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Quantifying Psychotropic Treatment and Illness Outcome in Cohort Studies using Record-Linkage to Administrative Health Data

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Dedicated to my father Michael T. Hafferty

Abstract

The advent of powerful information technology and the increasing availability of so-called 'Big Data', in a multitude of forms, has had revolutionary impact on many aspects of society, such as commerce and communication. Within healthcare broadly and mental health research specifically, however, the progress of these techniques is considered relatively nascent. This is paradoxical, as the complexity and multi-factorial nature of mental health conditions, such as major depression and self-harm, makes them particularly tractable for more sophisticated data-driven approaches.

In this thesis I will apply the transformative potential of data science applications related to *record-linkage* for mental health research. I will demonstrate that record-linkage of cohort studies to administrative health data enables:

(i) improved signal and power for discoveries and the reduction of false associations
(ii) validation of research data and the identification of inaccuracies
(iii) transformation of cross-sectional studies into longitudinal studies; and
(iv) identification of new phenotypes for study.

Chapters 1, 2 and 3 provide an introductory overview. In Chapter 1, I will survey the current state of psychiatric research in major depressive disorder (MDD), antidepressant pharmacoepidemiology, self-harm and suicidal ideation. These inter-related aspects of mental illness are common, highly complex and place a high burden on society. They are thus particularly appropriate for the research methods I shall employ herein. In Chapter 2 I will discuss the evolution of data sciences approaches within psychiatry, and specifically of record-linkage techniques and their

application in medical epidemiology. In Chapter 3 I will also review the demographics and characteristics of the datasets used in this thesis, namely Generation Scotland (GS:SFHS), UK Biobank (UKB), the Scottish Morbidity Records (SMR) and the Prescribing Information System (PIS) of NHS Scotland.

Chapter 4 demonstrates the application of record-linkage to administrative health data for *validation* in psychiatric research. Using national prescribing data in PIS as the 'gold standard', I compare the accuracy of GS:SFHS cohort self-reported psychiatric drug use, which is often thought to be relatively under-reported for reasons such as self-stigma, compared to other commonly prescribed medications. Our study finds that under-reporting is not found for all psychiatric medications, indeed antidepressants show very good agreement between self-report and prescribing data (κ=0.85,(95% Confidence Interval(CI)0.84-0.87)), similar to antihypertensives (κ=0.90, (CI 0.89-0.91)) which are another commonly prescribed medicine. However, for mood stabilizers the agreement is relatively poor (κ=0.42, CI 0.33-0.50). A number of medication-related and patient-level factors are analysed, with relevant past medical history being the strongest predictor of self-report sensitivity. By contrast, general intelligence is not found to be predictive. The chapter concludes that there is no simple relationship between psychiatric medication use and medication under-reporting. In addition, that no patient-level factor produces greater accuracy of self-report across all medications studied, although history of indicated illness – where this could be defined - predicted more accurate self-report.

In Chapter 5 the potential of record-linkage to *transform cross-sectional research studies into longitudinal studies*, is investigated using the problem of quantifying antidepressant prevalence. Antidepressants are the most commonly prescribed

psychiatric medication, but concerns have been raised about significant increases in their usage. By linking PIS prescribing data with the phenotypic data in a subset of GS:SFHS, the study is able to determine new measures of antidepressant prevalence, incidence, adherence, prescribing patterns with other medications, and patient-level predictors of usage. An antidepressant prevalence of almost one third of the cohort (28%, 95% CI 26.9-29.1), defined as dispensing of at least one PIS antidepressant prescription in the five-year period 2012-16, is described. This is a 36.2% increase in annual prevalence between 2010 and 2016. Incidence is calculated as 2.4(2.1-2.7)% per year, which is not significantly changed from previous estimates. The majority of antidepressant episodes (57.6%) are found to be greater than 9 months duration and adherence, using the Proportion of Days Covered (PDC) measure, is found to be generally high(69%). In time-to-antidepressant-use Cox regression analysis of the 5 years following individual GS:SFHS enrolment, predictors of new antidepressant use included: history of affective disorder; being female; physical comorbidities; higher neuroticism scores; and lower cognitive function scores. The chapter finds that this research supports the hypothesis that increased long-term use among existing (and returning) users, along with wider range of indications of antidepressants, has significantly increased the prevalence of these medications.

In Chapter 6 the potential of record-linkage to *identify new phenotypes for study* within psychiatric cohorts is examined using the example of self-harm. Self-harm is a common and debilitating behaviour but often difficult to research as there may be unwillingness in sufferers to disclose. Using record-linkage to hospital morbidity data(SMR), I identified individuals with hospital-treated self-harm in GS:SFHS and compared these to a replication cohort drawn from UK Biobank, with self-reported

hospital-treated self-harm. I further demonstrated that neuroticism, a stable personality trait associated with depression, is independently positively associated with self-harm (per Eysenck Personality Questionnaire Short-Form(EPQ-SF) unit Odds Ratio 1.2 95% Credible Interval 1.1-1.2, P_{FDR} <0.001), even when adjusted for a range of relevant covariates. I further replicated this finding in UK Biobank (per EPQ-SF unit Odds Ratio 1.1, 1.1-1.2, p_{FDR} <0.001). In a follow-up recontact study of GS:SFHS, STRADL, where self-reported suicidal ideation was recorded, I find that neuroticism, and the neuroticism-correlated coping style, emotion-oriented coping (EoC), were also associated with suicidal ideation in multivariable models. Therefore the chapter concludes that neuroticism is an independent predictor of hospital-treated self-harm risk, and is therefore independent of major depressive disorder in this respect, and is also (along with emotion-oriented coping), an independent predictor of suicidal ideation.

Chapter 7 summarises the empirical findings presented in Chapters 4 to 6. The Chapter will also recapitulate the strengths and limitations of the record-linkage approaches used in this thesis. Finally, suggestions for future research avenues for record-linkage studies using psychiatric cohorts, and psychiatric data science as an evolving field, are discussed.

Lay Summary

We know that modern computer technology has changed many aspects of how we work, learn, communicate and trade. It also has enormous potential to improve how we understand our health, in particular research into the complex world of our mental health (how we think, feel, behave and relate to each other). We have learned a lot from previous studies of mental health, which often involve recruiting large groups of volunteers followed by collecting detailed health-related information and performing tests. However, these studies often have problems, such as not having enough information about the volunteers to make robust conclusions about the topics being studied; or only having information from a particular point in time rather than a broader view across many years; or by the fact that people may be understandably unwilling to talk about some personal aspects of their mental health. A new computer technology called 'record-linkage', which enables the connecting of willing research volunteers with information stored about them in other places, such as in hospital records, in an anonymous and confidential way, has great potential to help. This PhD thesis demonstrates how record-linkage can improve research into mental health, in particular addressing questions central to research in major depressive disorder (MDD).

In the first research chapter (Chapter 4) I will investigate the accuracy of people's recollection and reporting of the medications they are using. In particular, whether those who are on psychiatric medications are less likely to self-report accurately, due to factors such as feeling stigmatised. This is done by comparing NHS prescriptions data (collected by pharmacies) as a trusted gold standard with the self-report of participants in the Generation Scotland cohort(GS:SFHS). What I will show is that accuracy of self-report is high across most of the medicines studied (psychiatric and

non-psychiatric), thus drugs for depression (antidepressants) are roughly as accurately self-reported as drugs for blood pressure (antihypertensives). However, I also find that self-report for another psychiatric drug group (mood stabilisers) is much less accurate and discuss potential reasons for this including that many patients may be confused at what 'mood stabilisers' means. I consider various factors that may lead to more accurate self-report and find that the strongest is having a history of an illness related to the medication in question.

In Chapter 5, I explore how commonly people are using antidepressants (drugs for depression) which has become an important question as prescribing rates of antidepressants has reached unprecedented levels in the UK. I use record-linkage to prescribing data to try to provide reliable figures for which groups of people use antidepressants most frequently, how regularly they are taking them, how many new people are starting them, and what other medications they might be taking. I demonstrate that antidepressant exposure is indeed significantly higher in the Generation Scotland cohort than previous reports would indicate. Indeed, almost one third of the cohort had been dispensed at least one antidepressant prescription in the five years studied (2012-16). However, I also show that the number of new users (incidence) has not significantly increased. This suggests that antidepressant use has risen mainly because of longer periods of usage, better compliance with antidepressant treatment and previous users returning to use. I also determine a number of predictors of antidepressant use, including history of depressive illness, being female, physical illness, sensitivity to stress (neuroticism) and lower intellectual performance.

Finally, the last research chapter(Chapter 6) looks at a very important aspect of mental health and depressive illness that people are often unwilling to discuss with clinical and research professionals: self-harm and thoughts of suicide. I show that record-linkage can help identify sufferers of these conditions in an anonymous and confidential way, by linking Generation Scotland with the NHS hospital records (Scottish Morbidity Records). Having defined those who have a history of self-harm, I am able to demonstrate that those who tend to find the world more stressful and threatening (high neuroticism) are at particular risk of self-harm. I am able to repeat this finding using another large cohort study (UK Biobank). In the second part of the study I examine a smaller subgroup of Generation Scotland(STRADL) who were re-contacted some years after their original enrolment and completed a questionnaire on the coping skills they use in response to stressful events. I find that those who tend to cope with problems through their emotions are more likely to have ideas of suicide. This chapter concludes that neuroticism is an important predictor of self-harm risk which is associated with, but independent of, major depressive disorder. This research can potentially help us improve access to care for these individuals who might be at risk.

Declaration

I hereby authorise the University of Edinburgh to publish the abstract of this thesis, and to authorise others to do so, for scholarly purposes and with proper acknowledgement of authorship.

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Signed

Dr Jonathan Hafferty

Date 11/06/2021

Publications

A list of first-author publications that are based directly on the work constituting this thesis are presented below, with appropriate acknowledgement of the contribution of co-authors to the work presented herein :

Chapter 4:

Hafferty, JD., Campbell, AI., Navrady, LB., Adams, MJ., MacIntyre, D., Lawrie, SM., Nicodemus, KK., Porteous, DJ., McIntosh, AM. (2018)

"Self-reported medication use validated through record linkage to national prescribing data" *J Clin Epidemiol. 94. 132-142.*

This study was conceived by JDH, AIC and AMM. JDH performed the analysis, wrote the manuscript and prepared all the tables and figures. AMM was the main supervisor for the project, with co-supervision provided by KKN and DJP. LBN, AIC and MJA aided in the data preparation and/or statistical analysis. All authors reviewed the manuscript for publication.

Chapter 5:

Hafferty, JD., Wigmore, EM., Howard, DM., Adams, MJ., Clarke, TK., Campbell, AI., MacIntyre, DJ., Nicodemus, KK., Lawrie, SM., Porteous, DJ., McIntosh, AM. (2019)

"Pharmaco-epidemiology of antidepressant exposure in a UK cohort record-linkage study" *J Psychopharmacol.* 33(4)482-493

The study was conceived by JDH and AMM. JDH performed the analysis, wrote the manuscript and prepared all the tables and figures. AMM was the main supervisor for the project, with co-supervision provided by KKN and DJP. EMW, DMH, MJA, TKC and AIC aided in the data preparation and/or statistical analysis. All authors reviewed the manuscript for publication.

Chapter 6:

Hafferty, JD., Navrady, LB., Adams, MJ., Howard, DM., Campbell, AI., Whalley, HC., Lawrie, SM., Nicodemus, KK., Porteous, DJ., Deary, IJ., McIntosh, AM. (2019)

"The role of neuroticism in self-harm and suicidal ideation: results from two UK population-based cohorts" *Soc Psychiatry Psychiatr Epidemiol.* doi. 10.1007/s00127-019-01725-7. Epub ahead of print.

The study was conceived by JDH, LBN and AMM. JDH performed the analysis, wrote the manuscript and prepared all the tables and figures. AMM was the main supervisor for the project, with co-supervision provided by KKN and DJP, and additional supervision by IJD. LBN, MJA, DMH and AIC aided in the data preparation and/or statistical analysis. All authors reviewed the manuscript for publication.

A completed list of publications (first- and co-author) received as part of the work done during this PhD are presented in Appendix A.

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I'd like to thank my friend and brilliant fellow psychiatrist Dr Tomasz Bajorek for his continued camaraderie during my studies. I think turning up to rescue me at the Oxford bus station in the middle of the night while also on call was above and beyond the call of duty!

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faith in me. There aren't many families that would have been so supportive and understanding during the three years of this fellowship and I am very lucky to have them.

It's been a wonderful three years and I hope this thesis goes some way to recognise the contributions of all that have helped me along the way.

List of Abbreviations

AIC	Akaike Information Criterion
AoC	Avoidance-oriented Coping
ATC	Anatomical Therapeutic Chemical Classification System
BDNF	Brain Derived Neurotrophic Factor
BNF	British National Formulary
BRS	Brief Resilience Scale
CBT	Cognitive–behavioural therapy
CHI	Community Heath Index number
95% CI	95% confidence interval / 95% credible interval
CIDI-SF	Composite International Diagnostic Interview – Short Form
CISS	Coping Inventory for Stressful Situations
CPRD	Clinical Practice Research Datalink
CRIS	Clinical Record Interactive Search
DDD	Defined daily doses
DSH	Deliberate Self-Harm
DSM	Diagnostic and Statistical Manual of Mental Disorders
eDRIS	(Scottish NHS) eData Research and Innovation Service
EHR	Electronic Health Records
EoC	Emotion-oriented Coping
EPQ-SF	Eysenck Personality Questionnaire Short Form-Revised
FDR	False Discovery Rate
g	General intelligence
GDPR	(EU) General Data Protection Regulations

GEE	Generalized Estimating Equations
GHQ	General Health Questionnaire-28
GP	General Practitioner
GS	Generation Scotland
GS:SFHS	Generation Scotland: Scottish Family Health Study
GWAS	Genome-wide association study
5-HT	5-hydroxytryptamine (serotonin)
HR	Hazard ratio
ICD	International Classification of Diseases
ISD	(Scottish NHS) Information Services Division
LTE	List of Threatening Experiences
MAOI	Monoamine Oxidase Inhibitor
MAR	Missing at Random
MCAR	Missing Completely at Random
MCMCglmm	Markov Chain Monte Carlo generalised linear mixed model
MD	Major Depression
MDD	Major Depressive Disorder
MICE	Multiple imputation by chained equations
MPR	Medication possession ratio
MRC	Medical Research Council
NaSSA	Noradrenergic and Specific Serotonergic Antidepressant
NCMH	(Welsh) National Centre for Mental Health
NIMH	(US) National Institute of Mental Health
NMAR	Not Missing at Random
NMDA	N-methyl-D-aspartate glutamate receptor
NHS	National Health Service (UK)

NSS	National Services Scotland
NSSI	Non-Suicidal Self-Injury
OR	Odds ratio
OCT	Over-the-counter (medications)
p	Associated p-value of a test statistic
PAC	Privacy Advisory Committee
PC	Principal component
PCA	Principal component analysis
PDC	Proportion of days covered (medication adherence metric)
PGC	Psychiatric Genomics Consortium
PHQ	Patient Health Questionnaire–9
PIS	(Scottish) Prescribing Information System
PPV	Positive Predictive Value
RCT	Randomised Controlled Trial
RDoC	Research Domain Criteria
SA	Suicide Attempts
SAIL	(Welsh) Secure Anonymised Information Linkage
SBR	Scottish Birth Records
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	Standard deviation
SDMD	Scottish Drug Misuse Database
SH	Self-Harm
SIMD	Scottish Index of Multiple Deprivation
SMR	Scottish Morbidity Records
SMR00	SMR relating to outpatient medical and psychiatric contacts
SMR01	SMR relating to inpatient and daycase medical admissions

SMR02	SMR relating to maternity records
SMR04	SMR relating to inpatient and daycase psychiatric admissions
SMR06	SMR relating to cancer admissions
SMR11	SMR relating to neonatal records now replaced by SBR
SNRI	Serotonin and noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor(s)
STRADL	Stratifying Resilience and Depression Longitudinally
TCA	Tricyclic antidepressant(s)
ToC	Task-oriented Coping
WHO	World Health Organisation

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Chapter 1 : Introduction

A leitmotiv of this thesis is the transformative potential of record-linkage to administrative health data in addressing some of the most important issues in mental health research. In particular, I will assess the ways in which record-linkage (introduced and discussed in detail in the next Chapter) can provide phenotyping information that is often missing, unvalidated or incomplete in conventional cohort studies. In the chapters that follow I shall look in particular at research pertinent to major depressive disorder, which is the most common mood disorder in the UK and USA (Hillhouse and Porter, 2015). In particular, this thesis will examine two psychiatric topics – antidepressant use and self-harming behaviour - which are closely entwined with MDD research, but which have in the past generated concerns about methodological issues including (a)unreliable self-report, (b) potentially untrustworthy prevalences, and (c)non-representativeness of the research populations previously studied compared to real world experience.

In the research chapters that follow, three specific research objectives will be addressed. These are to provide answers to the following questions:

1. Are users of psychiatric medications less likely to accurately self-report their usage in research studies compared to users of other medications?
2. Has exposure to antidepressant medications significantly increased in recent years and, if so, is this due to a change in how antidepressants are used ?
3. Is the psychological trait of neuroticism an independent risk factor for the MDD-associated outcomes of antidepressant use and self-harm ?

In this introductory chapter, I will introduce the reader to the main topic area of this thesis, Major Depressive Disorder (MDD), before providing a brief introduction to antidepressant and self-harm research. Due to the wide range of content to be discussed, including epidemiology, pathophysiology, genetics, diagnostic sub-categorisations and treatment of depressive illness; the psychological trait of neuroticism; and self-harm and suicidality; the approach taken here is, of necessity, that of a narrative review rather than a systematic literature review. Major reviews are however cited and can be found in the Bibliography and References.

1.1 Major Depressive Disorder

Major depressive disorder (MDD) is a highly debilitating syndrome characterised by persistent low mood and anhedonia (reduced enjoyment in activities previously found pleasurable) as well as a number of cognitive, psychological and physiological symptoms. A diagnosis of MDD is based on a number of potential symptom clusters which differ to an extent with individual presentations (see Table 1.1), but a central characteristic of major depression is its persistence, pervasiveness and pathological extent (McIntosh et al., 2019).

Major depression is a leading cause of global disability, accounting for more than 4% of all years lived with disability (Vos et al., 2017). Depression occupies a higher rank over time in the global burden of disease than many conditions which receive much greater levels of research funding (McIntosh et al., 2019; Woelbert et al., 2019). Major depression is associated with social disadvantage, physical morbidity and mortality (Chesney et al., 2014) and significant economic and social impact.

1.2 Epidemiology of MDD

Studies originating in the United States have found that the reported annual population prevalence of depression has increased (probably reflecting improved reporting and diagnosis) from 3.33% (1991-92) to 7.06%(2001-02)(Compton et al., 2006), to 8.3% in 2011 (Kessler and Bromet, 2013; Bromet et al., 2011). The lifetime prevalence of depression in the United States, in a study published in 2011, was found to be 19.2% (Kessler and Bromet, 2013; Bromet et al., 2011). The prevalence of depression in females is fairly consistently found to be approximately double that of males (Gelder et al., 2012). Median age of onset, symptomatology, disorder severity and sociodemographic profiles of depression are mostly comparable across countries and cultures (Kendler et al., 2015), although there are variations in depression annual prevalence (or presentation) between countries, varying from 2.2% in Japan to 10.4% in Brazil (Kessler and Bromet, 2013).

Depression tends to first occur between later adolescence and the early 40s, with a median age of onset of major depressive disorder of 25 years (Bromet et al., 2011). While overall depression prevalence rates are thought to be broadly comparable between high-income and lower-income countries, only an estimated 10% of sufferers receive treatment for depression in lower-income countries compared to 60% for higher-income countries (Wang et al., 2007).

