancer at the age of 20-80 years between 2001-2009	I-IV	ND	4.5 (4.5), 0-10 (median (IQR) duration of follow up: 4.4 (4.5))	Population based 452,507 women randomly selected from the respondents to the 1990 census	EHR, being prescribed an anxiolytic (group N05B of the ATC classification system)	Cumulative incidence: 6.4%	Cumulative incidence: 2.5%	SIR= 2.52 *	95%CI: 2.43-2.62	
									By age group: 20-44: SIR= 3.96 * 45-54: SIR= 3.04 * 55-64: SIR= 2.50 * 65-80: SIR= 2.04 *	By age group: 95%CI: 3.56-4.40 95%CI: 2.81-3.30 95%CI: 2.33-2.68 95%CI: 1.91-2.17	
				0-0.5			-	-	SIR= 6.13 *	95%CI: 5.81-6.47	
				0.5-1			-	-	SIR= 1.90 *	95%CI: 1.72-2.10	
				1-2			-	-	SIR= 1.47 *	95%CI: 1.35-1.61	
				2-4.5			-	-	SIR= 1.38 *	95%CI: 1.26-1.52	
Studies involving scales											
Cohen et al., 2011 [5] Israel	Convenience sample 56 married Israeli Arab breast cancer survivors, post treatment and free of disease recruited from one hospital.	I-III (ND%)	Srg, C: 48.2% Srg, M: 51.8% Srg, R: 12.5% CT: 85.7% RT: 85.7% HT: 58.9%	4.8 (4.2), 1-17	Convenience sample 66 married and 'healthy' Arab women living in Israel, approached in community settings; individually matched for age and education (matching categories not reported).	BSI-18	BSI-18 mean score (SD): 2.7 (1.2)	BSI-18 mean score (SD): 2.2 (0.9)	-	P<0.05 *	Higher levels of anxiety associated with higher levels of depression, somatization and emotional distress in both groups (P<0.001). Higher levels of anxiety associated with lower body image in breast cancer survivors only (P=0.05).

Boehmer et al., 2015 [6] ND	Convenience sample 85 lesbian or bisexual breast cancer survivors post-active treatment recruited via advertisements, flyers, etc. (3.5% of whom had had cancer recurrence).	I-III (100%)	ND	4.5 (ND), 1-10	Convenience sample 85 lesbian or bisexual women with no history of cancer, not using hormone therapy, recruited via flyers, advertisements, etc.; individually matched for age (± 3 years) and partner status (partnered vs. unpartnered).	Anxiolytics intake (self-reported)	Prevalence: 3.5%	Prevalence: 1.2%	PR=2.92 †	95%CI: 0.31-27.1	Anxiety was more common in women taking any psycho pharmacological medication, compared to those who did not (OR=3.78, 95%CI: 1.76 to 8.09).
						HADS score ≥8	Prevalence: 45.2%	Prevalence: 36.5%	PR=1.24 †	95%CI: 0.86-1.78	
Calvio et al., 2010 [7] United States	Convenience sample 122 breast cancer survivors, working full-time for ≥1 year, with computer and internet, recruited via advertisements and flyers.	I (36.9%) II (44.3%) III (17.2%)	Srg, ND: 96.7% CT: 82.8% RT: 73.0% HT: 45.9% IT: 13.1%	3.1 (2.4), 1-10	Convenience sample 113 women without cancer, working full-time for ≥1 year, with computer and internet, recruited via advertisements and flyers.	HADS	HADS mean score (SD): 7.8 (3.0)	HADS mean score (SD): 7.1 (2.6)	-	P<0.01 *	Higher HADS scores indicate more anxiety symptoms. Mean scores adjusted for marital status (cohabitating with partner vs. single/not cohabitating), race (Caucasian vs. non-Caucasian), ethnicity (Hispanic vs. non-Hispanic), age (<40, 41-50, 51-65), income (0-39,000; 40-59,000; 60-79,000; 80-89,000; 80-99,000; ≥100,000), and menopausal status (currently going through, premenopausal, postmenopausal).
Dahl et al., 2011 [8] Norway	Convenience sample 337 tumor free breast cancer survivors treated with radiotherapy during 1998 and 2002 in one hospital.	II (ND) III (ND)	Srg, C: 24% Srg, M: 76% CT: 82% RT: 100% HT: 81%	3.9 (ND), 2.6-6.9	Convenience sample 1,685 women randomly selected from a population-based sample of women with no history of cancer who provided questionnaires with complete data; individually matched for age (± 5 years).	HADS	HADS mean score (SD): 6.3 (2.8)	HADS mean score (SD): 4.8 (3.7)	-	P<0.001 *	Higher HADS score indicates more anxiety symptoms. Mean scores adjusted for level of education, on disability pension and menopausal status. Higher scores of HADS for anxiety were associated with more insomnia symptoms in breast cancer survivors and in controls (p<0.001).
Miao et al., 2016 [9] China	Convenience sample 23 patients with breast cancer who had been treated with chemotherapy at a local hospital.	I-III (100%)	CT: 100%	3 (0.3),	Convenience sample 26 age-matched healthy controls selected amongst patients relatives and local universities; matched for age (matching method not reported).	HRS-A	HRS-A mean score (SD): 4.96 (1.43)	HRS-A mean score (SD): 4.5 (1.22)	-	P=0.232	Higher HRS-A score indicates more anxiety symptoms.

Rubino et al., 2007 [10] Italy	Convenience sample 33 consecutive patients who had had breast-reconstruction after mastectomy, in 2001-2002.	ND	Srg, M: 100% Srg, R: 100%	ND (ND), >1	Convenience sample 33 'healthy' women, randomly selected amongst the personnel of the local university.	HRS-A, applied during psychiatric interview Cut-off score: >14	Prevalence: 24.2%	Prevalence: 0.0%	PR=7.99 * †	95%CI: 1.06-60.34	PR calculated by the authors of the present study. For calculation purposes, it was assumed that one person in the non-cancer group had the outcome.
Boele et al., 2015 [11] The Netherlands	Convenience sample Post-menopausal breast cancer survivors with no diagnosis of psychiatric illness, not treated with adjuvant CT, selected from the medical records of the Cancer Institute.	ND	Srg, ND: 95% CT: 0% RT: 65% HT: 100% / 0%	Exposure to HT: 3.2 (1.9), 1.5-7; Unexposed to HT: 2.8 (0.3), 2.3-3.3.	Convenience sample 44 friends or family members of the women who had had breast cancer, with no history of breast cancer, matched for age and education (method of matching not reported).	HSCL-25	HSCL-25 mean score (SD): HT: 11.17 (10.39) No HT: 13.57 (11.74)	HSCL-25 mean score (SD): 9.92 (10.55)	-	P=0.30	Higher HSCL-25 score indicates more anxiety symptoms. P adjusted for age and estimated premorbid IQ. Women with higher anxiety levels had significantly lower processing speed evaluated as part of cognitive function.
Kreukels et al., 2008 [12] The Netherlands	Convenience sample 63 women who had non-metastatic breast cancer, with no history of psychiatric diseases.	I-III (100%)	CT: 100% HT: 40%	~ 1 (follow up at 12 months after CT)	Convenience sample 60 friends or family of the patients with the same age who never had cancer, matched for age (method of matching not reported).	HSCL-25	HSCL-25 mean score (SD): 16.3 (12.2)	HSCL-25 mean score (SD): 8.7 (7.9)	-	P<0.001 *	Higher HSCL-25 score indicates more anxiety symptoms.
Amir et al., 2002 [13] Israel	Convenience sample 39 women free of cancer symptoms for ≥3 years and not under active treatment, identified through 2 hospitals.	I (46%) II (46%) III (8%)	Srg, C: 20% Srg, M: 80% CT: 66% RT: 41% HT: 46%	6.5 (ND), ≥5	Convenience sample 39 women who did not experience life-threatening disease, recruited by unknown methods, matched for age and education (method of matching not reported).	SCL-90	SCL-90 mean score (SD): 0.87 (0.96)	SCL-90 mean score (SD): 0.49 (0.35)	-	P<0.001 *	Higher SCL-90 scores indicate more anxiety symptoms. Women who had breast cancer and reported PTSD symptoms had higher anxiety levels than those who did not report PTSD symptoms: 1.81 (1.23) vs. 0.67 (0.76), P<0.01.
Garcia-Torres et al., 2013 [14] Spain	Convenience sample 22 breast cancer survivors, free of relapse, identified by staff of the local association against cancer.	ND	Srg, M: 100% CT: 72.7%	8.2 (5.6), 1-21	Convenience sample 22 women with no history of cancer who volunteered with the same association against cancer.	ISRA (trait anxiety)	ISRA mean score (SD): 155.13 (71.51)	ISRA mean score (SD): 157.29 (82.45)	-	P=0.92	Correlation between anxiety and depression: r = 0.46, p<0.05.

Castellon et al., 2004 [15] United States	Convenience sample 53 women who had breast cancer at or before the age of 50, with no evidence of disease or recurrence, and no history of psychiatric disorder.	0-II (100%)	CT: 34% CT+HT: 34%	ND (ND), 2-5	Convenience sample 19 Healthy women recruited via fliers, newsletter articles and advertisements, or amongst the acquaintances of the hospital staff.	STAI (trait anxiety)	STAI mean score (SD), by treatment No CT: 31.9 (7.3) CT: 33.1 (8.1)	STAI mean score (SD): 38.0 (9.3)	-	P=0.075	Higher STAI scores indicate more anxiety symptoms.
Weitzner et al., 1997 [16] ‡ United States	Convenience sample 60 women with age <70 years, education ≥6th grade, no history of psychiatric diagnoses, >5 years disease-free, selected from those returning to the hospital for long-term follow up of cancer.	I (15%) II (63%) III (22%)	Srg, M: 100%	ND (ND), ≥5	Convenience sample 93 employees or volunteer workers at the same hospital with no personal or family history of breast cancer, age <70 years, education ≥6th grade, and no history of psychiatric diagnosis.	STAI (mild to moderate trait anxiety)	Prevalence: 27%	Prevalence: 15%	PR=1.8 †	95%CI: 0.95-3.41	Cut-off to be identified as case defined as >1 standard deviation above the mean.
						STAI (trait anxiety)	STAI mean score (SD): 35 (ND)	STAI mean score (SD): 33 (ND)	-	P<0.05 *	Adjusted for years of age and years of education. Women with stage III breast cancer at diagnosis had more trait anxiety compared to the other breast cancer survivors (P<0.004). Trait anxiety in breast cancer survivors was predictive of all domains of quality of life, except family functioning.
Root et al., 2015 [17] United States	Convenience sample 113 women aged <70 years who had breast cancer, were post-menopausal at diagnosis, receiving HT at recruitment, with no recurrence, no neurological or psychiatric diagnoses and who did not report sleep disturbances.	I (58%) II (0%) III (33%) IV (8%)	Srg, C: 75% Srg, M: 32% CT: 52% RT: 78% HT: 52%	4.2 (1.2)	Convenience sample 37 health women with no history of cancer or cancer treatment, post-menopausal, with no neurological or psychiatric diagnoses, matched for age and education (method of matching not reported).	STAI	STAI mean score (SD): 32.4 (8.6)	STAI mean score (SD): 33.1 (1.4)	-	P=0.62	Higher STAI scores indicate more anxiety symptoms.
Castellon et al., 2004 [15] United States	Convenience sample 53 women who had breast cancer at or before the age of 50, with no evidence of disease or recurrence, and no history of psychiatric disorder.	0-II (100%)	CT: 34% CT+HT: 34%	ND (ND), 2-5	Convenience sample 19 Healthy women recruited via fliers, newsletter articles and advertisements, or amongst the acquaintances of the hospital staff.	STAI (state anxiety)	STAI mean score (SD), by treatment No CT: 24.6 (3.6) CT: 28.6 (8.8)	STAI mean score (SD): 33.2 (8.0)	-	P=0.01 *	Higher STAI scores indicate more anxiety symptoms.

Conroy et al., 2013 [18] United States	Convenience sample 24 breast cancer survivors with history of non-metastatic disease and chemotherapy treated.	I (29%) IIa (33%) IIb (25%) IIIa (8%) IIIb (4%)	CT: 100% RT: 79%	6.4 (2.1), 3.2-10.2	Convenience sample 23 healthy women matched for age and education (categories of matching not reported)	STAI (state anxiety)	STAI mean score (SD): 30.2 (7.9)	STAI mean score (SD): 31.9 (9.1)	-	P>0.05	Higher STAI scores indicate more anxiety symptoms.
McDonald et al., 2010 [19] ND	Convenience sample 29 female breast cancer patients without neurobehavioral risk factors including neurologic, medical, or psychiatric conditions, except history of depression or anxiety.	0 (14%) I (35%) II (48%) IIIA (3%)	CT: 59% RT: 69%	~1.5 (0.15)	Convenience sample 18 healthy controls 'demographically matched' (method of matching not reported).	STAI (state anxiety)	STAI mean score (SD): CT: 27.6 (8.8) No CT: 28.3 (11.3)	STAI mean score (SD): 25.6 (7.2)	-	P>0.05	-
							Prevalence of anxiety: 7%	Prevalence of anxiety: 0%	PR= 1.25 †	95%CI: 0.12-12.65	Cut off for case: STAI-S T-score ≥65
Klein et al., 2011 [20] France	Population based 652 breast cancer survivors >5 post active-treatment, randomly selected from 3 population-based cancer registries by year of diagnosis.	0-IV (ND)	Srg, C: 64.7% Srg, M: 34.6% CT: 45.8% RT: 83.0% HT: 68.0%	Diagnosed in: 2000: 5.6 (1.0), 5.0-5.9 1995: 10.3 (0.6), 10.0-10.9 1990: 15.6 (1.0), 15.0-15.9	Population based 1,188 women with no history of cancer randomly selected from the electoral rolls; individually matched by age (±10 years) and place of residence (area of the cancer registry, and urban/rural).	STAI (state anxiety)	STAI mean score (SD): Diagnosed in: 2000: 34.4 (ND) 1995: 34.7 (ND) 1990: 33.2 (ND)	STAI mean score (SD): 28.5 (ND)	-	P<0.001 *	Higher STAI scores indicate more anxiety symptoms. Mean scores adjusted for age group, marital status, education, employment status, household monthly income comorbidities and hospitalization in the last 12 months.
Saleeba et al., 1996 [21] ‡ United States	52 women aged <70 years, education ≥6th grade, no history of psychiatric diagnoses, >5 years disease-free, selected from those under long-term follow up of breast cancer.	I (13%) II (63%) III (23%)	Srg, C: 0% Srg, M: 100%	8.5 (ND), 5-18	88 women aged <70 years, with ≥6th grade of education, no history of psychiatric diagnoses and undergoing routine low risk breast cancer screening.	STAI (mild to moderate state anxiety)	Prevalence: 21%	Prevalence: 7%	PR=3.0 * †	95%CI: 1.19-7.57	Cases defined as state anxiety scores above the 85th percentile for respective age group.
						STAI (state anxiety)	STAI mean score (SD): 33.08 (11.50)	STAI mean score (SD): 31.82 (8.40)	-	P>0.05	Higher STAI scores indicate more anxiety symptoms.

ATC = Anatomic Therapeutic Chemical classification system; BSI-18 = Brief Symptom Inventory 18 [22]; CT = chemotherapy; EHR = electronic health records; HADS = Hospital Anxiety and Depression Scale [23]; HRS-A = Hamilton Rating Scale for Anxiety [24]; HSCL-25 = The Hopkins Symptom Checklist-25 [25]; HT = hormone therapy; ICD-8 = The International Classification of Diseases, Eight Revision; ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10 =

The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; IQR = interquartile range; ISRA = Inventory of Situations and Responses to Anxiety [26]; IT = immunotherapy; ND = not defined; OR = odds ratio; PR = prevalence ratio; RR = relative risk; RT = radiotherapy; SCL-90 = Anxiety subscale of the Symptoms Checklist-90 [27]; SD = standard deviation; SIR = standardised incidence ratio; Srg, C = Breast conserving surgery; Srg, ND = Surgery, not further specified; Srg, M = Mastectomy; Srg, R = Breast reconstructive surgery; STAI = State-Trait Anxiety Inventory [28]; yrs = years; 95%CI = 95% confidence interval.

* There was some statistical evidence ($P<0.05$) for a different prevalence, risk or severity of anxiety between breast cancer survivors and women who did not have cancer.

† Prevalence ratio calculated by the authors of the present study.

‡ The two studies provided results for different components of anxiety (trait and state) based on the same sample of patients.

Supplementary Table 4. Depression: main characteristics and results of the studies that evaluated the risk of depression, or the prevalence or severity of depressive symptoms, in breast cancer survivors (>1 year) and women who did not have cancer.

First author, year of publication Country	Breast cancer survivors				Comparison group	Outcome assessment	Quantitative measure of the outcome		Relative risk estimate (RR, OR, SIR, PR)	P-value or 95% confidence interval	Notes
	Type of population and main characteristics	Stage at diagnosis (%)	Breast cancer treatments (%)	Time since diagnosis/ treatment in years: mean/ median (SD), range	Type of population and main characteristics		Breast cancer survivors	Comparison group			
Electronic health records											
Suppli et al., 2014 [29] Denmark (continues)	Population-based All 44,494 women born in 1920-1981 and living in Denmark, who had breast cancer diagnosed in 1998-2011, without history of other cancers or major psychiatric disorder.	All	ND	5 (ND), 0-15	Population-based 1,997,669 women born in 1920-1981 and living in Denmark, without history of cancer or major psychiatric disorder	EHR, first hospital contact (in- or outpatient) for unipolar depression, as registered in the Danish Psychiatric Central Registry. ICD-8 codes: 296.09, 296.29; ICD-10 codes: F32-33.9	Incidence rate: 215 per 100,000 person-years Cumulative incidence: 1.1%	Incidence rate: 171 per 100,000 person-years Cumulative incidence: 0.8%	All patients: RR= 1.39 *	All patients: 95%CI: 1.27-1.52	Includes patients diagnosed with breast cancer at <1yr.
									By age: 30-39: RR= 0.78 40-49: RR= 1.56 * 50-59: RR= 1.35 * 60-69: RR= 1.41 * 70-79: RR= 1.25 * ≥80: RR= 1.56 *	By age: 95%CI: 0.39-1.55 95%CI: 1.23-1.96 95%CI: 1.11-1.63 95%CI: 1.16-1.71 95%CI: 1.03-1.51 95%CI: 1.25-1.93	RR adjusted for age (5-year intervals), calendar period (1998-2000, 2001-2004, 2005-2008, 2009-2011) and Charlson comorbidity index score (0, 1, ≥2).
									By Charlson comorbidity index: 0: RR= 1.47 * 1: RR= 1.41 * ≥2: RR= 1.02	By Charlson comorbidity index: 95%CI: 1.31-1.64 95%CI: 1.18-1.69 95%CI: 0.77-1.34	RR adjusted for age (5-year intervals), calendar period (1998-2000, 2001-2004, 2005-2008, 2009-2011).
							Cumulative incidence:	Cumulative incidence:			RR adjusted for age (5-year intervals), calendar period (1998-2000, 2001-2004, 2005-2008, 2009-2011) and Charlson comorbidity index score (0, 1, ≥2). Significant predictors of depression among breast cancer survivors: Age at diagnosis and living alone.
				0-1			0.3%	0.2%	RR= 1.70 *	95%CI: 1.41-2.05	
				1-2			0.2%	0.2%	RR= 1.48 *	95%CI: 1.19-1.83	
				2-3			0.3%	0.2%	RR= 1.64 *	95%CI: 1.31-2.06	
				3-4			0.2%	0.2%	RR= 1.20	95%CI: 0.90-1.60	
				4-5			0.2%	0.2%	RR= 1.40 *	95%CI: 1.04-1.87	
				6-8			0.2%	0.2%	RR= 1.13	95%CI: 0.90-1.41	
				9-14			0.2%	0.1%	RR= 1.09	95%CI: 0.80-1.46	
	Population-based All 35,286 women born in 1920-1981 and living in Denmark, who had breast cancer diagnosed in 1998-2011 and did not use antidepressants in the 3 years before study entry, without history of other cancers or major psychiatric disorder.	All	ND	5 (ND), 0-15	Population based 1,860,552 women born in 1920-1981 and living in Denmark, without history of cancer or major psychiatric disorder and who did not use antidepressants during the three years prior to study entry.	EHR, first redeemed prescription of antidepressants (group N06A of the ATC classification system)	Incidence rate: 3,772 per 100,000 person-years Cumulative incidence: 17.1%	Incidence rate: 1,971 per 100,000 person-years Cumulative incidence: 9.4%	RR= 1.82 *	95%CI: 1.77-1.86	RR adjusted for age (5-year intervals), calendar period (1998-2000, 2001-2004, 2005-2008, 2009-2011) and Charlson comorbidity index score (0, 1, ≥2). Predictors of depression among breast cancer survivors: age at diagnosis, living alone, not having higher education, having comorbidities, positive lymph node metastasis.

Suppli et al., 2014 [29] Denmark (continued)	Population-based All 35,286 women born in 1920-1981 and living in Denmark, who had breast cancer diagnosed in 1998-2011 and did not use antidepressants in the 3 years before study entry, without history of other cancers or major psychiatric disorder.	All	ND	5 (ND), 0-15	Population based 1,860,552 women born in 1920-1981 and living in Denmark, without history of cancer or major psychiatric disorder and who did not use antidepressants during the three years prior to study entry.	EHR, first redeemed prescription of antidepressants (group N06A of the ATC classification system)	Incidence rate: 3,772 per 100,000 person-years Cumulative incidence: 17.1%	Incidence rate: 1,971 per 100,000 person-years Cumulative incidence: 9.4%	By Charlson comorbidity index score: 0: RR= 2.06 * 1: RR= 1.49 * ≥2: RR= 1.25 *	By Charlson comorbidity index score: 95%CI: 2.00-2.12 95%CI: 1.40-1.58 95%CI: 1.15-1.36	RR adjusted for age (5-year intervals), calendar period (1998-2000, 2001-2004, 2005-2008, 2009-2011).
									By age: 30-39: RR= 2.07 * 40-49: RR= 2.12 * 50-59: RR= 2.12 * 60-69: RR= 1.89 * 70-79: RR= 1.59 * ≥80: RR= 1.29 *	By age: 95%CI: 1.77-2.43 95%CI: 1.98-2.27 95%CI: 2.02-2.23 95%CI: 1.80-1.99 95%CI: 1.51-1.68 95%CI: 1.19-1.40	Includes patients diagnosed with breast cancer at <1yr. RR adjusted for age (5-year intervals), calendar period (1998-2000, 2001-2004, 2005-2008, 2009-2011) and Charlson comorbidity index score (0, 1, ≥2).
				5 (ND), 0-15			Cumulative incidence: 17%	Cumulative incidence: 9.4%	RR= 1.82 *	95%CI: 1.77-1.86	
				0-1			6.4%	2.1%	RR= 3.09 *	95%CI: 2.95-3.22	
				1-2			4.2%	2.1%	RR= 2.06 *	95%CI: 1.94-2.18	
				2-3			3.3%	2.1%	RR= 1.60 *	95%CI: 1.49-1.72	
				3-4			3.3%	2.1%	RR= 1.59 *	95%CI: 1.46-1.72	
				4-5			2.7%	2.1%	RR= 1.30 *	95%CI: 1.18-1.44	
				6-8			2.6%	2.1%	RR= 1.23 *	95%CI: 1.15-1.32	
				9-14			2.2%	2.0%	RR= 1.08	95%CI: 0.98-1.19	
Hjerl et al., 2002 [1] Denmark (continues)	Population-based All 60,431 women aged >15 years with first invasive breast cancer registered in the national Cancer Registry in 1970-1993.	All	ND	4 (ND), 0-15 (Median cohort follow up: 4 years since diagnosis; range: 0 to 15)	Population-based Danish female population aged >15 years.	EHR, first ever psychiatric admission with affective disorders, as registered in the Danish Psychiatric Central Registry ICD-8 codes: 296.19-296.99, 298.09, 301.19, 300.49	Cumulative incidence: 0.7%	Cumulative incidence: 0.5%	SIR= 1.49 *	95%CI: 1.35-1.63	Standardised incidence ratio estimated considering all follow up time since diagnosis.
									By calendar period: 1970-74: SIR=1.68 * 1975-79: SIR=1.60 * 1980-84: SIR=1.56 * 1985-89: SIR=1.46 * 1990-93: SIR=1.25	By calendar period: 95%CI: 1.20-2.27 95%CI: 1.30-1.94 95%CI: 1.28-1.88 95%CI: 1.19-1.77 95%CI: 0.99-1.55	

Hjerl et al., 2002 [1] Denmark (continued)	Population-based All 60,431 women aged >15 years with first invasive breast cancer registered in the national Cancer Registry in 1970-1993.	All	ND	4 (ND), 0-15 (Median cohort follow up: 4 years since diagnosis; range: 0 to 15)	Population-based Danish female population aged >15 years.	EHR, first ever psychiatric admission with affective disorders, as registered in the Danish Psychiatric Central Registry ICD-8 codes: 296.19-296.99, 298.09, 301.19, 300.49	-	-	By age group: 15-29: SIR= 3.24 30-34: SIR= 0.67 35-39: SIR= 1.96 40-44: SIR= 2.92 * 45-49: SIR= 1.46 * 50-54: SIR= 2.14 * 55-59: SIR= 1.39 * 60-64: SIR= 1.46 * 65-69: SIR= 1.32 70-74: SIR= 1.22 75-79: SIR= 1.09 80-84: SIR= 1.00 85-89: SIR= 1.28 ≥90: SIR= 2.43	By age group: 95%CI: 0.19-14.3 95%CI: 0.04-2.94 95%CI: 0.98-3.44 95%CI: 2.06-4.00 95%CI: 1.03-2.00 95%CI: 1.69-2.67 95%CI: 1.05-1.81 95%CI: 1.11-1.89 95%CI: 0.99-1.73 95%CI: 0.90-1.61 95%CI: 0.75-1.51 95%CI: 0.60-1.53 95%CI: 0.59-2.39 95%CI: 0.60-6.30	Standardised incidence ratio estimated considering all follow up time since diagnosis.
	Women aged >15 years with first invasive breast cancer registered in the national Cancer Registry in 1970-1993 and living in Copenhagen city area (metropolitan).	All	ND	4 (ND), 0-15	Female population aged >15 years and living in Copenhagen city area.	EHR, first ever psychiatric admission with affective disorders, as registered in the Danish Psychiatric Central Registry ICD-8 codes: 296.19-296.99, 298.09, 301.19, 300.49	-	-	SIR= 1.19	95%CI: 0.95-1.48	Standardised incidence ratio estimated considering all follow up time since diagnosis.
				1.5			-	-	SIR= 0.9	95%CI: 0.5-1.7	Approximate values estimated from the graphics provided in the original study.
				2.5			-	-	SIR= 1.2	95%CI: 0.6-2.0	
				3.5			-	-	SIR= 0.9	95%CI: 0.4-1.9	
				4.5			-	-	SIR= 1.1	95%CI: 0.4-2.3	
				5.5			-	-	SIR= 1.7	95%CI: 0.7-3.1	
				6.5			-	-	SIR= 1.3	95%CI: 0.4-2.8	
				7.5			-	-	SIR= 0.6	95%CI: 0.1-1.9	
				8.5			-	-	SIR= 0.7	95%CI: 0.1-2.2	
				9.5			-	-	SIR= 0.4	95%CI: 0.0-1.9	
				10.5			-	-	SIR= 2.5	95%CI: 0.9-5.4	
				13.0			-	-	SIR= 0.2 *	95%CI: 0.0-0.9	
	Women aged >15 years with first invasive breast cancer registered in the national Cancer Registry in 1970-1993 and living outside Copenhagen city area.	All	ND	4 (ND), 0-15	Female population aged >15 years and living outside Copenhagen city area.	EHR, first ever psychiatric admission with affective disorders, as registered in the Danish Psychiatric Central Registry ICD-8 codes: 296.19-296.99, 298.09, 301.19, 300.49	-	-	SIR= 1.57 *	95%CI: 1.41-1.75	Standardised incidence ratio estimated considering all follow up time since diagnosis. Approximate values estimated from the graphics provided in the original study.
				1.5			-	-	SIR= 2.1 *	95%CI: 1.6-2.6	
				2.5			-	-	SIR= 1.3	95%CI: 0.9-1.8	
				3.5			-	-	SIR= 1.5 *	95%CI: 1.1-2.1	
				4.5			-	-	SIR= 1.4	95%CI: 0.9-2.0	
				5.5			-	-	SIR= 1.6 *	95%CI: 1.1-2.4	
				6.5			-	-	SIR= 1.4	95%CI: 0.8-1.9	
				7.5			-	-	SIR= 1.1	95%CI: 0.6-1.8	
				8.5			-	-	SIR= 1.0	95%CI: 0.5-1.8	
				9.5			-	-	SIR= 0.8	95%CI: 0.3-1.6	
				10.5			-	-	SIR= 0.9	95%CI: 0.4-1.8	
				11.5			-	-	SIR= 0.9	95%CI: 0.3-1.9	
				12.5			-	-	SIR= 1.1	95%CI: 0.4-2.3	
				13.5			-	-	SIR= 1.6	95%CI: 0.6-3.1	

Hung et al., 2013 [2] Taiwan	Population-based 26,629 women with no prior mood disorder and cancer, with breast cancer registered in the National Health Insurance Database in 2000-2005.	All	ND	2.7 (ND), ND-7 (median follow up years for breast cancer survivors: 2.7; for matched cohort: 3.21)	Population-based 26,629 women randomly selected from 1 million women who did not have breast cancer registered in the National Health Insurance Database; matched for age and Charlson comorbidity score (matching, categories not reported).	EHR, recorded in the Registry for Catastrophic Illness with an ICD-9-CM code for major depressive disorder (296.2X-296.3X, 300.4, 311.X)	Incidence rate: 14.55 per 1,000 person-years Cumulative incidence= 4.4%	Incidence rate: 7.51 per 1,000 person-years Cumulative incidence= 2.6%	RR=1.94 *	95%CI: 1.76-2.13	Includes patients diagnosed with breast cancer at <1yr.
				2			4%	2%	RR=2.0 * †	95%CI: 1.80-2.22	Approximate cumulative incidence values estimated from the graphics provided in the original study. P value for the log-rank test comparing the Kaplan-Meier curves: P<0.001
				4			5%	3%	RR=1.7 * †	95%CI: 1.53-1.82	
				6			6%	4%	RR=1.5 * †	95%CI: 1.39-1.62	
Earle et al., 2007 [30] United States	Convenience sample 463 women who had non-metastatic cancer registered with a private health care insurance company and not receiving active treatment; patients had no evidence of recurrence.	Non-metastatic	ND	ND (ND), ≥5	Convenience sample 3,108 women without cancer registered with a private health care insure company; matched for age and clinic location (individual matching, categories not reported).	EHR, ICD-9 codes for diagnoses of psychotic depression and dysthymia in an administrative database from a health care plan.	Prevalence: 22.5%	Prevalence: 18.1%	PR=1.24 * †	95%CI: 1.03-1.50 P=0.04	Breast cancer survivors had more visits with mental health providers compared to women without cancer.
Kim et al., 2017 [31] Korea	Population based 2,130 women who had mastectomy for breast cancer, randomly selected from the National Health Insurance Database	All	Srg, M: 100%	0	Population based 8,520 women never diagnosed with cancer randomly selected from the same database as the cases matched for age, income, region, pre-operative depression (individual matching, categories not reported).	EHR, ICD-10 codes for depression	Prevalence: 5.5%	Prevalence: 2.5%	PR= 2.20 * †	95%CI: 1.76-2.74	-
				1			4.8%	3.1%	PR= 1.55 * †	95%CI: 1.24-1.94	
				2			4.4%	3.0%	PR= 1.47 * †	95%CI: 1.14-1.89	
				3			4.4%	3.1%	PR= 1.42 * †	95%CI: 1.08-1.87	
				4			4.1%	4.0%	PR= 1.03 †	95%CI: 0.76-1.39	
				5			4.4%	3.5%	PR= 1.26 †	95%CI: 0.91-1.75	
				6			4.5%	4.3%	PR= 1.05 †	95%CI: 0.73-1.49	
				7			5.0%	3.9%	PR= 1.28 †	95%CI: 0.86-1.91	
				8			6.0%	3.9%	PR= 1.54 †	95%CI: 0.99-2.39	
				9			5.4%	4.7%	PR= 1.15 †	95%CI: 0.67-1.98	
				10			8.1%	4.5%	PR= 1.80 †	95%CI: 0.93-3.47	

Yang et al., 2017 [4] Sweden	Population based All 4,402 women diagnosed with an in situ breast cancer at the age of 20-80 years between 2001-2009	0	ND	4.7 (4.4), 0-10 (median (IQR) duration of follow up: 4.7 (4.4))	Population based 452,507 women randomly selected from the respondents to the 1990 census	EHR, ICD-10 diagnostic codes for depression (F32-F33) at in patient or outpatient hospital visits	Cumulative incidence: 1.3%	Cumulative incidence: 1.2%	SIR= 1.03 By age group: 20-44: SIR= 1.48 45-54: SIR= 0.84 55-64: SIR= 1.01 65-80: SIR= 1.07	95%CI: 0.80-1.34 By age group: 95%CI: 0.84-2.61 95%CI: 0.51-1.36 95%CI: 0.61-1.68 95%CI: 0.62-1.85	Standardised incidence ratios were standardised by calendar period (1-year categories), age (5-year categories), and region of residence (North, Stockholm- Gotland, South, Southeast, Uppsala-Orebro, West).
				0-0.5			0.1%	0.1%	SIR= 0.77	95%CI: 0.29-2.05	
				0.5-1			0.1%	0.1%	SIR= 1.14	95%CI: 0.51-2.54	
				1-2			0.2%	0.2%	SIR= 0.91	95%CI: 0.47-1.74	
				2-5			0.6%	0.5%	SIR= 1.15	95%CI: 0.78-1.70	
				5-10			0.3%	0.3%	SIR= 1.00	95%CI: 0.57-1.76	
				4.7 (4.4), 0-10 (median (IQR) duration of follow up: 4.7 (4.4))		EHR, being prescribed an antidepressant (group N06A of the ATC classification system)	Cumulative incidence: 3.6%	Cumulative incidence: 2.3%	SIR= 1.58 * By age group: 20-44: SIR= 1.36 45-54: SIR= 1.93 * 55-64: SIR= 1.54 * 65-80: SIR= 1.40 *	95%CI: 1.36-1.85 By age group: 95%CI: 0.84-2.23 95%CI: 1.48-2.53 95%CI: 1.15-2.07 95%CI: 1.05-1.87	Standardised incidence ratios were standardised by calendar period (1-year categories), age (5-year categories), and region of residence (North, Stockholm- Gotland, South, Southeast, Uppsala-Orebro, West).
				0-0.5			-	-	SIR= 2.09	95%CI: 1.57-2.79	
				0.5-1			-	-	SIR= 1.49	95%CI: 1.04-2.13	
				1-2			-	-	SIR= 1.70	95%CI: 1.30-2.22	
				2-4.5			-	-	SIR= 1.12	95%CI: 0.79-1.59	
	Population based All 40,849 women diagnosed with an invasive breast cancer at the age of 20-80 years between 2001-2009	I-IV	ND	4.5 (4.5), 0-10 (median (IQR) duration of follow up: 4.4 (4.5))	Population based 452,507 women randomly selected from the respondents to the 1990 census	EHR, ICD-10 diagnostic codes for depression (F32-F33) at in patient or outpatient hospital visits	Cumulative incidence: 1.9%	Cumulative incidence: 1.2%	SIR= 1.57 * By age group: 20-44: SIR= 1.69 45-54: SIR= 1.70 55-64: SIR= 1.56 65-80: SIR= 1.38	95%CI: 1.46-1.69 By age group: 95%CI: 1.42-2.01 95%CI: 1.50-1.93 95%CI: 1.36-1.79 95%CI: 1.19-1.59	SIR standardised by calendar period, age, and region. Predictors of depression among breast cancer survivors: having comorbidities and positive lymph nodes.
				0-0.5			0.2%	0.1%	SIR= 1.83 *	95%CI: 1.48-2.26	
				0.5-1			0.3%	0.1%	SIR= 2.48 *	95%CI: 2.07-2.97	
				1-2			0.4%	0.2%	SIR= 2.04 *	95%CI: 1.76-2.36	
				2-5			0.6%	0.5%	SIR= 1.29 *	95%CI: 1.14-1.46	
				5-10			0.3%	0.3%	SIR= 1.18	95%CI: 0.99-1.41	
				4.5 (4.5), 0-10 (median (IQR) duration of follow up: 4.4 (4.5))		EHR, being prescribed an antidepressant (group N06A of the ATC classification system)	Cumulative incidence: 9.2%	Cumulative incidence: 2.2%	SIR= 1.95 * By age group: 20-44: SIR= 2.43 * 45-54: SIR= 2.23 * 55-64: SIR= 2.00 * 65-80: SIR= 1.64 *	95%CI: 1.86-2.04 By age group: 95%CI: 2.14-2.76 95%CI: 2.02-2.45 95%CI: 1.83-2.18 95%CI: 1.51-1.77	SIR standardised by calendar period, age, and region.
				0-0.5			-	-	SIR= 2.14 *	95%CI: 1.95-2.36	
				0.5-1			-	-	SIR= 2.62 *	95%CI: 2.40-2.87	
				1-2			-	-	SIR= 1.92 *	95%CI: 1.76-2.09	
				2-4.5			-	-	SIR= 1.34 *	95%CI: 1.20-1.49	

Khan et al., 2010 [3] United Kingdom	Population-based 16,938 women aged ≥30 with breast cancer registered in the UK General Practice Research Database.	All	ND	ND (ND), ≥5	Population-based 67,649 women who did not have breast or colorectal cancer at beginning of follow; individual matching for age (± 1 year) and primary care practice (small area).	EHR, primary care consultations for depression recorded with Read codes	Prevalence: 9.6%	Prevalence: 8.9%	OR= 1.06	95%CI: 1.00-1.14	Odds ratio adjusted for Charlson comorbidity score, previous history of depression and death.
						EHR, ≥1 prescription of antidepressants	Prevalence: 23.7%	Prevalence: 20.2%	OR= 1.16 *	95%CI: 1.11-1.22	Odds ratio adjusted for Charlson comorbidity score, number of consultations, and death.
Cohort studies involving scales											
Aerts et al., 2014 [32] ND	Convenience sample 66 women who had breast-conserving surgery for early breast cancer and no recurrence during follow up.	'Early-stage' (100%)	Srg, C: 100% CT: 24.7% RT: 76.5% HT: 70.3%	~ 1 (follow up at 1 year)	Convenience sample 149 women with no history of cancer recruited in: a gynaecology outpatient clinic, an organisation for elderly women and online; matched for age (method not reported).	BDI	BDI mean score (SD) 7.71 (8.00)	BDI mean score (SD) 5.28 (5.34)	-	P=0.02 *	Higher CES-D scores indicate more depressive symptoms. Women who had advanced stage or had had relapse were excluded at baseline, as were those who had recurrence or a second cancer during follow up.
	Convenience sample 48 women who had mastectomy for early breast cancer at one university hospital and no recurrence during follow up.	'Early-stage' (100%)	Srg, M: 100% CT: 44.1% RT: 45.6% HT: 54.4%	~ 1 (follow up at 1 year)			BDI mean score (SD) 8.85 (6.79)	BDI mean score (SD) 5.28 (5.34)	-	P<0.01 *	
Ancoli-Israel et al., 2014 [33] United States	Convenience sample 44 women who had been diagnosed with breast cancer 1 year before, and scheduled to receive ≥4 cycles of CT, with no psychological impairments and not receiving RT at recruitment.	I (27.9%) II (39.7%) III (30.9%) Unknown (1.5%)	Srg, C: 45.6% Srg, M: 49.7% CT: 100%	~ 1 (follow up at 1 year after CT)	Convenience sample 35 cancer-free friends of the women who had breast cancer with no psychological impairments at the time of recruitment; individual matching for age (±5 years), ethnicity and education (categories of ethnicity and education not reported).	CES-D	CES-D mean score (SD) 10.0 (ND)	CES-D mean score (SD) 4.8 (ND)	-	P=0.04 *	Higher CES-D scores indicate more depressive symptoms. Mean scores adjusted for age and body mass index.

Kesler et al., 2013 [34] United States	Convenience sample 44 women who had breast cancer recruited via support groups and advertisements; patients excluded if they had had disease recurrence or relapse.	I-IIIA	Srg, ND: 100% CT: 100%	4.8 (3.4), 1-12	Convenience sample 38 healthy female controls recruited through advertisements	CAD	CAD mean score (SD): 48.8 (8.2)	CAD mean score (SD): 48.0 (7.2)	-	P=0.08	-
Bailey et al., 2010 [35] United States	Convenience sample 515 patients with first primary breast cancer, aged >40 years, with no cognitive impairment or prior history of breast cancer, post active treatment and who spoke English.	0 (34.4%) I (51.4%) IIA (14.2%)	Srg, ND: 100%	~ 1 (follow up at 12 months after surgery)	Convenience sample 496 women who had a normal/benign mammogram, aged >40 years, with no cognitive impairment or prior history of breast cancer, and who spoke English; frequency matched for age (40-50, 50-69, ≥70 years).	CES-D Cut-off score for case: ≥16	Prevalence: 47.4%	Prevalence: 52.6%	PR= 0.9 †	95%CI: 0.80-1.02	Women with more advanced disease at diagnosis (stage IIA) had significantly more depression compared to those diagnosed at earlier stages.
Hermelink et al., 2017 [36] Germany	Convenience sample 150 women aged 18-65 years, newly diagnosed with breast cancer, with no previous history of neurological or psychotic disorders and no previous systemic treatment for cancer	0 (7%) I (42%) II (41.4%) III (%9.6)	CT: 100% HT: 73.9% vs. CT: 0% HT: 80.7%	~ 1 (follow up at 1 year after diagnosis)	Convenience sample 56 women aged 18-65 years, who never had cancer, and attended the same institution as cases for breast imagining and did not require further tests.	PHQ-D	PHQ-D mean score CT: 4.7 (4.5) No CT: 4.2 (4.5)	PHQ-D mean score 2.7 (3.0)	-	P=0.03 * (for differences between the three groups)	Higher PHQ-D mean scores indicate more depressive symptoms.
Lee et al., 2011 [37] Korea	Convenience sample 206 patients aged ≥18 years who had been diagnosed with breast cancer 1 year before	I-IIA (71.2%) IIB-III (25.0%)	Srg, C: 82.5% Srg, M: 16.4% CT: 86.7% RT: 82.5% HT: 82.2%	~ 1 (follow up at 1 year after diagnosis)	Population-based Nationally representative sample of 496 adult women.	SDS	SDS mean score 38.1 (0.94)	SDS mean score 38.8 (0.37)		P=0.514	Mean scores adjusted for age, menopausal status, comorbidity, marital status, educational level, religious practice, job status, monthly income, body mass index, smoking status, drinking status, regular exercise, propensity score, and subscales of social support.
							Prevalence: 49.3%	Prevalence: 46.6%	PR=1.06 †	95%CI: 0.89-1.25 P=0.516	Cut-off score for case: ≥50

Cross-sectional studies involving scales											
Bizetti Pelai et al., 2012 [38]	Convenience sample 89 women who had surgery for breast cancer at <10 years	ND (ND)	Srg, BCS: 37% Srg, M: 50-63% RT: 2-11% CT: 24-30% CT+RT: 54-60%	3.7 (ND), ≤10	Convenience sample 43 women without breast cancer, or neurological or orthopaedic impairments of the upper limbs	BDI	Prevalence: 41.6%	Prevalence: 28.0%	PR=1.49 †	95%CI: 0.97-2.28	Cut-off score for case: ≥10
Castellon et al., 2004 [15] United States	Convenience sample 53 women who had breast cancer at or before the age of 50, with no evidence of disease or recurrence, and no history of psychiatric disorder.	0-II (100%)	CT: 34% CT+HT: 34%	ND (ND), 2-5	Convenience sample 19 Healthy women recruited via fliers, newsletter articles and advertisements, or amongst the acquaintances of the hospital staff.	BDI	BDI mean score (SD): No CT: 7.0 (4.5) CT: 6.3 (5.1)	BDI mean score (SD): 7.8 (7.9)	-	P=0.63	-
Weitzner et al., 1997 [16] United States	Convenience sample 60 women with age <70 years, education ≥6th grade, no history of psychiatric diagnoses, >5 years disease-free, selected from those returning to the hospital for long-term follow up of cancer.	I (15%) II (63%) III (22%)	Srg, M: 100%	ND (ND), ≥5	Convenience sample 93 employees or volunteer workers at the same hospital with no personal or family history of breast cancer, age <70 years, education ≥6th grade, and no psychiatric history.	BDI Scale applied as part of a psychiatric interview	BDI mean score (SD): 7 (ND)	BDI mean score (SD): 5 (ND)	-	P<0.003 *	Adjusted for years of age and years of education. Among breast cancer survivors, lower BDI scores, indicating less depression, were associated with better quality of life for all domains (P<0.02), except in the family one.
							Prevalence: 29%	Prevalence: 15%	PR= 1.93 * †	95%CI: 1.03-3.61	Cut-off score for case: >12 (mild to moderate depression)
Garcia-Torres et al., 2013 [14] Spain	Convenience sample 22 breast cancer survivors free of relapse identified by staff of the local association against cancer.	ND	Srg, M: 100% CT: 72.7%	8.2 (5.6), 1-21	Convenience sample 22 women with no history of cancer who volunteered with the same association against cancer.	BDI-II	BDI-II mean score (SD): 13.13 (7.83)	BDI-II mean score (SD): 8.18 (7.78)	-	P=0.02 *	Correlation between anxiety and depression: r = 0.46, p<0.05; Cut-off score for case: >14 (slight to severe depression)
							Cognitive-affective component: 5.86 (4.06)	Cognitive-affective component: 3.72 (3.88)	-	P=0.03 *	
							Motivational-somatic component: 6.81 (5.07)	Motivational-somatic component: 3.81 (2.92)		P=0.02 *	
							Prevalence: 40%	Prevalence: 18%	PR= 2.22 †	95%CI: 0.79-6.21	

Nguyen et al., 2013 [39] United States	Convenience sample 57 women survivors of breast cancer, aged over 65 years, without recurrence, recruited from a cancer registry	I-IIIA (100%)	RT: 53% CT: 47%	>10	Convenience sample 30 healthy female adults, selected in the community for a previous study.	BDI-II	BDI-II mean score (SD): 4.86 (4.07)	BDI-II mean score (SD): 4.03 (3.38)	-	P=0.39	-
Cohen et al., 2011 [5] Israel	Convenience sample 56 married Israeli Arab breast cancer survivors, post treatment and free of disease recruited from one hospital.	I-III (ND%)	Srg, C: 48.2% Srg, M: 51.8% Srg, R: 12.5% CT: 85.7% RT: 85.7% HT: 58.9%	4.8 (4.2), 1-17	Convenience sample 66 married and healthy Arab women living in Israel, approached in community settings; individual matching for age and education (matching categories not reported).	BSI-18	BSI-18 mean score (SD): 2.0 (1.1)	BSI-18 mean score (SD): 1.8 (0.8)	-	P>0.05	Higher levels of depression associated with higher levels of anxiety and somatization, and lower levels of support in both groups (P<0.05). Higher levels of depression associated with lower body image in breast cancer survivors (P=0.05).
Broeckel et al., 2002 [40] United States	Convenience sample 58 breast cancer survivors who had a spouse or partner, free of recurrence for >5 years, with no known neurological disorder, and no history of other cancer.	I (26%) II (62%) III (10%) Unknown (2%)	Srg, C: 50% Srg, M: 47% CT: 100% RT: 71% HT: 48%	7.7 (2.3), 5.2-15.2	Convenience sample 61 women with no history of cancer who had a spouse or partner, recruited among the friends of the women who had breast cancer; individual matching for age (± 6 years).	CES-D	CES-D mean score (SD): 8.01 (6.34)	CES-D mean score (SD): 4.75 (4.12)	-	P≤0.05 *	Higher CES-D score indicates more depressive symptoms. Correlation between depression scores and problems in sexual function: r = 0.27, P≤0.05
Claus et al., 2006 [41] United States	Population-based All 795 women diagnosed with DCIS in 1994-1998, with no history of invasive breast cancer; reinterviewed on average 6.2 years after first interview.	0 (100%)	Srg, C: 35.5% Srg, M: 14.0%	5.8 (1.0), ND	Population based 702 women selected by random-digit-dialling methods, with no history of DCIS or invasive breast cancer; frequency matched for age (± 5 years) and geography. Reinterviewed on average at 6.0 (0.6) years after first interview.	CES-D	CES-D mean score (95%CI): 8.3 (7.7-8.9)	CES-D mean score (95%CI): 7.2 (6.6-7.8)	-	P<0.05 *	Higher CES-D score indicates more depressive symptoms. Mean scores adjusted for age at diagnosis/interview, race (white/non-white), education (college degree/no college) menopausal status, comorbid conditions (myocardial infarction, stroke, cancer), marital status (married/living as married vs. not), time since diagnosis and case/control status.
			Srg, C: 100%	5.7 (1.1)			CES-D mean score (SD): 8.1 (7.2-9.0)	CES-D mean score (SD): 7.2 (6.6-7.8)	-	P>0.05	
			Srg, C: 100% RT: 100%	5.7 (1.1)			CES-D mean score (SD): 8.7 (7.9-9.5)	CES-D mean score (SD): 7.2 (6.6-7.8)	-	P<0.05 *	
			Srg, M: 100%	6.0 (0.9)			CES-D mean score (SD): 7.4 (5.8-8.9)	CES-D mean score (SD): 7.2 (6.6-7.8)	-	P>0.05	

Conroy et al., 2013 [18]	Convenience sample 24 breast cancer survivors with history of non-metastatic disease and CT treated.	I (29%) IIa (33%) IIb (25%) IIIa (8%) IIIb (4%)	CT: 100% RT: 79%	6.4 (2.1), 3.2-10.2	Convenience sample 23 healthy women matched for age and education (matching method not reported).	CES-D	CES-D mean score (SD): 7.5 (5.8)	CES-D mean score (SD): 8.7 (6.9)	-	P>0.05	Higher CES-D score indicates more depressive symptoms.
Koppelmans et al., 2012 [42] The Netherlands	Convenience sample 196 women who had been treated for breast cancer between 1976 and 1995, were aged between 50 and 80 years in 2008, did not have recurrence or a second primary cancer and never used adjuvant hormone therapy.	I-III (100%)	HT: 0% CT: 100%	21 (4.4), ND	Convenience sample All 1,509 women without a history of cancer who were between 50 and 80 years of age at the time of the assessments, selected from a larger population-based cohort.	CES-D	CES-D mean score (SD): 4.7 (8.0)	CES-D mean score (SD): 6.7 (8.4)	-	P<0.05 *	Mean score adjusted for age (format of the variable not reported). Higher CES-D score indicates more depressive symptoms.
McDonald et al., 2010 [19] ND	Convenience sample 29 female breast cancer patients without neurobehavioral risk factors including neurologic, medical, or psychiatric conditions, except history of depression or anxiety	0 (14%) I (35%) II (48%) IIIA (3%)	CT: 59% RT: 69%	~1.5 (0.15)	Convenience sample 18 healthy controls 'demographically matched' (matching method not reported).	CES-D	CES-D mean score (SD): CT: 6.8 (6.2) No CT: 7.5 (10.4)	CES-D mean score (SD): 4.7 (8.9)	-	P>0.05	Higher CES-D score indicates more depressive symptoms.
							Prevalence of depression: 13.8%	Prevalence of depression: 5.6%	PR= 2.46 †	95%CI: 0.30 - 20.20	Cut-off for case: CES-D score ≥16
Otte et al., 2010 [43] United States	Convenience sample 246 breast cancer survivors free of cancer at recruitment, with no history of other cancers and able to speak, read and write English	I (ND) II (ND) III (ND)	Srg, C: 42% Srg, M: 59% CT: 89% RT: ND HT: 33%	5.6 (2.0), 2-10	Convenience sample 246 women in general good health with no history of breast cancer recruited by acquaintance referral, self-referral or from corporative group; individual matching for age (±5 years).	CES-D	CES-D mean score (SD): 11.53 (9.60)	CES-D mean score (SD): 9.00 (9.20)	-	P<0.01 *	Higher CES-D score indicates more depressive symptoms. Depressive scores were correlated with sleep-wake disturbances (p<0.05).

Root et al., 2015 [17]	Convenience sample 113 women aged <70 years who had breast cancer, were post-menopausal at diagnosis, receiving HT at recruitment, with no recurrence, no neurological or psychiatric diagnoses and who did not report sleep disturbances.	I (58%) II (0%) III (33%) IV (8%)	Srg, C: 75% Srg, M: 32% CT: 52% RT: 78% HT: 52%	4.2 (1.2)	Convenience sample 37 health women with no history of cancer or cancer treatment, post-menopausal, with no neurological or psychiatric diagnoses, matched for age and education (matching method not reported).	CES-D	CES-D mean score (SD): 8.6 (8.2)	CES-D mean score (SD): 7.8 (6.5)	-	P=0.59	Higher CES-D score indicates more depressive symptoms.
Von Ah et al., 2009 [44] United States	Convenience sample 52 women aged ≥40 years, who had breast cancer and had completed primary treatment ≥1 year ago, no cancer relapse, no metastatic disease or other cancer, and no history of psychiatric illnesses, recruited from cancer support groups, advertisements in churches and community centres, or by referral of enrolled participants.	I-II (50%) III (ND)	Srg, C: 66% Srg, M: 33% CT: 55.8% RT: 80.8% HT: 79%	4.6 (2.8), 1.2-15.8	Convenience sample 52 women aged ≥40 years, with no history of cancer, no history of psychiatric illnesses, recruited from cancer support groups, advertisements in churches and community centres, or by referral of enrolled participants; individual matching for age (±5 years) and education (±3 years).	CES-D	CES-D mean score (SD): 10.8 (8.1)	CES-D mean score (SD): 9.5 (8.2)	-	P=0.415	Higher CES-D score indicates more depressive symptoms.
Von Ah et al., 2012 [45] United States	Convenience sample 62 non-Hispanic African American women diagnosed with non-metastatic breast cancer and able to read and write English, recruited by medical record review and by self-referral.	I-IIB (85.7%) IIIB (14.3%)	Srg, C: 0% Srg, M: 60.3% CT & RT: 54.6% HT: ND	5.0 (2.7), 2-10	Convenience sample 78 African American women with no history of breast cancer, recruited through community advertisements and events.	CES-D	CES-D mean score (SD): 12.2 (11.7)	CES-D mean score (SD): 11.6 (11.0)	-	P=0.757	Higher CES-D score indicates more depressive symptoms. Mean scores adjusted for age, income, years of education and body mass index.

Frazzetto et al., 2012 [46] Italy	Convenience sample 32 women aged 66-75 years, with breast cancer recurrence ≥10 years after initial diagnosis, recruited in one hospital.	ND	ND	ND (ND), ≥10	Convenience sample 35 women in 'good health' previously recruited in a hospital for a study on health-related quality of life	GDS	Prevalence: 33.3%	Prevalence: 20.0%	PR= 1.67 †	95%CI: 0.73-3.80	Cut-off score for case: 10-19 (mild depression)
							Prevalence: 50.0%	Prevalence: 8.6%	PR= 5.81 * †	95%CI: 1.87-18.08	Cut-off score for case: 20-30 (severe depression)
							Prevalence: 83.3%	Prevalence: 28.6%	PR= 2.91 * †	95%CI: 1.69-5.03	Cut-off score for case: ≥10 (mild to severe depression)
Calvio et al., 2010 [7] United States	Convenience sample 122 breast cancer survivors ≥1 year post treatment, working full-time for ≥1 year, with computer and internet, recruited via advertisements and flyers.	I (36.9%) II (44.3%) III (17.2%)	Srg, ND: 96.7% CT: 82.8% RT: 73.0% HT: 45.9% IT: 13.1%	3.1 (2.4), 1-10	Convenience sample 113 women without a previous cancer diagnosis, working full-time for ≥1 year, with computer and Internet, recruited via advertisements and flyers.	HADS	HADS mean score (SD): 4.6 (3.3)	HADS mean score (SD): 3.2 (2.7)	-	P<0.001 *	Higher scores indicate more depressive symptoms. Mean scores adjusted for marital status (cohabitating with partner vs. single/not cohabitating), race (Caucasian vs. non-Caucasian), ethnicity (Hispanic vs. non-Hispanic), age (<40, 41-50, 51-65), income (0-39,000; 40-59,000; 60-79,000; 80-89,000; 80-99,000; ≥100,000), and menopausal status (currently going through, premenopausal, postmenopausal).
Boehmer et al., 2015 [6] ND	Convenience sample 85 lesbian or bisexual breast cancer survivors post-active treatment recruited via advertisements, flyers, etc. (3.5% of whom had had cancer recurrence)	I-III (100%)	ND	4.5 (ND), 1-10	Convenience sample 85 lesbian or bisexual women with no history of cancer, no prophylactic mastectomy or oophorectomy, and not using hormone therapy, recruited via flyers, advertisements, etc.; individual matching for age (± 3 years) and partner status (partnered vs. unpartnered).	Antidepressants intake (self-reported)	Prevalence: 34.1%	Prevalence: 21.2%	PR=1.61 †	95%CI: 0.97-2.67	Depression was more common in women taking any psychopharmacological medication, compared to those who did not (OR=2.29, 95%CI: 1.02 to 5.15), and less common in women with higher levels of physical activity (OR= 0.31, 95%CI: 0.11-0.84).
						HADS score ≥8	Prevalence: 15.3%	Prevalence: 12.9%	PR=1.19 †	95%CI: 0.56-2.50	

Dahl et al., 2011 [8] Norway	Convenience sample 337 tumor free breast cancer survivors treated with radiotherapy during 1998 and 2002 in one hospital.	II (ND) III (ND)	Srg, C: 24% Srg, M: 76% CT: 82% RT: 100% HT: 81%	3.9 (ND), 2.6-6.9	Convenience sample 1,685 women randomly selected from a population-based sample with no history of cancer and had complete data for questionnaires; individual matching for age (± 5 years).	HADS	HADS mean score (SD): 3.1 (3.3)	HADS mean score (SD): 3.7 (3.1)	-	P<0.001 *	Mean scores adjusted for level of education, on disability pension and menopausal status. Higher scores of HADS for depression were associated in univariate analysis with more insomnia symptoms in breast cancer survivors and in controls (P<0.05).
Miao et al., 2016 [9]	Convenience sample 23 patients with breast cancer who had been treated with chemotherapy at a local hospital	I-III (100%)	CT: 100%	3 (0.3),	Convenience sample 26 age matched healthy controls selected amongst patients relatives and local universities (matching method not reported).	HRS-D	Mean score (SD) 5.04 (1.19)	Mean score (SD) 4.88 (1.23)	-	P=0.650	Higher score indicates more anxiety symptoms
Rubino et al., 2007 [10] Italy	Convenience sample 33 consecutive patients who had had breast-reconstruction after mastectomy, in 2001-2002.	ND	Srg, M: 100% Srg, R: 100%	ND (ND), >1	Convenience sample 33 women, randomly selected amongst university staff.	HRS-D ‡ Score ≥8	Prevalence: 45.4%	Prevalence: 12.1%	PR=3.76 * †	95%CI: 1.39-10.14	A P-value of 0.02 was reported in the article, for the chi-square test of differences in depression between groups.
Boele et al., 2015 [11] The Netherlands	Convenience sample Post-menopausal breast cancer survivors with no psychiatric history, who did not receive CT, selected from medical records. 20 exposed to HT, 43 in the Srg+RT group.	ND	Srg, ND: 95% CT: 0% RT: 65% HT: 100% / 0%	Exposure to HT: 3.2 (1.9), 1.5-7; Unexposed to HT: 2.8 (0.3), 2.3-3.3.	Convenience sample 44 friends or family members of the women who had had breast cancer, with no history of breast cancer; matched for age and education (method of matching not reported).	HSCL-25	HSCL-25 mean score (SD): HT: 12.89 (8.40) No HT: 15.46 (15.82)	HSCL-25 mean score (SD): 11.92 (10.97)	-	P=0.43	Higher HSCL-25 score indicates more depressive symptoms. P-value adjusted for age and premorbid IQ.

Kreukels et al., 2008 [12] The Netherlands	Convenience sample 63 women who had non-metastatic breast cancer, with no history of psychiatric diseases.	I-III (100%)	CT: 100% HT: 40%	~ 1	Convenience sample 60 friends or family of the patients with the same age who never had cancer; matched for age (matching method not reported).	HSCL-25	HSCL-25 mean score (SD): 17.1 (13.6)	HSCL-25 mean score (SD): 9.6 (9.2)	-	P<0.001 *	Higher HSCL-25 score indicates more depressive symptoms.
Min et al., 2010 [47] Korea	Convenience sample 52 women who had breast cancer treated with mastectomy and followed up immediate reconstruction with latissimus dorsi myocutaneous flap, recruited in one cancer center (3% had disease recurrence).	0 (15.4%) I (40.4%) II (30.7%) III (13.5%) IV (0%)	Srg, M: 100% Srg, R: 100%	3.1 (1.3), ND	Convenience sample 104 'healthy female volunteers' matched for age (matching method not reported).	SDS	SDS mean score (SD): 48.5 (11.6)	SDS mean score (SD): 39.9 (9.1)	-	P<0.001 *	Mean SDS scores in breast cancer survivors were significantly higher in women who had neo adjuvant chemotherapy compared to those who did not.
Amir et al., 2002 [13] Israel	Convenience sample 39 women free of cancer symptoms for ≥3 years and not under active treatment, identified through two hospitals.	I (46%) II (46%) III (8%)	Srg, C: 20% Srg, M: 80% CT: 66% RT: 41% HT: 46%	6.5 (ND), ≥5	Convenience sample 39 women who did not experience any life-threatening disease; matched for age and education (matching method not reported).	SCL-90	SCL-90 mean score (SD): 0.99 (1.07)	SCL-90 mean score (SD): 0.66 (0.55)	-	P<0.001 *	Higher SCL-90 scores indicate more depressive symptoms. Women who had breast cancer and reported PTSD symptoms had more depressive symptoms than those who did not: 2.13 (1.22) vs. 0.75 (0.75), P<0.01.

ATC = Anatomic Therapeutic Chemical classification system; BC = breast cancer; BDI = Beck Depression Inventory [48]; BDI-II = Beck Depression Inventory-II [49]; BSI-18 = Brief Symptom Inventory-18 [22]; CAD = Clinical Assessment of Depression [50]; CES-D = The Center for Epidemiologic Studies, Depression Scale [51]; CT = chemotherapy; EHR = electronic health records; GDS = Geriatric Depression Scale [52]; HADS = Hospital Anxiety and Depression Scale [23]; HRS-D = Hamilton Rating Scale for Depression [53]; HSCL-25 = Hopkins Symptom Checklist-25 [25]; HT = hormone therapy; ICD-8 = The International Classification of Diseases, Eight Revision; ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10 = The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; ND = not defined; OR = odds ratio; PHQ-D = Patient Health Questionnaire - Depression [54]; PR = prevalence ratio; RR = relative risk; RT = radiotherapy; SCL-90 = Depression subscale of Symptoms Checlist-90 [27]; SD = standard deviation; SDS = Zung's self-rating depression scale [55]; SIR = standardised incidence ratio; Srg, C = Breast conserving surgery; Srg, ND = Surgery, not further specified; Srg, M = Mastectomy; Srg, R = Breast reconstructive surgery; yrs = years.

* There was some statistical evidence (P<0.05) for a different prevalence, risk or severity of anxiety between breast cancer survivors and women who did not have cancer.

† Prevalence ratio calculated by the authors of the present study.

Supplementary Table 5. Neurocognitive dysfunction: main characteristics and results of the studies that evaluated the cognitive dysfunction or its domains in breast cancer survivors (>1 year) and women who did not have cancer.

First author, year of publication Country	Breast cancer survivors				Comparison group	Outcome assessment	Quantitative measure of the outcome		Relative risk estimate (RR, OR, SIR, PR)	P-value or 95% confidence interval	Notes
	Type of population and main characteristics	Stage at diagnosis (%)	Breast cancer treatments (%)	Time since diagnosis/ treatment in years: mean/median (SD), range	Type of population and main characteristics		Breast cancer survivors	Comparison group			
Cohort studies involving neurocognitive assessment batteries											
Ahles et al., 2010 [56] United States	Convenience sample 46 women, aged 18-70 years, newly diagnosed with breast cancer, without history of neurologic disorders or axis I psychiatric disorders, consecutively recruited from one centre.	0 (16.7%) I (47.0%) II (28.0%) IIIA (8.3%)	CT: 100%	~1.5 (follow up at 18 months after treatment)	Convenience sample 39 women without cancer recruited through community advertisements; frequency matched for age and education (categories of matching not reported).	Change in the standardised scores for processing speed since baseline assessment prior to CT. Processing speed: Digit Symbol-Coding (WAIS-III), Trail Making Test (D-KEFS), Color-Word Interference Test (D-KEFS), and Grooved Pegboard. Verbal ability: Vocabulary [WASI, Verbal Fluency Test (D-KEFS)]. Verbal memory: CVLT-II, Logical Memory I and II (WMS-III). Visual memory: Faces I and II (WMS-III). Working memory: PASAT. Sorting: Sorting Test (D-KEFS). Distractibility: CPT. Reaction time: CPT.	Mean score (SD) Processing speed -0.01 (0.45) Verbal ability 0.17 (0.87) Verbal memory 0.68 (0.80) Visual memory 1.04 (0.69) Working memory 0.69 (0.65) Sorting 0.52 (0.91) Distractibility 0.20 (0.45) Reaction time -0.57 (1.14) Block design 0.11 (0.84)	Mean score (SD) Processing speed 0.25 (0.52) Verbal ability 0.17 (0.71) Verbal memory 0.69 (0.69) Visual memory 1.05 (0.80) Working memory 0.64 (0.92) Sorting 0.55 (0.73) Distractibility 0.16 (0.81) Reaction time 0.16 (0.88) Block design 0.18 (0.76)	-	-	Domain scores adjusted for age, education, and baseline score. The linear mixed-methods model indicated that older patients who received chemotherapy had lower post-treatment processing speed performance (z-score difference,-0.16 per 10 years increase in age; 95%CI: -0.29 to -0.04) compared with healthy controls.
	Convenience sample 64 women, aged 18-70 years, newly diagnosed with breast cancer, without history of neurologic disorders or axis I psychiatric disorders, consecutively recruited from one centre.	0 (16.7%) I (47.0%) II (28.0%) IIIA (8.3%)	CT: 0%	~1.5 (follow up at 18 months after treatment)	Convenience sample 39 women without cancer recruited through community advertisements; frequency matched for age and education (categories of matching not reported).		Mean score (SD) Processing speed -0.09 (0.65) Verbal ability -0.04 (0.73) Verbal memory 0.38 (0.93) Visual memory 1.02 (0.71) Working memory 0.44 (0.95) Sorting 0.21 (0.86) Distractibility -0.02 (1.05) Reaction time -0.28 (0.95) Block design -0.07 (0.82)	Mean score (SD) Processing speed 0.25 (0.52) Verbal ability 0.17 (0.71) Verbal memory 0.69 (0.69) Visual memory 1.05 (0.80) Working memory 0.64 (0.92) Sorting 0.55 (0.73) Distractibility 0.16 (0.81) Reaction time 0.16 (0.88) Block design 0.18 (0.76)	-	-	Domain scores adjusted for age, education, and baseline score. The linear mixed-methods model indicated that older patients not exposed to chemotherapy had lower post-treatment Processing Speed performance (z-score difference, -0.11; 95%CI, -0.21 to -0.001).

Collins et al., 2014 [57] Canada	Convenience sample 60 women, aged 18-65 years, with at least the 8th grade of education, newly diagnosed with non-metastatic breast cancer, scheduled to receive CT, recruited in one hospital; patients who had disease progression during follow up were excluded.	I-III (100%)	CT: 100%	~ 1 (follow up at 12 months after CT)	Convenience sample 60 women recruited through hospital advertisements and peer nomination, with at least the 8th grade of education; matched on age, education and first language (categories of matching not reported).	Processing Speed: Digit-Symbol Coding & Symbol Search (WAIS-III); TMT-A; TMT-B; Processing speed & Reaction time indices (CNS-VS). Working Memory: Digit Span & Letter-Number-Sequencing (WAIS-III); PASAT; ACTT; COWA; Flexibility & working memory indices (CNS-VS). Visual Memory Visual memory index (CNS-VS). Verbal Memory HVLT-; verbal memory index (CNS-VS).	Prevalence: 22%	Prevalence: 6%	PR= 3.67* †	95%CI: 1.21-11.12	Cut off for case: A standardised-regression based score of ≥ -2.0 on 3 or more of the 19 cognitive measures
Fan et al., 2005 [58] Canada	Convenience sample 91 women with breast cancer without relapse, with no psychiatric history and no use of psychotropic medications other than benzodiazepines for nausea, sleep, or anxiety.	ND	CT: 100% RT: 65% HT: 67%	~ 1 (follow up at 1 year after CT)	Convenience sample 102 healthy women, acquaintances or relatives of the patients; individual matching for age (± 5 years).	HSCS, mild dysfunction	Prevalence: 30.8%	Prevalence: 19.3%	PR= 1.60 †	95%CI: 0.93-2.73	-
						HSCS, moderate to severe dysfunction	Prevalence: 4.4%	Prevalence: 3.6%	PR= 1.22 †	95%CI: 0.28-5.31	
						TMT-A	Median score: 44.0	Median score: 45.0	-	P= 0.25	
						TMT-B	Median score: 49.0	Median score: 54.0	-	P= 0.0005 *	
				~ 2 (follow up at 2 year after CT)		HSCS, mild dysfunction	Prevalence: 21.3%	Prevalence: 11.1%	PR= 1.92 †	95%CI: 0.91-4.04	
						HSCS, moderate to severe dysfunction	Prevalence: 3.8%	Prevalence: 0.0%	PR= 3.88 †	95%CI: 0.33-28.77	
						TMT-A	Median score: 47.0	Median score: 49.0	-	P= 0.61	
						TMT-B	Median score: 50.0	Median score: 53.0	-	P= 0.048 *	
Hermelink et al., 2017 [36] Germany	Convenience sample 150 women with breast cancer, aged 18-65 years, with no history of neurological disorders and no previous systemic treatment.	0 (7%) I (42%) II (41.4%) III (%9.6)	CT: 100% HT: 73.9% vs. CT: 0% HT: 80.7%	~ 1 (follow up at 1 year after diagnosis)	Convenience sample 56 women aged 18-65 years, who never had cancer, and attended the same institution as cases for breast imagining and did not require further tests.	Attention TAP; TMT-A, Memory Digit span (WSM-R); VLMT. Executive function TMT-B; lexical and semantic search (RWT).	Composite z-score: No CT: 0.04 (0.45); CT: -0.10 (0.42)	Composite z-score: 0.10 (0.38)	-	P= 0.01 *	Composite score of overall performance calculated as the mean across all age- and education-adjusted cognitive indices (age and education categories in the models not reported). Cognitive change scores were further adjusted for cognitive scores at baseline.
							Composite score, change in the first year of diagnosis: No CT: -0.01 (0.38) CT: -0.07 (0.37)	Composite score, change in the first year of diagnosis 0.11 (0.35)	-	P=0.02 *	
							Prevalence: 17.7%	Prevalence: 5.3%	RR= 2.43	95% CI: 0.89 - 6.65	≥5 scores below 1.5 SD and/or ≥4 scores below 2 SD.

Jenkins et al., 2006 [59] United Kingdom	Convenience sample 128 women diagnosed with early breast cancer across the UK, with no disease progression	'early breast cancer'	Srg, M: 26% CT: 66.4%	~ 1 (follow up at 12 months after CT)	Convenience sample 49 healthy women who were friends or family of the patients, or from the local women's support group	Verbal memory Logical memory (WMS); Immediate & delayed recall (AVLT). Visual memory Complex figure task. Executive function The Stroop task Working memory Spatial span, letter/number sequencing & digit span (WMS-III) Processing speed Letter cancellation task.	Prevalence of decline on ≥2 measures as measured by the reliable change index: 16.8%	Prevalence of decline on ≥2 measures as measured by the reliable change index: 10.6%	PR= 1.58 †	95%CI: 0.64-3.90	Reliable change index corrected for practice effects.
Phillips et al., 2012 [60] United States	Convenience sample 129 women diagnosed with breast cancer and scheduled to receive CT or RT; patients with recurrence were excluded	0 (10%) I (53%) II (37%)	Srg, M: 91.5% Srg, C: 8.5% HT: 62%	3 (follow up at 26 months after RT)	Convenience sample 184 women with no history of cancer, individual matching for age (±5 years) and ZIP code.	Attention Trial 1 Color Trails Test; Digit & Spatial Span (WAIS-III). Executive functioning Digit Symbol Coding (WAIS-III); Trial 2 Color Trails Test; COWAT. Nonverbal memory Visual Reproduction test (WMS-III). Processing speed Ruff 2 & 7 Test. Verbal memory CVLT.	Score Means (SE) CT group: Attention 53.55 (0.72) Executive functioning 51.87 (0.81) Nonverbal memory 56.24 (0.95) Processing speed 49.90 (0.84) Verbal memory 50.67 (1.11) RT group: Attention 51.59 (0.68) Executive functioning 52.30 (0.77) Nonverbal memory 54.97 (0.90) Processing speed 49.03 (0.80) Verbal memory 50.75 (1.05)	Score Means (SE) Attention 51.78 (0.41) Executive functioning 54.63 (0.46) Nonverbal memory 55.90 (0.54) Processing speed 51.38 (0.48) Verbal memory 51.26 (0.63)	-	P<0.05 *	Score means are adjusted for age, T1 National Adult Reading Test scores, and time from T1 to T2 assessments. Significant group x time interaction detected for processing speed (P=0.009).
Schagen et al., 2006 [61] The Netherlands	Convenience sample 57 women who had breast cancer treated with RT but not CT, and no relapse	I (100%)	RT: 100% CT: 0% HT: 0%	~1	Convenience sample 60 healthy women, friends of the participants in the study	24 test indices, covering the following domains: focused-sustained attention, working-verbal-visual memory, processing speed, executive function, and verbal/motor function	Prevalence: 22.8%	Prevalence: 6.7%	OR= 2.1	95%CI: 0.5-8.4	Odds ratio adjusted for age and IQ. Cognitive impairment defined as scoring 2 SD below the mean of the control group for ≥3 of the 24 tests.

Cross-sectional studies involving neurocognitive assessment batteries											
Boele et al., 2015 [11] The Netherlands	Convenience sample Post-menopausal breast cancer survivors with no psychiatric history, who did not receive CT, selected from medical records.	ND	Srg, ND: 95% CT: 0% RT: 65% HT: 100% / 0%	Exposure to HT: 3.2 (1.9), 1.5-7; Unexposed to HT: 2.8 (0.3), 2.3-3.3.	Convenience sample 44 friends or family members of the women who had had breast cancer, with no history of breast cancer; matched for age and education (method of matching not reported).	Verbal memory AVLT; Visual association test. Visual memory WMS. Working memory Letter-number sequencing (WAIS-III) Executive functioning Stroop; TMT-B. Processing speed Stroop; TMT-A Reaction speed Fepsy reaction times Fluency Category fluency, letter fluency Motor functioning Fepsy tapping	Domain z-scores by treatment group: Verbal memory HT: -0.49 (0.66) Srg+RT: -0.01 (0.63) Visual memory HT: 0.136 (0.80) Srg+RT: -0.25 (1.09) Working memory HT: -0.144 (0.82) Srg+RT: 0.08 (1.06) Executive functioning HT: -0.10 (0.92) Srg+RT: 0.07 (0.93) Processing speed HT: -0.06 (0.65) Srg+RT: -0.01 (0.82) Reaction speed HT: 0.24 (0.79) Srg+RT: -0.12 (1.07) Fluency HT: -0.41 (0.78) Srg+RT: -0.31 (0.70) Motor functioning HT: 0.29 (0.70) Srg+RT: 0.14 (0.84)	Domain z-scores: Verbal memory -0.001 (0.81) Visual memory 0.000 (0.95) Working memory 0.001 (1.00) Executive functioning 0.000 (0.88) Processing speed 0.000 (0.79) Reaction speed 0.000 (0.91) Fluency 0.000 (0.88) Motor functioning 0.000 (0.96)	-	Verbal memory P=0.009 * Visual memory P=0.339 Working memory P=0.965 Executive functioning P=0.444 Processing speed P=0.554 Reaction speed P=0.529 Fluency P=0.012 * Motor functioning P=0.667	P-value for the three-group comparison. Z-scores corrected for age and estimated premorbid IQ.
Brezden et al., 2000 [62] Canada	Convenience sample 40 women who had completed CT for breast cancer, at least the 8th grade of education, with no history of cognitive dysfunction or psychiatric illnesses and with no clinical evidence of recurrence or metastases.	I-II (ND)	CT (100%)	2 (ND), >1	Convenience sample 36 healthy female relatives of the patients or hospital personnel who volunteered for the study.	HSCS	Median score: 34.5 Prevalence of moderate and severe cognitive impairment: 50%	Median score: 26.0 Prevalence of moderate and severe cognitive impairment: 11%	- PR= 4.5 * †	P>0.05 95%CI: 1.71-12.11	When adjusted for age, menopausal status, and level of education (categories not reported), the difference was significant (P=0.046). -

Calvio et al., 2010 [7] United States	Convenience sample 122 breast cancer survivors ≥1 year post treatment, working full-time for ≥1 year, with computer and internet, recruited via advertisements and flyers.	I (36.9%) II (44.3%) III (17.2%)	Srg, ND: 96.7% CT: 82.8% RT: 73.0% HT: 45.9% IT: 13.1%	3.1 (2.4), 1-10	Convenience sample 113 women without a previous cancer diagnosis, working full-time for ≥1 year, with computer and Internet, recruited via advertisements and flyers.	CNS-VS battery Composite memory Verbal memory Visual memory Executive function Attention	Composite memory: 101.7 (18.1) Verbal memory: 99.8 (16.6) Visual memory: 102.8 (17.1) Executive function: 98.6 (9.2) Attention: 83.8 (10.3)	Composite memory: 97.1 (19.8) Verbal memory: 96.0 (20.0) Visual memory: 99.3 (17.1) Executive function: 94.5 (16.4) Attention: 80.2 (17.7)	-	Executive function: P<0.001 * Attention: P<0.05 * All other domains P>0.05	Lower scores indicate poorer functioning. Mean scores adjusted for marital status (cohabitating with partner vs. single/not cohabitating), race (Caucasian vs. non-Caucasian), ethnicity (Hispanic vs. non-Hispanic), age (<40, 41-50, 51-65), income (0-39,000; 40-59,000; 60-79,000; 80-89,000; 80-99,000; ≥100,000), and menopausal status (currently going through, premenopausal, postmenopausal).
Castellon et al., 2004 [15] United States	Convenience sample 53 women who had breast cancer at or before the age of 50, with no evidence of disease or recurrence, and no history of psychiatric disorder.	0-II (100%)	CT: 34% CT+HT: 34%	2-5	Convenience sample 19 Healthy women recruited via fliers, newsletter articles and advertisements, or amongst the acquaintances of the hospital staff.	Verbal Fluency COWA. Verbal Learning CVLT. Verbal Memory Logical memory (WMS-R). Visual Memory Visual Reproduction (WMS-R); RCFT. Visuospatial Function Block Design (WAIS-III); Copy Trial (RCFT). Psychomotor Speed Digit Symbol (WAIS-III); TMT-A; TMT-B. Reaction Time CCAP Executive Attention PASAT; Stroop Test.	z-scores, no CT nor HT: Fluency: -0.36 Verbal Learning: 0.54 Verbal memory: 0.21 Visual memory: 0.45 Visuospatial: 0.42 Reaction time: -0.20 Psychomotor speed: 0.22 Executive attention: -0.01 z-scores, CT (with or without HT): Fluency: -0.64 Verbal learning: 0.03 Verbal memory: -0.35 Visual memory: -0.39 Visuospatial: -0.51 Reaction time: -0.49 Psychomotor speed: 0.03 Executive attention: -0.41	Ref the mean scores of the healthy women used to calculate the z-scores.	-	Verbal Fluency: P=0.007 * All other domains: p>0.05	-

Conroy et al., 2013 [18] United States	Convenience sample 24 breast cancer survivors with history of non-metastatic disease and chemotherapy treated.	I (29%) IIa (33%) IIb (25%) IIIa (8%) IIIb (4%)	CT: 100% RT: 79%	6.4 (2.1), 3.2-10.2	Convenience sample 23 healthy women; matched for age and education (matching method not reported).	Learning AVLT; BLT. Memory AVLT; BLT. Attention Digit span (WAIS-III); PASAT. Language WRAT-4; Word Reading test; Vocabulary (WASI). Visuospatial Block Design (WASI) Executive Digit span; COWA; Color-Word Test, Sorting Test, & Trail Making Test (D-KEFS). Psychomotor Symbol Digit, and Grooved Pegboard.	Age-adjusted domain z-scores: Learning: -0.2 (0.7) Memory: -0.3 (0.6) Attention: 0.4 (0.6) Language: 0.3 (0.8) Visuospatial: -0.5 (1.0) Executive: -0.04 (0.7) Psychomotor: -0.1 (0.4) Average: -0.1 (0.5)	Age-adjusted domain z-scores: Learning: 0.1 (0.7) Memory: 0.2 (0.7) Attention: 0.03 (0.5) Language: -0.03 (0.9) Visuospatial: 0.1 (0.9) Executive: 0.04 (0.6) Psychomotor: 0.04 (0.4) Average: 0.1 (0.4)	-	Memory: P≤0.05 * All other domains: P>0.05	-
Ernst et al., 2002 [63] United States	Convenience sample 16 women aged 65-80 years, recruited via advertisements.	'localised breast cancer'	HT: 100% Srg, ND: 100% CT: 0%	4.4 (1.7), 2-10	Convenience sample 33 women with no history of breast cancer; matched for age (matching method not reported).	Digit symbol substitution test	Nr of correct substitutions (SD): 7.5 (3.1)	Nr of correct substitutions (SD): 7.2 (2.1)	-	P>0.05	-
						TMT-A	Time required (SD): 44.2 (12.2)	Time required (SD): 36.9 (10.4)	-	P>0.05	-
Inagaki et al., 2006 [64] Japan	Convenience sample 105 women who had breast cancer aged 18-55 years, with no history of neurological or psychiatric disorders other than affective or anxiety; tumor free at recruitment.	0-I (27.5%)	Srg, C: 49% CT: 100% HT: 39% RT: 48%	1	Convenience sample 55 healthy subjects who lived in the same area as the patients recruited via advertisements in the local newspaper; matched for region (matching method not reported).	WMS-R	Mean domain score (SD): Attention 99.4 (12.5) Verbal memory 96.9 (13.0) Visual memory 101.9 (12.1) Delayed recall 100.3 (10.4)	Mean domain score (SD): Attention 99.6 (13.0) Verbal memory 99.2 (14.4) Visual memory 101.4 (10.3) Delayed recall 100.7 (12.6)	-	For all domains: P>0.05	-

Kesler et al., 2013 [34] United States	Convenience sample 44 women who had breast cancer recruited via support groups and advertisements; patients excluded if they had had disease recurrence or relapse	I-IIIA	Srg, ND: 100% CT: 100%	4.8 (3.4), 1-12	Convenience sample 38 healthy female controls recruited through advertisements	MMQ; HVLT-R; WAIS	Mean scores (SD): HVLT-R total recall: 49.3 (8.0) HVLT-R delayed recall: 49.8 (6.4) MMQ: 42.2 (11.2) WAIS-IQ: 112 (11)	Mean score (SD): HVLT-R total recall: 57.1 (9.6) HVLT-R delayed recall: 56.0 (8.1) MMQ: 59.3 (7.4) WAIS-IQ: 115 (13)	-	P=0.03 * P=0.02 * P<0.001 * P=0.29	-
Koppelmans et al., 2012 [42] The Netherlands	Convenience sample 196 women who had been treated for breast cancer between 1976 and 1995, were aged 50-80 years in 2008, did not have recurrence or a second primary cancer and never used adjuvant hormone therapy.	I-III (100%)	HT: 0% CT: 100%	21 (4.4), ND	Convenience sample All 1,509 women without a history of cancer who were 50-80 years of age at the time of the assessments, selected from a larger population-based cohort.	Learning and memory (15-WLT)	Trial 1: 5.5 (2.2) Trial 2: 8.6 (2.4) Trial 3: 10.3 (2.6) Total: 24.3 (6.2) Delayed recall: 8.0 (2.9) Recognition: 13.8 (1.8)	Trial 1: 5.9 (2.4) Trial 2: 9.0 (2.7) Trial 3: 10.6 (2.9) Total: 25.5 (6.9) Delayed recall: 8.7 (3.2) Recognition: 13.8 (2.0)	-	P=0.008 * P=0.02 * P=0.17 P=0.02 * P=0.002 * P=0.76	Adjusted for age and education (categories of the variables used in the models not reported).
						Processing speed (LDST)	Total correct: 31.8 (6.7)	Total correct: 32.5 (7.5)	-	P=0.14	
						Stroop color-word test	Word card: 16.8 (3.3) Color card: 23.3 (4.4) Color-word card: 45.8 (12.6)	Word card: 16.5 (3.7) Color card: 22.2 (4.9) Color-word card: 43.5 (14.0)	-	P=0.14 P=0.001 * P=0.02 *	
						Verbal fluency (WTF)	Total: 24.1 (6.1) 15sec: 13.8 (4.8)	Total: 24.2 (6.8) 15sec: 13.8 (5.4)	-	P=0.89 P=0.95	
						Visuospatial (DOT)	Total correct: 28.9 (9.2)	Total correct: 28.9 (9.7)	-	P=0.99	
						Motor speed (PPB)	Both hands: 11.1 (1.6) Dominant hand: 13.8 (1.9) Nondominant hand: 12.9 (1.8)	Both hands: 11.2 (1.8) Dominant hand: 13.8 (2.1) Nondominant hand: 13.4 (2.0)	-	P=0.56 P=0.81 P=0.001 *	
Kreukels et al., 2008 [12] The Netherlands	Convenience sample 63 women who had been treated with CT for non-metastatic breast cancer, with no history of psychiatric diseases	I-III (100%)	CT: 100% HT: 40%	~ 1	Convenience sample 60 Female friends or relatives of the patients with the same approximate age who never had cancer; matched for age (matching method not reported).	TMT-A; Digit Symbol (WAIS); Stroop Color Word Test; Eriksen Task, Working-Memory Updating, CVLT, Visual Reproduction of the WMS, AFM Task, TMT-B, Word Fluency, Fepsy Finger Tapping.	Prevalence of cognitive impairment: 33.3%	Prevalence of cognitive impairment: 10%	RR= 5.51 *	95%CI: 1.86-16.28	Cognitive impairment defined as 2 standard deviations below the mean of the healthy control group on ≥ 3 tests. RR adjusted for age and premorbid IQ.

Lejbak et al., 2010 [65] Canada	Convenience sample 28 post menopausal women with oestrogen positive breast cancer, aged 40 and 80 years, recruited from the local cancer registry and oncology centre	I (100%)	HT: 100% Srg, ND: 83% RT: 67%	3 (1), 2-5	Convenience sample 37 age-equivalent controls recruited through mailed invitations	Immediate verbal memory: List Learning, Story Memory. Delayed verbal memory List Recall, Story Recall. Complex visuomotor attention: Coding Letter fluency: COWA Object location memory task Speeded manual dexterity: Grooved Pegboard Complex working memory Verbal n-Back	Mean score (SD): List Learning 29.0 (5.1) List Recall 7.1 (2.2) Story Memory 17.1 (3.6) Story Recall 9.0 (2.3) Coding 42.9 (9.5) Letter Fluency 40.0 (10.8) Object-Location 47.5 (21.1) Grooved Pegboard 80.9 (17.1) Verbal n-Back 119.9 (9.7)	Mean score (SD) List Learning 30.3 (3.8) List Recall 6.8 (2.2) Story Memory 18.4 (3.3) Story Recall 9.7 (2.1) Coding 49.3 (9.2) Letter Fluency 44.3 (11.2) Object-Location 44.4 (20.0) Grooved Pegboard 67.76 (12.7) Verbal n-Back 123.0 (9.5)	- - - - - - - - -	P=0.24 P=0.58 P=0.15 P=0.23 P=0.01 * P=0.03 * P=0.55 P<0.01 * P=0.23	Higher scores indicate better performance.
Miao et al., 2016 [9] China	Convenience sample 23 patients with breast cancer who had been treated with chemotherapy at a local hospital	I-III (100%)	CT: 100%	3 (0.3),	Convenience sample 26 age matched healthy controls selected amongst patients relatives and local universities; matched for age (matching method not reported).	Stroop interference test; MoCA	Mean score (SD) Stroop: 35.04 (8.96) MoCA: 26.00 (1.34)	Mean score (SD) Stroop: 30.17 (6.49) MoCA: 26.58 (1.74)	-	P=0.04 * P>0.05	Higher score in the Stroop interference test indicates worse performance.
Myers et al., 2015 [66] United States	Convenience sample 156 breast cancer patients recruited across 24 states using newsletters and flyers	I (26%) II (47%) III (14%) IV (5%)	CT: 100% RT: 71.2% HT: 49.4%	1-2 2-5 >5	Convenience sample 46 healthy controls recruited using flyers	FACT-COG, Perceived cognitive impairments (PCI) Perceived cognitive abilities (PCA)	Mean score (SD): PCI: 48.6 (17.2) PCA: 17.6 (7.2) PCI: 41.7 (18.3) PCA: 15.9 (6.8) PCI: 50.4 (18.2) PCA: 19.0 (6.9)	Mean score (SD): PCI: 61.1 (9.4) PCA: 19.1 (8.8) PCI: 61.1 (9.4) PCA: 19.1 (8.8) PCI: 61.1 (9.4) PCA: 19.1 (8.8)	- - - -	P<0.05 * P>0.05 P<0.05 * P<0.05 * P<0.05 * P<0.05 *	Higher scores indicate higher cognitive function.

Nguyen et al., 2013 [39] United States	Convenience sample 57 women survivors of breast cancer, aged over 65 years, without recurrence, recruited from the cancer registry	I-IIIA (100%)	RT: 53% CT: 100%	>10	Convenience sample 30 healthy female adults, selected in the community for a previous study	Intelligence and mental status WASI; Wide Range Achievement Test-III reading subtest; Folstein mini mental state examination. Attention and working memory Digit Span, Letter-Number Sequencing, and Arithmetic subtests (WAIS-III) Psychomotor speed TMT-A. Language COWA; Boston Naming Test Visuospatial RCFT-Copy Condition; Benton Facial; Recognition Test. Memory AVLT; RCFT-Delay Condition. Benton Visual Retention Test-Revised. Executive functioning Wisconsin Card Sorting Test. TMT-B.	WASI Vocabulary: 64.5 (7.8) Block design: 33.9 (12.3) Similarities: 36.8 (4.8) Matrix design: 20.6 (6.5) Wide Range Achievement Test-III Reading: 48.1 (4.7) Digit span: 15.5 (3.4) Letter–Number Seq 9.1 (2.1) Arithmetic total 12.4 (2.8) TMT A time: 37.8 (8.9) B-time: 97.0 (35.5) COWA: 39.4 (15.1) Boston Naming Test 57.0 (2.5) Rey–Osterrieth Complex Figure Copy: 33.3 (2.0) Delay: 15.9 (5.1) Benton Faces total 44.4 (3.4) Benton Visual Retention Test total 5.3 (2.2) Rey Auditory-Verbal Learning Test Total: 48.6 (8.3) Delay: 10.2 (2.6) IED: 3.2 (4.2) Wisconsin: Perseverative: 12.5 (6.9) Errors: 11.0 (5.7) Categories: 2.9 (1.6)	WASI Vocabulary: 63.7 (6.9) Block design: 34.8 (11.9) Similarities: 36.6 (3.0) Matrix design: 21.8 (6.8) Wide Range Achievement Test-III Reading: 50.2 (5.0) Digit span: 16.9 (4.4) Letter–Number Seq 11.0 (2.0) Arithmetic total 13.7 (3.2) TMT A time: 29.3 (8.7) B-time: 72.4 (26.6) COWA: 38.8 (11.1) Boston Naming Test 56.1 (3.0) Rey–Osterrieth Complex Figure Copy: 32.0 (2.9) Delay: 15.6 (5.6) Benton Faces total 45.5 (3.8) Benton Visual Retention Test total 4.4 (2.8) Rey Auditory-Verbal Learning Test Total: 49.4 (8.7); Delay: 10.6 (2.3). IED: 1.3 (1.0) Wisconsin: Perseverative: 16.6 (12.2) Errors: 14.9 (11.0) Categories: 5.0 (1.9)	-	P<0.05 *: Letter–Number Seq; Trail making test A and B; Boston naming test; Rey–Osterrieth Complex Figure; Benton Visual Retention; Rey Auditory-Verbal Learning; IED; Wisconsin Card Sorting categories. P>0.05 All other tests.	-

Root et al., 2015 [17] United States	Convenience sample 113 women aged <70 years who had breast cancer, post-menopausal at diagnosis, with no recurrence, no neurological or psychiatric diagnoses.	I (58%) II (0%) III (33%) IV (8%)	Srg, C: 75% Srg, M: 32% CT: 52% RT: 78% HT: 52%	4.2 (1.2)	Convenience sample 37 health women with no history of cancer or cancer treatment, post-menopausal, with no neurological or psychiatric diagnoses; matched for age and education (method of matching not reported).	FACT-COG	Mean score (SD) Memory: 20.4 (5.9) Verbal 18.5 (4.8) Concentration 12.4 (3.2) Mental acuity 12.0 (3.4) QoL impact 13.7 (3.0) PCI: 56.5 (12.7) PCA: 19.5 (6.3)	Mean score (SD): Memory: 23.5 (3.2) Verbal: 19.2 (3.6) Concentration: 13.6 (2.4) Mental acuity: 13.4 (2.0) QoL impact: 14.3 (2.4) PCI: 59.4 (8.3) PCA: 22.7 (4.5)	-	P=0.003 * P=0.42 P=0.04 * P=0.02 * P=0.27 P=0.20 P=0.005 *	-
Silverman et al., 2007 [67] United States	Convenience sample 24 women who had breast cancer and were right handed.	ND	CT+HT: 52% CT: 24%	ND (ND), 5-10	Convenience sample 10 healthy controls who had undergone PET studies before, free of cognitive impairments.	RCFT- recall test	Mean (SD): 20.6 (4.8)	Mean (SD): 23.8 (6.3)	-	P>0.05	Lower scores represent worse functioning.
Von Ah et al., 2009 [44] United States	Convenience sample 52 women aged ≥40 years, who had breast cancer, recruited from cancer support groups, advertisements in the community centres, or by referral of enrolled participants.	I-II (50%) III (ND)	Srg, C: 66% Srg, M: 33% CT: 55.8% RT: 80.8% HT: 79%	4.6 (2.8), 1.2-15.8	Convenience sample 52 women aged ≥40 years, with no history of cancer, no history of psychiatric illnesses, recruited from advertisements in churches and community centres, or by referral of enrolled participants; individual matching for age (±5 years) and education (±3 years).	Memory: AVLT	Sum recall: 48.5 (7.2) Delayed recall: 9.6 (2.8)	Sum recall: 52.4 (8.1) Delayed recall: 10.9 (2.8)	--	P=0.01 *	-
						Attention: Digit span (WAIS-III)	17.8 (4.0)	17.7 (4.1)		P=0.89	-
						Attention: Symbol digit modalities test	53.6 (8.2)	54.1 (10.4)		P=0.79	-
						Executive function: COWA	38.2 (10.9)	42.2 (12.4)		P=0.08	-
						Subjective memory function: Squire SRS	92.9 (17.9)	102.9 (22.6)		P=0.01 *	-

ACTT = Auditory Consonant Trigrams Test [68]; AFM = Additive factors method task [69]; AVLT = Rey Auditory Verbal Learning Test [70]; BC = breast cancer; BLT = Brown Learning Test [71]; CCAP - California Computerized Assessment Package [72]; CNS-VS = CNS vital signs battery [73, 74]; COWA = Controlled Oral Word Association [75]; CPT = Continuous Performance test [76]; CT = chemotherapy; CVLT = California Verbal Learning Test [77]; D-KEFS = Delis-Kaplan Executive Function System [78]; DOT = Design organization test [79]; EORTC-QLQ-CF = the European Organization for Research and Treatment of Cancer [80]; FACT-COG = Functional Assessment of Cancer Therapy for Cognition [81]; HSCS = High Sensitivity Cognitive Screen [82]; HT = hormone therapy; HVLT-R = Hopkins verbal learning test revised [83]; IT = immunotherapy; LDST = Letter Digit Substitution Test [84]; MoCA = Montreal Cognitive Assessment Test [85]; Multifactorial Memory Questionnaire Ability Scale [86]; ND = not defined; OR = odds ratio; PASAT = Paced Auditory Serial Addition Test [87]; PCA = Perceived cognitive abilities; PCI = Perceived cognitive impairments; PPB = Purdue Pegboard test [88]; PR = prevalence ratio; RCFT = Rey-Osterrieth Complex Figure Test, Copy Condition [89-91]; RT = radiotherapy; RWT = Regensburg word fluency test [92]; SD = standard deviation; Srg, C = Breast conserving surgery; Srg, ND = Surgery, not further specified; Srg, M = Mastectomy; Srg, R = Breast reconstructive surgery; SRS = Squire self-report scale [93]; TAP = Test of Attentional Performance [94]; TMT-A = Trail Making Test-A [95]; TMT-B = Trail Making Test-B [95]; WAIS-III = Wechsler Adult Intelligence Scale-III [96]; WASI = Wechsler Abbreviated Scale of Intelligence [97]; 15-WLT = 15-Word Learning Test [98]; WMS-R = Wechsler Memory Scale-Revised [99]; WRAT = Wide Range Achievement Test [100]; WTF = Word Fluency Test [101]; yrs = years; 95%CI = 95% confidence interval.

* There was some statistical evidence (P<0.05) for a different prevalence, risk or severity of anxiety between breast cancer survivors and women who did not have cancer.

† Prevalence ratio calculated by the authors of the present study.

Supplementary Table 6. Sexual dysfunction: main characteristics and results of the studies that provided data on the frequency and/or severity of sexual dysfunction in breast cancer survivors (>1 year) and women who did not have cancer.

First author, year of publication Country	Breast cancer survivors				Comparison group	Outcome assessment	Prevalence / cumulative incidence of the outcome		Relative risk estimate (RR, OR, SIR, PR)	P-value or 95% confidence interval	Notes
	Type of population and main characteristics	Stage at diagnosis (%)	Breast cancer treatments: %	Time since diagnosis/ treatment in years: mean/ median (SD), range	Type of population and main characteristics		Breast cancer survivors	Comparison group			
Cross-sectional studies											
Boehmer et al., 2014 [102] United States	Convenience sample 85 lesbian or bisexual breast cancer survivors, with no metastatic breast cancer or secondary cancers, recruited via advertisements, flyers, and other promotional materials distributed online and in print media (<5% had cancer recurrence).	0 (16.5%) I (28.2%) II (37.7%) III (8.2%) Unknown (9.4%)	Srg C: 41.2% Srg, M: 40.0% CT: 61.2% RT: 58.8% HT: 45.9%	4.5 (2.3), 1-10	Convenience sample 85 lesbian or bisexual women with no history of cancer, not using hormone replacement therapy, recruited via flyers, advertisements, etc.; individual matching for age (± 3 years) and partner status (partnered vs. unpartnered).	Scale: FSFI	Prevalence: 52.5%	Prevalence: 4.3%	All women: OR=1.44 Sexually active: OR=1.79	All women: 95%CI: 0.72-2.90 Sexually active: 95%CI 0.78-4.07	40% of the cases and 31% of the controls were sexually inactive.
						Scale: FSFI Overall score	Mean score (SD): 24.0 (7.2)	Mean score (SD): 26.0 (5.3)	-	P=0.08	
						Subscales: Desire	4.3 (2.0)	5.7 (2.2)	-	P<0.01 *	
						Arousal	13.2 (5.3)	14.9 (4.5)	-	P=0.07	
						Lubrication	13.5 (6.0)	11.6 (1.1)	-	P=0.03 *	
						Orgasm	11.1 (4.1)	12.6 (3.2)	-	P=0.04 *	
						Satisfaction	11.0 (3.2)	11.8 (3.2)	-	P=0.22	
						Pain	12.8 (3.2)	14.1 (1.8)	-	P=0.03 *	
Safarinejad et al., 2013 [103] Iran (continues)	Convenience sample 186 women cancer survivors aged 25-45, with BMI<30 kg/m², in a relationship and attempted intercourse weekly, with no breast cancer recurrence, no other cancer, no psychopathology, no relationship disturbances, no diabetes or cardiac, renal, neurological, or liver disease, among others; identified from the cancer registry.	I (62.4%) II (37.6%)	Srg, C: 100% Srg, M: 0% CT: 67.7% RT: 46.2% HT: 79.6%	2.4 (ND), >1	Convenience sample 204 women without cancer aged 25-45 in a relationship, who attempted intercourse weekly, in same geographical area of cases, with BMI<30kg/m², no psychopathology, no relationship disturbances, no diabetes or cardiac, renal, neurological, or liver disease, among others, recruited from a private clinic; matched for age (matching method not reported).	Scale: FSFI	Prevalence of dysfunction: 52.5% By treatment: RT+CT: 44.6% CT+HT: 46.2% CT+RT+HT: 66.7%	Prevalence: of dysfunction: 28.7%	PR=1.81 * † By treatment: PR= 1.55 * PR= 1.61 * OR= 8.2 *	95%CI: 1.40-2.34 By treatment: 95%CI: 1.13-1.98 95%CI: 1.32-1.90 95%CI: 6.5-14.2	Odds ration adjusted for age, body mass index, occupational status, educational level, smoking history, serum hormonal levels, tumour stage and grading. The categorization of the variables included in the model were not reported.
						FSFI Subscales: Desire	All treatments: 41.9% By treatment: RT+CT: 33% CT+HT: 42% CT+RT+HT: 53%	28.0%	PR=1.50 * † By treatment: OR= 1.8 OR= 3.6 * OR= 4.7 *	95%CI: 1.13-1.98 By treatment: 95%CI: 0.9-2.2 95%CI: 2.6-6.8 95%CI: 2.8-8.7	
						Arousal	All treatments: 33.9% By treatment: RT+CT: 31% CT+HT: 30% CT+RT+HT: 50%	25.0%	PR=1.36 † By treatment: OR= 1.6 OR= 1.5 OR= 4.2 *	95%CI: 0.99-1.85 By treatment: 95%CI: 0.8-2.8 95%CI: 0.8-2.8 95%CI: 2.6-8.2	
						Orgasm	All treatments: 41.9% By treatment: RT+CT: 33% CT+HT: 41% CT+RT+HT: 56%	29.0%	PR=1.44 * † By treatment: OR= 2.1 OR= 3.2 * OR= 5.2 *	95%CI: 1.10-1.90 By treatment: 95%CI: 0.8-3.4 95%CI: 2.4-7.1 95%CI: 3.7-10.2	

Safarinejad et al., 2013 [103] Iran (continued)	Convenience sample 186 women cancer survivors aged 25-45, with BMI<30 kg/m^2, in a relationship and attempted intercourse weekly, with no breast cancer recurrence, no other cancer, no psychopathology, no relationship disturbances, no diabetes or cardiac, renal, neurological, or liver disease, among others; identified from the cancer registry.	I (62.4%) II (37.6%)	Srg, C: 100% Srg, M: 0% CT: 67.7% RT: 46.2% HT: 79.6%	2.4 (ND), >1	Convenience sample 204 women without cancer aged 25-45 in a relationship, who attempted intercourse weekly, in same geographical area of cases, with BMI<30kg/m^2, no psychopathology, no relationship disturbances, no diabetes or cardiac, renal, neurological, or liver disease, among others, recruited from a private clinic; matched for age (matching method not reported).	Pain	All treatments: 39.2% By treatment: RT+CT: 31% CT+HT: 36% CT+RT+HT: 59%	Prevalence: 30.0%	PR=1.31 † By treatment: OR= 1.2 OR= 2.2 * OR= 5.6 *	95%CI: 0.99-1.72 By treatment: 95%CI: 0.96-1.8 95%CI: 1.5-3.8 95%CI: 3.2-11.4	Odds ratio adjusted for age, body mass index, occupational status, educational level, smoking history, serum hormonal levels, tumour stage and grading. The categorization of the variables included in the model were not reported.
						Lubrication	All treatments: 58.1% By treatment: RT+CT: 56% CT+HT: 55% CT+RT+HT: 61%	31.0%	PR=1.87 * † By treatment: OR= 4.2 * OR= 4.1 * OR= 6.4 *	95%CI: 1.48-2.38 By treatment: 95%CI: 3.4-8.7 95%CI: 3.2-8.4 95%CI: 4.6-12.6	
						Satisfaction	All treatments: 53.8% By treatment: RT+CT: 50% CT+HT: 53% CT+RT+HT: 59%	29.0%	PR=1.86 * † By treatment: OR= 3.4 * OR= 3.8 * OR= 5.7 *	95%CI: 1.44-2.39 By treatment: 95%CI: 1.8-5.8 95%CI: 2.2-6.1 95%CI: 3.4-11.4	
						Desire	Mean score (95%CI): 3.7 (3.1-4.3) By treatment: RT+CT: 4.4 (3.8-4.7) CT+HT: 3.6 (2.9-4.4) CT+RT+HT: 3.1 (2.6-3.6)	Mean score (95%CI): 4.8 (3.6-5.6)	-	P<0.05 * By treatment: P>0.05 P<0.05 * P<0.05 *	Women who had RT+CT+HT reported more sexual dysfunction problems than women who had RT+CT for all domains, and more impairments than women who had CT+HT for arousal, lubrication, satisfaction and pain.
						Arousal	4.0 (3.3-4.3) By treatment: RT+CT: 4.4 (3.6-4.6) CT+HT: 4.3 3.6-4.6() CT+RT+HT: 3.3 (2.7-3.7)	4.9 (3.5-5.4)	-	P<0.05 * By treatment: P>0.05 P>0.05 P<0.05 *	
						Lubrication	2.8 (2.4-3.3) By treatment: RT+CT: 3.1 (2.6-3.6) CT+HT: 3.1 (2.6-3.5) CT+RT+HT: 2.4 (1.9-2.8)	5.1 (3.5-5.8)	-	P<0.05 * By treatment: P<0.05 * P<0.05 * P<0.05 *	
						Orgasm	3.7 (3.1-4.1) By treatment: RT+CT: 4.3 (3.6-4.7) CT+HT: 3.6 (3.1-3.9) CT+RT+HT: 3.2 (2.7-3.6)	4.7 (3.8-5.8)	-	P<0.05 * By treatment: P>0.05 P<0.05 * P<0.05 *	
						Satisfaction	3.3 (2.9-3.7) By treatment: RT+CT: 3.4 (3.0-3.9) CT+HT: 3.5 (3.1-4.0) CT+RT+HT: 2.9 (2.5-3.3)	5.1 (3.7-5.7)	-	P<0.05 * By treatment: P<0.05 * P<0.05 * P<0.05 *	
						Pain	4.6 (3.8-4.7) By treatment: RT+CT: 4.9 (4.5-5.0) CT+HT: 4.4 (4.1-4.6) CT+RT+HT: 3.1 (2.7-3.5)	5.1 (3.8-5.5)	-	P>0.05 By treatment: P>0.05 P<0.05 * P<0.05 *	

Claus et al., 2006 [41] United States	Population-based All 795 women in Connecticut diagnosed with DCIS in 1994-1998, with history of invasive breast cancer	0 (100%)	Srg, C: 35.5% Srg, M: 14.0%	5.8 (1.0), ND	Population based 702 women selected by random-digit-dialling methods, with no history of DCIS or invasive breast cancer; frequency matched by age (± 5 years) and geography.	Scale: MOS-SFS, Lack of interest	Prevalence: 27.9% By treatment: Srg, C: 25.6% Srg, C + RT: 31.0% Srg, M: 22.6%	Prevalence: 22.3%	PR= 1.25 * † By treatment: PR= 1.15 † PR= 1.39 * † PR= 1.01 †	95%CI: 1.05-1.49 By treatment: 95%CI: 0.90-1.46 95%CI: 1.14-1.70 95%CI: 0.70-1.47	Cut-off for case: "somewhat of a problem" or "very much of a problem".
						Unable to relax	Prevalence: 19.2% By treatment: Srg, C: 20.1% Srg, C + RT: 18.6% Srg, M: 18.7%	Prevalence:12.8%	PR=1.50 * † By treatment: PR= 1.57 * † PR= 1.45 * † PR= 1.46 †	95%CI: 1.16-1.91 By treatment: 95%CI: 1.16-2.12 95%CI: 1.10-1.93 95%CI: 0.95-2.25	
						Difficulty with arousal	Prevalence: 23.0% By treatment: Srg, C: 25.6% Srg, C + RT: 22.3% Srg, M: 18.7%	Prevalence:15.2%	PR=1.51 * † By treatment: PR= 1.68 * † PR= 1.47 * † PR= 1.23 †	95%CI: 1.22-1.88 By treatment: 95%CI: 1.29-2.19 95%CI: 1.14-1.89 95%CI: 0.80-1.87	
						Difficulty with orgasm	Prevalence: 20.4% By treatment: Srg, C: 21.3% Srg, C + RT: 20.8% Srg, M: 16.8%	Prevalence:14.8%	PR=1.38 * † By treatment: PR= 1.44 * † PR= 1.41 * † PR= 1.14 †	95%CI: 1.10-1.73 By treatment: 95%CI: 1.08-1.92 95%CI: 1.08-1.83 95%CI: 0.72-1.78	
Broeckel et al., 2002 [40] United States	Convenience sample 58 breast cancer survivors who had a spouse or partner, free of recurrence for >5 years, with no known neurological disorder, and no history of other cancer.	I (26%) II (62%) III (10%) Unknown (2%)	Srg, C: 50% Srg, M: 47% CT: 100% RT: 71% HT: 48%	7.7 (2.3), 5.2-15.2	Convenience sample 61 women with no history of cancer who had a spouse or partner, recruited among the friends of the women who had breast cancer; individual matching for age (± 6 years).	Scale: MOS-SFS Overall	Mean score (SD): 1.95 (1.05)	Mean score (SD): 1.50 (0.70)	-	P≤0.01 *	Sexual dysfunction positively correlated with vaginal dryness in breast cancer survivors.
						Interest	2.06 (1.16)	1.67 (0.83)	-	P≤0.05 *	
						Enjoyment	1.72 (0.94)	1.38 (0.74)	-	P≤0.01 *	
						Arousal	1.87 (1.08)	1.40 (0.83)	-	P≤0.01 *	
						Orgasm	1.78 (1.01)	1.44 (0.80)	-	P≤0.05 *	
Rubino et al., 2007 [10] Italy	Convenience sample 33 consecutive patients who had had breast-reconstruction after mastectomy, in 2001-2002, in one hospital.	ND	Srg, M: 100% Srg, R: 100%	ND (ND), >1	Convenience sample 33 healthy women, randomly selected amongst the personnel of the local university.	Psychiatric interview	Prevalence: 18.5%	Prevalence: 9.1%	PR=2.03 †	95%CI: 0.19-21.26	-

Vazquez-Ortiz et al., 2010 [104] Spain	Convenience sample 30 women aged 25-59 years who had mastectomy ≥1 year ago, were free of disease, in a stable heterosexual relationship, able to read and write and with no psychological or psychiatric treatment in the last 10 years, recruited from hospitals.	I (13.3%) II (60.0%) III-A (26.7%)	Srg, M: 100%	ND (ND), 2-5	Convenience sample 30 women without breast cancer aged 25-59, assistants to talks and workshops about woman's health, who did not have an incapacitating or severe disease.	Scale: SAI-E Arousal	Mean score (SD): 68.5 (23.9)	Mean score (SD): 72.6 (23.7)	-	P=0.690	-
						Scale: SAI-E Satisfaction	Mean score (SD): 72.3 (23.3)	Mean score (SD): 76.9 (23.9)	-	P=0.524	
						Scale: WSQ Sex frequency per month: 0	10.0%	3.3%	PR=3.33 †	95%CI: 0.33-33.27	-
						1-3	20.0%	13.3%	PR=1.50 †	95%CI: 0.47-4.80	
						4-6	33.3%	30.0%	PR=1.11 †	95%CI: 0.53-2.34	
						7-9	13.3%	20.0%	PR=0.67 †	95%CI: 0.21-2.12	
						>9	23.3%	33.3%	PR=0.70 †	95%CI: 0.31-1.59	
						Orgasm frequency during sex Never (0%)	7.1%	3.3%	PR=2.15 †	95%CI: 0.21-22.11	-
						Sometimes (1-29%)	14.3%	10.0%	PR=1.43 †	95%CI: 0.36-5.72	
						Often (30-58%)	17.9%	23.3%	PR=0.77 †	95%CI: 0.28-2.10	
						Most of the time (60-89%)	21.4%	16.7%	PR=1.28 †	95%CI: 0.45-3.67	
						Almost always (90-100%)	39.3%	46.7%	PR=0.84 †	95%CI: 0.47-1.51	

BC = breast cancer; CT = chemotherapy; FSFI = Female Sexual Functioning Index [105];
HT = hormone therapy; MOS-SFS = MOS Sexual Functioning Scale [106]; ND = not defined; PR = prevalence ratio; RT = radiotherapy; SAI-E = Sexual Arousal and Satisfaction Scale - Expanded [107]; SD = standard deviation; Srg, C = Breast conserving surgery; Srg, M = Mastectomy; Srg, R = Breast reconstructive surgery; WSQ = Women's Sexuality Questionnaire [108].

* There was some statistical evidence (P<0.05) for a different prevalence, risk or severity of anxiety between breast cancer survivors and women who did not have cancer.

† Prevalence ratio calculated by the authors of the present study.

Supplementary Table 7. Other outcomes: characteristics and results of the studies that provided data on the frequency and/or severity of bipolar disorders, obsessive-compulsive problems, post-traumatic stress, sleep-wake disturbances, somatization and suicide in breast cancer survivors (>1 year) and women who did not have cancer.

First author, year of publication Country	Breast cancer survivors				Comparison group	Outcome assessment	Prevalence / cumulative incidence of the outcome		Relative risk estimate (RR, OR, SIR, PR)	P-value or 95% confidence interval	Notes
	Type of population and main characteristics	Stage at diagnosis (%)	Breast cancer treatments (%)	Time since diagnosis/ treatment in years: mean/ median (SD), range	Type of population and main characteristics		Breast cancer survivors	Comparison group			
Bipolar disorder											
Hung et al., 2013 [2] Taiwan	Population-based 26,629 women with no prior mood disorder and cancer, with primary breast cancer registered in the National Health Insurance Database in 2000-2005.	All	ND	2.7 (ND), ND-7 (median follow up years for breast cancer survivors: 2.7; for matched cohort: 3.21)	Population-based 26,629 women randomly selected from 1 million women with no history of breast cancer in the same database; individual matching for age and Charlson comorbidity score (categories of matching not reported).	EHR, recorded in the Registry for Catastrophic Illness with an ICD-9-CM code for anxiety (ICD-9-CM codes: 296.0X-296.1X, 296.4X-296.8X)	Cumulative incidence: 0.3%	Cumulative incidence: 0.1%	RR=2.06 *	95%CI: 1.37-3.15	Approximate cumulative incidence values estimated from the graphics provided in the original study. P value for the log-rank test comparing the Kaplan-Meier curves: P<0.001
				2			0.3%	0.1%	RR=3.0 * †	95%CI: 2.56-3.39	
				4			0.4%	0.2%	RR=2.0 * †	95%CI: 1.82-2.19	
				6			0.6%	0.3%	RR=2.0 * †	95%CI: 1.86-2.16	
Obsessive-compulsive problems											
Amir et al., 2002 [13] Israel	Convenience sample 39 women free of cancer symptoms for ≥3 years and not under active treatment, identified in 2 hospitals.	I (46%) II (46%) III (8%)	Srg, C: 20% Srg, M: 80% CT: 66% RT: 41% HT: 46%	6.5 (ND), ≥5	Convenience sample 39 women without any life-threatening disease, recruited by unknown methods; matched for age and education; matched for age and education (method of matching not reported).	Scale: SCL-90	SCL-90 mean score (SD): 0.92 (0.70)	SCL-90 mean score (SD): 0.68 (0.42)	-	P<0.001 *	Higher SCL-90 scores indicate more obsessive-compulsive symptoms. Women who had breast cancer and PTSD symptoms had more obsessive-compulsive problems than those who did not have PTSD symptoms (P<0.01).
Post-traumatic stress											
Gurevich et al., 2004 [109] Canada	Convenience sample 66 women with a good working knowledge of English ≥1 year post breast cancer treatments with negative mammography before.	Local (61%) Regional (30.5%) Distant (2%) Unknown (11%)	Srg: 96.6% CT: 48% RT: 71% HT: 48%	6.6 (4.5), ≥1	Convenience sample 69 'healthy' women undergoing surveillance mammography in the same hospital.	Scale: SASRQ	SASRQ mean scores (SD): Dissociative: 1.07 (1.05) Re-experiencing: 1.23 (1.25) Avoidance: 1.34 (1.21) Arousal: 1.96 (1.40) Impairment: 1.29 (1.30) Total acute stress: 1.37 (1.05)	SASRQ mean scores (SD): 0.45 (0.80) 0.58 (0.95) 0.83 (1.17) 1.00 (1.21) 0.66 (1.10) 0.69 (0.91)	-	P<0.0001 * P<0.001 * P<0.02 * P<0.0001 * P<0.003 * P<0.0001 *	-

Voigt et al., 2016 [110] Germany	Convenience sample 150 women aged 18-65 years, newly diagnosed with breast cancer at recruitment, with no history of psychotic disorders	0 (7%) I (42%) II (41.4%) IIIc (%9.6)	Srg, M: 26% Srg, C: 74% CT: 58%	~ 1	Convenience sample 56 women aged 18-65 years, who never had cancer, who attended the same institution as cases for breast imagining and did not require further tests	SCID, number of PTSD symptoms	Prevalence of PTSD related to BC: 2.0% Prevalence of PTSD related to stressors other than BC: 0%	Prevalence of PTSD related to stressors other than BC: 0%	PR= 1.51 †	95%CI: 0.17-13.20	Mean number of PTSD symptoms (SD) in breast cancer survivors: 1.7 (2.3); significantly different from the mean number of symptoms in controls (P<0.001).
Yang et al., 2017 [4] Sweden	Population based All 40,849 women diagnosed with an invasive breast cancer at the age of 20-80 years between 2001-2009	I-IV	ND	4.5 (4.5), 0-10 (median (IQR) duration of follow up: 4.4 (4.5))	Population based 452,507 women randomly selected from the respondents to the 1990 census	EHR, ICD-10 diagnostic codes for stress-related disorders (F430-2, F438-9) at in patient or outpatient hospital visits	Cumulative incidence: 0.9%	Cumulative incidence: 0.5%	SIR= 1.77 * By age group: 20-44: SIR= 1.68 * 45-54: SIR= 1.78 * 55-64: SIR= 1.89 * 65-80: SIR= 1.64 *	95%CI: 1.60-1.95 By age group: 95%CI: 1.36-2.08 95%CI: 1.52-2.09 95%CI: 1.56-2.28 95%CI: 1.23-2.19	Standardised incidence ratios were standardised by calendar period (1-year categories), age (5-year categories), and region of residence (North, Stockholm-Gotland, South, Southeast, Uppsala-Orebro, West).
				0-0.5			-	-	SIR= 4.22 *	95%CI: 3.44-5.19	
				0.5-1			-	-	SIR= 2.73 *	95%CI: 2.11-3.52	
				1-2			-	-	SIR= 1.72 *	95%CI: 1.36-2.17	
				2-5			-	-	SIR= 1.36 *	95%CI: 1.14-1.63	
				5-10			-	-	SIR= 0.98	95%CI: 0.73-1.32	
	Population based All 40,849 women diagnosed with an invasive breast cancer at the age of 20-80 years between 2001-2009	0	ND	4.5 (4.5), 0-10 (median (IQR) duration of follow up: 4.4 (4.5))	Population based 452,507 women randomly selected from the respondents to the 1990 census	EHR, ICD-10 diagnostic codes for stress-related disorders (F430-2, F438-9) at in patient or outpatient hospital visits	Cumulative incidence: 0.6%	Cumulative incidence: 0.5%	SIR= 1.02 By age group: 20-44: SIR= 0.38 45-54: SIR= 1.06 55-64: SIR= 1.46 65-80: SIR= 1.15	95%CI: 0.70-1.50 By age group: 95%CI: 0.09-1.51 95%CI: 0.60-1.87 95%CI: 0.76-2.81 95%CI: 0.37-3.56	
				0-0.5			-	-	SIR= 2.76 *	95%CI: 1.31-5.79	
				0.5-1			-	-	SIR= 0.78	95%CI: 0.20-3.14	
				1-2			-	-	SIR= 1.04	95%CI: 0.43-2.51	
				2-5			-	-	SIR= 0.88	95%CI: 0.46-1.69	
				5-10			-	-	SIR= 0.57	95%CI: 0.18-1.76	
Sleep-wake disturbances											
Ancoli-Israel et al., 2014 [33] United States	Convenience sample 44 women who had been newly diagnosed with breast cancer 1 year before, and scheduled to receive ≥4 cycles of CT, with no psychological impairments and not receiving RT at recruitment.	I (27.9%) II (39.7%) III (30.9%) Unknown (1.5%)	Srg, C: 45.6% Srg, M: 49.7% CT: 100%	~ 1 (follow up at 1 year after CT)	Convenience sample 35 cancer-free friends of the women who had breast cancer, or 'volunteers', with no psychological impairments at the time of recruitment individual matching for age (±5 years), ethnicity and education (categories of ethnicity and education not reported).	Nocturnal total sleep time	Mean time (SD), hours: 7.01 (0.74)	Mean time (SD), hours: 7.07 (0.66)	-	P>0.05	Sleep measure by wrist activity, using an actigraph during 72 consecutive hours.
						Daytime total nap time	Mean time (SD), hours: 0.49 (0.47)	Mean time (SD), hours: 0.36 (0.44)		P=0.63	
						Scale: PSQI	PSQI mean scores (SD): 7.4 (ND)	PSQI mean scores (SD): 5.0 (ND)	-	P=0.02 *	

El Rafihi-Ferreira et al., 2011 [111] Brazil	Convenience sample 50 women with a previous diagnosis of breast cancer without encephalopathies or severe psychiatric disorders. Patients were all disease free at enrolment.	I-II (100%)	Srg, ND: 40% CT: 66% RT: 54% HT: 77%	3.8 (2.8), 1-10	Convenience sample 50 women without a previous cancer diagnosis, encephalopathies or severe psychiatric disorders.	Scale: PSQI	Prevalence:40%	Prevalence: 50%	PR=0.8 †	95%CI: 0.52-1.24	Cut-off for case: score >5
						Cannot get to sleep in 30 min	Prevalence: 42%	Prevalence: 38%	PR= 1.1 †	95%CI: 0.68-1.79	Cut-off for case: reported problems three or more times a week. Worse sleep quality associated with poorer quality of life for the social domain, and domains of physical and psychological health (P<0.05). Women who had had breast cancer and had worse quality of sleep reported higher depressive symptomatology compared to those with good quality of sleep (SDS mean scores 20.8 (7.12) vs. 16.6 (3.76), P<0.05).
						Wake up in the middle of the night or early morning	40%	22%	PR= 1.82 †	95%CI: 0.98-3.39	
						Get up to use the bathroom	52%	26%	PR= 2.0 * †	95%CI: 1.17-3.43	
						Cannot breathe comfortably	8%	8%	PR= 1.0 †	-	
						Cough or snore loudly	16%	16%	PR= 1.0 †	-	
						Feel too cold	4%	6%	PR= 0.67 †	95%CI: 0.12-3.82	
						Feel too hot	36%	14%	PR= 2.57 * †	95%CI: 1.18-5.61	
						Pain	14%	20%	PR= 0.70 †	95%CI: 0.29-1.69	
						Sleep medication	12%	16%	PR= 0.75 †	95%CI: 0.28-2.00	
						Daytime sleepiness	2%	4%	PR= 0.50 †	95%CI: 0.05-5.34	
						<6h of sleep	18%	14%	PR= 1.29 †	95%CI: 0.52-3.18	
Otte et al., 2010 [43] United States	Convenience sample 246 breast cancer survivors free of cancer at recruitment, with no history of other cancers and able to speak, read and write English	I (ND) II (ND) III (ND)	Srg, C: 42% Srg, M: 59% CT: 89% RT: ND HT: 33%	5.6 (2.0), 2-10	Convenience sample 246 women in general good health with no history of breast cancer recruited by acquaintance referral, self-referral or from corporative group; individual matching for age (±5 years).	Scale: PSQI Overall score	PSQI mean scores (SD): 7.31 (3.80)	PSQI mean scores (SD): 5.80 (3.45)	-	P<0.01 *	Adjusted for race (minority vs. not minority) and menopausal status (pre or post menopausal). Determinants sleep-wake disorders in women who had breast cancer: race other than Caucasian, having hot flashes, poor physical functioning and depression.
						Sleep quality	1.20 (ND)	0.85 (ND)	-	P<0.01 *	
						Sleep latency	1.39 (ND)	1.00 (ND)	-	P<0.01 *	
						Sleep disturbance	1.50 (ND)	1.31 (ND)	-	P<0.01 *	
						Sleep medication	0.65 (ND)	0.61 (ND)	-	P=0.70	
						Sleep efficiency	0.59 (ND)	0.57 (ND)	-	P=0.77	
						Sleep duration	0.98 (ND)	0.84 (ND)	-	P=0.03 *	Adjusted for race.
						Daytime dysfunction	0.96 (ND)	0.70 (ND)	-	P<0.01 *	-
Dahl et al., 2011 [8] Norway	Convenience sample 337 tumor free breast cancer survivors treated with radiotherapy during 1998 and 2002 in one hospital.	II (ND) III (ND)	Srg, C: 24% Srg, M: 76% CT: 82% RT: 100% HT: 81%	3.9 (ND), 2.6-6.9	Convenience sample 1,685 women randomly selected from a population-based sample of women with no history of cancer whose questionnaires had complete data; matched individual matching for age (± 5 years).	Prevalence of regular use of hypnotics	Prevalence: 15%	Prevalence: 4%	PR=3.75 * †	95%CI: 2.65-5.30	Adjusted for level of education, on disability pension and menopausal status.

Von Ah et al., 2012 [45] United States	Convenience sample 62 non-Hispanic African American women diagnosed with non-metastatic breast cancer and able to read and write English, recruited by medical record review and by self-referral.	I-IIB (85.7%) IIIB (14.3%)	Srg, C: 0% Srg, M: 60.3% CT & RT: 54.6% HT: ND	5.0 (2.7), 2-10	Convenience sample 78 African American women with no history of breast cancer, recruited through community advertisements and events.	Scale: PSQI	PSQI mean scores (SD): 9.0 (4.2)	PSQI mean scores (SD): 6.1 (4.0)	-	P=<0.001 *	Mean scores adjusted for age, income, years of education and body mass index.
Somatization											
Cohen et al., 2011 [5] Israel	Convenience sample 56 married Israeli Arab breast cancer survivors, post treatment and free of disease recruited from one hospital.	I-III (ND%)	Srg, C: 48.2% Srg, M: 51.8% Srg, R: 12.5% CT: 85.7% RT: 85.7% HT: 58.9%	4.8 (4.2), 1-17	Convenience sample 66 married and 'healthy' Arab women living in northern Israel, approached in community settings; individual matching for age and education (matching categories not reported).	Scale: BSI-18	BSI-18 mean score (SD): 2.6 (1.2)	BSI-18 mean score (SD): 1.8 (0.8)	-	P<0.001 *	More somatic symptoms in breast cancer survivors were associated with lower education, religiosity, depression, anxiety, emotional distress and lower body image (P<0.05).
Amir et al., 2002 [13] Israel	Convenience sample 39 women free of cancer symptoms for ≥3 years and not under active treatment, identified through two hospitals.	I (46%) II (46%) III (8%)	Srg, C: 20% Srg, M: 80% CT: 66% RT: 41% HT: 46%	6.5 (ND), ≥5	Convenience sample 39 women who did not experience any life-threatening disease, recruited by unknown methods; matched for age and education (method of matching not reported).	SCL-90	SCL-90 mean score: 0.92 (0.86)	SCL-90 mean score: 0.51 (0.47)	-	P<0.001 *	Higher SCL-90 scores indicate more somatic symptoms. Women who had breast cancer and reported PTSD symptoms had more somatic symptoms than women who did not have PTSD symptoms: 1.61 (1.06) vs. 0.77 (0.60), P<0.01.
Suicide											
Schairer et al., 2006 [112] Denmark, Finland, Norway, Sweden, United States (continues)	Population based 723,810 one-year breast cancer survivors diagnosed between 1953 and 2001.	All	ND	8.7 (ND), 1-49 (mean follow up duration: 7.7 years, range <1 month to 49 years)	Population-based General female population in each of the countries	Official mortality databases in each country. ICD-7 codes: E963 and E970 - 979; ICD-8 and ICD-9: E950 - E959; and ICD-10: X60 - X84.	Incidence rate: 1.5 per 10,000 person-years Cumulative incidence of suicide by time since diagnosis: 5 yrs: 0.05% 10 yrs: 0.10% 20 yrs: 0.16% 30 yrs: 0.20%	Incidence rate: 1.09 per 10,000 person-years	SIR= 1.37 *	95%CI: 1.28-1.47	-
									By country US: SIR= 1.49 * Sweden: SIR= 1.27 * Denmark: SIR= 1.25* Finland: SIR= 1.53 * Norway: SIR= 1.40 *	By country 95%CI: 1.32-1.70 95%CI: 1.12-1.45 95%CI: 1.07-1.46 95%CI: 1.28-1.83 95%CI: 1.07-1.81	-
									By calendar period 1953-59: SIR=1.86* 1960-69: SIR=1.72* 1970-79: SIR=1.31* 1980-89: SIR=1.29* 1990-2001: SIR=1.36*	By calendar period 95%CI: 1.20-2.78 95%CI: 1.42-2.07 95%CI: 1.15-1.49 95%CI: 1.15-1.46 95%CI: 1.18-1.57	-

Schairer et al., 2006 [112] Denmark, Finland, Norway, Sweden, United States (continued)	Population based 723,810 one-year breast cancer survivors diagnosed between 1953 and 2001.	All	ND	8.7 (ND), 1-49	Population-based General female population in each of the countries	Official mortality databases in each country. ICD-7 codes: E963 and E970 - 979; ICD-8 and ICD-9: E950 - E959; and ICD-10: X60 - X84.	Incidence rate: 1.5 per 10,000 person-years Cumulative incidence of suicide by time since diagnosis: 5 yrs: 0.05% 10 yrs: 0.10% 20 yrs: 0.16% 30 yrs: 0.20%	Incidence rate: 1.09 per 10,000 person-years	By race White: SIR=1.36 * Black: SIR=2.88 * Other: SIR=1.02	By race 95%CI: 1.27-1.46 95%CI: 1.44-5.17 95%CI: 0.44-2.01	-
									By age <40: SIR=1.34 * 40-49: SIR=1.42 * 50-59: SIR=1.50 * 60-69: SIR=1.26 * ≥70: SIR=1.24 *	By age 95%CI: 1.24-1.62 95%CI: 1.32-1.71 95%CI: 1.09-1.47 95%CI: 1.04-1.48 95%CI: 1.24-1.62	-
									By time since diagnosis, years 1: SIR=1.51 * 2: SIR=1.49 * 3: SIR=1.57 * 4: SIR=1.31 * 5-9: SIR=1.30 * 10-14: SIR=1.28 * 15-19: SIR=1.25 20-24: SIR=1.32 ≥25: SIR=1.35	By time since diagnosis, years 95%CI: 1.25-1.82 95%CI: 1.22-1.82 95%CI: 1.27-1.93 95%CI: 1.02-1.66 95%CI: 1.14-1.49 95%CI: 1.07-1.54 95%CI: 0.95-1.62 95%CI: 0.89-1.90 95%CI: 0.82-2.12	
									By stage at diagnosis Local: SIR=1.38 * Regional: SIR=1.55* Distant: SIR=2.11 * Unknown: SIR=1.05*	By stage at diagnosis 95%CI: 1.24-1.53 95%CI: 1.34-1.79 95%CI: 1.16-3.55 95%CI: 0.73-1.50	Includes only patients from the US, Demark, Finland and Norway.
									By treatment Surgery only SIR= 1.40 * Radiotherapy, no chemotherapy SIR= 1.46 * Chemotherapy, no radiotherapy SIR= 1.12 Radiotherapy and chemotherapy SIR= 1.50 * Other/none/unknown SIR= 1.84 *	By treatment 95%CI: 1.24-1.58 95%CI: 1.27-1.67 95%CI: 0.80-1.55 95%CI: 1.09-2.02 95%CI: 1.14-2.96	Refers to initial course of treatment only; Includes only patients from the US, Demark, Finland and Norway.
									Breast conserving surgery SIR= 1.22 Radical mastectomy SIR= 1.30 *	 95%CI: 0.89-1.64 95%CI: 1.04-1.63	US women only, 1983-2001.

Fang et al., 2012 [113]	Population based 74,977 women diagnosed with primary breast cancer between 1991 and 2006	All	ND	>1 (Mean follow up time of the all cancer cohorts was 4.07 years (median 2.65, range 0 to 15.99)	Population based Women not diagnosed with cancer during follow up.	ICD-9 codes E950–E959 and ICD-10 codes X60–X84 and Y870	-	-	RR= 1.6 *	95%CI: 1.2-2.1	RR adjusted for age at follow-up (≤49 years, 5-yr groups for 50 to 74 yrs, ≥75 yrs), calendar period at follow-up (5-year groups), civil status (cohabitation or non-cohabitation), socioeconomic status (blue-collar, white-collar, self-employed, or unclassified), and education (≥9 years, <9 years, or missing).

BC = breast cancer; BSI-18 = Brief Symptom Inventory-18 [22]; CT = chemotherapy; EHR = electronic health records; HT = hormone therapy; ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification; IRR = incidence rate ratio; ND = not defined; PR = prevalence ratio; PSQI = Pittsburgh Sleep Quality Index [114]; RR = relative risk; RT = radiotherapy; SASRQ = Stanford Acute Stress Reaction Questionnaire [115]; SCL-90 = Somatization subscale of Symptoms Checklist-90 [27]; SD = standard deviation; Srg, C = Breast conserving surgery; Srg, M = Mastectomy.

* There was some statistical evidence (P<0.05) for a different prevalence, risk or severity of anxiety between breast cancer survivors and women who did not have cancer.

† Prevalence ratio calculated by the authors of the present study.

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11.2 Appendix 2 Supplementary materials to the paper in Chapter 5

Carreira H, Williams R, Strongman H, Bhaskaran K

Identification of mental health and quality of life outcomes in primary care databases in the UK: a systematic review

BMJ Open. 2019 Jul 2;9(7):e029227

Contents

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Supplementary appendix 4, table 7. ICD codes used in the studies of dementia.

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Supplementary appendix 4, table 10. List of Read codes used in the studies of male sexual dysfunction.

Supplementary appendix 4, table 11. List of Read codes used in the studies of sleep disorder.

Supplementary appendix 4, table 12. List of Read codes used in the studies of fatal and non-fatal self-harm.

Supplementary appendix 4, table 13. ICD codes used in the studies of fatal self-harm.

Supplementary Appendix 1.

MEDLINE search expression, applied via OVID, 28 June 2018

1. CPRD.mp.
2. Clinical Practice Research.mp.
3. GPRD.mp.
4. General Practice Research Database.mp.
5. The Health Improvement Network.mp.
6. QRESEARCH.mp.
7. DIN-LINK.mp.
8. VAMP.mp.
9. Value Added Information Medical.mp.
10. (THIN adj1 (database or dataset or data)).mp.
11. (Read adj1 (term* or code# or codification)).mp.
12. (diagnostic adj1 (term* or code#)).mp.
13. Disease Analyzer.mp.
14. Primary care clinical informatics unit.mp.
15. PCCIU.mp.
16. (optimum patient care adj4 data*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. OPCRD.mp.
18. health information network.mp.
19. health improvement network.mp.
20. Q research.mp.
21. (ResearchOne or (Research One adj2 data*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
22. Doctors Independent Network.mp.
23. SAIL.mp.
24. (SAIL adj4 data*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25. mediplus.mp.
26. ((general practice or primary care or primary health care) adj4 data*).mp.
27. longitudinal patient database.mp.
28. ((EHR or eletronic health record*) adj4 data*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
29. health care database*.mp.
30. exp "mental disorders"/
31. exp "behavior and behavior mechanisms"/
32. exp "behavioral disciplines and activities"/
33. exp Psychological Phenomena/
34. exp fatigue/
35. exp pain/
36. exp "Sleep Wake Disorders"/
37. exp central nervous system depressants/
38. exp muscle relaxants, central/
39. exp psychotropic drugs/
40. exp sleep aids, pharmaceutical/
41. (anxiety or anxious* or panic or anxiolytic* or (stress not oxidat*) or depressi* or dysthymia or antidepress* or sexual or erectile or suicid* or self-harm or hopeless* or sleep or insomnia or hypnotic* or cognit* or chemo-fog or chemo-brain or pain or fatigue or (mental adj1 (disorder or disorders)) or antipsychotic).mp.
42. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. exp United Kingdom/
44. (UK or Britain or British or England or English or Scotland or Scottish or Wales or Welsh Ireland).mp.
45. 43 or 44
46. or/1-29
47. 42 and 45 and 46

EMBASE search expression, applied via OVID, 28 June 2018

1. CPRD.mp.
2. Clinical Practice Research.mp.
3. GPRD.mp.
4. General Practice Research Database.mp.
5. The Health Improvement Network.mp.
6. QRESEARCH.mp.
7. DIN-LINK.mp.
8. VAMP.mp.
9. Value Added Information Medical.mp.
10. (THIN adj1 (database or dataset or data)).mp.
11. (Read adj1 (term* or code# or codification)).mp.
12. (diagnostic adj1 (term* or code#)).mp.
13. Disease Analyzer.mp.
14. Primary care clinical informatics unit.mp.
15. PCCIU.mp.
16. (optimum patient care adj4 data*).mp.
17. OPCRD.mp.
18. health information network.mp.
19. health improvement network.mp.
20. Q research.mp.
21. (ResearchOne or (Research One adj2 data*)).mp.
22. Doctors Independent Network.mp.
23. SAIL.mp.
24. (SAIL adj4 data*).mp.
25. mediplus.mp.
26. ((general practice or primary care or primary health care) adj4 data*).mp.
27. longitudinal patient database.mp.
28. ((EHR or eletronic health record*) adj4 data*).mp.
29. health care database*.mp.
30. or/1-29
31. UK.mp.
32. United Kingdom.mp.
33. England.mp.
34. Wales.mp.
35. Scotland.mp.
36. Northern Ireland.mp.
37. 31 or 32 or 33 or 34 or 35 or 36
38. exp central depressant agent/
39. exp central muscle relaxant/
40. exp psychotropic agent/
41. antidepress*.mp.
42. antipsychotic.mp.
43. anxiolytic.mp.
44. exp mental capacity/ or exp mental compliance/ or exp mental concentration/ or exp mental deficiency/ or exp mental deterioration/ or exp mental development/ or exp mental development assessment/ or exp mental disease/ or exp mental disease assessment/ or exp mental dissociation/ or mental function/ or exp mental health/ or exp mental health care/ or exp mental health center/ or exp mental health organization/ or exp mental health research/ or exp mental health service/ or exp mental hospital/ or exp mental stress/
45. depressi*.mp.
46. dysthymia.mp.
47. catatonia.mp.
48. self-injur*.mp.
49. self injury.mp.
50. self mutilation.mp.
51. suicid*.mp.
52. self-harm.mp.
53. anxious*.mp.
54. anxiety.mp.
55. panic.mp.
56. catastrophi*.mp.
57. phobia.mp.
58. phobic.mp.
59. neurotic.mp.
60. compulsive.mp.
61. bipolar.mp.
62. neurotic.mp.

63. personality.mp.
64. psychotic.mp.
65. psychosis.mp.
66. paranoid.mp.
67. delusional.mp.
68. sexual.mp.
69. insomnia.mp.
70. exp insomnia/
71. exp sleep/ or exp sleep disorder/
72. exp somatoform disorder/
73. exp substance abuse/ or exp "substance use"/
74. exp stress/
75. or/38-74
76. 30 and 37 and 75

Supplementary Appendix 2. Template email sent to corresponding authors of the studies for which a list of codes wasn't provided in the publication.

Dear [corresponding author],

I'm currently doing a PhD about mental health and quality of life in breast cancer survivors. As part of my PhD, I'm conducting a systematic review of the studies that assessed mental health outcomes using electronic health records. The aim of the review is to summarise how studies have identified these outcomes in primary care databases in the UK; the review will be part of my PhD thesis and we are also planning to publish it in a peer-reviewed journal in due course.
I'm writing to you because a study in which you are the corresponding author was identified as eligible (please see title below), and I would kindly ask if you could be of assistance with the issues described below.

[title]
[description of the list of codes needed]

I look forward to hearing from you and thank you in advance for your help.

Best wishes,
Helena

Supplementary appendix 3, table 1. Main characteristics of the eligible studies: anxiety.

Author, year of publication	Study title	Type of study	Database(s)	Study period (years)	Outcome description	List of codes available	Validation of list of codes	EHR-related eligibility criteria for the study // Follow up requirements	Handling of outcomes occurring prior to exposure	Notes
Bouras, 2016 [1]	Linked and primary care database analysis of the incidence and impact of psychiatric morbidity following gastrointestinal cancer surgery in England	Cohort study	CPRD, HES	1997-2012	"Diagnosis code [for anxiety] in CPRD or HES, or a prescription code [for Diazepam or Lorazepam] between 36 months before and 12 months after surgery."	Yes	None stated	Data available for >3 years before the index date // Follow up duration: 1 year after index date	Study quantified the psychiatric morbidity before and after the index date.	-
Fardet, 2012 [2]	Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care	Cohort study	THIN	1990-2008	Read and Multilex list of codes for diagnoses of panic disorder or panic attack excluding c odes for anxiety	No	None stated	≥6 months of registration with the primary care practice	Hazards ratios adjusted for past history of neuropsychiatric disorders (yes/no)	Outcome was eligible if there was no record of the outcome in the previous 6 months
Granerod, 2016 [3]	Increased rates of sequelae post-encephalitis in individuals attending primary care practices in the United Kingdom: a population-based retrospective cohort study	Cohort study	CPRD	1998-2012	"Anxiety disorders (including both symptom codes and diagnoses such as generalised anxiety disorder, panic disorder, post-traumatic stress disorder and obsessive compulsive disorder)"	Yes	None stated	None stated // At least one contact with the GP practice in the two years after the index date	Analysis restricted to those at risk of a new-onset outcome, defined as no code in the year prior to the index date.	-
Hesdorffer, 2012 [4]	Epilepsy, suicidality, and psychiatric disorders: a bidirectional association	Matched cohort study	CPRD	1990-2008	Anxiety, not further specified	No	None stated	At least 3 years of data before the index date, 1 year after the index date, and at least 1 code for a medical or drug code in the 6 months before the index // Follow up 3 years after index date	Excluded subjects with a record of the outcome before the study date.	-

Khan, 2010 [5]	Consulting and prescribing behaviour for anxiety and depression in long-term survivors of cancer in the UK	Cohort study	CPRD	2003-2006	Consultations for anxiety and prescriptions of benzodiazepines and Buspirone	No	None stated	None stated	History of anxiety prior to the analysis period included in the models	Outcomes occurred within a 3-year period chosen for the study
Kurd, 2005 [6]	The risk of depression, anxiety, and suicidality in patients with psoriasis: A population-based cohort study	Cohort study	CPRD	1987-2002	"clinician diagnosis of anxiety and related disorders in which anxiety symptoms are common"	No (refers using the same codes of previous studies)	None stated	None stated	Patients with history of anxiety in the 6 months before the index date were excluded in a sensitivity analysis.	-
Lurie, 2015 [7]	Antibiotic exposure and the risk for depression, anxiety, or psychosis: A nested case-control study	Nested case control study	THIN	1995-2013	Anxiety, including codes for diagnosis of generalised anxiety disorder and phobic anxiety	Yes	None stated	Only records from patients that had been registered with the GP for more than 183 days // Outcomes were considered incident if occurring at more than 183 days after the index date.	Patients who had pharmacological treatment for a specific psychiatric diagnosis more than 90 days before the diagnosis was first recorded were excluded.	Patients with mixed anxiety and depression were excluded from the analysis
Martin-Merino, 2010 [8]	Prevalence, incidence, morbidity and treatment patterns in a cohort of patients diagnosed with anxiety in UK primary care	Cohort study	THIN	2002-2004	"Identification codes included all Read codes describing anxiety. These included codes ranging from mild anxiousness symptoms to other disorders such as phobia, panic attack and generalized and mixed anxiety disorders"	Yes	Yes Record review/ questionnaires	Enrolled for at least 2 years with the practice and have received one prescription in the previous year; patients aged ≥70 years had to have at least 2 visits registered in the follow up period of >1 year.	Patients with previous anxiety diagnoses were excluded, as well as those who had 5 or more prescriptions of anxiolytics before the diagnosis.	-

Meier, 2004 [9]	The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials	Cohort study	CPRD	1990-1999	First time diagnosis of panic attack, regardless of referral or treatment, identified by OXMIS- and/or- ICD-8-codes	No	Yes 'reviewed a list of all cases to determine inclusion/ exclusion'	≥1 year of data available before index date and "some GPRD activity (diagnoses or prescriptions) recorded after the index date" // Patients were censored 18 months after exposure date	"The base population for person-time analyses consisted of all subjects free of (…) panic attacks at the start of follow up."	-
Schneider, 2013 [10]	Antimalarial chemoprophylaxis and the risk of neuropsychiatric disorders	Nested case control study	CPRD	2001-2009	Incident diagnosis of anxiety, not further specified	No	None stated	At least 1 year of date before the index date // some activity (diagnoses or prescriptions) recorded after the index date	Excluded patients with the outcome of interest observed before the index date	-
Sheehan, 2015 [11]	Mental illness, challenging behaviour, and psychotropic drug prescribing in people with intellectual disability: UK population based cohort study	Cohort study	THIN	1999-2013	Anxiety, including codes for symptoms and diagnoses	Yes	None stated	Entry in the cohort at least one year after registration with the practice	None stated	Excludes cases of mixed anxiety and depression
Walters, 2012 [12]	Recent trends in the incidence of anxiety diagnoses and symptoms in primary care	Cohort study	THIN	1998-2008	Anxiety, including symptoms, diagnosis, mixed anxiety and depression, panic attacks and panic disorder Results were also provided separately for: - anxiety disorders (eg. chronic anxiety, generalised anxiety disorder, anxiety state); - anxiety symptoms (e.g. 'anxiousness'); - mixed anxiety and depression; - panic attacks and panic disorder.	No	None stated	≥1 year of data since registration with the practice and 'consistent recording of at least one medical record (e.g. a diagnostic entry), one additional health data record (e.g. blood test result) and >1 prescriptions on average for the practice per patient per year.	Excluded patients with an entry for anxiety recorded in the previous year.	Participants could have had more than one episode during the follow up, provided that they were separated for more than 12 months.

CPRD – Clinical Practice Research Datalink; HES – Hospital Episodes Statistics; ICD-10 – International Classification of Diseases, edition 10; ND – not defined; OXMIS – Oxford Medical Information System; PCCIU – Primary Care Clinical Informatics Unit Research; THIN – The Health Improvement Network.

Supplementary appendix 3, table 2. Main characteristics of the eligible studies: depression.

Author, year of publication Title	Study title	Type of study	Database(s)	Study period (years)	Outcome description	List of codes available	Validation of list of codes	EHR-related eligibility criteria for the study // Follow up requirements	Handling of outcomes occurring prior to exposure	Notes
Becker, 2011 [13]	Risk of incident depression in patients with Parkinson disease in the UK	Nested case-control study	CPRD	1994-2005	'To be included in the analysis as a valid depression case, a patient had to have a code recorded for an affective disorder (depression, manic disorders, bipolar disorders, or unspecified affective disorders) during follow-up.'	Yes	Yes Pharmacological treatment with antidepressive drugs	At least 3 years of computer EHR prior to the index date // None stated.	Cases who had depression diagnosed prior to the index date were excluded;	-
Booth, 2015 [14]	Impact of bariatric surgery on clinical depression. Interrupted time series study with matched controls	Controlled interrupted time-series study	CPRD	2000-2012	Clinical depression was identified through medical diagnoses for depression recorded in clinical or referral records as well as through prescriptions for anti-depressant drugs.	Yes	None stated	At least one year of registration with the practice prior to the index date	Not applicable	-
Bornand, 2016 [15]	The risk of new onset depression in association with influenza - A population-based observational study	Nested case-control study	CPRD	2000-2013	Minimum of three prescriptions for one or more antidepressant drugs recorded after the incident major depression diagnosis (i.e. the index date), identified by READ-codes based on ICD-10 codes (F32), if they started the antidepressant therapy within 90 days of the depression diagnosis	Yes	None stated	A minimum of three years of history before the index date.	Excluded patients with more than two prescriptions for antidepressants at any time prior to the index date. Adjusted for history of affective disorders in the models.	Provides data for depression severity: general depression; mild depression; moderate depression; severe depression; other.

Bouras, 2016 [1]	Linked Hospital and Primary Care Database Analysis of the Incidence and Impact of Psychiatric Morbidity Following Gastrointestinal Cancer Surgery in England	Cohort study	CPRD HES	1997-2012	"Codes for the diagnoses of (…) depression were measured in CPRD (…) In HES, ICD-10 codes recorded in the first position of a hospital episode (signifying the main condition treated) for the diagnoses of depression. (…) Prescription data (…) including antidepressants (Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram, Mitrazapine, and Venlafaxine), (…) anxiolytics (Diazepam and Lorazepam)."	Yes	None stated	Data available for >3 years before the study index date // Follow up duration: 1 year post diagnosis	Not applicable	-
Claxton, 2000 [16]	Selective serotonin reuptake inhibitor treatment in the UK: Risk of relapse or recurrence of depression	Cohort study	MediPlus	1993-1995	Re-initiation of any antidepressant after a gap of at least 6 months with no antidepressant prescription; suicide attempt, referral to psychotherapy or psychiatrist, admission to a mental health facility, emergency room use related to mental disorders, or electroconvulsive therapy and re-initiation of antidepressant one of the above. Depression first defined as treatment with a SSRI and a Read code within 1 month of the prescription.	Yes	None stated	Only patients with contact with the services during the previous 2 years of the index date; // Follow up duration of 18 months post index date	Not applicable (all patients had been treated with SSRI)	Patients dementia, schizophrenia, psychosis and manic depression were excluded.
Clifford, 2002 [17]	Drug or symptom-induced depression in men treated with apha1-blockers for benign prostatic hyperplasia? A nested-case control study	Nested case-control study	CPRD	1992-1999	Proxy of antidepressant prescription (first prescription of antidepressant)	No	None stated	Registered in CPRD for at least 12 months // ND	None stated	-

Dave, 2010 [18]	Incidence of Maternal and Paternal Depression in Primary Care	Cohort study	THIN	1993-2007	"Read code entry for unipolar depression and/or a prescription for an antidepressant at the appropriate therapeutic dose for treatment of depression on a given consultation date (…) we eliminated those who had an entry for anxiety or panic disorder but had no entry for depression in their entire computerized medical record." New episode was considered when no diagnosis or prescription had been registered in the past year.	No Available on request	None stated	None stated	Results stratified by history of previous mental disorder	Mixed anxiety and depression was included.
Fardet, 2012 [2]	Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care	Cohort study	THIN	1990-2008	'Read code for unipolar depression, for symptoms of depression, or for a prescription for an antidepressant. Diagnoses were considered first; prescriptions of antidepressants were used in defining the outcome only when there was no recorded diagnosis of a neuropsychiatric illness and no other recorded indication for the prescription. To exclude patients who may have received prescriptions for antidepressants for anxiety rather than for depression, we eliminated those who had an entry for anxiety or panic disorder but had no entry for depression in their entire computerized medical record.'	No	None stated	≥6 months of registration with the primary care practice.	Hazards ratios adjusted for past history of neuropsychiatric disorders (yes/no)	Outcome was eligible if there was no record of the outcome in the previous 6 months

Gunnell, 2009 [19]	Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database	Cohort study	CPRD	2006-2008	Depression defined as the start of antidepressant therapy	No	None stated	At least 1 years of CPRD record before index date // ND	People who had been prescribed an antidepressant within the previous 6 months before index date were excluded. Previous psychiatric consultations considered in the models.	-
Granerod, 2016 [3]	Increased rates of sequelae post-encephalitis in individuals attending primary care practices in the United Kingdom: a population-based retrospective cohort study	Matched cohort study	CPRD	1998-2012	Depression, consisting of codes for depression diagnosis and symptoms if evidence of pharmacological treatment was present.	Yes	None stated	None stated // At least one contact with the GP practice in the two years after the index date.	Analysis restricted to those at risk of a new-onset outcome, defined as no code in the year prior to the index date.	-
Hagberg, 2017 [20]	Risk of Incident Antidepressant-Treated Depression Associated with Use of 5alpha-Reductase Inhibitors Compared with Use of alpha-Blockers in Men with Benign Prostatic Hyperplasia: A Population-Based Study Using the Clinical Practice Research Datalink	Nested case-control study	CPRD	1992-2013	A Read code for a depression diagnosis and a prescription for an antidepressant within 90 days of the depression diagnosis.	No	None stated	At least 1 year of recorded history in the database before cohort entry;	Excluded men with a diagnosis of depression or suicidal behaviors (ideation or attempts), or men who received prescriptions for antidepressant medications prior to cohort entry.	-

Hagberg, 2016 [21]	Incidence rates of suicidal behaviors and treated depression in patients with and without psoriatic arthritis using the Clinical Practice Research Datalink	Nested case control study	CPRD	1998-2012	'A patient was required to have at least one prescription for an antidepressant drug in addition to a diagnosis code for depression within 60 days of each other to qualify as a case of treated depression.'	No	Yes, record review	At least one year of registration with the practice prior to the index date	Any patient who had a diagnosis of depression or a prescription for an antidepressant drug recorded before the cohort entry date was excluded from the Treated Depression sub-cohort.	-
Harris, 2011 [22]	Depression indicators in a national sample of older community and care home patients: applying the Quality and Outcomes Framework	Cohort study	THIN	ND-2008	(i) depression case finding with assessment tool validated for primary care; (ii) assessment of depression severity in patients with a new depression episode. 'Quality and Outcomes Framework Read Codes were used in both cases, but no account was taken of exceptions recorded by GPs, as these may bias comparisons between community and care home samples.'	Yes	None stated	Patients registered for at least 90 days with a new diagnosis of depression in period 91-450 days from end of follow up and no depression severity assessment >365 days before end of follow up.	Not applicable	Only practices contributing with data up to at least March 2008 were included.
Hesdorffer, 2012 [4]	Epilepsy, suicidality, and psychiatric disorders: a bidirectional association	Matched cohort study	CPRD	1990-2008	Incident major depression, not further specified	No	None stated	At least 3 years of data before the index date, 1 year after the index date, and at least 1 code for a medical or drug code in the 6 months before the index // Follow up 3 years after index date	Excluded subjects with a record of the outcome before the study date.	-

Jacob, 2017 [23]	Depression Risk in Patients with Rheumatoid Arthritis in the United Kingdom	Cohort study	Disease Analyser database	2000-2014	Diagnoses of depression, according to the ICD-10 codes	No	None stated	None stated // Incidence in the first 5 years of the index date	None stated	-
Jenkins-Jones, 2018 [24]	Poor compliance and increased mortality, depression and healthcare costs in patients with congenital adrenal hyperplasia	Matched cohort study	CPRD, ONS, HES inpatient and outpatient	?	Depression defined by Read Codes in CPRD, by ICD-10 code in HES inpatient data, or by the prescription of antidepressants. Depression was identified not only from ongoing records but also from patients' clinical histories dating from before the start of data follow-up. A sensitivity analysis considered only those depression outcomes identified by both diagnostic (Read or ICD-10) code and at least one antidepressant prescription.	Yes	None stated	None stated	Not applicable: the outcome was lifetime prevalence of depression rather than incident occurrence.	-
John, 2016 [25]	Recent trends in primary-care antidepressant prescribing to children and young people: an e-cohort study	Cohort study	SAIL	2003-2013	Incident episode: a Read code for a diagnosis or symptom of depression, or antidepressant, with no record of the given subtype (antidepressant prescription or depression diagnosis or depression symptom) in the previous 12 months; Participants could have more than one episode recorded across the study period as long a period of at least 12 months existed between entries within that subtype. Prevalent episode: any record of the given subtype (antidepressant prescription or depression diagnosis or depression symptom) in a target year Annual recurrent episode: defined as the first record in a given year of a given subtype where a record of that subtype exists previously in that individuals GP record.	Yes	None stated	Registered with the GP practice for at least 1 year	Not applicable	Explored the indication of the antidepressants

Kendrick, 2015 [26]	Changes in rates of recorded depression in English primary care 2003-2013: time trend analyses of effects of the economic recession, and the GP contract quality outcomes framework	Cohort study	CPRD	2003-2013	"had clinical or referral events recorded which included a Read code for non-psychotic depressive symptoms or diagnoses, or for assessment using depression symptom questionnaires." Prevalence of depression: Read code present in the year or quarter; Incidence of depression: limited to patients who had no code for depression recorded in the previous 12 months. Incidence of first-ever depression: no previous code for depression diagnosis, symptoms or antidepressant treatment recorded within 10 year study period, and no previous record of depression or antidepressant treatment recorded.	Yes	None stated	None stated	Not applicable	"We excluded patients with psychotic diagnoses including bipolar disorder, psychotic depression, and schizoaffective psychosis, and patients prescribed antidepressants for other indications besides depression."
Khan, 2010 [5]	Consulting and prescribing behaviour for anxiety and depression in long-term survivors of cancer in the UK	Matched cohort study	CPRD	2003-2006	Consultations for depression and prescriptions of as tricyclics, SSRIs and MAOIs	No (Available on request)	None stated	None stated // Follow up duration: 3 years	History of anxiety prior to the analysis period was included in the models	-
Kotz, 2017 [27]	Cardiovascular and neuropsychiatric risks of varenicline and bupropion in smokers with chronic obstructive pulmonary disease	Matched cohort study	QResearch	2001-2012	Depression, not further specified	No	None stated	Registered for >12 months before data extraction // Follow up duration 6 months	History of neuropsychiatric events before the index date were considered as confounders	-
Kotz, 2015 [28]	Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study	Matched cohort study	QResearch	2007-2012	Depression, not further specified	No	None stated	Registered for >12 months before data extraction // Follow up duration 6 months	History of neuropsychiatric events before the index date were considered as confounders	-

Kurd, 2005 [6]	The risk of depression, anxiety, and suicidality in patients with psoriasis: A population-based cohort study	Matched cohort study	CPRD	1987-2002	Depression included all clinician diagnoses of depressive symptomology including bipolar disorder, defined by diagnostic Read or OXMIS codes	No (refers using the same codes of previous studies)	None stated	None stated	Patients with history of anxiety in the 6 months before the index date were excluded in a sensitivity analysis.	-
Lurie, 2015 [7]	Antibiotic exposure and the risk for depression, anxiety, or psychosis: A nested case-control study	Nested case control study	THIN	1995-2013	At least one Read code of depression; not further specified.	Yes	None stated	Only records from patients that had been registered with the GP for more than 183 days // Outcomes were considered incidence if occurring at more than 183 days after the index date.	Patients who had pharmacological treatment for a specific psychiatric diagnosis more than 90 days before the diagnosis was first recorded were excluded.	Patients with mixed anxiety and depression were excluded from the analysis
Martin-Merino, 2010 [29]	Study of a cohort of patients newly diagnosed with depression in general practice: Prevalence, incidence, comorbidity, and treatment patterns	Cohort study, descriptive and analytical	THIN	2002-2004	Patients with incident depression during the follow up but excluding those who had 5 or more prescriptions of an antidepressant before the depression diagnosis.	No	Yes GP questionnaires	Registered for >2 years with their GP practice prior to the index date; Excluded patients aged >69 years who had fewer than 2 visits during the follow-up.	All subjects who had a record of depression before the index date were excluded.	Prevalence of depression calculated as the sum of all patients who had the outcome during the study, plus those who had the outcome in the two years before the study start date.