The disorder is associated with a number of biological, psychological and socio-demographic risk factors. In one landmark study using the Virginia Twin Registry, Kendler (Kendler et al., 2002) was able to predict over 50% of the variance in the liability to develop major depression in the proceeding 12 months (in females). The strongest predictors for depression were (1) stressful life events (2) genetic factors,

both direct and indirect (3) previous history of major depression and (4) the psychological trait of neuroticism. Depression is also associated with other factors including childhood adversity, sexual abuse, marital discord, unemployment, physical illness, and is comorbid with a number of mental and physical health problems, especially anxiety disorder, substance abuse disorders and personality disorders (Gelder et al., 2012).

1.3 Pathophysiology and Genetics of Major Depression

The pathophysiological basis of the majority of cases of major depression remains unknown. As discussed below, the accidentally discovered antidepressant action of drugs promoting monoamine transmission led to the development of a 'monoamine hypothesis', relating depression to deficiencies in monoamine networks in the brain (Bunney and Davis, 1965). There is some evidence that stress and hypothalamus-pituitary-adrenal (HPA) axis activation can induce reduction in monoamine levels and is associated with depression onset (Cowen, 2002). Stress has also been implicated with decreases in neuronal growth and survival, such as that mediated by brain-derived neurotrophic factor (BDNF) (Belmaker and Agam, 2008). There is some evidence that synaptogenesis can be upregulated, and stress-induced neuronal atrophy counteracted, by glutamate NMDA-receptor antagonists, leading to an interest in ketamine as a potential antidepressant (Duman and Li, 2012).

Another major theoretical framework for understanding depression is as a neuroinflammatory process (Maes et al., 1990; Bullmore, 2018). MDD has well established comorbidities with a variety of inflammatory diseases (Graff et al., 2009;

Carney et al., 1988) and chronic stress can induce cytokine dysregulation leading to chronic neuroinflammation (Kim et al., 2016). Intriguingly, interferons – a superfamily of proinflammatory cytokines used in the treatment of a variety of autoimmune conditions – have been found to induce depression in up to a third of those treated (Bullmore, 2018). This has also led to recent interest in anti-inflammatory medications as potential antidepressants.

Early twin heritability studies of major depression estimated a genetic heritability of between 31 and 42% (Sullivan et al., 2000). To date, linkage analysis, candidate gene studies and re-sequencing studies have not produced robust, replicable findings regarding the underlying genetic basis for depression (McIntosh et al., 2019).

Another approach is to use haplotype analysis (based on a group of genes inherited together from a single parent), which has recently identified a haplotype in 6q21 (a region previously associated with bipolar disorder) in Generation Scotland (GS:SFHS, n=18,773) which also replicates ($P<0.05$) in UK Biobank (UKB, n=25,035) (Howard et al., 2017). This study is significant within the context of this research thesis, as it employed record-linkage techniques (including work by the present author) to link GS:SFHS to administrative health data in the Scottish Morbidity Record to screen the case and control group, identifying false positives (cases of MDD that had other significant diagnoses such as bipolar disorder and schizophrenia) and false negatives (members of the control group with diagnoses of MDD). This is an example of record-linkage being used to improve signal and power for discoveries and reduce false associations, as will be discussed further in the following chapters.

The implication of linkage, candidate gene and genome-wide association studies (GWAS) performed to date are that the underlying liability depression is polygenic and no loci of major effect exist (Ripke et al., 2013). A recent large-scale meta-analysis performed on 246,363 cases and 561,190 controls from the three largest genome-wide association studies of depression to date and replicated into an independent sample of 414,055 cases and 892,299 controls (Howard et al., 2019), identified 102 independent variants (87 replicated) and a heritability of major depression of 8.9% (95% Confidence Interval 8.3-9.5%). Larger sample sizes with denser imputation, plus greater use of next-generation/whole-genome sequencing technology, are awaited to uncover more of the genetic component of major depression indicated by the twin heritability studies.

1.4 Historical Overview of Depression Diagnosis in Research and Clinical Practice

Depressed mood is a common psychological symptom and part of the normal range of normal human emotional experience. While depressed mood is often transient and non-pathological, this symptom can/may be sustained, severely and adversely impacting many areas of functioning. The Greek physician Hippocrates (460-377 BC) recognised a condition of unremitting and persistent “fear or sadness” and described associated symptoms including aversion to food, insomnia, psychomotor restlessness, irritability and hopelessness or despondency. This was termed *melancholia*. Additional insight was provided by Galen (131-201 AD) who made the important point that melancholia, ascribed to an excess of ‘black bile’, produced symptoms that were prolonged and disproportionate to any external circumstances that may have affected the sufferer.

In *The Anatomy of Melancholy* (1621) (Burton, 1621), the Oxford University scholar Robert Burton described melancholia as a *"sorrow…without any evident cause*" and which consisted of mood, cognitive and physical components. During the 19th century, with the development of psychiatry as a distinct medical discipline, Emil Kraepelin (1856-1926) identified melancholia as consisting of *"morbid emotions* [that] *are distinguished from healthy emotions chiefly through the lack of a sufficient cause, as well as by their intensity and persistence*" (Kraepelin, 1915). Having differentiated schizophrenia (dementia praecox) from manic-depressive insanity, Kraepelin initially defined melancholia as a separate disorder but was later persuaded that melancholia and manic-depressive insanity has the *"same morbid process"* (Kraepelin, 1921).

While Kraepelin's insights mostly evolved from work within asylums, the work of (principally) outpatient neurologists and psychiatrists, especially Jean-Martin Charcot (1825-1893) and Sigmund Freud (1856-1939) led to the development of an alternative understanding of depression. Freud's background was in neurology, where a differentiation was made between *neuroses*, afflictions of the nerves without an obvious neuropathology, and neuritis where inflammation or other pathological processes were observable (e.g. via microscopy). The neuroses included a variety of conditions seen by outpatient clinicians (tending to an, often, wealthy clientele), including *hysteria* (conversion disorder, somatization, fugue and amnesia), phobias and anxieties, obsessions and depressed mood. In Freudian psychiatry, neuroses began to be understood as being more psychological than neurological in basis, reflecting defence mechanisms against anxiety, the manifestation of unconscious processes and desires, and the products of psychosocial adversities such as loss of a love object.

Thus by the turn of the 20th century, depression was often conceptualised as two distinct conditions (Shorter, 2007). Melancholia (often understood as part of manic-depressive insanity) was characterised by mental anguish, hopelessness, joylessness, stupor and often suicidal thoughts or actions. It was typically chronic and recurrent and often treated by alienists. Neurosis, by contrast, encompassed anxiety, fatigue, somatic preoccupations, obsessions and low mood. It was more likely to be treated by outpatient neurologists and spa doctors. In 1920 Kurt Schneider formalised this distinction by differentiation of *endogenous depression* (evolved from melancholia) from *reactive depression* (evolved from neurosis).

The experience of the First and Second World Wars had a profound effect on psychiatry, which had to respond to epidemics of 'shell shock' and 'combat fatigue'. This led to greater professionalism within psychiatry, greater pragmatism regarding treatments, and a greater public understanding of the existence of mental illness and the requirement for treatment (Gelder et al., 2012). This was further informed by the emergence of the first antipsychotic and antidepressant treatments in the 1950s and the rise of 'biological psychiatry' with its emphasis on neuropathological processes in mental illness such as disruption of neurotransmitter systems.

The first edition of the *Diagnostic and Statistical Manual of the American Psychiatric Association* (American Psychiatric Association, 1952) grouped melancholia and 'manic-depressive reaction' with psychotic disorders (schizophrenic and paranoid reactions), while grouping neurotic depression with anxiety disorders. DSM-II (American Psychiatric Association, 1968) maintained the distinction between 'manic-depressive illness' and psychoneurotic disorders. By the 1970s, there were a wide

range of depressions treated within both the psychodynamic and biological psychiatric traditions, and were surveyed in a landmark paper by Kendell (Kendell, 1976) as including psychotic and nonpsychotic, endogenous versus reactive, melancholic versus psychoneurotic and (following the work of Karl Kleist), bipolar versus unipolar.

Meanwhile, the Freudian concept of neurosis was adapted and transformed by the work of Hans Eysenck (Eysenck, 1967) and his developing taxonomy of personality. The modern concept of *neuroticism* (not to be confused with neurotic depression) came to be seen as a trait of emotionality, in particularly a tendency to arouse quickly when stimulated, and to inhibit emotions slowly, with a propensity to experience negative emotions (Ormel et al., 2013). As such neuroticism came to be regarded as one of the 'Big Five' personality traits, along with extraversion, agreeableness, conscientiousness and openness to experience. As will be demonstrated in the research chapters to follow, neuroticism is conceptually distinct from major depression but is closely associated with it.

1.5 Diagnosis of Major Depression in Research Studies

The foundational basis of the diagnosis of depression in current clinical and research practice is the *operationalised* definitions of mental illness adopted in DSM-III (American Psychiatric Association, 1980) and ICD-10 (World Health Organisation, 2017). This approach is most closely associated with Robert Spitzer (1932-2015), a highly influential psychiatrist of the latter 20th century, and influenced by a number of studies which called the credibility and consistency of psychiatric diagnosis into question (Rosenhan, 1973; US-UK Cross-National Project, 1974).

Operationalism is a philosophical tradition whereby a concept can only be understood if there is an appropriate means of measurement of it, subserved by a set of operations. Developed from conceptual work in the field of physics (Bridgman, 1927), operationalism was developed within psychology and psychiatry by the logical positivist philosopher Hempel (1966). In Hempel's model a mental state could be observed by an assessor, leading to a totalising of a symptom list, which is compared to specified duration and severity criteria, and also to specified exclusion, sub-type and other multi-axial dimensional criteria. One of the first attempts to make psychiatric diagnosis operationalised was the "St Louis Classification" of Washington University (Feighner et al., 1972).

The Research Diagnostic Criteria (Spitzer et al., 1975) separated 'major depression' which had many subtypes including endogenous depression, from 'minor depression' – a lesser form of depression which occurred with or without anxiety, and these were also distinguished from bipolar disorder. This provided the basis of DSM-III (American Psychiatric Association, 1980) which formally separated bipolar disorder and major depression (on the basis of presence or absence of manic symptoms) and replaced the concept of 'minor depression' with dysthymic disorder (or depressive neurosis, understood to be a persistent low grade depressive condition recurring throughout life). Melancholic depression and endogenous depression were removed as concepts and, despite some later efforts to resurrect them, Major Depressive Disorder has persisted since as a unitary concept describing a clinically heterogenous condition (Table 1.1), although melancholia can theoretically (along with psychotic and atypical depression) be sub-classified.

Table 1.1 – Diagnostic Criteria for Major Depressive Disorder in DSM-5 and ICD-10, Adapted from McIntosh et al. (2019)

DSM-V Major Depressive Disorder	ICD-10 'Moderate Depressive Episode'
Five or more symptoms, at least one of which must come from the "A" criteria.	Two or more symptoms from the following :
"A" criteria	
1. Depressed mood	1. Depressed mood
2. Markedly diminished interest or pleasure in almost all activities	2. Loss of interest and enjoyment
	3. Reduced energy leading to increased fatigability and diminished activity
"B" criteria	Three or more typical symptoms from the following:
1. Significant weight loss/gain or decrease/increase in appetite	1. Reduced concentration and attention
2. Insomnia or excessive sleep	2. Reduced self-esteem and self-confidence
3. Psychomotor agitation or retardation	3. Ideas of guilt and unworthiness (even in mild type of episode)
4. Fatigue or loss of energy	4. Bleak and pessimistic views of the future
5. Feelings of worthlessness or excessive/inappropriate guilt	5. Ideas or acts of self-harm or suicide
6. Diminished concentration or indecisiveness	6. Disturbed sleep
7. Recurrent thoughts of death, suicidal ideation, plans or an attempt	7. Diminished appetite

Both sets of criteria require a minimum symptom duration of 2 weeks, significant functional impairment and for the disorder to not be better accounted for by another medical/psychiatric condition.

1.6 Alternative Research Definitions of Depression

In a recent literature review aimed at understanding the phenomenology of major depression and the representativeness of DSM criteria, Kendler (2016) has argued that current diagnostic criteria place heavy emphasis on neurovegetative features of depression at the expense of changes in cognitive functioning, attitudinal change and

somatic symptoms previously understood to be important features of depression. Kendler cautions against the 'category mistake' of conflating DSM criteria with the syndrome of depression as one and the same, given that the ICD/DSM will of their nature select criteria that require lesser levels of inference (to improve reliability), hence emphasis on readily quantifiable symptoms like weight, appetite and sleep.

In 2013, Thomas R. Insel, Director of the US National Institute of Mental Health (NIMH), stated that the agency would be "*re-orienting its research away from DSM categories*" (Insel, 2013), citing a lack of validity given that, unlike diseases like ischaemic heart disease, there are no objective laboratory measures yet developed for major depression and schizophrenia. Insel proposed the development of Research Domain Criteria (RDoC) to be used by future research projects, that would incorporate genetics, imaging, cognitive science and other sources of objective data. While this is an aspiration for the future, such criteria are not yet in common use in research studies.

A further recent development in depression diagnosis within psychiatric research has been the increased use of *self-reported depression*, outside of operationalised clinical diagnostic systems. Partly, this has been the result of the creation of very large study samples and biobanks enabling, for example, massive genome-wide association studies, which may not have access to formal DSM/ICD diagnostic evaluation. The company 23andMe recently provided a sample of in excess of one million individuals self-reporting the presence or absence of a depression diagnosis made by a healthcare individual (Howard et al., 2019). This leads to uncertainty about whether the full DSM or ICD criteria have been met in these cases, to which end the Psychiatric Genomics Consortium (PGC) have developed the concept of "Major

Depression" (MD) to include more 'minimally phenotyped' samples (McIntosh et al., 2019).

MD cases include those who self-declare diagnosis of depression by a healthcare professional or who meet research diagnostic criteria, or both. For example, in UK Biobank depression like traits can be broadly defined by questions such as '*Have you seen a doctor (GP) for nerves, anxiety, tension or depression*' (UKB Data-Field 2090) and *'Have you seen a psychiatrist for nerves, anxiety, tension or depression'* (UKB Data-Field 2100). This can lead to debate as to the extent to which MD and MDD describe the same condition, which is further complicated as many with MDD do not present to a healthcare professional for diagnosis (a necessary condition for MD that has not been ascertained by diagnostic criteria), and many individuals with anxiety disorders are not depressed. Nevertheless, two recent studies have identified high correlation at the genetic level between self-declared depression and DSM-diagnosed depression (Zeng et al., 2016; Howard et al., 2018) , although a further (pre-print) study suggests that the relationship may be more nuanced between minimal phenotyping GWAS hits and specificity for major depression (Cai et al., 2018).

In addition to large-scale genetic and biobank studies which have led to the development of minimally phenotyped MD as a research diagnosis, another significant factor for depression phenotyping is increased access to record-linkage of administrative health and prescribing data (McIntosh et al., 2019). This enables other means of phenotyping depression cases, such as record-linkage to DSM/ICD diagnostic codes within health data (Davis et al., 2018), neuro-linguistic programming based text mining of health data for depression related keywords (Smoller, 2018) and

identifying depression cases through analysis of antidepressant users in prescribing records (Wigmore et al., 2019) (Table 1.2). An advantage of using record-linkage to administrative health data to identify cases is that it is well known that sufferers from depression may forget or fail to report past depressive episodes in self-report (recall bias) (Gelder et al., 2012).

Table 1.2 : Methods of Phenotyping Depression in Research Studies, Adapted From McIntosh et al. (2019)

	DATA SOURCE		
	Self-rated	**Electronic Health Records**	**Trained interview e.g. research nurse**
Diagnostic Standard	Self-report questionnaire e.g. CIDI-SF used in STRADL	Recorded diagnostic codes e.g. ICD-10 in Scottish Morbidity Records / NHS data	Structured diagnostic interview e.g. SCID used in GS:SFHS
Single item (sub-diagnostic)	Single question self-report e.g. 'have you ever seen a health professional for depression?'	Single-word searches of record-link data e.g. searches for "depression" or "antidepressant"	Evoked recollection of previous history of depression
Multiple item (sub-diagnostic)	Multiple item self-report e.g. UKB self-reported depression	Multiple search term text mining e.g. Clinical Record Interactive Search (CRIS)	Sub-diagnostic rating scale of psychological distress e.g. PHQ-9 depression rating scale

1.7 Neuroticism and Major Depression

As we have seen, neuroticism is a stable personality trait described by Eysenck and characterised by negative emotional response and stress sensitivity. Numerous studies have demonstrated an association between neuroticism and major depression (Chan et al., 2007; Kendler et al., 2006) and a large meta-analysis has demonstrated this relationship between neuroticism and depressed mood or dysthymia (Kotov et al., 2010). However, much of the research linking neuroticism and major depression is cross-sectional, and thus it is difficult to discriminate associative relationships from causal ones. Furthermore, there is debate as to the extent to which neuroticism plays a mediating role between adversity and mental health outcomes (Lardinois et al., 2011). Thus it has been argued that negative life events in childhood promote the development of neuroticism, which then increases the vulnerability to major depression (Roy, 2002).

Neuroticism is itself a partially heritable trait, and twin studies have suggested a genetic correlation between neuroticism and major depressive disorder of between 0.43 and 0.69 (Kendler et al., 2006; Kendler and Myers, 2010; Hettema et al., 2006). A recent large neuroticism GWAS has identified four loci are also of nominal significance in a GWAS of MDD (Okbay et al., 2016). In summary, neuroticism and major depression appear to be genetically and phenotypically distinct, although with significantly overlapping and intertwined underlying architecture at the gene and behavioural level.

1.8 Antidepressants

There are a number of treatment options for MDD, including pharmacological, psychological (e.g. cognitive behavioural therapy), electroconvulsive therapy, exercise and occupational therapies. The majority of moderate to severe MDD cases are treated by antidepressants (Donoghue, 2019). For most patients there is a delayed onset of efficacy of antidepressant therapy before adequate remission of symptoms is achieved (Uher et al., 2011). Nevertheless, it is estimated that some 34-46% of MDD patients do not adequately respond to treatment (Fava et al., 2005).

Imipramine, the first antidepressant, was discovered serendipitously by Roland Kuhn in 1957 (Kuhn, 1958). At the time Kuhn was researching antipsychotics (Healy, 1998). Imipramine was the first of a new class of tricyclic antidepressants (TCAs), many of which are molecularly modified from the classic antihistamine chemical structure. In that same year, while researching anti-tuberculosis compounds, Nathan Kline discovered the first of the monoamine oxidase inhibitor class (MAOI) of antidepressants, iproniazid (Loomer et al., 1957). In 1965, in one of the first randomised controlled trials, the Medical Research Council demonstrated that, in treatment of depression, imipramine and electro-convulsive therapy (ECT) were superior to placebo (and phenelzine) (Thiery, 1965). Interestingly, further clinical experience and research demonstrated that while many responded to imipramine, many did not, and some of those who were treatment resistant to imipramine did respond to iproniazid (Healy, 2016).

In the early 1960s it was discovered that tricyclic antidepressants exerted their action by blocking the reuptake of monoamines, principally noradrenaline and serotonin. The monoamines (dopamine, noradrenaline and serotonin) are neurotransmitters in

the central nervous system (CNS) which are involved in neural networks subsuming a variety of functions, including emotion, arousal, movement and some types of memory. The 'monoamine hypothesis' postulates that the pathophysiology of depression relates to diminished concentrations of monoamines within the brain (Bunney and Davis, 1965). In addition to the monoaminergic-related (putative) action of antidepressants, the monoamine hypothesis noted that medications that deplete serotonin and catecholamines (such as the early antihypertensive drug reserpine), precipitate depression in some patients (Hillhouse and Porter, 2015).

In the 1970s Arvid Carlsson developed zimelidine, the first antidepressant which (relatively) selectively blocked serotonin reuptake (Carlsson and Wong, 1997). Zimelidine and fluoxetine (Wong et al., 1974) were the first of the Selective Serotonin Reuptake Inhibitors (SSRIs), which were followed in due course by paroxetine, citalopram, escitalopram and sertraline, among others (zimelidine was subsequently withdrawn).

There remains considerable debate about the extent to which noradrenaline reuptake block is an important property of the antidepressant class. Healy (2016) has noted that, some time before the production of zimelidine, it was known that the tricyclic antidepressants nortriptyline and desipramine were relatively selective for noradrenaline reuptake, and yet were effective antidepressants. Therefore the relationship between serotonin reuptake blockade and antidepressant efficacy is arguably not as straightforward as that, for example, between dopamine D2 receptor block and antipsychotic efficacy. It has also been noted that SSRIs are less effective for more severe or hospitalized depression(Healy, 2016) than medications which also target the noradrenergic system.

The monoamine hypothesis of depression has been repeatedly challenged in more recent times and is no longer considered an all-encompassing explanation of MDD pathophysiology. It has been noted that monoamine depletion in healthy subjects does not consistently produce depressive symptoms and that tryptophan depletion in MDD patients does not worsen depressive symptoms (Hillhouse and Porter, 2015).

Following the development of the SSRIs, there was interest in developing antidepressants which also targeted the noradrenergic system, but which had a more favourable toxicity profile than TCAs or MAOIs. Shortly after the introduction of fluoxetine, the 'atypical' antidepressant bupropion was released. Bupropion is primarily a dopamine-noradrenaline reuptake inhibitor and has highest binding affinity for dopamine transports and minimal binding affinity for serotonin transporters. Nevertheless, it is an efficacious antidepressant (Feighner et al., 1986) although in the UK, unlike the USA, bupropion is not licensed for depression and only used as an " off-label " antidepressant.

The next class of antidepressants to be released, in 1993, were the serotonin-noradrenaline reuptake inhibitors (SNRIs), of which venlafaxine and duloxetine are the most prominent examples in UK clinical practice. Reboxetine was developed to more specifically target the noradrenergic reuptake system, with the idea that it could prove useful for more atypical forms of depression, but it has had a relatively chequered reception in clinical practice (Cipriani et al., 2018).

Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), was released in 1996 and acts by antagonising adrenergic alpha-2 autoreceptors as well as by antagonising 5-HT2 and 5-HT3 receptors, thereby enhancing noradrenaline

and serotonin synaptic transmission (Anttila and Leinonen, 2001). Mirtazapine has become a clinically popular alternative antidepressant in outpatient practice from the SSRI/SNRI/TCA antidepressants. Other examples of atypical antidepressants include low dose oral antipsychotics (especially flupentixol), the serotonin precursor tryptamine, the 5-HT2A receptor and alpha-1-adrenoceptor antagonist trazodone, and the melatonin receptor agonist agomelatine.

In 2013, vortioxetine, a serotonin receptor agonist, antagonist and reuptake-inhibitor (with dopamine and noradrenaline reuptake inhibiting properties), was released, but was not in common clinical practice during the period analysed in this thesis. Other experimental or novel treatments that were not in common clinical use during the period studied include glutamatergic agents, NMDA receptor antagonists (e.g. ketamine) and glycine-like modulators.

The British National Formulary (BNF) (Joint Formulary Committee, 2012) classifies antidepressants in Chapter 4, Section 3, and provides the following classes : TCA, SSRI, MAOI and “other” antidepressants. The BNF is the standard formulary used in UK clinical practice, and is also in clinical use worldwide, and is the standard therefore adopted in this thesis. However, other standards exist, including the Anatomical Therapeutic Chemical Classification System (ATC) of the World Health Organisation (2012), which defines antidepressants under ATC code N06 (psychoanaleptics): Section A (antidepressants), incorporates non-selective monoamine reuptake inhibitors, SSRIs, non-selective MAOIs, monoamine oxidase-A inhibitors and ‘other’ antidepressants. Another recently adopted convention within the European Union is Neuroscience-based Nomenclature (Worley, 2017) which names medication via their mechanism of action (thus citalopram is a ‘serotonin reuptake inhibitor’). This reflects

an understanding that the names of many psychiatric medication classes are historic and not necessarily specific (i.e. 'antidepressants' are also commonly used for anxiety, and also are not thought to work by chemically counteracting or opposing depression but through a more complex mechanism). Nevertheless, throughout this thesis, the BNF approach has been adopted, in accordance with common UK clinical practice and its use in routinely-collected administrative health data within the UK. In some cases, however, the SNRIs have been distinguished from the rest of BNF Section 4.3.4 "other antidepressant drugs", as will be specified where applicable.

It is also important to recognise that antidepressant medications are not the only medications which treat depression. The BNF additionally lists a class of medications which have been variously described as "mood stabilizers", including lithium carbonate, lithium citrate, a number of anticonvulsants (including sodium valproate, carbamazepine and lamotrigine), a number of antipsychotics (including olanzapine, quetiapine and aripiprazole) and medications under development as antidepressants such as ketamine (used off-label). It is also the case that anxiolytic, sedative and antihistamine medications can be beneficial in depression. The description of a particular medication as "antidepressant" is therefore to a degree arbitrary rather than definitive, as reflected by expert consensus in the BNF. In this study when discussing "antidepressants" I have defined this as those agents within BNF Chapter 4 Section 3, which are understood to be licensed for and employed for the treatment of major depressive disorder, in both primary and secondary care. Where possible and practical I have provided additional information on the medications that can be described as "mood stabilizers" (although as discussed in Chapter 4 there is considerable confusion about this concept) and also other anxiolytic agents.

It is equally important to appreciate that BNF Chapter 4 Section 3 antidepressants have wider indications that simply the treatment of depression, and in fact the number of indications is growing, with considerable pharmaco-epidemiological significance, as discussed in Chapter 5. Clomipramine, the TCA with the most serotonergic action, has been found to be a useful anxiolytic with specific indications for phobic and obsessional states (Healy, 2016). The SSRI class has widespread use in the treatment of anxiety states ranging from generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) to panic disorder and social phobia (Joint Formulary Committee, 2012). Additionally, antidepressant drugs often have clinical uses outside of psychiatry. Amitriptyline, a tricyclic antidepressant, is now more commonly prescribed for non-psychiatric purposes such as chronic pain, fibromyalgia, insomnia and headache than it is for depression or anxiety, as discussed in Chapter 5. SSRIs are commonly prescribed to treat sexual disorders, bed-wetting and premenstrual dysphoria. Duloxetine, a SNRI, is commonly prescribed to treat urinary incontinence in women. As discussed in Chapters 4 and 5, the widespread use of antidepressants for a growing number of indications places particular challenges on research into antidepressant pharmaco-epidemiology and exposure.

1.9 Self-Harm, Suicidality and Attempted Suicide

Self-harm (SH) is defined as self-injury or self-poisoning, irrespective of the apparent purpose of the act (National Collaborating Centre for Mental Health, 2004). Self-harm is distinguished from purely accidental injury (at least theoretically). Terms like ‘deliberate self-harm’ (DSH) are no longer preferred in research due to their potentially judgemental overtones (Chapter 6) and the difficulty of distinguishing causality for self-injury in research and clinical practice. The aetiology, epidemiology,

comorbidities and nosological issues of self-harm are discussed in detail in Chapter 6. Distinction can be made theoretically between nonsuicidal self-injury (NSSI), suicide attempts (SA), suicidal ideation and completed suicide, although in many cases such distinctions are more difficult to make in practice.

While self-harm as a behaviour can occur in the absence of depressive illness, individuals with major depressive disorder are 20-times more likely to die by suicide in comparison to the general population (Chesney et al., 2014) and individuals with depression have a risk ratio of 14.1 (95% Confidence Interval 14.0-14.3) for self-harm in a record-linkage study of patients presenting to hospital as admissions or day cases (Singhal et al., 2014). It is further estimated that 50% of worldwide suicides annually are attributable to major depressive disorder (Otte et al., 2016).

Information on self-harm in research studies is typically collected retrospectively through self-report (Marrs, 2016). However, given its emotive content the self-report of self-harm is particularly likely to be affected by reporting issues including denial, self-stigma, problems with recall, misinterpretation of study questions and response bias (Velting et al., 1998). Research of self-harm in adolescents has demonstrated that individuals are two to three times less likely to disclose suicide attempts if their anonymity is not guaranteed (Safer, 1997). There is also evidence that those individuals who self-harm are more likely to be non-responders or lost to follow up in research studies (Wolke et al., 2009; Kidger et al., 2012).

In this context, record linkage to administrative data has significant potential to ameliorate under-reporting of self-harm in research studies (or at least that self-harm which can be detected in administrative data, such as self-harm associated with

hospital or general practice attendance). For example, a data linkage study comparing self-harm questionnaire responders and non-responders in the ALSPAC adolescent cohort found that self-harm leading to hospital admission was greater in non-responders (2.0%) than responders (1.2%) (Marrs, 2016). Thus research studies that combine self-report with other sources of data, including linkage to administrative health data, are arguably more likely to produce accurate phenotyping of cases, particularly for hospital-associated self-harm which, while less common (the majority of self-harm does not present to hospital), is potentially more clinically serious (see Chapter 6).

1.10 Concluding Remarks

This chapter has provided background to the epidemiology, aetiology and conceptual development of the major outcomes of interest in this thesis (antidepressant usage and self-harm) and the major associated covariates (major depressive disorder and neuroticism). Emphasised throughout is that while major depression is clearly linked with antidepressant usage and also with self-harm, the overlap is certainly not complete. Similarly, while depression (especially neurotic depression) and neuroticism share a common history in the development of psychopathological ideas, they are similarly distinct entities – the former a mental illness and the latter a dimension of personality.

This chapter has also shown that contemporary research into major depression, antidepressant usage and self-harm has benefited in recent years from the availability of linked data studies. In Chapter 2, I shall discuss the conceptual and methodological basis for the record-linkage techniques which will be utilised in the research chapters to follow.

Chapter 2 : Record-Linkage as Applied to Mental Health Research

2.1 Data Linkage, 'Big Data' and Psychiatric Research

Note : Some of the material presented here is based on material also published in Hafferty et al. "Invited Commentary on Stewart and Davis "'Big Data' in mental health research- current status and emerging possibilities" *Soc Psychiatry Psychiatr Epidemiolol* (2017) 52:127-129; and Russ TC, Woelbert E, Davis KAS, Hafferty JD et al. "How data science can advance mental health research", *Nature Human Behaviour*, (2019) Vol 3, 24-32.

* * *

In recent years there has been a revolution in the way data is processed, utilised and analysed for a variety of enterprises, with psychiatric research being no exception. An entirely new research discipline, *data science,* has been at the forefront of this change. 'Data science' was reportedly coined as recently as 2008 (Davenport and Patil, 2012) and has been defined as "*a set of fundamental principles that support and guide the principle extraction of information and knowledge from data*" (Provost and Fawcett, 2013).

These principles encompass computer-driven processes, algorithms and methods (such as data linkage, data mining and machine-learning) as applied to quantities of high-dimensional (i.e. multi-layered) structured (i.e. highly formatted and organised) and unstructured data. Critics have sometimes disparagingly referred to data science as a synonym for a (perhaps less robust and principled form of) statistics, or within the medical sciences as an 'old-wine-in-new-bottles' rebadging of computational

epidemiology. More positively, data science can be seen as a 'fourth paradigm' of science (alongside theoretical, empirical and computational science) which lies at the interface between mathematical/statistical methods, cutting-edge computational applications and skills, and evidence-based domain knowledge (see Figure 2.1) (Russ et al., 2019).

Figure 2.1 – The Meaning of Data Science

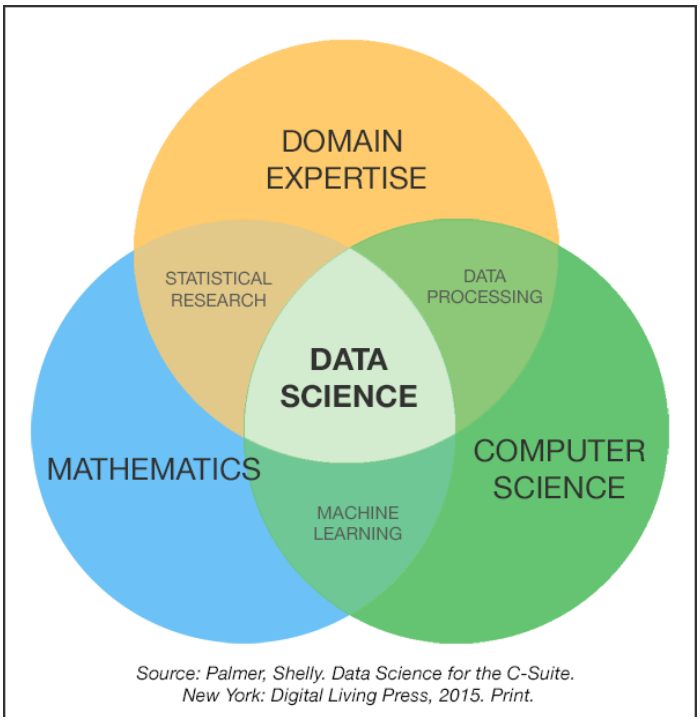


Image source : http://www.datascienceassn.org/content/data-science-venn-diagram-shelly-palmer-2015 [Accessed 07-06-19]

Data science can be conceptualised as a means of "*generating new knowledge from real-world data*" (Russ et al., 2019). Within medicine, this has already had significant impact. Firstly, with the establishment of new research enterprises dedicated to the exploitation of data for medical purposes, such as Health Data Research UK (https://www.hdruk.ac.uk) and the Farr Institute of Health Informatics Research (https://farrinstitute.org). Secondly, with advancements related to the use of this data for medical science, such as data-driven approaches to the study of aetiology and

pathogenesis of cancer (Hamada et al., 2017), data mining for heart disease prediction (Singh et al., 2018) and the development of anonymised electronic mental health record databases for mental health research (McIntosh et al., 2016b; Stewart and Davis, 2016).

Closely allied with the development of data science is the accumulation of 'big data'. 'Big data' has been defined as data sets which are so large in size, so fast to change and so complex in structure that traditional data processing techniques are overwhelmed (Hafferty et al., 2017). 'Big data' has become possible due to technological advances in data processing and storage, computer networking, mobile technology, the internet-of-things and platforms for data manipulation.

The challenges of working with such data are typically described through the taxonomy of 'Vs' – especially volume, velocity and variety of data – as originally described by Laney (2011). In this context, *volume* reflects the size of the datasets in terms of the number of cases and also the quantity of data attached per record (which can be massive if imaging and genetic data is included). *Velocity* reflects the speed at which the data is changed and updated, which can even be in near real-time in datasets which use medical health records and/or data provided by sensors. *Variety* reflects the sources of data and the data organisation principles within them, which can be very different in the case of, for example, datasets combining administrative health data whose predominant function is for financial/billing purposes, free-text medical notes used by clinicians, standardised psychological research instruments and tests, output from sensors, and repositories of biological data. '*Veracity*' and '*variability*' are often added to reflect the range and potential unreliability of

information arising from some sources, especially when datasets are combined (Stewart and Davis, 2016).

The opportunities for using data science and 'Big Data' in mental health research have been reviewed by McIntosh (2016b) and Stewart and Davis (2016). One of the most tractable approaches within the UK is to apply these techniques to massive population cohorts which are deeply phenotyped with clinical, psychological and sociodemographic data in addition to genetic, imaging and other biological data (examples include two of the cohorts that will be further discussed in this study, UK Biobank and Generation Scotland, other examples include the Avon Longitudinal Study of Parents and Children and, outside the UK, the US Million Veteran Programme and the BioBank Japan Project).

An exciting development which will be further explored within this study is the ability to use *record-linkage* (discussed below) to combine these cohorts with routinely collected healthcare and other administrative data. This can be done within population-based cohorts as described, and also to more domain-specific cohorts focused on mental health (examples include the collaboration of the Welsh National Centre for Mental Health (NCMH) cohort of approximately 6000 individuals with the Secure Anonymised Information Linkage (SAIL) databank of healthcare, child health, education, deprivation and demographic data). Additionally, cohorts can be created de novo using electronic health records, data structuring techniques and deidentification pipelines, as has been done with the Clinical Practice Research Datalink (CPRD) of GP practices and more recently with the Clinical Record Interactive Search (CRIS) database of mental health records developed at South

London and Maudsley NHS Foundation Trust in 2007 and since extended further in London as well as Oxford and Cambridge. These are summarised in Table 2.1

Table 2.1 United Kingdom 'Big Data' Resources for Psychiatric Research, adapted from Stewart and Davis (2016)

Name	Mental Health Specific?	Description	Size
Clinical Practice Research Datalink (CPRD)	No	National sample based on a sample of primary care providers	
Clinical Record Interactive Search (CRIS)	Yes	Local secondary care psychiatry anonymised case register – London, Oxford, Cambridge	200,000+ (London)
Generation Scotland	No	Regional family- and population-based research cohort with record-linkage to administrative data	21,000+
GriST	Yes	Primary and secondary care psychiatry records, multiple locations	
Public Health England Mental Health Dementia and Neurology Intelligence Network	Yes	Regional study from mixed administrative sources	
Qresearch GP database	No	Database of national sample of primary care providers (600 practices)	Approx. 12m
The Health Improvement Network (THIN)	No	Database of national sample of primary care providers	Approx. 10m
UK Biobank	No	National sample of volunteers with record-linkage to administrative data	500,000+
Secure Anonymised Information Linkage (SAIL)	No	Linked data from variety of sources for Welsh population	Approx. 3m
PsyCymru	Yes	E-cohort of psychosis cases linked to SAIL	12,000

Source : Adapted from Stewart and Davis *"'Big data' in mental health research : current status and emerging possibilities*" Soc Psychiatry Psychiatr Epidemiol (2016) 51:1055-1072

2.2 Record-linkage

Record-linkage, also known as *data matching*, is a discipline with a long history which predated the computer age and is described by Christen (2012). The appeal of linking patient medical records with other types of information is well understood within epidemiology. Within psychiatric research, routine clinical data has been employed in some of the earliest studies of asylum records through to the growth of 'case register' series in the middle part of the twentieth century (Stewart and Davis, 2016). However, early studies were often linked between records 'by hand' and were cumbersome and time consuming as well as prone to matching and other errors. With the development of Electronic Health Records (EHRs) larger volumes and varieties of information are now accumulated than would have been conceivable in traditional epidemiological research, posing both a tremendous transformative research opportunity and a considerable technical challenge to investigators.

The term *record linkage* was coined by Dunn in 1946 (Dunn, 1946) as a proposal for a *'Book of Life'* for every individual, which would start with birth records, link to educational, health, marriage and social security records and end with death records, and would provide a solid foundation to plan services, research public health and improve national statistics. At an early stage, Dunn recognised the potential challenges of variability within the data, including errors and difficulties providing reliable linkage for records of individuals with common names. The idea of using computers to automate and standardise the data matching process was proposed by Newcombe et al. (1959) who also utilised a distinction between (a)*deterministic record linkage* which is a wholly automatic process where a fixed criterion (such as a combination of name, birth date, gender and postcode; or a unique identifier number) is used to link individuals, and (b)*probabilistic record linkage* where statistical

techniques are used to apply probabilistic weights within an algorithm, to determine the likelihood that records relate to the same individual.

For example, the relative likelihood that a pair of records belong to the same individual can be made using the calculation of probability weights (Fellegi and Sunter, 1969) based on the founding principle of frequency ratios (Fleming et al., 2012; Newcombe et al., 1959). In comparing two records, an algorithm can be used to compute a weighted score proportional to the probability that the records belong to the same person. The '*m probability*' measures the reliability, quality, accuracy and stability of a variable and the probability that a given identifier will agree for a pair of records that truly belong to the same individual. The *'u probability*' is the probability that a given variable will randomly match across two records(Fleming et al., 2012; Mason and Tu, 2008). Varying levels of positive and negative weight are produced based on the levels of agreement or disagreement between an identifier and two records being compared. Once a weight is calculated for each variable in the linkage process, the sum of all weights for all variables utilised is made to provide an overall weight for the record pairing, which is then used to determine if the threshold for a link has been met.

Deterministic record linkage is fast but depends on the ability to define linkage criteria of sufficient granularity to be truly discriminatory, which may be difficult across wide ranges of datasets. Probabilistic record linkage allows multiple data sets, where there may not be a unique identifier, to be integrated. However, it is a statistically complex method which requires significant clerical review to minimise error rates.