Meier, 2004 [9]	The Risk of Severe Depression, Psychosis or Panic Attacks with Prophylactic Antimalarials	Cohort study	CPRD	1990-1999	Depression referred to specialist or hospital, or if received treatment with antidepressants at or after the diagnosis date identified by OXMIS- and/or- ICD-8-codes	No	Yes 'reviewed a list of all cases to determine inclusion/ exclusion'	≥1 year of data available before index date and "some GPRD activity (diagnoses or prescriptions) recorded after the index date" // Patients were censored 18 months after exposure date	"The base population for person-time analyses consisted of all subjects free of depression at the start of follow up."	-
Millson, 2000 [30]	Are triptans with enhanced lipophilicity used for the acute treatment of migraine associated with an increased consulting rate for depressive illness?	Cohort study, analytical	CPRD, data for the West Midlands	1993-1997	'consulting at least once for depression'	Yes	No	None stated	None Stated	-
Milojevic, 2017 [31]	Mental health impacts of flooding: a controlled interrupted time series analysis of prescribing data in England	Cohort study	General practice prescribing data	2010-2015	Antidepressants prescription	No (but list of antidepressants provided in appendix)	Not applicable	None stated	Not applicable	-
Moore, 2009 [32]	Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database	Cohort study	CPRD	1993-2005	Depression: "first ever antidepressant prescription for depression diagnosed up to 180 days before or 90 days after the prescribing event, or received a first ever diagnosis of depression without an associated prescription for antidepressants."	No	None stated	Registered with practices contributing with up to standard quality data for the entire study period	Patients only included if it was the first ever events during the follow up period.	Provides data for treatment patterns: chronic treatment; intermittent treatment; short-term treatment; delayed treatment; no treatment.

Morgan, 2014 [33]	General practice-recorded depression and antidepressant use in young people with newly diagnosed Type 1 diabetes: a cohort study using the Clinical Practice Research Datalink	Matched cohort study	CPRD	1988-2010	Depression identified from diagnosis codes (Oxford Medical Information System and Read), along with at least one antidepressant prescription (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants or other antidepressants).	No	None stated	None stated	Participants with depression diagnoses or prescriptions prior to diabetes diagnosis (or prior to the start date for control subjects) were excluded.	-
Petersen, 2006 [34]	Risk and predictors of fatigue after infectious mononucleosis in a large primary-care cohort	Nested case control cohort study	CPRD	1989-2000	Depression, not further specified	No (available from the authors)	None stated	At least one year of data before diagnosis // At least one year of complete follow up after diagnosis	Included patients who did not have fatigue in the year before onset	-
Rait, 2009 [35]	Recent trends in the incidence of recorded depression in primary care	Cohort study	THIN	1996-2006	"Diagnoses of depression (e.g. 'depressive disorder') and recorded depressive symptoms (e.g. 'low mood'). new episode of diagnosed depression was defined as an entry in the records where there was no previous diagnosis of depression coded in the previous year. A new episode of depressive symptoms was also defined as an entry where there had been no previous recorded depressive symptom code in the previous year."	No	None stated	At least one year of follow up data // ND	None stated	Provides results separately for diagnoses and symptoms of depression.
Shah, 2016 [36]	The mental health and mortality impact of death of a partner with dementia	Nested case control study	THIN	2005-2008	Depression, not further specified	Yes	None stated	At least one year of data with the practice	None stated	-

Schneider, 2013 [10]	Antimalarial chemoprophylaxis and the risk of neuropsychiatric disorders	Nested case control study	CPRD	2001-2009	Incident diagnosis of depression, not further specified	Yes	None stated	At least 1 year of date before the index date // some activity (diagnoses or prescriptions) recorded after the index date	Excluded patients with the outcome of interest observed before the index date	Excluded patients with history of cancer, alcoholism, and rheumatoid arthritis.
Schneider, 2010 [37]	COPD and the risk of depression	Cohort study	CPRD	1995-2005	Diagnosis of depression, not further specified In sensitivity analysis, only cases with an incident diagnosis of depression who receive pharmacological treatment within 6 months of diagnosis were included	Yes	None stated	Excluded patients with less than 3 years of active recording history prior to the date of the COPD diagnosis	Patients with previous history of depression, suicide, suicidal ideation, etc., prior to the index date were excluded	Excluded patients with history of cancer, HIV, drug abuse, or alcoholism prior to the index date
Sheehan, 2015 [11]	Mental illness, challenging behaviour, and psychotropic drug prescribing in people with intellectual disability: UK population based cohort study	Cohort study, analytical	THIN	1999-2013	Read codes for depression (including mixed depression-anxiety) that the authors' used in previous studies.	Yes	None stated	Entry in the cohort at least one year after registration with the practice	None stated	Excludes cases of mixed anxiety and depression
Smeeth, 2008 [38]	Effect of statins on a wide range of health outcomes: A cohort study validated by comparison with randomized trials	Cohort study	THIN	1995-2006	Depression defined as the start of antidepressant pharmacotherapy	No	None stated	None stated	People with a previous history of the outcome prior to the index date were excluded from the analysis of that outcome.	First year of follow up was excluded.

Smith, 2014 [39]	Depression and multimorbidity: a cross-sectional study of 1,751,841 patients in primary care	Cross-sectional	PCCIU	ND-2007	"Read code for depression recorded within last year and/or 4 or more antidepressant prescriptions (excluding low-dose tricyclic antidepressants) within the last year. Low-dose tricyclic antidepressants were excluded because they are commonly prescribed for chronic pain syndromes rather than depression."	No	None stated	Patients alive and permanently registered with a general practice at the date of the study	None stated	-
Thomas, 2013 [40]	Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study	Nested case-control study	CPRD HES ONS	2006-2011	"Incident episodes of depression as measured by the date that antidepressant treatment was initiated (treated depression)" // For comparison with previous study, depression was also defined with Read codes only in CPRD	Yes	None stated	At least one year of registration with the practice prior to the index date // ND	Previous psychiatric illness, and use of psychotropic medication considered as potential confounders.	-
Tyrer, 1999 [41]	A study of cardiovascular disease, depression and antidepressants on a computerised general practice database	Cohort study	UK MediPlus	1995-1996	'new diagnosis of depression and treatment, classified by the first antidepressant prescribed.'	No	None stated	At least 12 months of data before the index date // Follow up duration 12 months	Patients with depression in the 12 months period before the cardiac event were excluded.	-
Vallerand, 2018 [42]	Risk of depression among patients with acne in the U.K.: a population-based cohort study	Cohort study, analytical	THIN	1986-2012	Read code for major depressive disorder	Yes	None stated	None stated // Follow up for > 2 years after index date	Patients with MDD Read code prior to the start of follow up were excluded	-
Walters, 2011 [43]	The relationship between asthma and depression in primary care patients: A historical cohort and nested case control study	Cohort study and nested case control study	CPRD	1995-2006	GP recorded diagnosis of depression, as defined by Read/OXMIS codes) during the study period	No (codes available from the authors)	None stated	All patients had at least 24 months of 'up to standard' data prior to the index date of the case.	All cases with a recorded medical diagnosis of depression or depressive symptoms before the index date were excluded from the cohort.	-

Yang, 2003 [44]	Lipid-lowering drugs and the risk of depression and suicidal behavior	Matched cohort study	CPRD	1991 onwards	Treated depression (with antidepressants) referred to a consultant or patient hospitalized for depression; excluded patients who also had diagnosis of anxiety or with specific causes for depression (e.g. post-partum depression)	No	Yes List of patients referred to hospital or consultant were manually reviewed; referral letters reviewed.	≥1 year of data available before index date	Patients with history of depression prior to study start were excluded	-

CPRD – Clinical Practice Research Datalink; EHR – electronic health records; HES – Hospital Episodes Statistics; ICD-10 – International Classification of Diseases, edition 10; ND – not defined; PCCIU – Primary Care Clinical Informatics Unit Research; SAIL – SAIL Databank - The Secure Anonymised Information Linkage Databank; THIN – The Health Improvement Network; ONS – Office for National Statistics.

Supplementary appendix 3, table 3. Main characteristics of the eligible studies: composite outcomes, anxiety and depression.

Author, year of publication Title	Study title	Type of study	Database(s)	Study period (years)	Outcome description	List of codes available	Validation of list of codes	EHR-related eligibility criteria for the study // Follow up requirements	Handling of outcomes occurring prior to exposure	Notes
John, 2016 [45]	Case-finding for common mental disorders of anxiety and depression in primary care: an external validation of routinely collected data	Validation study using patient reported outcomes	SAIL	2000-2009	Outcome: Common mental disorders, defined as anxiety and depression. Read codes for: i) anxiety diagnosis, e.g. generalised anxiety disorder; ii) anxiety symptoms e.g. anxiousness; iii) mixed anxiety and depression; iv) panic attacks and panic disorders; v) depression diagnoses; vi) depression symptoms. Treatment defined as having at least one prescription for an antidepressant, anxiolytic or hypnotic within the year around the date of the survey answer. Excluded codes for other psychosis, phobias, obsessive compulsive disorders, post traumatic stress disorder, behavioural disorders, hyperkinetic disorders, conduct disorders, disorders of social functioning, and adjustment disorders. Defined 12 algorithms with current and historical symptoms, diagnosis and treatment.	Yes	Yes Patient reported outcomes	At least 6 months after registration with the practice	Not applicable (no exposure under study). Incidence outcome were those where no previous entry had been recorded around 1 year of the date of the survey answer. Other outcomes were considered historical.	-
Turner, 2016 [46]	Ongoing impairments following transient ischaemic attack: retrospective cohort study	Nested case control study	THIN	2009-2013	Outcome: Psychological impairment, defined as anxiety, depression and post-traumatic stress disorder. First consultation after the index date with a Read code for symptoms or diagnosis of anxiety, depression or post-traumatic stress, plus a first prescription of an antianxiety or antidepressant drug	Yes	None stated	Practice with at least one year of up to standard data, and patients registered for at least one year with the practice. // Patient alive and registered with the practice 1 month after index	Not stated.	-

SAIL – SAIL Databank - The Secure Anonymised Information Linkage Databank; THIN – The Health Improvement Network.

Supplementary appendix 3, table 4. Main characteristics of the eligible studies: dementia.

Author, year of publication Title	Study title	Type of study	Database(s)	Study period (years)	Outcome description	List of codes available	Validation of list of codes	EHR-related eligibility criteria for the study // Follow up requirements	Handling of outcomes occurring prior to exposure	Notes
Brown, 2016 [47]	Comparison of dementia recorded in routinely collected hospital admission data in England with dementia recorded in primary care	Validation study	CPRD HES	1990-2012	Read codes for dementia and/or a code for a drug specifically prescribed for dementia (i.e. donepezil, galantamine, memantine and rivastigmine).	Yes	Yes GP questionnaire	At least 12 months before and 12 months after the first HES record of dementia	Not applicable	-
Davies, 2014 [48]	Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias	Nested case-control study	CPRD	1997-2008	Alzheimer's disease, vascular dementia, or unspecified/other dementias Created four categories: probable Alzheimer's disease, possible Alzheimer's disease, vascular dementia, combine unspecified or other dementia.	Yes	No	None stated	Not applicable	-
Donegan, 2017 [49]	Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study	Cohort study	CPRD	2005-2015	Dementia defined using Read codes listed for the condition in the Quality and Outcomes Framework	No	No	Patients were eligible for analysis if registered with the practice for the entire quarter of the year being analysed;	Not applicable (descriptive study of the incident cases of dementia)	-
Dregan, 2015 [50]	Are Inflammation and Related Therapy Associated with All-Cause Dementia in a Primary Care Population?	Matched cohort study	CPRD	2002-2013	"Medical diagnostic codes were used to identify new diagnoses of dementia including Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, dementia in other conditions, and unspecified dementia."	No	No	None stated	Considered incident cases only	-

Dregan, 2015 [51]	Patterns of anti-inflammatory drug use and risk of dementia: a matched case-control study	Matched case control study	CPRD	1992-2014	"Medical diagnostic codes were used to identify new diagnoses of dementia and include non-specific dementia (Eu02z), Alzheimer disease (F110), vascular dementia (Eu01), Lewy body dementia (Eu025), senile dementia (E00) and dementia in other conditions (Eu02)."	Yes	No	None stated	Considered incident diagnosis	-
Dunn, 2005 [52]	Does lithium therapy protect against the onset of dementia?	Nested case control study	CPRD	1992-2002	'Cases with definite diagnosis of Alzheimer disease, vascular dementia (with which there is a diagnostic overlap), and those with uncertain cause of dementia'	No	Yes GP Questionn aire	"At least 4 years o research standard data preceding the date of the diagnosis" //	Considered incident cases only	-
Dunn, 2005 [53]	Association between dementia and infectious disease: evidence from a case-control study	Nested case control study	CPRD	1992-2002	"We identified cases as all those patients with an incident dementia, as diagnosed by their GP, a GP colleague, or a hospital specialist (…) We included cases with a recorded diagnosis of Alzheimer disease, vascular dementia (with which there is diagnostic overlap), and those with uncertain cause of dementia. Other specified causes of dementia were excluded (eg, dementia in Parkinson's disease)."	No	Yes GP questionna ires	"At least 4 years of research standard data preceding the date of first diagnosis (median time from onset of symptoms to diagnosis has been estimated at 4 years)." // ND	Considered incident cases only	Cases further classified as probable or possible cases of dementia.
Emdin, 2016 [54]	Blood Pressure and Risk of Vascular Dementia: Evidence From a Primary Care Registry and a Cohort Study of Transient Ischemic Attack and Stroke	Cohort study	CPRD HES ONS	1990-2003	First record of vascular dementia, in one of the databases. For the primary analysis, cases of Alzheimer's disease and vascular dementia (i.e. mixed dementia) were included.	Yes	No	Registered with the GP practice for at least one year // First 4 years of follow up excluded from analysis	First 4 years of follow up excluded from analysis	-
Goh, 2014 [55]	Angiotensin receptor blockers and risk of dementia: cohort study in UK Clinical Practice Research Datalink	Cohort study	CPRD	1995-2010	New diagnosis of dementia, defined by Read codes, excluding specific causes of dementia (e.g. dementia in neoplastic disease).	Yes	No	At least 6 months of registration with the GP practice // Outcome occurring in the first year after the index date were not considered	Excluded all individuals with a record of dementia or cognitive impairment prior to the date of entry in the study	-

Granerod, 2016 [3]	Increased rates of sequelae post-encephalitis in individuals attending primary care practices in the United Kingdom: a population-based retrospective cohort study	Nested case control study	CPRD	1998-2012	"cognitive problems (including memory loss, aphasia, difficulty processing information, difficulty reasoning, difficulty concentrating and learning disability)"	Not provided in the original study but obtained from the authors	None stated	None stated // At least one contact with the GP practice in the two years after the index date.	Analysis restricted to those at risk of a new-onset outcome, defined as no code in the year prior to the index date.	Dementia diagnosis were considered separately
Hippisley-Cox, 2010 [56]	Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database	Cohort study	QResearch	2002-2008	Dementia, defined with Read codes, not further specified.	No; states that code list is available on request	No	At least one year of registration with the practice // ND	Incident cases included in the study	-
Imfeld, 2012 [57]	Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: a population-based case-control study	Nested case control study	CPRD	1998-2008	"either a diagnosis of AD followed by at least one prescription for an AD drug or vice versa; a diagnosis of dementia followed by at least two prescriptions for an AD drug; at least two recordings of an AD diagnosis; an AD diagnosis after a specific dementia test (e.g., Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), or Abbreviated Mental Test (7-min screen)), a referral to a specialist (e.g., neurologist, geriatrician, or psychogeriatrician), an assessment based on a neuroimaging technique (e.g., magnetic resonance imaging (MRI), computed tomography (CT), or single-photon emission CT (SPECT)); or an AD diagnosis preceded or followed by any recorded dementia symptoms (e.g., memory impairment, aphasia, apraxia, or agnosia)."	No	Yes GP questionnaire	Patients with >3 years of active history in the database were excluded.	First time diagnosis of Alzheimer's disease included	-

Imfeld, 2013 [58]	Epidemiology, co-morbidities, and medication use of patients with Alzheimer's disease or vascular dementia in the UK	Descriptive cohort study	CPRD	1998-2008	"A patient was required to have either: 1) a diagnosis of AD followed by at least one prescription for an AD drug or vice versa; 2) a diagnosis of unspecific dementia followed by at least two prescriptions for an AD drug; 3) at least two recordings of an AD diagnosis; 4) an AD diagnosis after a specific dementia test (e.g., Mini Mental State Examination, Clock Drawing Test, or Abbreviated Mental Test [7-Minute Screen]), a referral to a specialist (e.g., neurologist, geriatrician or psycho-geriatrician), or an assessment based on neuroimaging technique (e.g., magnetic resonance imaging, computed tomography, or single photon emission computed tomography); or 5) an AD diagnosis preceded or followed by any recorded dementia symptoms (e.g., memory impairment, aphasia, apraxia, or agnosia). In addition, AD patients with a recording of any other specific dementia diagnosis (e.g., VaD, Pick's disease, or dementia with Lewy bodies) after the index date were not eligible, as well as those AD patients with a recording of stroke within two years prior to the index date."	No	Yes GP questionnaires	None stated	Considered incident cases during the study period only	"cases were not eligible if they had had a stroke before the index date (because this is more indicative of a diagnosis of vascular dementia (VaD)16) or a recording of any other specific dementia diagnosis (e.g., VaD, Pick's disease, or Lewy body dementia) after the index date."

Imfeld, 2015 [59]	Benzodiazepine Use and Risk of Developing Alzheimer's Disease or Vascular Dementia: A Case-Control Analysis	Case control	CPRD	1998-2013	"first time diagnosis of AD, VaD, or any unspecified dementia (based on Read codes) (…), or who received a first-time prescription for an acetylcholinesterase inhibitor (i.e. donepezil, rivastigmine, galantamine, or tacrine) or the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (…) To increase the probability of including only well-defined AD or VaD cases, a validated algorithm was applied (…) this algorithm was based on recordings of specific dementia tests [e.g. Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), or Abbreviated Mental Test (7-Minute Screen)], referrals to specialists (e.g. neurologists, geriatricians or psycho-geriatricians), brain imaging [computed tomography (CT), magnetic resonance imaging (MRI), or single photon emission computed tomography (SPECT)], or dementia symptoms (memory impairment, aphasia, apraxia, or agnosia) supportive of a diagnosis of a specific dementia subtype (i.e. AD or VaD)."	No	Yes GP questionnaire	At least three years of active history in the database before diagnosis // ND	Considered incident cases during the study period only	-
Jick, 2000 [60]	Statins and the risk of dementia	Nested case control study	CPRD	1992-1998	First time diagnosis of dementia or Alzheimer's disease	No	No but refers to previous study where the validity of the same list of codes was assessed	None stated	Incidence cases considered only	-

Judge, 2017 [61]	Protective effect of anti-rheumatic drugs on dementia in rheumatoid arthritis patients		CPRD	1995-2011	Dementia, including Alzheimer's dementia, vascular dementia, and mixed dementia.	Yes	No	At least one year of up to standard registration data before the index date // ND	Considered incident cases only	-
Khan, 2011 [62]	Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors	Cohort study	CPRD	2003-2006	Dementia, defined with Read codes, not further specified	No; states that codes are available upon request	No	None stated	Only incident cases were considered	-
Khosrow-Khavar, 2017 [63]	Androgen deprivation therapy and the risk of dementia in patients with prostate cancer	Cohort study	CPRD	1988-2016	All incident cases of dementia, including Alzheimer's disease	Yes	None stated (refers to validation in previous studies)	Patients with less than 1 year of history in CPRD were excluded // All patients had to have at least 1 year of follow up data	Excluded patients with previous diagnosis of any dementia	-
Lu, 2016 [64]	Gout and the risk of Alzheimer's disease: a population-based, BMI-matched cohort study	Cohort study	THIN	1995-2013	Alzheimer's disease	Yes	Not in the original study; refers to a previous validation study	None stated	First diagnoses only	-
Mehta, 2017 [65]	Association of Hypoglycaemia With Subsequent Dementia in Older Patients With Type 2 Diabetes Mellitus	Cohort study	CPRD	2002-2012	Dementia defined by Read codes; used the same list of codes as another previous study.	No	None stated	None stated	Excluded patients with dementia diagnosed in the year prior to the index date	-
Mehta, 2016 [66]	Development and validation of the RxDx-Dementia risk index to predict dementia in patients with type 2 diabetes and hypertension	Cohort study	CPRD	2003-2012	Dementia, defined with a previously validated algorithm (refers to previous publication)	No	None stated	None stated	Considered incident cases only	Sensitivity analysis include the definition of dementia as clinical diagnosis or drug prescription

Perera, 2018 [67]	Dementia prevalence and incidence in a federation of European Electronic Health Record databases: The European Medical Informatics Framework resource	Cohort study	THIN	2004-2012	'Codes that clearly indicated a dementia diagnosis, rather than those that were suggestive'	Yes	No	None stated	Not applicable (calculated incidence estimates)	-
Qizilbash, 2015 [68]	BMI and risk of dementia in two million people over two decades: a retrospective cohort study	Cohort study	CPRD	1992-2007	"Patients were classified as having dementia if, any of the following terms were recorded during follow-up: dementia, Alzheimer, Lewy body disease, Pick's disease. Dementia recorded on a death certificate was also used."	No	None stated	None stated	Excluded patients with dementia diagnosed in the year prior to the index date	-
Seshadri, 2001 [69]	Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease	Cohort study	CPRD	1992-1998	First-time diagnosis of Alzheimer's disease, senile dementia or presenile dementia	No	Yes Case review	None stated	Only first time diagnosis were included	-
Strom, 2015 [70]	Statin therapy and risk of acute memory impairment	Nested case-control study	THIN	1987-2013	"The outcome for this study was the onset of acute, reversible memory impairment. Using Read codes Clinical Terms, version 2 (…), we sought codes with descriptions specifically pertaining to memory loss including amnesia, amnesia symptom, memory loss symptom, temporary loss of memory, short-term memory loss, transient global amnesia, drug-induced amnestic syndrome, non-alcoholic amnestic syndrome, amnesia (retrograde), memory lapses, minor memory lapses, and mild memory disturbance."	Yes	Yes GP questionnaire for a random sample	At least one 365 of registration with the GP practice	Patients with codes for acute memory loss before the index date were excluded.	Excluded patients diagnosed with dementia

Turner, 2016 [46]	Ongoing impairments following transient ischaemic attack: retrospective cohort study	Matched-cohort study	THIN	2009-2013	Read codes for diagnoses (such as 28E0.00: mild cognitive impairment) and symptoms (such as 1B1A.12: memory loss symptom) related to overall cognitive impairment and impaired individual cognitive domains. 'Cognitive impairment included memory, attention, spatial awareness, perception, apraxia and executive functioning impairments but not a diagnosis of dementia.'	Not provided in the original study but obtained from the authors	None stated	Patients alive and registered with the practice 1 month after the index date	Excluded patients with fatigue recorded on the index date	Dementia diagnosis were not included
Walters, 2016 [71]	Predicting dementia risk in primary care: development and validation of the Dementia risk score using routinely collected data		THIN	2000-2011	Newly recorded dementia diagnoses, including Alzheimer's disease, vascular dementia, and unspecified or mixed dementia. Excluding dementia associated with Parkinson's disease, Lewy body dementia, Huntingdon, Picks, HIV and drug induced and alcohol-related dementia.	No but available upon request from the authors	No	Excluded patients with less than one year of follow up data // follow up restricted to a maximum of 5 years	Excluded patients with dementia, cognitive impairment or memory symptoms at baseline	-

CPRD – Clinical Practice Research Datalink; GP – general practitioner; HES – Hospital Episodes Statistics; THIN – The Health Improvement Network; ONS – Office for National Statistics.

Supplementary appendix 3, table 5. Main characteristics of the eligible studies: fatigue.

Author, year of publication Title	Study title	Type of study	Database(s)	Study period (years)	Outcome description	List of codes available	Validation of list of codes	EHR-related eligibility criteria for the study // Follow up requirements	Handling of outcomes occurring prior to exposure	Notes
Donegan, 2013 [72]	Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK	Ecological and self-controlled case series	CPRD	2000-2011 and 2008-2011	Chronic fatigue syndrome including chronic fatigue syndrome/myalgic asthenia, post-viral fatigue syndrome, fibromyalgia, and neurasthenia.	No (Obtained from the authors)	None stated	None stated // At least one year of follow up available	None stated	Sensitivity analysis considered 'incident fatigue' at the earliest recording of symptoms, referrals or diagnoses.
Collin, 2017 [73]	Trends in the incidence of chronic fatigue syndrome and fibromyalgia in the UK, 2001-2013: a Clinical Practice Research Datalink Study	Descriptive cohort study	CPRD	2001-2013	Diagnoses of chronic fatigue syndrome, fibromyalgia, post-viral fatigue syndrome, or asthenia/ debility diagnosis or referral to a specialist service	Yes	None stated	At least 12 months of up to standard data	Only new first ever diagnosis were considered	Symptoms of fatigue were considered separately.
Gallagher, 2004 [74]	Incidence of fatigue symptoms and diagnoses presenting in UK primary care from 1990 to 2001.	Descriptive cohort study	CPRD	1990-2001	Read codes for diagnosis of chronic fatigue syndrome; post-viral fatigue syndrome; asthenia/debility. Read codes for symptoms were classified separately.	No (Stated that was available from the authors but could not be obtained)	None stated	Data prior to 1990 not shown due to lower numbers than expected and being the first years of data collection of the database.	Fatigue diagnosis was incident if there was no record of diagnoses in the previous year, with or without previous symptoms; symptoms were incident if there was no symptoms or diagnoses in the previous year.	-

Hamilton, 2009 [75]	Risk markers for both chronic fatigue and irritable bowel syndromes: A prospective case-control study in primary care	Nested case control study	CPRD	1988-2001	List of diagnostic codes for post-viral fatigue syndrome; chronic fatigue syndrome.	No (refers to another publication)	None stated	Only patients with complete records for 3 years prior to the index date were included	Not applicable	-
Petersen, 2006 [34]	Risk and predictors of fatigue after infectious mononucleosis in a large primary-care cohort	Nested case control cohort study	CPRD	1989-2000	Read codes for diagnoses of post-viral debility, post-viral fatigue syndromes, post-influenza debility and syndrome post-viral; symptoms of tiredness, malaise, lethargy, debility, and fatigue.	No (Stated that was available from the authors but could not be obtained)	None stated	At least one year of data before diagnosis // At least one year of complete follow up after diagnosis	Included patients who did not have fatigue in the year before onset	-
Turner, 2016 [46]	Ongoing impairments following transient ischaemic attack: retrospective cohort study	Nested case-cohort study	THIN	2009-2013	First consultation after the index date with a Read code for symptoms or diagnosis of fatigue	No Obtained from the authors	None stated	Practice with at least one year of up to standard data, and patients registered for at least one year with the practice. // Patient alive and registered with the practice 1 month after index	Excluded patients with fatigue recorded on the index date.	-

CPRD – Clinical Practice Research Datalink; THIN – The Health Improvement Network.

Supplementary appendix 3, table 6. Main characteristics of the eligible studies: pain.

Author, year of publication	Study title	Type of study	Database(s)	Study period (years)	Outcome description	List of codes available	Validation of list of codes	EHR-related eligibility criteria for the study // Follow up requirements	Handling of outcomes occurring prior to exposure	Notes
Becker, 2007 [76]	Migraine incidence, comorbidity and health resource utilization in the UK	Nested case-control study	CPRD	1994-2001	Migraine diagnosis	No	Yes GP questionnaire	None stated	First-time diagnosis only	-
Campbell, 2015 [77]	In sickness and in health: A cross-sectional analysis of concordance for musculoskeletal pain in 13,507 couples	Descriptive	CiPCA	2005-2006	Widespread body pain: "All relevant codes were formed into the five most common consultation body regions (back, knee, neck, shoulder, foot), as well as codes for osteoarthritis consultations. A further category of 'any musculoskeletal' consultations were formed inclusive of the above body regions and conditions, as well as consultations for unspecified pain (e.g. arthralgia), widespread pain conditions and other single body regions where the proportion of consultations were too few to perform meaningful separate analysis (e.g. head, arm, elbow, wrist, hand, hip, pelvis, thigh and buttock)."	Yes	None stated	None stated	None stated	-

Hall, 2006 [78]	Epidemiology and treatment of neurophatic pain: the UK primary care perspective	Descriptive	CPRD	1992-2002	"A post-herpetic neuralgia record was a specific term for post-herpetic neuralgia or an acute herpes zoster term plus either neuropathy, or neuropathic pain, 3-6 months after the first acute herpes zoster entry. A trigeminal neuralgia record had a specific term for this diagnosis. Phantom limb pain was defined as a specific term or a term for amputation plus either a neuropathy or neuropathic pain record 3–24 months after the first amputation code. Patients were included in the painful diabetic neuropathy cohort if their record contained a specific term; a term for diabetic neuropathy with a prescription for a treatment for pain current at the date of diagnosis; a record of diabetes and neuropathic pain or record of diabetes and both neuralgia and a treatment for pain current on the date of the neuralgia code."	No	None stated	At least year of up to standard data	None stated	-

Hall, 2013 [79]	An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population	Cohort study, descriptive	CPRD	2005-2010	"Five neuropathic pain cohorts (post-herpetic neuralgia, painful diabetic neuropathy, phantom limb pain, neuropathic back pain and neuropathic postoperative pain) were identified from (…) a single specific Read code, or a combination of Read and therapy codes as specified in a case definition. Postherpetic neuralgia was defined as a specific code for post-herpetic neuralgia, or a code for acute zoster plus either a code for neuropathy, or neuropathic pain, between three and six months after the first acute zoster entry. Phantom limb pain (PLP) was defined as a specific code, or a code for amputation plus either a code for neuropathy or neuropathic pain between three and twenty-four months after the first amputation code. The painful diabetic neuropathy cohort included patients with a specific code for painful diabetic neuropathy; those with a code for diabetes and a general code for neuropathic pain and a third group with a code for diabetic neuropathy (or diabetes and neuralgia) with a prescription for a neuropathic pain treatment which was initiated within 28 days of the date of the neuropathy/ neuralgia code."	No	Yes GP questionnaires	At least of 1 year of data of good quality for research	None stated

Mansfield, 2017 [80]	Identifying patients with chronic widespread pain in primary care	Cross sectional	CiPCA	2005-2009	(A) Recurrent region pain, define as: "In a period of 5 consecutive years, a patient fulfils all of 1-4: 1. At least 1 consultation for a musculoskeletal complaint in the axial skeleton (neck and back); 2. At least 1 consultation for an upper- or lower-limb complaint; 3. At least 1 consultation for a regional musculoskeletal complaint in each of 3 separate years; 4. At least 4 consultations for regional musculoskeletal complaints during the 5-year period." (B) "Non specific generalized pain conditions, including fibromyalgia, fibrositis, rheumatism, myalgia, arthralgia, and polyalgia"	Yes	Yes	Patients not registered with the practice for the full 5-year period were excluded	Not applicable (cross sectional analysis)	-
Ruigomez, 2006 [81]	Chest pain in general practice: incidence, comorbidity and mortality	Case control study	CPRD	1996	Chest pain: Codes for chest pain that did specify the type or location of the symptom.	Yes	None stated	Registered with the GP for at least 2 years // At least one entry in the records in the last 3 years before the study	Excluded patients with history of pain the past 2 years	-
Wallander, 2007 [82]	Unspecified abdominal pain in primary care: The role of gastrointestinal morbidity	Matched cohort study	CPRD	Before 1996	Abdominal pain: Diagnosis of abdominal pain	Yes	None stated	At least one entry to the data in the three years prior to the study start.	Patients were excluded if they had a record of abdominal pain of any abdominal site or type in the 2 years before the study started.	-

Zondervan, 1999 [83]	Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database	Cohort study	Mediplus UK primary care database	1991-1995	Chronic pelvic pain: pain in the lower abdominal region persisting for at least six months. "Episode of chronic pelvic pain: pelvic pain on two or more contacts, with at least six months (≥ 183 days) between the first and the last contact but with no period of more than one year (> 365 days) without a pelvic pain contact. An episode of chronic pelvic pain was defined as starting six months after the first contact and finishing at the contact preceding a pain-free, one-year interval (if any)." "Excluded pain due to malignancy; chronic inflammatory and other defined bowel diseases such as Crohn's, coeliac disease, ulcerative colitis; acute conditions verified by having surgery such as appendicectomy, cholecystectomy; or pregnancy. Women with pelvic pain occurring only during menstruation (dysmenorrhoea) or sexual intercourse (dyspareunia) were also excluded."	No	None stated	None stated	Not applicable. Monthly incidence estimated as the number of new episodes in a given month as a proportion of	-

CiPCA - The Consultations in Primary Care Archive; CPRD – Clinical Practice Research Datalink;. NSAIDS - Nonsteroidal anti-inflammatory drug.

Supplementary appendix 3, table 7. Main characteristics of the eligible studies: sexual dysfunction.

Author, year of publication Title	Study title	Type of study	Database(s)	Study period (years)	Outcome description	List of codes available	Validation of list of codes	EHR-related eligibility criteria for the study // Follow up requirements	Handling of outcomes occurring prior to exposure	Notes
Blumentals, 2003 [84]	Antihypertensive treatment and erectile dysfunction in a cohort of type II diabetes patients	Nested case-control study	CPRD	1987-2001	Erectile dysfunction, ascertained from the diagnosis codes, not further specified	No	None stated	None stated	None stated	-
Hagberg, 2016 [85]	Risk of erectile dysfunction associated with use of 5-alpha reductase inhibitors for benign prostatic hyperplasia or alopecia: population based studies using the Clinical Practice Research Datalink	Nested case control study	CPRD	1992-2011	Erectile dysfunction: "diagnosis of erectile dysfunction or impotence, prescription for a phosphodiesterase type 5 inhibitor (eg, sildenafil, tadalafil, or vardenafil) where the strength and quantity prescribed was indicated for treatment of erectile dysfunction, or record of procedures for treatment of erectile dysfunction (eg, penile prosthesis, penile injection, or other operations for treatment of erectile dysfunction)." Non-erectile dysfunction: including ejaculatory disorder, psychosexual dysfunction, or low libido	No	None stated	At least 3 years of history before the cohort entry date;	Incident cases considered after the index date.	-
Khan, 2011 [62]	Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study	Cohort study	CPRD	2003-2006	Erectile dysfunction: "new prescriptions for sildenafil (Viagra, Pfizer, NY, United States), apomorphone hydrochloride, vardenafil (Levitra, Bayer Healthcare Pharmaceuticals, New Haven, USA), alprostadil (an injectable treatment) and tadalafil (Cialis, Lilly, USA)"	No	None stated	None stated	Excluded patients with erectile dysfunction recorded before the index date	-
Morant, 2008 [86]	Increased sexual dysfunction in men with storage and voiding lower urinary tract symptoms	Cross-sectional analysis	THIN	2000-2007	Male sexual dysfunction	Yes	None stated	None stated	None stated	-

Schlesinger, 2018 [87]	Gout and the Risk of Incident Erectile Dysfunction: A Body Mass Index-matched Population-based Study	Cohort study	THIN	1995-2012	Erectile dysfunction noted by the presence of the Read code E227311	Yes	None stated	At least one year of registration with the practice before the index date	Excluded prevalent cases at baseline	-
Sultan, 2017 [88]	Gout and subsequent erectile dysfunction: a population-based cohort study from England	Cohort study	CPRD, HES	1998-2004	Erectile dysfunction, ascertained from the medical codes, not further specified	Yes	None stated	At least 1 year of follow up data	Only incident cases after the index date were considered; cases in the first 6 months of registration were considered prevalent.	-

CPRD – Clinical Practice Research Datalink; HES – Hospital Episodes Statistics; THIN – The Health Improvement Network.

Supplementary appendix 3, table 8. Main characteristics of the eligible studies: sleep disorder.

Author, year of publication Title	Study title	Type of study	Database(s)	Study period (years)	Outcome description	List of codes available	Validation of list of codes	EHR-related eligibility criteria for the study // Follow up requirements	Handling of outcomes occurring prior to exposure	Notes
Roddy, 2013 [89]	The association of gout with sleep disorders: A cross-sectional study in primary care	Matched cohort study	CiPCA and PiPCA	2001-2008	Read codes for sleep disorders, excluding codes for sleep apnoea which were classified separately	Yes	None stated	None stated	None stated	-
Wallander, 2007 [90]	Morbidity associated with sleep disorders in primary care: A longitudinal cohort study	Cohort study	CPRD	1996	Read codes for sleep disorder including insomnia, hypersomnia, and sleep disturbance	Yes	None stated	Registered with a general practitioner for at least 2 years and having at least 1 entry in CPRD in the previous 3 years.	Patients with a consultation for sleep disorders during the 2 years before the start of the study were excluded.	-

CPRD – Clinical Practice Research Datalink; CiPCA - The Consultations in Primary Care Archive; PiPCA - The Prescriptions in Primary Care Archive.

Supplementary appendix 3, table 9. Main characteristics of the eligible studies: fatal and non-fatal self-harm.

Author, year of publication Title	Study title	Type of study	Database(s)	Study period (years)	Outcome description	List of codes available	Validation of list of codes	EHR-related eligibility criteria for the study // Follow up requirements	Handling of outcomes occurring prior to exposure (applicable to self-harm only)	Notes
Andersohn, 2010 [91]	Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behaviour	Nested case-control study	CPRD	1990-2005	"Potential cases were identified using predefined medical codes of self-harm (i.e., without a clear suicidal intention [intentional self-harm]) or suicidal behaviour (i.e., with a clear suicidal intention [attempted suicide]). Patients who died were also considered as potential cases if suicidal thoughts were recorded within 4 weeks before death."	Yes	Yes, record review	At least one year of data with the GP practice	Models adjusted for history of self-harm at baseline	In an additional analysis, the patients with codes for self-harm without explicitly mention to suicidal behaviour were excluded.
Arana, 2010 [92]	Suicide-related events in patients treated with antiepileptic drugs	Cohort study	THIN	1988-2008	"Cases of suicide-related events were based on codes for suicide, attempted suicide, and intentional self-inflicted injuries plus suicide. A completed suicide was defined as a code for suicidality followed by a code for death in the following month and a final date of any administrative activity in the database or disenrollment within 6 months after the suicidality code. If the disenrollment date occurred more than 6 months after a suicidality code, we reviewed the patient's profile. Patients with a last medical or other health related code that was recorded within 1 month after the suicide date were also considered to have completed suicide."	No	Yes GP questionnaire, record and death certificate review	Patients were eligible if they were enrolled with a clinical practice for at least 6 months during the study period	Patients with personal or family history of suicide attempt were excluded	-

Carr, 2016 [93]	The epidemiology of self-harm in a UK-wide primary care patient cohort, 2001-2013	Descriptive cohort study	CPRD	2001-2013	"Read codes incorporating all cases across the spectrum from milder forms of non-suicidal behaviour through to near-fatal suicide attempts (…) We excluded codes that referred only to thoughts of self-harm or suicidal ideation and alcohol-related codes, unless intent to actively harm oneself was specified.	Yes	None stated	None stated	None stated	None stated
Carr, 2017 [94]	Premature Death Among Primary Care Patients With a History of Self-Harm	Cohort study	CPRD ONS	2001-2013	Suicide, ascertained with ICD-10 codes in the ONS mortality data; including open verdicts.	Yes	Not applicable	At least one year of registration with the practice prior to the index date;	Not applicable.	-
Coupland, 2011 [95]	Antidepressant use and risk of adverse outcomes in older people: Population based cohort study	Cohort study	QResearch, ONS	1996-2007	Read codes for attempted suicide or self-harm, not further specified	No	None stated	At least one year of registration with the practice prior to the index date;	None stated	Suicide was also an outcome, but data for this outcome was not analysed due to small numbers.
Coupland, 2015 [96]	Antidepressant use and risk of suicide and attempted suicide or self-harm in people aged 20 to 64: cohort study using a primary care database	Cohort study	QResearch, ONS	2000-2011	"code for suicide or an open verdict in their linked death certificate, or patients who had a Read code for attempted suicide or self-harm who died within 30 days.	No (refers to codes used in other studies	None stated	At least one year of registration with the practice prior to the index date; // Most analysis restricted to the first 5 years of follow up.	Excluded patients with a previous attempted suicide or self-harm event recorded at baseline	-
Fardet, 2012 [2]	Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care	Cohort study	THIN	1990-2008	Cases of suicide or suicide attempt	No	Yes Review of death certificates	≥6 months of registration with the primary care practice	Hazards ratios adjusted for past history of neuropsychiatric disorders (yes/no)	Outcome was eligible if there was no record of the outcome in the previous 6 months
Donovan, 1996 [97]	The use of the General Practice Research Database (GPRD) to examine potential links between antidepressant medication and the incidence of suicide	Cohort study	CPRD	1988-1993	Suicide, not further specified	No	None stated	None stated	Prior suicidal history considered as a risk factor for suicide	-

Doyle, 2016 [98]	Suicide risk in primary care patients diagnosed with a personality disorder: a nested case control study	Nested case control study	CPRD, ONS	2002-2011	Suicides and open verdicts ascertained via linkage to ONS mortality data	Yes (ICD-10 codes)	Not applicable (Data linked to the gold-standard)	At least one year of up to standard CPRD data	Not applicable	-
Gao, 2013 [99]	Association between body mass index and suicide, and suicide attempt among British adults: The health improvement network database	Cohort study	THIN	2000-2007	Suicide: "defined in two ways (…): 1) patients with a Read code of suicide attempt confirmed by death within 3 months or 2) patients who did not have a Read code of suicide attempt, but whose cause of death might be suicide. To identify patients using the second approach, we first searched for all deaths (…) the cause of death was reviewed. In addition, free text records were searched for potential suicide as cause of death, including suicide, deliberate drug overdose or self-harm, self-inflicted injuries, poisoning, asphyxiation, trauma, and acute or multiple organ failure. Death certificates for these patients were requested for the final verdict of the cause of death. Suicide attempt: "identified using the Read codes for suicide and then by confirming that the patient was still alive for at least 3 months from the time of the event."	No	None stated	None stated	None stated	-
Gunnell, 2009 [19]	Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database	Cohort study	CPRD	2006-2008	OXMIS and Read terms for fatal and non-fatal self-harm.	No	Yes Record review	At least 1 years of CPRD records before index date;	Considered the potential confounding effect of previous self-harm or suicidal thoughts in analysis.	-

Hall, 2009 [100]	Validation of death and suicide recording on the THIN UK primary care database	Validation study	THIN	2002-2004	"Coded and free text records were searched to identify any entry for suicide or a medical cause of death which might indicate suicide, including trauma, poisoning, overdose, asphyxiation, acute or multiple organ failure or a suggestion that death was intentional. An electronic record of suicide was accepted."	Yes	Yes (Validation study, record review)	None stated	Not applicable (validation study)	-
Hagberg, 2016 [21]	Incidence rates of suicidal behaviors and treated depression in patients with and without psoriatic arthritis using the Clinical Practice Research Datalink	Cohort study	CPRD	1998-2012	Suicidal behaviours, defined as: "diagnosis of suicidal ideation, suicide attempt, and/or suicide recorded after the cohort entry date. (…) If a patient had a code for suicide, but had not died, the event was classified as a suicide attempt. Suicidal ideation, attempts, and suicide were considered separately; thus a patient may have been included in more than one analysis.	No	Yes, record review	At least one year of registration with the practice prior to the index date	Patients with suicidal behaviors were included "because patients could recover from suicidal behaviors with treatment or consultation."	-
Hayes, 2016 [101]	Self-harm, Unintentional Injury, and Suicide in Bipolar Disorder During Maintenance Mood Stabilizer Treatment: A UK Population-Based Electronic Health Records Study	Cohort study	THIN	1995-2013	"emergency department or primary care attendance for self-harm during the period of drug exposure and the 3 months afterward. This outcome included Read codes for intentional poisoning, intentional self injurious behavior, and self-harm acts of uncertain intent. (…) Secondary outcomes were unintentional injury (eg, falls or motor vehicle crashes) seen in primary or secondary care and a record of the patient's suicide during this period"	No	Refers to previous validation of the list of codes	None stated	Not applicable (the outcome was diagnoses during the exposure period)	-

Hesdorffer, 2012 [4]	Epilepsy, suicidality, and psychiatric disorders: a bidirectional association	Cohort study	CPRD	1990-2008	Read codes for suicidality including codes for attempted suicide and completed suicide.	No	None stated	At least 3 years of data before the index date, and at least 1 code for a medical or drug code in the 6 months before the index // At least 1 day of data after index date; follow up duration: 3 years after index date	Excluded subjects with a record of the outcome before the study date.	-
Hesdorffer, 2016 [102]	Occurrence and Recurrence of Attempted Suicide Among People With Epilepsy	Cohort study	CPRD	1988-2013	Diagnoses of attempted suicide identified with Read codes, not further specified. Suicide attempts divided into incident or recurrent.	No	None stated	At least 6 month of complete records before the index date and ≥1 medical or drug codes for a condition other than epilepsy in the 6 months before the index date. // At least 1 day of data post index date	None stated	-
Haste, 1998 [103]	Potential for suicide prevention in primary care? An analysis of factors associated with suicide.	Matched cohort study	CPRD	1991-1993	Suicide: "were identified from the database in two ways: 1. Patients with a record of suicide in the notes; and 2. Patients who did not have a record of suicide, but whose record of cause of death on the database suggested that suicide might be possible. These causes included death from carbon monoxide poisoning (excluding accidental poisoning), hanging, suicidal or accidental overdose, and reference to self-inflicted injury. (…) Cases where the verdict was open were included."	No	Yes GP confirmation, review of death certificates	None stated	Not applicable (cases of completed suicide only)	-

Jick, 1995 [104]	Antidepressants and suicide	Cohort study	CPRD	1988-1993	"Cases of suicide were identified from the computer record from among all the study subjects who died. When the cause of death was recorded as suicide or was considered to be uncertain, we obtained further information from the general practitioner and the death certificate to determine the final diagnosis and means of committing suicide."	No	Yes, GP questionnaire	At least 6 month of registration with the practice prior to the index date	Not applicable (cases of completed suicide only)	-
Jick, 1998 [105]	A study of the relation of exposure to quinolones and suicidal behaviour	Nested case control study	CPRD	1991-1995	Three case groups: 1) committed suicide; 2) had a diagnosis of attempted suicide; 3) had a diagnosis of suicidal ideation. "If the subject had more than one case diagnosis during the study period, only the first such diagnosis was considered."	Yes	None stated	>18 months of information on drugs prescribed and diagnoses recorded prior to the index.	None stated	-
Jick, 2000 [106]	Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide	Cohort study	CPRD	?	Suicide and inpatient or outpatient code for attempted suicide	Yes	None stated	Between 5 years and 6 months of clinical records before the index date // At least 1 year of records post index date	Controlled for history of attempted suicide	-
Jick, 2004 [107]	Antidepressants and risk of suicidal behaviours	Cohort study	CPRD	1993-1999	Nonfatal suicidal behaviour: "Cases were those who (1) had a first-time recorded diagnosis of nonfatal suicidal ideation (…) or attempted suicide" Suicide: patients who committed suicide, not further specified.	Yes	None stated	At least 2 years of registration with the practice prior to the index date	None stated	-
Jick, 2009 [108]	Rate of suicide in patients taking montelukast	Cohort study	CPRD	1998-2007	'computer recorded diagnosis of suicide'	No	None stated	None stated	None stated	

Kurd, 2010 [6]	The risk of depression, anxiety, and suicidality in patients with psoriasis: A population-based cohort study	Matched cohort study	CPRD	1987-2002	'Suicidality was defined as diagnosis of suicidal ideation, suicide attempt, or suicide', defined by diagnostic Read or OXMIS codes.	No Refers to diagnostic codes used in other publications.	None stated	None stated	In sensitivity analysis, the patients with a diagnosis of the outcome measured prior to or within six months of the index date were excluded.	-
Kotz, 2015 [28]	Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study	Cohort study	QResearch	2007-2012	Fatal and non-fatal self-harm, not further specified	None stated	None stated	Registered for >12 months before data extraction // Follow up duration 6 months	History of neuropsychiatric events considered as confounders	-
Kotz, 2017 [27]	Cardiovascular and neuropsychiatric risks of varenicline and bupropion in smokers with chronic obstructive pulmonary disease	Cohort study	QResearch	2001-2012	Fatal and non-fatal self-harm, not further specified	None stated	None stated	None stated // Follow up duration 6 months	History of neuropsychiatric events considered as confounders	-
Lalmohamed, 2012 [109]	Causes of death in patients with multiple sclerosis and matched referent subjects: A population-based cohort study	Cohort study	CPRD HES ONS mortality	2001-2008	Death by accident or suicide ascertained in the ONS mortality database	Yes (ICD-10 codes)	Not applicable (ONS mortality database, ICD-10 codes)	≥1 year of data available before index date	None stated	-
Martinez, 2005 [110]	Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode of depression: nested case-control study	Nested case control study	CPRD	1995-2001	Non-fatal self-harm (drug overdose, deliberate self-laceration, poisoning, and non-fatal suicide attempts using other methods) Suicide, identified by OXMIS and Read codes	No Obtained from the authors	Yes, Review of the death certificates and free text entries	≥1 year of data available before index date	Model adjusted for history of non-fatal self-harm	"People with an episode of non-fatal self harm were not censored in analyses with suicide as the end point."

Meier, 2004 [9]	The Risk of Severe Depression, Psychosis or Panic Attacks with Prophylactic Antimalarials	Cohort study	CPRD	1990-1999	Suicide defined by OXMIS and/or ICD-8 codes	No	Yes 'reviewed a list of all cases to determine inclusion/ exclusion'	≥1 year of data available before index date and "some GPRD activity (diagnoses or prescriptions) recorded after the index date" // Patients were censored 18 months after exposure date	Not applicable (suicide as an outcome only)	-
Mines, 2005 [111]	Prevalence of risk factors for suicide in patients prescribed venlafaxine, fluoxetine, and citalopram	Cohort study	CPRD	1995-2002	Suicidal behaviour in the year prior to index date	Yes	None stated	≥1 year of data available	None stated	-
Osborn, 2008 [112]	Suicide and severe mental illnesses. Cohort study within the UK general practice research database	Matched cohort study	CPRD	1987-2002	Suicide, not further specified	No	None stated	None stated	None stated	
Rubino, 2007 [113]	Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study	Cohort study	CPRD	1995-2005	Completed suicide: coding for death associated with mention of suicide in free text or by code for suicide in the medical record and a statement of death in the administrative record (30 days either way); First attempted suicide (non-fatal event).	Yes	Yes Free text search	At least one year of registration with the practice prior to the index date	Suicide attempts considered as a confounder in the models	"excluded records that at the review of free text notes did not seem to represent attempted suicide - for example, unintentional overdose or self harm without suicidal intent"

Schneider, 2010 [37]	COPD and the risk of depression	Cohort study	CPRD	1995-2005	'incident suicide or suicidal ideation', not further specified	No Obtained from the authors	None stated	Patients with less than 3 years of active recording history prior to the date of the COPD diagnosis were excluded;	Patients with previous history of depression, suicide, suicidal ideation, etc., prior to the index date were excluded	-
Schuerch, 2016 [114]	Impact of varying outcomes and definitions of suicidality on the associations of antiepileptic drugs and suicidality: comparisons from UK Clinical Practice Research Datalink (CPRD) and Danish national registries (DNR)	Validation study	CPRD HES ONS	1996-2009	<u>Suicidal ideation/intent:</u> "Recorded medical terms from the clinical and referral module, plus reasons for transfer out of the general practices to identify patients with one of these outcomes" <u>Suicide attempt:</u> "Recorded medical terms from the clinical and referral module, plus reasons for transfer out of the GP-practice to identify patients with one of these outcomes from CPRD." <u>Completed suicide:</u> "Term of suicidal attempt or ideation occurring simultaneously with a recording of death (+/- 4 weeks), death recorded as reason for leaving the practice (registering out), and a final date of any administrative activity in the database of disenrollment within six months after suicidality code."	Yes	Yes (validation study)	At least 6 months of data before the index date //	Patients with history of suicide attempts, self-harm or suicidal ideation/intent in the 6 months before index were excluded	-
Thomas, 2013 [40]	Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study	Nested case-control study	CPRD, HES and ONS mortality data	2006-2011	Incidence fatal and non-fatal self-harm (as measured by death from suicide in the ONS mortality database) and hospital admission for self-harm (as recorded in the HES database). Includes open verdicts.	Yes for ONS database; no for Read codes.	None stated	At least one year of registration with the practice prior to the index date	Previous self-harm considered as a potential confounder in analysis	-

Thomas, 2013 [115]	Validation of suicide and self-harm records in the Clinical Practice Research Datalink	Validation study	CPRD, HES, ONS mortality data, and Multicentre study of self-harm	1998-2010	"Cases of suicide and self-harm (the 'events') were identified by extracting all records with Read codes for suicide, attempted suicide and self-harm (…). Given that suicide-related Read codes may refer to both fatal and nonfatal suicide attempts, completed suicides within the CPRD were identified using the conventional CPRD approach of linking patient deaths to Read codes for suicide that were recorded within 95 days of the CPRD derived death dates"	Yes	Yes (Validation study)	Registered with a practice contributing with up to standard data, and having acceptable records for research.	Not applicable (descriptive study on the incidence of self-harm)	-
Tyrrell, 2016 [116]	Changes in poisonings among adolescents in the UK between 1992 and 2012: a population based cohort study	Cohort study	THIN	1992-2012	"poisonings [categorised] as intentional, unintentional, unknown intent or alcohol related. Where Read codes explicitly described the intent using the words 'deliberate' or 'intentional' (intentional); 'accidental' (unintentional); and 'unknown' or 'unspecified' (unknown) then they were classified as such. The words 'suicide', 'self-inflicted', 'self-poisoning' or 'overdose' were also used to categorise a poisoning as intentional, unless otherwise specified."	No	None stated	None stated	First poisoning within the observation period	Multiple events occurring in the same individual within a month were counted as one event only
Webb, 2012 [117]	Risk of self-harm in physically ill patients in UK primary care	Nested case control study	CPRD	2001-2008	Suicidal ideation, defined by Read coding descriptions that included the terms 'suicide and self-inflicted,' 'suicide and self-harm,' 'para-suicide' or 'attempted suicide.' Cases that died following the code were excluded.	No	None stated	At least two years of up to standard CPRD data	None stated	-
Webb, 2012 [118]	Suicide risk in primary care patients with major physical diseases: A case-control study	Nested case control study	CPRD and ONS mortality data	2001-2008	Suicides as mentioned in the death certificate, and open verdicts.	Yes	Not applicable (ONS mortality data)	At least two years of up to standard CPRD data	Not applicable (study of suicide only)	-

Wijlaars, 2013 [119]	Suicide-related events in young people following prescription of SSRIs and other antidepressants: A self-controlled case series analysis	Nested case control study	THIN	1995-2009	Suicide attempts, suicidal ideation and completed suicide. Completed suicides: "Read codes that were confirmed by a date of death within 2 weeks of the suicide event date. We searched a cause of death, if available." Excluded cases classified as open verdicts.	No Refers to a previous list, that was updated for the study	Yes Record review	At least 6 months of up to standard CPRD data	Accounted for in analysis	-
Windfuhr, 2016 [120]	Suicide risk linked with clinical consultation frequency, psychiatric diagnoses and psychotropic medication prescribing in a national study of primary-care patients	Nested case-control study	CPRD and ONS mortality data	2002-2011	International Classification of Disease version 10 (ICD-10) codes X60-84, Y10-34 (excluding Y33.9), Y87.0, Y87.2 Includes open verdicts	Yes	Not applicable (ONS mortality data)	≥1 year of data available after up to standard data	None stated	-
Yang, 2003 [44]	Lipid-lowering drugs and the risk of depression and suicidal behaviour	Matched cohort study	CPRD	1991 onwards	Suicidal behaviour, ideation suicidal, suicidal plan, suicidal thoughts, attempted suicide, threat suicide, suicidal drug overdose, drug overdose, para suicide and suicide.	Yes	No (refers to previous studies assessing suitability of the records)	Patients with history of suicidal behaviour prior to study start were excluded	None stated	-

CPRD – Clinical Practice Research Datalink; THIN – The Health Improvement Network; PCCIU – Primary Care Clinical Informatics Unit; SSRI - selective serotonin re-uptake inhibitors; GP – General practice; MAOIs - monoamine oxidase inhibitors; CiPCA - Consultations in primary care archive; PiPCA - Prescriptions in primary care archive.

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Supplementary appendix 4, table 1. List of Read codes used in the studies of anxiety.

Read code	Description	Number of studies
Eu41.00	[X]Other anxiety disorders	5
Eu41100	[X]Generalized anxiety disorder	5
Eu41z11	[X]Anxiety NOS	5
Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]	4
Eu05400	[X]Organic anxiety disorder	4
Eu41112	[X]Anxiety reaction	4
Eu41111	[X]Anxiety neurosis	4
Eu41z00	[X]Anxiety disorder, unspecified	4
E202.12	Phobic anxiety	4
E200200	Generalised anxiety disorder	4
E200.00	Anxiety states	4
E200000	Anxiety state unspecified	4
E200z00	Anxiety state NOS	4
Eu40.00	[X]Phobic anxiety disorders	3
Eu40z00	[X]Phobic anxiety disorder, unspecified	3
Eu41012	[X]Panic state	3
Eu41011	[X]Panic attack	3
Eu41y00	[X]Other specified anxiety disorders	3
Eu41300	[X]Other mixed anxiety disorders	3
Eu41211	[X]Mild anxiety depression	3
Eu41113	[X]Anxiety state	3
E200500	Recurrent anxiety	3
E200100	Panic disorder	3
E200111	Panic attack	3
E200400	Chronic anxiety	3
1B1V.00	C/O - panic attack	3
1B13.11	Anxiousness - symptom	3
1B13.00	Anxiousness	3
E200300	Anxiety with depression	3
Eu93200	[X]Social anxiety disorder of childhood	2
Eu34114	[X]Persistant anxiety depression	2
Eu40012	[X]Panic disorder with agoraphobia	2
Eu40y00	[X]Other phobic anxiety disorders	2
Eu41200	[X]Mixed anxiety and depressive disorder	2
Eu93y12	[X]Childhood overanxious disorder	2
Eu41y11	[X]Anxiety hysteria	2
E2D0.00	Disturbance of anxiety and fearfulness childhood/adolescent	2
E2D0z00	Disturbance anxiety and fearfulness childhood/adolescent NOS	2
E202100	Agoraphobia with panic attacks	2
E292400	Adjustment reaction with anxious mood	2
E280.00	Acute panic state due to acute stress reaction	2
Z4I7.00	Acknowledging anxiety	2
Eu40100	[X]Social phobias	1
Eu40112	[X]Social neurosis	1
Eu93000	[X]Separation anxiety disorder of childhood	1
Eu42100	[X]Predominantly compulsive acts [obsessional rituals]	1
Eu93100	[X]Phobic anxiety disorder of childhood	1
Eu42.12	[X]Obsessive-compulsive neurosis	1
Eu42.00	[X]Obsessive - compulsive disorder	1
Eu45215	[X]Nosophobia	1
Eu46z11	[X]Neurosis NOS	1
Eu40300	[X]Needle phobia	1
Eu45213	[X]Hypochondriacal neurosis	1
Eu45212	[X]Dysmorphophobia nondelusional	1
Eu51511	[X]Dream anxiety disorder	1
Eu40213	[X]Claustrophobia	1
Eu60600	[X]Anxious [avoidant] personality disorder	1
Eu42.11	[X]Anankastic neurosis	1
Eu40011	[X]Agoraphobia without history of panic disorder	1
Eu40000	[X]Agoraphobia	1
R2y2.00	[D]Nervousness	1
R2y2.12	[D]Nervous tension	1
R2y2.11	[D]Nerves	1
1BK..00	Worried	1
1B12.12	Tension - nervous	1
E202300	Social phobia, fear of eating in public	1
E112000	Single major depressive episode, unspecified	1
E292000	Separation anxiety disorder	1
Z4I7211	Reducing anxiety	1
Z4I7100	Recognising anxiety	1
E29y100	Other post-traumatic stress disorder	1
E203z00	Obsessive-compulsive disorder NOS	1
E203100	Obsessional neurosis	1

Read code	Description	Number of studies
225J.00	O/E - panic attack	1
2258.00	O/E - anxious	1
1465.00	H/O: depression	1
1466.00	H/O: anxiety state	1
1B1..00	General nervous symptoms	1
E275711	Compulsive water drinking	1
E203000	Compulsive neurosis	1
1P3..00	Compulsive behaviour	1
E202800	Claustrophobia	1
E2D0000	Childhood and adolescent overanxiousness disturbance	1
1B13.12	Anxious	1
8G94.00	Anxiety management training	1
Z4L1.00	Anxiety counselling	1
E203.11	Anancastic neurosis	1
Z4I7200	Alleviating anxiety	1
E202200	Agoraphobia without mention of panic attacks	1
1B12.00	'Nerves' - nervousness	1
1B12.11	'Nerves'	1

Supplementary appendix 4, table 2. ICD codes used in the studies of anxiety.

Study	Databases	ICD version	List of codes
Bouras, 2016	CPRD + HES	ICD-10	F40-F48

CPRD – Clinical Practice Research Datalink; HES – Hospital Episode Statistics; ICD - International Classification of Diseases.

Supplementary appendix 4, table 3. List of Read codes used in the studies of depression.

Read code	Description	Number of studies
E112.00	Single major depressive episode	14
E112000	Single major depressive episode, unspecified	14
E112100	Single major depressive episode, mild	14
E112200	Single major depressive episode, moderate	14
E112300	Single major depressive episode, severe, without psychosis	14
E112z00	Single major depressive episode NOS	14
E135.00	Agitated depression	14
E112.11	Agitated depression	13
E112.12	Endogenous depression first episode	13
E112.13	Endogenous depression first episode	13
E112.14	Endogenous depression	13
E112500	Single major depressive episode, partial or unspec remission	13
E2B..00	Depressive disorder NEC	13
E2B1.00	Chronic depression	13
Eu32.00	[X]Depressive episode	13
E113.00	Recurrent major depressive episode	12
E11y200	Atypical depressive disorder	12
E11z200	Masked depression	12
Eu32.11	[X]Single episode of depressive reaction	12
Eu32.12	[X]Single episode of psychogenic depression	12
Eu32.13	[X]Single episode of reactive depression	12
Eu32000	[X]Mild depressive episode	12
Eu32100	[X]Moderate depressive episode	12
Eu32200	[X]Severe depressive episode without psychotic symptoms	12
Eu32400	[X]Mild depression	12
Eu32y00	[X]Other depressive episodes	12
Eu32z00	[X]Depressive episode, unspecified	12
Eu33.00	[X]Recurrent depressive disorder	12
E112400	Single major depressive episode, severe, with psychosis	11
E113.11	Endogenous depression - recurrent	11
E130.11	Psychotic reactive depression	11
Eu32212	[X]Single episode major depression w'out psychotic symptoms	11
Eu32y11	[X]Atypical depression	11
Eu32z11	[X]Depression NOS	11
Eu32z12	[X]Depressive disorder NOS	11
1B17.00	Depressed	10
E112600	Single major depressive episode, in full remission	10
E113000	Recurrent major depressive episodes, unspecified	10
E113100	Recurrent major depressive episodes, mild	10
E113200	Recurrent major depressive episodes, moderate	10
E113300	Recurrent major depressive episodes, severe, no psychosis	10
E113500	Recurrent major depressive episodes,partial/unspec remission	10
E113700	Recurrent depression	10
E113z00	Recurrent major depressive episode NOS	10
E130.00	Reactive depressive psychosis	10
E200300	Anxiety with depression	10
E291.00	Prolonged depressive reaction	10
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms	10
Eu32213	[X]Single episode vital depression w'out psychotic symptoms	10
Eu32311	[X]Single episode of major depression and psychotic symptoms	10
Eu32313	[X]Single episode of psychotic depression	10
Eu32y12	[X]Single episode of masked depression NOS	10
Eu32z13	[X]Prolonged single episode of reactive depression	10
Eu33.11	[X]Recurrent episodes of depressive reaction	10
Eu33.12	[X]Recurrent episodes of psychogenic depression	10
Eu33.13	[X]Recurrent episodes of reactive depression	10
Eu33000	[X]Recurrent depressive disorder, current episode mild	10
Eu33100	[X]Recurrent depressive disorder, current episode moderate	10
Eu33211	[X]Endogenous depression without psychotic symptoms	10

Read code	Description	Number of studies
Eu33y00	[X]Other recurrent depressive disorders	10
Eu33z00	[X]Recurrent depressive disorder, unspecified	10
Eu34114	[X]Persistant anxiety depression	10
1B1U.00	Symptoms of depression	9
1B1U.11	Depressive symptoms	9
E113600	Recurrent major depressive episodes, in full remission	9
Eu32300	[X]Severe depressive episode with psychotic symptoms	9
Eu32312	[X]Single episode of psychogenic depressive psychosis	9
Eu32314	[X]Single episode of reactive depressive psychosis	9
Eu32500	[X]Major depression, mild	9
Eu32600	[X]Major depression, moderately severe	9
Eu32700	[X]Major depression, severe without psychotic symptoms	9
Eu32z14	[X] Reactive depression NOS	9
Eu33214	[X]Vital depression, recurrent without psychotic symptoms	9
Eu33311	[X]Endogenous depression with psychotic symptoms	9
Eu33z11	[X]Monopolar depression NOS	9
Eu34113	[X]Neurotic depression	9
Eu41200	[X]Mixed anxiety and depressive disorder	9
Eu41211	[X]Mild anxiety depression	9
1B17.11	C/O - feeling depressed	8
E113400	Recurrent major depressive episodes, severe, with psychosis	8
E204.00	Neurotic depression reactive type	8
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt	8
Eu33212	[X]Major depression, recurrent without psychotic symptoms	8
Eu33400	[X]Recurrent depressive disorder, currently in remission	8
Eu34111	[X]Depressive neurosis	8
Eu3y111	[X]Recurrent brief depressive episodes	8
1BT..00	Depressed mood	7
2257.00	O/E - depressed	7
E11..12	Depressive psychoses	7
Eu32800	[X]Major depression, severe with psychotic symptoms	7
Eu33.14	[X]Seasonal depressive disorder	7
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom	7
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis	7
Eu33315	[X]Recurrent severe episodes of psychotic depression	7
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis	7
9H90.00	Depression annual review	6
9H91.00	Depression medication review	6
9H92.00	Depression interim review	6
9HA0.00	On depression register	6
E290.00	Brief depressive reaction	6
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp	6
Eu34100	[X]Dysthymia	6
E118.00	Seasonal affective disorder	5
E204.11	Postnatal depression	5
E290z00	Brief depressive reaction NOS	5
Eu53011	[X]Postnatal depression NOS	5
Eu53012	[X]Postpartum depression NOS	5
1465.00	H/O: depression	4
1BQ..00	Loss of capacity for enjoyment	4
8HHq.00	Referral for guided self-help for depression	4
E02y300	Drug-induced depressive state	4
Eu33.15	[X]SAD - Seasonal affective disorder	4
R007z13	[D]Postoperative depression	4
1BP0.00	Loss of interest in previously enjoyable activity	3
1BT..11	Low mood	3
1BU..00	Loss of hope for the future	3
212S.00	Depression resolved	3
8CAa.00	Patient given advice about management of depression	3
9Ov0.00	Depression monitoring first letter	3
9Ov1.00	Depression monitoring second letter	3

Read code	Description	Number of studies
9Ov2.00	Depression monitoring third letter	3
9Ov3.00	Depression monitoring verbal invite	3
9Ov4.00	Depression monitoring telephone invite	3
9k4..00	Depression - enhanced services administration	3
E001300	Presenile dementia with depression	3
E002100	Senile dementia with depression	3
E2B0.00	Postviral depression	3
Eu20400	[X]Post-schizophrenic depression	3
Eu34112	[X]Depressive personality disorder	3
Eu92000	[X]Depressive conduct disorder	3
1JJ..00	Suspected depression	2
8BK0.00	Depression management programme	2
9HA1.00	Removed from depression register	2
9Ov..00	Depression monitoring administration	2
9k40.00	Depression - enhanced service completed	2
9kQ..00	On full dose long term treatment depression - enh serv admin	2
E115.00	Bipolar affective disorder, currently depressed	2
E11y.00	Other and unspecified manic-depressive psychoses	2
E211200	Depressive personality disorder	2
Eu25100	[X]Schizoaffective disorder, depressive type	2
Eu25111	[X]Schizoaffective psychosis, depressive type	2
Eu25112	[X]Schizophreniform psychosis, depressive type	2
Eu32B00	[X]Antenatal depression	2
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms	2
Eu34y00	[X]Other persistent mood affective disorders	2
Eu34z00	[X]Persistent mood affective disorder, unspecified	2
Eu3y100	[X]Other recurrent mood affective disorders	2
Eu3z.00	[X]Unspecified mood affective disorder	2
1645.00	Excessive fluid intake	1
1B1J.00	Emotional problem	1
1B1J.11	Emotional upset	1
1BO..00	Mood swings	1
1BP..00	Loss of interest	1
1BT..12	Sad mood	1
1S4..00	Mood observations	1
1S40.00	Dysphoric mood	1
388J.00	Hospital anxiety and depression scale	1
388K.00	Geriatric depression scale	1
388P.00	HAD scale: depression score	1
388g.00	Beck depression inventory second edition score	1
62T1.00	Puerperal depression	1
6896.00	Depression screening using questions	1
8O82.00	Emotional and psychosocial support and advice	1
9ON3.00	Stress monitoring default	1
9ON4.00	Stress monitoring 1st letter	1
9ON5.00	Stress monitoring 2nd letter	1
9ON6.00	Stress monitoring 3rd letter	1
9ON7.00	Stress monitoring verbal inv.	1
9ON8.00	Stress monitoring phone invite	1
9ON9.00	Stress monitoring deleted	1
9ONA.00	Stress monitoring check done	1
9ONZ.00	Stress monitoring admin.NOS	1
E002.00	Senile dementia with depressive or paranoid features	1
E002z00	Senile dementia with depressive or paranoid features NOS	1
E004300	Arteriosclerotic dementia with depression	1
E115.11	Manic-depressive - now depressed	1
E115000	Bipolar affective disorder, currently depressed, unspecified	1
E115100	Bipolar affective disorder, currently depressed, mild	1
E115200	Bipolar affective disorder, currently depressed, moderate	1
E115300	Bipolar affect disord, now depressed, severe, no psychosis	1
E115400	Bipolar affect disord, now depressed, severe with psychosis	1

Read code	Description	Number of studies
E115500	Bipolar affect disord, now depressed, part/unspec remission	1
E115600	Bipolar affective disorder, now depressed, in full remission	1
E115z00	Bipolar affective disorder, currently depressed, NOS	1
E11y000	Unspecified manic-depressive psychoses	1
E11z100	Rebound mood swings	1
E222		1
E283.00	Other acute stress reactions	1
E283z00	Other acute stress reaction NOS	1
E284.00	Stress reaction causing mixed disturbance of emotion/conduct	1
E28z.00	Acute stress reaction NOS	1
E292.00	Adjustment reaction, predominant disturbance other emotions	1
E292400	Adjustment reaction with anxious mood	1
E292y00	Adjustment reaction with mixed disturbance of emotion	1
E292z00	Adjustment reaction with disturbance of other emotion NOS	1
E294.00	Adjustment reaction with disturbance emotion and conduct	1
E2C4.00	Mixed disturbance of conduct and emotion	1
E2C4z00	Mixed disturbance of conduct and emotion NOS	1
E35		1
E4J5		1
Eu02z16	[X] Senile dementia, depressed or paranoid type	1
Eu3..00	[X]Mood - affective disorders	1
Eu31.11	[X]Manic-depressive illness	1
Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn	1
Eu31400	[X]Bipol aff disord, curr epis sev depress, no psychot symp	1
Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp	1
Eu31600	[X]Bipolar affective disorder, current episode mixed	1
Eu31y00	[X]Other bipolar affective disorders	1
Eu31y11	[X]Bipolar II disorder	1
Eu31z00	[X]Bipolar affective disorder, unspecified	1
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms	1
Eu34.00	[X]Persistent mood affective disorders	1
Eu3y.00	[X]Other mood affective disorders	1
Eu3y000	[X]Other single mood affective disorders	1
Eu3y011	[X]Mixed affective episode	1
Eu3yy00	[X]Other specified mood affective disorders	1
Eu4..00	[X]Neurotic, stress - related and somoform disorders	1
Eu43.00	[X]Reaction to severe stress, and adjustment disorders	1
Eu43000	[X]Acute stress reaction	1
Eu43012	[X]Acute reaction to stress	1
Eu43y00	[X]Other reactions to severe stress	1
Eu43z00	[X]Reaction to severe stress, unspecified	1
Eu92.11	[X]Emotional behavioural problems	1
R007z14	[D]Work stress	1
ZR2A.00	Beck depression inventory	1
ZR2A.11	BDI - Beck depression inventory	1
ZR2B.00	Beck hopelessness scale	1
ZR2G.00	Behaviour and mood disturbance scale	1
ZR2h.00	Brief depression rating scale	1
ZR7..00	Depression anxiety scale	1
ZR8..00	Depression self rating scale	1
ZR8..11	DSRS - Depression self rating scale	1
ZRBY.00	Edinburgh postnatal depression scale	1
ZRBY.11	EPDS - Edinburgh postnatal depression scale	1
ZRL6.00	Geriatric depression scale	1
ZRL6.11	GDS - Geriatric depression scale	1
ZRL6.12	Geriatric depression score	1
ZRLU.00	Hamilton rating scale for depression	1
ZRLU.11	HAMD - Hamilton rating scale for depression	1
ZRLU.12	HRSD - Hamilton rating scale for depression	1
ZRLfH00	Health of the Nation Outcome Scale item 7 - depressed mood	1
ZRLfI00	Health of the Nation Outcome Scale item 7 - depressed mood	1

Read code	Description	Number of studies
ZRLn.00	Hopelessness scale	1
ZRLr.00	Hospital anxiety and depression scale	1
ZRLr.11	HAD - Hospital anxiety and depression scale	1
ZRLr.12	HADS - Hospital anxiety and depression scale	1
ZRVM.00	Leeds scale for the self-assessment of anxiety & depression	1
ZRaH.00	Mood affective checklist	1
ZRaH.11	MACL - Mood affective checklist	1
ZRbS.00	Positive and negative affect schedule	1
ZRby.00	Profile of mood states	1
ZRby.11	POMS - Profile of mood states	1
ZRrI.00	Wakefield self-assessment depression inventory	1
ZRrY.00	WHO depression scale	1
ZRrc.00	Zung self-rating depression scale	1
ZRrc.11	SDS - Zung self-rating depression scale	1
ZV11100	[V]Personal history of affective disorder	1
ZV11111	[V]Personal history of manic-depressive psychosis	1
ZV11112	[V]Personal history of manic-depressive psychosis	1

Supplementary appendix 4, table 4. ICD codes used in the studies of depression.