More recently, another important research area within record linkage has been that of *data cleaning*, especially the eradication of duplicate records and the processing of variables into an appropriate form for statistical analysis. Another important principle, especially for sensitive health data, is that of *privacy-preserving record linkage,* whereby the need for exchange of private and confidential data between organisations involved in data matching is minimised.

The accurate and deterministic linkage of data is significantly aided in those countries which have utilised an unique identification number for its health and other records. The Nordic European countries are relatively well-known for this, allowing large population-based register record-linkage studies in Sweden, Denmark and Finland (Hargreaves et al., 2015). As will be discussed below, Scottish studies have also been able to apply these techniques through the existence since the 1970s of an unique Community Health Index (CHI) number for every individual registered to a GP practice in Scotland. This is a 10-character code consisting of the patient's date of birth (in six-digit format), two assigned digits, a digit which is odd for males and even for females, and an arithmetical check digit.

An advantage of record-linkage of administrative data to large population-based cohorts is that such studies potentially offer much larger patient numbers, wider parameters of study, and longer timescales of follow-up, than are typical of randomised control trials (RCTs) or standard cross-sectional or cohort studies (Hafferty et al., 2017). A further advantage of record-linked administrative health data is that it necessarily arises out of naturalistic clinical settings, in terms of both clinical practice and patient health and comorbidity, thereby obviating one of the criticisms of the RCT, the 'gold standard' of medical research, which can be prone to unrealistically

overly-strict exclusion criteria. Routine clinical data sets can, therefore, be complementary to RCT data, while also making research findings more relevant to everyday clinical practice. In addition, the quantity of clinical 'big data' potentially allows analysis of rarer clinical conditions, or subject areas that would be unlikely to meet ethical approval for more conventional studies (for example, medication usage in pregnancy). 'Big data' record-linked studies thereby potentially provide the scale and breadth of patient numbers required for stratified, predictive and personalised medicine research.

Such methods do, however, have important drawbacks. As discussed, an important consideration in the use of 'Big Data' is *veracity* of data. It is important to remember when employing record-linkage to administrative data that this data has not usually been collected with consideration for its use in research. It may indeed have factors in the recording of information which introduce biases or errors for research studies. For example, when using data employing diagnostic codes (such as the International Statistical Classification of Diseases 10th Revision, ICD-10, (World Health Organisation, 2017)) the coding is likely to have been inputted by an administrator rather than a clinician, and the necessity to input codes in a highly structured format often means that underlying clinical uncertainties are not accurately reflected in the coding (and there is often no supplementary clinical information to draw on in later research). This can be a particular challenge in psychiatry, as a number of important diagnoses are relatively under-recognised in clinical records, including dementia, major depression and anxiety, although their recognition and reporting is improving in recent years (Stewart and Davis, 2016).

2.3 Privacy and Research Governance in Record-Linkage Studies

Additional important considerations in record-linkage studies are public trust, ethics, privacy and clinical data governance. This area is arguably under-researched. Privacy, informed consent, data stewardship, and the long-term ownership of data by academic and commercial entities are becoming ever more pertinent issues as the pace of data accumulation increases. Data collected from individuals with psychiatric illnesses may come with additional privacy concerns as attitudes research suggests that mental health data are among the most personal and sensitive (Taylor and Taylor, 2014).

It is important, however, that legitimate concerns about privacy do not inadvertently create an excessively restrictive regulatory environment. There is a critical role for policymakers in striking the right balance between privacy and realising the research potential of big data, as was recently illustrated in the debate regarding what become the EU General Data Protection Regulation (GDPR) in the research community (Mittelstadt and Floridi, 2016). The MRC Farr Institute, the European Data in Health Research Alliance, and Patients4Data group have all promoted the importance of data sharing for research and health-care improvement while acknowledging the potential risks of inaccurately recorded information and data breaches (McIntosh et al., 2016b).

Within this context, it is encouraging that the majority of mental health service users agree to the use of their health records for research, especially when they are provided with appropriate communication and opportunity for informed consent about use and potential benefits (McIntosh et al., 2016b). The UK Biobank model of consent

is a good example of public willingness to consent to multiple uses of their data for research purposes (Russ et al., 2019).

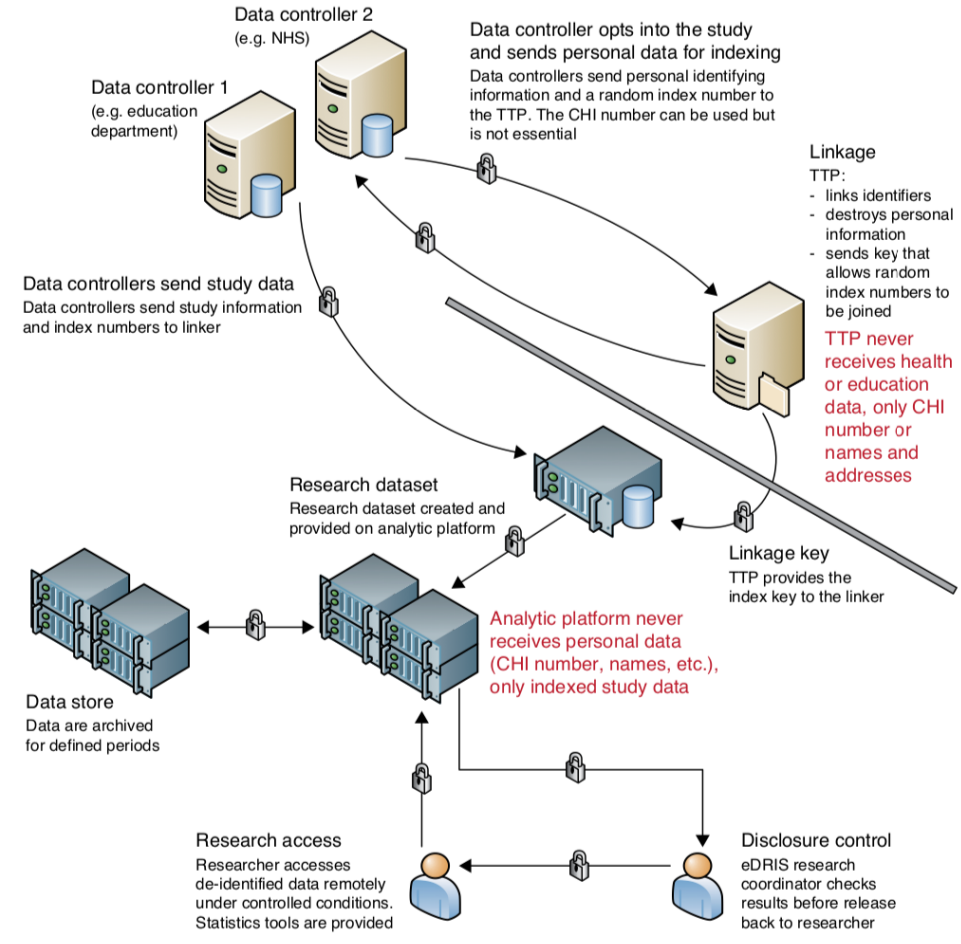
However, this has to be weighed against the relatively low response rate for population-based cohort studies, even very large ones. For example, in UK Biobank approximately 9.2m individuals were invited but only 5.45% (approximately 500,000) were recruited(Fry et al., 2017). Also, there was evidence of a “healthy volunteer” selection bias (participants were less likely to be obese, to smoke, drink alcohol and had lower all-case morbidity and mortality than found in the general population). This has led to calls for caution in terms of the generalizability and external validity of findings that might not apply to the target population(Keyes and Westreich, 2019).

2.4 Health Data-Linkage Studies in Scotland

Scotland is one region of the UK where research governance procedures for linked data have been particularly well established (Figure 2.2**)**. There are several reasons why this is the case. Firstly, through the existence of the ten-digit Community Health Index (CHI) number, which covers between 96.5-99.9% of the Scottish population of 5 million, and which allows for pseudonymised data linkage between a variety of health records from birth to death as discussed (Figure 2.3) (Pavis and Morris, 2015). Secondly, Scotland possesses and has developed over considerable time a robust research governance framework, underpinned by the Scotland Data Protection Act 1998 and overseen in the health research sphere by the Privacy Advisory Committee (PAC), which also mandates significant public input for review of grant applications. Thirdly, Scotland possesses a network of safe and transparent repositories of clinical data involving the Scottish branch of the Farr Institute of Health Informatics Research

(involving a consortium of six Scottish universities and the NHS), and National Service Scotland (NSS) Information Services Division (ISD) and its associated National Safe Haven (https://www.isdscotland.org/Products-and-services/Edris/Use-of-the-National-Safe-Haven/). Finally, further support to researchers is provided by an eData Research and Innovation Service (eDRIS) to help researchers navigate the system and understand which data is available and the access procedures involved (Pavis and Morris, 2015).

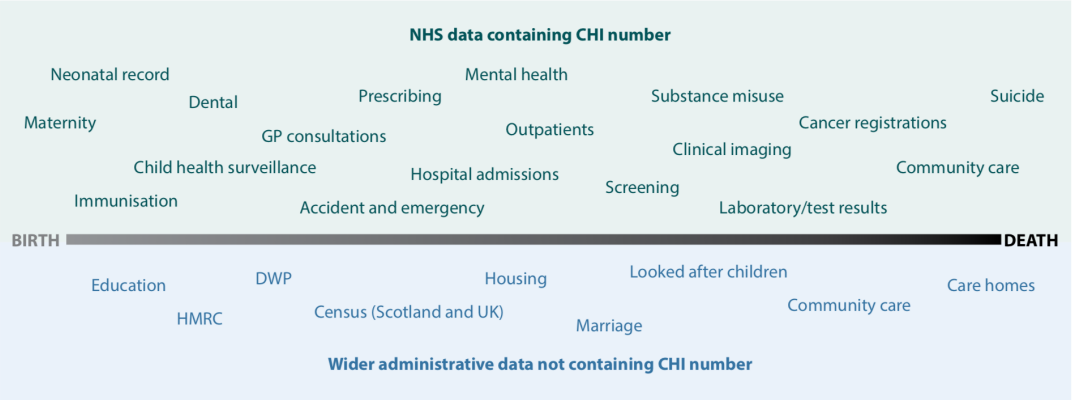
Figure 2.2 The 'Scottish Model' of Data Linkage using the Principle of Separation of Functions, from Pavis and Morris (2015)



CHI = Community Health Index; eDRIS = eData Research and Innovation Service; NHS = National Health Service; TTP = trusted third party

Source: Pavis S and Morris AD, *"Unleashing the power of administrative health data: the Scottish model"* Public Health Research & Practice. September 2015. Vol 25(4):e2541541

Figure 2.3 Scottish national-level data resources which employ the CHI number, from Pavis and Morris (2015)



CHI = Community Health Index; DWP = Department for Works and Pensions; HMRC = HM Revenue and Customs; NHS = National Health Service

Source: Pavis S and Morris AD, *"Unleashing the power of administrative health data : the Scottish model"* Public Health Research & Practice. September 2015. Vol 25(4):e2541541

2.5 Record-Linkage to Administrative Data and Psychiatric Research

The research literature of computer-based record-linkage studies in psychiatry dates back to the 1970s (Baldwin, 1971). An early application of the technique was the linking of death registers to psychiatric medical records to investigate suicide in psychiatric patients (Barner-Rasmussen et al., 1986; Black et al., 1985). Making use of the availability of deterministic linkage via Swedish personal identification numbers, linkage between inpatient registers with diagnostic information and cause-of-death registries enabled one of the first large scale (N=8895) analyses of predictors for completed suicide (Allgulander and Fisher, 1990), although the authors commented that the lack of detailed psychological and sociodemographic phenotyping constrained the specificity and utility of the predictors found. Such studies were extended to investigate other causes of potentially avoidable mortality in the psychiatric population by linking community health records to local mortality databases (Amaddeo et al., 2007).

A pioneering record-linkage study comparing self-reported use of mental health services with administrative healthcare records as 'gold standard' was performed in 36,892 individuals in Ontario, Canada. It found that there were significant discrepancies in those (mostly depressed) individuals self-reporting mental health service use and the usage ascertained from their records (Rhodes and Fung, 2004). This was an early attempt to utilise record-linkage as a means of validating self-reported research variables (see Chapter 4).

Using the Oxford Record Linkage study, which collated brief abstracts of medical and psychiatric hospital contacts and mortality in the former Oxford NHS Region 1963-1999, Goldacre et al. conducted an innovative study exploring the potential link between major depression (and anxiety) and development of cancer (Goldacre et al., 2007). The study demonstrated a potential link between depression and brain and lung cancers (smoking was not controlled for and the authors pointed out this was likely to be significant), but the risk ratios for other cancers was not significant (0.98, 95% Confidence Interval 0.92-1.04). A large Canadian record-linkage study (N=247,344) linking primary care and mental health records with oncology and death registries found evidence of increased cancer mortality in the mentally ill although this was not evidently due to increased incidence (Kisely et al., 2008).

The potential for utilising record-linkage to ICD coding in physician billing and hospital discharge abstracts for the purposes of ascertaining psychiatric disease prevalence was employed in a Canadian study which was able to thereby estimate the prevalence of mood and/or anxiety disorders in four Canadian provinces as between 8-10%. The authors commented that administrative data provided an economical and useful tool for disease surveillance, but that the lack of specificity in disease coding

and data capture limited the granularity of the estimates (Kisely et al., 2009). By linking patient registers to national prescribing databases, researchers were able to make similar prevalence estimates for use of psychiatric medication. A Norwegian study employing this technique found a significant increase in antidepressant use among the adolescent population 2004-2013 (Hartz et al., 2016).

In 1996, Womersley published an opinion piece arguing for greater use of the Community Health Index (CHI) number for record-linkage studies based in Scotland (Womersley, 1996). An early initiative was the foundation of the Medicines Monitoring Unit (MEMO) in Tayside, a university-based organization that used record-linkage to construct an observational pharmaco-epidemiological and pharmaco-vigilance database of 400,000 people (Evans et al., 2001). Using this population, MacDonald and colleagues conducted an early study of antidepressant usage and the duration of antidepressant episodes which indicated that – at this time – many doses and treatment durations for TCAs and SSRIs were probably sub-therapeutic (MacDonald et al., 1996). Chapter 5 provides a significant update to this early research making use of CHI-based record-linkage to Scottish prescribing data, in a population-based cohort including the Tayside population.

2.6 Concluding Remarks

In this chapter I have charted the evolution of record-linkage from a relatively labour intensive and small-scale practice undertaken at the local hospital level to the massively scaled, computer-based and nationally applicable technology which exists today. Future developments of this technology include more sophisticated data mining, machine learning and Bayesian modelling approaches as will be discussed in Chapter 7.

The success of record-linkage research depends upon the fidelity of the data linkage and also on the quality and depth of the datasets being thereby connected. In the next chapter I will overview the population-based cohorts and nationally based administrative databases that will be employed in the research chapters of this thesis.

Chapter 3: Profiles of Cohorts and Datasets

3.1 Introductory Remarks

In this chapter I will review the two main cohorts that will be utilised in this study, which are Generation Scotland (and including the follow-on STRADL re-contact study) and UK Biobank. I will also survey the main administrative health datasets that will be employed for record-linkage purposes, the Scottish Morbidity Records and Prescribing Information System. Some of this information will be repeated, as appropriate, in the Methods sections of the research chapters which follow, although this chapter is dedicated to a move general overview of the datasets which will be used herein.

3.2 Generation Scotland : Scottish Family Health Study (GS:SFHS)

Generation Scotland:Scottish Family Health Study (GS:SFHS) is a population- and family-based epidemiology study (N=21,474), with socio-demographic, clinical and genetic phenotyping. A full cohort profile is provided in Smith et al. “Cohort Profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness” *International Journal of Epidemiology* 2013: 42:689-700 (Smith et al., 2006; Smith et al., 2013a).

A list of General Practices willing to participate in GS:SFHS was generated with General Practice involvement being assisted by the Scottish Practices and Professionals Involved in Research (SPPIRe) network(Smith et al., 2006). An

independent party, based in the NHS, generated a list of eligible people registered with each collaborating general practice, by utilising the Community Health Index (CHI) number (randomisation technique not stated). The names of all potential participants were then screened by their GP, and individuals who it would be inappropriate to approach (e.g. terminal illness, unable to consent to research) were excluded(Smith et al., 2006). Letters of invitation to eligible participants were then generated on practice-headed notepaper and signed by one of the GP principals. These letters were then dispatched by an independent party and up to two reminders were permitted. The invitation was for agreement to discuss the study with family members with a view to potential involvement. If the contacted person returned the consent slip, their name and contact details would be provided to the research team.

In the UK, 96% of the population is registered with a GP and thus this recruitment method was favoured for recruiting a population-based sample. Invitations to participate were blinded to health status.

Potential participants were invited to the study and also to identify at least one first-degree relative (aged 18+) who would also participate. Nominated first-degree relatives could be from any location. The first recruitment phase (2006-10) involved potential participants aged 33-65 years and at least one nominated first-degree relative (aged 18+) from GP practices in Glasgow and Tayside areas of Scotland. In the second phase (2010-2011) the study was extended to include Aryshire, Arran and North-eastern Scotland, and the age of potential participants was broadened to 18-65 years (invited relatives remaining aged 18+).

In total, 126,000 potential participants were invited and 12.3% volunteered and met study criteria. Not all participants were recruited, for logistical reasons or due to failure to recruit additional family members, leaving a total recruitment of 6665 (5.3% overall response rate). An additional 1288 individuals volunteered directly (age >18 years and at least one additional relative who agreed to participate). A further 16,007 family members associated with these invited participants and volunteers were also recruited, giving a total of 23,960.

A total of 21,474 individuals attended Generation Scotland research clinics in Glasgow, Dundee, Perth, Aberdeen or Kilmarnock. Prior to their appointment they completed a pre-clinic questionnaire. At the clinic appointment, a variety of measures were taken by trained clinic staff. This included screening for emotional and psychiatric problems using the structured clinical interview for DSM-IV disorders (SCID) (99.6% of cohort completed) (First et al., 2002). In the case of positive screening, the mood sections of the SCID were then completed (18.8% completed).

Psychological traits of neuroticism and extraversion were self-reported using the Eysenck Personality Questionnaire Short-Form Revised (99.4% completed) (Eysenck et al., 1985), consisting of twenty four questions with total scores on each subscale ranging from 0-12. Four groups of cognitive tests measuring intelligence were also administered during the clinic assessment. Processing speed was measured by the Wechsler Digit Symbol Substitution Task (98.8% completed) (Wechsler, 1958). Verbal declarative memory was measured using one paragraph from the Wechsler Logical Memory Test I & II (98.7% completed) (Wechsler, 1945). Vocabulary was measured using the Mill-Hill Vocabulary Scale (98.2% completed) (Raven, 1958), using combined junior and senior synonyms. Executive function was

measured using a Verbal Fluency Test employing phonemic lists of C, F and L (Wechsler, 1958) (99.3% completed).

Psychological distress was self-reported using the General Health Questionnaire (GHQ-28), involving the scoring of 28 questions concerning recent psychological symptoms from 0 (*"not at all"*) to 3 *("much more than usual*") with total scores ranging from 0 to 84 (Goldberg and Hillier, 1979), higher scores indicating greater psychological distress. Socioeconomic deprivation was measured using the Scottish Index of Multiple Deprivation (Payne and Abel, 2012) which is an official tool utilised by the Scottish government which scores deprivation by combining different indicators (e.g. income levels, crime levels) into a single index. The SIMD (in this thesis the 2012 version of SIMD is used) divides Scotland into 6505 small geo-zones (called datazones) with roughly equal populations, based on participant postcode. Each datazone is assigned a relative ranking from 1 (most deprived) to 6505 (least deprived). The Scottish population is 5.45m (2019) and thus a typical datazone would contain 838 people. Rural datazones would be significantly larger geographically than urban ones.

Written informed consent was also obtained for 98% of GS:SFHS for data linkage to routinely collected health records and only those individuals who provided consent were used in this study.

3.3 STRADL

In 2015, a project entitled 'STRADL: Stratifying Resilience and Depression Longitudinally' was launched to re-contact participants from GS:SFHS. The purpose

of the study was to obtain additional information (by questionnaire) from GS:SFHS participants regarding their mental health (especially presence of Major Depressive Disorder), and additional psychological measures relevant to psychological resilience (the ability to maintain psychopathological health despite exposure to known risk factors) (Luthar et al., 2006). A full cohort profile is provided in Navrady et al. "Cohort Profile : Stratifying Resilience and Depression Longitudinally (STRADL): A questionnaire follow-up of the Generation Scotland: Scottish Family Health Study (GS:SFHS)" *International Journal of Epidemiology* (2017) (Navrady et al., 2018).

Individuals were eligible to be re-contacted for the STRADL study if they (i) had originally taken part in GS:SFHS (ii) had a Community Health Index (CHI) number, thereby enabling record linkage to administrative health data (iii)were alive and living in Scotland (iv) had given informed consent for re-contact. On this basis, 21,525(89%) of GS:SFHS participants were eligible for recontact and all were sent a questionnaire booklet by an independent party. In total 785 completed an online questionnaire and 8833 returned a paper copy (total STRADL respondents 9,618, 45%) (Navrady et al., 2018).

STRADL respondents also consented to the use of their data for *'future medical research into health, illness and medical treatment*' on the basis that this data would remain anonymous and be added to that already securely held as part of the GS:SFHS study. All components of STRADL received formal, national ethical approval from NHS Tayside Committee on Research Ethics (Reference 14/SS/0039).

The STRADL cohort was predominantly female (62%, compared to 59% for GS:SFHS and 52% for Scottish population) with a mean age of 50.48 (SD=13.41)

(Navrady et al., 2018) (mean age Scottish population 38). Compared to the Scottish population, the STRADL cohort was generally healthier and wealthier and better educated. The prevalence of having a degree qualification was 37% (Scottish population 33%) and having no qualifications was 5% (Scottish population 33%). The average SIMD was 4123 compared to a Scottish population average of 3252. 18% were retired compared to a Scottish population average of 15.1%, and 71% were in employment compared to a Scottish population average of 62.8%(Smith BH, 2012). Nevertheless, the cohort contained significant representation from all the Scottish Index of Multiple Deprivation (SIMD) strata.

STRADL participants completed the Composite International Diagnostic Interview - Short Form (CIDI-SF) (Kessler, 1998). The CIDI-SF is a self-report questionnaire (by contrast with the SCID used in GS:SFHS, which is scored by a researcher). The CIDI-SF is based on DSM-IV (American Psychiatric Association, 2003) criteria for Major Depressive Disorder as part of a larger Composite International Diagnostic Interview developed by the World Health Organization (Robins et al., 1988). CIDI-SF employs two symptomatic screening questions related to low mood or anhedonia, with a minimum of four other symptoms requiring endorsement to meet criteria for caseness. In the entire STRADL cohort, 16% of respondents met the CIDI-SF criteria for lifetime history of MDD (N=1,506) and a further 16% of these individuals reported being currently depressed (Navrady et al., 2018).

With regard to psychological measurements, the General Health Questionnaire-28 (Goldberg and Hillier, 1979), also used in GS:SFHS, was repeated in STRADL. Responses were scored using the Likert method (0-3), with higher scores representing greater levels of psychological distress. Psychological resilience was

scored using the Brief Resilience Scale (Smith et al., 2008). Coping styles employed in response to stress (defined and discussed further in Chapter 6) were self-reported using the Coping Inventory for Stressful Situations (CISS) (Endler, 1990) which categorised coping styles along three distinct scales : task-oriented, emotion-orientated and avoidance-oriented coping (see Chapter 6 for further details). Self-report was also obtained of experience of twelve common and threatening life events that may have occurred in the previous six months and the contextual response to these (List of Threatening Experiences, LTE, (Brugha et al., 1985).

3.4 UK Biobank

UK Biobank (UKB) is a population-based cohort (N=502,682) recruited across the UK in 2006-10. UKB consists of adults aged between 40 and 69. UK Biobank was recruited by the investigators sending 9,238,453 postal invitations to individuals registered with the National Health Service and living within approximately 25 miles of one of 22 assessment centres located in England, Wales and Scotland(Fry et al., 2017).

The average age in UK Biobank was 56.52 years (UK mean age 40.2 in 2019). The proportion of females was 54.4% (UK proportion of females 51.2%). The proportion unemployed was 6.9% (UK proportion unemployed 2020 4.8%). The proportion with college education or above was 47.1% (UK 2018 proportion 49%). The proportion with no qualifications was 14.5% (UK 2015 figure 8.4%). The average Townsend Deprivation Index (see below) was -1.29 (UK mean score 0)(Hewitt et al., 2016; Zhang et al., 2021). Note that these comparisons are influenced by the age restriction in UK Biobank to 40-69.

Like GS:SFHS, UKB contains biological, physical, socio-demographic, psychological, cognitive and mental health data, much of which was collected by a touch-screen questionnaire (Smith et al., 2013b).

In UK Biobank, lifetime history of depression was ascertained using self-reported lifetime history of depressive symptoms and contact with mental health services (for an overview of the methodology see Smith et al. (2013b).

Neuroticism was assessed using the same Eysenck Personality Questionnaire Short Form-Revised (EPQ-SF) (Eysenck, 1985) as also used in GS:SFHS, assessed using 12 questions administered via touch-screen questionnaire.

Cognitive ability was also measured using a touch-screen questionnaire. This consisted of measurements of bespoke indicators of reaction time (mean response over 12 trials), verbal-numerical reasoning (number of correct answers within 2 minutes) and visual memory (number of errors when matching card pairs) (Smith et al., 2013b).

Measurement of socio-economic deprivation was also made in UK Biobank, using the Townsend Deprivation Index (Townsend, 1987). This consists of a single index of a variety of factors (including household overcrowding, unemployment, and non-home ownership) within small geographical zones based on postcode information.

3.5 Scottish National Prescribing Information System

The Scottish National Prescribing Information System (PIS) is an NHS data system which is managed by NHS National Services Scotland (NHS NSS). It is described comprehensively in Alvarez-Madrazo et al. “Data Resource Profile : The Scottish National Prescribing Information System (PIS)” *International Journal of Epidemiology* (Alvarez-Madrazo et al., 2016).

PIS provides for NHS prescriptions prescribed, dispensed and reimbursed within the community (i.e. does not include hospital-dispensed prescriptions). These prescriptions are written by a wide variety of practitioners, including General Practitioners (GPs), dentists, nurse prescribers, pharmacists, hospital doctors and non-medical prescribers.

PIS covers the entire geography of Scotland with its population of 5.3 million people. Summary information on reimbursed medicines has been available via PIS since 1993 but from April 2009 individual-level prescribing and dispensing data is available. Data linkage to PIS is made possible through the Community Health Index (CHI) number. New prescribing data is uploaded to PIS on a monthly cycle and usually made available approximately two months after the prescription was dispensed to the patient. As of 2014, PIS contained records of 507 million individual items prescribed and 344 million items dispensed since 2009 (Alvarez-Madrazo et al., 2016).

The availability of fine-grained patient-level data within PIS is described by the CHI capture rate, and has attained almost 100% coverage for prescribed and dispensed items within PIS, excluding only those who have an invalid CHI number (Alvarez-

Madrazo et al., 2016). Prescriptions are free in Scotland, and records show that in the calendar year 2014 in excess of 70% of men and 85% of women had at least one prescription reimbursed.

PIS records a variety of data about each prescription. This includes patient-level data, such as the CHI number, age, gender and SIMD socio-economic ranking. Prescriber data includes the profession and location where the prescription was written, and some demographic data of the associated GP practice if applicable. Dispenser data includes the type and geographical location of dispensing practice. Drug/medication data includes the approved name of the medication (normally listed using the International Non-proprietary Names (INN) standard), product name, formulation and strength of medication. Quantity of medication is expressed as the number of tablets (for example) supplied and the corresponding World Health Organisation Defined Daily Doses (WHO, 2011), a standard for making comparisons of typical daily doses within medication types. Each medication is also identifiable and searchable via its British National Formulary (Joint Formulary Committee, 2012) structured code.

It is important to state that the *indication* for medication usage is not recorded in PIS, although some basic assumptions can be made using the BNF structured code (which differs, for example, when a medication such as duloxetine is used as an antidepressant versus being used for urinary incontinence).

In accordance with research information governance procedures, PIS data is provided to researchers via the electronic Data Research and Innovation Services (eDRIS) using pseudo-anonymised extracts (i.e. CHI numbers replaced by unique study numbers and other personal identifiers removed). The specific PIS variables

included with the extract are tailored to the individual research project and must be specifically justified within the study grant and application to the Privacy Advisory Committee (PAC), which oversees the process. The PIS extracts undergo significant data cleaning processes, including more than 10 stages of quality checking (Alvarez-Madrazo et al., 2016) before they are released to researchers for further data checking and cleaning.

Over-the-counter (OTC) medication sales are not recorded in PIS, unless the medication is supplied in community pharmacies under specific schemes such as the Minor Ailments Service (MAS). The vast majority of OTC medications utilised by patients are therefore not included in PIS.

3.6 Scottish Morbidity Records

Healthcare data for Scottish NHS patients is collected by Information Services Division (ISD) Scotland as a series of Scottish Morbidity Records (SMR) which provide a continuum of data from birth to death. In this respect Scotland has some of the best health service data in the world, combining high levels of data integrity and consistency, nationwide coverage, and ability to securely record-link for research purposes (Information Services Division, 2019). Patient-identifiable records of hospital discharges, cancer registrations and deaths have been held in central systems in Scotland since 1968 and have been further computerised since the 1980s (Fleming et al., 2012).

At present there are two main permanently linked data sets held by ISD Scotland: (1)the Scottish Morbidity Database, containing records related to non-obstetric

hospital contacts plus cancer and death registrations since 1980/81; and (2)the Maternity and Neonatal Linked Database, containing mother and baby records since 1975. Records for individual patients are completed and submitted by hospitals and NHS boards to ISD Scotland who record-link and securely maintain them. Record-linkage is performed on the basis of deterministic CHI-linkage and probability matching techniques based on surname, full forename and first initial, sex, date of birth and postcode (Fleming et al., 2012). Utilising the two techniques prevents errors that might arise from using CHI-linkage alone, where problems can be caused by CHI mis-coding, or an individual having multiple CHI numbers in error. The methodology employed to probabilistically record-link SMR records includes 'blocking' whereby only those record pairs which share a minimum amount of initial similarity are subjected to the matching process (Kendrick, 1997).

SMR01 is an episode-based record of all inpatient and day cases discharged from non-psychiatric, non-obstetric hospital wards in Scotland (i.e. acute hospital admissions). These records have been available in computerised form since 1968 but the current SMR01 records are from 1981 to the present. A new record is formed each time a patient is discharged from hospital, transferred to a new hospital or a different hospital department, or changes consultant responsible for care. Over 1.5 million records are created annually (Scottish Public Health Observatory, 2019). SMR01 is used to plan the financial management of hospitals, but curated releases of this data are also available to researchers using CHI-based data linkage. SMR01 contains information of a clinical and non-clinical nature for each record, including duration of admission, admitting department, diagnostic information utilising ICD-10 coding (World Health Organisation, 2017) (and in older records ICD-9) and details of any operations or procedures. The completion of SMR01 records is often delegated

to clerical staff who are not routinely supervised by clinicians. As a result, regular quality assessments are undertaken by Information Services Division (ISD) Scotland to maintain quality assurance of the records.

SMR00 is an episode-based based record of all outpatients receiving care when an outpatient clinic is attended (whether in hospital clinic, nurse run clinic or outpatient session at the patient's home). SMR00 contains details of the patient's identifier (CHI based), date of attendance, specialty code of hospital specialty (which includes medicine, surgery and psychiatry specialities) and related ICD-10 diagnostic codes.

SMR04 is an episode-based counterpart to SMR01, but detailing inpatients and day cases discharged from psychiatric hospitals in Scotland (1981-present). A new record is created for any new admission, transfer to another hospital or transfer to new consultant. Diagnoses are based on ICD-10 coding and include a list of admission diagnoses and discharge diagnoses.

Maternity records are detailed in SMR02 (Scottish Maternity Record) which collects data on inpatient and day case discharges within obstetrics and covers 98% of all births and pregnancies in Scotland (Scottish Public Health Observatory, 2019) from 1975 to the present. Birth records detailing all a baby's neonatal care are included in the Scottish Birth Record (SBR) and in its forerunner, SMR11, which operated from 1975 to 2002.

SMR06 is the Scottish Cancer Registry which contains information about Scottish residents diagnosed with tumours (malignant and some benign) from 1980 to the present. The registry began in 1956 and since 1997 has been fully electronic,

recording details of tumour stage, grade and treatment information as well as sociodemographic data.

The Scottish Drug Misuse Database (SDMD, SMR25) is an SMR-related dataset which is also curated by ISD Scotland, which provides systematic recording of clients seen at services from drug misuse. The database includes diagnostic information (ICD-10) for each record, as well as details of related prescriptions, contact with services, illicit drug profile, injecting/sharing details and sociodemographic information.

Since 1st January 2000, deaths in Scotland have been coded in accordance with ICD-10 and have been stored in a database of deaths that is available with SMR records.

Access to the data within the Scottish Morbidity Records requires compliance with the information and data governance infrastructures of the Scottish NHS, to maintain public confidence in secondary use of data. The SMR data is quality assured and held in the Information Services Division (ISD) on behalf of NHS Scotland. The ISD is a branch of a special Health Board in NHS Scotland, named National Services Scotland(NSS). It is in turn regulated by the UK Statistics Authority. Release of data must be compliant with legislation including the Data Protections Act(1998), Human Rights Act(1998), Freedom of Information Scotland Act (2002) and the General Data Protection Regulation (2018)(Murray, 2019).

The Privacy Advisory Committee (PAC) is an advisory committee to the NSS Board and Registrar General of Scotland, which is responsible for confidentiality, data protection and information governance of SMR. Applications to access the SMR data

must go through the PAC. It is an important principal of PAC applications that the data requested is justified and is no more than is required to complete the research. Once PAC approval has been gained, the ISD will begin to compile and release the data. Any further data releases, or requests for additional data, require further permissions from the PAC. This can cause some practical difficulties and delays for research studies that are looking to take a longitudinal approach, and certainly prevents 'near real time' data upload as has been developed with CRIS. The ISD also requires a period of some months to compile and quality check the SMR data. Annual releases of data in a rolling manner became possible in 2019, but any further changes require additional PAC approval.

3.7 Concluding Remarks

This chapter has summarised the population-based cohorts and datasets of administrative health data that will be utilised in the research chapters to follow. It is clear that the Scottish provenance of GS:SFHS and the existence of the Scottish CHI number as a basis for linkage provided an unique opportunity for psychiatric linked data research, as the forthcoming research chapters will hopefully show. As record-linkage technology and governance processes develop over time, the potential to utilise these methods on other large cohorts and datasets such as UK Biobank, CPRD and CRIS will surely grow, as will be discussed further in Chapter 7.

In the following three research chapters, I return to the objectives stated in Chapter 1, which are to address the following questions :

1. Are users of psychiatric medications less likely to accurately self-report their usage in research studies compared to users of other medications?
2. Has exposure to antidepressant medications significantly increased in recent years and, if so, is this due to a change in how antidepressants are used ?
3. Is the psychological trait of neuroticism an independent risk factor for the MDD-associated outcomes of antidepressant use and self-harm ?

I will begin by addressing the first of these objectives in the next chapter.

Chapter 4 : Validating Pharmacoepidemiological Research Data using Record-Linkage

4.1 Introductory Remarks

In Chapter 2, we saw that a major potential application of record-linkage to administrative health data in psychiatric research is *validation*. Cohort studies depend on complete and accurate ascertainment of potential risk factors and outcomes of interest in order to reach meaningful conclusions. For many research variables there can be considered a "gold standard" approach which ensures maximum fidelity for the research data (such as detailed patient interview by a trained professional or exhaustive survey of medical notes) but such methods are often so resource intensive to be rendered impractical, particularly for very large studies and/or over large periods of time. Resultantly, more practical approaches to phenotyping, such as self-report (discussed in Chapters 1 and 2) are often utilised. However, self-report is subject to a range of potential biases and researchers need a means to be confident about its veracity.

In this chapter I will demonstrate the utility of routinely collected national prescribing data for the validation of self-reported medication usage in the cohort GS:SFHS. Participants were asked to self-report their regular usage of a number of common medication types, including two psychiatric classes (antidepressants and mood stabilizers) which are commonly used in major depression and other affective disorders. Concerns have been raised about the quality of self-report of medications in general (potentially due to factors such as participant recall errors) and psychiatric medications in particular (potentially due to factors such as respondent bias and self-stigma) (Van den Brandt et al., 1991; Cotterchio et al., 1999; Knudsen, 2002). The

ability to link the participants of GS:SFHS to national prescribing data via the Prescribing Information System (PIS) provided a significant opportunity to validate the medication self-report, using prescribing data as the 'gold standard'.

The following chapter has been published in the *Journal of Clinical Epidemiology* (Hafferty et al., 2018). As the first author of the publication I jointly conceived the study, performed the analysis, wrote the manuscript and prepared all the tables and figures. To acknowledge the contribution of the co-authors (see also Publications section of this thesis for breakdown of author contributions) the term "we" rather than "I" is used throughout this chapter.

4.2 Paper: Self-Reported Medication Use Validated Through Record Linkage to National Prescribing Data

4.3 Abstract

4.3.1 Objective

Researchers need to be confident about the reliability of epidemiological studies that quantify medication use through self-report. Some evidence suggests that psychiatric medications are systemically under-reported. Modern record linkage enables validation of self-report with national prescribing data as gold standard. Here, we investigated the validity of medication self-report for multiple medication types.

4.3.2 Study Design and Setting

Participants in the Generation Scotland population-based cohort (N=10,244) recruited 2009-11 self-reported regular usage of several commonly prescribed medication classes. This was matched against Scottish NHS prescriptions data using three- and six-month fixed time windows. Potential predictors of discordant self-report, including general intelligence and psychological distress, were studied via multivariable logistic regression.

4.3.3 Results

Antidepressants self-report showed very good agreement (κ=0.85, (95% Confidence Interval (CI) 0.84-0.87)), comparable to antihypertensives (κ=0.90, (0.89-0.91)). Self-report of mood stabilizers showed moderate-poor agreement (κ=0.42 CI 0.33-0.50). Relevant past medical history was the strongest predictor of self-report sensitivity, whereas general intelligence was not predictive.

4.3.4 Conclusion

In this large population-based study, we found self-report validity varied among medication classes, with no simple relationship between psychiatric medication and under-reporting. History of indicated illness predicted more accurate self-report, for both psychiatric and non-psychiatric medications. Although other patient-level factors influenced self-report for some medications, none predicted greater accuracy across all medications studied.

4.3.5 What is New In This Study

- Self-reported medication use shows high validity in the general population although there is variation between medication classes.
- A simple relationship between psychiatric medications and under-reporting was not found. Mood stabilizers show moderate-poor agreement, due to both under-report and false positives, whereas antidepressant reporting is comparable to other long-term non-psychiatric medications.
- Medical history of an indicated health condition is the strongest predictor of accurate report. General intelligence was not associated with the accuracy of reporting.
- Medication-related factors such as range of indications, prescribing cycles, and phrasing of self-report question may also influence accuracy of self-report.
- When matching self-report to prescribing data, longer fixed time windows produce higher levels of agreement and positive predictive values, at the expense of some loss of sensitivity.