Study	Databases	ICD version	List of codes
Bouras, 2016	CPRD + HES	ICD-10	F32, F33
Jenkins-Jones, 2018	CPRD + HES	ICD-10	F32, F33, F41.2, F92.0

CPRD – Clinical Practice Research Datalink; HES – Hospital Episode Statistics; ICD - International Classification of Diseases.

Supplementary appendix 4, table 5. List of Read codes used in the studies of composite outcomes of anxiety and depression.

Read code	Description	Number of studies
Eu32200	[X]Severe depressive episode without psychotic symptoms	2
Eu33z00	[X]Recurrent depressive disorder, unspecified	2
Eu33400	[X]Recurrent depressive disorder, currently in remission	2
Eu33100	[X]Recurrent depressive disorder, current episode moderate	2
Eu33000	[X]Recurrent depressive disorder, current episode mild	2
Eu33.00	[X]Recurrent depressive disorder	2
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt	2
Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]	2
Eu41y00	[X]Other specified anxiety disorders	2
Eu33y00	[X]Other recurrent depressive disorders	2
Eu32y00	[X]Other depressive episodes	2
Eu41.00	[X]Other anxiety disorders	2
Eu32100	[X]Moderate depressive episode	2
Eu41200	[X]Mixed anxiety and depressive disorder	2
Eu32000	[X]Mild depressive episode	2
Eu32400	[X]Mild depression	2
Eu41100	[X]Generalized anxiety disorder	2
Eu34100	[X]Dysthymia	2
Eu32z00	[X]Depressive episode, unspecified	2
Eu32.00	[X]Depressive episode	2
Eu41z00	[X]Anxiety disorder, unspecified	2
1B1U.00	Symptoms of depression	2
E112000	Single major depressive episode, unspecified	2
E112300	Single major depressive episode, severe, without psychosis	2
E112500	Single major depressive episode, partial or unspec remission	2
E112200	Single major depressive episode, moderate	2
E112100	Single major depressive episode, mild	2
E112600	Single major depressive episode, in full remission	2
E112z00	Single major depressive episode NOS	2
E112.00	Single major depressive episode	2
E118.00	Seasonal affective disorder	2
E113500	Recurrent major depressive episodes,partial/unspec remission	2
E113000	Recurrent major depressive episodes, unspecified	2
E113300	Recurrent major depressive episodes, severe, no psychosis	2
E113200	Recurrent major depressive episodes, moderate	2
E113100	Recurrent major depressive episodes, mild	2
E113600	Recurrent major depressive episodes, in full remission	2
E113z00	Recurrent major depressive episode NOS	2
E113.00	Recurrent major depressive episode	2
E113700	Recurrent depression	2
E200500	Recurrent anxiety	2
E291.00	Prolonged depressive reaction	2
E2B0.00	Postviral depression	2
E200100	Panic disorder	2
2257.00	O/E - depressed	2
E204.00	Neurotic depression reactive type	2
E200200	Generalised anxiety disorder	2
E2B..00	Depressive disorder NEC	2
1BT..00	Depressed mood	2
1B17.00	Depressed	2
E2B1.00	Chronic depression	2
E200400	Chronic anxiety	2
E200300	Anxiety with depression	2
E200.00	Anxiety states	2
E200000	Anxiety state unspecified	2
E200z00	Anxiety state NOS	2
E135.00	Agitated depression	2
Eu33214	[X]Vital depression, recurrent without psychotic symptoms	1
Eu3z.00	[X]Unspecified mood affective disorder	1
Eu40100	[X]Social phobias	1
Eu40112	[X]Social neurosis	1
Eu32213	[X]Single episode vital depression w'out psychotic symptoms	1
Eu32314	[X]Single episode of reactive depressive psychosis	1
Eu32.13	[X]Single episode of reactive depression	1
Eu32313	[X]Single episode of psychotic depression	1
Eu32312	[X]Single episode of psychogenic depressive psychosis	1
Eu32.12	[X]Single episode of psychogenic depression	1
Eu32y12	[X]Single episode of masked depression NOS	1
Eu32311	[X]Single episode of major depression and psychotic symptoms	1
Eu32.11	[X]Single episode of depressive reaction	1
Eu32212	[X]Single episode major depression w'out psychotic symptoms	1

Read code	Description	Number of studies
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms	1
Eu32300	[X]Severe depressive episode with psychotic symptoms	1
Eu33.14	[X]Seasonal depressive disorder	1
Eu33.15	[X]SAD - Seasonal affective disorder	1
Eu06y11	[X]Right hemispheric organic affective disorder	1
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis	1
Eu33315	[X]Recurrent severe episodes of psychotic depression	1
Eu33.13	[X]Recurrent episodes of reactive depression	1
Eu33.12	[X]Recurrent episodes of psychogenic depression	1
Eu33.11	[X]Recurrent episodes of depressive reaction	1
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp	1
Eu3y111	[X]Recurrent brief depressive episodes	1
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis	1
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom	1
Eu43z00	[X]Reaction to severe stress, unspecified	1
Eu43.00	[X]Reaction to severe stress, and adjustment disorders	1
Eu32z13	[X]Prolonged single episode of reactive depression	1
Eu42100	[X]Predominantly compulsive acts [obsessional rituals]	1
Eu20400	[X]Post-schizophrenic depression	1
Eu43100	[X]Post - traumatic stress disorder	1
Eu40.00	[X]Phobic anxiety disorders	1
Eu34.00	[X]Persistent mood affective disorders	1
Eu34z00	[X]Persistent mood affective disorder, unspecified	1
Eu34114	[X]Persistant anxiety depression	1
Eu41012	[X]Panic state	1
Eu40012	[X]Panic disorder with agoraphobia	1
Eu41011	[X]Panic attack	1
Eu3yy00	[X]Other specified mood affective disorders	1
Eu3y000	[X]Other single mood affective disorders	1
Eu3y100	[X]Other recurrent mood affective disorders	1
Eu43y00	[X]Other reactions to severe stress	1
Eu34y00	[X]Other persistent mood affective disorders	1
Eu42y00	[X]Other obsessive-compulsive disorders	1
Eu3y.00	[X]Other mood affective disorders	1
Eu41300	[X]Other mixed anxiety disorders	1
Eu31y00	[X]Other bipolar affective disorders	1
Eu05300	[X]Organic mood [affective] disorders	1
Eu05400	[X]Organic anxiety disorder	1
Eu60513	[X]Obsessive-compulsive personality disorder	1
Eu42.12	[X]Obsessive-compulsive neurosis	1
Eu42z00	[X]Obsessive-compulsive disorder, unspecified	1
Eu42.00	[X]Obsessive - compulsive disorder	1
Eu4..00	[X]Neurotic, stress - related and somoform disorders	1
Eu34113	[X]Neurotic depression	1
Eu3..00	[X]Mood - affective disorders	1
Eu33z11	[X]Monopolar depression NOS	1
Eu3y011	[X]Mixed affective episode	1
Eu41211	[X]Mild anxiety depression	1
Eu31.13	[X]Manic-depressive reaction	1
Eu31.12	[X]Manic-depressive psychosis	1
Eu31.11	[X]Manic-depressive illness	1
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms	1
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms	1
Eu32700	[X]Major depression, severe without psychotic symptoms	1
Eu32800	[X]Major depression, severe with psychotic symptoms	1
Eu33212	[X]Major depression, recurrent without psychotic symptoms	1
Eu32600	[X]Major depression, moderately severe	1
Eu32500	[X]Major depression, mild	1
Eu33211	[X]Endogenous depression without psychotic symptoms	1
Eu33311	[X]Endogenous depression with psychotic symptoms	1
Eu51511	[X]Dream anxiety disorder	1
Eu34112	[X]Depressive personality disorder	1
Eu34111	[X]Depressive neurosis	1
Eu32z12	[X]Depressive disorder NOS	1
Eu92000	[X]Depressive conduct disorder	1
Eu32z11	[X]Depression NOS	1
Eu60511	[X]Compulsive personality disorder	1
Eu63011	[X]Compulsive gambling	1
Eu43013	[X]Combat fatigue	1
Eu31z00	[X]Bipolar affective disorder, unspecified	1
Eu31700	[X]Bipolar affective disorder, currently in remission	1
Eu31600	[X]Bipolar affective disorder, current episode mixed	1
Eu31900	[X]Bipolar affective disorder type II	1
Eu31800	[X]Bipolar affective disorder type I	1
Eu31.00	[X]Bipolar affective disorder	1

Read code	Description	Number of studies
Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn	1
Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp	1
Eu31y11	[X]Bipolar II disorder	1
Eu31911	[X]Bipolar II disorder	1
Eu31400	[X]Bipol aff disord, curr epis sev depress, no psychot symp	1
Eu32y11	[X]Atypical depression	1
Eu41113	[X]Anxiety state	1
Eu41112	[X]Anxiety reaction	1
Eu41111	[X]Anxiety neurosis	1
Eu41y11	[X]Anxiety hysteria	1
Eu41z11	[X]Anxiety NOS	1
Eu42.11	[X]Anankastic neurosis	1
Eu40011	[X]Agoraphobia without history of panic disorder	1
Eu40000	[X]Agoraphobia	1
Eu3z.11	[X]Affective psychosis NOS	1
Eu34011	[X]Affective personality disorder	1
Eu43000	[X]Acute stress reaction	1
Eu43012	[X]Acute reaction to stress	1
Eu32z14	[X] Reactive depression NOS	1
ZV11112	[V]Personal history of manic-depressive psychosis	1
ZV11111	[V]Personal history of manic-depressive psychosis	1
ZV11100	[V]Personal history of affective disorder	1
R2y2.00	[D]Nervousness	1
1BK..00	Worried	1
E11y000	Unspecified manic-depressive psychoses	1
E117400	Unspecified bipolar affective disorder,severe with psychosis	1
E117000	Unspecified bipolar affective disorder, unspecified	1
E117300	Unspecified bipolar affective disorder, severe, no psychosis	1
E117200	Unspecified bipolar affective disorder, moderate	1
E117100	Unspecified bipolar affective disorder, mild	1
E117600	Unspecified bipolar affective disorder, in full remission	1
E117z00	Unspecified bipolar affective disorder, NOS	1
E117.00	Unspecified bipolar affective disorder	1
E117500	Unspecified bipolar affect disord, partial/unspec remission	1
E11z000	Unspecified affective psychoses NOS	1
E211000	Unspecified affective personality disorder	1
1JJ..00	Suspected depression	1
E284.00	Stress reaction causing mixed disturbance of emotion/conduct	1
67J..00	Stress counselling	1
E202.11	Social phobic disorders	1
E112400	Single major depressive episode, severe, with psychosis	1
E002z00	Senile dementia with depressive or paranoid features NOS	1
E002.00	Senile dementia with depressive or paranoid features	1
E002100	Senile dementia with depression	1
1BT..12	Sad mood	1
8HHq.00	Referral for guided self-help for depression	1
8HHp.00	Referral for guided self-help for anxiety	1
Z4I7211	Reducing anxiety	1
E113400	Recurrent major depressive episodes, severe, with psychosis	1
Z4I7100	Recognising anxiety	1
E11z100	Rebound mood swings	1
E130.00	Reactive depressive psychosis	1
E130.11	Psychotic reactive depression	1
E001300	Presenile dementia with depression	1
E2A2.11	Post-traumatic brain syndrome	1
E202.00	Phobic disorders	1
E202.12	Phobic anxiety	1
E202000	Phobia unspecified	1
8CAa.00	Patient given advice about management of depression	1
E200111	Panic attack	1
E29y100	Other post-traumatic stress disorder	1
E11y300	Other mixed manic-depressive psychoses	1
E11yz00	Other and unspecified manic-depressive psychoses NOS	1
E11y.00	Other and unspecified manic-depressive psychoses	1
E11z.00	Other and unspecified affective psychoses	1
E11zz00	Other affective psychosis NOS	1
E283.00	Other acute stress reactions	1
E283z00	Other acute stress reaction NOS	1
E03y200	Organic affective syndrome	1
9kQ..00	On full dose long term treatment depression - enh serv admin	1
9HA0.00	On depression register	1
E203.00	Obsessive-compulsive disorders	1
E203z00	Obsessive-compulsive disorder NOS	1
E214100	Obsessional personality	1
E203100	Obsessional neurosis	1

Read code	Description	Number of studies
225J.00	O/E - panic attack	1
2259.00	O/E - nervous	1
225K.00	O/E - fearful mood	1
2253.00	O/E - distressed	1
2258.00	O/E - anxious	1
E116000	Mixed bipolar affective disorder, unspecified	1
E116300	Mixed bipolar affective disorder, severe, without psychosis	1
E116400	Mixed bipolar affective disorder, severe, with psychosis	1
E116500	Mixed bipolar affective disorder, partial/unspec remission	1
E116200	Mixed bipolar affective disorder, moderate	1
E116100	Mixed bipolar affective disorder, mild	1
E116600	Mixed bipolar affective disorder, in full remission	1
E116z00	Mixed bipolar affective disorder, NOS	1
E116.00	Mixed bipolar affective disorder	1
E11z200	Masked depression	1
E115.11	Manic-depressive - now depressed	1
13Y3.00	Manic-depression association member	1
1BT..11	Low mood	1
1BU..00	Loss of hope for the future	1
1BQ..00	Loss of capacity for enjoyment	1
146D.00	H/O: manic depressive disorder	1
1465.00	H/O: depression	1
1466.00	H/O: anxiety state	1
1B1H.00	Frightened	1
Z522600	Flooding - obsessional compulsive disorder	1
1B1T.00	Feeling stressed	1
16ZB100	Feeling low or worried	1
E202D00	Fear of death	1
1B1H.11	Fear	1
9hC..00	Exception reporting: depression quality indicators	1
9hC0.00	Excepted from depression quality indicators: Patient unsuita	1
9hC1.00	Excepted from depression quality indicators: Informed dissen	1
E112.13	Endogenous depression first episode	1
E112.12	Endogenous depression first episode	1
E113.11	Endogenous depression - recurrent	1
E112.14	Endogenous depression	1
9N54.00	Encounter for fear	1
1B1U.11	Depressive symptoms	1
E11..12	Depressive psychoses	1
E211200	Depressive personality disorder	1
9Ov3.00	Depression monitoring verbal invite	1
9Ov2.00	Depression monitoring third letter	1
9Ov4.00	Depression monitoring telephone invite	1
9Ov1.00	Depression monitoring second letter	1
9Ov0.00	Depression monitoring first letter	1
9Ov..00	Depression monitoring administration	1
9H91.00	Depression medication review	1
8BK0.00	Depression management programme	1
9H92.00	Depression interim review	1
9H90.00	Depression annual review	1
9k4..00	Depression - enhanced services administration	1
9k40.00	Depression - enhanced service completed	1
E214.00	Compulsive personality disorders	1
E214z00	Compulsive personality disorder NOS	1
E203000	Compulsive neurosis	1
1P3..00	Compulsive behaviour	1
E28..11	Combat fatigue	1
1B1V.00	C/O - panic attack	1
1B17.11	C/O - feeling depressed	1
E290z00	Brief depressive reaction NOS	1
E290.00	Brief depressive reaction	1
E11..11	Bipolar psychoses	1
E115600	Bipolar affective disorder, now depressed, in full remission	1
E115000	Bipolar affective disorder, currently depressed, unspecified	1
E115200	Bipolar affective disorder, currently depressed, moderate	1
E115100	Bipolar affective disorder, currently depressed, mild	1
E115z00	Bipolar affective disorder, currently depressed, NOS	1
E115.00	Bipolar affective disorder, currently depressed	1
E115300	Bipolar affect disord, now depressed, severe, no psychosis	1
E115400	Bipolar affect disord, now depressed, severe with psychosis	1
E115500	Bipolar affect disord, now depressed, part/unspec remission	1
E11y200	Atypical depressive disorder	1
E004300	Arteriosclerotic dementia with depression	1
1B1H.12	Apprehension	1
1B13.00	Anxiousness	1

Read code	Description	Number of studies
8G94.00	Anxiety management training	1
Z4L1.00	Anxiety counselling	1
173f.00	Anxiety about breathlessness	1
6659000	Antidepressant drug treatment started	1
E214000	Anankastic personality	1
E203.11	Anancastic neurosis	1
Z4I7200	Alleviating anxiety	1
E202200	Agoraphobia without mention of panic attacks	1
E202100	Agoraphobia with panic attacks	1
E112.11	Agitated depression	1
E11..00	Affective psychoses	1
E211.00	Affective personality disorder	1
E292400	Adjustment reaction with anxious mood	1
E282.00	Acute stupor state due to acute stress reaction	1
E28z.00	Acute stress reaction NOS	1
E28..00	Acute reaction to stress	1
E283100	Acute posttrauma stress state	1
E280.00	Acute panic state due to acute stress reaction	1
E281.00	Acute fugue state due to acute stress reaction	1
Z4I7.00	Acknowledging anxiety	1
1B12.00	'Nerves' - nervousness	1
9kQ..11		1

Supplementary appendix 4, table 6. List of Read codes used in the studies of cognitive impairment.

Read code	Description	Number of studies
Eu01.00	[X]Vascular dementia	13
Eu01200	[X]Subcortical vascular dementia	13
Eu00112	[X]Senile dementia,Alzheimer's type	13
Eu00011	[X]Presenile dementia,Alzheimer's type	13
Eu01100	[X]Multi-infarct dementia	13
Eu00.00	[X]Dementia in Alzheimer's disease	13
Eu01.11	[X]Arteriosclerotic dementia	13
Eu00z11	[X]Alzheimer's dementia unspec	13
E000.00	Uncomplicated senile dementia	13
E004.11	Multi infarct dementia	13
E004.00	Arteriosclerotic dementia	13
F110000	Alzheimer's disease with early onset	13
F110.00	Alzheimer's disease	13
Eu01z00	[X]Vascular dementia, unspecified	12
Eu01000	[X]Vascular dementia of acute onset	12
Eu00012	[X]Primary degen dementia, Alzheimer's type, presenile onset	12
Eu00113	[X]Primary degen dementia of Alzheimer's type, senile onset	12
Eu01111	[X]Predominantly cortical dementia	12
Eu00z00	[X]Dementia in Alzheimer's disease, unspecified	12
Eu00100	[X]Dementia in Alzheimer's disease with late onset	12
Eu00000	[X]Dementia in Alzheimer's disease with early onset	12
Eu00200	[X]Dementia in Alzheimer's dis, atypical or mixed type	12
Eu00013	[X]Alzheimer's disease type 2	12
Eu00111	[X]Alzheimer's disease type 1	12
E004000	Uncomplicated arteriosclerotic dementia	12
E004200	Arteriosclerotic dementia with paranoia	12
E004300	Arteriosclerotic dementia with depression	12
E004100	Arteriosclerotic dementia with delirium	12
E004z00	Arteriosclerotic dementia NOS	12
F110100	Alzheimer's disease with late onset	12
Eu01y00	[X]Other vascular dementia	11
Eu01300	[X]Mixed cortical and subcortical vascular dementia	11
Eu02.00	[X]Dementia in other diseases classified elsewhere	11
Eu02300	[X]Dementia in Parkinson's disease	11
Eu02z00	[X] Unspecified dementia	11
Eu02z14	[X] Senile dementia NOS	11
E00..12	Senile/presenile dementia	11
E002000	Senile dementia with paranoia	11
E002100	Senile dementia with depression	11
E001.00	Presenile dementia	11
E041.00	Dementia in conditions EC	11
Fyu3000	[X]Other Alzheimer's disease	10
Eu02500	[X]Lewy body dementia	10
Eu02y00	[X]Dementia in other specified diseases classif elsewhere	10
Eu04100	[X]Delirium superimposed on dementia	10
Eu02z16	[X] Senile dementia, depressed or paranoid type	10
Eu02z13	[X] Primary degenerative dementia NOS	10
Eu02z11	[X] Presenile dementia NOS	10
E001000	Uncomplicated presenile dementia	10
E002z00	Senile dementia with depressive or paranoid features NOS	10
E002.00	Senile dementia with depressive or paranoid features	10
E003.00	Senile dementia with delirium	10
E00..11	Senile dementia	10
E001200	Presenile dementia with paranoia	10
E001300	Presenile dementia with depression	10
E001100	Presenile dementia with delirium	10
E001z00	Presenile dementia NOS	10
Eu02000	[X]Dementia in Pick's disease	9
Eu02200	[X]Dementia in Huntington's disease	9
Eu02400	[X]Dementia in human immunodef virus [HIV] disease	8
Eu02100	[X]Dementia in Creutzfeldt-Jakob disease	8
F112.00	Senile degeneration of brain	8
F116.00	Lewy body disease	8
F111.00	Pick's disease	7
E012.00	Other alcoholic dementia	6
E012.11	Alcoholic dementia NOS	6
Eu10711	[X]Alcoholic dementia NOS	5
E00z.00	Senile or presenile psychoses NOS	5
6AB..00	Dementia annual review	5
Eu02z15	[X] Senile psychosis NOS	4
Eu02z12	[X] Presenile psychosis NOS	4

Read code	Description	Number of studies
ZS7C500	Language disorder of dementia	4
E02y100	Drug-induced dementia	4
66h..00	Dementia monitoring	4
R00z011	[D]Memory deficit	3
e000.00	Uncomplicated senile dementia	3
Z7CEG00	Transient memory loss	3
Z7CF811	Short-term memory loss	3
E00..00	Senile and presenile organic psychotic conditions	3
2900	SENILE DEMENTIA	3
Z7CF800	Poor short-term memory	3
Z7CEH15	Poor memory	3
2901A	PRESENILE DEMENTIA	3
E00y.00	Other senile and presenile organic psychoses	3
3A30.00	Memory: present place not knwn	3
Z7CEH14	Memory problem	3
1B1A.12	Memory loss symptom	3
1B1A.00	Memory loss - amnesia	3
Z7CE611	Memory loss	3
Z7CEJ00	Memory lapses	3
Z7CEH00	Memory impairment	3
1B1A.13	Memory disturbance	3
Z7CEC11	Loss of memory for recent events	3
Z7CE615	Loss of memory	3
1461.00	H/O: dementia	3
3AE6.00	GDS level 7 - very severe cognitive decline	3
3AE5.00	GDS level 6 - severe cognitive decline	3
3AE4.00	GDS level 5 - moderately severe cognitive decline	3
3AE3.00	GDS level 4 - moderate cognitive decline	3
3AE2.00	GDS level 3 - mild cognitive decline	3
3AE1.00	GDS level 2 - very mild cognitive decline	3
2930	DEMENTIA ARTERIOSCLEROTIC	3
299 G	DEMENTIA AGGRESSIVE	3
299 B	DEMENTIA	3
E012000	Chronic alcoholic brain syndrome	3
1B1A.11	Amnesia symptom	3
ZR1K.00	Alzheimer's disease assessment scale	3
2901B	ALZHEIMER'S DISEASE	3
ZR1K.11	ADAS - Alzheimer's disease assessment scale	3
Eu80200	[X]Receptive language disorder	2
R00z000	[D]Amnesia (retrograde)	2
ZS78D00	Wernicke's dysphasia	2
ZS78D13	Wernicke's aphasia	2
Z7C3500	Unable to use verbal reasoning	2
Z7C3200	Unable to reason	2
Z7C5100	Unable to concentrate	2
1B1A000	Temporary loss of memory	2
Z7CEF00	Temporary loss of memory	2
Z7C5313	Short concentration span	2
Z7C5312	Short attention span	2
1BR0.11	Short attention span	2
8HTY.00	Referral to memory clinic	2
8HIa.00	Referral to dementia care advisor	2
Z7C5300	Reduced concentration span	2
1BR..00	Reduced concentration	2
Z7C5311	Reduced attention span	2
E00y.11	Presbyophrenic psychosis	2
Z7CEB12	Poor memory for remote events	2
Z7CFO00	Poor long-term memory	2
1BW..00	Poor concentration	2
Z7CEC12	No memory for recent events	2
Z7CEK00	Minor memory lapses	2
Z7CEL00	Mild memory disturbance	2
E2A1000	Mild memory disturbance	2
3A40.00	Memory: present year not known	2
3A20.00	Memory: present time not known	2
3A10.00	Memory: own age not known	2
3A50.00	Memory: own DOB not known	2
3A70.00	Memory: important event not kn	2
3A80.00	Memory: import.person not knwn	2
3A91.00	Memory: count down unsuccess.	2
3AA1.00	Memory: address recall unsucc.	2
Z7A1500	Memory retraining	2
Z7CE412	Memory loss symptom	2
Z7CE614	Memory loss - amnesia	2
Z7CE413	Memory loss - amnesia	2

Read code	Description	Number of studies
Z7CE612	Memory gone	2
Z7CEH11	Memory dysfunction	2
Z7CE400	Memory disturbance (& amnesia (& symptom))	2
Z7CE414	Memory disturbance	2
Z7CEH12	Memory deficit	2
Z7CFx00	Memory aided by use of labels	2
Z7CE415	Loss of memory	2
Z7CFO11	Long-term memory loss	2
Z7C5111	Lack of concentration	2
Z7CE616	LOM - Loss of memory	2
2901D	JACOB- CREUZFELDT DISEASE WITH DEMENTIA	2
Z7CEN11	Invents experiences to compensate for loss of memory	2
Z7CEA11	Impairment of working memory	2
Z7CEA13	Impairment of primary memory	2
Z7C1.00	Impaired cognition	2
129B.00	FH: Alzheimer's disease	2
Z7A1A00	Executive functions training	2
9hD0.00	Excepted from dementia quality indicators: Patient unsuitabl	2
9hD1.00	Excepted from dementia quality indicators: Informed dissent	2
1S21.00	Disturbance of memory for order of events	2
Z7C3C00	Difficulty using visuospatial reasoning	2
Z7C3600	Difficulty using verbal reasoning	2
Z7C3300	Difficulty reasoning	2
Z7C4A00	Difficulty processing information at normal speed	2
Z7C4700	Difficulty processing information accurately	2
Z7C4300	Difficulty processing information	2
Z7CI100	Difficulty making plans	2
ZR3V.13	Dementia rating scale	2
9Ou4.00	Dementia monitoring verbal invite	2
9Ou3.00	Dementia monitoring third letter	2
9Ou5.00	Dementia monitoring telephone invite	2
9Ou2.00	Dementia monitoring second letter	2
9Ou1.00	Dementia monitoring first letter	2
3A...12	Dementia assessment	2
Z7CGP00	Delayed verbal memory	2
ZR3V.11	DRS - Clinical dementia rating scale	2
Y0601JS	DEMENTIA CLINIC ATTENDANCE	2
Y060 JS	DEMENTIA CLINIC	2
2919	DEMENTIA ALCOHOLIC	2
Z73..00	Cognitive intervention strategies	2
28E..00	Cognitive decline	2
ZR3V.00	Clinical dementia rating scale	2
ZR3V.12	CDR - Clinical dementia rating scale	2
Z7CEH13	Bad memory	2
ZR2X.12	BDRS - Blessed dementia rating scale	2
Z7A1400	Attention training	2
Z7CE600	Amnesia	2
EU02y..0		2
X0034		2
AE..00		2
Ryu5.00	[X]Symptoms/signs inv cognit, percept, emotion state & behav	1
Eu80000	[X]Specific speech articulation disorder	1
Eu81500	[X]Severe learning disability	1
Eu81700	[X]Profound learning disability	1
Ryu5000	[X]Other amnesia	1
Ryu5100	[X]Oth & unspec symptom/sign involv cognit funct/awareness	1
Eu81600	[X]Mild learning disability	1
Eu05700	[X]Mild cognitive disorder	1
Eu81z12	[X]Learning disorder NOS	1
Eu81z11	[X]Learning disability NOS	1
Eu81z13	[X]Learn acquisition disab NOS	1
Eu03.11	[X]Korsakov's psychosis, nonalcoholic	1
Eu10611	[X]Korsakov's psychosis, alcohol induced	1
Eu80014	[X]Functional speech articulation disorder	1
Eu80100	[X]Expressive language disorder	1
Eu90000	[X]Disturbance of activity and attention	1
Eu44000	[X]Dissociative amnesia	1
Ryu5700	[X]Disorientation, unspecified	1
Eu10712	[X]Chronic alcoholic brain syndrome	1
Eu80600	[X]Auditory processing disorder	1
Eu90011	[X]Attention deficit hyperactivity disorder	1
Eu9y700	[X]Attention deficit disorder	1
ZS91.12	[X]Attention deficit disorder	1
Eu04.12	[X]Acute / subacute confusional state, nonalcoholic	1
ZV40000	[V]Problems with learning	1

Read code	Description	Number of studies
R045100	[D]Dysphasia	1
R00zX00	[D]Disorientation, unspecified	1
R043.00	[D]Aphasia	1
R00z500	[D]Anterograde amnesia	1
E011200	Wernicke-Korsakov syndrome	1
C253.00	Wernicke's encephalopathy	1
C251.11	Wernicke's encephalopathy	1
Z7CMB00	Visuospatial agnosia	1
Z7A1800	Visual processing training	1
F481J00	Visual disorientation syndrome	1
F584000	Unspecified other abnormal auditory perception	1
Z7CH300	Unrealistic planning	1
Z7C7200	Unable to write	1
ZT46200	Unable to use verbal communication	1
ZT49200	Unable to use non-verbal communication	1
ZT47200	Unable to use language	1
Z7CI500	Unable to use decision-making strategies	1
Z7C6200	Unable to tell the time	1
ZT4f200	Unable to responds to communication by others	1
Z7C2600	Unable to recognise surroundings	1
Z7C2200	Unable to recognise sounds	1
Z7C2D00	Unable to recognise parts of own body	1
Z7C2L11	Unable to recognise objects visually	1
Z7C2L00	Unable to recognise objects by sight	1
Z7C2H00	Unable to recognise objects	1
Z7C2T00	Unable to recognise familiar people	1
Z7C2R00	Unable to recognise faces by sight	1
Z7C2P00	Unable to recognise faces	1
Z7CFC00	Unable to recall five digit number at five minutes	1
Z7C8200	Unable to read	1
Z7C4900	Unable to process information at normal speed	1
Z7C4600	Unable to process information accurately	1
Z7C4200	Unable to process information	1
ZM18200	Unable to plan meals	1
Z7CH200	Unable to plan	1
ZN28200	Unable to organise a journey	1
Z7CI900	Unable to make considered choices	1
Z7C4C00	Unable to analyse information	1
1B1S.00	Transient global amnesia	1
Z7CE700	Transient global amnesia	1
ZS78600	Transcortical sensory dysphasia	1
ZS78411	Transcortical motor aphasia	1
Z7CE711	TGA - Transient global amnesia	1
ZS78300	Subcortical aphasia	1
E031.00	Subacute confusional state	1
Z7A2200	Strategy training for perceptual skills	1
ZS5..00	Speech and language dyspraxias	1
ZS...00	Speech and language disorder	1
ZS73.00	Specific language impairment	1
ZS73.11	Specific language disorder	1
Z7CC700	Spatial disorientation	1
Z7CD400	Slow learner	1
F483200	Simultaneous visual perception without fusion	1
1B1A100	Short-term memory loss	1
28E2.00	Severe cognitive impairment	1
ZS78A00	Semantic dysphasia	1
9Nk1.00	Seen in memory clinic	1
9N0y.00	Seen in learning disabilities clinic	1
342 CP	SENILE PARKINSONISM	1
Z7CE900	Retrograde amnesia	1
8HHP.00	Referral to learning disability team	1
8H4f.00	Referral to learning disabilities psychiatrist	1
1BR0.00	Reduced concentration span	1
ZS72.00	Receptive language impairment	1
ZS78C00	Receptive dysphasia	1
ZS78C11	Receptive aphasia	1
Z7A1700	Reality orientation	1
Z7A1711	RO - Reality orientation	1
Z7CE911	RA - Retrograde amnesia	1
ZRbf.00	Psycholinguistic assessments of language process in aphasia	1
ZD38300	Promoting aphasics communication effectiveness programme	1
8G96.00	Problem solving therapy	1
ZS78F00	Posterior dysphasia	1
1B1Y.00	Poor visual sequential memory	1
1B1a.00	Poor auditory sequential memory	1

Read code	Description	Number of studies
F591z00	Perceptive hearing loss NOS	1
F591.14	Perceptive hearing loss	1
F591.13	Perceptive deafness	1
Z7CL700	Perception that things appear grey	1
Z7CL800	Perception that things appear flat	1
Z7CLE00	Perception of things changing size	1
Z7CLH00	Perception of things changing shape	1
Z7CL911	Perception of things changing colour	1
E2F2.00	Other specific learning difficulty	1
F584z00	Other abnormal auditory perception NOS	1
F584.00	Other abnormal auditory perception	1
Z7A1600	Orientation training	1
Z7CC312	Orientation poor	1
Z7CC311	Orientation confused	1
E2A1100	Organic memory impairment	1
918e.00	On learning disability register	1
29J4.00	O/E - sensory inattention	1
2B46.11	O/E - sensory dysphasia	1
2B43.00	O/E - sensory aphasia	1
2BM3.11	O/E - perceptive deafness	1
2B45.11	O/E - motor dysphasia	1
2B42.00	O/E - motor aphasia	1
2B46.00	O/E - dysphasia - sensory	1
2B45.00	O/E - dysphasia - motor	1
2B47.00	O/E - dysphasia - NOS	1
2B4..12	O/E - dysphasia	1
2B44.00	O/E - aphasia NOS	1
2B4..11	O/E - aphasia	1
ZS78I00	Non-fluent dysphasia	1
ZS78I11	Non-fluent aphasia	1
28E1.00	Moderate cognitive impairment	1
ZS78200	Mixed transcortical dysphasia	1
ZS78900	Mixed dysphasia	1
ZS78911	Mixed aphasia	1
Z7C2700	Mistakes people's identity	1
28E0.00	Mild cognitive impairment	1
3A60.00	Memory: present month not knwn	1
3A11.00	Memory: own age known	1
Z7A1300	Memory skills training	1
Z7CFz00	Memory aided by use of lists	1
Z7CFw00	Memory aided by use of diary	1
ZS34.11	Learning disability	1
9HB2.00	Learning disabilities health action plan reviewed	1
9HB1.00	Learning disabilities health action plan offered	1
9HB0.00	Learning disabilities health action plan declined	1
9HB4.00	Learning disabilities health action plan completed	1
9HB6.11	Learning disabilities annual health check declined	1
9HB6.00	Learning disabilities annual health assessment declined	1
9HB5.00	Learning disabilities annual health assessment	1
Z7CD200	Learning difficulties	1
ZS3..00	Language-related cognitive disorder	1
ZS7..00	Language impairment	1
ZS7C600	Language disorder associated with thought disorder	1
13ZA.00	Language difficulty	1
E011100	Korsakov's alcoholic psychosis with peripheral neuritis	1
E011000	Korsakov's alcoholic psychosis	1
E040.11	Korsakoff's non-alcoholic psychosis	1
ZS78D12	Jargon dysphasia	1
ZS78D11	Jargon aphasia	1
A411.00	Jakob-Creutzfeldt disease	1
ZS78212	Isolation dysphasia	1
Z7CEA12	Impairment of immediate recall	1
Z7CD300	Impaired ability to learn new material	1
E201700	Hysterical amnesia	1
Z7CL100	Heightened visual perception	1
Z7CL511	Heightened perception of touch	1
Z7CLO00	Heightened perception of taste	1
Z7CLP11	Heightened perception of sound	1
Z7CLN11	Heightened perception of smells	1
Z7CLN12	Heightened perception of odours	1
Z7CLN00	Heightened olfactory perception	1
Z7CLP00	Heightened auditory perception	1
ZRLfE00	Health of the Nation Outcome Scale item 4 - cognitive probl	1
Z7CF200	Has delayed recall	1
ZS78800	Global dysphasia	1

Read code	Description	Number of studies
3AE..00	Global deterioration scale: assessment of prim deg dementia	1
ZS78811	Global aphasia	1
Z7CE500	Forgetful	1
ZS78E11	Fluent aphasia	1
1281.00	FH: Senile dementia	1
ZS71.00	Expressive language impairment	1
ZS84.00	Expressive language disorder	1
ZS78G11	Expressive aphasia	1
9hD..00	Exception reporting: dementia quality indicators	1
ZS78K00	Efferent motor dysphasia	1
ZS78K11	Efferent motor aphasia	1
ZS78.00	Dysphasia	1
ZT46400	Does not use verbal communication	1
ZT4J400	Does not use the elements of language	1
ZT49400	Does not use non-verbal communication	1
ZT4f400	Does not respond to communication by others	1
Z7C2900	Does not recognise self	1
Z7C2A00	Does not recognise photographs of self	1
Z7CEM00	Distortion of memory	1
Z7CC600	Disorientation for person	1
Z7C7300	Difficulty writing	1
ZT46500	Difficulty using verbal communication	1
ZT49500	Difficulty using non-verbal communication	1
Z7CI600	Difficulty using decision-making strategies	1
ZT4A500	Difficulty using a non-speech system for communication	1
Z7CJ100	Difficulty solving problems	1
Z7C8300	Difficulty reading	1
ZM18500	Difficulty planning meals	1
Z7C9300	Difficulty performing logical sequencing	1
ZN28500	Difficulty organising a journey	1
Z7CI200	Difficulty making decisions	1
Z7CIA00	Difficulty making considered choices	1
ZT4g500	Difficulty imitating forms of communication	1
Z7C4D00	Difficulty analysing information	1
9HB7.11	Did not attend learning disabilities annual health check	1
9HB7.00	Did not attend learning disabilities annual health assessmnt	1
9Ou..00	Dementia monitoring administration	1
ZS93.11	DAMP - Deficits in attention motor control and perception	1
ZS78B11	Conduction aphasia	1
F591y00	Combined perceptive hearing loss	1
Z7A1.00	Cognitive skills training	1
ZD15.00	Cognitive neuropsychological language therapy	1
ZD38200	Cognitive behavioural language therapy	1
E2E0z00	Child attention deficit disorder NOS	1
E2E0.00	Child attention deficit disorder	1
Z7CLK00	Changed perception of time	1
F11x700	Cerebral degeneration due to Jakob - Creutzfeldt disease	1
ZS78H00	Broca's dysphasia	1
ZS78H11	Broca's aphasia	1
ZS76.00	Auditory processing disorder	1
E2E0000	Attention deficit without hyperactivity	1
ZS91.00	Attention deficit disorder	1
ZS78.11	Aphasia	1
Z7CE811	Antegrade amnesia	1
ZS78511	Anomic aphasia	1
ZS78500	Anomia	1
Z7CEB00	Amnesia for remote events	1
Z7CEC00	Amnesia for recent events	1
Z7CEE00	Amnesia for important personal information	1
Z7CED00	Amnesia for day to day facts	1
13Y7.00	Alzheimer's disease society member	1
ZS7C.00	Acquired language disorder	1
ZS78100	Acquired dysphasias	1
9OIA.00	ADHD monitoring invitation third letter	1
9OI8.00	ADHD monitoring invitation first letter	1
ZS91.11	ADD - Attention deficit disorder	1
Z7C2N00		1
E0120		1
6AB.00		1
Z7C3800		1
Xa25J		1
Z7CEB11		1
Z7CC800		1
Z7C2J00		1
X00Rk		1

Read code	Description	Number of studies
Z7C3B00		1
Z7A1100		1
Z7C6300		1
Z7C9200		1
Z7C3900		1
Z7C2F00		1
Z7C2B00		1
Z7A1712		1
Z7A2100		1
Z7A2300		1

Supplementary appendix 4, table 7. ICD codes used in the studies of dementia.

Study	Databases	ICD version	List of codes
Brown, 2016	CPRD + HES	ICD-10	E512, F00, F01, F02, F03, F10.6, F10.7, G30, G31.0
Emdin, 2016	CPRD + HES	ICD-10	F01

CPRD – Clinical Practice Research Datalink; HES – Hospital Episode Statistics; ICD - International Classification of Diseases.

Supplementary appendix 4, table 8. List of Read codes used in the studies of fatigue.

Read code	Description	Number of studies
168..00	Tiredness symptom	3
168..11	Fatigue - symptom	3
168..12	Lethargy - symptom	3
1682.00	Fatigue	3
1683.00	Tired all the time	3
1684.11	C/O - debility - malaise	3
168Z.00	Tiredness symptom NOS	3
8HkW.00	Referral to chronic fatigue syndrome specialist team	3
8HIL.00	Referral for chronic fatigue syndrome activity management	3
8Q1..00	Activity management for chronic fatigue syndrome	3
E205.00	Neurasthenia - nervous debility	3
E205.12	Tired all the time	3
Eu46011	[X]Fatigue syndrome	3
F286.00	Chronic fatigue syndrome	3
F286.11	CFS - Chronic fatigue syndrome	3
F286.12	Postviral fatigue syndrome	3
F286.13	PVFS - Postviral fatigue syn	3
F286.14	Post-viral fatigue syndrome	3
F286.15	Myalgic encephalomyelitis	3
F286.16	ME - Myalgic encephalomyelitis	3
F286000	Mild chronic fatigue syndrome	3
F286100	Moderate chronic fatigue syndrome	3
F286200	Severe chronic fatigue syndrome	3
R007.00	[D]Malaise and fatigue	3
R007100	[D]Fatigue	3
R007211	[D]General weakness	3
R007300	[D]Lethargy	3
R007400	[D]Postviral (asthenic) syndrome	3
R007411	[D]Post viral debility	3
R007500	[D]Tiredness	3
R007z00	[D]Malaise and fatigue NOS	3
168..13	Malaise - symptom	2
1683.11	C/O - 'tired all the time'	2
1684.00	Malaise/lethargy	2
1684.13	C/O - postviral syndrome	2
1688.00	Exhaustion	2
1B3..12	Weakness symptoms	2
E205.11	Nervous exhaustion	2
Eu46000	[X]Neurasthenia	2
F03y.12	Myalgic encephalomyelitis	2
N239.00	Fibromyalgia	2
N248.00	Fibromyalgia	2
R007000	[D]Malaise	2
R007200	[D]Asthenia NOS	2
R2y3.00	[D]Debility, unspecified	2
168..14	C/O 'Muzzy head'	1
1B32.00	Weakness present	1
8HkW.11	Referral to myalgic encephalomyelitis specialist team	1
8Q1..11	Activity management for myalgic encephalopathy	1
A4zy300	Encephalitis lethargica	1
Eu46y14	[X]Psychasthenia	1
Eu46y15	[X]Psychasthenia neurosis	1
R007600	[D]Post polio exhaustion	1
R007z11	[D]Lassitude	1
R202.00	[D]Senile asthenia	1
SN44.00	Exhaustion due to exposure	1

Supplementary appendix 4, table 9. List of Read codes used in the studies of pain.

Read code	Description	Number of studies
NyuAG	[X]Uns sof tis d,use/overu/prs	2
NyuA	[X]Other soft tissue disorders	2
Nyu80	[X]Other myositis	2
Nyu3	[X]Other joint disorders	2
Ryu70	[X]Other chronic pain	2
NyuAF	[X]Oth spcf soft tissu disords	2
Nyu85	[X]Oth spcf disorders/muscle	2
NyuAA	[X]Oth sft tis diso/oth dis CE	2
Nyu8A	[X]Oth disordrs/muscle/dis CE	2
Nyu9	[X]Disorders/synovium+tendon	2
Nyu8	[X]Disorders of muscles	2
Nyu8B	[X]Disorder of muscle, unspec	2
R01zz	[D]Nerv/musculoskel.sympt.NOS	2
R01z	[D]Nerv/musculoskel.symp.other	2
R01	[D]Musculoskeletal symptoms	2
R01z2	[D]Musculoskeletal pain	2
R00z2	[D]General aches and pains	2
N22z	Synovium/tendon/bursa dis.NOS	2
N0950	Stiff joint NEC-site unspecif.	2
N0958	Stiff joint NEC-other specif.	2
N240	Rheumatism/fibrositis NOS	2
N2	Rheumatism, excl.the back	2
N240z	Rheumatism or fibrositis NOS	2
N2400	Rheumatism NOS - shoulder	2
N2403	Rheumatic pain	2
N24z	Polyalgia	2
N09	Other/unspecif.joint disorders	2
N22yz	Other tendon disorder NOS	2
N233z	Other specif.musc.disorder NOS	2
N06yz	Other specif.arthropathy NOS	2
N06y9	Other spec.arthr.-multipl.site	2
N09y	Other spec. joint disorders	2
N24	Other soft tissue disorders	2
N3z	Other musculoskeletal dis. NOS	2
N247	Other musculoskel.limb sympts.	2
N23y	Other muscle/ligament/fascia	2
N23yz	Other musc./lig./fasc.dis.NOS	2
N096z	Other joint symptoms NOS	2
N0968	Other joint sympt.-other spec.	2
N0969	Other joint sympt.-multip.site	2
N09yz	Other joint disorders NOS	2
N09y0	Other joint dis.-site unspec.	2
N09y8	Other joint dis.-other specif.	2
N09y9	Other joint dis.-multiple site	2
N2y	Nonarticular rheumatism OS	2
N2z	Nonarticular rheumatism NOS	2
N39	Nonallopathic lesions, NEC	2
N39z	Nonallopathic lesion NEC NOS	2
N2411	Myositis unspecified	2
N2480	Myofascial pain syndrome	2
N241	Myalgia/myositis unspecified	2
N241z	Myalgia/myositis NOS	2
N3y	Musculoskeletal disorders OS	2
Ny	Musculoskeletal diseases OS	2
Nz	Musculoskeletal diseases NOS	2
N2402	Muscular rheumatism	2
N23z	Muscle/ligament/fascia dis.NOS	2
N2410	Muscle pain	2
N0959	Multiple joint stiffness	2
N0450	Juv ankylosing spondylitis	2
N095z	Joint stiffness NEC NOS	2
N095	Joint stiffness NEC	2
N09zz	Joint disorders NOS	2
N09z	Joint disorder NOS	2
N09z0	Joint disord.NOS-site unspecif	2
N09z8	Joint disord.NOS-other specif.	2
N09z9	Joint disord.NOS-multiple site	2
N096	Joint crepitus	2
N2401	Fibrositis unspecified	2
N2412	Fibromyositis NOS	2
N248	Fibromyalgia	2
N239	Fibromyalgia	2

Read code	Description	Number of studies
N23	Fascia disorders	2
N06zB	Chronic arthritis	2
N06z0	Arthropathy NOS-site unspecif.	2
N06z8	Arthropathy NOS-other specif.	2
N06z9	Arthropathy NOS-multiple sites	2
N06zz	Arthropathy NOS	2
N0z	Arthropathies NOS	2
N06z	Arthritis	2
N0949	Arthralgia of multiple joints	2
N094z	Arthralgia NOS	2
N0940	Arthralgia - site unspecified	2
N0948	Arthralgia - other specified	2
N094	Ache in joint	2
OX7179KB	viral myalgia /ox	1
7K6T1	release of Torticollis	1
N2452	neuropathic pain	1
OX7289CH	back pain /ox	1
Syu4E	[X]Unspecif inj should/up arm	1
NyuB8	[X]Unsp osteopor + pathol frac	1
Nyu28	[X]Unilat second gonarthrosis	1
Nyu25	[X]Unilat primary gonarthrosis	1
Nyu4	[X]Systmc connctv tis disordrs	1
Nyu4C	[X]Sys diso/connctv t/o dis CE	1
Nyu95	[X]Synovitis+tenosyn/bact d CE	1
Nyu97	[X]Synovial hypertrophy, NEC	1
Ryu3	[X]Sym/sign inv nv/muscskel sy	1
Syu12	[X]Superf inj neck part unsp	1
Syu84	[X]Sprn/str oth unsp part knee	1
Syu46	[X]Spr/str oth/un part shl gir	1
Syu36	[X]Spr/str ot/un pt lum sp/pel	1
Syu18	[X]Spr/str jt/lg ot/un pt neck	1
Nyu92	[X]Spontans ruptr/oth tendons	1
Nyu68	[X]Spondylpthy/oth diseases CE	1
Nyu66	[X]Spondylpth/o inf+paras d CE	1
Nyu69	[X]Spondylopathy unspecified	1
Nyu6	[X]Spondylopathies	1
Nyu5B	[X]Spin osteochondrosis, unsp	1
Nyu1G	[X]Seroposit rheum arthr, unsp	1
Nyu10	[X]Rheum arthrit+inv/o org/sys	1
Nyu05	[X]Reactv arthropathy/o dis CE	1
Eu45y	[X]Psychogenic torticollis	1
NyuE4	[X]Postproc muscsk disord,unsp	1
Nyu2F	[X]Post-traum arthr oth joints	1
NyuC9	[X]Periostitis/oth inf dis CE	1
Nyu51	[X]Other+unspecified kyphosis	1
Nyu64	[X]Other spondylosis	1
Nyu2D	[X]Other specified arthrosis	1
Nyu1B	[X]Other specified arthritis	1
Nyu65	[X]Other spcfd spondylopathies	1
Nyu3D	[X]Other spcfd joint disorders	1
NyuAB	[X]Other shoulder lesions	1
Nyu54	[X]Other secondary scoliosis	1
Nyu50	[X]Other secondary kyphosis	1
Nyu17	[X]Other secondary gout	1
Nyu21	[X]Other primary coxarthrosis	1
Nyu20	[X]Other polyarthrosis	1
Nyu46	[X]Other overlap syndromes	1
NyuB1	[X]Other osteoporosis	1
NyuC	[X]Other osteopathies	1
NyuC5	[X]Other osteonecrosis	1
NyuC3	[X]Other osteomyelitis	1
Nyu82	[X]Other ossification/muscle	1
Nyu37	[X]Other meniscus derangements	1
Nyu52	[X]Other lordosis	1
Nyu15	[X]Other juvenile arthritis	1
Nyu3C	[X]Other instability of joint	1
NyuA4	[X]Other infective bursitis	1
Nyu53	[X]Other idiopathic scoliosis	1
Nyu41	[X]Other giant cell arteritis	1
Nyu56	[X]Other fusion of spine	1
Nyu55	[X]Other forms of scoliosis	1
NyuAE	[X]Other enthesopathies,NEC	1
Nyu7	[X]Other dorsopathies	1
Nyu7A	[X]Other dorsalgia	1

Read code	Description	Number of studies
Nyu36	[X]Other disorders of patella	1
Nyu44	[X]Other dermatomyositis	1
Nyu35	[X]Other derangements/patella	1
NyuB6	[X]Other cyst of bone	1
NyuC2	[X]Other chronic osteomyelitis	1
Nyu18	[X]Other chondrocalcinosis	1
Nyu81	[X]Other calcification/muscle	1
NyuA1	[X]Other bursitis of knee	1
NyuA6	[X]Other bursitis NEC	1
NyuA5	[X]Other bursal cyst	1
NyuA7	[X]Other bursa disorder	1
NyuE3	[X]Other biomechanical lesions	1
NyuB4	[X]Other adult osteomalacia	1
NyuC0	[X]Other acute osteomyelitis	1
NyuC4	[X]Other 2ndary osteonecrosis	1
Nyu47	[X]Oth syst dis/connctv tissue	1
Nyu91	[X]Oth synovitis+tenosynovitis	1
Syu40	[X]Oth sup inj should/upp arm	1
Nyu62	[X]Oth spondylosis+myelopathy	1
Nyu79	[X]Oth specified dorsopathies	1
NyuC8	[X]Oth spcfd disorders of bone	1
Nyu1A	[X]Oth spcfc arthropathies,NEC	1
Nyu12	[X]Oth spcf rheumatd arthritis	1
Nyu61	[X]Oth spcf inflam spondylpath	1
NyuD4	[X]Oth spcf disordrs/cartilage	1
Nyu59	[X]Oth spcf deform dorsopaths	1
NyuD3	[X]Oth spc osteochondropathies	1
Syu3K	[X]Oth sp inj abd/low back/pel	1
Nyu2E	[X]Oth secondary coxarthrosis	1
Nyu83	[X]Oth ruptr/muscl(nontraumtc)	1
Nyu58	[X]Oth recur vertebrl subluxtn	1
Nyu03	[X]Oth reactive arthropathies	1
Nyu13	[X]Oth psoriatic arthropathies	1
Nyu26	[X]Oth post-traum gonarthrosis	1
Nyu23	[X]Oth post-traum coxarthrosis	1
NyuB0	[X]Oth osteoporosis+patholog #	1
Nyu39	[X]Oth intrnl derangemnts/knee	1
Nyu90	[X]Oth infectve(teno)synovitis	1
Nyu60	[X]Oth infectv spondylopathies	1
Nyu45	[X]Oth forms/systemc sclerosis	1
Nyu43	[X]Oth forms/sys lup erythemat	1
NyuA9	[X]Oth fibroblastic disorders	1
Nyu22	[X]Oth dysplastic coxarthrosis	1
NyuB5	[X]Oth diso/continuity of bone	1
NyuC6	[X]Oth diso/bone dvlpmnt+grwth	1
NyuE	[X]Oth dis musculosk+connect	1
Nyu70	[X]Oth cervicl disc displacmnt	1
Nyu71	[X]Oth cervicl disc degeneratn	1
Nyu72	[X]Oth cervical disc disorders	1
Nyu3A	[X]Oth articulr cartilag disor	1
Nyu27	[X]Oth 2ndry gonarthrsis,bilat	1
Nyu24	[X]Oth 2ndry coxarthrsis,bilat	1
NyuB2	[X]Osteoporosis/oth disords CE	1
NyuBC	[X]Osteopenia	1
NyuCA	[X]Osteopathy/other inf dis CE	1
NyuCF	[X]Osteopathy/oth diseases CE	1
NyuCC	[X]Osteonecrosis/other dis CE	1
NyuCB	[X]Osteonecros/h'moglobnpth CE	1
NyuCD	[X]Osteitis defrmn/neop dis CE	1
SR1z1	[X]Op multiple fractures unsp	1
Nyu00	[X]O strep arthritis+polyarthr	1
Nyu38	[X]O spontn disrptn/lig(s)knee	1
Nyu63	[X]O spondylosis+radiculopathy	1
NyuD2	[X]O spf juvnl osteochondrosis	1
Nyu42	[X]O spcf necrotiz vasculopath	1
Nyu3B	[X]O spcf joint derangmnts,NEC	1
Nyu77	[X]O spcf intrvrtbrl disc diso	1
Nyu94	[X]O spcf diso/synovium+tendon	1
Nyu19	[X]O spcf crystl arthropathies	1
Nyu76	[X]O spc intrvrtbl disc degenr	1
Nyu75	[X]O spc intervert disc displm	1
NyuB7	[X]O spc diso/bne dnsity+struc	1
NyuE0	[X]O spc acq defrm/muscskl sys	1
NyuA3	[X]O sft t d rl/use,overu+prss	1

Read code	Description	Number of studies
Nyu11	[X]O sero+ve rheumat arthritis	1
Nyu57	[X]O recur atlantoaxl subluxtn	1
NyuE2	[X]O postproced muscskel disor	1
Nyu04	[X]O postinf arthropath/dis CE	1
NyuC7	[X]O hypertrophc osteoarthrpth	1
Nyu14	[X]O enteropathic arthrpathies	1
NyuB3	[X]O drug-indc osteomalac/adlt	1
Nyu96	[X]O diso/synovm+tendon/dis CE	1
Nyu93	[X]O contractre/tendon(sheath)	1
Nyu40	[X]O cond relt/polyarterit nod	1
NyuC1	[X]O chr h'matogens osteomylit	1
Nyu4D	[X]Necrotis vasculopathy, unsp	1
Nyu87	[X]Myosits/protzl+paras inf CE	1
Nyu88	[X]Myositis/oth infects dis CE	1
Nyu89	[X]Myositis in sarcoidosis CE	1
Nyu86	[X]Myositi/bacterial dis CE	1
Nyu84	[X]Muscle wasting and atrophy NEC	1
SyuA4	[X]Multi disloc/spr/strns,unsp	1
Nyu4F	[X]Mixed connective tissue disease	1
Nyu74	[X]Lumb+o intvt disc d+radiclp	1
Nyu73	[X]Lumb+o intrvrt disc d+mylop	1
Nyu5A	[X]Lordosis, unspecified	1
Nyu16	[X]Juvenile arthritis/o dis CE	1
Syu1	[X]Injuries to the neck	1
Syu3	[X]Injabd/low back/lum sp/pel	1
Syu4	[X]Inj to shoulder/upper arm	1
Syu8	[X]Inj to knee and lower leg	1
Nyu1	[X]Inflammatory polyarthropathies	1
Nyu0	[X]Infectious arthropathies	1
Nyu1C	[X]Gt arthpth/enz d+o inh d CE	1
Syu16	[X]Fracture other parts neck	1
Syu44	[X]Fract should/upp arm unsp	1
Syu15	[X]Fract oth spec cervic vert	1
SyuA2	[X]Fract inv oth comb bod regn	1
NyuAH	[X]Fibroblastic disord, unspec	1
NyuA8	[X]Fasciitis,NEC	1
NyuBB	[X]Erosion of bone	1
SyuA3	[X]Dsl/spr/str,oth comb bod rg	1
SyuB3	[X]Dsl/sp/st un jt/l leg,lv un	1
NyuB	[X]Disordrs/bone dens+structur	1
Nyu3E	[X]Disorder of patella, unspec	1
NyuDE	[X]Disorder cartilage, unspec	1
NyuBA	[X]Disord bone dens/struc,unsp	1
Syu17	[X]Disloc oth unsp parts neck	1
SyuBC	[X]Disl/spr/str unsp body reg	1
Nyu4E	[X]Dermatopolymyositis, unspec	1
Nyu48	[X]Dermat(poly)myosit/neo d CE	1
Nyu5	[X]Deforming dorsopathies	1
Nyu1D	[X]Crys arthpth/o meta diso,CE	1
Nyu67	[X]Collapsd vertebra in dis CE	1
SR1z0	[X]Clsd multiple fracts unspec	1
NyuD	[X]Chondropathies	1
Nyu7B	[X]Cervical disc disord, unsp	1
Nyu4B	[X]Arthrpthy/hyprsens react CE	1
Nyu1F	[X]Arthrpth/o spcf diseases CE	1
Nyu1E	[X]Arthrpth/o en,nut+meta diso	1
Nyu2	[X]Arthrosis	1
Nyu4A	[X]Arthropathy/o bld disord CE	1
Nyu49	[X]Arthropathy/neoplast dis CE	1
Nyu02	[X]Arthrits/o inf+paras dis CE	1
Nyu01	[X]Arthrit+polyarth/o s bact a	1
NyuB9	[X]Adult osteomalacia, unspec	1
Nyu	[X]Ad muscskl+con t dis cls tm	1
NyuCE	[X]#bone/neoplastic disease CE	1
NyuE1	[X]#/bne f insrt/o i,j pr,bn p	1
EMISREQ|7N945(9)	[SO]Lumbosacral joint -Req.	1
HNGZ018	[RFC] Arthritis	1
R0420	[D]Swelling in head or neck	1
R042	[D]Swell.masslump head/neck	1
R027	[D]Spontaneous bruising	1
R065A	[D]Musculoskeletal chest pain	1
R137	[D]Musculoskel.ray/scan abnorm	1
R137z	[D]Musculosc xray/scan abn NOS	1
R022C	[D]Lump on knee	1

Read code	Description	Number of studies
R04zz	[D]Head and neck symptoms NOS	1
R04	[D]Head and neck symptoms	1
R04z	[D]Head and neck other sympt.	1
R00z2-1	[D]General aches and pains	1
R065000	[D]CHEST PAIN, UNSPECIFIED	1
R065z00	[D]CHEST PAIN NOS	1
R065.00	[D]CHEST PAIN	1
R090z00	[D]Abdominal pain	1
R090.00	[D]Abdominal pain	1
DEGRADE_EVENT_1730_49	[DEGRADE Muscle Injury]	1
DEGRADE_EVENT_2469_340	[DEGRADE Knee Pain]	1
DEGRADE_EVENT_3154_40	[DEGRADE Knee Pain]	1
N135z-2	Wry neck	1
N05z3	Wrist osteoarthritis NOS	1
N0943-1	Wrist joint pain	1
N06z3-1	Wrist arthritis NOS	1
S5704	Whiplash injury	1
EGTONWE2	Wedge Compression # Of Dorsal Spine	1
EGTONWE1	Wedge Compression # Lumbar Spine	1
N2432	Weber - Christian disease	1
N2430	Weber - Christian disease	1
N0974	Walking difficulty-other spec.	1
N0975	Walking difficulty-multip.site	1
N0970	Walking difficulty due to unspecified site	1
N2413	Viral myalgia	1
N092M	Villonodular synovitis of knee	1
N092z	Villonodular synovitis NOS	1
N092	Villonodular synovitis	1
N0920	Villonod.synovitis-site unspec	1
N0921	Villonod.synovitis-shoulder	1
N0928	Villonod.synovitis-other spec.	1
N0929	Villonod.synovitis-mult.sites	1
N2208	Villonod synovitis-tend sheath	1
N092B	Villonod synovitis-sternclav j	1
N092A	Villonod synovitis-shoulder	1
N092C	Villonod synovitis-acromclav j	1
N330B	Vertebral osteoporosis	1
N320	Vertebral epiphysitis	1
N1	Vertebral column syndromes	1
N1y	Vertebral column disorders OS	1
N1z	Vertebral column disorder NOS	1
N0966-2	Unstable knee	1
N0967-1	Unstable ankle	1
N066z	Unspecified monoarthritis NOS	1
N066	Unspecified monoarthritis	1
N1290	Unspec.disc disorder+myelop.	1
N0650	Unsp.polyarthr.-site unspecif.	1
N065000	Unsp.polyarthr.-site unspecif.	1
N0651	Unsp.polyarthr.-shoulder	1
N065800	Unsp.polyarthr.-other specif.	1
N0658	Unsp.polyarthr.-other specif.	1
N065900	Unsp.polyarthr.-multiple site	1
N0659	Unsp.polyarthr.-multiple site	1
N3020	Unsp.osteomyelitis-site unspec	1
N3021	Unsp.osteomyelitis-shoulder	1
N3028	Unsp.osteomyelitis-other spec.	1
N3029	Unsp.osteomyelitis-mult.site	1
N302z	Unsp.osteomyelitis NOS	1
N0660	Unsp.monoarthr.-site unspecif.	1
N0661	Unsp.monoarthr.-shoulder	1
N0668	Unsp.monoarthr.-other specif.	1
N1121	Two lev th spondyl-no myelop	1
N11B1	Two lev th spondyl + radiculop	1
N1131	Two lev th spondyl + myelop	1
N1141	Two lev lumbsac spond-no myelo	1
N1151	Two lev lumbsac spond + myelop	1
N1101	Two lev Cx spondyl-no myelop	1
N1191	Two lev Cx spondyl + radiculop	1
N1111	Two lev Cx spondyl + myelop	1
N018	Tuberculous arthritis	1
N3041	Tuberculosis of thoracic spine	1
N304	Tuberculosis of spine	1
N306	Tuberculosis of other bones	1
N3042	Tuberculosis of lumbar spine	1

Read code	Description	Number of studies
N3040	Tuberculosis of cervical spine	1
N3060	Tuberculosis bone-site unspec.	1
N3061	Tuberculosis bone-shoulder	1
N3064	Tuberculosis bone-other sites	1
N3065	Tuberculosis bone-multip.sites	1
N306z	Tuberculosis bone NOS	1
N22yD	Tuberc infec - tendon sheath	1
N2155	Trochanteric tendinitis	1
N2157	Trochanteric bursitis	1
N0874	Triangular fibrocartilage tear	1
N0875	Triangular fibrocartil detach	1
N118	Traumatic spondylopathy	1
N2312	Traumatic myositis ossificans	1
SE46	Traumatic haematoma	1
SK	Traumatic complicat./unsp.inj.	1
N061A	Traumatic arthropathy-shoulder	1
N061M	Traumatic arthropathy-knee	1
N061z	Traumatic arthropathy NOS	1
N061	Traumatic arthropathy	1
N0610	Traumatic arthr.-site unspecif	1
N0611	Traumatic arthr.-shoulder	1
N0618	Traumatic arthr.-other specif.	1
N0619	Traumatic arthr.-multiple site	1
N061B	Traumat arthrop-sternoclav jt	1
N061C	Traumat arthrop-acromioclav jt	1
S906	Traumat amp at shoulder joint	1
SA72	Traum.unil.amput.>knee-no comp	1
N220Q	Transient synovitis	1
N064A	Transient arthropathy-shoulder	1
N064M	Transient arthropathy-knee	1
N064z	Transient arthropathy NOS	1
N064	Transient arthropathy	1
N064B	Transient arthrop-sternoclav j	1
N0640	Transient arthr.-site unspecif	1
N0641	Transient arthr.-shoulder	1
N0648	Transient arthr.-other specif.	1
N0649	Transient arthr.-multiple site	1
N064C	Transient arthr-acromioclav jt	1
N135	Torticollis unspecified	1
Q20y9	Torticollis due to birth injury	1
16A3	Torticollis - symptom	1
N2451-1	Toe pain	1
N2162	Tibial collateral lig.bursitis	1
N2450-1	Thumb pain	1
N05z4-2	Thumb osteoarthritis NOS	1
N3735	Thoracogenic scoliosis	1
N1485	Thoraco-lumbar ankylosis	1
N144	Thoracic/lumbosacral neuritis	1
N144z	Thoracic/lumbosac.neuritis NOS	1
N112-1	Thoracic spondylosis	1
N112	Thoracic spond.-no myelopathy	1
N113	Thoracic spond.+ myelopathy	1
N148B	Thoracic spine instability	1
N1484	Thoracic spine ankylosis	1
N1401	Thoracic spinal stenosis	1
N12A2	Thoracic postlaminectomy syndr	1
N1440	Thoracic nerve root pain	1
N12z8	Thoracic discitis	1
N121	Thoracic disc displ.-no myelop	1
N1292	Thoracic disc disord.+myelop.	1
N126	Thoracic disc degeneration	1
S571	Thoracic back sprain	1
EMISNQTH14	Thoracic back pain	1
N245-8	Thigh pain	1
N11B	Th spondyl + radiculop	1
N1406	Th spin stenos due to oth dis	1
N12C1	Th disc prolapse+radiculopathy	1
N12B1	Th disc prolapse + myelopathy	1
N2132-1	Tennis elbow	1
N2202	Tendon sheath giant cell tumor	1
ASDFGTE2	Tendon Symptoms	1
N2456	Tender heel pad	1
S46B	Tear/articulr cart/knee,currnt	1
S545	Tear of ligament of knee joint	1

Read code	Description	Number of studies
N000*	Systemic lupus erythematosus	1
N000	Systemic lupus erythematosus	1
N000z	Systemic lupus erythematos.NOS	1
N0012	Syst scleros induc drugs/chems	1
N0003	Syst lup eryth + organ/sys inv	1
N2227	Syphilitic bursitis	1
N2200	Synovitis or tenosynovitis NOS	1
N220z-2	Synovitis of knee	1
N220z	Synovitis of knee	1
N220V	Synovitis of knee	1
N220	Synovitis and tenosynovitis	1
N220T	Synovitis NOS	1
N2201	Synovit./tenosynovitis+dis EC	1
N22y4	Synovial plica	1
N098	Synovial osteochondromatosis	1
N2240	Synovial cyst unspecified	1
N0980	Synov osteochondromat-shoulder	1
N098B	Synov osteochondromat-knee	1
N0981	Synov osteochondromat st-cla j	1
N0982	Synov osteochondromat ac-cla j	1
1D24	Symptom: trunk posterior	1
16J4	Swollen knee	1
16J3	Swollen joint	1
16J7	Swollen foot	1
1834-1	Swollen finger	1
1JG	Suspected inflammatory arthritis	1
N21z2	Supraspinatus tendonitis	1
N2113	Supraspinatus tendinitis	1
N230	Suppurative myositis	1
SD1y4	Supl inj bk NOS-no mj opn wnd	1
SD9	Superficialinjuriesunspecif.	1
SD097	Superficiallnjury:Neck	1
SD2y1	Superficial injury of scapular NOS	1
SD6y2	Superficial injury of knee NOS	1
SDz	Superficial injuries NOS	1
SD0	Superficial Injury: Neck	1
SD2y0	Superfic injury shoulder NOS	1
SD2	Superf.inj.shoulder/upper arm	1
SD1z4	Superf.back inj.NOS+infect.	1
N3371	Sudek's atrophy	1
N2167	Subpatellar bursitis	1
N3y01	Subluxatn complex (vertebral)	1
N3y02	Sublux stenos of neural canal	1
N3081	Subacute osteomyelitis-th spin	1
N3082	Subacute osteomyelitis-lu spin	1
N3080	Subacute osteomyelitis-Cx spin	1
N309	Subacute osteomyelitis	1
N308	Subacute osteomyelitis	1
N2122	Subacromial impingement	1
N2116	Subacromial bursitis	1
S3z2	Stress fracture	1
N095B	Stiff sternoclavic joint NEC	1
N095A	Stiff shoulder NEC	1
16AZ	Stiff neck symptom NOS	1
16A	Stiff neck symptom	1
N135z	Stiff neck NOS	1
16A2	Stiff neck	1
N095M	Stiff knee NEC	1
N095C	Stiff acromioclavicular joint NEC	1
S5y41	Sternoclavicular sprain	1
N0108	Staphylococc arthrit/polyarthr	1
S5410	Sprn,knee jt,medial collat	1
S5400	Sprn,knee jt,lat collat lgmt	1
S520D	Sprn triangular fibrocartilage	1
S520G	Sprn shrt intrnsc lgmnt non-sp	1
S5	Sprains and strains	1
S50	Sprained shoulder	1
S54y-99	Sprained knee NOS	1
S54-99	Sprained knee	1
S560	Sprain, lumbosacral ligament	1
S564	Sprain, iliolumbar ligament	1
S501	Sprain, coraco-clav ligament	1
S506	Sprain supraspinatus tendon	1
S505	Sprain subscapularis tendon	1

Read code	Description	Number of studies
S5071	Sprain shoulder joint posterior	1
S5070	Sprain shoulder joint anterior	1
S507	Sprain shoulder joint	1
S534	Sprain patellar tendon	1
S503	Sprain infraspinatus tendon	1
S500	Sprain acromio-clav ligament	1
S542	Sprain -cruciate knee ligament	1
S541	Sprain - medial knee ligament	1
S541-99	Sprain - medial knee ligament	1
S540-99	Sprain - lateral knee ligament	1
S540	Sprain - lateral knee ligament	1
SC07	Sprain - late effect	1
S57X	Spr/str ot/un pt lum sp/pel	1
ASDFGSP5	Sports Injury	1
N082	Spontaneous joint dislocation	1
16B3	Spontaneous bruising	1
N11z0	Spondylosis-no myelopathy,NOS	1
N11zz	Spondylosis NOS	1
N11z1	Spondylosis + myelopathy, NOS	1
N388	Spondylolysis	1
OXL7561C	Spondylolisthesis /ox	1
N10z	Spondylitis NOS	1
N374	Spine curvature+other condits.	1
N374z	Spine curvature+other cond.NOS	1
N1400	Spinal stenosis unspec.region	1
N140z	Spinal stenosis NOS	1
N140-1	Spinal stenosis	1
N140	Spinal stenosis	1
N101	Spinal enthesopathy	1
N222z	Specific bursitides NOS	1
N222	Specific bursitides	1
F1382	Spasmodic Torticollis	1
N23y4	Spasm of muscle	1
N23yE	Spasm of back muscles	1
EGTON309	Sore Neck	1
N3321	Solitary bone cyst	1
N0878	Snapping shoulder	1
N32y	Slipped radial epiphysis	1
N33zA	Skeletal fluorosis	1
N002*	Sicca (Sjogren's) syndrome	1
N2125	Shoulder tendonitis	1
S50y	Shoulder sprain NOS	1
N245-7	Shoulder pain	1
N245	Shoulder pain	1
N2457	Shoulder pain	1
N0951	Shoulder joint stiffness	1
UNMAPPC0	Shoulder injury	1
S221	Shoulder fracture - open	1
N22y5	Short tendon	1
N011	Sex acquired reactive arthrop	1
N0110	Sex acqd reac arthrop-unspec	1
N0111	Sex acqd reac arthrop-shoulder	1
N011y	Sex acqd reac arthrop-oth spec	1
N011x	Sex acqd reac arthrop-multiple	1
N011z	Sex acq reac arthropathy NOS	1
SRz0	Severe multiple injuries	1
N047	Seropositive errosive RA	1
N04X	Seroposit rheum arthr unsp	1
N040P	Seronegative rheumat arthritis	1
EGTONSE2	Sero-Negative Polyarthritis	1
N04y1	Sero negative arthritis	1
N04y10	Sero negative arthritis	1
N3301	Senile osteoporosis	1
N2169	Semimembranosus tendinitis	1
EGTON131	Semi Frozen Shoulder	1
N3y00	Segmental & somatic dysfunctn	1
N0505	Secondary multiple arthrosis	1
N050500	Secondary multiple arthrosis	1
EMISNQSC20	Scoliosis of thoracic spine	1
N374A	Scoliosis in skelet dysplasia	1
N374C	Scoliosis in neurofibromatosis	1
N374D	Scoliosis in conn tiss anomal	1
N3739	Scoliosis due to oth treatment	1
OX735AA	Scoliosis Acquired /ox	1

Read code	Description	Number of studies
N3743	Scoliosis + other condition	1
N001	Scleroderma	1
OX353C	Sciatica Chronic /ox	1
N1240	Schmorl's nodes-unspec. region	1
N1241	Schmorl's nodes-thoracic regn.	1
N124z	Schmorl's nodes-region NOS	1
N1242	Schmorl's nodes-lumbar region	1
N124	Schmorl's nodes	1
N3201	Scheuermann's disease	1
N2121	Scapulohumeral fibrositis	1
N146z-1	Sacroiliac strain	1
N1466	Sacroiliac disorder	1
S5731	Sacral/coccyx sprain	1
N0004	SLE with pericarditis	1
N25	SAPHO syndrome	1
S5Q2	Rupture supraspinatus tendon	1
S5Q1	Rupture subscapularis tendon	1
S5U2	Rupture patellar tendon	1
N2250	Rupture of synovium unspecif.	1
N225z	Rupture of synovium NOS	1
N2251-99	Rupture of synovium - knee	1
N225	Rupture of synovium	1
S5Q0	Rupture infraspinatus tendon	1
N2251	Ruptur poplit space synov cyst	1
N2110	Rotator cuff syndrome unspecif	1
S504	Rotator cuff sprain	1
N211	Rotator cuff shoulder syndrome	1
N2261	Rotator cuff complete rupture	1
N3385	Rotational mal-union of #	1
182B	Rib pain	1
EGTON425	Rheumatology	1
N040N	Rheumatoid vasculitis	1
N0422	Rheumatoid nodule	1
N040R	Rheumatoid nodule	1
N0421	Rheumatoid lung disease	1
N040Q	Rheumatoid bursitis	1
N0402	Rheumatoid arthritis-shoulder	1
N0400	Rheumatoid arthritis-Cx spine	1
N040D	Rheumatoid arthritis of knee	1
N040	Rheumatoid arthritis	1
N0403	Rheumatoid arthr-sternoclav jt	1
N0404	Rheumatoid arthr-acromioclav j	1
N1351	Rheumatic torticollis	1
N0420	Rheumatic carditis	1
OX7149A	Rheumatic Arthritis /ox	1
N040S	Rheumat arthr - multiple joint	1
N2333	Rhabdomyolysis	1
N042z	Rh.arthr.+visc/syst.dis.NOS	1
N080A	Reverse Hill-Sachs lesion	1
N0871	Reverse Bankart lesion	1
N12zA	Resorption of thoracic disc	1
N12zE	Resorption of lumbar disc	1
N12z6	Resorption of cervical disc	1
N3732	Resolving infant.idiopath.scol	1
N246	Residual soft tiss.foreign bod	1
N339	Residual foreign body in bone	1
Ny2	Repetitive strain injury	1
N33z5	Relapsing polychondritis	1
N337	Reflex sympathetic dystrophy	1
N083	Redislocation of joint	1
S46D	Recurrent subluxation of patella	1
N083D	Recurrent sublux shoulder-post	1
N083F	Recurrent sublux shoulder-inf	1
N083C	Recurrent sublux shoulder-ant	1
N083H	Recurrent sublux shoulder-ant	1
N083q	Recurrent sublux - patella	1
N083z	Recurrent joint dislocat.NOS	1
N0839	Recurrent disloc-multip joints	1
N083B	Recurrent disloc shoulder-post	1
N083E	Recurrent disloc shoulder-inf	1
N083A	Recurrent disloc shoulder-ant	1
N083G	Recurrent disloc shoulder-ant	1
N083p	Recurrent disloc - patella	1
N083n	Recurrent disloc - knee	1

Read code	Description	Number of studies
N0830	Recurr.joint disloc.-site unsp	1
N0838	Recurr.joint disloc-other spec	1
N0831	Recur. disloc.- shoulder joint	1
N0836-99	Recur. disloc. - knee joint	1
N083K	Recur sublux shoulder-multidir	1
N083J	Recur disloc shoulder-multidir	1
N1y0	Rec atlantoax subl + myelopath	1
N01w0	Reactive arthropathy-shoulder	1
N01w	Reactive arthropathy unspecified	1
N01wB	Reactive arthropathy of knee	1
N038	Reactive arthropathies	1
N01w2	Reactive arthrop-sternoclav jt	1
N01w1	Reactive arthr-acromioclav jt	1
EGTON436	Radiculopathy	1
N2422	Radiculitis unspecified	1
N3734	Radiation scoliosis	1
N3711	Radiation kyphosis	1
N0706	Radial tear of medial meniscus	1
N0717	Radial tear of lateral meniscus	1
N2204	Radial styloid tenosynovitis	1
N22yC	Pyogenic infec - tendon sheath	1
N010	Pyogenic arthritis	1
N0100	Pyogenic arthr.-site unspecif.	1
N0101	Pyogenic arthr.-shoulder regn.	1
N010y	Pyogenic arthr.-other specif.	1
N010x	Pyogenic arthr.-multiple sites	1
N010z	Pyogenic arthr.-NOS	1
S57z0	Pulled back muscle	1
OX848ML	Pulled Muscle /ox	1
E2601	Psychogenic Torticollis	1
N2373	Pseudosarcomatous fibromatosis	1
N33zC	Pseudarth after fusn/arthrodes	1
S5422	Prt tr,knee,post cruciate lgmt	1
N12C4	Prol lumb interv disc sciatic	1
N0010	Progressive systemic sclerosis	1
N2311	Progressive myositis ossific.	1
N3733	Progressive infant.idiop.scol.	1
N051B	Primary gonarthrosis, bilat	1
N050400	Primary general osteoarthrosis	1
N0504	Primary general osteoarthrosis	1
N0519	Primary coxarthrosis bilateral	1
N051C	Primary arthrosis of first carpometacarpal joints, bilateral	1
N2165	Prepatellar bursitis	1
N3736	Postural scoliosis	1
N3307	Postsurg malabsorp osteoporos	1
N3314	Postsur malab osteop+path frct	1
NyX	Postproc muscsk disord,unsp	1
N2313	Postop.heterotopic calcificat.	1
N3306	Postoophorectomy osteoporosis	1
N3312	Postoophorc osteopor+path frct	1
N3302	Postmenopausal osteoporosis	1
N331B	Postmenop osteopor+path fract	1
N0380	Postmeningococcal arthritis	1
N12Az	Postlaminectomy syndrome NOS	1
N12A	Postlaminectomy syndrome	1
N12A0	Postlaminectomy syndr.unspec.	1
N0381	Postinf arthropath in syphilis	1
N037	Postimmunization arthropathy	1
N013	Postdysenteric react arthrop	1
N0130	Postdys react arthrop-unspec	1
N0131	Postdys react arthrop-shoulder	1
N013y	Postdys react arthrop-oth spec	1
N013x	Postdys react arthrop-multiple	1
N013z	Postdys react arthrop NOS	1
16B4	Post-traumatic bruising	1
N052B	Post-traumatic arthrosis of first carpometacarpal joints, bilateral	1
N052C	Post-trauma gonarth, unilat	1
N052A	Post-traum gonarthrosis, bilat	1
N0529	Post-traum coxarthrosis, bilat	1
N3738	Post-surgical scoliosis	1
N3721	Post-laminectomy lordosis	1
N3712	Post-laminectomy kyphosis	1
N2314	Polymyositis ossificans	1
N004	Polymyositis	1

Read code	Description	Number of studies
N20*	Polymyalgia rheumatica	1
N20	Polymyalgia	1
N065-1	Polyarthropathy NEC	1
N065.11	Polyarthropathy NEC	1
N065	Polyarthropathy NEC	1
N065z	Polyarthritis	1
N065z00	Polyarthritis	1
N307z	Poliomyelitis osteopathy NOS	1
N3070	Polio.osteopathy-site unspecif	1
N3071	Polio.osteopathy-shoulder	1
N3078	Polio.osteopathy-other sites	1
N3079	Polio.osteopathy-multiple site	1
N0109	Pneumococc arthrit & polyarthr	1
N2179	Plantar fasciitis	1
N2209	Plant thorn synovitis	1
N2161	Pes anserinus tendin./bursitis	1
SJz-98	Peripheral nerve injury NOS	1
N21zz	Peripheral enthesopathy NOS	1
N21	Peripheral enthesopathies	1
N0705	Periph detach-medial meniscus	1
N0716	Periph detach-lateral meniscus	1
N303	Periostitis, no osteomyelitis	1
N303B	Periostitis, no osteomye-th sp	1
N303C	Periostitis, no osteomye-lu sp	1
N303A	Periostitis, no osteomye-Cx sp	1
N303z	Periostitis no osteomyel NOS	1
N3030	Periostitis - site unspecified	1
N3031	Periostitis - shoulder	1
N3038	Periostitis - other sites	1
N3039	Periostitis - multiple sites	1
N2120	Periarthritis of shoulder	1
N21z1	Periarthritis NOS	1
N3843	Pedicular spondylolisthesis	1
N0432	Pauciarticular juvenile R.A.	1
N0456	Pauciartic onset juv ch arth	1
N331y	Pathological fracture OS	1
N331z	Pathological fracture NOS	1
N082z	Pathological dislocation NOS	1
N331C	Pathological # cervical vert	1
N0820	Patholog.disloc.-site unspecif	1
N0821	Patholog.disloc.-shoulder	1
N0828	Patholog.disloc.-other specif.	1
N082A	Path disloc-shoulder joint	1
N082R	Path disloc-patellofem joint	1
N082B	Path disloc-oth joint-shoulder	1
N0829	Path disloc-multiple joints	1
N082Q	Path disloc-knee joint	1
N0536-1	Patellofemoral osteoarthritis	1
N0536	Patellofemoral osteoarthritis	1
N07y6	Patellofemoral maltracking	1
N09A	Patellofemoral disorder	1
N2266	Patellar tendon nontraum.rupt.	1
N2164	Patellar tendinitis	1
N33z9	Partial epiphyseal arrest	1
S5421	Part tr,knee,ant cruciate lgmt	1
N2114	Part thickn rotator cuff tear	1
S5411	Part tear,knee,mdl collat lgmt	1
S5401	Part tear,knee,lat collat lgmt	1
N1y2	Pars interarticular strss frct	1
N0704	Parr beak tear-post/med menisc	1
N0715	Parr beak tear-post/lat menisc	1
N2316	Paralytic calcific/ossif muscl	1
N243	Panniculitis unspecified	1
N136	Panniculitis of neck	1
N243z	Panniculitis NOS	1
N093z	Palindromic rheumatism NOS	1
N093	Palindromic rheumatism	1
N0930	Palindromic rheum.-site unspec	1
N0931	Palindromic rheum.-shoulder	1
N0938	Palindromic rheum.-other spec.	1
N0939	Palindromic rheum.-multip.site	1
N211z	Painful arc syndrome	1
N211z-1	Painful arc syndrome	1
EGTON224	Painful Shoulder	1

Read code	Description	Number of studies
EGTON279	Painful Right Knee	1
N131-1	Pain in cervical spine	1
N245-9	Pain in buttock	1
N2453	Pain in arm	1
OX7280AD	Pain Neck /ox	1
OX7873E	Pain Knee /ox	1
N245-95	Pain In Right Leg	1
N245-97	Pain In Right Arm	1
N245-96	Pain In Left Leg	1
N3101	Paget's disease-thoracic spine	1
N3106	Paget's disease-scapula	1
N310F	Paget's disease-patella	1
N310x	Paget's disease-multiple sites	1
N3102	Paget's disease-lumbar spine	1
N3105	Paget's disease-clavicle	1
N3100	Paget's disease-cervical spine	1
N310y	Paget's disease OS	1
N310z	Paget's disease NOS	1
N122-1	PID - prolapsed lumbar disc	1
N129	PID - prol i/v disc + myelop	1
S102y	Othr spec clsd # thorac vert	1
S411y	Othr opn trmtc disloctn shlder	1
S410y	Othr cls trmtc disloc shoulder	1
SK12z	Othershould/upperarminj.NOS	1
SE08	Othercontusionneck	1
N06..00	Other/unspecif. arthropathies	1
N12z2	Other thoracic disc disorders	1
N22	Other synovium/tendon/bursa	1
N22y	Other synovium/tendon/bursa	1
N096B	Other symptoms - sternoclav jt	1
N096A	Other symptoms - shoulder	1
N096M	Other symptoms - knee	1
N096D	Other symptoms - elbow	1
N096C	Other symptoms - acromioclav j	1
SD9y	Other superficial injury, without mention of infection, NOS	1
S5y	Other sprains and strains	1
S5yz	Other sprains NOS	1
N11y	Other spondyloses/allied dis.	1
S5W	Other specified tendon rupture	1
S54w	Other specified knee sprain	1
SK1	Other specified injury	1
N06y	Other specified arthropathy	1
N233	Other specific muscle disorder	1
N04y	Other specif.infl.polyarthrop.	1
N32yz	Other spec.osteochondrop.NOS	1
N04yz	Other spec.infl.polyarthr.NOS	1
N00y	Other spec.diff.collagen dis.	1
N06y0	Other spec.arthr.-site unspec.	1
N06y1	Other spec.arthr.-shoulder	1
N06y8	Other spec.arthr.-other specif	1
S5yy	Other spec sprains and strains	1
S50w	Other shoulder sprain	1
SK122	Other shoulder injuries	1
N212	Other shoulder affections NEC	1
N212z	Other shoulder affect.NEC NOS	1
SK121	Other scapular region injuries	1
N042	Other rh.arthr.+visc/syst.dis.	1
N3722	Other post-surgical lordosis	1
N21y	Other periph. enthesopathies	1
N3272	Other osteochondr dissec-knee	1
S466	Other opn trm dslctn knee	1
S497	Other open trmtc dislocation	1
S49Fz	Other open subluxation NOS	1
S4J3	Other open #-subluxation	1
S4J1	Other open #-dislocation	1
N226z	Other nontraumatic tendon rupt	1
SK10y	Other neck injuries	1
SK1x	Other multiple injuries	1
N12z3	Other lumbar disc disorders	1
N07yy	Other knee lig. old disruption	1
SK170	Other knee injury	1
N368	Other knee deformity	1
N045	Other juvenile arthritis	1
N326	Other juven.osteochondroses	1

Read code	Description	Number of studies
N0960	Other joint sympt.-site unspec	1
N0961	Other joint sympt.-shoulder	1
N09y1	Other joint dis.-shoulder	1
N08yz	Other joint derange.NEC NOS	1
SK112	Other interscapular injuries	1
N07yz	Other intern.knee derang.NOS	1
SK1z	Other injury NOS	1
N10y	Other inflamm.spondylopathies	1
N10yz	Other inflamm.spondylop.NOS	1
N30y	Other infections+bone disease	1
N03x	Other general dis.+arthropathy	1
N237z	Other fibromatoses NOS	1
N237	Other fibromatoses	1
SK10z	Other face and neck injuries NOS	1
S49z	Other dislocation NOS	1
N12z0	Other disc disorders unspecif.	1
N08	Other derangement of joint	1
N36y	Other deformity of bone	1
N37y	Other curvatures of spine	1
N02yz	Other crystal arthropathy NOS	1
N02y	Other crystal arthropathies	1
N02y0	Other crystal arth.-site unsp.	1
N02y1	Other crystal arth.-shoulder	1
N02yy	Other crystal arth.-other spec	1
N02yx	Other crystal arth.-mult.sites	1
S465	Other cls trm dslctn knee	1
S49E	Other closed traumatic sublux	1
S4J2	Other closed #-sublux	1
S4J0	Other closed #-dislocation	1
N13yz	Other cervical syndromes NOS	1
N13y	Other cervical syndromes	1
N12z1	Other cervical disc disorders	1
N33	Other bone/cartilage disorders	1
N31y	Other bone involve.in dis.EC	1
SK114	Other back injuries	1
N374X	Other and unspecified kyphosis	1
N06	Other and unspecified arthropathies	1
S462	Other acute meniscus tear	1
N38yz	Other acquired deformity NOS	1
N38y	Other acquired deformity	1
N38	Other acquired deformity	1
S4J	Other #-dslc or subluxation	1
N08y0	Oth.joint deran.NEC-site unsp.	1
N08y1	Oth.joint deran.NEC-shoulder	1
N08y8	Oth.joint deran.NEC-other spec	1
N08y9	Oth.joint deran.NEC-mult.sites	1
N30y0	Oth.inf.+bone dis-site unspec.	1
N30y1	Oth.inf.+bone dis-shoulder	1
N30y8	Oth.inf.+bone dis-other sites	1
N30y9	Oth.inf.+bone dis-multip.site	1
N30yz	Oth.inf.+bone dis-NOS	1
N07y	Oth. internal knee derangement	1
S49	Oth, mlti+ill-def dislc/sublux	1
N0401	Oth rheumatoid arthritis-spine	1
S49F	Oth open traumatic subluxation	1
SRy	Oth inj inv mult body reg NEC	1
S496	Oth cls trmatic dislocation	1
S49Ez	Oth closed subluxation NOS	1
N33B	Osteoradionecrosis	1
N3746	Osteoporotic kyphosis	1
N3300	Osteoporosis unspecified	1
N330C	Osteoporosis localized spine	1
N330A	Osteoporosis in endocr disord	1
N330z	Osteoporosis NOS	1
N330	Osteoporosis	1
N330D	Osteoporos due corticosteroid	1
N3309	Osteopor,multiple myelomatosis	1
N3319	Osteopor path # thor vertebrae	1
N3318	Osteopor path # lumb vertebrae	1
N331A	Osteopor path # cerv vertebrae	1
N3313	Osteopor of disuse + path frct	1
N09B	Osteophyte	1
N307	Osteopathy from poliomyelitis	1
ASDFGOS1	Osteopaenia	1

Read code	Description	Number of studies
N334B	Osteonecrosis in caisson dis	1
N3349	Osteonecrosis due to drugs	1
N334A	Osteonecr due to prev trauma	1
N334C	Osteonecr due haemoglobinopath	1
N30	Osteomyelitis/periostitis	1
N302a	Osteomyelitis of vertebra	1
N302	Osteomyelitis NOS	1
N33zH	Osteolytic lesion	1
N33zD	Osteolysis	1
N32z3	Osteochondrosis NOS	1
N32z	Osteochondropathy NOS	1
N32zz	Osteochondropathy NOS	1
N32	Osteochondropathies	1
N32z2	Osteochondritis of knee	1
N3270	Osteochondritis dissec-patella	1
N327y	Osteochondr dissec-other site	1
N3274	Osteochondr dissec-capitellum	1
N327	Osteochond dissecans	1
OX7130E	Osteoarthrosis Shoulder /ox	1
OX7130B	Osteoarthrosis Knee(S) /ox	1
OX7131A	Osteoarthrosis Cervical Spine /ox	1
N11z	Osteoarthritis spine	1
N11D1	Osteoarthritis of thoracic spine	1
N11D3	Osteoarthritis of spine NOS	1
N11-2	Osteoarthritis of spine	1
N11D	Osteoarthritis of spine	1
N11D2	Osteoarthritis of lumbar spine	1
N11D0	Osteoarthritis of cervical spine	1
N110-2	Osteoarthritis cervical spine	1
N05z0	Osteoarthritis NOS-site unspec	1
N05z000	Osteoarthritis NOS-site unspec	1
N05z7	Osteoarthritis NOS-ankle/foot	1
N05zM	Osteoarthritis NOS, of tibio-fibular joint	1
N05zQ	Osteoarthritis NOS, of talonavicular joint	1
N05zK	Osteoarthritis NOS, of sacro-iliac joint	1
N05zR	Osteoarthritis NOS, of other tarsal joint	1
N05zF	Osteoarthritis NOS, of metacarpophalangeal joint	1
N05zT	Osteoarthritis NOS, of lesser metatarsophalangeal joint	1
N05zU	Osteoarthritis NOS, of interphalangeal joint of toe	1
N05zD	Osteoarthritis NOS, of distal radio-ulnar joint	1
N05zE	Osteoarthritis NOS of wrist	1
N05z4	Osteoarthritis NOS of the hand	1
N05z9	Osteoarthritis NOS of shoulder	1
N05zL	Osteoarthritis NOS of knee	1
N05zJ	Osteoarthritis NOS of hip	1
N05zC	Osteoarthritis NOS of elbow	1
N05zN	Osteoarthritis NOS of ankle	1
N05zz00	Osteoarthritis NOS	1
N05zz	Osteoarthritis NOS	1
N05z1	Osteoarthritis -shoulder joint	1
N05z800	Osteoarthritis - other joint	1
N05z8	Osteoarthritis - other joint	1
N05z6-99	Osteoarthritis - knee joint	1
N05..11	Osteoarthritis	1
N094K	Osteoarthritis	1
N05	Osteoarthritis	1
N310	Osteitis deformans-Paget's dis	1
N311	Osteitis deformans+disease EC	1
N3350	Osteitis condensans ilii	1
N335	Osteitis condensans	1
N31	Osteit.deform./osteop.+dis.EC	1
N3110	Osteit deformans,neoplast dis	1
N3y03	Osseous stenos of neural canal	1
N3y06	Oss/sublx sten intervert foram	1
S900z	Opn wound shoulder+up limb,NOS	1
SA10	Opn wnd kneelg+ank-no cmplctn	1
S46A6	Opn trmtc sublux,head fibula	1
S413z	Opn trmtc sublux shoulder NOS	1
S468	Opn trmtc sublux pat-fem jt	1
S46A0	Opn trmtc sublux knee jt,unsp	1
S46A2	Opn trmtc sublux knee jt,post	1
S46A4	Opn trmtc sublux knee jt,ltrl	1
S46A1	Opn trmtc sublux knee jt,ant	1
S46A	Opn trmtc sublux knee jt	1

Read code	Description	Number of studies
S4112	Opn trmtc dslctn shldr jt,post	1
S411z	Opn trmtc dislоctn shouldr NOS	1
S4110	Opn trmtc dislctn shoulder jnt	1
S49F4	Opn trm sublux,st-clav jt,post	1
S49F3	Opn trm sublux,st-clav jt,ant	1
S49F2	Opn trm sublux st-clav jt	1
S4681	Opn trm sublux pat-fem jt,med	1
S4680	Opn trm sublux pat-fem jt,ltrl	1
S49F5	Opn trm sublux laryngl cartlge	1
S46A5	Opn trm sublux knee jt,rotatry	1
S46A3	Opn trm sublux knee jt,medial	1
S4131	Opn trm sublux acromio-clav jt	1
S4666	Opn trm dslctn, head fibula	1
S464	Opn trm dslctn patello-fem jt	1
S4641	Opn trm dslctn pat-fem jt,med	1
S4640	Opn trm dslctn pat-fem jt lat	1
S4660	Opn trm dslctn knee, unspec	1
S4664	Opn trm dslctn knee jt,lateral	1
S4662	Opn trm dslctn knee jt, post	1
S4663	Opn trm dslctn knee jt, medial	1
S4661	Opn trm dslctn knee jt, ant	1
S4665	Opn trm dslct knee jt,rotatory	1
S4973	Opn trm dslc,stern-clav jt,ant	1
S4972	Opn trm dslc sterno-clav jt	1
S4974	Opn trm dsl,stern-clav jt,post	1
S4114	Opn trm dislc acromio-clav jt	1
S413	Opn traumtc subluxatn shoulder	1
S4130	Opn traumtc sublux shouldr jnt	1
S411	Opn traumtc dislоctn shoulder	1
S4115	Opn traumatic dislоctn scapula	1
S49B	Opn sublux thrcic+lmbr vertbra	1
S49B1	Opn sublux thoracic spine	1
S499x	Opn sublux mlti cerv vertebrae	1
S499z	Opn sublux cerv vertebra NOS	1
S4991	Opn sublux atlanto-occipitl jt	1
S493C	Opn spnl dslc+cauda equina lsn	1
S4934	Opn spnl dslc+ant thrc crd lsn	1
S4939	Opn spnl dslc+ant lmbr crd lsn	1
S491B	Opn spnl dslc+ant cerv crd lsn	1
S493B	Opn spnl dsl+post lmbr crd lsn	1
S491D	Opn spnl dsl+post cerv crd lsn	1
S4933	Opn spnl dsl+comp thrc crd lsn	1
S4938	Opn spnl dsl+comp lmbr crd lsn	1
S4919	Opn spnl dsl+cerv crd lsn,unsp	1
S4932	Opn spn dslc+thrc crd lsn,unsp	1
S4936	Opn spn dslc+post thrc crd lsn	1
S491C	Opn spn dslc+ctrl cerv crd lsn	1
S491A	Opn spn dslc+comp cerv crd lsn	1
S4935	Opn spn dslc+cent thrc crd lsn	1
S493A	Opn spn dslc+cent lmbr crd lsn	1
S1150	Opn spn # + unsp lumb crd lesn	1
S1154	Opn spn # + post lumb crd lesn	1
S1151	Opn spn # + comp lumb crd lesn	1
S1153	Opn spn # + cent lumb crd lesn	1
S1155	Opn spn # + cauda equina lesn	1
S1152	Opn spn # + ant lumbr crd lesn	1
S5P1z	Opn dvsn,thyroid regn lgmt NOS	1
S5P1	Opn dvsn,thyroid region lgmt	1
S5P12	Opn dvsn,thyroid cartilge lgmt	1
S5P30	Opn dvsn,sternoclavicular lgmt	1
S5N	Opn dvsn,lgmt other part back	1
S5P11	Opn dvsn,cricothyroid ligament	1
S5P10	Opn dvsn,cricoarytenoid lgmt	1
S5K1	Opn dvsn mdl collat lgmt knee	1
S5K0	Opn dvsn lat collat lgmt knee	1
S5F1	Opn dvsn coracoclavicular lgmt	1
S5F0	Opn dvsn acromioclavic lgmt	1
S5K2	Opn dvs post cruciate lgm knee	1
S5K3	Opn dvs ant cruciate lgmt knee	1
S4931	Opn dslc thoracic spine	1
S4975	Opn dslc laryngl cartilage	1
S1034	Opn # thorc vert-trnsvrse prcs	1
S1032	Opn # thorc vert-spondylolysis	1
S1033	Opn # thorc vert-spinous prcs	1

Read code	Description	Number of studies
S1036	Opn # thor vert-tricolumnar	1
S1035	Opn # thor vert-posterior arch	1
S1055	Opn # lumb vert,posterior arch	1
S1054	Opn # lumb vert, trnsvrse prcs	1
S1056	Opn # lumb vert, tricolumnar	1
S1052	Opn # lumb vert, spondylolysis	1
S1053	Opn # lumb vert, spinous prcs	1
S101L	Opn # cerv vert, trnsvrse prcs	1
S101N	Opn # cerv vert, tricolumnar	1
S101J	Opn # cerv vert, spondylolysis	1
S101K	Opn # cerv vert, spinous prcs	1
S101M	Opn # cerv vert, post arch	1
S101D	Opn # axis, trnsvrse process	1
S1018	Opn # atlas-isol arch/art prcs	1
S89z	Open wounds NOS	1
S90	Open wound shoulder/upper limb	1
S9020	Open wound shoulder+tendon inv	1
S9010	Open wound shoulder+complicat.	1
S9021	Open wound scapular+tendon inv	1
S900	Open wound of shoulder/upper limb without complication	1
S9000	Open wound of shoulder region	1
S87	Open wound of sacroiliac reg.	1
S84	Open wound of neck	1
SA100	Open wound of knee	1
S86	Open wound of back	1
SA110	Open wound knee+complication	1
S8z	Open wound head/neck/trunk NOS	1
S8	Open wound head/neck/trunk	1
S113z	Open thoracic #+cord lesn.NOS	1
S113	Open thoracic #+cord lesion	1
S49Dz	Open subluxation of spine NOS	1
S49B0	Open subluxation lumbar spine	1
S4998	Open subluxation C7/T1	1
S4997	Open subluxation C6/C7	1
S4996	Open subluxation C5/C6	1
S4995	Open subluxation C4/C5	1
S4994	Open subluxation C3/C4	1
S4993	Open subluxation C2/C3	1
S49D0	Open sublux spine, unspecified	1
S49D	Open sublux other vertebra	1
S4990	Open sublux cerv spine, unsp	1
S499	Open sublux cerv spine	1
S4992	Open sublux atlanto-axial jt	1
S49y	Open multiple/ill-def.disloc.	1
S2921	Open mult fract clav scap hum	1
S115	Open lumbar # + cord lesion	1
S2115	Open fracture scapula, spine	1
S2116	Open fracture scapula, neck	1
S2113	Open fracture scapula, glenoid	1
S2114	Open fracture scapula, blade	1
S321	Open fracture of the patella	1
S105	Open fracture lumbar vertebra	1
S1260	Open fracture larynx	1
S2012	Open fracture clavicle, shaft	1
S101	Open fracture cervical spine	1
S1012	Open fracture axis	1
S1011	Open fracture atlas	1
S5N0	Open dvsn, neck ligament	1
S5Fz	Open dvsn shoulder lgmt NOS	1
S4911	Open dslc atlanto-occipital jt	1
S4912	Open dslc atlanto-axial jt	1
S5Nz	Open divisn, back ligament NOS	1
S5N1	Open division,thoracic lgmt	1
S5P	Open division, other ligament	1
S5Pz	Open division, other lig NOS	1
S5N2	Open division, lumbar ligament	1
S5F	Open division shoulder lgmt	1
S5Ky	Open division other knee lgmt	1
S5M5	Open division lumbosacral lgmt	1
S5K	Open division ligament knee	1
S5Kz	Open division knee lgmt NOS	1
S5M4	Open division iliolumbar lgmt	1
S4950	Open dislocation spine unspec.	1
S495z	Open dislocation spine NOS	1

Read code	Description	Number of studies
S491	Open dislocation of neck	1
S4930	Open dislocation lumbar spine	1
S466z	Open dislocation knee NOS	1
S497z	Open dislocation NOS	1
S4918	Open dislocation C7/T1	1
S4917	Open dislocation C6/C7	1
S4916	Open dislocation C5/C6	1
S4915	Open dislocation C4/C5	1
S4914	Open dislocation C3/C4	1
S4913	Open dislocation C2/C3	1
S493	Open disloc.thoracic/lumbar	1
S493z	Open disloc.thorac./lumbar NOS	1
S495	Open disloc.other vertebra	1
S491x	Open disloc.mult.cerv.vertebra	1
S491z	Open disloc.cervical vert.NOS	1
S4910	Open disloc.cerv.spine unspec.	1
S111z	Open cervical#+cord lesion NOS	1
S111	Open cervical #+cord lesion	1
S1263	Open #trachea	1
S1262	Open #thyroid cartilage	1
S11y	Open #spine+cord lesion unsp.	1
S2110	Open #scapula-unspecified	1
S211z	Open #scapula NOS	1
S126z	Open #larynx/trachea NOS	1
S1261	Open #hyoid bone	1
S2010	Open #clavicle unspecified	1
S201z	Open #clavicle NOS	1
S3z1	Open #bones unspecified	1
S4F7	Open #-sublux,patello-fem jt	1
S4J33	Open #-sublux st-clav jt,post	1
S4J32	Open #-sublux st-clav jt,ant	1
S4A30	Open #-sublux shoulder joint	1
S4A3	Open #-sublux shoulder	1
S4F3	Open #-sublux knee joint	1
S4A31	Open #-sublux acrom-clav joint	1
S4F5	Open #-dslc,patello-fem jt	1
S4F1	Open #-dslc, knee joint	1
S4J13	Open #-dslc st-clav jt,post	1
S4J12	Open #-dslc st-clav jt,ant	1
S4A10	Open #-dslc shoulder joint	1
S4A1	Open #-dslc shoulder	1
S4A11	Open #-dslc acrom-clav joint	1
S1010	Open # unsp cerv vertebra	1
S103	Open # thoracic vertebra	1
S1031	Open # thorac vert, wedge	1
S1030	Open # thorac vert, burst	1
S1013	Open # third cerv vertebra	1
S10y	Open # spine, unspecif	1
S1016	Open # sixth cerv vertebra	1
S1017	Open # seventh cerv vert	1
S2112	Open # scapula, coracoid	1
S2111	Open # scapula, acromion	1
S211	Open # scapula	1
S3213	Open # patella, vertical	1
S3210	Open # patella, transverse	1
S3214	Open # patella, stellate	1
S3211	Open # patella, proximal pole	1
S3212	Open # patella, distal pole	1
S1051	Open # lumbar vert, wedge	1
S1050	Open # lumbar vert, burst	1
S126	Open # larynx and trachea	1
S1014	Open # fourth cerv vertebra	1
S1015	Open # fifth cerv vertebra	1
S2011	Open # clavicle, medial end	1
S2013	Open # clavicle, lateral end	1
S201	Open # clavicle	1
S101H	Open # cerv vert, wedge	1
S101G	Open # cerv vert, burst	1
S101z	Open # cerv spine NOS	1
S101F	Open # axis, tricolumnar	1
S101B	Open # axis, spondylolysis	1
S101C	Open # axis, spinous procss	1
S101E	Open # axis, posterior arch	1
S101A	Open # axis, odontoid prcss	1

Read code	Description	Number of studies
S1019	Open # atlas, comminuted	1
S4113	Op tr ds shd jt,inf(infr-glen)	1
S4111	Op tr dis shld jt,ant(sub-cor)	1
S49Bz	Op sublx thrc+lmbr vertbra NOS	1
S49B2	Op spn sublx+thrc crd lsn,unsp	1
S49B6	Op spn sublx+post thrc crd lsn	1
S49BB	Op spn sublx+post lmbr crd lsn	1
S49B7	Op spn sublx+lmbr crd lsn,unsp	1
S49B3	Op spn sublx+comp thrc crd lsn	1
S49B8	Op spn sublx+comp lmbr crd lsn	1
S499A	Op spn sublx+comp cerv crd lsn	1
S499C	Op spn sublx+cntrl crv crd lsn	1
S4999	Op spn sublx+cerv crd lsn,unsp	1
S49B5	Op spn sublx+cent thrc crd lsn	1
S49BA	Op spn sublx+cent lmbr crd lsn	1
S49BC	Op spn sublx+cauda equina lsn	1
S49B4	Op spn sublx+ant thrc crd lsn	1
S499D	Op spn sublux+post crv crd lsn	1
S49B9	Op spn sublux+ant lmbr crd lsn	1
S499B	Op spn sublux+ant cerv crd lsn	1
S4937	Op spn dsl+lmbr crd lsn unsp	1
S1134	Op spn #+pst thor crd lsn,T1-6	1
S1133	Op spn #+cnt thor crd lsn,T1-6	1
S1132	Op spn #+ant thor crd lsn,T1-6	1
S115z	Op spn # incmp lmb crd lsn NOS	1
S1130	Op sp #+unsp thor crd lsn,T1-6	1
S1136	Op sp #+unsp thor cd lsn,T7-12	1
S113A	Op sp #+pst thor crd lsn,T7-12	1
S1139	Op sp #+cnt thor crd lsn,T7-12	1
S1131	Op sp #+cmpl thor crd lsn,T1-6	1
S1137	Op sp #+cmp thor crd lsn,T7-12	1
S1138	Op sp #+ant thor crd lsn,T7-12	1
S1501	Op multi fractur of thor spine	1
SR161	Op fract/th wth lw bck+plv+lmb	1
SR101	Op fract invol head with neck	1
S113B	Op # T7-12incomp cord lsn NOS	1
S1135	Op # T1-6 incomp cord lsn NOS	1
S1116	Op # C5-7 unspec cord lesion	1
S111A	Op # C5-7 posterior cord lesn	1
S111B	Op # C5-7 incomp cord les NOS	1
S1117	Op # C5-7 compl cord lesion	1
S1119	Op # C5-7 central cord les	1
S1118	Op # C5-7 anterior cord les	1
S1110	Op # C1-C4 unspec cord les	1
S1114	Op # C1-4 post cord lesion	1
S1115	Op # C1-4 cord les. NOS	1
S1111	Op # C1-4 compl cord lesion	1
S1113	Op # C1-4 cent cord lesion	1
S1112	Op # C1-4 ant cord lesion	1
N1120	One lev th spondyl-no myelop	1
N11B0	One lev th spondyl + radiculop	1
N1130	One lev th spondyl + myelop	1
N1140	One lev lumbsac spond-no myelo	1
N1150	One lev lumbsac spond + myelop	1
N1100	One lev Cx spondyl-no myelop	1
N1190	One lev Cx spondyl + radiculop	1
N1110	One lev Cx spondyl + myelop	1
N0542	Oligoarticular osteoarthritis, unspecified, of upper arm	1
N0545	Oligoarticular osteoarthritis, unspecified, of the pelvic region and thigh	1
N0546	Oligoarticular osteoarthritis, unspecified, of lower leg	1
N0544	Oligoarticular osteoarthritis, unspecified, of hand	1
N0543	Oligoarticular osteoarthritis, unspecified, of forearm	1
N0547	Oligoarticular osteoarthritis, unspecified, of ankle and foot	1
N054	Oligoarticular OA unspecified	1
N0541	Oligoartic OA, unspec-shoulder	1
N0549	Oligoartic OA, unspec-multiple	1
N0540	Oligoartic OA, unsp-unsp sites	1
N0548	Oligoartic OA unspec-oth site	1
N2133	Olecranon bursitis	1
N0720	Old torn meniscus of knee	1
N070B	Old tear post horn med menis	1
N070A	Old tear of medial meniscus	1
N071C	Old tear of lateral meniscus	1

Read code	Description	Number of studies
N07y9	Old post/lat caps complex tear	1
N07y3	Old post.cruciate lig.disrupt.	1
N07yF	Old part tear post cruciat lig	1
N07yA	Old part tear med collat lig	1
N07y7	Old part tear lat collat lig	1
N07yD	Old part tear ant cruciate lig	1
N07y1	Old med.collat.lig.disruption	1
N07yC	Old med capsular complex tear	1
N07y0	Old lat.collat.lig.disruption	1
N07yB	Old compl tear med collat lig	1
N07y8	Old compl tear lat collat lig	1
N07yG	Old comp tear post cruciat lig	1
N07yE	Old comp tear ant cruciate lig	1
N07y4	Old capsular knee lig.disrupt.	1
N0701	Old bucket handle tear-medial	1
N0711	Old bucket handle tear-lat men	1
N07y2	Old ant.cruciate lig.disrupt.	1
N067	Ochronotic arthropathy	1
N054z	OA,1 site +,unspecified NOS	1
N05zP	OA NOS-subtalar joint	1
N05zA	OA NOS-sternoclavicular joint	1
N05zB	OA NOS-acromioclavicular join	1
N05zG	OA NOS-PIP joint of finger	1
N05zH	OA NOS-DIP joint of finger	1
N05zS	OA NOS-1st MTP joint	1
N3381	Nonunion of fracture	1
N226	Nontraumatic tendon subluxatn	1
N23y2	Nontraumatic muscle rupture	1
N2260	Nontraum.unspec.tendon rupture	1
N392	Nonallopathic lesion-thoracic	1
N393	Nonallopathic lesion-lumbar	1
N391	Nonallopathic lesion-cervical	1
N082Z	Non-trau subl acromiocl joint	1
N044	Nodular fibrositis-chr. rheum.	1
N2372	Nodular fasciitis	1
16A1	No stiff neck	1
16C1	No backache	1
1229	No FH: Osteoporosis	1
N2471	Night cramps	1
N11y2	Neuropathic spondylopathy	1
N2423	Neuropathic pain	1
N374B	Neuromuscular scoliosis	1
N3749	Neuromuscular lordosis	1
N3745	Neuromuscular kyphosis	1
N14A	Neurogenic claudication	1
N2421	Neuritis unspecified	1
N2420	Neuralgia unspecified	1
N242z	Neuralg./neurit./radiculit.NOS	1
N242	Neuralg./neurit./radicul.unsp.	1
SJ	Nerve/spinal cord injuries	1
EMISNQNE5	Nerve root pain present	1
SJz	Nerve and spinal cord injury NOS	1
S5700	Neck sprain unspecified	1
S570z	Neck sprain NOS	1
S570	Neck sprain	1
N12D	Narrowing disc space	1
N2332	Myositis in sarcoidosis	1
N2321	Myofibrosis	1
N241-97	Myalgia/myositis - shoulder	1
EGTON307	Myalgia	1
EMISNQMU15	Musculoskeletal symptom	1
EMISNQMU5	Musculoskeletal pain severe	1
EMISNQMU2	Musculoskeletal pain present	1
EMISNQMU4	Musculoskeletal pain moderate	1
N096-2	Musculoskeletal pain - joints	1
MAWBYMU1	Musculoskeletal Symptoms	1
N3	Musculosk.inflam/deform.+other	1
N232z	Muscle wasting/atrophy NEC NOS	1
N232	Muscle wasting and disuse atrophy NEC	1
N2322	Muscle wasting NEC	1
UNMAPM4AB	Muscle strain	1
N23yD	Muscle strain	1
N2410-2	Muscle pain	1
N231	Muscle ossification	1

Read code	Description	Number of studies
S5yz1	Muscle injury / strain	1
N238	Muscle contracture	1
N231z	Muscle calcif./ossificat.NOS	1
N230D	Muscle abscess-shoulder	1
N230B	Muscle abscess-neck	1
N230C	Muscle abscess-back	1
N230A	Muscle abscess	1
ASDFGMU2	Muscle Symptoms	1
EGTON110	Muscle Injury	1
M4A8	Muscle Injury	1
N2310	Musc.calcif./ossif.unspecified	1
N0719	Multiple tears-lat meniscus	1
N0708	Multiple tears of medial meniscus	1
S101x	Multiple open # cerv vert	1
SR1z	Multiple fractures unspecified	1
S100x	Multiple clsd # cerv vert	1
N099A	Multiple clicking joints	1
S3y	Multiple #legs/arms/ribs/stern	1
S10A2	Multip fracture/cervical spin	1
N11C2	Multi lev lumbsac spond+radicu	1
S150	Multi fractures/thoracic spine	1
S3y1	Mult.open #legs/arms/ribs	1
S3y0	Mult.closed #legs/arms/ribs	1
N1122	Mult lev th spondyl-no myelop	1
N11B2	Mult lev th spondyl+radiculop	1
N1132	Mult lev th spondyl + myelop	1
N1142	Mult lev lumbsac spond-no myel	1
N1152	Mult lev lumbsac spond + myelo	1
N1102	Mult lev Cx spondyl-no myelop	1
N1192	Mult lev Cx spondyl+radiculop	1
N1112	Mult lev Cx spondyl + myelop	1
S10B6	Mult fractur/lumbar spine+pelv	1
S292	Mult fract/clav,scapula+humrus	1
1D17	Morning stiffness - joint	1
N3323	Monostotic fibrous dysplasia	1
N0433	Monarticular juvenile R.A.	1
EMISNQMI188	Mixed connective tissue disease	1
OX6954MC	Mixed Connective Tissue Disease /ox	1
N2224	Miners' knee	1
N2172	Metatarsalgia NOS	1
N063.11	Menopausal arthritis	1
N063	Menopausal arthritis	1
N072	Meniscus derangement NEC	1
N070	Medial meniscus derangement	1
N070z	Medial meniscus derange.NOS	1
N0703	Medial menisc.post.horn derang	1
N0700	Medial menisc.derang.unspecif	1
N0702	Medial menisc.ant.horn derang.	1
N2131	Medial epicondylitis - elbow	1
16CA	Mechanical low back pain	1
N3380	Malunion of fracture	1
N338	Malunion and nonunion of fracture	1
N11C	Lumbosacral spondylosis with radiculopathy	1
N115	Lumbosacral spond.+ myelopathy	1
SJ35	Lumbosacral plexus injury	1
N1441	Lumbosacral neuritis unspecif.	1
N1463	Lumbosacral instability	1
N1460	Lumbosacral ankylosis	1
N114-2	Lumbar spondylosis	1
N148C	Lumbar spine instability	1
N1486	Lumbar spine ankylosis	1
N1402	Lumbar spinal stenosis	1
N12A3	Lumbar postlaminectomy syndr.	1
SJ321	Lumbar nerve root injury - L2	1
N12zC	Lumbar discitis	1
N122	Lumbar disc displacement	1
N1293	Lumbar disc disord.+myelopathy	1
N127	Lumbar disc degeneration	1
S572	Lumbar back sprain	1
N1420	Lumbago with sciatica	1
N142-4	Lumbago	1
N140A	Lu spin stenos due to oth dis	1
N12C2	Lu disc prolapse+radiculopathy	1
N12B2	Lu disc prolapse + myelopathy	1

Read code	Description	Number of studies
N12C3	Lu disc prol+caud eq compress	1
N142-1	Low back pain	1
EGTON264	Low Back Pain	1
N374W	Lordosis unspecified	1
N3747	Lordosis in skeletal dysplasia	1
N3748	Lordosis in hip disease	1
N3742	Lordosis + other condition	1
N0818	Loose joint body-multip joints	1
N081z	Loose joint body (ex.knee)NOS	1
N081A	Loose body, oth joint-shoulder	1
N0811	Loose body joint-shoulder	1
N0819	Loose body in shoulder joint	1
N073	Loose body in knee	1
N081	Loose body in joint-excl.knee	1
N0817	Loose body in joint, joint OS	1
N0810	Loose body in joint	1
N07yH	Locking knee	1
N07y5	Locked knee	1
N0522	Localised, secondary osteoarthritis of the upper arm	1
N0525	Localised, secondary osteoarthritis of the pelvic region and thigh	1
N0526	Localised, secondary osteoarthritis of the lower leg	1
N0524	Localised, secondary osteoarthritis of the hand	1
N0523	Localised, secondary osteoarthritis of the forearm	1
N0527	Localised, secondary osteoarthritis of the ankle and foot	1
N051E	Localised, primary osteoarthritis of toe	1
N0512	Localised, primary osteoarthritis of the upper arm	1
N0515	Localised, primary osteoarthritis of the pelvic region and thigh	1
N0513	Localised, primary osteoarthritis of the forearm	1
N0517	Localised, primary osteoarthritis of the ankle and foot	1
N051F	Localised, primary osteoarthritis of elbow	1
N052z	Localised secondary OA NOS	1
N051z	Localised primary OA NOS	1
N0532	Localised osteoarthritis, unspecified, of the upper arm	1
N0537	Localised osteoarthritis, unspecified, of the ankle and foot	1
N053z	Localised OA unspecified NOS	1
N053	Localised OA unspecified	1
N052	Local.secondary osteoarthritis	1
N0520	Local.secondary OA-site unsp.	1
N0521	Local.secondary OA-shoulder	1
N0528	Local.secondary OA-other spec.	1
N051	Local.primary osteoarthritis	1
N0510	Local.primary OA-site unspec.	1
N0511	Local.primary OA-shoulder regn	1
N0518	Local.primary OA-other specif	1
N0516	Local.primary OA-lower leg	1
N0514	Local.primary OA-hand	1
N0530	Local.OA unsp.-site unspecif.	1
N0531	Local.OA unsp.-shoulder region	1
N0538	Local.OA unsp.-other specified	1
N0534	Local.OA unsp.-hand	1
N0533	Local.OA unsp.-forearm	1
N051D	Local prim osteoarth wrist	1
N3308	Local osteoporosis - Lequesne	1
S5z	Ligament sprain NOS	1
N0001	Libman-Sacks disease	1
N245-6	Leg pain	1
N234	Laxity of ligament	1
SJ43	Latrl cutaneous branch T12 inj	1
N071	Lateral meniscus derangement	1
N0714	Lateral meniscus derangem.NOS	1
N0713	Lateral menisc.post.horn deran	1
N0710	Lateral menisc.derang.unspecif	1
N0712	Lateral menisc.ant.horn derang	1
N2132	Lateral epicondylitis of the elbow	1
MHTBALA9	Lateral Patella Release	1
SC08	Late effect-tendon injury	1
SC05	Late effect-mult./other #bones	1
SC06	Late effect-dislocation	1
SC01	Late effect-#spine-no cord les	1
SC011	Late effect # thoracic vert	1
SC012	Late effect # lumbar vertebra	1
SC010	Late effect # cervic vertebra	1
EGTON119	Laceration Nos	1
N3744	Kyphosis in skeletal dysplasia	1

Read code	Description	Number of studies
N3713	Kyphosis due to oth treatment	1
N3741	Kyphosis + other condition	1
N373z	Kyphoscoliosis or scoliosis NOS	1
N373	Kyphoscoliosis and scoliosis	1
N3241	Kohler's dis.(prim.patell.ctr)	1
N0956	Knee stiff	1
S54y	Knee sprain NOS	1
S54	Knee sprain	1
N0106	Knee pyogenic arthritis	1
N0826	Knee pathological dislocation	1
1M10	Knee pain	1
N05z6	Knee osteoarthritis NOS	1
N05z6-1	Knee osteoarthritis NOS	1
N0946-1	Knee joint pain	1
N0946	Knee joint pain	1
N0846	Knee joint contracture	1
N0856	Knee joint ankylosis	1
N0966	Knee gives way	1
N216z	Knee enthesopathy NOS	1
N06z6-1	Knee arthritis NOS	1
N06z6	Knee arthritis NOS	1
ASDFGKN2	Knee Pain?	1
ASDFGKN6	Knee Pain Does Not Affect Sleep	1
ASDFGKN4	Knee Pain Affects Sleep?	1
ASDFGKN5	Knee Pain Affects Sleep	1
ASDFGKN3	Knee Pain	1
MUNNUKN1	Knee Pain	1
MAWBYKN1	Knee Pain	1
N0836	Knee - recurrent dislocation	1
N13y1	Klippel's disease	1
N116	Kissing spine	1
N002	Keratoconjunctivitis sicca	1
N0600	Kaschin-Beck dis.-site unspec.	1
N0601	Kaschin-Beck dis.-shoulder	1
N0608	Kaschin-Beck dis.-other specif	1
N0609	Kaschin-Beck dis.-multipl.site	1
N060z	Kaschin-Beck dis.-NOS	1
N060	Kaschin - Beck disease	1
N320z	Juvenile spine osteochondr.NOS	1
N3200	Juvenile spine osteochond.unsp	1
N0455	Juvenile rheumatoid arthritis	1
N0430	Juvenile rheumatoid arthr.unsp	1
N043z	Juvenile rheumatoid arthr.NOS	1
N3263	Juvenile osteochondrosis NOS	1
N326z	Juvenile osteochondroses NOS	1
N3262	Juvenile osteochondritis NOS	1
N3261	Juvenile epiphysitis NOS	1
N0030	Juvenile dermatomyositis	1
N3260	Juvenile apophysitis NOS	1
N043	Juvenile R.A.- Still's disease	1
OX7120DA	Juvenile Arthritis /ox	1
N3243	Juv.osteoch.secondary.pat.ctre	1
N0451	Juv seronegative polyarthritis	1
N328	Juv osteochondrosis of spine	1
N0452	Juv arthritis in psoriasis	1
N0453	Juv arthritis in Crohn's dis	1
N0454	Juv arth in ulcerative colitis	1
N0900	Joint effusion-site unspecif.	1
N0901	Joint effusion-shoulder region	1
N0908	Joint effusion-other specif.	1
N09z1	Joint disord.NOS-shoulder	1
N08z	Joint derangement NOS	1
N08zz	Joint derangement NOS	1
N08z0	Joint derange.NOS-site unspec.	1
N08z1	Joint derange.NOS-shoulder	1
N08z7	Joint derange.NOS-other spec.	1
N08z8	Joint derange.NOS-multipl.site	1
N05z.11	Joint degeneration	1
N05z	Joint degeneration	1
N0840	Joint contracture-site unspec	1
N0841	Joint contracture-shoulder	1
N0848	Joint contracture-other specif	1
N0850	Joint ankylosis-site unspecif.	1
N0851	Joint ankylosis-shoulder	1

Read code	Description	Number of studies
N0858	Joint ankylosis-other specif.	1
ASDFGJO2	Joint Symptoms	1
ASDFGJO3	Joint Pain	1
N3841	Isthmic spondylolisthesis	1
S531	Ischiocapsular sprain	1
N23yB	Ischaemic infarction of muscle	1
N123-1	Intervertebral disc prol. NOS	1
N12z	Intervertebral disc lesion NOS	1
OX7259AP	Intervertebral Disc Prolapsed /ox	1
N3y05	Intervert disc sten neur canal	1
N23y0	Interstitial myositis	1
N07z	Internal knee derangement NOS	1
N07	Internal derangement of knee	1
N1350	Intermittent torticollis	1
N090W	Intermittent hydrarthrosis	1
N084E	Int rotat contracture-shoulder	1
N08y	Instability of joint	1
SJ7z	Injury to other nerve NOS	1
SKz	Injury NOS	1
OX9967C	Injury Knee /ox	1
SJ9	Injur/nerv+spinl crd/thorx lev	1
SJB	Inj/nerves/should+upp arm levl	1
S46C	Inj/multipl structures of knee	1
S5Q6	Inj tendon rotator cuff should	1
N2166	Infrapatellar bursitis	1
N10	Inflammatory spondylopathies	1
N04	Inflammatory polyarthropathy	1
N04*	Inflammatory arthropathy	1
N10y0	Inflamm.spondylop.in dis. EC	1
N04z	Inflamm.polyarthropathy NOS	1
S4103	Inferior dislocation shoulder	1
N2302	Infective myositis-shoulder	1
N2300	Infective myositis-neck	1
N2301	Infective myositis-back	1
N01z	Infective arthritis NOS	1
N01zz	Infective arthritis NOS	1
N302B	Infection of thoracic spine	1
N302G	Infection of scapula	1
N302R	Infection of patella	1
N302Z	Infection of multiple bones	1
N302C	Infection of lumbar spine	1
N302F	Infection of clavicle	1
N302A	Infection of cervical spine	1
N01z0	Infect.arthr.NOS-site unspecif	1
N01z1	Infect.arthr.NOS-shoulder reg	1
N01zy	Infect.arthr.NOS-other specifi	1
N01zx	Infect.arthr.NOS-multiple site	1
N12zG	Infect intervert disc - pyogen	1
N01z8	Infec arthritis NOS-shoulder	1
N01zK	Infec arthritis NOS-knee	1
N01z9	Infec arthr NOS-sternoclav jt	1
N01zA	Infec arth NOS-acromioclav jt	1
N23y5	Inappropriate firing of muscle	1
N2124	Impingement syndr of shoulder	1
N2331	Immobility syndrome	1
N2159	Iliotibial band syndrome	1
N1403	Idiopathic th spinal stenosis	1
N3730	Idiopathic scoliosis	1
N3303	Idiopathic osteoporosis	1
N1407	Idiopathic lu spinal stenosis	1
N3731	Idiopathic kyphoscoliosis	1
N33z7	Idiopathic hypertrophy of bone	1
N1300	Idiopathic Cx spinal stenosis	1
N3316	Idiopath osteopor + path fract	1
N3348	Idiopath asep necrosis of bone	1
N1405	Iatrogenic th spinal stenosis	1
N1409	Iatrogenic lu spinal stenosis	1
N1302	Iatrogenic Cx spinal stenosis	1
C04*	Hypothyroidism	1
N2431	Hypertrophy of knee fat pad	1
N33z4	Hypertrophy of bone	1
N3382	Hypertrophic non-union of #	1
N312	Hypertroph.pulm.osteoarthrop.	1
N02y8	Hydroxyapatite deposition dis	1

Read code	Description	Number of studies
N2225	Housemaids knee	1
N0707	Horiz cleavage tear-med menisc	1
N0718	Horiz cleavage tear-lat menisc	1
N094K-2	Hip pain	1
N05z5	Hip osteoarthritis NOS	1
N05z5-1	Hip osteoarthritis NOS	1
N0535	Hip osteoarthitis NOS	1
N0535-2	Hip osteoarthitis NOS	1
N06z5	Hip arthritis NOS	1
N0809	Hill-Sachs lesion	1
N245-5	Heel pain	1
N0507	Heberden's nodes with arthropathy	1
N245-4	Hand pain	1
N2450	Hand pain	1
N0944-1	Hand joint pain	1
N06z4-1	Hand arthritis NOS	1
N068	Haemophilic arthropathy	1
N091B	Haemarthrosis-sternoclav joint	1
N0910	Haemarthrosis-site unspecified	1
N0911	Haemarthrosis-shoulder	1
N0918	Haemarthrosis-other specified	1
N0919	Haemarthrosis-multiple joints	1
N091C	Haemarthrosis-acromioclav jt	1
N0916	Haemarthrosis of the knee	1
N091A	Haemarthrosis of shoulder	1
N091M	Haemarthrosis of knee	1
N091z	Haemarthrosis NOS	1
N091	Haemarthrosis	1
N083M	Habitual sublux shoulder	1
N083L	Habitual disloc shoulder	1
N083r	Habitual disloc - patella	1
14G8	H/O: vertebral fracture	1
14G1	H/O: rheumatoid arthritis	1
14G2	H/O: osteoarthritis	1
14GZ	H/O: musculo-skeletal dis. NOS	1
14G3	H/O: knee problem	1
14J	H/O: injury	1
14G4	H/O: back problem	1
14T5	H/O: artificial joint	1
14V5	H/O: arthrodesis	1
14G	H/O: arthritis	1
14N30	H/O Spinal surgery	1
16Z2	Growing pains	1
S3z00	Greenstick fracture	1
N0230	Gouty arthritis-site unspecif.	1
N0231	Gouty arthritis-shoulder	1
N023y	Gouty arthritis-other specif.	1
N023x	Gouty arthritis-multiple sites	1
N023z	Gouty arthritis NOS	1
N023	Gouty arthritis	1
N2131-1	Golfer's elbow	1
N200	Gnt cell arter+polymyalg rheum	1
EGTON444	Gluteal Muscle Injury	1
N0873	Glenoid labrum tear	1
N0872	Glenoid labrum detachment	1
N365	Genu recurvatum - acquired	1
N050z	Generalised osteoarthritis NOS	1
N050z00	Generalised osteoarthritis NOS	1
N050	Generalised osteoarthritis - OA	1
N050.0	Generalised osteoarthritis - OA	1
N065A	Generalised arthritis	1
N065A00	Generalised arthritis	1
N05000	Generalised OA-site unspecif.	1
N0500	Generalised OA-site unspecif.	1
N050200	Generalised OA-multiple sites	1
N0502	Generalised OA-multiple sites	1
N0501	Generalised OA-hand	1
N224z	Ganglion/synovial cyst NOS	1
N224	Ganglion/synov.cyst - knee	1
N224-92	Ganglion/synov.cyst - knee	1
N2243	Ganglion unspecified	1
N2245	Ganglion of wrist	1
N2242	Ganglion of tendon sheath	1
N2246	Ganglion of knee	1

Read code	Description	Number of studies
N2241	Ganglion of joint	1
N224C	Ganglion of foot	1
EMISR4QFU2	Fusion Of Lumbar Spine	1
EMISR4QFU1	Fusion Of Cervical Spine	1
N2115	Full thickn rotator cuff tear	1
N210-2	Frozen shoulder	1
N331N	Fragility fracture	1
N331M	Fragility # unsp osteoporosis	1
S10B	Fracture/lumbar spine+pelvis	1
S10A1	Fracture/2nd cervical vertebra	1
S10A0	Fracture/1st cervical vertebra	1
S15	Fracture of thoracic vertebra	1
S1z	Fracture of neck and trunk NOS	1
S1	Fracture of neck and trunk	1
S10A	Fracture of neck	1
S10B0	Fracture of lumbar vertebra	1
N338z	Fracture malunion or nonunion NOS	1
SR1	Fracture involv multi body reg	1
SR10	Fracture involv head with neck	1
S4	Fracture dislocation/subluxat	1
OX8056	Fracture Spine /ox	1
S3z	Fracture NOS	1
OXL8056LV	Fracture Lumbar Vertebra /ox	1
SR16	Fract/thorx wth lw bck+plv+lmb	1
N3317	Fract of bone in neoplast dis	1
N2451	Foot pain	1
N245-3	Foot pain	1
1M11	Foot pain	1
N220B	Flexor tenosynovitis of finger	1
N3660	Flexion deformity of knee	1
N369	Flexion deformity	1
N084A	Flexion contracture-shoulder	1
N084a	Flexion contracture-knee	1
N374E	Flatback syndrome	1
N040T	Flare of rheumatoid arthritis	1
N08yA	Flail joint	1
N09C	Fistula of joint	1
N2450-2	Finger pain	1
N05z4-1	Finger osteoarthritis NOS	1
N2163	Fibular collat.lig.bursitis	1
N3324	Fibrous cortical defect	1
N2405	Fibrositis of neck	1
N00y1	Fibrosclerosis systemic	1
N087	Fibrocartilage lesion of joint	1
MHTBAFH1	Fh: Osteoporosis	1
N041	Felty's syndrome	1
N1y1	Fatigue fracture of vertebra	1
N244	Fasciitis unspecified	1
N024	Familial chondrocalcinosis	1
N14y	Facet joint syndrome	1
12I1	FH: Rheumatoid arthritis	1
1268	FH: Osteoporosis	1
12I2	FH: Osteoarthritis	1
12IZ	FH: Musculo-skeletal dis. NOS	1
12I	FH: Arthritis	1
N220D	Extensor tenosynovitis of wrist	1
N220F	Extensor tenosynovitis of thumb	1
N220E	Extensor tenosynovitis of finger	1
N084B	Extension contracture-shoulder	1
N084F	Ext rotat contracture-shoulder	1
N21z7	Exostosis	1
16C8	Exacerbation of backache	1
N0506	Erosive osteoarthrosis	1
N32z1	Epiphysitis NOS	1
N33z1	Epiphyseal arrest	1
N00y0	Eosinophilic fasciitis	1
N216	Enthesopathy of knee	1
N21z	Enthesopathy NOS	1
N11y1	Enterobacterial spondylitis	1
1M00-1	Elbow pain	1
1M00	Elbow pain	1
N05z2	Elbow osteoarthritis NOS	1
N06z2	Elbow arthritis NOS	1
N090B	Effusion of sternoclav joint	1

Read code	Description	Number of studies
N090A	Effusion of shoulder	1
N0909	Effusion of multiple joints	1
N090M	Effusion of knee	1
N090z	Effusion of joint NOS	1
N090	Effusion of joint	1
N090C	Effusion of acromioclav joint	1
N0906	Effusion - knee joint	1
N0906-99	Effusion - knee joint	1
N3840	Dysplastic spondylolisthesis	1
N2361	Dupuyt dis-palm + nod no cont	1
N3305	Drug-induced osteoporosis	1
N0002	Drug-ind systemic lupus eryth	1
N3315	Drug-ind osteopor + path fract	1
N235	Double-jointed (hypermobility)	1
N1123	Dorsal spondylo w/o myelopath	1
N3370	Disuse atrophy of bone	1
N3304	Dissuse osteoporosis	1
N0000	Disseminated lupus erythemat.	1
N09AX	Disorder of patella unspecified	1
N33zG	Disorder of cartilage, unspec	1
N33zF	Disorder of bone unspecified	1
S46	Dislocation or subluxation of knee	1
S4z	Dislocation or subluxation NOS	1
S41z	Dislocation of shoulder NOS	1
S46z	Dislocation of knee NOS	1
S41	Dislocated shoulder	1
S463-99	Dislocated patella	1
SR20	Disloc,sprns+strns inv hd+neck	1
SR2	Dislc,sprns+strns/mult bdy reg	1
N071B	Discoid lateral meniscus	1
N123	Disc unsp.displ.-no myelopathy	1
N12B	Disc prolapse with myelopathy	1
N12C	Disc prolapse + radiculopathy	1
N12zz	Disc disorders NOS	1
N129z	Disc disorder+myelopathy NOS	1
N00	Diffuse connective tissue dis.	1
N097z	Difficulty in walking NOS	1
N097	Difficulty in walking	1
N23yA	Diastasis of muscle	1
N33z3	Diaphysitis	1
N0300	Diabetic cheiroarthropathy	1
N0301	Diabetic Charcot arthropathy	1
N003X	Dermatopolymyositis, unspec	1
N0031	Dermatopolymyosit,neoplast dis	1
N003	Dermatomyositis	1
SC0z	Delayed union of fracture	1
N3386	Delayed union of fracture	1
S9030	Degloving injury,shoulder area	1
SA130	Degloving injury knee	1
N3842	Degenerative spondylolisthesis	1
N128	Degenerative disc disease NOS	1
N1404	Degenerativ th spinal stenosis	1
N1408	Degenerativ lu spinal stenosis	1
N1301	Degenerativ Cx spinal stenosis	1
N114	Degeneration of lumbar spine	1
N114-1	Degeneration of lumbar spine	1
N0721	Degen lesion artic cart knee	1
N36y4	Deformity of scapula	1
N36yD	Deformity of patella	1
N36y3	Deformity of clavicle	1
N36y2	Deformity of bone	1
N224D	Cyst of tendon sheath	1
N0722	Cyst of semilunar cartilage	1
N0709	Cyst of medial meniscus	1
N071A	Cyst of lateral meniscus	1
N2244	Cyst of bursa	1
N332z	Cyst of bone NOS	1
N332	Cyst of bone	1
N11A	Cx spondyl + vasc compression	1
N1303	Cx spin stenos due to oth dis	1
N12C0	Cx disc prolapse+radiculopathy	1
N12B0	Cx disc prolapse + myelopathy	1
N3740	Curvature of spine unspecified	1
N37zz	Curvature of spine NOS	1

Read code	Description	Number of studies
N37z	Curvature of spine NOS	1
N37	Curvature of spine	1
N02zK	Crystal arthropathy NOS-knee	1
N02zz	Crystal arthropathy NOS	1
N02z	Crystal arthropathy NOS	1
N02z0	Crystal arthr.NOS-site unspec.	1
N02z1	Crystal arthr.NOS-shoulder	1
N02zy	Crystal arthr.NOS-other spec.	1
N02zx	Crystal arthr.NOS-multipl.site	1
N02z9	Cryst arthr NOS-sternoclav jt	1
N02zA	Cryst arthr NOS-acromioclav jt	1
N02z8	Crys arthr NOS-shoulder	1
SF20z	Crushinjuryshlder+uparmNOS	1
SFz	Crushing injury NOS	1
SF	Crushing injury	1
SF40	Crush injury multiple sites NEC	1
SF021	Crush injury larynx	1
SF311	Crush injury knee	1
SF110	Crush injury back	1
SF4z	Crush injury	1
N13y2	Crick in neck	1
N2472	Cramp	1
N051A	Coxarthr from dysplasia, bilat	1
N3216	Coxa plana	1
182B0	Costal margin chest pain	1
N2123	Coracoid impingement	1
S502	Coracohumeral sprain	1
SE30z	Contusionshlder+uer arm NOS	1
SE44	Contusionlwr limbmlti sites	1
SE00	Contusion, forehead	1
SEz	Contusion with skin intact NOS	1
SE30	Contusion shoulder or upper arm	1
SE300	Contusion shoulder area	1
SE301	Contusion scapular area	1
SE231	Contusion of lower back	1
SE232	Contusion of lower back	1
SE4y	Contusion multiple sites NEC	1
SE41z	Contusion knee and lower leg NOS	1
SE411	Contusion knee	1
SE0z	Contusion face scalp+neck NOS	1
SE304	Contusion clavicular area	1
SE23z	Contusion back NOS	1
SE	Contusion (bruise) with intact skin	1
N22y0	Contracture of tendon sheath	1
N23yC	Contracture of muscle	1
N0849	Contracture of multiple joints	1
N084z	Contracture of joint NOS	1
N084	Contracture of joint	1
N	Connective tissue diseases	1
N3y04	Connect tiss sten neural canal	1
PE1	Congenital sternomastoid torticollis	1
N3y07	Con tis/disc sten intervrt for	1
N33C	Complex regionl pain syndrom I	1
S5C	Complete tear, knee ligament	1
S58z	Complete tear shoulder joint NOS	1
S58	Complete tear shoulder joint	1
N33z8	Complete epiphyseal arrest	1
N33z6	Compensatory hypertrophy-bone	1
SK0y	Compartmentsyndrome	1
S5A0D	Comp tr shrt intr lig non-sp	1
N331D	Collapsed vertebra NOS	1
N331	Collapse of vertebra NOS	1
N331F	Collapse of thoracic vertebra	1
N3310	Collapse of thoracic vertebra	1
N3311	Collapse of lumbar vertebra	1
N331G	Collapse of lumbar vertebra	1
N331E	Collapse of cervical vertebra	1
N331L	Collap vert due osteopor NOS	1
N331J	Collap lumb vert due to osteo	1
N331H	Collap cerv vert due to osteop	1
N00z	Collagen disease NOS	1
N331K	Coll thorac vert due osteopor	1
N147z	Coccyx disorder NOS	1
N1472	Coccygodynia	1

Read code	Description	Number of studies
S5E1	Cmplt tr,thyroid region lgmt	1
S5E30	Cmplt tr,sternoclavicular lgmt	1
S5Ez	Cmplt tr,other lgmt NOS	1
S5Cy	Cmplt tr,other knee lgmt	1
S5C1	Cmplt tr,knee,mdl collat lgmt	1
S5C0	Cmplt tr,knee,lat collat lgmt	1
S5Cz	Cmplt tr,knee lgmt NOS	1
S581	Cmplt tr,coraco-clav lgmt	1
S580	Cmplt tr,acromio-clav lgmt	1
S5A0A	Cmplt tr triang fibrocartilage	1
S5C3	Cmpl tr,knee,ant cruciate lgmt	1
S5y57	Cmpl tear,lumbosacral lgmt	1
S5y56	Cmpl tear,iliolumbar lgmt	1
S5C2	Cmp tr,knee,post cruciate lgmt	1
S2920	Clsd mult fract clav scap hum	1
S1000	Clsd # unsp cerv vertebra	1
S1024	Clsd # thorc vert-trnsvrs prcs	1
S1026	Clsd # thorc vert - tricolumnr	1
S1025	Clsd # thorc vert - post prcs	1
S1020	Clsd # thoracic vert, burst	1
S1021	Clsd # thoracic vert wedge	1
S102z	Clsd # thorac vert NOS	1
S1023	Clsd # thor vert-spinous prcss	1
S1003	Clsd # third cerv vertebra	1
S2102	Clsd # scapula, coracoid	1
S1041	Clsd # lumbar vert wedge	1
S1040	Clsd # lumbar vert burst	1
S1046	Clsd # lumb vert - tricolumnar	1
S1004	Clsd # fourth cerv vertebra	1
S1005	Clsd # fifth cerv vertebra	1
S2001	Clsd # clavicle medial end	1
S2003	Clsd # clavical lateral end	1
S100H	Clsd # cerv vert, wedge	1
S100G	Clsd # cerv vert, burst	1
S100z	Clsd # cerv spine NOS	1
S100F	Clsd # axis, tricolumnar	1
S100D	Clsd # axis, transvrse process	1
S100B	Clsd # axis, spondylolysis	1
S100C	Clsd # axis, spinous process	1
S100E	Clsd # axis, posterior arch	1
S100A	Clsd # axis odontoid process	1
S1009	Clsd # atlas, comminuted	1
S1106	Clsd # C5-C7 unspec cord les	1
S110A	Clsd # C5-C7 post cord lesion	1
S110B	Clsd # C5-C7 incomp cord les	1
S1107	Clsd # C5-C7 complete cord les	1
S1109	Clsd # C5-C7 cent cord lesion	1
S1108	Clsd # C5-C7 ant cord lesion	1
S1100	Clsd # C1-C4 unspec cord les	1
S1104	Clsd # C1-C4 post cord lesion	1
S1105	Clsd # C1-C4 incomp cord les	1
S1101	Clsd # C1-C4 complete cord les	1
S1103	Clsd # C1-C4 cent cord lesion	1
S1102	Clsd # C1-C4 ant cord lesion	1
S4120	Cls trmtc subluxatn shldr jnt	1
S4696	Cls trmtc sublux,head fibula	1
S467	Cls trmtc sublux pat-fem jt	1
S4690	Cls trmtc sublux knee jt,unsp	1
S4692	Cls trmtc sublux knee jt,post	1
S4694	Cls trmtc sublux knee jt,ltrl	1
S4691	Cls trmtc sublux knee jt,ant	1
S469	Cls trmtc sublux knee jt	1
S4102	Cls trmtc dslctn shldr jtpost	1
S410z	Cls trmtc dislctn shoulder NOS	1
S49E4	Cls trm sublux,st-clav jt,post	1
S49E3	Cls trm sublux,st-clav jt,ant	1
S49E2	Cls trm sublux st-clav jt	1
S4671	Cls trm sublux pat-fem jt,med	1
S4670	Cls trm sublux pat-fem jt,ltrl	1
S49E5	Cls trm sublux laryngl cart	1
S4695	Cls trm sublux knee jt,rotatry	1
S4693	Cls trm sublux knee jt,medial	1
S4121	Cls trm sublux acromio-clav jt	1
S4656	Cls trm dslctn, head fibula	1

Read code	Description	Number of studies
S4631	Cls trm dslctn pat-fem jt,med	1
S4630	Cls trm dslctn pat-fem jt,lat	1
S4650	Cls trm dslctn knee, unspec	1
S4654	Cls trm dslctn knee jt,lateral	1
S4652	Cls trm dslctn knee jt, post	1
S4653	Cls trm dslctn knee jt, medial	1
S4651	Cls trm dslctn knee jt, ant	1
S465z	Cls trm dslctn knee NOS	1
S4655	Cls trm dslct knee jt,rotatory	1
S4963	Cls trm dslc,stern-clav jt,ant	1
S4962	Cls trm dslc sterno-clav jt	1
S4965	Cls trm dslc laryngl cartilage	1
S4964	Cls trm dsl,stern-clav jt,post	1
S412	Cls traumtc subluxatn shoulder	1
S410	Cls traumtc disloctn shoulder	1
S4105	Cls traumatic disloctn scapula	1
S49A	Cls sublux thrcic+lumbar spine	1
S49A1	Cls sublux thrcic spine	1
S49Az	Cls sublux thrc+lmbr spine NOS	1
S498x	Cls sublux mlti cerv vertebrae	1
S4980	Cls sublux cervical spine,unsp	1
S498	Cls sublux cervical spine	1
S498z	Cls sublux cerv vertebra NOS	1
S4981	Cls sublux atlanto-occiptl jt	1
S4982	Cls sublux atlanto-axial jt	1
S492C	Cls spnl dslc+cauda equina lsn	1
S4924	Cls spnl dslc+ant thrc crd lsn	1
S4929	Cls spnl dslc+ant lmbr crd lsn	1
S490B	Cls spnl dslc+ant cerv crd lsn	1
S492B	Cls spnl dsl+post lmbr crd lsn	1
S4923	Cls spnl dsl+comp thrc crd lsn	1
S4928	Cls spnl dsl+comp lmbr crd lsn	1
S4922	Cls spn dslc+thrc crd lsn,unsp	1
S4926	Cls spn dslc+post thrc crd lsn	1
S490D	Cls spn dslc+post cerv crd lsn	1
S4925	Cls spn dslc+cent thrc crd lsn	1
S492A	Cls spn dslc+cent lmbr crd lsn	1
S1140	Cls spn # + unsp lumb crd lesn	1
S1144	Cls spn # + post lumb crd lesn	1
S1141	Cls spn # + comp lumb crd lesn	1
S1143	Cls spn # + cent lumb crd lesn	1
S1145	Cls spn # + cauda equina lesn	1
S1142	Cls spn # + ant lumbr crd lesn	1
SR100	Cls fract invol head with neck	1
S492z	Cls dslc thrcic+lmbr spine NOS	1
S492	Cls dslc thoracic+lumbar spine	1
S4921	Cls dslc thoracic vertebra	1
S4920	Cls dslc lumbar spine	1
S4901	Cls dslc atlanto-occipital jnt	1
S4902	Cls dslc atlanto-axial joint	1
S4F6	Cls #-sublux,patello-fem jt	1
S4J23	Cls #-sublux st-clav jt,post	1
S4J22	Cls #-sublux st-clav jt,ant	1
S4F4	Cls #-dslc,patello-fem jt	1
S4J03	Cls #-dslc st-clav jt,post	1
S4J02	Cls #-dslc st-clav jt,ant	1
S1022	Cls # thorc vert-spondylolysis	1
S1044	Cls # lumbr vert-trnsvrse prcs	1
S1042	Cls # lumbr vert-spondylolysis	1
S1043	Cls # lumbr vert-spinous prcss	1
S1045	Cls # lumb vert-posterior arch	1
S100L	Cls # cerv vert, trnsvrse prcs	1
S100N	Cls # cerv vert, tricolumnar	1
S100J	Cls # cerv vert, spondylolysis	1
S100K	Cls # cerv vert, spinous prcss	1
S100M	Cls # cerv vert, post arch	1
S1008	Cls # atlas-isol arch/art prcs	1
S412z	Closed traumatic subluxation shoulder NOS	1
S496z	Closed traumatic disloctn NOS	1
S4100	Closed traumatic dislocation shoulder joint, unspecified	1
S463	Closed traumatic dislocation of patello-femoral joint	1
S112z	Closed thoracic#+cord lesn.NOS	1
S112	Closed thoracic #+cord lesion	1
S49Cz	Closed subluxation spine NOS	1

Read code	Description	Number of studies
S49A0	Closed subluxation lumbar spine	1
S4988	Closed subluxation C7/T1	1
S4987	Closed subluxation C6/C7	1
S4986	Closed subluxation C5/C6	1
S4985	Closed subluxation C4/C5	1
S4984	Closed subluxation C3/C4	1
S4983	Closed subluxation C2/C3	1
S49C0	Closed sublux spine, unsp	1
S49C	Closed sublux other vertebra	1
S026	Closed orbital blow-out fracture	1
S114	Closed lumbar # + cord lesion	1
S102	Closed fracture thoracic vertebra	1
S2104	Closed fracture scapula, blade	1
S2105	Closed fracture scapula spine	1
S2106	Closed fracture scapula neck	1
S2103	Closed fracture scapula glenoid	1
S2101	Closed fracture scapula acromion	1
S3204	Closed fracture patella, comminuted (stellate)	1
S320	Closed fracture of the patella	1
S1250	Closed fracture larynx	1
S2002	Closed fracture clavicle shaft	1
S1002	Closed fracture axis	1
S1001	Closed fracture atlas	1
S4940	Closed dislocation spine unsp.	1
S494z	Closed dislocation spine NOS	1
S490	Closed dislocation cervical spine	1
S4908	Closed dislocation C7/T1	1
S4907	Closed dislocation C6/C7	1
S4906	Closed dislocation C5/C6	1
S4905	Closed dislocation C4/C5	1
S4904	Closed dislocation C3/C4	1
S4903	Closed dislocation C2/C3	1
S494	Closed disloc.other vertebra	1
S490x	Closed disloc.mult.cerv.vert.	1
S490z	Closed disloc.cervic.vert.NOS	1
S4900	Closed disloc.cerv.spine unsp.	1
S4960	Closed disloc sternoclavic. jt	1
S4104	Closed disloc acromioclavic.jt	1
S110z	Closed cervical#+cord lesn.NOS	1
S110	Closed cervical #+cord lesion	1
S1253	Closed #trachea	1
S1252	Closed #thyroid cartilage	1
S11x	Closed #spine+cord lesn.unsp.	1
S2100	Closed #scapula-unspecified	1
S210z	Closed #scapula NOS	1
S125z	Closed #larynx/trachea NOS	1
S1251	Closed #hyoid bone	1
S2000	Closed #clavicle unspecified	1
S200z	Closed #clavicle NOS	1
S3z0	Closed #bones unspecified	1
S4F2	Closed #-sublux, knee joint	1
S4A20	Closed #-sublux shoulder joint	1
S4A2	Closed #-sublux shoulder	1
S4A21	Closed #-sublux acrom-clav jt	1
S4A00	Closed #-dslc shoulder joint	1
S4A0	Closed #-dslc shoulder	1
S4F0	Closed #-dslc knee joint	1
S4A01	Closed #-dslc acrom-clav joint	1
S10x	Closed # spine unspecif	1
S210	Closed # scapula	1
S3201	Closed # patella,proximal pole	1
S3203	Closed # patella, vertical	1
S3200	Closed # patella transverse	1
S3202	Closed # patella distal pole	1
S200	Closed # clavicle	1
S100	Closed # cervical spine	1
N063000	Climacteric arthr.-site unsp.	1
N0630	Climacteric arthr.-site unsp.	1
N0631	Climacteric arthr.-shoulder	1
N0638	Climacteric arthr.-other spec.	1
N063800	Climacteric arthr.-other spec.	1
N0639	Climacteric arthr.-multip.site	1
N063900	Climacteric arthr.-multip.site	1
N063z	Climacteric arthr.-NOS	1