4.4 Introduction

Cohort studies, and other epidemiological studies using self-reported data, depend on the accuracy of the self-report to make accurate and reliable conclusions. This includes pharmaco-epidemiological and large-scale biobanking studies which are based on self-reported medication use. Self-reported medication use can be determined by questionnaire (Lokkegaard et al., 2004; Rauma et al., 2013); by telephone or internet survey (West et al., 1995); or by face-to-face interview (Nielsen et al., 2008; Goodman et al., 1990; Sjahid et al., 1998; Norell et al., 1998). However, self-report is subject to recall errors and biases (Klungel et al., 2000; Cotterchio et al., 1999) and patients may be less willing to disclose details of certain medications than others.

The accuracy of self-report can be verified by comparison to a trusted measure or "gold standard". For medication utilization, the choice of gold standard depends to an extent on the purpose of the study (i.e. estimating patient adherence, or monitoring prescribing behaviour of clinicians), and there is therefore no universally applicable and accepted gold standard (Kwon A, 2003) (Klungel et al., 1999). One option is for a third party to perform a home inventory (Lau et al., 1997) or record individual medications produced by the patient (Caskie et al., 2006), but these assessments are difficult to perform on a large scale. An alternative is to compare self-report data to prescriptions, healthcare insurance claims, or general practice medical records (Goodman et al., 1990; Monster et al., 2002; Nielsen et al., 2008; Klungel et al., 1999). Prescribing databases have been shown to be highly accurate in recording medication utilization (Tamblyn et al., 1995), at least for those medications that require prescriptions.

Among published studies comparing medication self-report to prescribing data, the majority have been relatively small in size (Nielsen et al., 2008; Caskie et al., 2006; Haukka et al., 2007; Lau et al., 1997; Saunders et al., 1998; Jain et al., 1999; Klungel et al., 1999; Kwon A, 2003; Norell et al., 1998; Sjahid et al., 1998). Many studies are restricted to certain medications or medication types, such as antihypertensives (Klungel et al., 1999); cardiovascular drugs (Sjahid et al., 1998); antidepressants (Saunders et al., 1998), or hormone replacement therapy (Lokkegaard et al., 2004); or to special populations, such as the elderly (Lau et al., 1997; Sjahid et al., 1998; Tamblyn et al., 1995); postmenopausal women (Goodman et al., 1990; Rauma et al., 2013); or psychiatric illnesses (Haukka et al., 2007). Few studies utilize large population-based samples (Monster et al., 2002; Nielsen et al., 2008; Caskie et al., 2006; Haapea et al., 2010) or multiple disparate medication types (Caskie et al., 2006; Haapea et al., 2010; Noize et al., 2009; Richardson et al., 2013). Such comparisons are important, however, for they enable study of systematic over- and under-reporting of medication utilization between drug classes.

Self-report can be compromised by a number of factors, including not understanding the question, poor recall, and intended non-disclosure (Nielsen et al., 2008). There is no consensus on patient-level factors predisposing to discordance between medication self-report and gold standard measures, but previous reports have implicated advancing age (Cotterchio et al., 1999; Haapea et al., 2010), being unmarried (Haapea et al., 2010; Richardson et al., 2013), number of medications regularly dispensed (Van den Brandt et al., 1991; Jain et al., 1999), suffering poor health (Haapea et al., 2010), and lower educational attainment (Richardson et al., 2013). Within medication classes, there is some evidence that psychiatric

medications are less likely to be accurately self-reported (Haapea et al., 2010; Van den Brandt et al., 1991). Potential explanations for this include confusion regarding medication indication but also non-disclosure due to social desirability bias (Cotterchio et al., 1999) or self-stigmatization (Knudsen, 2002; Nielsen et al., 2008; Rauma et al., 2013; Kwon A, 2003). Factors that have not to date been found to influence reporting include gender (Richardson et al., 2013; Haapea et al., 2010) and cognitive health (Richardson et al., 2013).

Prescribing data can be sourced from local health providers or insurers (Kwon A, 2003), pharmacy records (Caskie et al., 2006; Monster et al., 2002; Saunders et al., 1998; Klungel et al., 1999; Sjahid et al., 1998; Richardson et al., 2013), social insurance databases (Haukka et al., 2007; Haapea et al., 2010) or national health service databases (Nielsen et al., 2008; Rauma et al., 2013; Lokkegaard et al., 2004). The recording of the dispensing and collection of medication, as well as its prescribing, is important for studies that seek to measure patient utilization (although even collection of a medication is not a hard indicator of usage). The country of origin of the study, and respective prescription legislation, dispensing and reimbursement practices, are also relevant to interpreting self-report against prescribing data (for example, over-the-counter medications may not appear in this data), and to making comparisons between national studies.

In this study, we sought to ascertain agreement between medication self-report, derived from a large UK cohort study, compared to record-linked national prescribing data as gold standard, across a range of commonly used psychiatric and non-psychiatric medications. We hypothesised that agreement would be lower for psychiatric medication types, due to systemic under-reporting. To our knowledge this

is one of the largest population-based studies of medication self-report also incorporating a covariate analysis method across a range of medications.

4.5 Method

4.5.1 Study Population

Our study utilized the Generation Scotland: Scottish Family Health Study (GS:SFHS) family- and population-based cohort of Scottish adult volunteers (n=21,474), recruited February 2006-March 2011, which has been described elsewhere(Smith et al., 2006; Smith et al., 2013a). The cohort has a higher proportion of females (59%) and older median age (47 males: 48 females) than the Scottish population at the 2001 census (37 and 39 respectively) (Smith BH, 2012; Smith et al., 2013a). Written informed consent was obtained for 98% of GS:SFHS for data linkage to routinely collected healthcare records.

4.5.2 Medication Self Report Data

All participants in GS:SFHS were asked to complete a pre-clinic questionnaire prior to their enrolment in the study. The first phase of the study used a text-based questionnaire which is not part of this analysis. Those individuals recruited between June 2009 – March 2011 (n=10,980, 59.5% female) completed a coded questionnaire where the Medications section was a "Yes" versus "No" checkbox, with the accompanying question "*Are you regularly taking any of the following medications?*". The available options were: (1) "*Cholesterol lowering medication (e.g. Simvastatin)*" (2) "*Blood pressure lowering medication*" (3) "*Insulin*" (4) "*Hormone replacement therapy*" (5) "*Oral contraceptive pill or mini pill*" (6) "*Aspirin*" (7)"*Antidepressants*"

(8)“*Mood stabilizers*”. The completed questionnaires were then machine read and electronically recorded using anonymised patient linkers.

4.5.3 Additional Covariate Data

Additional sociodemographic information collected in the questionnaire included gender, age, educational attainment, smoking status and relationship status. Compared to the rest of GS:SFHS, our sample was moderately older and contained more individuals with no school qualifications and also more degree level educated individuals (Table 4.1, Figure 4.1). Lifetime history of affective disorder (major depression and bipolar disorder) was obtained using the Structured Clinical Interview for DSM-IV Disorders (SCID) (Smith et al., 2013a). Self-reported history of hypertension, heart disease and diabetes was recorded.

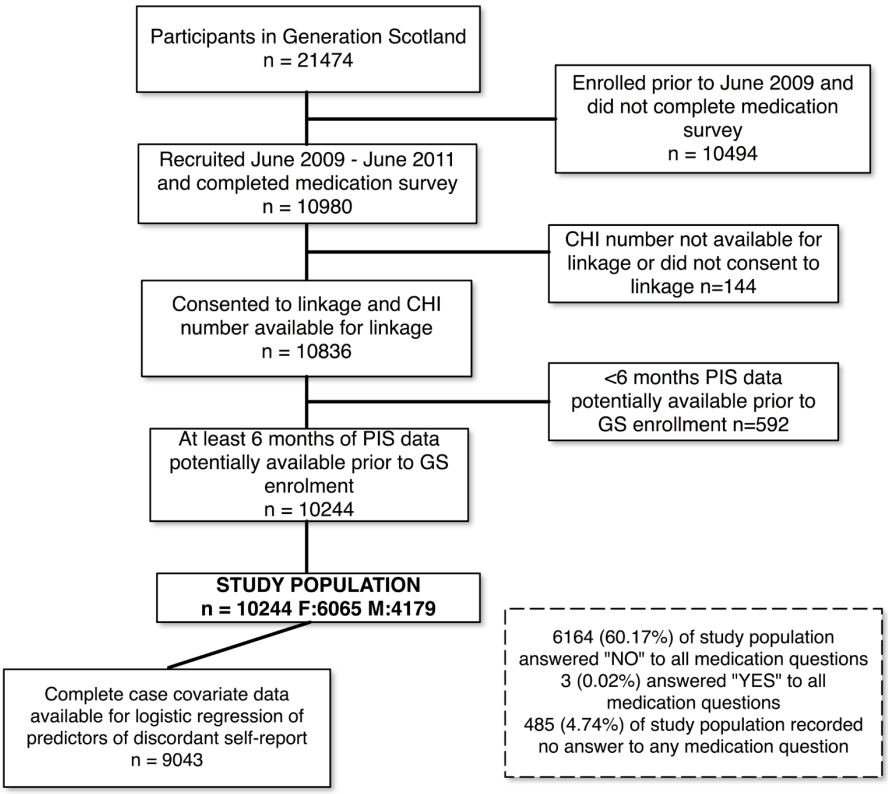
In addition, during the GS interview a variety of cognitive tests were performed (Smith et al., 2006). including (1) Digit Symbol Coding substitution task from the Wechsler Adult Intelligence Scale III (Wechsler D, 1998b),a screening instrument for neuropsychological dysfunction and processing speed with impairment of contributing ability yielding a low score (max score 133, typical range 24-116)(Habota et al., 2019); (2) Logical memory from the Wechsler Memory Scale III (Wechsler D, 1998a) which measures immediate and delayed recall of one paragraph (max score for combined test 50, typical range 9-48); (3) Mill-Hill Vocabulary Test (maximum score 44, typical range 16-44) which is used as a measure of acquired verbal intelligence; (4) Controlled Oral Word Association task(Verbal Fluency Test) which measures executive function through word generation using letters C, F and L each for one minute (no maximum score, typical range 12-88) (Lezak MD, 1995).

From these tests, we derived a measure of general intelligence (*g*) as the first un-rotated principle component, explaining 44% of the variance in scores (Navrady LB, 2017; Marioni et al., 2014). The loadings for processing speed, vocabulary, verbal declarative memory and executive function on the first principal component were 0.44, 0.53, 0.49 and 0.54 respectively. The range of *g* in the cohort was -4.48 to 8.92, mean 0.0, standard deviation 1.28. Psychological distress was measured using the General Health Questionnaire-28 (Likert scoring, maximum score 84) (Goldberg and Hillier, 1979).

4.5.4 Prescribing Data and Linkage

All Scottish citizens registered with a General Practitioner (more than 96% of the population) are assigned a unique identifier (Community Health Index (CHI) number). This was employed to record link GS:SFHS questionnaire data to the national Prescribing Information System (PIS) administered by NHS Services Scotland Information Services Division (Alvarez-Madrazo et al., 2016). PIS is a database of all Scottish NHS prescriptions for payments for medications prescribed by GPs; nurses; dentists; pharmacists; and hospitals where the medication was dispensed in the community. There is no prescription charge in Scotland. Hospital dispensed prescriptions and over-the-counter medications are not included. Patient level data has been available in PIS since April 2009 (Information Services Division, 2014). We obtained PIS prescribing data for April 2009-March 2011. We used the dates of dispensing, not prescription, when matching to self-report.

Figure 4.1. Flowchart of derivation of study population, and subset used in logistic regression analysis, from the Generation Scotland cohort.



Abbreviations : GS = Generation Scotland; PIS = Prescribing Information System; CHI = Community Health Index

Table 4.1. Socio-demographic, clinical and cognitive characteristics of study populations compared to whole Generation Scotland cohort.

	GS:SFHS (N=21474)	**Individuals in the current study** (N=10244)	**Subset of individuals in current study used in complete case multivariate logistic regression analysis** (N=9043)
Female	12674 (59.02%)	6065 (59.21%)	5329 (58.9%)
Age 18-39	6769 (31.52%)	3072(29.99%) †	2797(30.93%) ‡
Age 40-64	12346 (57.49%)	6015 (58.72%) †	5304(58.65%)
Age 65-99	2359 (10.99%)	1157(11.29%)	942(10.42%)
Affective Disorder (SCID)	2848 (13.26%)	1329 (12.97%)	1159 (12.82%)
Diabetes (Self-Report)	659 (3.07%)	323 (3.15%)	277 (3.06%)
Hypertension(Self-Report)	2836 (13.21%)	1297 (12.66%) †	1125 (12.44%)
Cardiac Disease(Self-Report)	777 (3.62%)	345 (3.37%) †	284 (3.14%) ‡
No School Certificate	2452 (11.42%)	1432 (13.98%) †	1296 (14.33%) ‡
Postgraduate Education	6323 (29.44%)	3273 (31.95%) †	3164 (34.99%) ‡
Smoker	3662 (17.05%)	1733 (16.92%)	1484 (16.41%) ‡
Relationship Status – Single	6720 (31.29%)	3236 (31.59%)	2866 (31.69%) ‡
GHQ Likert Score	*16 (8.87)*	*15.73 (8.74)* †	*15.66 (8.69)* ‡
Wechsler Logical Memory Test I &II	*30.7 (8.48)*	*30.95(8.15)*	*31.17 (8.05)* ‡
Mill-Hill Vocabulary Test	*30.06 (4.76)*	*30.09 (4.66)*	*30.23 (4.62)* ‡
Wechsler Digit Symbol Substitution Task	*72.23 (17.22)*	*71.71 (17.15)* †	*72.52 (16.88)* ‡
Verbal Fluency Test	*39.71 (11.72)*	*39.89 (11.70)* †	*40.22 (11.65)* ‡

Abbreviations: GS:SFHS, Generation Scotland : Scottish Family Health Study. GHQ, General Health Questionnaire.
All values are totals with percentages, unless shown in italics where they are means with standard deviations in parentheses.
† = Significant differences (alpha=0.05) between Generation Scotland and Study Population as determined by Chi square / t tests.
‡ = Significant differences (alpha=0.05) between Study Population and subset used in multivariate logistic regression analysis as determined by Chi square / t tests.

4.5.5 Matching Prescribing to Self-Report

For each individual and medication type, concordance with GS:SFHS self-report was checked against PIS prescribing record dispensing dates within a "fixed time window" (Nielsen et al., 2008; Rauma et al., 2013; Monster et al., 2002; Haukka et al., 2007) including the month of questionnaire completion, and two months preceding (total three months), and also five months preceding (total six months). The majority of prescriptions, including in Scotland, are dispensed in quantities of 90 days duration or less (Reid I, 2012; Caskie et al., 2006). A previous Dutch study (Lau et al., 1997) also found that fixed time windows shorter than 90 days are less sensitive, although the generalizability of this finding is uncertain. Accordingly, we employed two fixed time windows, three- and six-months duration, in order to assess their relative benefits in terms of agreement, sensitivity and positive predictive value.

To ensure all individuals had at least six months of potentially available prescribing records, we restricted analysis to GS:SFHS participants who had completed their medication questionnaire in September 2009 or later. This equated to 10,244 participants (6065 females and 4179 males) enrolled September 2009-March 2011 (Table 4.1, Figure 4.1). Of these, 96.5% had medication records available (the remainder were presumably not using prescribed medication) which compared to 95.6% for the whole GS cohort.

The PIS data allows medications to be identified by approved drug name and/or associated British National Formulary (Joint Formulary Committee, 2012) paragraph code. Medication indication is not recorded. Our matching criterion for each medication type is detailed in Table 4.2.

Table 4.2: Matching and exclusion criteria used for prescribing database searches.

Self-Reported Medication	*Matching criteria used in PIS*	*Exclusion criteria*
Cholesterol lowering medication (e.g. simvastatin)	BNF Paragraph code "212000".	
Antihypertensives	BNF Paragraph codes "205051" (ACE inhibitors); "205052" (Angiotensin II antagonists); "204000" (beta blockers); "206020" (calcium channel blockers); "202010" (thiazides and aldosterone antagonists); "202020" (loop diuretics); "202030" (potassium sparing diuretics); "205040" (alpha adrenoceptor blocking drugs); "202040" (combined K sparing diuretics); "205010" (vasodilator antihypertensive drugs); "205020" (centrally acting hypertensives); "205053" (renin inhibitors)	Records containing : "amiloride hydrochloride", "bumetanide", "eplerenone", "sotalol hydrochloride", "amiloride hydrochloride with bumetanide", "co-amilofruse", "triamterene with furosemide", "sildenafil", "clonidine hydrochloride" [These medications are not specifically indicated for hypertension]
Insulin	BNF Paragraph codes "601011" and "601012"	
Hormone replacement therapy	BNF Paragraph codes "604011"	
Oral contraceptive pill or mini pill	BNF Paragraph codes containing "^7030*"	BNF Paragraph codes "703050" (emergency contraceptives); "703040" (spermicidals); "703030" (contraceptive devices)
Aspirin	Prescribable Item Approved Name containing "aspirin"	Formulations containing aspirin as additional ingredient
Antidepressants	BNF Paragraph codes containing "^4030*": "403010" (tricyclic antidepressants), "403020"(monoamine oxidase inhibitors), "403030"(selective serotonin reuptake inhibitors) and "403040"(other antidepressant drugs).	Records containing: "amitriptyline" [An antidepressant which is no longer commonly prescribed for depression in the UK and which is often used short-term for other indications]
Mood stabilizers	Prescribable Item Approved Name containing : "lithium"; "carbamazepine"; "lamotrigine"; "valproate"; "amisulpride"; "olanzapine"; "aripiprazole"; "risperidone"; "quetiapine"	

4.5.6 Missing Data

The self-report questionnaire employed a 'Yes'/'No' checkbox, but some individuals ticked neither box (or data was otherwise missing, Table 4.3). In our main analysis we treated each medication separately, excluding the missing self-report values for each case. However, to mitigate the potential of hereby introducing biases, or not accounting for individuals who intended to deny medication use by leaving the section blank, we conducted two additional analyses – one with all individuals with any missing data excluded (n=7836), and the other with missing data coded as denial of medication use (Table 4.5).

4.5.7 Statistical Analysis

All analyses were carried out using R version 3.2.3 (R Core Team, 2015). Level of agreement between self-report and prescribing data was ascertained using Cohen's kappa (κ) method of rating inter-observer variation (Cohen, 1960). Kappa scores of <0.40 were considered fair to poor; 0.41-0.60 moderate; 0.61-0.8 substantial; and >0.81 good or better (Viera and Garrett, 2005; Landis JR, 1977). We also calculated sensitivity, specificity and positive predictive values (PPV). Ninety five percent confidence intervals (CI) were included.

We performed multivariable logistic regression analysis on predictors of false negative self-report compared to true positive (sensitivity). Due to some covariate missing data, the sample size of this analysis was reduced to 9043 for complete case

analysis (Table 4.1, Figure 4.1). Odds ratios with 95% CI were calculated. Multiple testing was adjusted for using the False Discovery Rate method with significance level (alpha) 0.05. As Generation Scotland is a partly family-based cohort, we adjusted for any correlation due to family relatedness using the Generalized Estimating Equations method (Hanley et al., 2003).