Read code	Description	Number of studies
N063z00	Climacteric arthr.-NOS	1
N0991	Clicking sternoclavic joint	1
N0990	Clicking shoulder	1
N099C	Clicking knee	1
N099	Clicking joint	1
N0992	Clicking acromioclavicular joint	1
N33A1	Clavicle pain	1
S490A	Cl spnl dslc+comp cerv crd lsn	1
S4909	Cl spnl dslc+cerv crd lsn,unsp	1
S49A2	Cl spn sublx+thrc crd lsn,unsp	1
S49A6	Cl spn sublx+post thrc crd lsn	1
S49AB	Cl spn sublx+post lmbr crd lsn	1
S49A7	Cl spn sublx+lmbr crd lsn,unsp	1
S49A3	Cl spn sublx+comp thrc crd lsn	1
S49A8	Cl spn sublx+comp lmbr crd lsn	1
S498A	Cl spn sublx+comp cerv crd lsn	1
S498C	Cl spn sublx+cntrl crv crd lsn	1
S4989	Cl spn sublx+cerv crd lsn,unsp	1
S49A5	Cl spn sublx+cent thrc crd lsn	1
S49AA	Cl spn sublx+cent lmbr crd lsn	1
S49AC	Cl spn sublx+cauda equina lsn	1
S49A4	Cl spn sublx+ant thrc crd lsn	1
S49A9	Cl spn sublx+ant lmbar crd lsn	1
S498D	Cl spn sublux+post crv crd lsn	1
S498B	Cl spn sublux+ant cerv crd lsn	1
S490C	Cl spn dslc+cntrl cerv crd lsn	1
S4927	Cl spn dsl+lmbr crd lsn unsp	1
S1124	Cl spn #+pst thor crd lsn,T1-6	1
S1123	Cl spn #+cnt thor crd lsn,T1-6	1
S1122	Cl spn #+ant thor crd lsn,T1-6	1
S1120	Cl sp #+unsp thor crd lsn,T1-6	1
S1126	Cl sp #+unsp thor cd lsn,T7-12	1
S112A	Cl sp #+pst thor crd lsn,T7-12	1
S1129	Cl sp #+cnt thor crd lsn,T7-12	1
S1121	Cl sp #+cmpl thor crd lsn,T1-6	1
S1127	Cl sp #+cmp thor crd lsn,T7-12	1
S1128	Cl sp #+ant thor crd lsn,T7-12	1
S1500	Cl multi fractur of thor spine	1
SR160	Cl fract/th wth lw bck+plv+lmb	1
S112B	Cl # T7-12incomp cord lsn NOS	1
S1125	Cl # T1-6 incmpl cord lesn NOS	1
N301B	Chronic osteomyelitis-th spine	1
N301C	Chronic osteomyelitis-lu spine	1
N301A	Chronic osteomyelitis-Cx spine	1
N301	Chronic osteomyelitis	1
C052*	Chronic lymphocytic thyroiditis (Hashimotos's disease)	1
16C9	Chronic low back pain	1
N090X	Chronic joint effusion	1
N3682	Chronic instability of knee	1
OX7289CB	Chronic Backache /ox	1
N3010	Chron.osteomyelitis-site unsp.	1
N3011	Chron.osteomyelitis-shoulder	1
N3018	Chron.osteomyelitis-other spec	1
N3019	Chron.osteomyelitis-mult.site	1
N301z	Chron.osteomyelitis NOS	1
N301L	Chron multifocal osteomyelitis	1
N301M	Chr osteomyel + draining sinus	1
N074	Chondromalacia patellae	1
N33z2	Chondromalacia NOS	1
N33zB	Chondrolysis	1
N022	Chondrocalcinosis unspecified	1
N022z	Chondrocalcinosis NOS	1
N02	Chondrocalcinosis	1
N0220	Chondrocalc.unsp.-site unspec.	1
N0221	Chondrocalc.unsp.-shoulder reg	1
N022y	Chondrocalc.unsp.-other spec.	1
N022x	Chondrocalc.unsp.-multipl.site	1
N020z	Chondrocalc.dicalc.phos.NOS	1
N021	Chondrocalc.-pyrophosph.cryst.	1
N021z	Chondrocalc.-pyrophosph.NOS	1
N020	Chondrocalc.-dicalc.phos.cryst	1
N0210	Chondroc.-pyrophos.-site unsp.	1
N0211	Chondroc.-pyrophos.-shoulder	1
N021y	Chondroc.-pyrophos.-other spec	1

Read code	Description	Number of studies
N021x	Chondroc.-pyrophos.-mult.sites	1
N0216	Chondroc.-pyrophos.-knee	1
N0200	Chondroc.-dical.ph.-site unsp.	1
N0201	Chondroc.-dical.ph.-shoulder	1
N020y	Chondroc.-dical.ph.-other spec	1
N020x	Chondroc.-dical.ph.-mult.sites	1
N33zJ	Chondritis	1
182C	Chest wall pain	1
N035	Charcots arthropathy	1
N132	Cervicocranial syndrome	1
N133	Cervicobrachial syndrome	1
N148A	Cervico-thoracic instability	1
N1483	Cervico-thoracic ankylosis	1
N131	Cervicalgia	1
N138	Cervicalgia	1
N13y0	Cervical syndrome NEC	1
N119	Cervical spondylosis with radiculopathy	1
N11E	Cervical spondylosis	1
N110-1	Cervical spondylosis	1
N110	Cervical spond.- no myelopathy	1
N111	Cervical spond.+ myelopathy	1
N1489	Cervical spine instability	1
N1482	Cervical spine ankylosis	1
N130	Cervical spinal stenosis	1
N13y3	Cervical root syndrome	1
N12A1	Cervical postlaminectomy syndr	1
N137	Cervical post.long.lig.ossific	1
SJ306	Cervical nerve root injury - C7	1
SJ305	Cervical nerve root injury - C6	1
SJ304	Cervical nerve root injury - C5	1
SJ303	Cervical nerve root injury - C4	1
SJ30	Cervical nerve root injury	1
N1113	Cervical myelopathy	1
N13	Cervical disorder NOS	1
N12z4	Cervical discitis	1
N120	Cervical disc displ.-no myelop	1
N1291	Cervical disc disord.+myelop.	1
N125	Cervical disc degeneration	1
S5701	Cervical ant.longit.lig.sprain	1
N13z	Cervical and neck disorders NOS	1
N12zH	Cerv disc disord + radiculopth	1
N21z0	Capsulitis NOS	1
N04y0	Caplan's syndrome	1
N3202	Calve's vertebral osteochondr.	1
N2454	Calf pain	1
N2226	Calcium deposit in bursa	1
N2111	Calcifying tendinitis shoulder	1
N12zB	Calcification of thoracic disc	1
N22y1	Calcification of tendon NOS	1
N12zF	Calcification of lumbar disc	1
N23y1	Calcification of ligament	1
N12z7	Calcification of cervical disc	1
N23y9	Calcific tendinitis	1
N2177	Calcaneal spur	1
N2315	Calc/ossif musc ass with burns	1
N0011	CREST syndrome	1
182Z.00	CHEST PAIN NOS	1
182..00	CHEST PAIN	1
S1007	C7 closed # - no cord lesion	1
S1006	C6 closed # - no cord lesion	1
1D12.00	C/O: stiffness	1
1D12	C/O: stiffness	1
16C7	C/O - upper back ache	1
1A53	C/O - lumbar pain	1
16C5	C/O - low back pain	1
N2118	Bursitis of shoulder	1
N223	Bursitis NOS	1
N2160-99	Bursitis - knee	1
N2160	Bursitis - knee	1
N221	Bunion	1
16BZ	Bruising symptom NOS	1
16B	Bruising symptom	1
16B2	Bruises easily	1
SE4z	Bruise NOS	1

Read code	Description	Number of studies
SE41	Bruise - knee/lower leg	1
SE41-99	Bruise - knee/lower leg	1
SE23	Bruise - back	1
N11y0	Brucella spondylitis	1
N3325	Brown tumour-hyperparathyroid	1
N301G	Brodie's abscess-thorac spine	1
N301H	Brodie's abscess-lumbar spine	1
N301F	Brodie's abscess-cervic spine	1
N302b	Brodie's abscess	1
N0503	Bouchard's nodes with arthropathy	1
N33z	Bone/cartilage disorder NOS	1
N33z0	Bone/cartilage dis.-unspecif.	1
N21z3	Bone spur NOS	1
N33A	Bone pain	1
N33zz	Bone or cartilage disorders NOS	1
N31z	Bone involvement in dis.EC NOS	1
N30z0	Bone infectn.NOS-site unspecif	1
N30z1	Bone infectn.NOS-shoulder	1
N30z9	Bone infectn.NOS-multiple site	1
N30z	Bone infection NOS	1
N30zz	Bone infection NOS	1
N3320	Bone cyst (localised),unspecif	1
N3y0	Biomec lesn,not elsewh clas	1
N2112	Bicipital tenosynovitis	1
N2134	Biceps tendinitis	1
N0120	Behcet's syndrome arthropathy	1
N2222	Beat knee	1
N0870	Bankart lesion	1
N224A	Baker's cyst	1
N224A-1	Baker's cyst	1
16	Baker's cyst	1
16C3	Backache with radiation	1
16CZ	Backache symptom NOS	1
16C	Backache symptom	1
16C2	Backache	1
N149	Back stiffness	1
S57	Back sprain excl. lumbosacral	1
16...	Back sprain NOS	1
S57z	Back sprain NOS	1
16C4	Back pain worse on sneezing	1
16C6	Back pain without radiat NOS	1
N145-2	Back pain unspecified	1
N143	Back pain - lower	1
UNMAPPC6	Back injury	1
N14	Back disorders - other	1
N14z	Back disorder/symptom NOS	1
OX8479	Back Strain/Sprain /ox	1
OX7289A	Back Pain With Sciatica /ox	1
N2455	Axillary pain	1
N3347	Avascular necrosis-other bone	1
N3345	Avascular necrosis, capitellum	1
N334	Avascular necrosis - bone	1
N334z	Avascular bone necrosis NOS	1
N3340	Avasc.bone necrosis site unsp.	1
N3383	Atrophic non-union of fracture	1
S5703	Atlanto-occipital joint sprain	1
N1487	Atlanto-occipital instability	1
N1480	Atlanto-occipital ankylosis	1
S5702	Atlanto-axial joint sprain	1
N1488	Atlanto-axial instability	1
N1481	Atlanto-axial ankylosis	1
14OD	At risk of osteoporotic fracture	1
14O9	At risk of osteoporosis	1
N080z	Articular cartilage disord.NOS	1
N080	Articular cart.disor.excl.knee	1
N0800	Artic.cart.dis.-site unspecif.	1
N0801	Artic.cart.dis.-shoulder	1
N0807	Artic.cart.dis.-other specif.	1
N0808	Artic.cart.dis.-multiple sites	1
N080B	Artic cart disord oth j-should	1
N0539	Arthrosis of first carpometacarpal joint, unspecified	1
OX7131C	Arthrosis Spine /ox	1
N0312	Arthropathy-Whipple's disease	1
N034	Arthropathy+respiratory disord	1

Read code	Description	Number of studies
N015	Arthropathy+other viral diseas	1
N01y	Arthropathy+other inf./parasit	1
N03y	Arthropathy+other condition EC	1
N015z	Arthropathy+oth.viral dis. NOS	1
N014	Arthropathy+oth.bacterial dis.	1
N017z	Arthropathy+helminthiasis NOS	1
N032	Arthropathy+haematological dis	1
N031	Arthropathy+gastrointestin.dis	1
N030	Arthropathy+endocr./metab.dis	1
N033	Arthropathy+dermatological dis	1
N01	Arthropathy with infections	1
N0310	Arthropathy in ulcerative colitis	1
N069	Arthropathy in neoplastic dis	1
N0302	Arthropathy in amyloidosis	1
N0148	Arthropathy in Whipple's disea	1
N0311	Arthropathy in Crohn's disease	1
N0320	Arthropathy due to haemophilia	1
N06z1	Arthropathy NOS-shoulder	1
N06z4	Arthropathy NOS-hand	1
N06z3	Arthropathy NOS-forearm	1
N06z7	Arthropathy NOS, of the ankle and foot	1
N017	Arthropathy + parasite infectn	1
N016z	Arthropathy + mycoses NOS	1
N016	Arthropathy + mycoses	1
N03z	Arthropathy + disorders EC NOS	1
N03	Arthropathy + disorders EC	1
N0y	Arthropathies OS	1
N0313	Arthropath follow intes bypass	1
N036	Arthrop-hypersensitivity reacn	1
N012	Arthrop+Behcet's syndrome	1
N0121	Arthrop+Behcet's synd-shoulder	1
N012y	Arthrop+Behcet's synd-oth spec	1
N012x	Arthrop+Behcet's synd-multiple	1
N012z	Arthrop+Behcet's synd NOS	1
N2330	Arthrogryposis	1
N0	Arthritis/arthrosis	1
N11	Arthritis of spine	1
N010A	Arthritis in Lyme disease	1
OX6960T	Arthritis Psoriatic /ox	1
N06z-1	Arthritis	1
N094F	Arthralgia of wrist	1
N094N	Arthralgia of tibio-fibular joint	1
N094A	Arthralgia of shoulder	1
N094M	Arthralgia of knee	1
N094D	Arthralgia of elbow	1
N094P	Arthralgia of ankle	1
N094H	Arthralgia of PIP joint of finger	1
N094G	Arthralgia of MCP joint	1
N094T	Arthralgia of 1st MTP joint	1
N0942	Arthralgia - upper arm	1
N094B	Arthralgia - sternoclav joint	1
N0941	Arthralgia - shoulder	1
N0945	Arthralgia - pelvic/thigh	1
N0944	Arthralgia - hand	1
N0943	Arthralgia - forearm	1
N0947	Arthralgia - ankle/foot	1
N094C	Arthralgia - acromioclav joint	1
EGTON1	Arthralgia	1
N0150	Arthr.+oth.viral dis-site unsp	1
N0151	Arthr.+oth.viral dis-shoulder	1
N0140	Arthr.+oth.bact.dis-site unsp.	1
N0141	Arthr.+oth.bact.dis-shoulder	1
N014y	Arthr.+oth.bact.dis-other spec	1
N014x	Arthr.+oth.bact.dis-mult.sites	1
N014z	Arthr.+oth bact. disease NOS	1
N0160	Arthr.+mycoses-site unspecif.	1
N0161	Arthr.+mycoses-shoulder region	1
N016y	Arthr.+mycoses-other specified	1
N016x	Arthr.+mycoses-multiple sites	1
N0170	Arthr.+helminth.-site unspec.	1
N0171	Arthr.+helminth.-shoulder regn	1
N017y	Arthr.+helminth.-other specif.	1
N017x	Arthr.+helminth.-multiple site	1
N015y	Arthr+oth.viral dis-other spec	1

Read code	Description	Number of studies
N015x	Arthr+oth.viral dis-mult.sites	1
N03x0	Arthr assoc oth dis-shoulder	1
N03xB	Arthr assoc oth dis-knee	1
N03x1	Arthr ass oth dis-sternoclav j	1
N03x2	Arthr ass oth dis-acromioclv j	1
N01yz	Arth+other infect./parasit.NOS	1
N01y0	Arth+oth.inf/para-site unspec.	1
N01y1	Arth+oth.inf/para-shoulder reg	1
N01yy	Arth+oth.inf/para-other specif	1
N01yx	Arth+oth.inf/para-multipl.site	1
N245-2	Arm pain	1
N32z0	Apophysitis NOS	1
N006	Antiphospholipid syndrome	1
1M12	Anterior knee pain	1
N094W	Anterior knee pain	1
S4101	Anterior dislocation of shoulder	1
N12z9	Annular tear of thoracic disc	1
N12zD	Annular tear of lumbar disc	1
N12z5	Annular tear of cervical disc	1
N148	Ankylosis/instab Cx,Th,Lu spin	1
N085B	Ankylosis other joint-shoulder	1
N085P	Ankylosis of the knee joint	1
N085A	Ankylosis of shoulder joint	1
N0859	Ankylosis of multiple joints	1
N085z	Ankylosis of joint NOS	1
N085	Ankylosis of joint	1
N117	Ankylosing verteb.hyperostosis	1
N100*	Ankylosing spondylitis	1
N100	Ankylosing spondylitis	1
N245-1	Ankle pain	1
1M13	Ankle pain	1
N05z7-1	Ankle osteoarthritis NOS	1
N3384	Angular mal-union of fracture	1
N3322	Aneurysmal bone cyst	1
N2320	Amyotrophia NOS	1
N0620	Allergic arthritis-site unsp.	1
N0621	Allergic arthritis-shoulder	1
N0628	Allergic arthritis-other spec.	1
N0629	Allergic arthritis-multip.site	1
N062z	Allergic arthritis-NOS	1
N062	Allergic arthritis	1
N337z	Algoneurodystrophy NOS	1
N3373	Algodystrophy of knee	1
N04y2	Adult-onset Still's disease	1
N32y0	Adult osteochondrosis of spine	1
N005	Adult Still's Disease	1
N370	Adolescent postural kyphosis	1
N3737	Adolescent idiopath scoliosis	1
N210	Adhesive capsulitis - shoulde	1
N2156	Adductor tendinitis	1
N084D	Adduction contracture-shoulder	1
N0431	Acute polyartic.juvenile R.A.	1
N300B	Acute osteomyelitis-thor spine	1
N3000	Acute osteomyelitis-site unsp.	1
N3001	Acute osteomyelitis-shoulder	1
N300G	Acute osteomyelitis-scapula	1
N300R	Acute osteomyelitis-patella	1
N3008	Acute osteomyelitis-other spec	1
N3009	Acute osteomyelitis-mult.site	1
N300C	Acute osteomyelitis-lumb spine	1
N300F	Acute osteomyelitis-clavicle	1
N300A	Acute osteomyelitis-cerv spine	1
N300z	Acute osteomyelitis NOS	1
N300	Acute osteomyelitis	1
S460	Acute meniscal tear medial	1
S461	Acute meniscal tear lateral	1
N090Y	Acute joint effusion	1
N300Z	Acute haematogen osteomyelitis	1
N145	Acute back pain - unspecified	1
N145-1	Acute back pain - unspecified	1
N141	Acute back pain - thoracic	1
N141-1	Acute back pain - thoracic	1
N142	Acute back pain - lumbar	1
N142-3	Acute back pain - lumbar	1

Read code	Description	Number of studies
N12	Acute back pain - disc	1
N143-1	Acute back pain + sciatica	1
N06zA	Acute arthritis	1
EGTONAC1	Acromio-Clavicular Dislocation	1
N384	Acquired spondylolisthesis	1
N3720	Acquired postural lordosis	1
N3710	Acquired postural kyphosis	1
N372z	Acquired lordosis NOS	1
N372	Acquired lordosis	1
N371z	Acquired kyphosis NOS	1
N371	Acquired kyphosis	1
N366	Acquired knee deformity NOS	1
N37z0	Acquired hunchback	1
N3641	Acquired genu varum	1
N364z	Acquired genu valgum/varum NOS	1
N364	Acquired genu valgum/varum	1
N3640	Acquired genu valgum	1
N385	Acquired deformity spine NOS	1
N382	Acquired deformity of neck	1
N38z	Acquired deformity NOS	1
N38y0	Acquired clavicle deformity	1
1DCC.00	Aching muscles	1
1DCC	Aching muscles	1
N220H	Achilles tenosynovitis	1
N2174	Achilles tendinitis	1
N094-1	Ache in joint	1
S4604	Ac mnscl tr,med,periph,dtchmt	1
S4614	Ac mnscl tr,lat,periph,dtchmt	1
S4605	Ac mnscl tear,med,horiz clvge	1
S4615	Ac mnscl tear,lat,horiz clvge	1
S4602	Ac menscl tear,med,bckt hndle	1
S4612	Ac menscl tear,lat,bckt hndle	1
S4603	Ac meniscal tear,med,radial	1
S4601	Ac meniscal tear,med,post horn	1
S4600	Ac meniscal tear,med,ant horn	1
S4613	Ac meniscal tear,lat,radial	1
S4611	Ac meniscal tear,lat,post horn	1
S4610	Ac meniscal tear,lat,ant horn	1
N22y2	Abscess of tendon	1
N22yE	Abscess of bursa-shoulder	1
N22yJ	Abscess of bursa-knee	1
N22y3	Abscess of bursa	1
SD	Abrasions	1
N084C	Abduction contracture-shoulder	1
1969.00	Abdominal pain	1
EGTON251	? Frozen Right Shoulder	1
N11C1	2 lev lumbsac spond+radiculop	1
N11C0	1 lev lumbsac spond+radiculop	1
HNG0160	(hn) Sports Injury	1
HNG0157	(hn) Spinal Injury	1
HNG0162	(hn) Soft tissue injuries	1
HNG0163	(hn) Rhematic problems	1
S11	#Vertebra + cord lesion	1
S10z	#Spine - no cord lesion - NOS	1
S10	#Spine - no cord lesion	1
S11z	#Spine + cord lesion NOS	1
S21z	#Scapula NOS	1
S21	#Scapula	1
S32z	#Patella NOS	1
S104	#Lumbar spine - no cord lesion	1
S32	#Knee-cap	1
S20z	#Clavicle NOS	1
S20	#Clavicle	1
S3zz	#Bones NOS	1
S4F	#-dslc/subluxation knee	1
S4A	#-dslc or subluxation shoulder	1

Supplementary appendix 4, table 10. List of Read codes used in the studies of male sexual dysfunction.

Read code	Description	Number of studies
E227311	Erectile dysfunction	3
K27y100	Impotence of organic origin	2
E227300	Impotence	2
Eu52213	[X]Psychogenic impotence	1
Eu52212	[X]Male erectile disorder	1
E227000	Unspecified psychosexual dysfunction	1
7C25E00	Treatment of erectile dysfunction NEC	1
7A6G000	Revascularisation for impotence	1
8IE8.00	Referral to erectile dysfunction clinic declined	1
8HTj.00	Referral to erectile dysfunction clinic	1
E227z00	Psychosexual dysfunction NOS	1
E227.00	Psychosexual dysfunction	1
E227700	Psychogenic dyspareunia	1
Z9E9.00	Provision of device for impotence	1
E227600	Premature ejaculation	1
7C25F00	Operations on penis for erectile dysfunction NEC	1
7A6G500	Ligation of penile veins for impotence	1
E227.11	Lack of libido	1
E227100	Inhibited sexual desire	1
E227500	Inhibited male orgasm	1
E227z11	Fear of ejaculation	1
K27y700	Erectile dysfunction due to diabetes mellitus	1
66Au.00	Diabetic erectile dysfunction review	1
66Av.00	Diabetic assessment of erectile dysfunction	1
1D1B.00	C/O erectile dysfunction	1
ZG43600	Advice on technique for impotence	1
67IA.00	Advice about impotence	1

Supplementary appendix 4, table 11. List of Read codes used in the studies of sleep disorder.

Read code	Description	Number of studies
1B1B.00	Cannot sleep - insomnia	1
1B1B.11	C/O - insomnia	1
1B1B100	Middle insomnia	1
1B1B200	Late insomnia	1
1B1Q.00	Poor sleep pattern	1
E274.00	Non-organic sleep disorders	1
E274.11	Hypersomnia of non-organic origin	1
E274.12	Insomnia due to nonorganic sleep disorder	1
E274000	Unspecified non-organic sleep disorder	1
E274100	Transient insomnia	1
E274111	Insomnia NOS	1
E274200	Persistent insomnia	1
E274300	Transient hypersomnia	1
E274311	Hypersomnia NOS	1
E274400	Persistent hypersomnia	1
E274500	Jet lag syndrome	1
E274600	Shifting sleep-work schedule	1
E274700	Somnambulism - sleep walking	1
E274800	Night terrors	1
E274900	Nightmares	1
E274A00	Sleep drunkenness	1
E274B00	Repeated rapid eye movement sleep interruptions	1
E274C00	Other sleep stage or arousal dysfunction	1
E274D00	Repetitive intrusions of sleep	1
E274D11	Restless sleep	1
E274E00	'Short-sleeper'	1
E274F00	Inversion of sleep rhythm	1
E274y00	Other non-organic sleep disorder	1
E274y11	Dreams	1
E274z00	Non-organic sleep disorder NOS	1
Eu51.00	[X]Nonorganic sleep disorders	1
Eu51000	[X]Nonorganic insomnia	1
Eu51100	[X]Nonorganic hypersomnia	1
Eu51200	[X]Nonorganic disorder of the sleep-wake schedule	1
Fy00.00	Disorders of initiating and maintaining sleep	1
Fy01.00	Disorders of excessive somnolence	1
Fy02.00	Disorders of the sleep-wake schedule	1
R005.00	[D]Sleep disturbances	1
R005.11	[D]Insomnia - symptom	1
R005.12	[D]Sleep rhythm problems	1
R005000	[D]Sleep disturbance, unspecified	1
R005100	[D]Insomnia with sleep apnoea	1
R005200	[D]Insomnia NOS	1
R005300	[D]Hypersomnia with sleep apnoea	1
R005311	[D]Sleep apnoea syndrome	1
R005312	[D]Syndrome sleep apnoea	1
R005400	[D]Hypersomnia NOS	1
R005500	[D]Sleep rhythm inversion	1
R005600	[D]Sleep rhythm irregular	1
R005700	[D]Sleep-wake rhythm non-24-hour cycle	1
R005800	[D]Sleep dysfunction with sleep stage disturbance	1
R005900	[D]Sleep dysfunction with arousal disturbance	1
R005z00	[D]Sleep dysfunction NOS	1

Supplementary appendix 4, table 12. List of Read codes used in the studies of fatal and non-fatal self-harm.

Read code	Description	Number of studies
TK1y.00	Suicide and selfinflicted poisoning by other utility gas	8
TK21.00	Suicide and selfinflicted poisoning by other carbon monoxide	8
TK01000	Suicide and self inflicted injury by Amylobarbitone	8
TK03.00	Suicide + selfinflicted poisoning tranquilliser/psychotropic	8
TK0z.00	Suicide + selfinflicted poisoning by solid/liquid subst NOS	8
TK04.00	Suicide + selfinflicted poisoning by other drugs/medicines	8
TK02.00	Suicide + selfinflicted poisoning by oth sedatives/hypnotics	8
TK20.00	Suicide + selfinflicted poisoning by motor veh exhaust gas	8
TK05.00	Suicide + selfinflicted poisoning by drug or medicine NOS	8
TK07.00	Suicide + selfinflicted poisoning by corrosive/caustic subst	8
TK01.00	Suicide + selfinflicted poisoning by barbiturates	8
TK00.00	Suicide + selfinflicted poisoning by analgesic/antipyretic	8
TK06.00	Suicide + selfinflicted poisoning by agricultural chemical	8
U200.00	[X]Intent self poison/exposure to nonopioid analgesic	7
U20..11	[X]Deliberate drug overdose / other poisoning	7
TK70.00	Suicide+selfinflicted injury-jump from residential premises	7
TK71.00	Suicide+selfinflicted injury-jump from oth manmade structure	7
TK72.00	Suicide+selfinflicted injury-jump from natural sites	7
TK7z.00	Suicide+selfinflicted injury-jump from high place NOS	7
TK61.00	Suicide and selfinflicted injury by stabbing	7
TK51.00	Suicide and selfinflicted injury by shotgun	7
TKx2.00	Suicide and selfinflicted injury by scald	7
TKxy.00	Suicide and selfinflicted injury by other specified means	7
TK54.00	Suicide and selfinflicted injury by other firearm	7
TK52.00	Suicide and selfinflicted injury by hunting rifle	7
TK30.00	Suicide and selfinflicted injury by hanging	7
TK6z.00	Suicide and selfinflicted injury by cutting and stabbing NOS	7
TK60.00	Suicide and selfinflicted injury by cutting	7
TKx5.00	Suicide and selfinflicted injury by crashing motor vehicle	7
TKx1.00	Suicide and selfinflicted injury by burns or fire	7
TK...00	Suicide and selfinflicted injury	7
TK01400	Suicide and self inflicted injury by Phenobarbitone	7
TK01100	Suicide and self inflicted injury by Barbitone	7
TK...14	Suicide and self harm	7
TK0..00	Suicide + selfinflicted poisoning by solid/liquid substances	7
TK2..00	Suicide + selfinflicted poisoning by other gases and vapours	7
TK11.00	Suicide + selfinflicted poisoning by liquified petrol gas	7
TK2z.00	Suicide + selfinflicted poisoning by gases and vapours NOS	7
TK10.00	Suicide + selfinflicted poisoning by gas via pipeline	7
TK1z.00	Suicide + selfinflicted poisoning by domestic gases NOS	7
TKx0000	Suicide + selfinflicted injury-jumping before moving object	7
TK31.00	Suicide + selfinflicted injury by suffocation by plastic bag	7
TK3y.00	Suicide + selfinflicted inj oth mean hang/strangle/suffocate	7
TK3z.00	Suicide + selfinflicted inj by hang/strangle/suffocate NOS	7
TK...13	Poisoning - self-inflicted	7
TK...17	Para-suicide	7
TK...11	Cause of overdose - deliberate	7
TK...15	Attempted suicide	7
U2...13	[X]Suicide	6
U20C.11	[X]Self poisoning with weedkiller	6
U20C.12	[X]Self poisoning with paraquat	6
U20A.11	[X]Self poisoning from glue solvent	6
U20B.11	[X]Self carbon monoxide poisoning	6
U2...15	[X]Para-suicide	6
U20..00	[X]Intentional self poisoning/exposure to noxious substances	6
U20A.00	[X]Intentional self poison organ solvent,halogen hydrocarb	6
U20y.00	[X]Intent self poison/exposure to unspecif chemical	6
U202.00	[X]Intent self poison/exposure to sedative hypnotic	6
U204.00	[X]Intent self poison/exposure to psychotropic drug	6
U20C.00	[X]Intent self poison/exposure to pesticide	6
U20B.00	[X]Intent self poison/exposure to other gas/vapour	6
U207.00	[X]Intent self poison/exposure to oth autonomic drug	6
U206.00	[X]Intent self poison/exposure to hallucinogen	6
U201.00	[X]Intent self poison/exposure to antiepileptic	6
U20yz00	[X]Intent self poison unspecif chemical unspecif place	6
U202z00	[X]Intent self poison sedative hypnotic unspecif place	6
U204z00	[X]Intent self poison psychotropic drug unspecif place	6
U204100	[X]Intent self poison psychotropic drug at res institut	6
U20Bz00	[X]Intent self poison other gas/vapour unspecif place	6
U208z00	[X]Intent self poison oth/unsp drug/medic unspecif place	6
U207z00	[X]Intent self poison oth autonomic drug unspecif place	6

Read code	Description	Number of studies
U200z00	[X]Intent self poison nonopioid analgesic unspecif place	6
U200100	[X]Intent self poison nonopioid analgesic at res institut	6
U205z00	[X]Intent self poison narcotic drug unspecif place	6
U201z00	[X]Intent self poison antiepileptic unspecif place	6
U206400	[X]Intent self pois hallucinogen in street/highway	6
U20y000	[X]Int self poison/exposure to unspecif chemical at home	6
U202000	[X]Int self poison/exposure to sedative hypnotic at home	6
U204000	[X]Int self poison/exposure to psychotropic drug at home	6
U20C000	[X]Int self poison/exposure to pesticide at home	6
U208.00	[X]Int self poison/exposure to other/unspec drug/medicament	6
U20B000	[X]Int self poison/exposure to other gas/vapour at home	6
U207000	[X]Int self poison/exposure to oth autonomic drug at home	6
U200000	[X]Int self poison/exposure to nonopioid analgesic at home	6
U205000	[X]Int self poison/exposure to narcotic drug at home	6
U201000	[X]Int self poison/exposure to antiepileptic at home	6
U20y200	[X]Int self poison unspecif chemical school/pub admin area	6
U202y00	[X]Int self poison sedative hypnotic other spec place	6
U204y00	[X]Int self poison psychotropic drug other spec place	6
U20Cy00	[X]Int self poison pesticide other spec place	6
U20B200	[X]Int self poison other gas/vapour school/pub admin area	6
U20By00	[X]Int self poison other gas/vapour other spec place	6
U208y00	[X]Int self poison oth/unsp drug/medic other spec place	6
U20A400	[X]Int self poison org solvent,halogen hydrocarb,in highway	6
U200y00	[X]Int self poison nonopioid analgesic other spec place	6
U205y00	[X]Int self poison narcotic drug other spec place	6
U2...14	[X]Attempted suicide	6
TKx7.00	Suicide and selfinflicted injury caustic subst, excl poison	6
TKxz.00	Suicide and selfinflicted injury by other means NOS	6
TKx..00	Suicide and selfinflicted injury by other means	6
TK7..00	Suicide and selfinflicted injury by jumping from high place	6
TKx3.00	Suicide and selfinflicted injury by extremes of cold	6
TKx4.00	Suicide and selfinflicted injury by electrocution	6
TK4..00	Suicide and selfinflicted injury by drowning	6
TK6..00	Suicide and selfinflicted injury by cutting and stabbing	6
TKz..00	Suicide and selfinflicted injury NOS	6
TK1..00	Suicide + selfinflicted poisoning by gases in domestic use	6
TKx0.00	Suicide + selfinflicted injury-jump/lie before moving object	6
TK3..00	Suicide + selfinflicted injury by hang/strangulate/suffocate	6
U2y0.00	[X]Intentionl self harm by oth specif means occurrn at home	5
U2z0.00	[X]Intentional self harm by unspecif means occurrn at home	5
U290.00	[X]Intentional self harm by sharp object occurrence at home	5
U29z.00	[X]Intentional self harm by sharp object occ unspecif place	5
U2A0.00	[X]Intentional self harm by blunt object occurrence at home	5
U270.00	[X]Intention self harm by smoke fire/flames occurrn at home	5
U294.00	[X]Intention self harm by sharp object occ street/highway	5
U29y.00	[X]Intention self harm by sharp object occ oth specif place	5
U205.00	[X]Intent self poison/exposure to narcotic drug	5
U209.00	[X]Intent self poison/exposure to alcohol	5
U209z00	[X]Intent self poison alcohol unspecif place	5
U202400	[X]Intent self pois sedative hypnotic in street/highway	5
U208400	[X]Intent self pois oth/unsp drug/medic in street/highway	5
U20A000	[X]Intent self pois organ solvent,halogen hydrocarb, home	5
U200500	[X]Intent self pois nonopioid analgesic trade/service area	5
U250.00	[X]Intent self harm oth/unspecif firearm disch occ at home	5
U2D6.00	[X]Intent self harm crash motor vehic occ indust/constr area	5
U2zy.00	[X]Intent self harm by unspecif means occ oth specif place	5
U2zz.00	[X]Intent self harm by unspecif means occ at unspecif place	5
U2z2.00	[X]Intent self harm by unspec mean occ sch/ins/pub adm area	5
U27z.00	[X]Intent self harm by smoke fire/flames occ unspecif place	5
U274.00	[X]Intent self harm by smoke fire/flame occ street/highway	5
U291.00	[X]Intent self harm by sharp object occ resident instit'n	5
U2yz.00	[X]Intent self harm by oth specif means occ unspecif place	5
U2y1.00	[X]Intent self harm by oth specif means occ resid instit'n	5
U2B0.00	[X]Intent self harm by jumping from high place occ at home	5
U2B4.00	[X]Intent self harm by jump from high place occ street/h'way	5
U211.00	[X]Intent self harm by hangng strangult/suffoct resid instit	5
U21z.00	[X]Intent self harm by hangng strangul/suffoct unspecif plce	5
U21y.00	[X]Intent self harm by hangng strangul/suffoct oth spec plce	5
U210.00	[X]Intent self harm by hanging strangulat/suffocat occ home	5
U221.00	[X]Intent self harm by drowning/submersn occ resid instit'n	5
U22z.00	[X]Intent self harm by drown/submersn occ unspecified place	5
U22y.00	[X]Intent self harm by drown/submersn occ oth specif place	5
U2D0.00	[X]Intent self harm by crash of motor vehicl occurrn at home	5
U2D4.00	[X]Intent self harm by crash motor vehicl occ street/highway	5
U2A3.00	[X]Intent self harm by blunt object occ sports/athlet area	5

Read code	Description	Number of studies
U2A1.00	[X]Intent self harm by blunt object occ resident instit'n	5
U242.00	[X]Int slf hrm rifl s'gun/lrg frarm dis sch/ins/pub adm area	5
U208000	[X]Int self poison/exposure to oth/unsp drug/medicam home	5
U209y00	[X]Int self poison alcohol other spec place	5
U20Az00	[X]Int self pois org solv,halogen hydrocarb, unspec place	5
U241.00	[X]Int self harm rifl s'gun/lrg frarm disch occ resid instit	5
U2C4.00	[X]Int self harm jump/lying befr mov obje occ street/highway	5
U2C1.00	[X]Int self harm jump/lying befr mov obje occ resid instit'n	5
U2Cy.00	[X]Int self harm jump/lying bef mov obje occ oth specif plce	5
U2Bz.00	[X]Int self harm by jump from high place occ unspecif place	5
U2By.00	[X]Int self harm by jump from high place occ oth specif plce	5
U2B6.00	[X]Int self harm by jump from high place indust/constr area	5
TK5z.00	Suicide and selfinflicted injury by firearms/explosives NOS	5
TK5..00	Suicide and selfinflicted injury by firearms and explosives	5
TKx6.00	Suicide and selfinflicted injury by crashing of aircraft	5
TK60111	Slashed wrists self inflicted	5
TK60100	Self inflicted lacerations to wrist	5
U202.13	[X]Overdose - temazepam	4
U202.11	[X]Overdose - sleeping tabs	4
U202.15	[X]Overdose - nitrazepam	4
U202.12	[X]Overdose - diazepam	4
U202.16	[X]Overdose - benzodiazepine	4
U202.17	[X]Overdose - barbiturate	4
U204.11	[X]Overdose - antidepressant	4
U202.18	[X]Overdose - amobarbital	4
U204.12	[X]Overdose - amitriptyline	4
U204.13	[X]Overdose - SSRI	4
U2z..00	[X]Intentional self harm by unspecified means	4
U27..00	[X]Intentional self harm by smoke, fire and flames	4
U29..00	[X]Intentional self harm by sharp object	4
U2y..00	[X]Intentional self harm by other specified means	4
U2B..00	[X]Intentional self harm by jumping from a high place	4
U26..00	[X]Intentional self harm by explosive material	4
U22..00	[X]Intentional self harm by drowning and submersion	4
U2D..00	[X]Intentional self harm by crashing of motor vehicle	4
U2A..00	[X]Intentional self harm by blunt object	4
U200400	[X]Intent self pois nonopioid analgesic in street/highway	4
U28z.00	[X]Intent self harm by steam hot vapour/obj occ unspec place	4
U280.00	[X]Intent self harm by steam hot vapour/hot obj occ at home	4
U24..00	[X]Intent self harm by rifle shotgun/larger firearm disch	4
U25..00	[X]Intent self harm by other/unspecified firearm discharge	4
U2C..00	[X]Intent self harm by jumping / lying before moving object	4
U21..00	[X]Intent self harm by hanging strangulation / suffocation	4
U212.00	[X]Inten slf harm hang strang/suffc sch oth ins/pub adm area	4
U209000	[X]Int self poison/exposure to alcohol at home	4
U41..00	[X]Hanging strangulation + suffocation undetermined intent	4
U4Bz.00	[X]Fall jump/push frm high plce undt intnt occ unspecif plce	4
U720.00	[X]Sequelae of intentional self-harm	3
U2...11	[X]Self inflicted injury	3
U44..00	[X]Rifle shotgun+larger firearm discharge undetermin intent	3
U40y.00	[X]Poisoning/exposure, ? intent, to unspecif chemical	3
U402.00	[X]Poisoning/exposure, ? intent, to sedative hypnotic	3
U404.00	[X]Poisoning/exposure, ? intent, to psychotropic drug	3
U40C.00	[X]Poisoning/exposure, ? intent, to pesticide	3
U40B.00	[X]Poisoning/exposure, ? intent, to other gas/vapour	3
U400.00	[X]Poisoning/exposure, ? intent, to nonopioid analgesic	3
U405.00	[X]Poisoning/exposure, ? intent, to narcotic drug	3
U409.00	[X]Poisoning/exposure, ? intent, to alcohol	3
U40..00	[X]Poisoning/expos to noxious substance,undetermined intent	3
U408.00	[X]Poison/exposure, ?intent, to other/unspec drug/medicament	3
U408000	[X]Poison/exposure ?intent, to oth/unsp drug/medicam home	3
U409000	[X]Poison/exposure ?intent, to alcohol at home	3
U40y600	[X]Poison/expos ?intent unspec chemic indust/construct area	3
U200.11	[X]Overdose - paracetamol	3
U200.12	[X]Overdose - ibuprofen	3
U200.13	[X]Overdose - aspirin	3
U45..00	[X]Other+unspecified firearm discharge undetermined intent	3
U2...00	[X]Intentional self-harm	3
U28..00	[X]Intentional self harm by steam hot vapours / hot objects	3
U216.00	[X]Intent self harm by hang strangl/suffc indust/constr area	3
U220.00	[X]Intent self harm by drowning/submersion occurrn at home	3
U206000	[X]Int self poison/exposure to hallucinogen at home	3
U2...12	[X]Injury - self-inflicted	3
U410.00	[X]Hanging strangulat+suffocat undet intent occurrn at home	3
U4B..00	[X]Falling jumping/pushed from high place undeterm intent	3

Read code	Description	Number of studies
U30..11	[X]Deliberate drug poisoning	3
ZX1R.00	Throwing self in front of vehicle	3
ZX1Q.00	Throwing self in front of train	3
TK53.00	Suicide and selfinflicted injury by military firearms	3
TK01z00	Suicide and self inflicted injury by barbiturates	3
TK2y.00	Suicide + selfinflicted poisoning by other gases and vapours	3
TKx0z00	Suicide + selfinflicted inj-jump/lie before moving obj NOS	3
ZX1N.00	Stabbing self	3
ZX1M.00	Shooting self	3
ZX1K.12	Setting self alight	3
ZX1K.11	Setting fire to self	3
ZX1H200	Self-suffocation	3
ZX1H100	Self-strangulation	3
ZX1K.00	Self-incineration	3
ZX1J.00	Self-electrocution	3
ZX1H.00	Self-asphyxiation	3
SL...15	Overdose of drug	3
SL...14	Overdose of biological substance	3
TKy..00	Late effects of selfinflicted injury	3
ZX1Q.11	Jumping under train	3
ZX1B.00	Jumping from height	3
ZX1B300	Jumping from cliff	3
ZX1B100	Jumping from building	3
ZX1B200	Jumping from bridge	3
TK...12	Injury - self-inflicted	3
ZX18.00	Hanging self	3
SLHz.00	Drug and medicament poisoning NOS	3
ZX15.00	Drowning self	3
U72..00	[X]Sequel intentn self-harm assault+event of undeterm intent	2
ZX1LD00	[X]Self mutilation	2
U40y000	[X]Poison/exposure ?intent, to unspecif chemical at home	2
U40C000	[X]Poison/exposure ?intent, to pesticide at home	2
U40A.00	[X]Pois/exposure,?intent,to organ solvent,halogen hydrocarb	2
U40y400	[X]Pois/expos ?intent unspecif chemical in street/highway	2
U40yz00	[X]Pois/expos ?intent to unspecif chemical unspecif place	2
U402z00	[X]Pois/expos ?intent to sedative hypnotic unspecif place	2
U408z00	[X]Pois/expos ?intent to oth/unsp drug/medic unspecif place	2
U409z00	[X]Pois/expos ?intent to alcohol unspecif place	2
U40B400	[X]Pois/expos ?intent other gas/vapour in street/highway	2
U409400	[X]Pois/expos ?intent alcohol in street/highway	2
U406y00	[X]Pois/exp ?intent to hallucinogen other spec place	2
U404300	[X]Pois/exp ?intent psychotropic drug in sport/athletic area	2
U40A300	[X]Pois/exp ?intent org solvent,halogen hydrocarb,sport area	2
U409200	[X]Pois/exp ?intent alcohol school/pub admin area	2
U205.11	[X]Overdose - heroin	2
U2Az.00	[X]Intentional self harm by blunt object occ unspecif place	2
U206z00	[X]Intent self poison hallucinogen unspecif place	2
U209400	[X]Intent self pois alcohol in street/highway	2
U292.00	[X]Intent self harm sharp obj occ sch oth ins/pub adm area	2
U2yy.00	[X]Intent self harm oth specif means occ oth specif place	2
U2y6.00	[X]Intent self harm oth specif means occ indust/constr area	2
U2z1.00	[X]Intent self harm by unspecif means occurrn resid instit'n	2
U27y.00	[X]Intent self harm by smoke fire/flame occ oth specif plce	2
U295.00	[X]Intent self harm by sharp object occ trade/service area	2
U296.00	[X]Intent self harm by sharp object occ indust/constr area	2
U2B1.00	[X]Intent self harm by jump from high place occ resid instit	2
U213.00	[X]Intent self harm by hang strangl/suffc sport/athlet area	2
U2Dz.00	[X]Intent self harm by crash motor vehic occ unspecif place	2
U2A2.00	[X]Intent self harm blunt obj occ sch oth ins/pub adm area	2
U20Ay00	[X]Int self pois org solv,halogen hydrocarb,oth spec place	2
U200600	[X]Int self pois nonopioid analgesic indust/construct area	2
U282.00	[X]Int self harm by steam hot vapor/obj sch/ins/pub adm area	2
U4C..00	[X]Falling lying running befor/into moving obj undet intent	2
U4B6.00	[X]Fall jump/push frm high plce undt intn indust/constr area	2
U47..00	[X]Exposure to smoke, fire and flames, undetermined intent	2
U470.00	[X]Exposure to smoke fire+flame undeterm intent occ at home	2
U42..00	[X]Drowning and submersion, undetermined intent	2
U4D7.00	[X]Crashng of motor vehicle undetermined intent occ on farm	2
U4D0.00	[X]Crashng of motor vehicle undetermined intent occ at home	2
U4D..00	[X]Crashing of motor vehicle, undetermined intent	2
U4D3.00	[X]Crash of motor vehicle undeterm intent sport/athlet area	2
U4A5.00	[X]Contct wth blunt obj undet intent occ trade/service area	2
U4A3.00	[X]Contct wth blunt obj undet intent occ sport/athletic area	2
U4A0.00	[X]Contact wth blunt object undetermined intent occ at home	2
U48..00	[X]Contact with steam hot vapours+objects undetermn intent	2

Read code	Description	Number of studies
U49..00	[X]Contact with sharp object, undetermined intent	2
U49z.00	[X]Contact with sharp obj undeterm intent occ unspecif place	2
U4A..00	[X]Contact with blunt object, undetermined intent	2
U4Az.00	[X]Contact with blunt obj undeterm intent occ unspecif place	2
ZX1S.00	Throwing self onto floor	2
1BDA.00	Thoughts of deliberate self harm	2
1BD3.00	Suicidal plans	2
1BD1.00	Suicidal ideation	2
1B19.11	Suicidal - symptom	2
1B19.00	Suicidal	2
ZX19200	Slapping self	2
ZX1I.00	Self-scalding	2
ZX1L300	Self-mutilation of penis	2
ZX1L100	Self-mutilation of hands	2
ZX1L200	Self-mutilation of genitalia	2
ZX1L600	Self-mutilation of ears	2
ZX1L.00	Self-mutilation	2
ZX1G.00	Scratches self	2
ZX19100	Punching self	2
TN...11	Poisoning undetermined - accidentally or purposely inflicted	2
ZX1E.00	Pinching self	2
ZX1C.00	Nipping self	2
14K1.00	Intentional overdose of prescription only medication	2
TN0..00	Injury ?accidental, poisoning by solid/liquid substances	2
TN0z.00	Injury ?accidental, poisoning by solid or liquid subst NOS	2
TN2y.00	Injury ?accidental, poisoning by other spec gas or vapour	2
TN04.00	Injury ?accidental, poisoning by other spec drug/medicament	2
TN02.00	Injury ?accidental, poisoning by other sedative/hypnotic	2
TN2..00	Injury ?accidental, poisoning by other gases	2
TN21.00	Injury ?accidental, poisoning by other carbon monoxide	2
TN20.00	Injury ?accidental, poisoning by motor vehicle exhaust gas	2
TN11.00	Injury ?accidental, poisoning by liquid petrol gas	2
TN1..00	Injury ?accidental, poisoning by gases in domestic use	2
TN1z.00	Injury ?accidental, poisoning by gas in domestic use NOS	2
TN10.00	Injury ?accidental, poisoning by gas distributed by pipeline	2
TN05.00	Injury ?accidental, poisoning by drug or medicament NOS	2
TN06.00	Injury ?accidental, poisoning by corrosive/caustic substance	2
TN08.00	Injury ?accidental, poisoning by arsenic or its compounds	2
TN00.00	Injury ?accidental, poisoning by analgesic or anti-pyretic	2
TN07.00	Injury ?accidental, poisoning by agricultural chemicals	2
TN3..00	Injury ?accidental, hanging, strangulation and suffocation	2
TN30.00	Injury ?accidental, hanging	2
TN01300	Injury ?accidental poisoning by Pentobarbitone	2
ZRLfC12	HoNOS item 2 - non-accidental self injury	2
ZX19.00	Hitting self	2
ZX13.00	Cutting self	2
ZX13.11	Cuts self	2
ZX12.00	Burning self	2
ZX11.00	Biting self	2
ZX11.11	Bites self	2
SL90.00	Antidepressant poisoning	2
8G6Z.00	Anti-suicide psychotherapy NOS	2
8G6..00	Anti-suicide psychotherapy	2
SL90z00	Anti-depressant poisoning NOS	2
U4z..00	[X]Unspecified event, undetermined intent	1
U4zz.00	[X]Unspecif event undeterm intent occurrn unspecif place	1
U4z3.00	[X]Unspecif event undeterm intent occurrn sport/athlet area	1
U4zy.00	[X]Unspecif event undeterm intent occurrn oth specif place	1
U4z6.00	[X]Unspecif event undeterm intent occurrn indust/constr area	1
SyuG.00	[X]Toxic effects of substances chiefly nonmedicinal source	1
SyuG700	[X]Toxic effects of other specified gases, fumes & vapours	1
SyuGH00	[X]Toxic effect of paints and dyes, NEC	1
SyuGJ00	[X]Toxic effect of other specified substances	1
SyuG900	[X]Toxic effect of other pesticides	1
SyuG800	[X]Toxic effect of other insecticides	1
SyuGC00	[X]Toxic effect of other ingested (parts of) plant(s)	1
SyuG000	[X]Toxic effect of other alcohols	1
U2E..00	[X]Self mutilation	1
U406.00	[X]Poisoning/exposure, ? intent, to hallucinogen	1
SyuFM00	[X]Poisoning by other psychotropic drugs, NEC	1
SyuFB00	[X]Poisoning by other opioids	1
SyuFW00	[X]Poisoning by other laxatives, incl intestin atonia drugs	1
SyuFT00	[X]Poisoning by other antihypertensive drugs, NEC	1
SyuFD00	[X]Poisoning by other and unspecified narcotics	1
SyuFA00	[X]Poisoning by other analgesics, not elsewhere classified	1

Read code	Description	Number of studies
SyuF900	[X]Poisoning by oth nonsteroidal anti-inflamm drugs [NSAID]	1
SyuFc00	[X]Poisoning by oth & unspecif drugs & biologic substances	1
SyuF.00	[X]Poisoning by drugs and biological substances	1
U40Bz00	[X]Pois/expos ?intent to other gas/vapour unspecif place	1
U409100	[X]Pois/expos ?intent to alcohol at res institut	1
U408400	[X]Pois/expos ?intent oth/unsp drug/medic in street/highway	1
U40yy00	[X]Pois/exp ?intent to unspecif chemical other spec place	1
U40By00	[X]Pois/exp ?intent to other gas/vapour other spec place	1
U202.14	[X]Overdose - flurazepam	1
U4y..00	[X]Other specified events, undetermined intent	1
U4y0.00	[X]Other specified event undetermind intent occurrn at home	1
U4y3.00	[X]Oth specif event undetermin intent occ sport/athlet area	1
Eu15000	[X]Mnt/beh dis due oth stim inc caffein: acute intoxication	1
Eu18000	[X]Mental & behav dis due vol solvents: acute intoxication	1
Eu17000	[X]Mental & behav dis due to use tobacco: acute intoxication	1
Eu11000	[X]Mental & behav dis due to use opioids: acute intoxication	1
Eu14000	[X]Mental & behav dis due to use cocaine: acute intoxication	1
Eu10000	[X]Mental & behav dis due to use alcohol: acute intoxication	1
Eu13000	[X]Mental & behav dis due seds/hypntcs: acute intoxication	1
Eu16000	[X]Mental & behav dis due hallucinogens: acute intoxicatn	1
Eu12000	[X]Mental & behav dis due cannabinoids: acute intoxication	1
Eu1A000	[X]Ment behav dis due use crack cocaine: acute intoxication	1
U39..11	[X]Intentionally shot with shotgun	1
U38..11	[X]Intentionally shot with handgun	1
U41z.00	[X]Hangng strangult+suffoct undet intent occ unspecif place	1
U4B0.00	[X]Fallng jumpng/push frm high place undet intent occ home	1
U81..00	[X]Evid of alcohol involv determind by level of intoxication	1
U4D1.00	[X]Crashng of motor vehicle undeterm intent resident instit	1
U466.00	[X]Contct wth explosiv materl undet intnt indust/constr area	1
U4A6.00	[X]Contct wth blunt obj undet intent occ industr/constr area	1
U46..00	[X]Contact with explosive material, undetermined intent	1
U4Ay.00	[X]Contact with blunt obj undeter intent occ oth specif plce	1
U1AC.11	[X]Accidental poisoning with weedkiller	1
U1A2.13	[X]Accidental poisoning with temazepam	1
U1A2.11	[X]Accidental poisoning with sleeping tablets	1
U1AC.12	[X]Accidental poisoning with paraquat	1
U1A0.11	[X]Accidental poisoning with paracetamol	1
U1A2.15	[X]Accidental poisoning with nitrazepam	1
U1A0.12	[X]Accidental poisoning with ibuprofen	1
U1A5.11	[X]Accidental poisoning with heroin	1
U1A2.12	[X]Accidental poisoning with diazepam	1
U1A2.16	[X]Accidental poisoning with benzodiazepine	1
U1A2.17	[X]Accidental poisoning with barbiturate	1
U1A0.13	[X]Accidental poisoning with aspirin	1
U1A4.11	[X]Accidental poisoning with antidepressant	1
U1A4.12	[X]Accidental poisoning with amitriptyline	1
U1A4.13	[X]Accidental poisoning with SSRI	1
U1AA.11	[X]Accidental poisoning from glue solvent	1
U1AD.00	[X]Accidental poisoning by and exposure to amfetamine	1
U1A..00	[X]Accidental poisoning by + exposure to noxious substances	1
U1A..12	[X]Accidental drug overdose / other poisoning	1
U1A..11	[X]Accidental drug / other poisoning	1
U1AB.11	[X]Accidental carbon monoxide poisoning	1
U1Ay.00	[X]Accident poisoning/exposure to unspecif chemical	1
U1A2.00	[X]Accident poisoning/exposure to sedative hypnotic	1
U1A4.00	[X]Accident poisoning/exposure to psychotropic drug	1
U1AC.00	[X]Accident poisoning/exposure to pesticide	1
U1AB.00	[X]Accident poisoning/exposure to other gas/vapour	1
U1A7.00	[X]Accident poisoning/exposure to oth autonomic drug	1
U1A0.00	[X]Accident poisoning/exposure to nonopioid analgesic	1
U1A5.00	[X]Accident poisoning/exposure to narcotic drug	1
U1A6.00	[X]Accident poisoning/exposure to hallucinogen	1
U1A3.00	[X]Accident poisoning/exposure to antiparkinson drug	1
U1A1.00	[X]Accident poisoning/exposure to antiepileptic	1
U1A9.00	[X]Accident poisoning/exposure to alcohol	1
U1AD000	[X]Accident poisoning by and exposure to amphetamine - home	1
U1Ay700	[X]Accident poison/exposure to unspecif chemical on farm	1
U1Ay000	[X]Accident poison/exposure to unspecif chemical at home	1
U1A2000	[X]Accident poison/exposure to sedative hypnotic at home	1
U1A4000	[X]Accident poison/exposure to psychotropic drug at home	1
U1AC700	[X]Accident poison/exposure to pesticide on farm	1
U1AC000	[X]Accident poison/exposure to pesticide at home	1
U1A8.00	[X]Accident poison/exposure to other/unspec drug/medicament	1
U1AB700	[X]Accident poison/exposure to other gas/vapour on farm	1
U1AB000	[X]Accident poison/exposure to other gas/vapour at home	1

Read code	Description	Number of studies
U1A8000	[X]Accident poison/exposure to oth/unsp drug/medicam home	1
U1A7000	[X]Accident poison/exposure to oth autonomic drug at home	1
U1A0000	[X]Accident poison/exposure to nonopioid analgesic at home	1
U1A5000	[X]Accident poison/exposure to narcotic drug at home	1
U1A1000	[X]Accident poison/exposure to antiepileptic at home	1
U1A9000	[X]Accident poison/exposure to alcohol at home	1
U1AA.00	[X]Accid poison/exposure to organ solvent,halogen hydrocarb	1
U1Ay500	[X]Accid poison/expos unspecif chemical trade/service area	1
U1Ayz00	[X]Accid poison/expos to unspecif chemical unspecif place	1
U1Ay100	[X]Accid poison/expos to unspecif chemical at res institut	1
U1A2z00	[X]Accid poison/expos to sedative hypnotic unspecif place	1
U1A4100	[X]Accid poison/expos to psychotropic drug at res institut	1
U1ABz00	[X]Accid poison/expos to other gas/vapour unspecif place	1
U1A8100	[X]Accid poison/expos to oth/unsp drug/medicam res institut	1
U1A8z00	[X]Accid poison/expos to oth/unsp drug/medic unspecif place	1
U1A7z00	[X]Accid poison/expos to oth autonomic drug unspecif place	1
U1A0z00	[X]Accid poison/expos to nonopioid analgesic unspecif place	1
U1A5z00	[X]Accid poison/expos to narcotic drug unspecif place	1
U1A9z00	[X]Accid poison/expos to alcohol unspecif place	1
U1AA000	[X]Accid poison/expos organ solvent,halogen hydrocarb, home	1
U1A3500	[X]Accid poison/expos antiparkinson drug trade/service area	1
U1A9500	[X]Accid poison/expos alcohol trade/service area	1
U1A9400	[X]Accid poison/expos alcohol in street/highway	1
U1Ay200	[X]Acc poison/expos unspecif chemical school/pub admin area	1
U1A4200	[X]Acc poison/expos psychotropic drug school/pub admin area	1
U1AA100	[X]Acc poison/expos org solvent,halogen hydrocarb,res instit	1
U1A9200	[X]Acc poison/expos alcohol school/pub admin area	1
U1ADz00	[X]Acc poison by and exposure to amphetamine - unspec places	1
Sy...00	[X] Injury and poisoning classification terms	1
U60F412	[X] Adverse reaction to acetylcysteine	1
ZV15600	[V]Personal history of poisoning	1
ZV4C400	[V]Occupational exposure to toxic agents in agriculture	1
ZV71A00	[V]Obs for suspected toxic effect from ingested substance	1
SLC7100	Zinc salt poisoning	1
SM01100	Wood alcohol causing toxic effect	1
SLEz.00	Water, mineral or uric acid metabolism poisoning NOS	1
SLE..00	Water, mineral and urate metabolism poisoning	1
SL42300	Warfarin sodium poisoning	1
SL42400	Warfarin poisoning	1
SL35z00	Vitamin poisoning NOS	1
SL35.00	Vitamin poisoning NEC	1
SL35100	Vitamin D poisoning	1
SL35000	Vitamin A poisoning	1
SL44300	Urokinase poisoning	1
SLE7.00	Uric acid drug poisoning	1
SLE7.11	Urate metabolism drug poisoning	1
SM9z.00	Unspecified substance causing toxic effect NOS	1
SL50000	Unspecified opium poisoning	1
SL30400	Tripelennamine poisoning	1
SL60100	Trimethadione poisoning	1
SL92200	Trifluperidol poisoning	1
SM23100	Trichloroethylene causing toxic effect	1
SL90300	Trazodone poisoning	1
SL95z00	Tranquilliser poisoning NOS	1
SL9..11	Tranquilliser poisoning	1
TE57.00	Toxic reactions caused by other plants	1
F036200	Toxic encephalitis due to thallium	1
F036100	Toxic encephalitis due to mercury	1
F036000	Toxic encephalitis due to lead	1
SMC..00	Toxic effect of tobacco and nicotine	1
SM57.00	Toxic effect of tin and its compounds	1
SM9A.00	Toxic effect of rodenticides	1
SMX..00	Toxic effect of paints and dyes, NEC	1
SM9X.00	Toxic effect of nitroglycerin & oth nitric acids & ester	1
SM79.00	Toxic effect of hydrogen sulfide	1
SM15.00	Toxic effect of homologues of benzene	1
SM98.00	Toxic effect of herbicides and fungicides	1
SMB..00	Toxic effect of formaldehyde	1
SM78.00	Toxic effect of fluorine gas and hydrogen fluoride	1
SM23200	Toxic effect of chloroform	1
SM7A.00	Toxic effect of carbon dioxide	1
SLG7.00	Topical dental drug poisoning	1
SL85.00	Topical and infiltration anaesthetic agent poisoning	1
SL16200	Tiabendazole poisoning	1
SL27.00	Thyroid hormone and thyroid derivatives poisoning	1

Read code	Description	Number of studies
SL27z00	Thyroid hormone and thyroid derivative poisoning NOS	1
SL27300	Thyroglobulin poisoning	1
SL91400	Thioridazine poisoning	1
SLE1100	Theophylline poisoning	1
SL04000	Tetracycline poisoning	1
SL04z00	Tetracycline group poisoning NOS	1
SL04.00	Tetracycline group poisoning	1
SM23000	Tetrachloroethylene causing toxic effect	1
SL85300	Tetracaine poisoning	1
SL21300	Testosterone poisoning	1
SLF5200	Terpin hydrate poisoning	1
SL3z.00	Systemic agent poisoning NOS	1
SLB2.00	Sympathomimetic poisoning	1
SM31200	Sulphuric acid causing toxic effect	1
SM73.00	Sulphur dioxide causing toxic effect	1
SL1x400	Sulphone poisoning	1
SL10.00	Sulphonamide poisoning	1
SL10200	Sulfamethoxazole poisoning	1
SL10000	Sulfadiazine poisoning	1
1BD4.00	Suicide risk	1
ZRn3.00	Suicide intent score subscale - attempt circumstances	1
SN47100	Suffocation by strangulation	1
SL06300	Streptomycin poisoning	1
SL44200	Streptokinase poisoning	1
SL97.11	Stimulant poisoning	1
SM2z.00	Solvents causing toxic effect NOS	1
SLC7000	Sodium morrhuate poisoning	1
SM32200	Sodium hydroxide causing toxic effect	1
SM90100	Sodium cyanide causing toxic effect	1
SM96.00	Soap and detergent causing toxic effect	1
SM96.12	Soap - toxic effect	1
SLF1.00	Smooth muscle relaxant poisoning	1
SL7z.11	Sleeping drug poisoning	1
SLF2.00	Skeletal muscle relaxant poisoning	1
ZX1..00	Self-injurious behaviour	1
ZX...00	Self-harm	1
ZX...11	Self-damage	1
SL7..12	Sedative poisoning	1
SL7z.00	Sedative and hypnotic drug poisoning NOS	1
SL7..00	Sedative and hypnotic drug poisoning	1
SL70500	Secobarbital poisoning	1
SL51100	Salicylic acid salt poisoning	1
SL51z00	Salicylate poisoning NOS	1
SL51.00	Salicylate poisoning	1
SLF7100	Salbutamol poisoning	1
ZX1..12	SIB - Self-injurious behaviour	1
SM02200	Rubbing alcohol causing toxic effect	1
SL06200	Rifampicin poisoning	1
SLF..12	Respiratory system drug poisoning	1
SL14500	Quinine poisoning	1
SLC0300	Quinidine poisoning	1
SL14400	Pyrimethamine poisoning	1
SL53.00	Pyrazole derivative poisoning	1
SL9z.00	Psychotropic agent poisoning NOS	1
SL9..00	Psychotropic agent poisoning	1
SL97.00	Psychostimulant poisoning	1
SL96400	Psilocybin poisoning	1
SL45100	Protamine sulphate poisoning	1
SLF0200	Prostaglandin poisoning	1
SLC0200	Propranolol poisoning	1
SM70100	Propane causing toxic effect	1
SL91300	Promazine poisoning	1
SL14300	Proguanil poisoning	1
SL22300	Progestogen poisoning	1
SL91200	Prochlorperazine poisoning	1
SLC0100	Procainamide poisoning	1
SL6x000	Primidone poisoning	1
8G61.00	Potential suicide care	1
SM32100	Potassium hydroxide causing toxic effect	1
SM90000	Potassium cyanide causing toxic effect	1
SL25.00	Posterior pituitary hormone poisoning	1
SL94600	Poisoning by temazepam	1
SLD3100	Poisoning by saline and osmotic laxatives	1
SL3..00	Poisoning by primarily systemic agents	1
SLX..00	Poisoning by oth & unspec antipsychotics & neuroleptics	1

Read code	Description	Number of studies
SL29.00	Poisoning by mineralocorticoids and their antagonists	1
SLD0200	Poisoning by histamine H2-receptor antagonists	1
SL20300	Poisoning by glucocorticoids and synthetic analogues	1
SL...16	Poisoning by drug and biological substances	1
SL6x100	Poisoning by carbamazepine	1
SLC9.00	Poisoning by calcium-channel blockers	1
SLC6400	Poisoning by angiotensin-converting-enzyme inhibitors	1
SL...00	Poisoning	1
SM82.12	Plants - toxic effect	1
1BDB.00	Plans for deliberate self harm without intent	1
SL16100	Piperazine poisoning	1
SLB0200	Pilocarpine poisoning	1
SM7y000	Phosgene causing toxic effect	1
SM93500	Phosdrin causing toxic effect	1
SL61000	Phenytoin poisoning	1
SL53100	Phenylbutazone poisoning	1
SLB3000	Phenoxybenzamine poisoning	1
SL91z00	Phenothiazine poisoning NOS	1
SL91.00	Phenothiazine poisoning	1
SLD1200	Phenolphthalein poisoning	1
SM30000	Phenol causing toxic effect	1
SL70400	Phenobarbital poisoning	1
SL42200	Phenindione poisoning	1
SL52200	Phenacetin poisoning	1
SLH4.00	Pharmaceutical excipient poisoning	1
SM1z.00	Petroleum product causing toxic effect NOS	1
SM1..00	Petroleum product causing toxic effect	1
SM14.00	Petroleum ether causing toxic effect	1
SM10.00	Petrol unspecified causing toxic effect	1
SL86.00	Peripheral nerve and plexus-blocking anaesthetic poisoning	1
SL70300	Pentobarbitone poisoning	1
SL34000	Penicillinase poisoning	1
SL00z00	Penicillin poisoning NOS	1
SL00.00	Penicillin poisoning	1
SL00300	Penicillin G poisoning	1
E022.00	Pathological drug intoxication	1
E014.00	Pathological alcohol intoxication	1
SM93300	Parathion causing toxic effect	1
SLB0.00	Parasympathomimetic poisoning	1
SL60000	Paramethadione poisoning	1
SM13.00	Paraffin wax causing toxic effect	1
SL52100	Paracetamol poisoning	1
SL1x300	Para-aminosalicylic acid poisoning	1
SLC5200	Papaverine poisoning	1
SLD4100	Papain poisoning	1
SLD4000	Pancreatin poisoning	1
SL04300	Oxytetracycline poisoning	1
SL21200	Oxymetholone poisoning	1
SL22z00	Ovarian hormone poisoning NOS	1
SL22.00	Ovarian hormone and synthetic substitute poisoning	1
SLC5.00	Other vasodilator poisoning	1
SL95.00	Other tranquilliser poisoning	1
F377.00	Other toxic agent polyneuropathy	1
SL3y.00	Other systemic agent poisoning	1
SM9y.00	Other substance causing toxic effect	1
SL0y.00	Other specific antibiotic poisoning	1
SM2yz00	Other solvents causing toxic effect NOS	1
SM2..00	Other solvents causing toxic effect	1
SM2y.00	Other solvents causing toxic effect	1
SLGx.00	Other skin and mucous membrane drug poisoning	1
SL7y.00	Other sedative and hypnotic poisoning	1
SLFy.00	Other respiratory system drug poisoning	1
SL9y.00	Other psychotropic agent poisoning	1
SM94.00	Other pesticides causing toxic effect NEC	1
SM8y.00	Other noxious substance eaten as food causing toxic effect	1
SM9..00	Other nonmedicinal substances causing toxic effect	1
SL5x.00	Other non-narcotic analgesic poisoning	1
SLF3.00	Other muscle drug poisoning	1
SLE6.00	Other mineral salt poisoning NEC	1
SM5y.00	Other metals causing toxic effect OS	1
SM5yz00	Other metals causing toxic effect NOS	1
SM5..00	Other metals causing toxic effect	1
SLC6.00	Other hypertensive agent poisoning	1
SM71.00	Other hydrocarbon gas causing toxic effect	1
SL2y.00	Other hormone or synthetic derivative poisoning	1

Read code	Description	Number of studies
SLDy.00	Other gastrointestinal agent poisoning	1
SM7..00	Other gases, fumes or vapours causing toxic effect	1
SM7y.00	Other gas, fume or vapour causing toxic effect	1
SM7yz00	Other gas, fume and vapour causing toxic effect NOS	1
SLHy.00	Other drug and medicament poisoning OS	1
SLHyz00	Other drug and medicament poisoning NOS	1
SLE4z00	Other diuretic poisoning NOS	1
SLC1100	Other digitalis glycoside poisoning	1
SLAy.00	Other central nervous system stimulant poisoning	1
SLD3.00	Other cathartic poisoning	1
SL93.00	Other antipsychotics/neuroleptics/tranquilliser poisoning	1
SL15.00	Other antiprotozoal drug poisoning	1
SL30x00	Other antihistamine poisoning	1
SL6x.00	Other anticonvulsant poisoning	1
SL1..00	Other anti-infective poisoning	1
SL1y.00	Other anti-infective poisoning	1
SLH..00	Other and unspecified drug and medicament poisoning	1
SL5yz00	Other analgesic or antipyretic poisoning NOS	1
SL5y.00	Other analgesic and antipyretic poisoning	1
SM0y.00	Other alcohol causing toxic effect	1
SM93z00	Organophosphate and carbamate causing toxic effect NOS	1
SM93.00	Organophosphate and carbamate causing toxic effect	1
SLF1100	Orciprenaline poisoning	1
SL22000	Oral contraceptive poisoning	1
SL50.12	Opiate poisoning	1
SL50z00	Opiate or narcotic poisoning NOS	1
SLA1z00	Opiate antagonist poisoning NOS	1
SLA1.00	Opiate antagonist poisoning	1
SL50.00	Opiate and narcotic poisoning	1
SL03100	Oleandomycin poisoning	1
SL22100	Oestrogen poisoning	1
SL01200	Nystatin poisoning	1
SM8z.00	Noxious substance eaten as food causing toxic effect NOS	1
SM8..00	Noxious substance eaten as food causing toxic effect	1
SLB2100	Noradrenalin poisoning	1
SM...00	Nonmedicinal agent causing toxic effects	1
SL5xz00	Non-narcotic analgesic poisoning NOS	1
SMz..00	Non-medicinal agent causing toxic effect NOS	1
SL82100	Nitrous oxide poisoning	1
SM72.00	Nitrogen oxides causing toxic effect	1
SM72000	Nitrogen dioxide causing toxic effect	1
SL1y100	Nitrofuran derivative poisoning	1
SM31100	Nitric acid causing toxic effect	1
SL94500	Nitrazepam poisoning	1
SLC4100	Nitrate poisoning	1
SM5y300	Nickel compounds causing toxic effect	1
SL50.11	Narcotic poisoning	1
SL54300	Naproxen poisoning	1
SL21100	Nandrolone poisoning	1
SM81.00	Mushrooms causing toxic effect	1
SLF..11	Muscle drug poisoning	1
SL50500	Morphine poisoning	1
1BD2.00	Morbid thoughts	1
SL90200	Monoamine oxidase inhibitor poisoning	1
1BD6.00	Moderate suicide risk	1
SL76.00	Mixed sedative poisoning NEC	1
SL07400	Mitomycin poisoning	1
SL04200	Minocycline poisoning	1
SM01.00	Methyl alcohol causing toxic effect	1
SL80100	Methocarbamol poisoning	1
SL74.00	Methaqualone compound poisoning	1
SM01000	Methanol causing toxic effect	1
SL50200	Methadone poisoning	1
SM5z.00	Metals causing toxic effect NOS	1
SL12300	Mercury compound poisoning	1
SM50.00	Mercury causing toxic effect	1
SL31600	Mercaptopurine poisoning	1
SL95100	Meprobamate poisoning	1
SL50400	Meperidine (pethidine) poisoning	1
SL54400	Mefenamic acid poisoning	1
SL...13	Medicinal poisoning	1
SL94400	Medazepam poisoning	1
SL96200	Marihuana poisoning	1
SM93200	Malathion causing toxic effect	1
SLD0100	Magnesium trisilicate poisoning	1

Read code	Description	Number of studies
SLD3000	Magnesium sulphate poisoning	1
T180.00	MVTA - accid poisoning - exhaust gas of moving motor vehicle	1
SL90211	MAOI - monoamine oxidase inhibitor poisoning	1
SL96100	Lysergide (LSD) poisoning	1
1BD7.00	Low suicide risk	1
SL94300	Lorazepam poisoning	1
SLG2.12	Local detergent poisoning	1
SLG2.11	Local astringent poisoning	1
SLG2.00	Local astringent and detergent poisoning	1
SLG0.00	Local anti-infective and anti-inflammatory poisoning	1
SL8z.00	Local anaesthetic poisoning NOS	1
SLA0000	Lobeline poisoning	1
44W8100	Lithium level high - toxic	1
SM70.00	Liquefied petrol gas causing toxic effect	1
SL85100	Lidocaine poisoning	1
SL27100	Levothyroxine sodium poisoning	1
SL6y200	Levodopa (L-dopa) poisoning	1
SL12200	Lead compound poisoning	1
SM4z.00	Lead compound causing toxic effect NOS	1
SM4..00	Lead and lead compounds causing toxic effect	1
SM41000	Lead acetate causing toxic effect	1
TH02.00	Late effects of accidental poisoning	1
SC...00	Late effects injury/poisoning/toxic effects/external causes	1
SC41.00	Late effect of poison due to nonmedical substance	1
SC40.00	Late effect of poison drug/medicament/biological substance	1
SC41.11	Late effect of poison	1
SCz..00	Late effect injury/poison/toxin effect/external cause NOS	1
SL83000	Ketamine poisoning	1
SM12.00	Kerosene causing toxic effect	1
SLG4.12	Keratoplastic poisoning	1
SL1x200	Isoniazid poisoning	1
SLD1.00	Irritant cathartic poisoning	1
SM5y200	Iron compounds causing toxic effect	1
SL40z00	Iron and iron compound poisoning NOS	1
SL40.00	Iron and iron compound poisoning	1
SL28000	Iodide poisoning	1
SP35000	Intoxication by serum	1
E250.14	Intoxication - alcohol	1
1BDC.00	Intent of deliberate self harm with detailed plans	1
SL23.00	Insulins and antidiabetic poisoning	1
SL23400	Insulin poisoning	1
TN...00	Injury undetermined whether accidentally/purposely inflicted	1
TNz..00	Injury undetermined accidental or purposely inflicted NOS	1
TM21.00	Injury due to legal intervention by poisoning by gas	1
Sz...00	Injury and poisoning NOS	1
S....00	Injury and poisoning	1
TN3y.00	Injury ?accidental, other means of hang/strangle/suffocate	1
TN9..00	Injury ?accidental, late effects	1
TN3z.00	Injury ?accidental, hanging/strangulation/suffocation NOS	1
TN70.00	Injury ?accidental, fall from residential premises	1
TN71.00	Injury ?accidental, fall from other man-made structure	1
TN72.00	Injury ?accidental, fall from natural site	1
TN7z.00	Injury ?accidental, fall from high place NOS	1
TN7..00	Injury ?accidental, fall from high place	1
TN4..00	Injury ?accidental, drowning	1
TN61.00	Injury ?accidental, by stabbing instrument	1
TN51.00	Injury ?accidental, by shotgun	1
TN82.00	Injury ?accidental, by scald	1
TN8y.00	Injury ?accidental, by other specified means	1
TN8..00	Injury ?accidental, by other means	1
TN54.00	Injury ?accidental, by other firearm	1
TN8z.00	Injury ?accidental, by means NOS	1
TN80100	Injury ?accidental, by lying before moving object	1
TN80.00	Injury ?accidental, by jumping or lying before moving object	1
TN80000	Injury ?accidental, by jumping before moving object	1
TN52.00	Injury ?accidental, by hunting rifle	1
TN50.00	Injury ?accidental, by handgun	1
TN5..00	Injury ?accidental, by firearms and explosives	1
TN5z.00	Injury ?accidental, by firearm or explosive NOS	1
TN83.00	Injury ?accidental, by extremes of cold	1
TN55.00	Injury ?accidental, by explosive	1
TN84.00	Injury ?accidental, by electrocution	1
TN6z.00	Injury ?accidental, by cutting or stabbing instrument NOS	1
TN60.00	Injury ?accidental, by cutting instrument	1
TN6..00	Injury ?accidental, by cutting and stabbing instruments	1

Read code	Description	Number of studies
TN85.00	Injury ?accidental, by crashing of motor vehicle	1
TN86.00	Injury ?accidental, by crashing of aircraft	1
TN87.00	Injury ?accidental, by caustic substances, except poisoning	1
TN81.00	Injury ?accidental, by burns or fire	1
SL54100	Indometacin poisoning	1
SL31.12	Immunosuppressive poisoning	1
SL90100	Imipramine poisoning	1
SL54200	Ibuprofen poisoning	1
SL7..11	Hypnotic poisoning	1
SLC6z00	Hypertensive agent poisoning NOS	1
SLB1200	Hyoscine poisoning	1
SL95000	Hydroxyzine poisoning	1
SL13.11	Hydroxyquinoline poisoning	1
SM31000	Hydrochloric acid causing toxic effect	1
SL61.00	Hydantoin derivative poisoning	1
SL47100	Human fibrinogen poisoning	1
SL2z.00	Hormone or synthetic substitute poisoning NOS	1
SL2..00	Hormone and synthetic substitute poisoning	1
1BD5.00	High suicide risk	1
SL50100	Heroin poisoning	1
SL42100	Heparin poisoning	1
SL12z00	Heavy metal anti-infective poisoning NOS	1
SL12.00	Heavy metal anti-infective poisoning	1
SL3y000	Heavy metal agonist poisoning	1
1BD..00	Harmful thoughts	1
SL81.00	Halothane poisoning	1
SL92000	Haloperidol poisoning	1
SL96z00	Hallucinogen poisoning NOS	1
SL96.00	Hallucinogen poisoning	1
SLG4.00	Hair treatment poisoning	1
14K0.00	H/O: repeated overdose	1
14K..00	H/O: poisoning	1
SL24211	Growth hormone poisoning	1
SL01100	Griseofulvin poisoning	1
SL24100	Gonadotrophin poisoning	1
SL54000	Gold salt poisoning	1
SLDz.00	Gastrointestinal agent poisoning NOS	1
SLD..00	Gastrointestinal agent poisoning	1
SM7z.00	Gases, fumes or vapours causing toxic effect NOS	1
SLC3z00	Ganglion-blocker poisoning NOS	1
SLC3.00	Ganglion-blocker poisoning	1
SM03z00	Fusel oil causing toxic effect NOS	1
SLE4100	Furosemide poisoning	1
SM74.00	Freon causing toxic effect	1
SL41000	Folic acid poisoning	1
SL94200	Flurazepam poisoning	1
SL91100	Fluphenazine poisoning	1
SL31500	Fluorouracil poisoning	1
SL1y000	Flucytosine poisoning	1
SL40100	Ferrous sulphate poisoning	1
SL40000	Ferric salt poisoning	1
SLG..00	Eye, otorhinolaryngological, skin and dental drug poisoning	1
SLG5z00	Eye drug poisoning NOS	1
SLG5.00	Eye drug poisoning NEC	1
SLG..12	Eye drug poisoning	1
SLF5.00	Expectorant poisoning	1
SM00z00	Ethyl alcohol causing toxic effect NOS	1
SM00.00	Ethyl alcohol causing toxic effect	1
SL6y100	Ethopropazine poisoning	1
SL82000	Ether poisoning	1
SM00000	Ethanol causing toxic effect	1
SL1x000	Ethambutol poisoning	1
SLE4000	Ethacrynic acid poisoning	1
SL03000	Erythromycin poisoning	1
SL03.00	Erythromycin and macrolide poisoning	1
SLF0000	Ergot alkaloid poisoning	1
E230200	Episodic acute alcoholic intoxication in alcoholism	1
SL34.00	Enzyme poisoning NEC	1
SLG3.00	Emollients, demulcents and protectant poisoning	1
SLD2.00	Emollient cathartic poisoning	1
SLD6.00	Emetic drug poisoning	1
SLE5.00	Electrolyte agent poisoning	1
SL97200	Ecstasy poisoning	1
SLG6.00	Ear, nose and throat drug poisoning NEC	1
SLz..00	Drug, medicament or biological substance poisoning NOS	1

Read code	Description	Number of studies
SL...12	Drug poisoning	1
SL04100	Doxycycline poisoning	1
SLE..11	Diuretic poisoning	1
SLC4000	Dipyridamole poisoning	1
SL30100	Diphenhydramine poisoning	1
SLD2000	Dioctyl sulphosuccinate poisoning	1
SM02000	Dimethyl carbinol causing toxic effect	1
SL50700	Dihydrocodeine poisoning	1
SLC1000	Digoxin poisoning	1
SLD4.00	Digestant poisoning	1
SL94100	Diazepam poisoning	1
SLHy100	Diagnostic agent NEC, poisoning	1
SL50600	Dextropropoxyphene poisoning	1
SLF4000	Dextromethorphan poisoning	1
SM96.11	Detergent toxic effect	1
SM00100	Denatured alcohol causing toxic effect	1
ZX1..13	Deliberate self-harm	1
SL07300	Daunorubicin poisoning	1
SL07100	Dactinomycin poisoning	1
SM92200	DDT causing toxic effect	1
SL31400	Cytarabine poisoning	1
SL31300	Cyclophosphamide poisoning	1
SLC5000	Cyclandelate poisoning	1
SM90z00	Cyanides causing toxic effect NOS	1
SM90.00	Cyanides and hydrocyanic acid causing toxic effect	1
ZX13100	Cutting own wrists	1
SL42000	Coumarin poisoning	1
SL20000	Cortisone derivative poisoning	1
SL24000	Corticotropin poisoning	1
SM3..00	Corrosives/acids/caustic alkalis causing toxic effect	1
SM3z.00	Corrosive/acid/caustic alkali causing toxic effect NOS	1
SM30z00	Corrosive aromatics causing toxic effect NOS	1
SLC4.00	Coronary vasodilator poisoning	1
SM5y100	Copper salts causing toxic effect	1
E230100	Continuous acute alcoholic intoxication in alcoholism	1
SL22200	Combined oestrogen and progesterone poisoning	1
SLE7100	Colchicine poisoning	1
SL50300	Codeine (methylmorphine) poisoning	1
SL85000	Cocaine poisoning	1
SLC6000	Clonidine poisoning	1
SM56.00	Chromium causing toxic effect	1
SLB0z00	Cholinergic poisoning NOS	1
SLB0.11	Cholinergic poisoning	1
SL91000	Chlorpromazine poisoning	1
SL30000	Chlorphenamine poisoning	1
SL14000	Chloroquine poisoning	1
SM75100	Chloroacetophenone causing toxic effect	1
SM76.00	Chlorine gas causing toxic effect	1
SM92.00	Chlorinated hydrocarbon causing toxic effect	1
SL94000	Chlordiazepoxide poisoning	1
SL02000	Chloramphenicol poisoning	1
SL31200	Chlorambucil poisoning	1
SL71.00	Chloral hydrate poisoning	1
SL13000	Chiniofon poisoning	1
SLH2.11	Chelating agent poisoning	1
SLAz.00	Central nervous system stimulant poisoning NOS	1
SLA..00	Central nervous system stimulant poisoning	1
SL80z00	Central nervous system muscle-tone depressant poisoning NOS	1
SL80.00	Central nervous system muscle-tone depressant poisoning	1
SL8..00	Central nervous system depressants and anaesthetic poisoning	1
SLH0000	Central appetite depressant poisoning	1
SL05000	Cefalexin poisoning	1
SM32z00	Caustic alkalis causing toxic effect NOS	1
SM32.00	Caustic alkalis causing toxic effect	1
Tz...00	Causes of injury and poisoning NOS	1
T....00	Causes of injury and poisoning	1
T8...11	Cause of overdose - accidental	1
SLC..00	Cardiovascular drug poisoning	1
SLCz.00	Cardiovascular agent poisoning NOS	1
SLC0.00	Cardiac rhythm drug poisoning	1
SLC1.00	Cardiac glycoside poisoning	1
SM21.00	Carbon tetrachloride causing toxic effect	1
SM6..00	Carbon monoxide causing toxic effect	1
SM93000	Carbaryl causing toxic effect	1
SL80000	Carbamate poisoning	1

Read code	Description	Number of studies
SLB1400	Caramiphen poisoning	1
SL96000	Cannabis poisoning	1
SL97100	Caffeine poisoning	1
SM55.00	Cadmium causing toxic effect	1
SM70000	Butane causing toxic effect	1
SL70200	Butabarbitone poisoning	1
SL31100	Busulfan poisoning	1
SL07200	Bleomycin poisoning	1
SL...11	Biological substance poisoning	1
SL23100	Biguanide poisoning	1
SLC0400	Beta blocker poisoning	1
SM53.00	Beryllium causing toxic effect	1
SM82.00	Berries and other plants causing toxic effect	1
SM82.11	Berries - toxic effect	1
SLE3000	Benzothiazide poisoning	1
SL94z00	Benzodiazepine poisoning NOS	1
SL94.00	Benzodiazepine poisoning	1
SM20.00	Benzene causing toxic effect	1
SL70z00	Barbiturate poisoning NOS	1
SL70.00	Barbiturate poisoning	1
SL70100	Barbitone poisoning	1
SL31000	Azathioprine poisoning	1
SLB..00	Autonomic nervous system drug poisoning	1
SLB1000	Atropine poisoning	1
1BD8.00	At risk of DSH - deliberate self harm	1
TL22.00	Assault by poisoning by other gases or vapours	1
TL20.00	Assault by poisoning by drugs or medicines	1
TL2z.00	Assault by poisoning NOS	1
TL2..00	Assault by poisoning	1
SL51000	Aspirin poisoning	1
SL11.00	Arsenical anti-infective poisoning	1
SM51.00	Arsenic causing toxic effect	1
SL52z00	Aromatic analgesic poisoning NOS	1
SL52.00	Aromatic analgesic poisoning NEC	1
SLF4z00	Antitussive poisoning NOS	1
SL28.00	Antithyroid agent poisoning	1
SL54z00	Antirheumatic poisoning NOS	1
SL54.00	Antirheumatic poisoning	1
SL5y200	Antipyretic poisoning, NEC	1
SL5..12	Antipyretic poisoning	1
SL6y.00	Antiparkinsonism drug poisoning	1
SL6yz00	Antiparkinsonian drug poisoning NOS	1
SL31z00	Antineoplastic or immunosuppressive poisoning NOS	1
SL07.00	Antineoplastic antibiotic poisoning	1
SL31.00	Antineoplastic and immunosuppressive poisoning	1
SL14z00	Antimalarial drug poisoning NOS	1
SL14.00	Antimalarial drug poisoning	1
SLC2.00	Antilipaemic and antiarteriosclerotic poisoning	1
SL30.13	Antihistamine poisoning	1
SL01.00	Antifungal antibiotic poisoning	1
SL30.12	Antiemetic poisoning	1
SLD5z00	Antidiarrhoeal poisoning NOS	1
SLD5.00	Antidiarrhoeal poisoning	1
SL6xz00	Anticonvulsant poisoning NOS	1
SL6..11	Anticonvulsant poisoning	1
SL6z.00	Anticonvulsant or antiparkinsonian drug poisoning NOS	1
SL6..00	Anticonvulsant and antiParkinsonian drug poisoning	1
SL42z00	Anticoagulant poisoning NOS	1
SL42.00	Anticoagulant poisoning	1
SL45z00	Anticoagulant agonist poisoning NOS	1
SL45.00	Anticoagulant agonist poisoning	1
SLB0100	Anticholinesterase poisoning	1
SL0z.00	Antibiotic poisoning NOS	1
SL0..00	Antibiotic poisoning	1
SLF7z00	Antiasthmatic poisoning NOS	1
SL30.00	Antiallergic and antiemetic drug poisoning	1
SL1z.00	Anti-infective poisoning NOS	1
SLD0.00	Anti-gastric acid drug poisoning	1
SLF6.00	Anti-common cold drug poisoning	1
SL16.00	Anthelmintic drug poisoning	1
SL24.00	Anterior pituitary hormone poisoning	1
SLD0z00	Antacid drug poisoning NOS	1
SLD0.11	Antacid drug poisoning	1
SL21.12	Androgen poisoning	1
SL21z00	Androgen or anabolic poisoning NOS	1

Read code	Description	Number of studies
SL21.00	Androgen and anabolic poisoning	1
SL5z.00	Analgesic, antipyretic or antirheumatic poisoning NOS	1
SL5..00	Analgesic, antipyretic and antirheumatic drug poisoning	1
SL5y100	Analgesic poisoning, NEC	1
SL5..11	Analgesic poisoning	1
SLA0.00	Analeptic poisoning	1
SL8..11	Anaesthetic poisoning	1
SL21.11	Anabolic steroid poisoning	1
SM03000	Amyl alcohol causing toxic effect	1
SL00000	Ampicillin poisoning	1
SL01000	Amphotericin B poisoning	1
SL70000	Amobarbital poisoning	1
SL90000	Amitriptyline poisoning	1
SLF7000	Aminophylline poisoning	1
SL97000	Amfetamine poisoning	1
SL6y000	Amantadine poisoning	1
SLD0000	Aluminium hydroxide poisoning	1
SLE7000	Allopurinol poisoning	1
SLH3.00	Alcohol deterrent poisoning	1
E230.11	Alcohol dependence with acute alcoholic intoxication	1
SM0z.00	Alcohol causing toxic effect NOS	1
SM0..00	Alcohol causing toxic effect	1
SL4..00	Agents affecting blood constituents, causing poisoning	1
TJF5100	Adverse reaction to ipecacuanha	1
TJF5000	Adverse reaction to acetylcysteine	1
SLC8000	Adrenochrome poisoning	1
SLB2.11	Adrenergic poisoning	1
SL20z00	Adrenal cortico-steroid poisoning NOS	1
SL20.00	Adrenal cortico-steroid poisoning	1
761H300	Administration of activated charcoal	1
E230000	Acute alcoholic intoxication, unspecified, in alcoholism	1
E230z00	Acute alcoholic intoxication in alcoholism NOS	1
E230.00	Acute alcoholic intoxication in alcoholism	1
SM31z00	Acids causing toxic effect NOS	1
SM31.00	Acids causing toxic effect	1
SL32.00	Acidifying agent poisoning	1
SLB0000	Acetylcholine poisoning	1
SM2y000	Acetone causing toxic effect	1
SL23000	Acetohexamide poisoning	1
SLE2000	Acetazolamide poisoning	1
T80yz00	Accidental poisoning-oth analgesic,antipyretic,antirheum NOS	1
T830z00	Accidental poisoning- phenothiazine-based tranquillisers NOS	1
T832z00	Accidental poisoning- benzodiazepine-based tranquilliser NOS	1
T953100	Accidental poisoning from seeds	1
T954.00	Accidental poisoning from other plants	1
T955y00	Accidental poisoning from other fungi	1
T955.00	Accidental poisoning from mushrooms and other fungi	1
T955z00	Accidental poisoning from mushrooms and fungi NOS	1
T955000	Accidental poisoning from mushrooms	1
T95..00	Accidental poisoning from foodstuffs and poisonous plants	1
T953z00	Accidental poisoning from berries or seeds NOS	1
T953.00	Accidental poisoning from berries and seeds	1
T953000	Accidental poisoning from berries	1
T937400	Accidental poisoning by zinc phosphide	1
T916300	Accidental poisoning by white washes	1
T885.00	Accidental poisoning by water,mineral,uric acid metab drugs	1
T937300	Accidental poisoning by warfarin	1
T981z00	Accidental poisoning by utility gas NOS	1
T88z.00	Accidental poisoning by unspecified drugs	1
T83z.00	Accidental poisoning by tranquillisers NOS	1
T83..00	Accidental poisoning by tranquillisers	1
T930500	Accidental poisoning by toxaphene	1
T964700	Accidental poisoning by thallium compounds	1
T937200	Accidental poisoning by thallium	1
T993.00	Accidental poisoning by tear gas	1
T910.00	Accidental poisoning by synthetic detergents and shampoos	1
T941200	Accidental poisoning by sulphuric acid	1
T991.00	Accidental poisoning by sulphur dioxide	1
T937100	Accidental poisoning by squill and derivatives	1
T92z.00	Accidental poisoning by solvent NOS	1
T96z.00	Accidental poisoning by solid and liquid substances NOS	1
T942000	Accidental poisoning by sodium hydroxide	1
T911.00	Accidental poisoning by soap products	1
T887z00	Accidental poisoning by skin, eye, ENT and dental drug NOS	1
T887000	Accidental poisoning by skin drugs	1

Read code	Description	Number of studies
T82z.00	Accidental poisoning by sedatives and hypnotics NOS	1
T903300	Accidental poisoning by secondary propyl alcohol	1
T913000	Accidental poisoning by scouring agents	1
T803z00	Accidental poisoning by salicylates NOS	1
T803.00	Accidental poisoning by salicylates	1
T937z00	Accidental poisoning by rodenticides NOS	1
T937.00	Accidental poisoning by rodenticides	1
T815.00	Accidental poisoning by quinalbarbitone	1
T805.00	Accidental poisoning by pyrazole derivatives	1
T84z.00	Accidental poisoning by psychotropic agents NOS	1
T841400	Accidental poisoning by psilocin	1
T932200	Accidental poisoning by propoxur	1
T980200	Accidental poisoning by propane	1
T830300	Accidental poisoning by promazine	1
T830200	Accidental poisoning by prochlorperazine	1
T881.00	Accidental poisoning by primarily systemic agents	1
T912.00	Accidental poisoning by polishes	1
T965z00	Accidental poisoning by plant foods and fertilisers NOS	1
T965.00	Accidental poisoning by plant foods and fertilisers	1
T965000	Accidental poisoning by plant food	1
T973.00	Accidental poisoning by piped natural gas	1
T938200	Accidental poisoning by phosphine	1
T805100	Accidental poisoning by phenylbutazone	1
T830.00	Accidental poisoning by phenothiazine-based tranquillisers	1
T940011	Accidental poisoning by phenol	1
T814.00	Accidental poisoning by phenobarbitone	1
T804200	Accidental poisoning by phenacetin	1
T920.00	Accidental poisoning by petroleum solvents	1
T923.00	Accidental poisoning by petroleum solids	1
T920200	Accidental poisoning by petroleum naphtha	1
T921.12	Accidental poisoning by petroleum fuels	1
T920z00	Accidental poisoning by petrol solvents NOS	1
T923z00	Accidental poisoning by petrol solids NOS	1
T92..00	Accidental poisoning by petrol products	1
T921.00	Accidental poisoning by petrol fuels and cleaners	1
T921z00	Accidental poisoning by petrol fuel or cleaner NOS	1
T921200	Accidental poisoning by petrol	1
T802100	Accidental poisoning by pethidine	1
T813.00	Accidental poisoning by pentobarbitone	1
T80y000	Accidental poisoning by pentazocine	1
T935500	Accidental poisoning by paraquat	1
T923000	Accidental poisoning by paraffin wax	1
T804100	Accidental poisoning by paracetamol	1
T916z00	Accidental poisoning by paint or varnish NOS	1
T887300	Accidental poisoning by otorhinolaryngological drugs	1
T98..00	Accidental poisoning by other utility gas + carbon monoxide	1
T981.00	Accidental poisoning by other utility gas	1
T83yz00	Accidental poisoning by other tranquillisers NOS	1
T83y.00	Accidental poisoning by other tranquillisers	1
T924z00	Accidental poisoning by other solvents NOS	1
T924.00	Accidental poisoning by other solvents	1
T96y.00	Accidental poisoning by other solid and liquid substances OS	1
T96..00	Accidental poisoning by other solid and liquid substances	1
T82y.00	Accidental poisoning by other sedatives and hypnotics OS	1
T82..00	Accidental poisoning by other sedatives and hypnotics	1
T84..00	Accidental poisoning by other psychotropic agents	1
T916.00	Accidental poisoning by other paints and varnishes	1
T802z00	Accidental poisoning by other opiates NOS	1
T802.00	Accidental poisoning by other opiates	1
T807.00	Accidental poisoning by other non-narcotic analgesics	1
T9...00	Accidental poisoning by other non-drug substances	1
T964.00	Accidental poisoning by other metals + compounds and fumes	1
T934.00	Accidental poisoning by other insecticides	1
T99y.00	Accidental poisoning by other gases and vapours OS	1
T99yz00	Accidental poisoning by other gases and vapours NOS	1
T99..00	Accidental poisoning by other gases and vapours	1
T95y.00	Accidental poisoning by other foods	1
T901.00	Accidental poisoning by other ethyl alcohol and its products	1
T85..00	Accidental poisoning by other drugs acting on nervous system	1
T88y.00	Accidental poisoning by other drugs OS	1
T88yz00	Accidental poisoning by other drugs NOS	1
T88..00	Accidental poisoning by other drugs	1
T94y.00	Accidental poisoning by other corrosives and caustics	1
T913z00	Accidental poisoning by other cleaning agents NOS	1
T913.00	Accidental poisoning by other cleaning agents	1

Read code	Description	Number of studies
T90y.00	Accidental poisoning by other alcohols	1
T966y00	Accidental poisoning by other adhesives	1
T851.00	Accidental poisoning by oth central nervous syst depressants	1
T80y.00	Accidental poisoning by oth analgesics,antipyretic,antirheum	1
T931z00	Accidental poisoning by organophosphorus insecticides NOS	1
T931.00	Accidental poisoning by organophosphorus insecticides	1
T930.00	Accidental poisoning by organochlorine insecticides	1
T936000	Accidental poisoning by organic mercurials	1
T802300	Accidental poisoning by opium	1
T843100	Accidental poisoning by opiate antagonists	1
T887200	Accidental poisoning by ophthalmological drugs	1
T855100	Accidental poisoning by noradrenalin	1
T807z00	Accidental poisoning by non-narcotic analgesics NOS	1
T916200	Accidental poisoning by non-lead paints	1
T990.00	Accidental poisoning by nitrogen oxides	1
T941100	Accidental poisoning by nitric acid	1
T832500	Accidental poisoning by nitrazepam	1
T964600	Accidental poisoning by nickel compounds	1
T806200	Accidental poisoning by naproxen	1
T886.00	Accidental poisoning by muscle + respiratory system drugs	1
T887100	Accidental poisoning by mucous membrane drugs	1
T982.00	Accidental poisoning by motor vehicle exhaust gas	1
T802200	Accidental poisoning by morphine	1
T840200	Accidental poisoning by monoamine oxidase inhibitors	1
T933.00	Accidental poisoning by mixtures of insecticides	1
T935400	Accidental poisoning by mixtures herbicides+plant food etc	1
T825.00	Accidental poisoning by mixed sedatives NEC	1
T901100	Accidental poisoning by methylated spirit	1
T938100	Accidental poisoning by methyl bromide	1
T902.00	Accidental poisoning by methyl alcohol	1
T823.00	Accidental poisoning by methaqualone compounds	1
T902000	Accidental poisoning by methanol	1
T801.00	Accidental poisoning by methadone	1
T964z00	Accidental poisoning by metals + compounds and fumes NOS	1
T961000	Accidental poisoning by mercury, unspecified	1
T961z00	Accidental poisoning by mercury, NOS	1
T961200	Accidental poisoning by mercury fumes	1
T961.00	Accidental poisoning by mercury and its compounds and fumes	1
T832400	Accidental poisoning by medazepam	1
T964500	Accidental poisoning by manganese and its compounds	1
T931300	Accidental poisoning by malathion	1
T841100	Accidental poisoning by lysergide, LSD	1
T922.00	Accidental poisoning by lubricating oils	1
T832300	Accidental poisoning by lorazepam	1
T852.00	Accidental poisoning by local anaesthetic	1
T852100	Accidental poisoning by lignocaine	1
T960000	Accidental poisoning by lead, unspecified	1
T960z00	Accidental poisoning by lead, NOS	1
T915.00	Accidental poisoning by lead paints	1
T960.00	Accidental poisoning by lead and its compounds and fumes	1
T916000	Accidental poisoning by lacquers	1
T806400	Accidental poisoning by ketoprofen	1
T921300	Accidental poisoning by kerosene	1
T903z00	Accidental poisoning by isopropyl alcohol NOS	1
T903100	Accidental poisoning by isopropanol	1
T964400	Accidental poisoning by iron compounds	1
T934z00	Accidental poisoning by insecticides NOS	1
T806100	Accidental poisoning by indomethacin	1
T840100	Accidental poisoning by imipramine	1
T806300	Accidental poisoning by ibuprofen	1
T854200	Accidental poisoning by hyoscine	1
T941000	Accidental poisoning by hydrochloric acid	1
T850100	Accidental poisoning by hydantoin derivatives	1
T91z.00	Accidental poisoning by household agents NOS	1
T91..00	Accidental poisoning by household agents	1
T880.00	Accidental poisoning by hormones and synthetic substitutes	1
T800.00	Accidental poisoning by heroin	1
T935z00	Accidental poisoning by herbicides NOS	1
T935.00	Accidental poisoning by herbicides	1
T981300	Accidental poisoning by heating gas NOS	1
T831000	Accidental poisoning by haloperidol	1
T851200	Accidental poisoning by halogenated hydrocarbon derivatives	1
T841.00	Accidental poisoning by hallucinogens	1
T841z00	Accidental poisoning by hallucinogen NOS	1
T806000	Accidental poisoning by gold salts	1

Read code	Description	Number of studies
T966z00	Accidental poisoning by glues and adhesives NOS	1
T966.00	Accidental poisoning by glues and adhesives	1
T966000	Accidental poisoning by glues	1
T884.00	Accidental poisoning by gastrointestinal system drugs	1
T470.00	Accidental poisoning by gases or fumes on ship	1
T99z.00	Accidental poisoning by gases and vapours NOS	1
T921100	Accidental poisoning by gas oils	1
T97..00	Accidental poisoning by gas distributed by pipeline	1
T936z00	Accidental poisoning by fungicides NOS	1
T936.00	Accidental poisoning by fungicides	1
T938.00	Accidental poisoning by fumigants	1
T95z.00	Accidental poisoning by foodstuffs and poisonous plants NOS	1
T965100	Accidental poisoning by fertilisers	1
T982000	Accidental poisoning by exhaust gas-stationary farm tractor	1
T982z00	Accidental poisoning by exhaust gas from motor vehicle NOS	1
T982100	Accidental poisoning by exhaust gas from gas engine	1
T901z00	Accidental poisoning by ethyl alcohol NOS	1
T901300	Accidental poisoning by ethanol, NOS	1
T8...00	Accidental poisoning by drugs, medicines and biologicals	1
T882.00	Accidental poisoning by drugs affecting blood constituents	1
T85z.00	Accidental poisoning by drugs acting on nervous system NOS	1
T8z..00	Accidental poisoning by drugs NOS	1
T914.00	Accidental poisoning by disinfectants	1
T935300	Accidental poisoning by diquat	1
T930300	Accidental poisoning by dieldrin	1
T832100	Accidental poisoning by diazepam	1
T800.11	Accidental poisoning by diamorphine	1
T887400	Accidental poisoning by dental drugs	1
T901000	Accidental poisoning by denatured alcohol	1
T938000	Accidental poisoning by cyanides	1
T967.00	Accidental poisoning by cosmetics	1
T94z.00	Accidental poisoning by corrosives and caustics NOS	1
T94..00	Accidental poisoning by corrosives and caustics NEC	1
T940.00	Accidental poisoning by corrosive aromatics	1
T964300	Accidental poisoning by copper salts	1
T981400	Accidental poisoning by cooking gas NOS	1
T802000	Accidental poisoning by codeine	1
T852000	Accidental poisoning by cocaine	1
T971.00	Accidental poisoning by coal gas NOS	1
T853.00	Accidental poisoning by cholinergics	1
T830000	Accidental poisoning by chlorpromazine	1
T99y000	Accidental poisoning by chlorine	1
T832000	Accidental poisoning by chlordiazepoxide	1
T930100	Accidental poisoning by chlordane	1
T935200	Accidental poisoning by chlorates	1
T820.00	Accidental poisoning by chloral hydrate	1
T88y000	Accidental poisoning by central appetite depressants	1
T942z00	Accidental poisoning by caustic alkalis NOS	1
T942.00	Accidental poisoning by caustic alkalis	1
T883.00	Accidental poisoning by cardiovascular system drugs	1
T983.00	Accidental poisoning by carbon monoxide-other domestic fuel	1
T970.00	Accidental poisoning by carbon monoxide from piped gas	1
T98y.00	Accidental poisoning by carbon monoxide from other sources	1
T98yz00	Accidental poisoning by carbon monoxide from oth source NOS	1
T98z.00	Accidental poisoning by carbon monoxide NOS	1
T983z00	Accidental poisoning by carbon monoxide - domestic fuel NOS	1
T940000	Accidental poisoning by carbolic acid	1
T932100	Accidental poisoning by carbaryl	1
T932.00	Accidental poisoning by carbamates	1
T841000	Accidental poisoning by cannabis derivatives	1
T842100	Accidental poisoning by caffeine	1
T964200	Accidental poisoning by cadmium and its compounds	1
T980100	Accidental poisoning by butane	1
T993000	Accidental poisoning by bromobenzyl cyanide	1
T822.00	Accidental poisoning by bromine compounds	1
T822000	Accidental poisoning by bromides	1
T964100	Accidental poisoning by brass fumes	1
T964000	Accidental poisoning by beryllium and its compounds	1
T832.00	Accidental poisoning by benzodiazepine-based tranquillisers	1
T930000	Accidental poisoning by benzene hexachlorine	1
T924000	Accidental poisoning by benzene	1
T81z.00	Accidental poisoning by barbiturates NOS	1
T81..00	Accidental poisoning by barbiturates	1
T811.00	Accidental poisoning by barbitone	1
T854000	Accidental poisoning by atropine	1

Read code	Description	Number of studies
T803000	Accidental poisoning by aspirin	1
T963000	Accidental poisoning by arsenic, unspecified	1
T963100	Accidental poisoning by arsenic compounds	1
T963.00	Accidental poisoning by arsenic and its compounds and fumes	1
T804.00	Accidental poisoning by aromatic analgesics NEC	1
T806z00	Accidental poisoning by antirheumatics NOS	1
T806.00	Accidental poisoning by antirheumatics	1
T840z00	Accidental poisoning by antidepressants NOS	1
T840.00	Accidental poisoning by antidepressants	1
T850z00	Accidental poisoning by anticonvulsant/anti-parkin drug NOS	1
T850.00	Accidental poisoning by anticonvulsant + anti-parkinson drug	1
T850.11	Accidental poisoning by anticonvulsant	1
T854.00	Accidental poisoning by anticholinergics	1
T86..00	Accidental poisoning by antibiotics	1
T850.12	Accidental poisoning by anti-parkinsonism drug	1
T87..00	Accidental poisoning by anti-infectives	1
T80..00	Accidental poisoning by analgesics,antipyretic,antirheumatic	1
T80z.00	Accidental poisoning by analgesics,antipyretic,antirheum NOS	1
T842000	Accidental poisoning by amphetamine	1
T840000	Accidental poisoning by amitriptyline	1
T900.00	Accidental poisoning by alcoholic beverages	1
T90..00	Accidental poisoning by alcohol, NEC	1
T90z.00	Accidental poisoning by alcohol NOS	1
T93..00	Accidental poisoning by agricultural chemical preparations	1
T855.00	Accidental poisoning by adrenergics	1
T855000	Accidental poisoning by adrenalin	1
T941z00	Accidental poisoning by acids NOS	1
T941.00	Accidental poisoning by acids	1
T981000	Accidental poisoning by acetylene	1
T930200	Accidental poisoning by DDT	1
T983300	Accidental poisoning by CO- kerosene in domestic stove/fire	1
T983100	Accidental poisoning by CO- coke in domestic stove/fireplace	1
T983000	Accidental poisoning by CO- coal in domestic stove/fireplace	1
T98y100	Accidental poisoning by CO - kiln vapour	1
T98y200	Accidental poisoning by CO - fuels in industrial use	1
T98y000	Accidental poisoning by CO - blast furnace gas	1
T93z.00	Accidental poisoning agricultural chemical preparations NOS	1
T9z..00	Accidental poisoning NOS	1
T77z.00	Accident/poisoning occurred in residential institution NOS	1
T85y.00	Accid. poisoning by other drugs acting on nervous system OS	1
T470500	Accid poison gas/fume on ship - swimmer injured	1
SL24011	ACTH - adrenocorticotropic hormone poisoning	1

Supplementary appendix 4, table 13. ICD codes used in the studies of fatal self-harm.

Study	ICD version	List of codes
Carr, 2017	ICD-10	V01-Y98
Coupland, 2015	ICD-10	not provided
Doyle, 2016	ICD-10	X60-X84, Y10-34 (excluding Y33.9), Y87.0 and Y87.2
Lalmohamed, 2012	ICD-10	V01-Y99
Meier, 2004	ICD-10	not provided
Schuerch, 2016	ICD-10	X60-X84, Y10-Y34
Thomas, 2013	ICD-10	X60-X84, Y10-34 (excluding Y33.9)
Webb, 2012	ICD-10	X60-X84, Y10-34 (excluding Y33.9)
Windfuhr, 2016	ICD-10	X60-X84, Y10-34 (excluding Y33.9), Y87.0 and Y87.2

ICD - International Classification of Diseases

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11.3 Appendix 3 Supplementary materials to the paper in Chapter 6

Carreira H, Williams R, Funston G, Stanway S, Krishnan Bhaskaran
Risk of adverse mental health outcomes in women with history of breast cancer: a matched population-based cohort study in the United Kingdom (1988-2018)

(submitted)

Contents

Medicines & Healthcare products Regulatory Agency

CPRD

Protocol Risk of adverse mental health outcomes in women with a history of breast cancer in the United Kingdom: a matched population-based cohort study

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*' and justification provided**
A. Study Title (Max. 255 characters) Risk of adverse mental health outcomes in women with a history of breast cancer in the United Kingdom: a matched population-based cohort study
B. Lay Summary (Max. 250 words) Women with a history of breast cancer are the largest group of cancer survivors in the general population. A breast cancer diagnosis may impact on mental health, and breast cancer treatments, which are necessary to control the disease, can result in side effects that may negatively affect the women's quality of life. This study aims to understand whether women who have had breast cancer have different mental health several years post-treatment, compared to women who did not have cancer. For this, we will compare the risk of being diagnosed with anxiety and depression, the primary outcomes of this study, in women who have had breast cancer and in women who never had cancer, attending general practitioner (GP) practices in the UK. We will also compare GP recorded declines in the patients' memory and thinking capacities, feelings of tiredness and weakness (fatigue), pain, insomnia, sexual problems, or self-harm and suicide (secondary outcomes), between the two groups, and explore factors that may be associated with increased risk of these outcomes. The results of this study can be used to better understand the needs of the women who carry on lives beyond breast cancer.
C. Technical Summary (Max. 300 words) The aim of this study is to estimate the relative risk of anxiety and depression (primary outcomes), and fatigue, pain, sleep disorders, neurocognitive and sexual dysfunctions, and fatal and non-fatal self-harm (secondary outcomes), in breast cancer survivors compared to non-cancer controls. This study will be a matched cohort study, utilising data from the CPRD GOLD primary care database. Outcome-specific algorithms will be developed and validated to identify outcomes in the data. Algorithm development will consider Read codes for diagnoses, prescriptions, referrals and symptoms; prevalence and incidence estimates by age-group and sex will be computed for a random sample of patients selected from CPRD GOLD primary care database. Validation will be against external sources of data, namely published data from population-based surveys in the UK. To estimate the associations between breast cancer survivorship and the primary and secondary outcomes, we will identify all women exposed to breast cancer in the CPRD GOLD primary care database, and randomly select an age- and primary-care-practice-matched cohort of women without prior cancer in a ratio of 1:4. Cox regression models will be used to estimate hazard ratios adjusted for important confounders, and to explore the role of effect modifiers; the proportionality of hazards will be tested graphically and inferentially.

D. Outcomes to be measured

- Anxiety
- Depression
- Fatigue
- Cognitive impairment
- Pain
- Sexual dysfunction
- Sleep disorders
- Completed suicide
- Self-harm

E. Objectives, Specific Aims and Rationale

General objective

To quantify the relative risk of common adverse mental health outcomes in breast cancer survivors compared to women who did not have cancer in the United Kingdom.

Specific aims

1. To develop and validate algorithms to identify patients with anxiety and depression (primary outcomes), and fatigue, mild cognitive impairment, pain, sleep disturbance, sexual dysfunction, and fatal and non-fatal self-harm (secondary outcomes) in the CPRD GOLD primary care database.
2. To compare the risk of developing anxiety and depression (primary outcomes), and of recorded fatigue, mild cognitive impairment, pain, sleep disturbance, sexual dysfunction, and fatal and non-fatal self-harm (secondary outcomes), between women with a history of breast cancer and women who did not have cancer.
3. To estimate association between breast cancer history and anxiety/depression by presence of common complications of the breast cancer treatments (i.e. lymphoedema, pain, mild cognitive impairment, fatigue, sexual dysfunction, sleep disorders) and exposure to endocrine therapy.

Rationale

It is currently unclear if the long-term mental health of breast cancer survivors differs from that of comparable women who never had cancer. This study will directly address this evidence gap, and help inform prevention and treatment needs relating to the mental health of breast cancer survivors.

F. Study Background

Women with a history of breast cancer are the largest group of cancer survivors in the United Kingdom (UK). Approximately 570,000 women were estimated to be living beyond a breast cancer diagnosis in 2010; this figure was projected to rise to1.5 million women by 2040 [1].

Evidence on the mental health of breast cancer survivors in the UK suggests high levels of distress in this group. Capelan et al [2] reported that 60% of women post treatment for early breast cancer had ≥1 unmet needs; the most common were hot flushes, fatigue, pain, worry, fear or anxiety, and sleep problems. A third of the women who participated in the Standardisation of Radiotherapy Trial (START) [3] had relevant symptoms of anxiety at baseline; five years later, this proportion was 29%. Similar results were observed for depression, albeit the absolute frequency was lower: 12% scored above normal level at baseline, and 11% at the five-year evaluation [3]. The worse recollections reported by a sample of women in the UK seven years after diagnosis included the anxiety related to the future's uncertainty (38%), the chemotherapy and related side effects (25%), and the shock of the cancer diagnosis (18%) [4]. Other reported concerns were the breast removal and body image implications in sexuality (8%), the suffering induced by their disease in their loved ones (7%), the co-morbidities (6%), and the side effects of radiotherapy and hormone therapy (6%) [4]. All of these may negatively affect the women's mental status. Indeed, a study on the quality of life of breast cancer survivors one to five years post-diagnosis in England described lower scores than what had been described in other studies of the general population [5].

In the UK, women post-treatment for breast cancer are often followed in hospital outpatient clinics, where they may receive psychological support, and in primary care [6]. In the latter setting, evidence on the relative risk of adverse mental health outcomes in breast cancer survivors, compared to women who did not have cancer, is scant. A systematic review of quantitative studies that evaluated adverse mental health outcomes in breast cancer survivors and in the background female population identified one single study from the UK. In this study, Khan et al [7] used routinely collected primary care data to study the pattern of consultations and prescriptions for anxiety and depression in women with a history of breast cancer for ≥5 years. The results showed significantly increased odds of being prescribed with antidepressants or anxiolytics, even though there was no strong statistical evidence of increased odds of consulting for these conditions. The frequency of anxiety and depression among women diagnosed at <5 years is unknown. Population-based studies conducted elsewhere [8-12] reported highest risks of anxiety and depression shortly after the breast diagnosis, which declined over time. It is currently unclear if this same pattern is observed in the UK. In addition, the studies identified in the systematic review suggest that breast cancer survivors may be at increased risk of other outcomes, such as sleep disturbance, neurocognitive and sexual dysfunctions; no study addressed these in population-based samples of breast cancer survivors in the UK. Furthermore, to our knowledge, the frequency of fatigue, pain, and fatal and non-fatal self-harm, in breast cancer survivors in the UK is unknown, even though these relate to unmet needs often reported by breast cancer survivors. The Clinical Practice Research Datalink primary care database includes data prospectively collected on symptoms, diagnoses, prescriptions, and referrals, for over 5.8 million women being followed in primary care since the late 1980s [13], and therefore it represents a unique opportunity to assess the risk of these outcomes at population-level.

The aim of this study is to quantify the relative risk of adverse mental health outcomes in women with a history of breast cancer the UK, compared to women with no cancer background. The primary outcomes will be anxiety and depression, two common mental disorders that are commonly managed in primary care settings. Secondary outcomes will be fatigue, mild cognitive impairment, pain, sleep disorder, sexual dysfunction, and fatal and non-fatal self-harm; part of the contribution of this study will be to establish the feasibility or otherwise of using electronic health records to assess some of these less-studied outcomes.

G. Study Type

Hypothesis testing

Study null hypothesis: There are no differences in the risks of anxiety and depression (primary outcomes), fatigue, mild cognitive impairment, pain, sleep disturbance, sexual dysfunction, and fatal and non-fatal self-harm (secondary outcomes), between women with a history of breast cancer and women who never had cancer receiving primary care in the UK.

H. Study Design

The research aims will be addressed with a matched cohort study design.

Two cohorts will be assembled from the CPRD GOLD primary care database:

(1) The exposed cohort will include women diagnosed with a breast cancer (list of Read codes available in appendix 2) after at least 12 months of uninterrupted up-to-standard follow-up in CPRD (to ensure that the breast cancer is an incident event).

(2) A comparison cohort will be assembled by randomly selecting, for each woman with a breast cancer diagnosis, up to 4 women of similar age (3-year range), attending the same GP practice and with at least 12 months of uninterrupted up-to-standard data quality for research, but with no history of cancer at the date of the breast cancer diagnosis of the matched breast cancer patient.

The index date will be the date of breast cancer diagnosis for the exposed group; comparison patients will take the same index date as their exposed match. Please see section L for more details.

Inclusion criteria for both cohorts are: female sex, aged ≥18 years, and having a clinical record with at least 12 months of uninterrupted up-to-standard data quality for research (as measured by CPRD) before the breast cancer diagnosis date (to ensure the cancer record represents incident disease). Exclusions will be the diagnosis of severe mental illness (i.e. organic mental disorder, mental disorders due to substances, schizophrenia, delusional disorders, or manic or bipolar episodes), having a history of the specified mental health outcome in the year before index date; and having had a diagnosis of any other cancer prior to the index date.

All women will be followed from the index date until the earliest date of: outcome observed, a cancer diagnosis, death recorded, transference out of the practice; last data collection for the practice.

Matching will allow close control of key covariates, include GP practice that is difficult to adjust for in a statistical model (too many levels), and has the practical advantage of reducing the size of the comparison group (which might otherwise include several million women) by restricting to the most relevant comparison patients.

I. Feasibility counts

Feasibility counts presented below are based on the January 2018 version of the CPRD GOLD primary care database.

We identified 65,136 women who had a diagnosis of breast cancer (Read codes provided in appendix 2) while aged between 18 and 80 years, registered with a primary care practice contributing with data to CPRD, and whose individual records were acceptable for research. Non-interrupted one year of follow up before the cancer diagnosis (index date) was not available for 6,757 women, and 6,044 women were further excluded because they had a lifetime diagnosis of severe mental illness or another cancer before their breast cancer diagnosis (see section J for the inclusion and exclusion criteria).

Hence, 52,335 women with a history of breast cancer were identified as eligible for this study; the table below provides details of the distribution by age and calendar period of diagnosis.

Table 1 Distribution of women with breast cancer history who are eligible for this study, by age and calendar period of diagnosis.

	N	%
All study participants	52,335	(100.0)
Calendar period of diagnosis		
1989-1994	3,184	(6.1)
1995-1999	4,768	(9.1)
2000-2004	10,934	(20.9)
2005-2009	14,705	(28.1)
2010-2014	13,805	(26.4)
≥2015	4,939	(9.4)
Age at diagnosis (years)		
18-24	24	(0.1)
25-34	771	(1.5)
35-44	4,916	(9.4)
45-54	12,235	(25.3)
55-64	14,910	(28.5)
65-74	12,811	(24.5)
75-80	5,668	(10.8)

A comparison group of women without cancer (4 controls per breast cancer case) will be randomly selected from the same data source, same primary care practice and within a 3-year age range.

Appendix 2 to this protocol (available from the authors) provides the list of Read codes used to identify women with a history of breast cancer in the CPRD GOLD primary care database. The list of Read codes used to identify cancer diagnoses other than the breast one (exclusion criterion) has been published elsewhere [14]. A provisional list of Read codes to identify women with several mental illnesses (exclusion criterion) was defined for the purpose of this calculation; the final list will be refined in due course.

J. Sample size considerations

Table 2 shows the minimum relative risk that could be detected with the 52,335 women identified in the CPRD GOLD primary care database, for different probabilities of type I (α) and type II error (β). These estimates were obtained with the command 'power' in Stata v15 [15].

Table 2 Minimum RR that can be detected with the 52,355 women with a history of breast cancer and 209,420 women who did not have cancer, for different probabilities of type I and type II errors, and baseline risk of the outcomes.

Outcome	α	β	% of outcome in unexposed group [ref]	Min. HR possible to be estimated	RR/HR estimated in other studies [ref]
Primary outcomes					
Anxiety, diagnoses	**0.05**	**0.20**	**5 [7]**	**1.05**	1.06 [7]
	0.01	**0.20**	**5 [7]**	**1.06**	1.08 [7]
	0.05	**0.10**	**5 [7]**	**1.06**	1.22 [11]
	0.01	0.10	5 [7]	1.07	1.25 [8]
	0.05	**0.20**	**20 [11]**	**1.02**	
	0.01	**0.20**	**20 [11]**	**1.03**	
	0.05	**0.10**	**20 [11]**	**1.03**	
	0.01	**0.10**	**20 [11]**	**1.03**	
Anxiety, prescription of anxiolytics	**0.05**	**0.20**	**3 [10]**	**1.07**	1.08 [7]
	0.01	**0.20**	**3 [10]**	**1.08**	2.52 [10]
	0.05	**0.10**	**3 [10]**	**1.08**	
	0.01	0.10	3 [10]	1.09	
	0.05	**0.20**	**8 [7]**	**1.04**	
	0.01	**0.20**	**8 [7]**	**1.05**	
	0.05	**0.10**	**8 [7]**	**1.05**	
	0.01	**0.10**	**8 [7]**	**1.06**	
Depression, diagnoses	0.05	0.20	3 [11]	1.07	1.06 [7]
	0.01	0.20	3 [11]	1.08	1.39 [9]
	0.05	0.10	3 [11]	1.08	1.49 [8]
	0.01	0.10	3 [11]	1.09	1.94 [11]
	0.05	**0.20**	**9 [7]**	**1.04**	
	0.01	**0.20**	**9 [7]**	**1.05**	
	0.05	**0.10**	**9 [7]**	**1.04**	
	0.01	**0.10**	**9 [7]**	**1.05**	
Depression, prescription of antidepressants	**0.05**	**0.20**	**2 [10]**	**1.08**	1.16 [7]
	0.01	**0.20**	**2 [10]**	**1.10**	1.95 [10]
	0.05	**0.10**	**2 [10]**	**1.09**	
	0.01	**0.10**	**2 [10]**	**1.11**	
	0.05	**0.20**	**20 [7]**	**1.02**	
	0.01	**0.20**	**20 [7]**	**1.03**	
	0.05	**0.10**	**20 [7]**	**1.03**	
	0.01	**0.10**	**20 [7]**	**1.03**	

(continues)

HR – hazard ratio. RR – risk ratio. Bold is used to denote where the minimum risk ratio that could be detected with the available sample size is lower than the lowest estimate reported in the literature.

Table 2 (continued) Minimum RR that can be detected with the 52,355 women with a history of breast cancer and 209,420 women who did not have cancer, for different probabilities of type I and type II errors, and baseline risk of the outcomes.

Outcome	α	β	% of outcome in unexposed group [ref]	Min. HR possible to be estimated	RR/HR estimated in other studies [ref]
Secondary outcomes *					
Sexual dysfunction	0.05	0.20	4.1 [16]	1.06	1.03 [16]
	0.01	0.20	4.1 [16]	1.07	2.27 [17]
	0.05	0.10	4.1 [16]	1.07	
	0.01	0.10	4.1 [16]	1.08	
	0.05	0.20	9.1 [17]	1.04	
	0.01	0.20	9.1 [17]	1.05	
	0.05	0.10	9.1 [17]	1.04	
	0.01	0.10	9.1 [17]	1.05	
Suicide	0.05	0.20	0.0008** [18]	1.47	1.37 [18]
	0.01	0.20	0.0008** [18]	1.60	1.6 [19]
	0.05	0.10	0.0008** [18]	1.57	
	0.01	0.10	0.0008** [18]	1.70	
Fatal and non-fatal self-harm	0.05	0.20	0.005 [18, 20]	1.17	1.03 [21]
	0.01	0.20	0.005 [18, 20]	1.21	1.37 [18]
	0.05	0.10	0.005 [18, 20]	1.20	
	0.01	0.10	0.005 [18, 20]	1.24	
Sleep disturbances	0.05	0.20	50 [22]	1.01	0.8 [22]
	0.01	0.20	50 [22]	1.02	
	0.05	0.10	50 [22]	1.02	
	0.01	0.10	50 [22]	1.02	
Prescription of hypnotics	**0.05**	**0.20**	**4 [23]**	**1.06**	3.75 [23]
	0.01	**0.20**	**4 [23]**	**1.07**	
	0.05	**0.10**	**4 [23]**	**1.07**	
	0.01	**0.10**	**4 [23]**	**1.08**	
Mild cognitive impairment	**0.05**	**0.20**	**5 [24]**	**1.05**	1.58 [25]
	0.01	**0.20**	**5 [24]**	**1.06**	1.60 [26]
	0.05	**0.10**	**5 [24]**	**1.06**	2.43 [24]
	0.01	**0.10**	**5 [24]**	**1.07**	3.67 [27]
	0.05	**0.20**	**19 [26]**	**1.02**	
	0.01	**0.20**	**19 [26]**	**1.03**	
	0.05	**0.10**	**19 [26]**	**1.03**	
	0.01	**0.10**	**19 [26]**	**1.04**	

HR – hazard ratio. RR – risk ratio. Bold is used to denote where the minimum risk ratio that could be detected with the available sample size is lower than the lowest estimate reported in the literature.

* No population-based studies have been identified reporting the relative risk of sexual dysfunctions, pain, fatigue, sleep disorders or cognitive dysfunction in breast cancer survivors compared to the non-cancer female population. Thus, the relative risk reported in the column for the other studies comes from studies involving convenience samples of cancer survivors. Pain and fatigue are often evaluated using psychometric instruments whose mean scores are summarised as means for between-group comparisons; no studies were identified providing data for the prevalence of pain and fatigue in breast cancer survivors and in women who did not have cancer, and thus these two outcomes were not included in the table.

** Calculated as the proportion of suicides in the exposed group divided by the inverse of the standardised mortality ratio reported in the original study.

The available sample size is expected to be sufficient for detecting clinically significant increases of anxiety and depression (primary outcomes) in breast cancer survivors compared to the women who did not have cancer.

For the secondary outcomes, sample size is likely to be enough to assess differences in sleep disturbance measured by hypnotics' prescription, and mild cognitive impairment. However, the available sample size will have

relatively small power to detect small differences in suicide between women with history of breast cancer and those who did not have cancer, because this is a rare outcome, but we will still have enough power to detect associations of a magnitude seen in some previous studies; data from our analysis can also contribute to future meta-analyses.

K. Planned use of linked data (if applicable):

The following linkages will be requested:

Death registration data from the Office for National Statistics (ONS)

HES Admitted Patient Care (HES-APC)

Index of Multiple Deprivation 2015 (IMD), practice and patient level

Data coming from these data sets will supplement information available in the CPRD GOLD primary care database, but linked data will be used in sensitivity analysis only.

Data from the ONS-mortality and HES-APC databases will be important to increase the completeness and validity of some outcomes. For example, for suicide, only 26% of the suicides registered in the ONS mortality data (gold standard) were captured in CPRD, indicating low sensitivity of this source [28]. Similarly for non-fatal self-harm, only 68% of the cases registered in HES-APC could be identified in CPRD [28]. Of note, patients who had the outcome recorded in the year prior to the index date will be excluded, and thus this finer definition of the outcomes will impact patients' selection and patients' who are identified as having had the outcome. Information on the exposure will not be supplemented by data from HES-APC.

Patient-level quintiles of IMD will be used to control for socioeconomic status, which is a major confounder of the association between breast cancer history and adverse mental health outcomes. Even though women in the comparison group are selected from the same primary care practice of the index-case, and thus IMD at practice level will not vary by matched set, the patient-level IMD will allow for a finer adjustment of socioeconomic status. Practice level of IMD is requested to allow us to study effect modification in the full dataset.

We acknowledge that analyses including linked data will be restricted to the subset of practices and patients who consent to the linkage scheme (~75% of the practices in England); the coverage periods for the dataset will be taken into account (see table below). This will result in reductions in sample size and potentially impact the power of the study to reject the null-hypothesis. Thus, these data will be used in sensitivity analysis only.

Table 3 Coverage period of the data included in the databases that will be linked to the CPRD GOLD primary care database.

Database	Coverage period
HES Admitted Patient Care (APC)	April 1997 – December 2017
ONS death registration	January 1998 – February 2018

L. Definition of the Study population

Breast cancer cohort

The study population will consist of all adult women recorded in the CPRD GOLD primary care database as having had an incident breast cancer (Read codes provided in appendix 2) diagnosed during up-to-standard follow-up and prior to the most recent version of the CPRD GOLD primary care database available after all approvals have been obtained.

Inclusion criteria:

1. Female sex, aged ≥18 years;
2. Recorded with a breast cancer diagnosis during CPRD follow-up;
3. Clinical record with at least 12 months of uninterrupted up-to-standard data quality for research (as measured by CPRD) before the breast cancer diagnosis date (to ensure the cancer record represents incident disease).

Exclusion criteria:

1. Diagnosis of severe mental illness before the breast cancer diagnosis (i.e. organic mental disorder, mental disorders due to substances, schizophrenia, delusional disorders, or manic or bipolar episodes) (a provisional list of Read codes was defined for feasibility counts);
2. History of the specified mental health outcome in analysis in the year before the breast cancer diagnosis (list of Read codes to be defined in objective 1 of this study);
3. Diagnosis of any other cancer prior to breast cancer (Read codes available from Ranopa et al. [14]).

M. Selection of comparison group(s) or controls

Non-cancer comparison cohort

A comparison cohort will be assembled by randomly selecting, for each index case, up to 4 women of similar age (3-year range), attending the same GP practice, but with no history of cancer at the index date. Matching will also consider the eligibility of the patients' data for linkage, to ensure that matched-sets have the same probability of having had the information recorded when conducting sub-set analysis using linked data. Controls will be selected using nearest neighbour matching methods without replacement [29]. Women in the non-cancer comparison cohort who meet one or more exclusion criteria will be excluded, as well as their index case.

Women diagnosed with breast cancer during the follow up period will be censored from the unexposed group at the date of the cancer diagnosis, but will be eligible to separately contribute in the exposed group from this date (with corresponding unexposed matches).

N. Exposures, Outcomes and Covariates

Exposure: breast cancer

Women will be considered exposed at the day of the breast cancer diagnosis (index date), denoted by the first entry of one or more of the Read codes provided in appendix 2.

Primary outcomes: anxiety and depression

To our knowledge, there is no validated list of Read codes to identify anxiety and depression in the CPRD GOLD primary care database. Algorithms will be developed and tested to identify anxiety and depression cases in CPRD. The algorithms will be chiefly determined by clinical diagnoses of anxiety and depression registered in the EHR with Read codes, and supplemented with information from drug prescriptions, referrals, and symptoms (if deemed suitable). Please see section N, plan of analysis for specific aim 1, for more details on the construction and validation of algorithms.

Secondary outcomes: fatigue, mild cognitive impairment, pain, sleep disturbance, sexual dysfunction, and fatal and non-fatal self-harm

Similarly, we will develop and test outcome-specific algorithms that identify events using a hierarchy of data on clinical diagnoses, prescriptions, referrals and symptoms.
In sensitivity analysis, we will consider linked data (see section J for data linkage requested) to develop more precise definitions of the outcomes, when possible. For example, two definitions of suicide will be considered: (1) considering Read codes only to identify suicides in CPRD; (2) considering Read codes for suicide as well as death registration data where suicide was recorded as primary cause of death (ICD-10 codes provided in appendix 3)

Covariates

Variables considered as potential confounders or effect modifiers of the association between breast cancer history and anxiety and depression (the primary outcomes of this study) are described below. The directed, acyclic graph (DAG) in appendix 4 (available from the authors) explicitly describes the assumptions of the causal relations between the variables that underpin the choice. Please refer to the data analysis (section N) for details on which variables will be considered for sensitivity analyses only.

Potential confounders

- Age at diagnosis (categorical variable, in 10-year age bands)
  Defined as the absolute difference between the year of breast cancer diagnosis and year of birth. Age is a strong risk factor for breast cancer and for mental disorders.
- Alcohol drinking habits at diagnosis (categorical variable: current drinker, former drinker, never drinker)
  Excess alcohol drinking is a well-established risk factor for breast cancer [30], besides being positively associated with anxiety and depression [31-33]. The most recent data on alcohol drinking habits prior to index date will be used in analysis. Current drinking will be further sub-divided into high, moderate, low or unknown intake of alcohol.
- Body mass index at diagnosis (categorical variable: underweight, normal weight, overweight, obesity class I, obesity class II and above)
  Calculated as BMI=(weight/height^2). Higher body mass index is protective against breast cancer in pre-menopausal women, but a risk factor for breast cancer post-menopause [34]. Obesity increases the risk of anxiety and depression [35, 36]. The most recent recording of BMI prior to index date will be used in analysis. The BMI values will be categorised into 5 categories: <18.5 kg/m^2 (underweight), 18.5-24.9 kg/m^2 (normal weight), 25.0-29.9 kg/m^2 (overweight), 30.0-34.9 kg/m^2 (obesity class I), ≥35.0 kg/m^2 (obesity class II and above). Read codes for body weight categories recorded in the year prior to the breast cancer diagnosed will be considered to supplement missing information for this variable.
- Calendar period of diagnosis (categorical variable: ≤1994; 1995-1999; 2000-2004; 2005-2009; 2010-2014; >2014)
  Even though calendar time *per se* does not change the risk of breast cancer, the risk of being diagnosed with breast cancer changed over time, probably due to increase awareness of the disease along with widespread use of mammography to screen for breast cancer. Time has also contributed for mental disorders being more likely to be diagnosed, due to raises awareness and increased recognition of the importance of mental disorders among health care professionals.
- Diabetes mellitus (dichotomous variable: yes/no)
  Diabetes mellitus has been associated with an increased risk of breast cancer [37] and depression [38]. Algorithms previously defined elsewhere will be applied to identify patients with diabetes mellitus in the CPRD GOLD primary care database [39, 40].
- Level of deprivation (categorical variable: quintiles of patient-level IMD).
  The IMD is an ecological measure of deprivation for small areas in England that combines information from seven domains (income, employment, education, health deprivation, crime, barriers to housing, and living environment), and ranks the small area from 1 (most deprived) to 32,844 (least deprived). Patients will be categorised in quintiles of IMD, with quintile 1 representing those least deprived and quintile 5 those most deprived.

- Menopausal status (dichotomous variable: premenopausal/postmenopausal)
  Menopausal status is a potential confounder of the association between breast cancer history and depression, as the risk of breast cancer increases with menopause [30], and so does the risk of depression [42]. However, information on menopausal status is not easily available in the CPRD database. We will therefore produce results stratified by an age cut-off, as a proxy of the menopausal status of the women. The cut-off will be the mean/median age at natural menopause in the UK.

- Smoking history at diagnosis (categorical variable: current smoker, former smoker, never smoker)
  Information on Read codes available on the data will be used to classify patients by smoking history. The most recent data on smoking prior to index date will be used in analysis.

Potential effect modifiers

- Living alone (dichotomous variable: yes/no)
  Ascertained from the CPRD GOLD primary care data using Read codes (list provided in [41]) and the patient's family number (variable 'famnum' from the patient file). Women living in household of <2 people will be classified as living alone.
- Residing in a care home (dichotomous variable: yes/no).
  This variable will be defined from the CPRD GOLD primary care database, using Read codes (list provided in [41]), and information gathered in the family number variable ('famnum'). For the latter, 'care home' will be defined as a household with >3 individuals aged ≥65 years and if their total count was more than of individuals <65 years.
- Ethnicity (categorical variable: White, South Asian, Black, Others and mixed)
  Ethnicity data recorded in the CPRD GOLD primary care database will be categorised in five groups, following the categories defined in the UK 2011 Census: White, South Asian, Black, Others and mixed. This variable will be derived from Read codes available in the CPRD GOLD primary care database and from HES, since the combined data sources increase completeness from 55% to 79% [41]. For analysis, four groups will be considered: White, South Asian, Black, Others and mixed.
- Previous mental health history (categorical variable: yes/no)
  Mental health history will be defined as having had an episode of anxiety- or depression-related disorders (primary outcomes) or any the secondary outcomes, ever recorded at more than 1 year before the breast cancer diagnosis (patients who had the outcome in the year before the breast cancer diagnosis will be excluded from the cohort). These will be identified based on the algorithms defined in aim 1 of this study.

- History of stroke or coronary heart disease at diagnosis (two dichotomous variables: yes/no)
  These will include ischaemic heart disease (angina and myocardial infarction) and stroke, which are amongst the leading causes of disability-adjusted life years in females in the UK. These will be identified through Read codes recorded in the CPRD GOLD primary care database.

- Socioeconomic status (IMD quintiles of deprivation)

  The IMD is an ecological measure of deprivation for small areas in England (Lower Super Output Areas). It combines information from seven domain indices (income, employment, education, health deprivation, crime, barriers to housing, and living environment). The index ranks the areas from 1 to 32,844; usually the quintiles are used for research purposes: from 1 (most deprived) up to 5 (least deprived). The IMD is linked to the primary care data using the postcode of the patient or practice.

Potential mediators of the association between breast cancer history and anxiety/depression

- Sequelae from cancer treatments (six separate binary variables (yes/no): lymphoedema, pain, mild cognitive impairment, fatigue, sexual dysfunction, sleep disorder)
  Lymphoedema will be defined using Read codes for the condition, in the CPRD GOLD primary care database. Pain, mild cognitive impairment, fatigue, sexual dysfunction, and sleep disorder are secondary outcomes of this study, and will be identified based on the algorithms defined in aim 1 of this study. Patients will be classified as having had one of these conditions if there was more than one record for these conditions within a 6-month interval.
- Exposed to endocrine treatment for breast cancer: binary variable (yes/no).
  This will be defined from the CPRD GOLD primary care database using Read codes for at least two prescriptions of anastrozole, tamoxifen, exemestane, or letrozole [43] within a 6-month period.

O. Data/ Statistical Analysis

Primary analyses

Specific aim 1. To develop and validate algorithms to identify patients with anxiety and depression

Algorithm development

A systematic review is currently under way to identify the lists of Read codes previously used to define anxiety and depression of primary care databases in the UK. The systematic review search expressions are provided in appendix 5.

(A) Raw data tabulations

We will estimate the number and proportion of patients recorded during the observation period with:

1) Diagnostic Read code for anxiety/depression;
2) Prescription of anxiolytics/antidepressants;
3) Referred to mental health services;
4) Symptoms of anxiety/depression.

Proportions will be estimated by calendar year.

(B) Simpler algorithm

We will estimate the additional contribution of prescriptions, referrals and symptoms to identify cases of anxiety/depression in CPRD. Referrals and prescriptions of anxiolytics/antidepressants will be considered as sufficient to identify cases of anxiety/depression if a Read code for symptoms of anxiety/depression, respectively, were recorded during the previous year. The reasons for this are threefold: (1) there is good evidence that GPs switched from anxiety/depression diagnostic codes to symptomatic ones [44, 45], following claims of over diagnosis of these conditions; (2) antidepressants and anxiolytics have also other indications, including anxiety disorders for antidepressants [46], which raise questions of the use of these data their own to identify these outcomes; (3) pharmacological treatment of mild depression has been discouraged since 2004 [47], and thus referrals to psychotherapy may help to capture milder cases.

(C) Complex algorithm

A more detailed algorithm will be developed considering that some drugs are prescribed for both depression and anxiety, in addition to manage vasomotor symptoms, which may be more frequent in breast cancer survivors than in women who did not have cancer. An example for depression is given in appendix 6. We will estimate the number of patients with anxiety/depression at each step, to evaluate how much each category adds to what has been previously recorded.

Algorithm validation

A random sample of 1 million patients of both sexes will be selected from the CPRD GOLD primary care database. We will apply each algorithm and produce descriptive statistics stratified by likelihood of having the outcome, including:

- Number and proportion of patients with the anxiety, depression or both, by 3-year calendar period;
- Number and proportion of patients with the anxiety, depression or both, by 3-year calendar period, age and sex;
- Number and proportion of patients with the anxiety and depression by 3-year calendar period and country in the UK.

For each outcome, we will compare the estimates obtained with others obtained from the literature, prioritising national surveys of population-based data such as the following:

- Adult Psychiatric Morbidity Survey 2007 [48] and 2014 [49];
- Measuring National Well-being programme, made available by the Office for National Statistics (includes prevalence of those in the UK with some evidence indicating depression or anxiety, since 2013, by country in the UK and English regions, and by 10-year age groups up to 75 years) [50].

The final algorithm will be chosen by considering information in the numeric value closer to the estimates obtained from the literature.

Sensitivity analysis

Proportion estimates considering the presence of symptomatic codes within the previous year will be re-calculated to consider shorter periods of time (i.e. 3 and 6 months).

Specific aim 2. Risk of mental health outcomes in women who had breast cancer compared to women who did not have cancer

Primary outcomes analysis – depression and anxiety

Main analysis

Descriptive statistics including number of events observed and person-years at risk will be computed, overall and stratified by the covariates listed in section M (see above). Medical procedures for the diagnosis of breast cancer are likely to cause anxiety. To deal with this we planned to exclude patients who had a record of anxiety diagnosed within 1 year before the breast cancer; this could result in patients with higher levels of trait anxiety being excluded from the analysis. We will calculate the number and proportion of patients who were excluded because they had the outcome in the year prior to the breast cancer, stratified by month. We will also describe how many of those who were excluded from analysis had an outcome after the breast cancer diagnosis by age-group. The quintiles of the

distribution of the number of consultations (defined using the 'consid' variable) will be described, as this can indicate the patterns of seeking care between women with a history of cancer, compared to those who did not.

The association between breast cancer history and anxiety and breast cancer history and depression, will be quantified using Cox regression models with time since index as the underlying time scale, and stratifying on matched set to account for matching by age and primary care practice. Follow up will begin at the index date (vide section M for definition of the exposure) and will terminate when an outcome is observed. Women will be censored at the earliest date of any of these: cancer recurrence, other cancer diagnosis, death, transference out of the practice; if these events don't occur, censoring will be observed at the date of last data collection for the practice. Crude measures of the association between breast cancer history and anxiety and depression will be reported stratifying by the covariates described in section M.

Cox multivariate regression analysis will be use to estimate hazard ratios adjusted for calendar period of breast cancer diagnosis, menopausal status, and diabetes mellitus at baseline (see list of confounders in section L, covariates, for the definition of these variables).
Interaction terms between the exposure and the following variables will be added, to explore effect modification by ethnicity (White, South Asian, Black, Others and mixed), place of residence (care home vs. household), co-habitation status (living alone vs. cohabiting), SES (quintiles of IMD), having mental health disorders history (yes vs. no), having history of stroke (yes vs. no) and coronary heart disease (yes vs. no).

Confidence intervals will be calculated using robust estimates of the standard errors, to account for the fact that patients may also contribute with time at risk in the unexposed cohort prior to their cancer diagnosis.

The proportional hazards assumption will be tested in two ways: 1) graphically, by plotting the cumulative rates on a log scale; 2) inferentially, by applying a likelihood ratio test to the estimates obtained for the entire period of observation and for time split into intervals.

Sensitivity analyses

Sensitivity analyses planned for this study will include a subset of patients only; this is because they use variables from linked data, which is available for a fraction of the patients only, and include variables amenable to have missing data (i.e. BMI, alcohol intake, smoking and patient-level IMD). Regarding the latter, we will quantify the completeness of each variable to decide on their inclusion in the final models. Analyses including variables with missing data will be restricted to patients with complete data for covariates (complete case analysis), if missing data is likely to be missing not a random. The following sensitivity analyses are planned:

1) The main analysis will be repeated further adjusting for age at diagnosis (continuous variable, since matching allowed for 3-year gap), patient quintile level of IMD, alcohol drinking patterns prior to index date, smoking history and body mass index categories prior to index date.

2) We will exclude women diagnosed with the outcome of interest in the year prior to the cancer diagnosis. To account for the fact that treatment for these conditions may often last for more than one year, and that mild anxiety and depression may be treated in psychological services and not result in visits to the GP, we will repeated the main analysis including only patients who had 5 years of complete follow up prior to the index date and did not have the outcome recorded at any point during this period.

Multiple comparisons

We acknowledge that this study includes multiple comparisons for each outcome, and several outcomes. Thus, P-values in the range ~0.01-0.05 be considered as some statistical evidence of an effect and interpreted cautiously. Sample size considerations considering a 0.01 probability of type I error (α) are provided in see section I.

Specific aim 3. To estimate association between breast cancer history and anxiety/depression by presence of lymphoedema, pain, mild cognitive impairment, fatigue, sexual dysfunction, sleep disorders, and having done endocrine therapy, during the follow up period.

We will estimate the cumulative incidence and period prevalence of lymphoedema, pain, mild cognitive impairment, fatigue, sexual dysfunction, and sleep disorders, in breast cancer survivors during the overall follow up period and by 5-year of follow up period.
We will estimate the hazards of developing anxiety and depression (the main outcomes) for three groups of patients: 1) breast cancer survivors who did not develop the common complication (i.e. lymphoedema, pain, mild cognitive impairment, fatigue, sexual dysfunction, sleep disorders) up to time *t*; 2) breast cancer survivors who have had the common complication at time *t*; 3) women who never had cancer. A Cox regression model will be used to estimate the association between time-updated exposure and the main outcomes (anxiety and depression), having as reference the hazard observed for the women who did not have cancer. The exposure variable will be time-updated; this means that women who develop a common complication will contribute with information to group 1 until the date at which they develop the complication of interest; after this point they will contribute with information to group 2. All models will be adjusted for calendar period of breast cancer diagnosis.
Confidence intervals will be calculated using robust estimates of the standard errors. Sensitivity analyses planned in objective 2 will be applied to this objective as well.

Secondary outcomes analyses – fatigue, mild cognitive impairment, pain, sleep disturbance, sexual dysfunction, fatal and non-fatal self-harm

The steps outlined above will be repeated for the secondary outcomes. Sensitivity analysis will follow the same rationale as described for the primary analysis.

P. Plan for addressing confounding

The confounding effect of age and socio-economic status (SES) will be limited at the study design phase, as women who had breast cancer will be individually matched to women who never had cancer by age and primary care practice. Variables considered as important confounders will be included in the multivariate Cox regression models (vide section M, covariates).

Q. Plans for addressing missing data

There are no plans for using multiple imputation methods in this study. Three variables in the main analysis are likely to have missing data: body mass index, smoking and alcohol intake. The probability of these values being recorded in the patients' medical records is likely to depend on the actual value (e.g. obese patients may have their weight more often assessed and smoking may be more often recorded in patients who visit the GP for complications of smoking (e.g. chronic obstructive pulmonary disease). This is a direct violation of the missing at random assumption needed for multiple imputation. We will therefore conduct a complete case analysis, which is a valid method when missingness is conditionally independent of the outcome [52].

R. Patient or user group involvement (if applicable)

Patients with history of breast cancer involved with the Independent Cancer Patients' Voice, a breast cancer support charity, commented on the study protocol.

S. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The results of this study will be presented at scientific conferences in the area, and submitted for publication in peer-reviewed journals.

Conflict of interest statement: Ms Williams reports that CPRD has financial relationships with its clients, including the London School of Hygiene and Tropical Medicine, in relation to providing access to research data and services outside the submitted work. Dr. Stanway reports personal fees from Roche, Clinigen, Eli Lilly, and Novartis, not related to this work. Dr. Bhaskaran reports grants from Wellcome Trust, the Royal Society, Medical Research Council, and British Heart Foundation, outside the submitted work.

T. Limitations of the study design, data sources, and analytic methods

Validity of the mental health diagnosis in the CPRD GOLD primary care database

The validity and the completeness of the recording of the mental disorders in CPRD have not been evaluated, and this will limit our results. The diagnosis and treatment of depression has also changed over time, as a result of the 2004 NICE guidelines (discouraging the treatment of mild depression with antidepressants) and the Quality and Outcomes Framework scheme in 2006, which recommended validated questionnaires to evaluate its severity [8, 9]. As for completeness, mental disorders such as depression and anxiety are managed at the primary care level, and therefore the potential for recording is high. Nevertheless, some of these conditions, especially in the sub-threshold or milder severities, may not result in GP visits and go therefore undiagnosed [10].

Unmeasured and residual confounding

This study is also limited by the lack of historical data on potential confounders, such as physical activity. Residual confounding will not be possible to rule out for variables such as smoking [53].

Multiple indications of the psychotropic medicines (complex algorithm definition)

In clinical practice, several classes of pharmacological agents are currently used to manage anxiety and depressive disorders, and many of these pharmacological agents are used to treat other physical and mental disorders (appendix 7). An example of this is illustrated by the guidelines. The National Institute for Health and Care Excellence (NICE) issued guidelines for recognition and management of depression in people who have a physical chronic condition such as cancer [54], and for management of generalized anxiety disorder (GAD) and panic disorder [46]. Low- or high-intensity psychological interventions (e.g. low intensity: individual non-facilitated or guided self-help; high intensity: cognitive behavioural therapy) are recommended as the first line for GAD, mild depression and long-term insomnia (>4 weeks) [46]. Pharmacological treatment is recommended for persisting GAD, moderate to severe depression and insomnia that causes severe daytime dysfunction. SSRI are currently recommended for GAD; benzodiazepines are most often restricted to crisis and not recommended for long-term use [46]. This will raise issues on the indication under which the patient has been prescribed the medicine. We will select all pharmacological agents used to treat each of the outcomes, and seek experts' advice on which drugs are often prescribed. In any case, this offers a potential for misclassification (thought to be non-differential).

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Methods1 Definition of outcomes

Search and selection of Read codes and pharmacological drugs

We searched the dictionary of codes using keywords defined by a general practitioner experienced in using the codes in clinical practice (GF). We then identified the relevant parent code for the outcome, and included all Read codes within that group. Finally, we added all codes identified in a comprehensive systematic review of the lists of Read codes used to identify mental health and quality of life outcomes in primary care databases of electronic health records in the UK (Carreira et al, BMJ Open, 2019). Two researchers (HC and GF) independently assigned each Read code to a certainty group, compared and agreed the final list of codes (available online).

Drugs for anxiety, depression, sleep disorders and pain were identified in product dictionary by searching formulations listed in the British National Formulary (BNF) as indicated to treat these conditions. The final list of products was checked for suitability by a GP (GF) and irrelevant products were excluded (e.g. doxepin topical).

Primary outcomes

Anxiety

Anxiety was defined with Read codes, if the Read code was considered sufficiently specific. When the Read code referred to typical symptoms of anxiety, which are not necessarily pathological, we considered the patient to have anxiety only if they had been prescribed with a drug with anxiety within 90 days of the Read code.

Read codes for the following conditions were included/excluded from our definition:

Included	Excluded
Generalised anxiety disorder	Specific phobias (e.g. heights)
Panic disorder	Somatic symptoms disorder
Agoraphobia	
Social anxiety disorder	
Mixed anxiety and depression	
Obsessive compulsive disorders *	
Trauma- and stress-related disorders* with anxiety, including PTSD, acute stress disorder, and adjustment disorder with anxiety	

N.B. 'Included' and 'Excluded' refer to *symptoms* and *diagnoses* of the conditions listed.

* In DSM-5, published in 2013, obsessive-compulsive and stress-related disorders are classified separately from anxiety disorders. This was a major change from previous editions of the DSM, in which these two categories were considered as anxiety disorders. The data for this study refer to patients under observation during 1988 and 2018 (or part of this period); it is unclear how, or if, the changes in nosology affected the use of Read codes by GPs at the point of patient care. In addition, the accuracy of the Read codes to identify each of the sub conditions is likely to be sub-optimal at any given point in time. For these reasons, we decided to include OCDs and stress-related disorders in our definition of anxiety. See below, in the depression section, a note about adjustment disorders with anxiety.

Drugs indicated to treat anxiety according to the British National Formulary:

Substance name
Alprazolam
Amitriptyline hydrochloride/ Chlordiazepoxide
Buspirone hydrochloride
Chlordiazepoxide hydrochloride
Diazepam
Duloxetine hydrochloride
Escitalopram oxalate
Lorazepam
Meprobamate
Moclobemide
Oxazepam
Oxprenolol hydrochloride
Paroxetine hydrochloride
Pericyazine
Perphenazine
Pregabalin
Trazodone hydrochloride
Venlafaxine hydrochloride

International Classification of Diseases, 10th revision, codes for anxiety:

ICD-10 codes	Description
F40	**1.** Phobic anxiety disorders
F41	**2.** Other anxiety disorders
F42	**3.** Obsessive-compulsive disorder
F43	**4.** Reaction to severe stress, and adjustment disorders
F44	**5.** Dissociative [conversion] disorders
F48	**6.** Other neurotic disorders

Definition used in sensitivity analysis including specific diagnoses:

Included (Read codes for diagnoses only)	Excluded
Panic disorder	All symptom codes (e.g. 'anxious')
Generalized anxiety disorder	
Mixed anxiety and depression	
Obsessive-compulsive disorder	
Acute stress disorder	
Post-traumatic stress disorder	
Anxiety disorder, NOS	

Depression

We used Read codes alone to classify patients with depression, if the Read code was considered sufficiently specific. When the Read code referred to typical symptoms of depression that could not be sufficient to classify as a depressive episode, we checked whether there as a prescription of a drug commonly used to depression within 90 days, and considered patients to be depressed if yes.