4.6 Results

Of the 10,244 individuals in the study, 6164 (60.17%) ticked 'No' to every medication question (Figure 4.1). In addition, 485 (4.74%) left blank or had missing data for every question. The proportion of completed responses differed between medications and was greatest for antihypertensives (86.44%) and lowest for mood stabilizers (77.87%, χ^2 =256.07, $p<2.2x10^{-16}$) (Table 4.3). The most commonly prescribed medication (six-month window) was antihypertensives, prevalence 19.05%, whereas antidepressants prevalence was 12.22% and mood stabilizers 1.32%. The prevalence of lifetime history of affective disorder in our sample was 12.66% (n=1297) for major depressive disorder and 0.31% for bipolar disorder (n=32). The self-reported prevalence of hypertension was 12.66% (n=1297), heart disease 3.37% (n=345) and diabetes 3.15% (n=323) (Table 4.1)

Table 4.3. *Medication self-report and prescribing data prevalences, agreements, sensitivities, specificities and positive predictive values, measured on two fixed time windows – 3 months and 6 months duration respectively – in the current study (n=10,244, including 6065 females)*

				3 MONTH FIXED TIME WINDOW				***6 MONTH FIXED TIME WINDOW***			
	Total (n) completed question, with Yes or No (%)	**Medication prevalence according to self report (%)**	**Medication prevalence according to PIS (%)***	**Agreement κ (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive predictive value (95% CI)**	**Agreement κ (95% CI)**	**Sensitivity (95% CI**	**Specificity (95% CI)**	**Positive predictive value (95% CI)**
Antidepressant**	8333 (81.35)	9.60	10.10	**0.84** (0.82-0.86)	**0.90** (0.87 – 0.92)	**0.99** (0.99-0.99)	**0.90** (0.87-0.92)	**0.85** (0.84-0.87)	**0.85** (0.82-0.87)	**0.99** (0.99-0.99)	**0.89** (0.87-0.91)
Mood stabilizer ***	7977 (77.87)	1.17	1.32	**0.40** (0.31-0.49)	**0.41** (0.31-0.52)	**0.99** (0.99-0.99)	**0.41** (0.31-0.52)	**0.42** (0.33-0.50)	**0.40** (0.31-0.50)	**0.99** (0.99-1.00)	**0.45** (0.35-0.56)
Cholesterol lowering medication	8789 (85.80)	13.97	13.81	**0.92** (0.91-0.94)	**0.97** (0.96-0.98)	**0.98** (0.98-0.99)	**0.90** (0.88-0.92)	**0.95** (0.94-0.96)	**0.97** (0.95-0.97)	**0.99** (0.99-0.99)	**0.95** (0.94-0.97)
Antihypertensive	8855 (86.44)	16.85	19.05	**0.90** (0.89-0.91)	**0.89** (0.87-0.91)	**0.99** (0.99-0.99)	**0.95** (0.94-0.96)	**0.90** (0.89-0.91)	**0.86** (0.85-0.88)	**1.00** (0.99-1.00)	**0.98** (0.97-0.98)
Aspirin	8445 (82.44)	9.28	7.63	**0.81** (0.78-0.83)	**0.97** (0.95-0.98)	**0.97** (0.97-0.98)	**0.72** (0.68-0.75)	**0.84** (0.82-0.86)	**0.95** (0.93-0.96)	**0.98** (0.97-0.98)	**0.78** (0.75-0.81)
Insulin	8016 (78.25)	1.11	0.97	**0.87** (0.82-0.93)	**1.00** (0.92-1.00)	**1.00** (1.00-1.00)	**0.78** (0.67-0.86)	**0.93** (0.89-0.97)	**1.00** (0.93-1.00)	**1.00** (1.00-1.00)	**0.88** (0.79-0.94)
HRT (female only)	*4794 (79.04)	5.97	4.59	**0.62** (0.57-0.68)	**0.92** (0.87-0.96)	**0.97** (0.96-0.97)	**0.49** (0.43-0.55)	**0.78** (0.74-0.82)	**0.91** (0.86-0.94)	**0.98** (0.98-0.98)	**0.70** (0.64-0.75)
Oral contraceptives (female only)	*4849 (79.95)	14.62	12.79	**0.55** (0.51-0.59)	**0.82** (0.78-0.86)	**0.92** (0.91-0.92)	**0.47** (0.43-0.51)	**0.73** (0.70-0.76)	**0.82** (0.79-0.85)	**0.95** (0.95-0.96)	**0.72** (0.68-0.75)

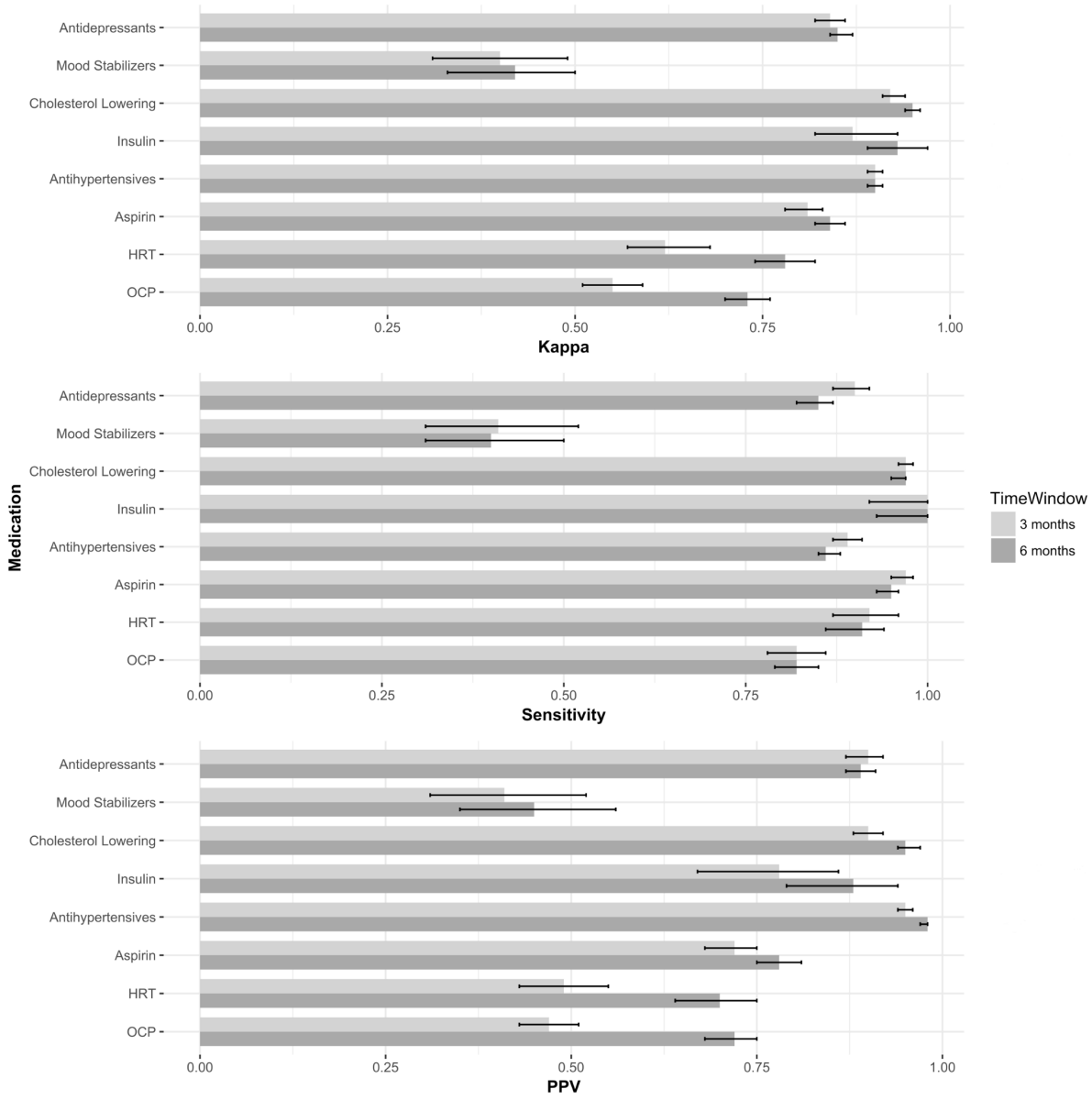
Abbreviations : PIS, Prescribing Information System. HRT, Hormone Replacement Therapy

** Six month time window employed*

*** Note that a broader definition of antidepressant than that shown in table, which included amitriptyline, returned an agreement of κ=0.83(0.81-0.85) at six month time window with sensitivity of 0.75(0.73-0.78)*

**** Note that a narrower definition of mood stabilizer than that shown in table, which comprised only lithium, sodium valproate, lamotrigine and carbamazepine, returned an agreement of κ=0.29(0.20-0.38) at six month time window with sensitivity of 0.21(0.22-0.43)*

Figure 4.2. Agreement and Validity of Medication Self-Report Compared With Prescribing Data As Gold Standard Using Three And Six Month Fixed Time Windows, With 95% Confidence Intervals



Abbreviations : PPV = Positive Predictive Value; HRT = Hormone Replacement Therapy; OCP = Oral Contraceptive Pill.

4.6.1 Agreement and Validity

Agreement (Table 4.3, Figure 4.2) between medication self-report and prescribing data was generally very good across medication classes. Greatest agreement was found for cholesterol lowering medication (κ=0.95, CI 0.94-0.96) (6-month fixed time window unless otherwise stated). Agreement for antidepressants (κ=0.85, CI 0.84-0.87) was lower than antihypertensives (κ=0.90, CI 0.89-0.91) but still within the highest kappa banding of >0.81. By contrast, agreement for mood stabilizers was moderate-poor (κ=0.42, CI 0.33-0.50). Comparing the six-month fixed time window to three-month, κ scores were higher, although only to a degree beyond 95% confidence intervals in the case of HRT and oral contraceptives.

Self-report sensitivity (Table 4.3, Figure 4.2) was slightly reduced in the six-month time window versus three-month, but was still greater than 0.80 for all medications except mood stabilizers. Antidepressant sensitivity (0.85, CI 0.82-0.87) was comparable to antihypertensives (0.86, CI 0.85-0.88). Sensitivity for mood stabilizers was comparatively poor (0.40, CI 0.31-0.50) indicating a high rate of false negatives.

The positive predictive value (Table 4.3, Figure 4.2) for antidepressant use (0.89, CI 0.87-0.91) was substantial, albeit less than antihypertensives and cholesterol lowering drugs, and contrasted with modest PPV for mood stabilizers (0.45 CI 0.35-0.56). The six-month fixed time window significantly improved PPV for most medication groups, with greatest effect for HRT and oral contraceptives (which nevertheless showed relatively moderate PPV in both time windows).

4.6.2 Predictors of Failure To Self-Report Medication Usage

Multivariable logistic regression (Table 4.4) found no covariates universally associated, across all medications, with failure to self-report medication usage, as determined by the prescribing data gold standard. General intelligence (*g*) was not associated with increased false negatives for any medication. Psychological distress (GHQ) reduced odds of false negatives for antidepressants (OR 0.98, CI 0.96-1.00, p_{FDR} 0.081) and mood stabilizers (OR 0.96 CI 0.91-1.01, p_{FDR} 0.197), but this relationship was not significant for multiple testing.

There was reduced discordant self-reporting for several medications if the patient had a history of an illness for which that medication was indicated, such as affective disorder and mood stabilisers (OR 0.09, CI 0.02-0.35 p_{FDR} 0.005), and hypertension and antihypertensives (OR 0.04, CI 0.02-0.06 p_{FDR}>0.001). Similar associations were found for affective disorder and antidepressants, and cardiac disease and aspirin, with p values of <0.1 after correcting for multiple testing.

Age and gender showed no consistent association, although older age was associated with lower false negatives for antihypertensives, antidepressants and possibly aspirin (p_{FDR} 0.074), and female gender was associated with increased false negatives for antihypertensives (OR 1.75, CI 1.16-2.62, p_{FDR} 0.020).

Table 4.4. Odds Ratios (with 95% Confidence Intervals) For Factors Associated With Failure To Self-Report Medication Use (False Negatives) As Determined By Prescribing Data As Gold Standard

	Anti-depressants	Mood stabilizers	Cholesterol lowering medication	Antihyper-tensives	Aspirin	Oral contra-ceptives (females only)
Female sex	0.67 (0.42-1.09)	0.75 (0.24-2.33)	1.62 (0.80-3.30)	**1.75 (1.16-2.62)**	1.14 (0.52-2.48)	-
Age	**0.97 (0.95-0.99)**	0.96 (0.91-1.02)	0.95 (0.92-0.99)	**0.94(0.92-0.96)**	*0.94 (0.90-0.99)*	1.01 (0.98-1.04)
Affective disorder	*0.55 (0.35-0.87)*	**0.09 (0.02-0.35)**	0.72 (0.22-2.42)	0.82 (0.47-1.44)	0.70 (0.19-2.51)	1.31 (0.69-2.49)
Diabetes	-	-	0.42 (0.13-1.40)	**0.30 (0.13-0.70)**	-	-
Hypertension	-	-	*0.28 (0.11-0.71)*	**0.04 (0.02-0.06)**	0.49 (0.23-1.06)	-
Heart disease	-	-	0.30 (0.07-1.25)	0.82 (0.45-1.50)	*0.15 (0.03-0.65)*	-
No school certificate	0.60 (0.26-1.32)	**17.0 (2.3-125.84)**	0.45 (0.12-1.72)	0.66 (0.37-1.17)	0.88 (0.28-2.82)	0.65 (0.07-5.89)
Higher education	1.17 (0.70-2.00)	1.27 (0.25-6.35)	1.63 (0.65-1.09)	0.85 (0.54-1.34)	1.27 (0.44-3.64)	1.41 (0.80-2.49)
Smoker	0.90 (0.52-1.54)	0.12 (0.02-0.082)	1.30 (0.45-3.76)	*1.84 (1.09-3.11)*	1.58 (0.59-4.21)	*1.98 (1.13-3.46)*
Ex-Smoker	0.66 (0.38-1.11)	0.44 (0.10-2.00)	1.32 (0.59-2.92)	1.40 (0.93-2.12)	0.71 (0.28-1.81)	1.18 (0.65-2.14)

	Anti-depressants	Mood stabilizers	Cholesterol lowering medication	Antihyper-tensives	Aspirin	Oral contra-ceptives (females only)
Relationship status – couple	0.89 (0.56-1.41)	2.03(0.59-7.01)	1.31 (0.58-2.97)	0.96 (0.63-1.47)	0.91 (0.40-2.08)	0.78 (0.48-1.28)
General intelligence (g)	0.85 (0.70-1.04)	0.76 (0.46-1.26)	0.85 (0.65-1.11)	1.02 (0.85-1.21)	1.17 (0.83-1.66)	0.92 (0.74-1.15)
Psychological distress (GHQ Likert)	*0.98 (0.96-1.00)*	0.96 (0.91-1.01)	0.99 (0.95-1.04)	0.99 (0.97-1.01)	1.00 (0.95-1.04)	1.02 (0.99-1.04)

Significant associations are shown in **bold** (alpha=0.05 and adjusted for multiple testing by False Discovery Rate method) and near-significant associations (alpha <0.10) are shown in *italics.*
The following factors were used as controls and do not appear in the table : male sex; age 18-39; secondary school education only; no affective disorder found on SCID; no history of self- reported high blood pressure/heart disease/diabetes; smoking status –never smoked; relationship status –single.
Insulin and hormone replacement therapy (HRT) are not shown in the table as no significant associations with predictors were found.

4.6.3 Influence of Missing Data

Recoding missing data as negative self-report (Table 4.5) resulted in somewhat lower levels of agreement and lower sensitivities for all medications. However, agreement remained good for antidepressants (κ=0.81 CI 0.79-0.83) and poor for mood stabilisers (0.34 CI 0.26-0.41). There was a demonstrable reduction in sensitivity for antidepressants (0.78 CI 0.75-0.80) but this reduction was not confined to psychiatric medications, being found also in antihypertensives (0.79 CI 0.77-0.81).

Table 4.5.

Comparison of Agreement (Cohen's kappa), Sensitivity and Positive Predictive Value with prescribing data for study population with:

(A) missing self-report medication data recoded as medication denied

(B) all records with any missing self-report medication data excluded

	A. All missing data recoded as medication denied, Six-month fixed time window (N=10,244)			**B.** Complete cases analysis with all missing data of medication responses excluded, Six-month fixed time window (N=7836)		
	Agreement κ	**Sensitivity**	**Positive Predictive Value**	**Agreement κ**	**Sensitivity**	**Positive Predictive Value**
Antidepressants	**0.81** (0.79-0.83)	**0.78** (0.75-0.80)	**0.89** (0.87-0.91)	**0.78** (0.75-0.81)	**0.73** (0.69-0.77)	**0.86** (0.82-0.89)
Mood stabilizers	**0.34** (0.26-0.41)	**0.28** (0.21-0.36)	**0.45** (0.35-0.56)	**0.29** (0.19-0.40)	**0.24** (0.15-0.35)	**0.39** (0.25-0.54)
Cholesterol lowering medication	**0.94** (0.93-0.95)	**0.93** (0.92-0.95)	**0.95** (0.94-0.97)	**0.93** (0.92-0.95)	**0.92** (0.89-0.94)	**0.96** (0.93-0.97)
Antihypertensives	**0.85** (0.84-0.86)	**0.79** (0.77-0.81)	**0.98** (0.97-0.98)	**0.82** (0.80-0.84)	**0.74** (0.70-0.77)	**0.97** (0.96-0.98)
Insulin	**0.91** (0.87-0.96)	**0.95** (0.88-0.99)	**0.88** (0.79-0.94)	**0.92** (0.86-0.98)	**1.00** (0.86-1.00)	**0.86** (0.72-0.95)
HRT (female only)	**0.76** (0.72-0.80)	**0.85** (0.80-0.90)	**0.70** (0.64-0.75)	**0.76** (0.70-0.82)	**0.84** (0.76-0.90)	**0.71** (0.62-0.78)
Contraceptive (female only)	**0.72** (0.69-0.75)	**0.79** (0.76-0.82)	**0.72** (0.68-0.75)	**0.71** (0.67-0.74)	**0.77** (0.73-0.81)	**0.71** (0.67-0.75)
Aspirin	**0.82** (0.80-0.85)	**0.90** (0.88-0.93)	**0.78** (0.75-0.81)	**0.80** (0.76-0.84)	**0.88** (0.83-0.91)	**0.77** (0.70-0.80)

4.7 Discussion

In this population-based cohort, we found substantial to very good agreement between medication self-report and electronic prescribing records, for most medications studied. We hypothesised that psychiatric medications would show less agreement and systematic under-reporting. Agreement for mood stabilizers was indeed considerably worse, although we found evidence of both under- and over-reporting (false positives). However, for antidepressants the agreement, sensitivity and PPV were broadly comparable to other medications studied. We did not identify any generalizable single predictors of failure to self-report prescribed medications, for psychiatric medications or for medications generally. However, past medical history of an indicated health condition showed the strongest effect in promoting self-report accuracy across classes, and this was also true for psychiatric medications.

In general, the six-month fixed time window outperformed the three-month for agreement and PPV, at the expense of modest loss of sensitivity. This was most evident for HRT and oral contraceptives in women, which could imply these medications are dispensed in longer time cycles, and require longer fixed time windows, relative to other medications.

4.7.1 Predictors of Discordant Self-Report

We found that a medical history of an indicated health condition for a given medication, such as affective disorder for mood stabilizers, or hypertension for antihypertensives, reduced the odds of false negatives. If systematic under-reporting of psychiatric medications due to self-stigma was taking place, we might have

expected to find the reverse. Relationship status and educational status did not predict discordance, except in the case of mood stabilizers where lack of school qualifications was associated with false negative reporting. This could indicate reduced understanding of the definition of "mood stabilizer" among the less educated. It might also represent association between lesser educational achievement and use of medications (such as antipsychotics) included in our definition of mood stabilizers.

We found that general intelligence (*g*) did not influence concordance of medication self-report with prescribing data, which to our knowledge has not been previously reported. We also believe we are the first to investigate psychological distress and medication self-report. Interestingly, while psychological distress might be posited as a potential factor in under-reporting psychiatric medications (e.g. through self-stigma), we found some evidence of a relationship between the increased GHQ score and greater sensitivity of self-reporting of antidepressants ($p<0.1$). Gender was not generally associated with accuracy, except in the case of antihypertensives, where increased odds of false negatives (OR 1.75 CI 1.16-2.62) were found, perhaps indicating greater usage of these medication types for non-antihypertensive purposes among females.

4.7.2 Questionnaire Phrasing

One possible explanation for the poor agreement, sensitivity and PPV for mood stabilizers is confusion among questionnaire respondents about the meaning of "mood stabilizer". There is no consensus definition of mood stabilizer among clinicians (Bauer and Mitchner, 2004) and laypersons may therefore be unsure as to its meaning. Klungel et al. (2000) have previously reported that sensitivity of

medication self-report is influenced by the specificity of question phrasing. In our matching to prescribing data we employed a broad definition of mood stabilizers, but when a narrower definition (excluding antipsychotics) was employed the agreement was even worse (κ=0.29, CI 0.20-0.38).