Read codes for the following conditions were included/excluded from our definition:

Included	Excluded
Major depressive disorder	Bipolar and related disorders (incl. bipolar I, II and cyclothymic disorder)
Dysthymia	Premenstrual dysphoric disorder
Recurrent depressive disorder	Suicide †
Mixed anxiety and depression	Self-harm †
Disruptive mood dysregulation disorder	Maternal depression
Depression in dementia (or other condition)	
Trauma- and stress-related disorders* with depressed mood, including adjustment disorders with depressed mood*	

N.B. 'Included' and 'Excluded' refer to symptoms and diagnoses of the conditions listed.

* See note on anxiety table. Adjustment disorders are considered to be a short-term reaction to a stressor (i.e. diagnosed usually within 3 months of the onset of the stressor). The core symptoms of adjustment disorders overlap with those of the anxiety and depressive disorders, which would be diagnosed if the symptoms persist for longer than a 6-month period after the terminus of the stressor. The potential for misclassification between adjustment and depressive disorders is high, as they share the same symptomatology and treatment. The data for this study will include patients recently diagnosed with breast cancer (included in the cohort in the day of the cancer recording in the CPRD GOLD primary care database). To avoid misclassification of the outcome, we included adjustment disorders in our definitions of anxiety and depression.

† Self-harm and suicide most often occur in patients with a depressive disorder. We will examine these two outcomes separately.

Drugs indicated to treat depression according to the British National Formulary:

Substance name
Agomelatine
Amitriptyline Hydrochloride
Amitriptyline Hydrochloride/ Perphenazine
Citalopram hydrobromide
Citalopram hydrochloride
Clomipramine hydrochloride
Dosulepin hydrochloride
Dosulepin Hydrochloride
Duloxetine hydrochloride
Escitalopram oxalate
Fluoxetine hydrochloride
Fluvoxamine maleate
Imipramine hydrochloride
Isocarboxazid
Lofepramine hydrochloride
Mianserin hydrochloride

Substance name
Mirtazapine
Moclobemide
Nortriptyline hydrochloride
Nortriptyline Hydrochloride
Paroxetine hydrochloride
Phenelzine sulfate
Reboxetine mesilate
Sertraline
Sertraline hydrochloride
Tranylcypromine sulfate
Trazodone Hydrochloride
Trimipramine maleate
Venlafaxine hydrochloride
Venlafaxine Hydrochloride
Vortioxetine hydrobromide

International Classification of Diseases, 10th revision codes for depression:

ICD-10 codes	Description
F32	**7.** Depressive episode
F33	**8.** Recurrent depressive disorder
F34	**9.** Persistent mood [affective] disorders
F41.2	**10.** Mixed anxiety and depressive disorder
F92.0	**11.** Depressive conduct disorder

Definition used in sensitivity analysis including specific diagnoses:

Included (Read codes for diagnoses only)	Excluded
Depressive episode	All symptom codes (e.g. 'depressed')
Major depression	
Seasonal affective disorder	
Dysthymia	
Mixed anxiety and depression	

Secondary outcomes

Cognitive dysfunction

Cognitive dysfunction was defined by Read codes for impairments in domain of cognitive function (e.g. 'amnesia symptom', 'orientation confused'), or Read codes related to cognitive assessments (e.g. 'mini-mental state examination', 'unable to remember own date of birth'), Read codes for dementia and drugs commonly used to treat dementia.

We used a broad definition of cognitive dysfunction because we were interested in mild cognitive dysfunction, which is often reported by women with history of breast cancer after diagnosis and treatment. However, changes to cognitive dysfunction, especially those in older adults, may not lead to primary care until it becomes troublesome for the patient or their family. At this point, the patient may be diagnosed with more severe levels of cognitive dysfunction, and we would not be able to identify an outcome of 'mild cognitive dysfunction' in the CPRD primary care database. As loss of cognitive function is a gradual process, we defined cognitive dysfunction using codes that ranged from mild cognitive dysfunction to dementia. We also included codes for scales/tests because we assumed that patients who have had a cognitive assessment registered by their GP might have relevant cognitive complains. Drugs were considered sufficient to ascertain the outcome because these are very specific to dementia.

Read codes for the following conditions were included/excluded from our definition:

Included	Excluded
Mild cognitive impairment	Delirium
Alzheimer's disease	Dementia in Creutzfeldt-Jakob disease †
Vascular dementia	Dementia in Huntington's disease †
Frontotemporal dementia	Dementia in Parkinson's disease †
Dementia in Pick's disease	Dementia in human immunodeficiency virus [HIV] disease †
Unspecified dementia	Normal pressure hydrocephalus †

† We excluded dementia with well-described cause, which is unlikely to be associated with a cancer history.

Drugs indicated to treat dementia according to the British National Formulary:

Substance name
Donepezil hydrochloride
Galantamine hydrobromide
Memantine hydrochloride

International Classification of Diseases, 10th revision codes for dementia:

ICD-10 codes	Description
F00	Dementia in Alzheimer disease
F01	Vascular dementia
F02.0	Dementia in Pick disease
F03	Unspecified dementia
F06.7	Mild cognitive disorder

Fatigue

Patients were classified as having had fatigue using Read codes (list of Read codes available online). We included/excluded the following conditions in our definition of fatigue:

Included	Excluded
Chronic fatigue syndrome/ myalgic encephalitis	Combat fatigue
Neurasthenia	Fatigue in pregnancy
Post viral fatigue syndrome *	Fibromyalgia †

N.B. 'Included' and 'Excluded' refer to *symptoms* and diagnoses of the conditions listed. We included symptoms such as 'tired all the time' because GPs may be less likely to diagnose chronic fatigue syndrome if symptoms can be attributed to the breast cancer treatments.

* Post-viral fatigue syndrome our definition of fatigue because there is a high potential for misclassification of these outcomes at primary care level, as viral infections are common.

† Studies have shown a considerable overlap between fatigue and fibromyalgia, with at least 75% of the patients diagnosed with fibromyalgia report fatigue (Clin Rev Allergy Immunol. 2015 Oct;49(2):100-51). We expect these patients to be captured by the terms for fatigue defined in the conditions of interest for this study.

Pain

Pain was defined using Read codes for pain of specific regions of the body (e.g. chest pain), and of known conditions that may be caused by treatments (e.g. arthralgia in patients who are treated with hormone therapy, or post-surgical pain), unspecified pain (e.g. pain symptom). Pain syndromes (e.g. fibromyalgia) were included. Read codes for pain scales were also considered as evidence of pain, as we assumed that this would not be offered to the patient if s/he did not complain of pain. Codes for rheumatoid arthritis and arthroses were excluded, as well as codes for fractures. We also excluded codes for pain of known aetiology that is unlikely to be related to breast cancer treatments (e.g. post-herpetic pain, diabetic neuropathic pain, menstrual pain, fractures, accidents, etc.).

Opioid analgesics

All opioid analgesics listed in the British National Formulary were considered eligible. We did not include codes for treatment of opioid dependency.

Sleep disorder

Sleep disorder was defined with Read codes, if the Read code was considered sufficiently specific. When the Read code referred to symptoms or possible treatment of sleep disorder (e.g. 'poor sleep pattern', 'sleep hygiene behaviour education'), we considered the patient to have a sleep disorder only if they had been prescribed with an anxiolytic/hypnotic (table below) within 90 days of the code.

Read codes for the following conditions were included/excluded from our definition:

Included	Excluded
Insomnia	Narcolepsy
Hypersomnia	Breathing-related disorders (including sleep apnoea)
Circadian rhythm sleep-wake disorders	Cataplexy
Parasomnias	

N.B. 'Included' and 'Excluded' refer to *symptoms* and diagnoses of the conditions listed.

Drugs indicated to treat sleep disorders according to the British National Formulary:

Substance name
Temazepam
Nitrazepam
Diazepam
Zopiclone
Clomethiazole
Promethazine hydrochloride
Promethazine teoclate
Zolpidem tartrate
Codeine phosphate/promethazine hydrochloride
Clomethiazole edisilate
Flunitrazepam
Flurazepam hydrochloride
Lormetazepam
Oxazepam
Promethazine hydrochloride/paracetamol
Loprazolam mesilate
Melatonin
Promethazine hydrochloride/pholcodine
Pethidine hydrochloride/promethazine hydrochloride
Paracetamol/promethazine hydrochloride/ dextromethorphan hydrobromide
Dextromethorphan hydrobromide/promethazine hydrochloride/ paracetamol

Female sexual dysfunction

We included only Read codes in our definition of sexual dysfunction. We included Read codes for scales of sexual function (e.g. Derogatis Sexual Dysfunction Inventory) because the patient is likely to have had subjective complains of sexual function in order for the GP to apply the test.

We considered the follow clinical disorders as relevant outcomes:

Included	Excluded
Female orgasmic disorder	Paraphilia
Female arousal disorder	Excess sex drive
Dyspareunia	Sexual orientation related codes

We acknowledge that codes for improved sexual function are likely to indicate that a disorder has been present; these were nevertheless excluded as the date of the disorder cannot be ascertained. In addition, prescriptions for sexual dysfunction are not likely to capture accurately the disorder, as it may include lubricants that are often sold over the counter, or creams containing oestrogen that may be under prescribed to breast cancer survivors due to concerns related with oestrogen positive receptor tumours.

Fatal and non-fatal self-harm

Fatal and non-fatal self-harm included codes for intentional self-harm and suicidal ideation, using an updated version of a previously validated list of Read codes (Br J Clin Pharmacol 2013; 76(1): 145-57), and International Classification of Diseases, tenth revision, (ICD-10) codes for completed suicide. Completed suicide was defined using the ICD-10 codes X60-X84 and Y10-34, excluding Y33.9 where the verdict is pending.

International Classification of Diseases, 10th revision codes for self-harm:

ICD-10 codes	Description
X60-X84	Intentional self-harm
Y10-Y34	Event of undetermined intent
Y87.0	Sequelae of intentional self-harm
Y87.2	Sequelae of events of undetermined intent

Methods2 Definition of covariates

Alcohol and smoking status

Information on alcohol drinking and smoking status was obtained from primary care records, and patients were assigned into the following categories for each variable: non-users, current users, and former users. For these three variables, we prioritised information registered in the year prior to the index date, or up to 30 days after the index date; where this was unavailable we used information recorded at any point prior to the index date, and if still missing, we used information recorded at any point in the clinical record.

Body mass index

Body mass index (BMI) (kg/m^2) was computed as weight divided by the square of height, using a previously defined algorithm to ascertain this information from the clinical records (BMJ Open 2013; 3(9): e003389). Patients were classified in BMI categories, according to the World Health Organization proposed cut-offs for Caucasian populations.

Cardiovascular comorbidity

Cardiovascular comorbidity was defined as having a record of stroke or ischaemic heart disease (angina and coronary heart disease) before the study index date, or up to 30 days after the index date.

Deprivation

Deprivation was defined by quintiles of the practice-postcode linked Index of Multiple Deprivation (IMD), which is an ecological measure of deprivation for small areas in England (Lower Super Output Areas). For a subset of patients, patient-postcode linked quintile of IMD was available.

Diabetes mellitus

Diabetes mellitus was defined as having had a Read code for type I or type II diabetes mellitus recorded up to 30 days after the index date (assuming that any event recorded within the first month would be prevalent).

Ethnicity

Ethnicity (White, South Asian, Black, Others and mixed) was defined in accordance with previously defined algorithms (J Public Health (Oxf) 2014; 36(4): 684-92).

Table 1(A) Characteristics of the patients excluded from analysis, and follow up time for anxiety, depression and cognitive dysfunction.

	Anxiety		Depression		Cognitive dysfunction	
	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed
Patients eligible for analysis, N (%)	230,067 (100.00)	57,571 (100.00)	230,067 (100.00)	57,571 (100.00)	230,067 (100.00)	57,571 (100.00)
Exclusions from outcome-specific analysis, N (%)	5,929 (2.58)	1,955 (3.40)	13,712 (5.96)	3,498 (6.08)	5,623 (2.44)	1,519 (2.64)
Patients excluded who had the outcome recorded *after* the index date, N (%)	2,707 (45.7)	896 (45.8)	8,511 (62.1)	2,175 (62.2)	- -	- -
Mean time (SD) between the mental health outcome diagnosis and the index date, days	214 (109)	218 (110)	212 (109)	214 (110)	- -	- -
Age at index date (years)						
Mean (SD)	60 (14)	60 (13)	61 (14)	61 (14)	74 (13.12)	74 (13.30)
Minimum-maximum	21-101	24-102	19-101	22-101	28-103	29-101
Total number of patients included in analysis (%)	**224,138 (97.42)**	**55,616 (96.60)**	**216,355 (94.04)**	**54,073 (93.92)**	**224,444 (97.56)**	**56,052 (97.36)**
Total number of person-years at risk	**1,306,784**	**288,115**	**1,202,647**	**261,081**	**1,385,179**	**315,453**
Duration of follow up (years)						
Mean (SD)	5.83 (4.79)	5.18 (4.57)	5.56 (4.74)	4.83 (4.48)	6.17 (4.94)	5.63 (4.71)
Median	4.61	3.89	4.26	3.44	5.00	4.38
Outcomes during follow-up, N	20,224	5,888	34,558	10,175	19,845	4,368

SD: standard deviation.

Table 1(B) Characteristics of the patients excluded from analysis, and follow up time for fatigue, sexual dysfunction and sleep disorders.

	Fatigue		Sexual dysfunction		Sleep disorder	
	Unexposed	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
Patients eligible for analysis, N (%)	230,067 (100.00)	57,571 (100.00)	230,067 (100.00)	57,571 (100.00)	230,067 (100.00)	57,571 (100.00)
Exclusions from outcome-specific analysis, N (%)	6,561 (2.85)	1,660 (2.88)	490 (0.21)	127 (0.22)	4,484 (1.95)	1,361 (2.36)
Patients excluded who had the outcome recorded *after* the index date, N (%)	2,409 (36.7)	609 (36.7)	87 (17.8)	12 (9.5)	1,822 (40.6)	622 (45.7)
Mean time (SD) between the mental health outcome diagnosis and the index date, days	208 (110)	211 (107)	203 (111)	202 (106)	206 (106)	215 (106)
Age at index date (years)						
Mean (SD)	62 (14)	63 (14)	53 (9)	51 (10)	67 (15)	65 (15)
Minimum-maximum	19-101	26-103	21-92	21-77	21-99	19-101
Total number of patients included in analysis (%)	**223,506 (97.10)**	**55,911 (97.10)**	**229,577 (99.8)**	**57,444 (99.8)**	**225,583 (98.10)**	**56,210 (97.60)**
Total number of person-years at risk	**1,266,975**	**280,982**	**1,435,837**	**325,393**	**1,338,065**	**290,786**
Duration of follow up (years)						
Mean (SD)	5.67 (4.73)	5.03 (4.48)	6.25 (4.98)	5.66 (4.75)	5.93 (4.85)	5.17 (4.60)
Median	4.44	3.69	5.09	4.40	4.71	3.86
Outcomes during follow-up, N	28,886	8,359	2,153	683	16,798	6,002

SD: standard deviation.

Table 1(C) Characteristics of the patients excluded from analysis, and follow up time for pain, opioid analgesics, and fatal/non-fatal self-harm.

	Pain		Opioids analgesics		Fatal and non-fatal self-harm	
	Unexposed	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
Patients eligible for analysis, N (%)	230,067 (100.00)	57,571 (100.00)	230,067 (100.00)	57,571 (100.00)	132,647 (100.00)	33,168 (100.00)
Exclusions from outcome-specific analysis, N (%)	68,030 (29.57)	18,800 (32.66)	16,877 (7.34)	4,899 (8.51)	315 (0.24)	63 (0.19)
Patients excluded who had the outcome recorded *after* the index date, N (%)	54,493 (80.10)	14867 (79.08)	12,547 (74.3)	3,855 (78.69)	80 (25.4)	14 (22.2)
Mean time (SD) between the mental health outcome diagnosis and the index date, days	215 (107.80)	214 (109.78)	217 (108)	215 (111)	229 (110)	218 (110)
Age at index date (years)						
Mean (SD)	63 (14)	63 (14)	66 (14)	67 (13)	54 (13)	52 (17)
Minimum-maximum	19-102	19-103	27-91	25-91	30-102	25-91
Total number of patients included in analysis (%)	**162,037 (70.43)**	**38,771 (67.34)**	**213,190 (92.7)**	**52,672 (91.5)**	**132,332 (99.8)**	**33,105 (99.8)**
Total number of person-years at risk	**505,451**	**100,312**	**1,181,155**	**248,654**	**831,516**	**190,182**
Duration of follow up (years)						
Mean (SD)	3.12 (3.30)	2.59 (2.88)	5.54 (4.70)	4.72 (4.49)	6.28 (4.98)	5.74 (4.76)
Median	1.99	1.59	4.27	3.36	5.13	4.50
Outcomes during follow-up, N	94,171	24,522	44,850	17,315	794	182

SD: standard deviation.

Table 2 Incidence of adverse mental health-related outcomes in breast cancer survivors and women who did not have cancer.

	Women with no history of cancer						Women with history of breast cancer					
	1 year		5 years		10 years		1 year		5 years		10 years	
	%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	95%CI
Anxiety	2.0	1.9 - 2.1	8.2	8.1 - 8.4	13.8	13.6 - 14.0	3.9	3.8 - 4.1	10.6	10.3 - 10.9	16.4	15.9 - 16.8
Depression	4.0	3.9 - 4.0	14.8	14.6 - 15.0	24.0	23.7 - 24.3	7.1	6.9 - 7.3	19.4	19.0 - 19.8	28.5	28.0 - 29.1
Cognitive dysfunction	1.1	1.1 - 1.2	5.8	5.7 - 5.9	13.2	12.9 - 13.4	1.0	0.9 - 1.1	5.7	5.4 - 5.9	13.1	12.7 - 13.6
Fatigue	2.7	2.6 - 2.8	11.4	11.3 - 11.6	19.9	19.7 - 20.2	4.0	3.8 - 4.1	15.2	14.8 - 15.5	23.9	23.4 - 24.5
Pain	22.1	21.9 - 22.4	61.0	60.7 - 61.3	79.1	78.8 - 79.4	27.0	26.6 - 27.5	69.7	69.2 - 70.3	85.6	85.1 - 86.2
Sexual dysfunction	0.2	0.2 - 0.2	0.8	0.8 - 0.9	1.5	1.4 - 1.5	0.2	0.2 - 0.3	1.2	1.1 - 1.4	2.0	1.8 - 2.1
Sleep disorder	1.6	1.5 - 1.6	6.6	6.5 - 6.8	11.6	11.4 - 11.7	4.7	4.6 - 4.9	10.8	10.5 - 11.1	16.0	15.5 - 16.4
Opioid analgesics	4.2	4.1 - 4.3	17.7	17.5 - 17.9	31.1	30.8 - 31.3	12.2	12.0 - 12.5	30.8	30.3 - 31.2	45.5	44.9 - 46.1
Fatal and non-fatal self-harm	0.1	0.1 - 0.1	0.5	0.5 - 0.6	0.9	0.8 - 1.0	0.1	0.1 - 0.2	0.5	0.5 - 0.6	0.9	0.8 - 1.0

95%CI: 95% confidence interval.

12.4 Appendix 4 Supplementary materials to the paper presented in Chapter 7

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Mental health and quality of life of female breast cancer survivors compared to women who did not have cancer

(in preparation)

Contents

Mental health and quality of life of female breast cancer survivors compared to women who did not have cancer

Study protocol

Version 4

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Summary

We aim to assess the quality of life (QoL), and presence and severity of anxiety and depressive symptoms, in women who have had breast cancer diagnosed at ≥1 year, compared to women who did not have cancer.

The Clinical Practice Research Datalink (CPRD) primary care database will be used to select a random sample of breast cancer survivors (≥1 year), whose general practitioner (GP) agrees to participate in the study (see below), and who were registered with the practice for ≥1 year before and after the breast cancer diagnosis. Age-matched women who never had cancer will be randomly selected from the same practice. Staff at each practice will mail the study materials to the eligible women, who will complete the questionnaires and send those to the CPRD Intervention Studies Team for processing.

In addition, a secondary objective of this study is to assess whether PROs can be reasonably studied by using electronic health records (EHR), as these would involve fewer resources. For this, the EHR of the participating women will be collated from the CPRD primary care database and the results will be compared to those reported by the patients.

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1 Background

Breast cancer is the most common malignancy diagnosed in women in the United Kingdom (UK), excluding non-melanoma skin cancer [1]. The five-year age-standardised net survival for patients diagnosed with breast cancer in 2005-09 was 81% [2]. Breast cancer survivors are the largest group of cancer survivors in the UK [3, 4]: approximately 570,000 women were estimated to be living with or beyond breast cancer in 2010; this corresponds to 1,803 per 100,000 women [4]. The increasing trends in incidence and survival [1, 2] suggest that the number of breast cancer survivors will continue to increase in the next decades [4].

Even though women now live longer after the breast cancer diagnosis, the disease is perceived as life threatening and a major cause of emotional distress [5]. Common reactions to the diagnosis include anxiety, feelings of loneliness, fear of death, hopelessness, anger, suicidal thoughts and existential issues [6, 7]. In addition to the sorrow of the diagnosis, most women undergo a long and complex journey of aggressive treatments [8] with iatrogenic effects that are likely to have a long-term negative impact on their mental health and health-related quality of life (HRQoL) [9, 10]. For example, surgery for tumour removal and lymph node status assessment may cause lymphoedema [11] and/or persistent pain [12], in addition to a life-long scar, which may change women's body image [13]. Chemotherapy may result in cognitive impairments [14, 15] and/or cause amenorrhea in pre-menopausal women, bringing fertility concerns (for women who want children) and vasomotor symptoms such as hot flushes, night sweats, breast sensitivity and/or pain [16, 17]. In the long-term, women also have to re-adapt to social and intimate relationships (including with their spouse [18] and offspring [19-21]), and deal with the fear of cancer recurrence and death [22].

Patients often report the social, mental and cognitive functioning as important outcomes of their disease [23-26]. However, few studies [27, 28] focused on the mental health and HRQoL of large samples of cancer survivors in the UK. The Clinical Practice Research Datalink (CPRD) primary care database gathers data for consultations occurring in a large number of general practices in the UK. This database currently includes data for more than 11.3 million patients, from over 600 general practices [29]. The cohort of cancer survivors in this database is one of the largest in the world with data prospectively and routinely collected at primary care level. As most mental disorders are also managed at primary care level [30, 31], the CPRD primary care database offers a unique opportunity to study long-term mental disorders in women who have had breast cancer. The information available for some domains of HRQoL may also represent an opportunity to study what are normally patient reported outcomes at a much lower cost but there has been no study evaluating the extent to which EHR data can be reasonably used to study HRQoL.

Khan *et al* used the CPRD primary care data to evaluate the pattern of consultations for anxiety and depression in 2003-2005, as well as the prescription of antidepressants and anxiolytics, among 16,938 breast cancer survivors (>5 years) and 67,649 women without breast cancer [27]. This study showed that breast cancer survivors had significantly increased odds of being prescribed antidepressants and anxiolytics but not of consulting for anxiety or depression, compared to women who did not have breast cancer [27]. The interpretation of these results is not straightforward because: 1) patients consulting for anxiety or depression are likely to represent the most severe cases, as these disorders, especially in the sub-threshold or milder severities, are often undiagnosed [31] and their burden underestimated; 2) cancer survivors may have more contact with the health services and be therefore more likely to be diagnosed and/or treated for anxiety or depressive symptoms, compared to women who did not have breast cancer; 3) antidepressants may also be prescribed to breast cancer survivors as treatment for hot flushes [32], one of the commonest side effects of endocrine treatments [33], and it is unclear if the frequency of prescription of antidepressants for hot flushes differs between women who have had breast cancer and women who never had cancer. Considering this, it is unclear how well the data registered in the EHR represent the burden of anxiety and depressive conditions in the population. In addition, a population-based cohort study conducted in Denmark described a significantly increased risk of depression in the first years after diagnosis, whose magnitude and significance reduced over time [34]. Corresponding estimates for the five years after the diagnosis are not available in the UK.

The aim of this study is to investigate the HRQoL, and the presence and severity of anxiety and depressive symptoms, in breast cancer survivors (>1 year) and in women who did not have cancer. A secondary objective of this study is to compare the outcomes reported by the patients to the data available in the EHR. In doing so, we will assess the feasibility of using EHR to study outcomes that are usually reported directly by patients.

2 Aims and objectives

Aims

The primary aim of this study is to investigate the health-related quality of life (HRQoL), and the presence and severity of anxiety and depressive symptoms, in female breast cancer survivors (>1 year) compared to women who did not have cancer.

The secondary aim is to assess the feasibility of studying outcomes that are usually reported directly be patients by relying on the EHR data.

Specific objectives

1. To describe cancer-specific measures of HRQoL in breast cancer survivors, and to explore the impact of demographic and clinical factors;
2. To compare measures of HRQoL between breast cancer survivors and women who did not have cancer and to evaluate the impact of clinical and demographic variables;
3. To compare the severity of anxiety and depressive symptoms in breast cancer survivors and in women who did not have cancer, and to assess the impact of demographic and clinical variables;
4. To compare patient reported HRQoL, and anxiety and depressive symptoms, with the information registered in the EHR for similar constructs.

3 Plan of investigation

3.1 Study type

Descriptive.

3.2 Study site

England, Wales, Scotland and Northern Ireland.

3.3 Study design

Cross-sectional.

3.4 Study population

Women aged 18 to 80 years old, diagnosed with a first primary cancer of the breast at one year or more ago at the recruitment date, and who had been registered for at least two years with a general practice contributing with 'up to standard' data to CPRD at the moment of the recruitment.

3.5 Comparison group

Adult women (18-80 years) without a previous cancer diagnosis, selected from the same primary care practices of the cancer patients.

3.6 Recruitment of the participants

Participants will be recruited from primary care practices contributing with data to the CPRD primary care database, via their GP. GPs working in practices considered 'active' (i.e. contributing with data to CPRD at the time of recruitment), and whose data quality at practice level has been judged as 'up to standard' by the CPRD internal quality procedures, will be invited by the CPRD Intervention Studies Team to participate in the study. Refusal to participate in the study will be recorded.

Breast cancer survivors

The EHR of the women registered with the GPs who accept to participate in the study will be collated. We will create a list of women who had a breast cancer recorded in the EHR using the list of Read codes provided in Appendix 1. We will then restrict the list to women aged

18-80 years, who were registered with the same primary care practice for at least one year before the breast cancer diagnosis, and who are currently alive, registered with the same practice, and have passed the first anniversary of their cancer diagnosis. A list of Read codes for other cancers [35] will be used to further exclude women who have had any other malignancy diagnosed before or after the breast cancer.

A random list of potentially eligible breast cancer survivors from each general practice will be selected. The number of women to be randomly selected from each practice will be calculated as the total number of women necessary for the study multiplied by the number of breast cancer survivors in the practice divided by the total number of potentially eligible breast cancer survivors in all practices.

The list of potentially eligible breast cancer survivors will be provided to the GP, and s/he will apply the following exclusion criteria:

a) The woman had a another cancer (not detected in the EHR), or has been treated for a non-invasive breast tumour;
b) The woman is considered unable to complete a self-administered questionnaire written in English for any reason.

The number of women excluded by the GP under each criterion will be recorded. Breast cancer survivors not excluded will be eligible for the study and invited to participate.

Women who did not have cancer

A list of Read codes [35] will be used to exclude patients who have had cancer from the list of patients attending the same practices as the cancer survivors. In addition, patients who have not been registered continuously for the last two years with the practice and outside the age range 18-80 years will be excluded. Women still in the list are potentially eligible.

The number of women to be selected from each practice will be calculated as: total number of women without cancer necessary for the study times the number of women without cancer in the practice divided by the total number of women without cancer in all practices.

For each practice, we will then calculate the proportion of breast cancer survivors in the following age groups: 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-80. The final list of potentially eligible controls will be created by randomly selecting women with the same age distribution as of the breast cancer survivors of that same practice.

This list of potentially eligible controls will be sent to the GPs, and s/he will confirm that the women did not have a cancer and apply exclusion criteria a) and b).

Women not excluded will be considered eligible controls and invited to participate in the study.

4 Data to be collected

4.1 Health-related quality of life

Information on HRQoL will be collected using the Quality of Life in Adult Cancer Survivors Scale (QLACS) [36]. The QLACS was developed to take into account the specific needs of long-term cancer survivors, including issues that continue after treatment, new issues that arise during the period post-cancer, late physical effects of the cancer treatments and positive aspects of surviving to cancer [36]. It includes 47 items, divided in 7 generic and 5 cancer-specific domains (Appendix 2).

Breast cancer survivors will be asked to reply to all 47 items of the QLCAS (Appendix 3). Women who never had cancer will reply to the 28 items of the generic domains (Appendix 4).

4.2 Anxiety and depression

Data on anxiety and depressive symptoms will be collected with the Hospital Anxiety and Depression Scale (HADS, 5) [37]. This is a 14-item self-reported screening tool for anxiety and depressive symptoms in the past week. It contains two sub-scales, one for anxiety (HADS-A) and another for depression (HADS-D), with 7 items each [37]. This scale has been validated for use in primary care [38] and was used in primary care studies in the UK [39-41].

4.3 Clinical and socio-demographic data

Breast cancer survivors will be asked to provide information about the type of treatments received, the stage of their disease at diagnosis, the time since the last treatment (excluding long-term hormonal therapy), their menopausal status before and after the treatment, and how the cancer responded to the treatment (Appendix 6).

For all women, we will also collect data on potential confounders of the association between cancer history and mental health outcomes: education, ethnicity and social support (Appendix 7). Information on other potential confounders, such as co-morbidities or age at diagnosis will be obtained from the EHR.

5 Data/statistical analysis

Proportion of participation and exclusions

The proportion of GPs who accept to participate in the study will be calculated for the whole of the UK, by country within the UK, and by region.

The proportion of patients considered by the GP as ineligible will be reported separately for breast cancer survivors and women who did not have cancer.

The proportion of breast cancer survivors who accept to participate in the study will be calculated, as well as the proportion of women who did not have cancer. The denominator will include all women in each group to whom questionnaires were sent, even though we expect a minor proportion of envelopes returned because the patient may have moved or died, or the address may not be correct.

Objective 1: To describe cancer-specific measures of HRQoL in breast cancer survivors, and to explore the impact of demographic and clinical factors.

The QLACS includes 19 items for 5 cancer-specific domains of HRQoL (Appendix 2). Answers are provided on an ordinal Likert-type of scale, with values for individual items ranging from 1 to 7 [36]. For each breast cancer survivor, we will group the items by domain and calculate the sum of the individual scores under each domain [36]. All but one domain include 4 items; the “family distress” domain includes 3 items, and the sum of the individual scores will be rescaled to make the metric comparable with other domains. Values for each domain will range between 4 and 28. The range (minimum and maximum) scores will be reported for each domain, as well as the proportion of patients who score at the minimum and maximum values (floor and ceiling effects, respectively).

A mean or median score (depending on distribution) for each domain will be calculated from the individual-level sums of scores of the breast cancer survivors. Standard deviation will be calculated to quantify the dispersion of the data. The correlation coefficient among the mean scores of the domains will be reported.

A summary score for the cancer specific domains will be calculated by adding the mean/median scores of four domains ('financial problems', 'distress-family', 'appearance', and 'distress-recurrence'); the mean/median score for 'benefits from cancer' is not included.

We will use linear regression models to estimate the association between the cancer-specific HRQoL domain scores and patients factors, such as stage at diagnosis or type of surgery. The dependent variable will be the sum of the individual items reported by each patient for that particular domain. The linear regression coefficients (β) from the regression models and the corresponding 95% confidence intervals will be reported.

Objective 2: To compare generic measures of HRQoL between breast cancer survivors and women who did not have cancer, and to evaluate the impact of demographic and clinical variables.

The QLACS includes 28 items for 7 generic domains of HRQoL, with values for individual items ranging from 1 to 7 [36] (Appendix 4).

The items will be grouped by domain (Appendix 2), and we will calculate, for each woman, the sum of the individual scores under each domain [36]. For each group of participants (i.e. breast cancer survivors and women who did not have cancer), the range (minimum and maximum) of the scores will be reported for each domain, as well as the proportion of women who score at the minimum and maximum values of the domain.

A mean or median score, depending on the distribution of the data, will be obtained for each group of women, by calculating the mean/median of the sum of the scores for each woman in that group. The respective standard deviation will be reported.

A summary score for the generic domains will be calculated as the sum of the individual domain scores.

The student's two-sample t-test, or a non-parametric alternative if needed (i.e. Mann-Whitney distribution free test), will be used to assess the evidence for a difference in the summary scores for each domain between the two groups.

Linear regression will be used to evaluate the impact of cancer diagnosis on the mean scores of HRQoL, adjusting for potential confounders. The role of socio-economic and clinical variables will be explored. The model fit and the linear regression coefficients (β) will be reported as well as the 95% confidence intervals.

Objective 3: To compare the severity of depressive and anxiety symptoms in breast cancer survivors and in women who did not have cancer, and to assess the impact of clinical and demographic variables.

The Hospital Anxiety and Depression Scale contains two sub-scales, one for anxiety (HADS-A) and another for depression (HADS-D), with 7 items each [37]. Each item is rated from 0 to 3 and the total score for each sub-scale ranges between 0 and 21; higher scores represent higher symptoms of depression or anxiety [37].

To evaluate the severity of the depressive and anxiety symptoms in each group, the mean or median score, as appropriate, will be calculated for each sub-scale. The student's t-test or the Mann-Whitney test will be used to compare the mean/median score of depressive and of anxiety symptoms between cancer survivors and women who did not have cancer.

To identify patients with clinically relevant symptoms of depression or anxiety, the authors of the scale propose the cut-off of 0-7 for non-cases, 8-10 for borderline cases and 11-21 for probable cases, in both subscales.

The proportion of patients falling into the three categories (non-case, borderline, probable case) will be estimated for breast cancer survivors and for controls.

A chi-squared test will be used to assess whether there is evidence of differences in the proportion of patients in these categories between the two groups. A test for trend will be used to evaluate if there are increasing changes over the categories in each group.

The participants will then be categorised as having or not having clinically relevant levels of depressive or anxiety symptoms (cut off >10). Logistic regression models will be used to estimate the association between breast cancer history and clinically relevant levels of anxiety, and breast cancer history and clinically relevant symptoms of depression. The impact of clinical and demographic variables will be explored in the regression models. Crude and adjusted odds ratios, and respective 95% confidence intervals, will be reported.

Alexander et al. [42] evaluated the performance of the HADS as a screening test for major depressive disorder and anxiety in breast cancer survivors who were between 3 months and 2 years after main treatment conclusion (gold standard: non-patient Structured Clinical Interview for the Diagnostic and Statistical Manual of mental disorders (SCID)). Using the proposed cut-off of >10, the HADS-D had a sensitivity of 50% (95% confidence interval (95%CI): 27 to 73) and a specificity of 97% (95%CI: 93 to 99) [42]. However, the HADS-A had a sensitivity of 71% (95%CI: 30 to 95) and specificity of 87% (95%CI: 81 to 91) [42]. Even though the optimal cut-off for this population has not been established, a sensitivity of 50% may be too low to be acceptable in clinical practice, and therefore we will conduct a

sensitivity analysis considering the cut-off of ≥8 to classify women as having clinically relevant symptoms of anxiety or depression.

Objective 4: To compare the information reported by the patients for HRQoL, and for depressive and anxiety symptoms, with the information registered in the EHR for similar constructs

HRQoL

The QLACS includes seven generic domains of HRQoL (Appendix 4). Of these, five are particularly suitable for comparison with the data recorded in the EHR because women with distressing levels for these domains may have visited their GP to seek help: 'negative feelings', 'cognitive problems', 'physical pain', 'sexual problems' and 'fatigue'. Read codes for the 'social avoidance' domain are also available, and therefore we included also this domain.

For each woman, we will calculate the mean score for each domain (mean values will range between 1 and 7). Then, we will consider as reporting important levels of distress all women with a mean score of ≥5 (corresponding to replies of frequently, very often or always to most questions) in the domains of negative feelings, cognitive problems, physical pain, sexual problems and fatigue. Two sensitivity analyses will be conducted: 1) using a lower cut-off of ≥3 (corresponding to replies of sometimes and as often as not, in addition to replies of frequently, very often or always to most questions); 2) considering as exposed to important levels of distress all women who replied ≥5 to at least one item in the domain.

To identify evidence of the corresponding outcomes in the EHR, we will produce a list of Read codes closely related to the QLACS items for each domain (table 1). This list of Read codes will be used to identify women (who have had and who did not have breast cancer) with these outcomes registered in their EHR in the previous year (or since the first anniversary of diagnosis, if a cancer was diagnosed at less than 2 years).

Table 1 Domains and respective items of the QLACS scale, and conditions related to each domain.

Domain	Items in the QLACS	Read codes* related to:
Negative feelings	19 Bothered by mood swings; 7 Felt blue or depressed; 9 Worried about little things; 24 Felt anxious	Depression, anxiety
Cognitive problems	3 Bothered by having a short attention span 4 Had trouble remembering things	Mild cognitive impairment Cognitive dysfunction

Domain	Items in the QLACS	Read codes* related to:
	2 Difficulty doing things requiring concentration	
	23 Bothered by forgetting what started to do	
Physical pain	13 Bothered by pain preventing activities	Pain reported as a symptom
	17 Mood disrupted by pain or its treatment	
	27 Pain interfered w/social activities	Prescriptions of analgesics
	21 Had aches or pains	
Sexual problems	Sexual interest:	Sexual dysfunction
	16 Lacked interest in sex	Hypoactive sexual disorder
	26 Avoided sexual activity	Prescription of topical oestrogens
	Sexual function	
	12 Dissatisfied w/sex life	
	10 Bothered by inability to function sexually	
Fatigue	11 Lacked energy to do things wanted to	Fatigue
	14 Felt tired a lot	Low energy
	1 Had energy to do things wanted to do	
	5 Felt fatigued	
Social avoidance	18 Avoided social gatherings	Social isolation
	20 Avoided friends	Social difficulties
	25 Reluctant to meet new people	Non aggressive unsocial conduct disorder
	15 Reluctant to start new relationships	

* This will also be based on the systematic review of the Read codes used to identify mental health outcomes in primary care databases.

We will estimate the proportion of women who reported distressing levels for these domains, and the proportion of women who have a recording of a similar construct in the EHR, separately for breast cancer survivors and for women who did not have cancer.

To estimate how much inquiring the patient adds to the information registered in the EHR, we will calculate the probability of:

1) having information for a particular domain registered in the EHR, among women who reported distressing levels for that domain (sensitivity);
2) not having any information registered in the EHR for a particular domain among women who did not report distressing levels for that domain (specificity);
3) reporting distressing levels for a particular domain among women who had information for that domain registered in the EHR (positive predictive value);
4) not reporting distressing levels for a particular domain among women who did not have data for that domain registered in the EHR (negative predictive value).

All probabilities will be calculated separately for breast cancer survivors and for women who did not have cancer.

Anxiety and depression

The scores of the HADS-A and HADS-D will be used to classify women as having clinically relevant levels of anxiety and of depressive symptoms, respectively, using >10 as cut-off. The proportion of women scoring above this threshold will be calculated.

Women with a diagnosis of an anxiety and/or depressive disorder will be identified in the EHR through a list of Read codes. This list will be based on a systematic review of the literature to identify mental disorders in primary care databases. Women with a Read code for a depressive or anxiety disorder diagnosed in the last year will be considered depressed or anxious. A sensitivity analysis will include Read codes for symptoms of depression and/or anxiety, to account for the difficulties in the diagnosis of these conditions.

We will calculate, for each group of women and for each disorder, the probability of:

1) having a diagnosis of anxiety/depression registered in the EHR among women who scored above the threshold in the HADS scale (sensitivity);
2) not having a diagnosis of anxiety/depression registered in the EHR among women who did not score above the threshold in the HADS scale (specificity);
3) scoring above the threshold in the HADS scale among women who had a diagnosis of anxiety/depression recorded in the EHR (positive predictive value);
4) not scoring above the threshold in the HADS scale among women who did not have a diagnosis of anxiety/depression recorded in the EHR (negative predictive value).

6 Plan for addressing missing data

We estimate that 5% of the women will have missing data for at least one item of the QLACS. This is a conservative estimate based on literature (the highest proportion of missing items was 3.2% [43]). The HADS has been shown to have excellent acceptability [37] and the proportion of missing items is usually small.

We will explore the pattern of missingness of the items by demographic and clinical variables. For that purpose, a variable will be created to denote records with incomplete information and we will explore the association between this variable and clinical and demographic variables. If the missingness can be explained by the other variables in the dataset, we will consider that it is missing at random, and specify a multiple imputation model to better represent the distribution from which the missing data came.

7 Sample size

We estimate that a sample of 260 breast cancer survivors and 260 women who did not have cancer are required to detect differences of the size reported in the literature. As participation rate in this type of studies has been low (approximately 20%), we believe that 1,400 women in each group need to be invited.

HRQoL

Table 2 provides details of the sample size calculation for the comparison of the summary scores of HRQoL, and of the mean scores of the generic domains of HRQoL, between breast cancer survivors and women who did not have cancer.

Table 2 Estimated sample size to compare the mean values of HRQoL in breast cancer survivors and women who did not have cancer.

	HRQoL mean score breast cancer survivors (SD)	HRQoL mean score normative data (SD)	Sample size per group †	Adjusted* sample size per group
Summary score	68.5 (22.7) [1]	60.9 (21.5)	133	800
Summary score	70.5 (26.6) [2]	60.9 (21.5)	100	600
Summary score	75.5 (26.3) [2]	60.9 (21.5)	43	350
Generic domains				
Negative feelings	9.7 (3.8)	7.1 (3.5)	31	300
Positive feelings	22.1 (4.7)	20.3 (6.3)	85	550
Cognitive problems	9.8 (5.0)	8.3 (2.7)	113	700
Sexual problems	11.8 (6.8)	9.0 (3.4)	58	400
Physical pain	9.7 (6.1)	7.8 (4.8)	131	800
Fatigue	11.8 (5.4)	10.3 (4.6)	**176**	**1,000**
Social avoidance	8.2 (4.3)	6.9 (2.8)	123	750

† Assuming an alpha of 0.05 and power of 80%.
* Calculated as the estimated sample size rounded upwards to the next 10 subjects (to take into account the uncertainty of the estimation process) divided by 0.2 (the estimated proportion of participation), and added a 100 patients to account for other variables to be studied.
[1] Women diagnosed with breast cancer at 18-24 months [44].
[2] Women diagnosed with breast cancer at 5 years of more [36, 43].

The summary mean scores for the generic domains of the QLACS among breast cancer survivors were obtained from the literature [36, 43, 44]. The mean/median scores of the generic domains among women who did not have cancer have not been reported. However, in a study involving long-term survivors of breast, bladder, head and neck, gynaecologic, prostate and colorectal cancer [36], patients with colorectal cancer ranked the lowest summary score (indicating better HRQoL) for the generic domains of HRQoL (mean 60.9,

SD=21.5). We used this score as a conservative estimate of the summary score of HRQoL in the general population, assuming that women who never have had cancer will not have worse HRQoL than the cancer patients who experience the best HRQoL. The same assumption was applied to estimate the sample size for the specific domains of HRQoL.

Anxiety and depression

Table 3 provides sample size estimates for the comparison of the mean scores of the two subscales of the HADS. As shown in the table, one study found a difference in mean HADS-Depression scores of just 0.6; to detect such a small difference would require 447 women per group, which would be beyond available resources. However, another study has calculated that differences of less than 1.4 in mean HADS-depression scores are not clinically important [45], and only around 75 patients per group would be required to detect differences above this level. For anxiety we would require 253 women per group to detect the minimum previously observed differences on the HADS scale.

Table 3 Estimated sample size to compare the mean scores of anxiety and depression between breast cancer survivors and women from the general population.

	Mean score breast cancer survivors (SD)	Mean score normative data (SD)	Sample size per group †	Adjusted* sample size per group
HADS-Anxiety	6.3 (2.8) [46]	4.8 (3.7) [46]	76	500
HADS-Anxiety	7.8 (3.0) [47]	7.1 (2.6) [47]	**253**	**1,400**
HADS-Depression	3.1 (3.3) [46]	3.7 (3.1) [46]	(447)	(2,350)
HADS-Depression	4.6 (3.3) [47]	3.2 (2.7) [47]	73	500

* Calculated as the estimated sample size rounded upwards to the next 10 subjects (to take into account the uncertainty of the estimation process) divided by 0.2 (the estimated proportion of participation), and added a 100 patients to account for other variables to be studied.

Table 4 provides estimates of the number of women necessary to compare the prevalences of anxiety and depression, as determined by the cut-offs of the HADS [48].

Table 4 Estimated sample size to compare the prevalences of anxiety and depression between breast cancer survivors and women from the general population.

Outcome	α	β	% of outcome in unexposed group [ref]	Estimated risk ratio [ref]	Sample size per group †	Adjusted* sample size per group
Anxiety	0.05	0.20	36.5 [48]	1.44 [48]	150	850
Depression	0.05	0.20	12.9 [48]	1.21 [48]	**2,614**	**13,170**

* Calculated as the estimate sample size rounded upwards to the next 10 subjects (to take into account the uncertainty of the estimation process) divided by 0.2 (the estimated proportion of participation), and added a 100 patients to account for other variables to be studied.

According to the calculations, over 13,000 breast cancer survivors and 13,000 women who did not have cancer would be needed to compare the prevalence of depression between the

two groups of women. Recruiting more than 1,500 women for this study is not feasible, and therefore we chose the sample size necessary to compare the mean scores of anxiety and depression between the two groups (n=1,400 in each group, as outlined above and in Table 3).

8 Feasibility counts

A total of 43,704 women with breast cancer, and who were at least one year post-diagnosis, were identified in the July 2015 cut of the CPRD primary care database. Of these, 21,564 women had acceptable records from practices contributing with 'up to standard' data. A total of 8,763 women were still registered in practices that contributed with data to CPRD during the year of 2016, of which 7,498 (86%) were aged between 18 and 80 years old. Table 5 describes the distribution of the patients by region within England.

Table 5 Number of women and general practices with active records (as per June 2016) in the CPRD primary care database, by region.

Region code	Region label	No. of practices	No. of patients
1	North East	3	91
2	North West	28	1,139
3	Yorkshire & The Humber	3	160
4	East Midlands	0	0
5	West Midlands	18	763
6	East of England	10	557
7	South West	17	658
8	South Central	27	1,304
9	London	35	1,007
10	South East Coast	47	1,819
	Total	188	7,437

The estimated sample size (1,400) corresponds to 19% of the women potentially eligible for the study.

9 Pilot study

We will invite all GPs working in practices contributing with ‘up to standard’ data to CPRD at the time of recruitment to participate in the study.

Packages containing paper questionnaires will be sent to 140 breast cancer survivors and 140 women who did not have cancer (10% of those to be invited), randomly selected from the list of patients attending the first practices to sign up for the study. The pilot phase will run for 1 month. After that time, we will estimate:

1) the proportion of participation in each group;
2) the age distribution of the participants in each group;
3) the number of questionnaires with missing items.

Sample size calculations will be revised, if necessary. Afterwards, paper questionnaires will be sent out to the remainder of women to be invited, up to the estimated sample size.

10 Limitations of the study design, data sources and analytical methods

We will use the CPRD primary care database to classify women as exposed or not to breast cancer. CPRD has been shown to capture more than 90% of the cancer diagnoses registered in the cancer registries [49]. This is considered acceptable for this project, even though a small proportion of the women may be incorrectly classified as unexposed. We will request that the GP revises the list of patients to exclude potentially misclassified cases.

We expect a substantial proportion of patients to decline to participate in the study, as shown by the proportion of participation in previous studies. Selection bias may occur if the patients who accept to participate in the study differ systematically from those who do not. We will compare the demographic characteristics of the women who participate in the study with the broad characteristics of the women who had breast cancer in the CPRD primary care database. Also, we assumed a similar participation rate by age-group between women with breast with and without cancer. We will compare the age-distribution of the final samples and take age into account in multivariate analyses if necessary.

Women who are unable to complete a self-administered questionnaire due to advanced disease (e.g. terminally ill, patients with dementia or severe mental illnesses) will be excluded from the study. Therefore, the generalizability of our results will be limited women with a relatively good cognitive function.

The QLACS was validated in the United States but not in the UK population of cancer survivors. However, no translation is required and the entire scale will be applied, which makes unlikely the occurrence of substantial bias.

This study will have limited power to detect a strong association between having had a breast cancer and depression as defined by the cut-offs of the HADS scale. Our primary outcome will be the difference of the mean scores of each sub-scale, for which this study will have enough power.

11 Patient or user group involvement

Two women who never had cancer revised the invitation letter, participant information sheets and questionnaires for women in the non-cancer comparison group.

Breast cancer survivors identified through the Independent Cancer Patients' Voice (a patient advocate group and charity) revised the materials for breast cancer survivors. Comments from each group were incorporated into the study materials.

We will also ask selected members of the public and breast cancer survivors to comment on the report produced to share the study results prior to making these available.

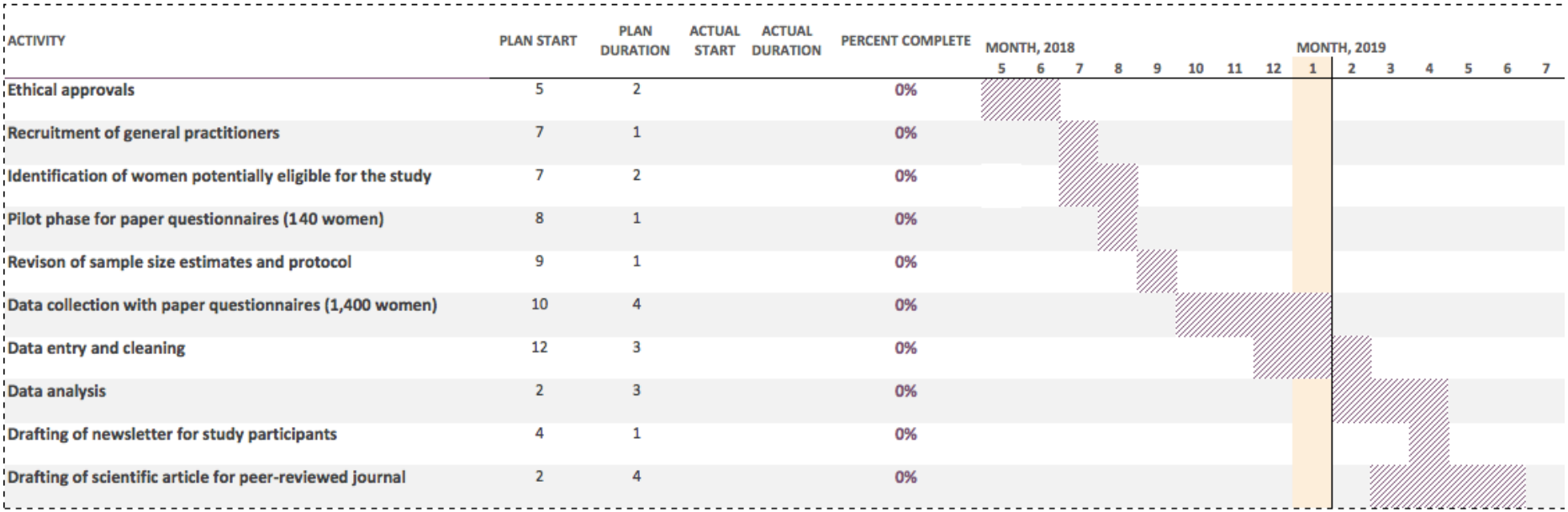
12 Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

We plan to disseminate the results with the publication of an article in a peer-reviewed scientific journal. We will also present preliminary finding at scientific meetings.

To share the results with the general public, we will make the study results publicly available online. We will create a study's webpage on the website of the London School of Hygiene & Tropical Medicine. The website address for this webpage will be included in the participant information packs. A summary of findings from the study will be posted on the study webpage in due course. Anyone visiting this webpage (whether a participant, invitee, general practitioner or any interested member of the public) will be able to provide a contact email address through the webpage to subscribe for updates. The study researchers will use these contact email addresses for the sole purpose of letting interested parties know about updates to the study webpage.

13 Timetable

ACTIVITY	PLAN START	PLAN DURATION	ACTUAL START	ACTUAL DURATION	PERCENT COMPLETE
Ethical approvals	5	2			0%
Recruitment of general practitioners	7	1			0%
Identification of women potentially eligible for the study	7	2			0%
Pilot phase for paper questionnaires (140 women)	8	1			0%
Revison of sample size estimates and protocol	9	1			0%
Data collection with paper questionnaires (1,400 women)	10	4			0%
Data entry and cleaning	12	3			0%
Data analysis	2	3			0%
Drafting of newsletter for study participants	4	1			0%
Drafting of scientific article for peer-reviewed journal	2	4			0%



Plan Duration

End of data collection

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15 Appendices

Appendix 1. List of read codes to identify breast cancer patients [50].

Read Code	Description
B34..11	CA FEMALE BREAST
B36..00	LOCAL RECURRENCE OF MALIGNANT TUMOUR OF BREAST
B340100	MALIGNANT NEOPLASM OF AREOLA OF FEMALE BREAST
B346.00	MALIGNANT NEOPLASM OF AXILLARY TAIL OF FEMALE BREAST
B341.00	MALIGNANT NEOPLASM OF CENTRAL PART OF FEMALE BREAST
B34y000	MALIGNANT NEOPLASM OF ECTOPIC SITE OF FEMALE BREAST
B34..00	MALIGNANT NEOPLASM OF FEMALE BREAST
B34z.00	MALIGNANT NEOPLASM OF FEMALE BREAST NOS
B343.00	MALIGNANT NEOPLASM OF LOWER-INNER QUADRANT OF FEMALE BREAST
B345.00	MALIGNANT NEOPLASM OF LOWER-OUTER QUADRANT OF FEMALE BREAST
B340.00	MALIGNANT NEOPLASM OF NIPPLE AND AREOLA OF FEMALE BREAST
B340000	MALIGNANT NEOPLASM OF NIPPLE OF FEMALE BREAST
B340z00	MALIGNANT NEOPLASM OF NIPPLE OR AREOLA OF FEMALE BREAST NOS
B34y.00	MALIGNANT NEOPLASM OF OTHER SITE OF FEMALE BREAST
B34yz00	MALIGNANT NEOPLASM OF OTHER SITE OF FEMALE BREAST NOS
B342.00	MALIGNANT NEOPLASM OF UPPER-INNER QUADRANT OF FEMALE BREAST
B344.00	MALIGNANT NEOPLASM OF UPPER-OUTER QUADRANT OF FEMALE BREAST
B347.00	MALIGNANT NEOPLASM, OVERLAPPING LESION OF BREAST
BB93.00	[M]COMEDOCARCINOMA NOS
BBM9.00	[M]CYSTOSARCOMA PHYLLODES, MALIGNANT
BB91100	[M]INFILTRATING DUCT AND LOBULAR CARCINOMA
BB91.00	[M]INFILTRATING DUCT CARCINOMA
BB9G.00	[M]INFILTRATING DUCTULAR CARCINOMA
BB9H.00	[M]INFLAMMATORY CARCINOMA
BB91000	[M]INTRADUCTAL PAPILLARY ADENOCARCINOMA WITH INVASION
BB94.00	[M]JUVENILE BREAST CARCINOMA
BB9F.00	[M]LOBULAR CARCINOMA NOS
BB9D.00	[M]MEDULLARY CARCINOMA WITH LYMPHOID STROMA
BB9K.00	[M]PAGET'S DISEASE AND INFILTRATING BREAST DUCT CARCINOMA
BB9K000	[M]PAGET'S DISEASE AND INTRADUCTAL CARCINOMA OF BREAST
BB9J.11	[M]PAGET'S DISEASE, BREAST
BB9J.00	[M]PAGET'S DISEASE, MAMMARY
BB94.11	[M]SECRETORY BREAST CARCINOMA
Byu6.00	[X]MALIGNANT NEOPLASM OF BREAST

Appendix 2. Items of the Quality of Life in Adult Cancer Survivors Scale (QLACS) grouped by domain

Domain	Item of the Quality of Life in Adult Cancer Survivors scale [36]
Generic	
Negative feelings	
	19 Bothered by mood swings
	7 Felt blue or depressed
	9 Worried about little things
	24 Felt anxious
Positive feelings	
	8 Enjoyed life
	28 Content with life
	6 Felt happy
	22 Had a positive outlook on life
Cognitive problems	
	3 Bothered by having a short attention span
	4 Had trouble remembering things
	2 Difficulty doing things requiring concentration
	23 Bothered by forgetting what started to do
Pain	
	13 Bothered by pain preventing activities
	17 Mood disrupted by pain or its treatment
	27 Pain interfered w/social activities
	21 Had aches or pains
Sexual interest	
	16 Lacked interest in sex
	26 Avoided sexual activity
Energy/fatigue	
	11 Lacked energy to do things wanted to
	14 Felt tired a lot
	1 Had energy to do things wanted to do
	5 Felt fatigued
Sexual function	
	12 Dissatisfied w/sex life
	10 Bothered by inability to function sexually
Social avoidance	
	18 Avoided social gatherings
	20 Avoided friends
	25 Reluctant to meet new people
	15 Reluctant to start new relationships

Domain	Item of the Quality of Life in Adult Cancer Survivors scale [36]
Cancer-specific	
Financial problems	
	43 Had money problems from cancer
	45 Financial problems from loss of income due to cancer
	30 Financial problems from cost of cancer surgery or tx
	37 Problems with insurance because of cancer
Benefits	
	40 Cancer helped recognize what important in life
	41 Better able to deal w/stress because of cancer
	32 Cancer helped cope better w/problems
	29 Appreciated life more because of cancer
Distress-family	
	34 Worried whether family had cancer causing genes
	31 Worried family members were at risk for cancer
	42 Worried family should have genetic tests - cancer
Appearance	
	35 Felt unattractive b/c of cancer or its treatment
	33 Self-conscious about appearance because of cancer
	44 Felt treated differently b/c of changes in appearance
	38 Bothered by hair loss from cancer treatments
Distress-recurrence	
	39 Worried about cancer coming back
	46 When felt pain, worried it was cancer again
	36 Worried about dying from cancer
	47 Preoccupied with concerns about cancer

Appendix 3. Quality of Life in Adult Cancer Survivors Scale (QLACS) [36]

We would like to ask you about some things that can affect the quality of people's lives. Some of these questions may sound similar, but please be sure to answer each one. Below is a scale ranging from never to always. Please indicate how often each of these statements has been true for you in the past four weeks. [Select one answer for each question]

		Never	Seldom	Sometimes	About as often as not	Frequently	Very often	Always
In the past 4 weeks…								
1	You had the energy to do the things you wanted to do.	1	2	3	4	5	6	7
2	You had difficulty doing activities that require concentrating.	1	2	3	4	5	6	7
3	You were bothered by having a short attention span.	1	2	3	4	5	6	7
4	You had trouble remembering things.	1	2	3	4	5	6	7
5	You felt fatigued.	1	2	3	4	5	6	7
6	You felt happy.	1	2	3	4	5	6	7
7	You felt blue or depressed.	1	2	3	4	5	6	7
8	You enjoyed life.	1	2	3	4	5	6	7
9	You worried about little things.	1	2	3	4	5	6	7
10	You were bothered by being unable to function sexually.	1	2	3	4	5	6	7
11	You didn't have energy to do the things you wanted to do.	1	2	3	4	5	6	7
12	You were dissatisfied with your sex life.	1	2	3	4	5	6	7
13	You were bothered by pain that kept you from doing the things you wanted to do.	1	2	3	4	5	6	7
14	You felt tired a lot.	1	2	3	4	5	6	7
15	You were reluctant to start new relationships.	1	2	3	4	5	6	7
16	You lacked interest in sex.	1	2	3	4	5	6	7
17	Your mood was disrupted by pain or its treatment.	1	2	3	4	5	6	7
18	You avoided social gatherings.	1	2	3	4	5	6	7
19	You were bothered by mood swings.	1	2	3	4	5	6	7
20	You avoided your friends.	1	2	3	4	5	6	7
21	You had aches or pains.	1	2	3	4	5	6	7
22	You had a positive outlook on life.	1	2	3	4	5	6	7
23	You were bothered by forgetting what you started to do.	1	2	3	4	5	6	7
24	You felt anxious.	1	2	3	4	5	6	7
25	You were reluctant to meet new people.	1	2	3	4	5	6	7
26	You avoided sexual activity.	1	2	3	4	5	6	7
27	Pain or its treatment interfered with your social activities.	1	2	3	4	5	6	7
28	You were content with your life.	1	2	3	4	5	6	7

		Never	Seldom	Sometimes	About as often as not	Frequently	Very often	Always
The next set of questions asks specifically about the effects of your cancer or its treatment. Again, for each statement, indicate how often each of these statements has been true for you in the past four weeks.								
29	You appreciated life more because of having had cancer.	1	2	3	4	5	6	7
30	You had financial problems because of the cost of cancer surgery or treatment.	1	2	3	4	5	6	7
31	You worried that your family members were at risk of getting cancer.	1	2	3	4	5	6	7
32	You realized that having had cancer helps you cope better with problems now.	1	2	3	4	5	6	7
33	You were self-conscious about the way you look because of your cancer or its treatment.	1	2	3	4	5	6	7
34	You worried about whether your family members might have cancer-causing genes.	1	2	3	4	5	6	7
35	You felt unattractive because of your cancer or its treatment.	1	2	3	4	5	6	7
36	You worried about dying from cancer.	1	2	3	4	5	6	7
37	You had problems with insurance because of cancer.	1	2	3	4	5	6	7
38	You were bothered by hair loss from cancer treatment.	1	2	3	4	5	6	7
39	You worried about cancer coming back.	1	2	3	4	5	6	7
40	You felt that cancer helped you to recognize what is important in life.	1	2	3	4	5	6	7
41	You felt better able to deal with stress because of having had cancer.	1	2	3	4	5	6	7
42	You worried about whether your family members should have genetic tests for cancer.	1	2	3	4	5	6	7
43	You had money problems that arose because you had cancer.	1	2	3	4	5	6	7
44	You felt people treated you differently because of changes to your appearance due to your cancer or its treatment.	1	2	3	4	5	6	7
45	You had financial problems due to a loss of income as a result of cancer.	1	2	3	4	5	6	7
46	Whenever you felt a pain, you worried that it might be cancer again.	1	2	3	4	5	6	7
47	You were preoccupied with concerns about cancer.	1	2	3	4	5	6	7

Appendix 4. Generic domains of HRQoL [36]

We would like to ask you about some things that can affect the quality of people's lives. Some of these questions may sound similar, but please be sure to answer each one. Below is a scale ranging from never to always. Please indicate how often each of these statements has been true for you in the past four weeks. [Select one answer for each question]

		Never	Seldom	Sometimes	About as often as not	Frequently	Very often	Always
In the past 4 weeks…								
1	You had the energy to do the things you wanted to do.	1	2	3	4	5	6	7
2	You had difficulty doing activities that require concentrating.	1	2	3	4	5	6	7
3	You were bothered by having a short attention span.	1	2	3	4	5	6	7
4	You had trouble remembering things.	1	2	3	4	5	6	7
5	You felt fatigued.	1	2	3	4	5	6	7
6	You felt happy.	1	2	3	4	5	6	7
7	You felt blue or depressed.	1	2	3	4	5	6	7
8	You enjoyed life.	1	2	3	4	5	6	7
9	You worried about little things.	1	2	3	4	5	6	7
10	You were bothered by being unable to function sexually.	1	2	3	4	5	6	7
11	You didn't have energy to do the things you wanted to do.	1	2	3	4	5	6	7
12	You were dissatisfied with your sex life.	1	2	3	4	5	6	7
13	You were bothered by pain that kept you from doing the things you wanted to do.	1	2	3	4	5	6	7
14	You felt tired a lot.	1	2	3	4	5	6	7
15	You were reluctant to start new relationships.	1	2	3	4	5	6	7
16	You lacked interest in sex.	1	2	3	4	5	6	7
17	Your mood was disrupted by pain or its treatment.	1	2	3	4	5	6	7
18	You avoided social gatherings.	1	2	3	4	5	6	7
19	You were bothered by mood swings.	1	2	3	4	5	6	7
20	You avoided your friends.	1	2	3	4	5	6	7
21	You had aches or pains.	1	2	3	4	5	6	7
22	You had a positive outlook on life.	1	2	3	4	5	6	7
23	You were bothered by forgetting what you started to do.	1	2	3	4	5	6	7
24	You felt anxious.	1	2	3	4	5	6	7
25	You were reluctant to meet new people.	1	2	3	4	5	6	7
26	You avoided sexual activity.	1	2	3	4	5	6	7
27	Pain or its treatment interfered with your social activities.	1	2	3	4	5	6	7
28	You were content with your life.	1	2	3	4	5	6	7

Appendix 5. Hospital Anxiety and Depression Scale [37]

Hospital Anxiety and Depression Scale (HADS)

This questionnaire is designed to help clinicians to know how you feel. Read each item below and underline the reply which comes closest to how you have been feeling in the past week.
Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

I feel tense or 'wound up'
- Most of the time
- A lot of the time
- From time to time, occasionally
- Not at all

I still enjoy the things I used to enjoy
- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

I get a sort of frightened feeling as if something awful is about to happen
- Very definitely and quite badly
- Yes, but not too badly
- A little, but it doesn't worry me
- Not at all

I can laugh and see the funny side of things
- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

Worrying thoughts go through my mind
- A great deal of the time
- A lot of the time
- Not too often
- Very little

I feel cheerful
- Never
- Not often
- Sometimes
- Most of the time

I can sit at ease and feel relaxed
- Definitely
- Usually
- Not often
- Not at all

I feel as if I am slowed down
- Nearly all the time
- Very often
- Sometimes
- Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach
- Not at all
- Occasionally
- Quite often
- Very often

I have lost interest in my appearance
- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

I feel restless as if I have to be on the move
- Very much indeed
- Quite a lot
- Not very much
- Not at all

I look forward with enjoyment to things
- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I get sudden feelings of panic
- Very often indeed
- Quite often
- Not very often
- Not at all

I can enjoy a good book or radio or television programme
- Often
- Sometimes
- Not often
- Very seldom

Now check that you have answered all the questions

Appendix 6. Clinical information

1. What treatments have you received for your breast cancer? (Tick all that apply)

- □ Surgery
- □ Radiotherapy
- □ Chemotherapy (excluding hormone treatment)
- □ Hormone treatment
- □ Monoclonal antibodies / immunotherapy
- □ Don't know / can't remember

1.1 If you have had breast surgery, do any of the following apply to you? (Tick all that apply)

- □ I have had a lumpectomy (partial removal of the breast)
- □ I have had a mastectomy (complete removal of the breast)
- □ I have had a bilateral mastectomy (complete removal of the two breasts)
- □ I have had a breast reconstruction
- □ I am awaiting or considering breast reconstruction
- □ None of these apply to me
- □ Don't know / can't remember

2. At the time of the diagnosis, your cancer was:

- □ Localised to the breast only (without involving lymph nodes)
- □ Spread to the lymph nodes in the axilla
- □ Spread beyond the breast and the lymph nodes (metastatic)
- □ Don't know / can't remember

2.1 Please select your stage at diagnosis:

- □ Stage I
- □ Stage II
- □ Stage III
- □ Stage IV
- □ Don't know / can't remember

3. How long is it since you completed your initial cancer treatment?
(Treatment includes any chemotherapy, radiotherapy or surgery for your breast cancer. When answering this question please do not include hormone treatments such as Tamoxifen.)

- □ I am still having my initial treatment
- □ It is less than 3 months since my initial treatment
- □ It is between 3 and 12 months since my initial treatment
- □ It is between 1 and 5 years since my initial treatment
- □ It is more than 5 years since my initial treatment
- □ Don't know / can't remember

4. Regarding your menopausal status before and after the breast cancer diagnosis:

- □ My menstrual periods had finished when my cancer was diagnosed
- □ My menstrual periods finished during my treatments for breast cancer
- □ I had periods before the cancer diagnosis and continued to have them during/after the treatments
- □ Don't know / can't remember

5. Is your cancer currently in remission? (Complete remission means that there is no sign of cancer in your body)

- □ Yes
- □ No
- □ Don't know

Appendix 7. Demographic information

1. Which of these qualifications do you have?

- □ Up to GCSEs, O levels, or equivalent
- □ A levels or equivalent
- □ Undergraduate degree (for example BA, BSc)
- □ Post-graduate degree
- □ Trade, technical or vocational training
- □ Do not wish to disclose

2. What is your ethnic group?

- □ White
- □ Mixed / Multiple ethnic groups
- □ Asian / Asian British
- □ Black / African / Caribbean / Black British
- □ Other ethnic group
- □ Do not wish to disclose

3. Which statement best describes your living arrangements?

- □ I live with partner / spouse
- □ I live with family / friends
- □ I live alone
- □ I live in a nursing home or other long term care home
- □ Other
- □ Do not wish to disclose

Health Research Authority

East of England - Cambridge South Research Ethics Committee
The Old Chapel
Royal Standard Place
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NG1 6FS

15 April 2019

Ms Helena I M Carreira
Keppel Street
EPH - NCDE
WC1E 7HT

Dear Ms Carreira,

Study title:	**Mental health and quality of life of female breast cancer survivors compared to women who did not have cancer, and feasibility of using electronic health records' data to study patient reported outcomes**
REC reference:	**17/EE/0403**
Amendment number:	
Amendment date:	**04 April 2019**
IRAS project ID:	**224561**

Thank you for submitting the above amendment, which was received on 04 April 2019. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 26 March 2019 refers).

The modified amendment has been considered on behalf of the Committee by the Chair.

Ethical opinion

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved are:

Document	*Version*	*Date*
Notice of Modified Amendment		04 April 2019
Participant information sheet (PIS)	5	29 March 2019

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

17/EE/0403:	**Please quote this number on all correspondence**

Yours sincerely,

Dr Leslie Gelling
Chair

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Observational / Interventions Research Ethics Committee

Ms Helena Carreira
LSHTM

10 August 2018

Dear Helena ,

Study Title: Mental health and quality of life of breast cancer survivors compared to women who did not have cancer, and feasibility of using electronic health records' data to study patient reported outcomes

LSHTM ethics ref: 14417

Thank you for your application for the above research, which has now been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	CV_HelenaCarreira	01/09/2017	1
Investigator CV	CV_KrishnanBhaskaran	01/09/2017	1
Investigator CV	CV_RachaelWilliams	01/09/2017	1
Protocol / Proposal	PRO_study_protocol_v1	18/09/2017	1
Protocol / Proposal	PRO_study_protocol_v3_tracked_changes	11/07/2018	3
Information Sheet	PIS_v3	11/07/2018	3
Advertisements	Invitation letter_BCS_v3	11/07/2018	3
Advertisements	Invitation_WWC_v3	11/07/2018	3
Local Approval	224561 17-0403 FIFO 24.11.2017	11/07/2018	1
Covering Letter	14417 REC_further clarifications_03082018	03/08/2018	2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Ms Helena I M Carreira
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Keppel street
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Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

13 September 2018

Dear Ms Carreira

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Mental health and quality of life of female breast cancer survivors compared to women who did not have cancer, and feasibility of using electronic health records' data to study patient reported outcomes**
IRAS project ID:	**224561**
REC reference:	**17/EE/0403**
Sponsor	**London School of Hygiene & Tropical Medicine**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Ms Patricia Henley
Tel: 44 (0) 20 7636 2268
Email: RGIO@lshtm.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **224561**. Please quote this on all correspondence.

Yours sincerely

Miss Lauren Allen
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Patricia Henley*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template [GP Site Agreement]		
Covering letter on headed paper [Cover letter]	1	11 September 2017
Covering letter on headed paper [Cover letter and further clarifications]	1	10 November 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor insurance details]	1	26 July 2017
IRAS Application Form [IRAS_Form_14092017]		14 September 2017
Letter from funder [Grant offer]	1	14 January 2015
Letter from sponsor [Sponsorship confirmation]	1	26 July 2017
Letter from statistician [Comments statistician]	1	25 August 2017
Letters of invitation to participant [Invitation to participate in research (GPs)]	2	10 November 2017
Letters of invitation to participant [Invitation letter_BCS - Clean]	3	13 July 2018
Letters of invitation to participant [Invitation letter_BCS - Tracked Changes]	3	13 July 2018
Letters of invitation to participant [Invitation_WWC - Clean]	3	13 July 2018
Letters of invitation to participant [Invitation_WWC - Tracked Changes]	3	13 July 2018
Non-validated questionnaire [Breast cancer clinical information]	1	11 September 2017
Non-validated questionnaire [Demographic information]	1	11 September 2017
Non-validated questionnaire [Contact details]	1	11 September 2017
Notice of Substantial Amendment (non-CTIMP)	Substantial Amendment 1	13 July 2018
Participant information sheet (PIS) [Clean]	3	13 July 2018
Participant information sheet (PIS) [Tracked Changes]	3	13 July 2018
Research protocol or project proposal [Clean]	3	01 May 2018
Research protocol or project proposal [Tracked Changes]	3	01 May 2018
Summary CV for Chief Investigator (CI) [Curriculum vitae]	1	07 September 2017
Summary CV for student [Curriculum vitae - Helena Carreira]	1	07 September 2017
Summary CV for supervisor (student research) [Curriculum vitae Rachael Williams]	1	07 September 2017
Summary CV for supervisor (student research) [Curriculum vitae Krishnan Bhaskaran]	1	07 September 2017
Validated questionnaire [Hospital Anxiety and Depression Scale]	1	11 September 2017
Validated questionnaire [Quality of Life in Adult Cancer Survivors Scale]	1	11 September 2017
Validated questionnaire [Quality of Life in Adult Cancer Survivors Scale - Generic Domains]	1	11 September 2017

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards?	Comments
1.1	IRAS application completed correctly	Yes	Participating GP surgeries have not yet been identified.
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The sponsor intends to use the GP practice agreement provided as the agreement with participating GP practices.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	A grant funding letter from the MRC has been provided. GPs will be reimbursed for checking the pre-screened list of patients codes and posting the survey to patients.
5.1	Compliance with the Data Protection Act and data	Yes	No comments

Section	HRA Assessment Criteria	Compliant with Standards?	Comments
	security issues assessed		
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
There is one site type. GP practices will be responsible for sending questionnaires to potential participants who have been identified using data held by the CPRD primary care database. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A key contact should be identified at the GP practices. The key contact will be responsible for sending study information to potential participants. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
All activity at the GP practices will be conducted by practice staff therefore access arrangements will not be applicable.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Supplementary table 1 Comparison between participants and non-participants, by group, age, country, and deprivation.

	No cancer group (No. 1,460)				Breast cancer survivors (No. 1,018)			
	Refused		Participated		Refused		Participated	
	No.	%	No.	%	No.	%	No.	%
Total	1,208	82.7	252	17.3	665	65.3	353	34.7
Age								
18-39	17	94.4	1	5.6	5	71.4	2	28.6
40-49	107	87.0	16	13.0	45	70.3	19	29.7
50-59	263	83.0	54	17.0	168	68.0	79	32.0
60-69	355	81.6	80	18.4	200	60.6	130	39.4
70-81	466	82.2	101	17.8	247	66.8	123	33.2
Country								
England	233	78.5	64	21.6	95	65.5	50	34.5
Northern Ireland	239	93.7	16	6.3	83	71.6	33	28.5
Scotland	356	82.8	74	17.2	241	67.9	114	32.1
Wales	380	79.5	98	20.5	246	61.2	156	38.8
Practice IMD								
1 (most deprived)	209	79.8	53	20.2	97	57.7	71	42.3
2	239	86.9	36	13.1	97	64.2	54	35.8
3	138	84.2	26	15.9	123	69.9	53	30.1
4	440	81.8	98	18.2	277	66.4	140	33.6
5 (least deprived)	182	82.4	39	17.7	71	67.0	35	33.0

IMD – Index of Multiple Deprivation.

Supplementary table 2 Correlation coefficients between the different domains of HRQoL (N=605).

	Generic domains of QLACS							Cancer-specific domains of QLACS				
	Negative feelings	Positive feelings	Cognitive problems	Pain	Sexual function	Energy/ fatigue	Avoidance	Financial problems	Benefits of cancer	Distress-family	Appearance	Distress-recurrence
Generic domains												
Negative feelings	1											
Positive feelings	-0.61	1										
Cognitive problems	0.62	-0.40	1									
Pain	0.49	-0.43	0.44	1								
Sexual interest	0.48	-0.41	0.44	0.40	1							
Energy/fatigue	0.68	-0.57	0.59	0.64	0.47	1						
Avoidance	0.70	-0.58	0.54	0.47	0.53	0.63	1					
Cancer-specific domains												
Financial problems	0.28	-0.26	0.37	0.36	0.26	0.29	0.31	1				
Benefits of cancer	-0.21	0.46	-0.13	-0.15	-0.17	-0.17	-0.19	0.03	1			
Distress-family	0.29	-0.19	0.32	0.25	0.13	0.28	0.25	0.36	0.11	1		
Appearance	0.49	-0.36	0.45	0.37	0.37	0.36	0.43	0.52	-0.04	0.41	1	
Distress-recurrence	0.53	-0.37	0.46	0.36	0.34	0.44	0.37	0.42	0.01	0.49	0.56	1

HRQoL = Health-Related Quality of Life; QLACS = Quality of Life in Adult Cancer Survivors scale.