4.7.3 Comparison with Other Studies

Table 4.6 describes the agreement of this present study, using the 6-month fixed time window, with other large published studies. We report a higher level of agreement (κ=0.86) for antidepressants than Nielsen (κ=0.66) (Nielsen et al., 2008), Rauma (κ=0.65) (Rauma et al., 2013) and Noize (κ=0.81) (Noize et al., 2009). When making comparisons with studies performed in other healthcare systems, it is important to recognise the variations between countries in prescribing legislation and access to medication. Scotland has a national health system, with no prescription charges, and prescribing data is collated nationally, which might explain a higher concordance with self-report and prescribing data than might be possible in some comparator studies.

Table 4.6. Comparison of Study Results With Other Published Studies Of Similar Methodology (Fixed Time Window).

Study and method	Medication	Kappa (95% CI)	Sensitivity	Specificity	PPV
Current Study 6 Month Fixed Time Window	**Antidepressants**	**0.85** (0.84-0.87)	**0.85** (0.82-0.87)	**0.99** (0.99-0.99)	**0.89** (0.87-0.91)
Nielsen et al (2008) (n=16,688) Interview based Danish nationally representative survey compared with national prescription records. Age 16+. 90-day time window (and legend time duration – not shown).	Antidepressants	0.66 (0.62-0.70)			
Caskie et al (2006) (n=1430) Longitudinal USA population based study ages 23-97 years. Comparison of medication "brown bag" interview with pharmacy prescription records (4 fixed month time window).	Antidepressants		0.86		
Rauma et al (2013) (n=11031) Postal questionnaire of postmenopausal Finnish women (age 58-67, mean age 62.3) compared to national prescription register, 4 month fixed time window (also 12 month fixed time window – not shown)	Antidepressants	0.65	0.55	0.99	
Haapea et al (2010) (n=7625) Postal questionnaire of Finnish birth cohort (all born 1966, data collected 1997) compared with register of social insurance institution, 6-month fixed time window	Antidepressants	0.68 (0.61-0.76)			
Richardson et al (2013) (n=2621) Irish Longitudinal Study on ageing. 50 years' age and older community dwelling population compared with pharmacy dispensing records, 6-month fixed time window	Psychoanaleptics	0.69 (0.65-0.73)			

Noize et al (2009) (n=4112) French older adult (65 years+) cohort study comparing questionnaire to national health insurance system, 60-day fixed time window (also 30 day – not shown)	Antidepressants	0.81 (0.77-0.84)	83	98.2	81.9
Haukka et al (2007) (n=905) Finnish population based genetic study of schizophrenia of which 422 had schizophrenia or bipolar disorder. Age range 30-65. Participants were interviewed about their medication and compared to social insurance prescription database. 180-day fixed time window.	Antidepressants	0.77			

Study and method	**Medication**	**Kappa (95% CI)**	**Sensitivity**	**Specificity**	**PPV**
Current Study 6 Month Fixed Time Window	**Mood stabilizers**	**0.42** (0.33-0.5)	**0.40** (0.31-0.50)	**0.99** (0.99-1.00)	**0.45** (0.35-0.56)
Haukka et al (2007)	Mood stabilizers Lithium	0.74 0.96			
Nielsen et al (2008)	Antipsychotics	0.73 (0.68-0.78)			
Rauma et al (2013)	Other psychoactive medication	0.30	0.29	0.97	
Haapea et al (2010)	Antipsychotics	0.77 (0.69-0.85)			
Noize et al (2009)	Antipsychotics	0.76 (0.66-0.84)	69.9	99.8	83.8
Richardson et al (2013)	Psychoanaleptics	0.59 (0.55-0.63)			

Study and method	**Medication**	**Kappa (95% CI)**	**Sensitivity**	**Specificity**	**PPV**
Current Study 6 Month Fixed Time Window	**Oral contraceptives**	**0.73** (0.70-0.76)	**0.82** (0.79-0.85)	**0.95** (0.95-0.96)	**0.72** (0.68-0.75)
Monster et al (2002)	Oral contraceptives	0.65	0.80		0.64

Study and method	Medication	Kappa (95% CI)	Sensitivity	Specificity	PPV
Current Study 6 Month Fixed Time Window	**Cholesterol lowering medication**	**0.95** (0.94-0.96)	**0.97** (0.95-0.97)	**0.99** (0.99-0.99)	**0.95** (0.94-0.97)
Monster et al (2002) (n=8592) Questionnaire from Netherlands population based study (ages 28-75 years, mean 49.5) compared with pharmacy data 1 year fixed time window	Lipid lowering drugs	0.81	0.85		0.79
Richardson et al (2013)	Lipid modifying agents	0.73 (0.69-0.77)			
Noize et al (2009)	Lipid lowering agents	0.85 (0.84-0.87)	0.86	0.98	0.95
Current Study 6 Month Fixed Time Window	**Antihypertensives**	**0.90** (0.89-0.91)	**0.86** (0.85-0.88)	**1.0**(0.99-1.00)	**0.98** (0.97-0.98)
Nielsen et al (2008)	Cardiovascular system	0.80 (0.78-0.81)			
Caskie et al (2006)	Beta blockers, Ca channel blockers, ACE inhibitors, diuretics		0.89 – 0.95		
Monster et al (2002)	Antihypertensives	0.69	0.89		0.62
Haapea et al (2010)	Beta blocking agents	0.55 (0.46-0.64)			
Richardson et al (2013)	Beta blocking agents, Calcium channel blockers, Diuretics	0.77 (0.73-0.81) – 0.80 (0.76-0.84)			
Noize et al (2009)	Antihypertensives	0.86 (0.84-0.87)	90.3	96.3	96.8
Sjahid et al (1998) (n=1682) Dutch cohort study of older adults (age 55+), patient interview compared with pharmacy records, 6 month fixed time window	Beta blocking agents, Calcium channel blockers, Diuretics	0.90-0.97			
Rauma et al (2013) (n=11031) Postal questionnaire of postmenopausal Finnish women (age 58-67, mean age 62.3) compared to national prescription register, 4 month fixed time window (also 12 month fixed time window – not shown)	Diuretics	0.82	0.83	0.98	

Study and method	Medication	Kappa (95% CI)	Sensitivity	Specificity	PPV
Current Study 6 Month Fixed Time Window	**Aspirin**	**0.84** (0.82-0.86)	**0.95** (0.93-0.96)	**0.98** (0.97-0.98)	**0.78** (0.75-0.81)
Nielsen et al (2008)	Antithrombotic agents	0.75 (0.70-0.80)			
Caskie et al (2006)	Salicylates		0.40		
Richardson et al (2013)	Antithrombotic agents	0.72 (0.68-0.76)			
Current Study 6 Month Fixed Time Window	**Insulin**	**0.93** (0.89-0.97)	**1.0**(0.93-1.00)	**1.0**(1.00-1.00)	**0.88** (0.79-0.94)
Nielsen et al (2008)	Insulins and analogues	0.82 (0.77-0.87)			
Caskie et al (2006)	Diabetic agents		0.97		
Haapea et al (2010)	Antidiabetics	0.92 (0.87-0.97)			
Richardson et al (2013)	Drugs used in diabetes	0.86(0.82-0.89)			
Noize et al (2009)	Drugs used in diabetes	0.93 (0.91-0.95)	0.91	0.99	0.96
Current Study 6 Month Fixed Time Window	**Hormone replacement therapy**	**0.78** (0.74-0.82)	**0.91** (0.86-0.94)	**0.98** (0.98-0.98)	**0.70** (0.64-0.75)
Nielsen et al (2008)	Hormone replacement therapy	0.51(0.47-0.55)			
Caskie et al (2006)	Oestrogens		0.82		
Monster et al (2002)	Hormone replacement therapy	0.49	0.60		0.46
Lokkegard et al (2004) Questionnaire to Danish nurses (n=2666) compared to administrative national health service prescribing databases (time window up to 9 years, non-fixed)	Hormone replacement therapy		0.74 (0.72-0.78)	0.98 (0.97-0.99)	

Kwon (2003) compared survey antidepressant self-report in a longitudinal depression study (n=164) with pharmacy claims data and a three-month fixed window and found substantial levels of agreement (κ=0.69). Interestingly, where there were discrepancies in prescription record antidepressant use, they found on notes review that most cases could be explained by antidepressants being used for other indications, or due to recent discontinuation. In our study, we attempted to minimise the rate of antidepressant false positives due to other indications by excluding amitriptyline from our searches (amitriptyline is widely prescribed but now rarely for depression in the UK).

With regard to mood stabilizers, a recent study comparing self-reported medication use in a genetic study of schizophrenia (n=905) (Haukka et al., 2007) found substantial levels of agreement (κ=0.74) between self-report of mood stabilizers and an administrative prescription database. This is a much higher level of agreement than found in our study, although we note that Haukka's was not a community-based sample and had a much higher prevalence of mood stabilizer use. A comparison of a postal medication survey (n=11,031) with national prescription records reported by Rauma et al. (2013) found substantial levels of agreement for antidepressant reporting (κ=0.65) but poor agreement (κ=0.30) for other psychoactive medications, a result more comparable with our own findings.

4.7.4 Study Strengths and Weaknesses

Our study used a large (n=10,244) population-based cohort linked to high fidelity Scottish PIS records (capture rate in excess of 95%) (Information Services Division, 2014). PIS collates data for the whole of Scotland and is therefore a comprehensive and 'closed' pharmacy recording system which also allows measurement of refills at several points in time. Such closed pharmacy systems enable measurement of the rate of refilling prescriptions which in turn gives an accurate measure of overall patient adherence, because the risk of patients obtaining refills elsewhere is greatly reduced(Osterberg and Blaschke, 2005). Self-report of medication use was via a short, simply worded questionnaire which obviated interviewer bias and did not require long-term recall of medication use. Response rate was high. We employed a variety of methods to compare the two data sources over two fixed time windows and performed covariate analysis of predictors of discordant self-report.

However, our method of verifying medication utilization took no account of dose and concordance with medication was assumed. Patients may be prescribed a drug but not fill their prescription (primary noncompliance). Although our use of date of dispensing rather than prescribing date would have obviated this to an extent, it would still be unknown if the dispensed drug was collected. A further issue is that the date of prescribing or dispensing may not be known, as only the "paid date" of financial settlement is always recorded in PIS. When the prescribed or dispensed date is missing it is frequently "back-filled" from the paid date. This therefore introduced some uncertainty in our determination of the dispensing date and potentially introducing false negatives and (particularly) false positives due to medication being apparently 'dispensed' weeks after it was in fact. However, the use of three- and six-month time

windows reduced the likelihood of false negatives and false positives compared to shorter fixed time windows.

In addition, patients may not take the drug, or not take as intended (secondary noncompliance), and concordance can be as low as 50% for antidepressants and antihypertensives (Haynes et al., 2008; Nielsen et al., 2008). In addition, the questionnaire referred to "regularly" taken medication whereas our method recorded any prescription within the fixed time window as positive use. The absence of data in PIS on medication indication increased the risk of over-inclusion and false positives, particularly for medications with broader indications, although we attempted to decrease this using our exclusion criteria (Table 4.2). Fixed time windows also potentially record false positives for medications discontinued during the window, but prior to self-report, although this is more common with medications taken acutely, such as antibiotics (Lau et al., 1997).

We must therefore concede that prescription data is by its nature an imperfect gold standard, although its use enables very large sample sizes which improve overall accuracy. The use of prescribing data as a gold standard involves some strong assumptions, including that the patient could not have obtained the medication without it being recorded in the prescribing data. The extent to which this is true depends on a variety of variables, including the medication type, prescribing legislation of the country of study, and the movement of individual patients between healthcare providers. Indeed, some studies are performed on the basis of self-report as gold standard to analyse the validity of clinical or prescribing records (Rikala et al., 2010). However, the advantage of prescribing data as a gold standard is that it is an objective measure, with definitions of medication usage that can be readily replicated

across studies and countries (whereas self-report questionnaires can vary considerably in definition and interpretation), which can be utilised at large scale across multiple medication types, and that is not subject to potential recall and desirability biases of self-report studies (Lam and Fresco, 2015).

Data linkage is also a fast-moving field, and though the PIS data from 2011 we used in this study had high fidelity and a capture in excess of 95%, future studies using larger datasets and more complex linkage may enable even more accurate estimates of validity. For example, as data linkage improves, cross referencing to other sources of clinical data such as GP and hospital records should assist identifying true cases and also reduce the incidence of false positives for those who have discontinued medication through the time windows analysed.

As discussed, the use of the term “mood stabilizer” may have caused confusion. Many individuals did not tick either checkbox, and moreover response rate differed between medication types, from 86.44% for antihypertensives to 77.87% for mood stabilizers. This may have reflected variations in understanding of, or willingness to answer, the question, and could have biased our results or inflated the kappa scores. However, we demonstrated that recoding this missing data as denial of use still produced substantial levels of agreement (Table 4.5). The Cohen’s kappa method itself may inflate values depending on the proportion of subjects in each category (Thompson and Walter, 1988), hence we have also tabulated the raw proportions (Table 4.7). GS:SFHS is a partly family-based cohort and this could potentially have introduced some correlation bias into our analysis, although we accounted for this in our multivariable regression through Generalized Estimating Equations.

Table 4.7: Self-Reported Medication Utilization Compared To Prescribing (PIS) Records (Six Month Fixed Time Window)

	SELF REPORT NEGATIVE *PRESCRIBING NEGATIVE* *TRUE NEGATIVES*	*%*	*SELF REPORT NEGATIVE* *PRESCRIBING POSITIVE* *FALSE NEGATIVES*	*%*	*SELF REPORT POSITIVE* *PRESCRIBING NEGATIVE* *FALSE POSITIVES*	*%*	*SELF REPORT POSITIVE* *PRESCRIBING POSITIVE* *TRUE POSITIVES*	*%*	*TOTAL (EXCLUDING MISSING DATA)*	*BLANK/ MISSING DATA*	*BLANK/ MISSING DATA AND PRESCRIBING POSITIVE*	*% BLANK/ MISSING AND PRESCRIBING POSITIVE*
ANTIDEPRESSANTS	7404	88.85	129	1.55	87	1.04	713	8.56	8333	1911	78	4.08%
MOOD STABILIZERS	7821	98.04	63	0.79	51	0.64	42	0.53	7977	2267	46	2.03%
CHOLESTEROL LOWERING MEDICATION	7519	85.55	42	0.48	56	0.64	1172	13.33	8789	1455	40	2.75%
ANTIHYPERTENSIVES	7134	80.56	229	2.59	34	0.38	1458	16.47	8855	1389	159	11.44%
ASPIRIN	7626	90.30	35	0.41	175	2.07	609	7.21	8445	1799	29	1.61%
INSULIN	7927	98.89	0	0.00	11	0.14	78	0.97	8016	2228	4	0.18%
HRT	4488	93.62	20	0.42	86	1.79	200	4.17	4794	1271	14	1.105
OCP	4029	83.09	111	2.29	200	4.12	509	10.50	4848	1216	24	1.97%

Abbreviations : HRT = Hormone Replacement Therapy. OCP = Oral Contraceptive Pill.

4.7.5 Conclusion

Our study provides convincing evidence that medication self-report is accurate compared to prescribing data, particularly for medication classes that are more precisely definable. We have shown that self-report of antidepressant use meets the highest threshold for Cohen's kappa agreement and can be considered valid for research and clinical purposes. Our analysis of potential patient-level predictors of reporting discordance, such as gender, age, education and general intelligence, did not identify generalizable factors across all medication classes, although there was some evidence that medical history of an indicated condition improves sensitivity of self-report. As discussed above, medication-level factors such as range of possible indications, and length of dispensing cycles, may also be important when validating self-report across a fixed time window with prescribing data as gold standard.

Our study also demonstrates the utility of record linkage of longitudinal population-based cohorts to nationally administered prescribing datasets, as a useful adjunct to epidemiological and large biobanking studies. Utilising administrative health data for verification and quality control of self-report has applications beyond epidemiological studies and can be potentially exploited in clinical applications, such as data-linked clinical support tools acting as adjuncts to clinical interview, and in formulating predictive models of disease risk(McIntosh et al., 2016b).

4.8 Concluding Remarks

In this chapter I have demonstrated the application of record-linkage to administrative health data in the validation of self-reported cohort phenotyping, in this case for medication usage. The first objective of this thesis, as described in Chapter 1, was to answer the question “are users of psychiatric medications less likely to accurately self-report their usage in research studies compared to users of other medications?”. Interestingly, the validation exercise did not provide evidence for our hypothesis that psychiatric medication was systematically under-reported. However, it did demonstrate clearly (in the case of mood stabilizers especially) the potential risks of relying on self-report alone.

I have also shown that there are potential risks inherent with over-reliance on either self-report or indeed record-linked administrative data. As stated in the chapter, the selection of record-linked prescribing data as ‘gold standard’, while clearly justifiable, was to an extent arbitrary because neither self-report nor prescribing data is an unimpeachable ‘gold standard’ for ascertaining medication use. While record-linked data can clearly be used for validation, this chapter has also hopefully shown the potential for linked data to be used *improve signal and power for discoveries and the reduction of false associations*. In other words, by combining self-report and linked data in defining cases and controls, future highly scaled research studies can significantly increase the veracity of their research data and its conclusions. In the following chapter, I shall show this technique can be applied to the problem of measuring antidepressant pharmaco-epidemiology, where through combining self-report and linked data, new research-grade measures of antidepressant usage can be produced.

Chapter 5 : Transforming Cross-Sectional Data on Antidepressant Use into a Longitudinal Study using Linked Data

5.1 Introductory Remarks

As discussed in Chapter 1, antidepressant medication is a mainstay of treatment for major depressive disorder, although it is more appropriately used for certain types of major depression and also is extensively used for a variety of other indications.

Recent reports that antidepressant prescriptions in the UK are now at the highest levels on record have caused considerable academic and media interest. There has been extensive debate about whether antidepressant medication levels are appropriate to clinical need or represent a significant overtreatment and medicalisation of aspects of the human condition which do not require pharmacological management (Information Services Division, 2014; Reid I, 2013; Spence D, 2013). Clearly, there is a need for a robust reassessment of antidepressant pharmaco-epidemiology in the general population.

In the following chapter record-linkage to national prescribing data is used to transform GS:SFHS into a longitudinal cohort for the study of antidepressant incidence, prevalence, adherence and patient-level factors indicating usage. This is used to demonstrate the potential of record-linked data generally in undertaking this type of longitudinal study, while answering two important public health questions relevant to mood disorder research : (a) has exposure to antidepressant medications significantly increased in recent years and, if so, is this due to a change in how antidepressants are used?, and (b) is the psychological trait of neuroticism an independent risk factor for the MDD-associated outcome of antidepressant use?

The following chapter has been published in the *Journal of Psychopharmacology* (Hafferty et al., 2019b). As the first author of the publication I jointly conceived the study, performed the analysis, wrote the manuscript and prepared all the tables and figures. To acknowledge the contribution of the co-authors (see also Publications section of this thesis for breakdown of author contributions) the term “we” rather than “I” is used throughout this chapter.

5.2 Paper : Pharmaco-epidemiology of Antidepressant Exposure in a UK Cohort Record-Linkage Study

5.3 Abstract

5.3.1 Objective

Antidepressants are the most commonly prescribed psychiatric medication, but concern has been raised about significant increases in their usage in high income countries. We aimed to quantify antidepressant prevalence, incidence, adherence and predictors of use in the adult population.

5.3.2 Method

The study record-linked administrative prescribing and morbidity data to the Generation Scotland cohort (N=11052), between 2009-16. Prevalence and incidence of any antidepressant use was determined. Antidepressant adherence was measured using Proportion of Days Covered (PDC) and Medication Possession Ratio (MPR)

metrics. Time-to-event analysis for incident antidepressant use within 5 years of GS:SFHS recruitment was performed to reveal patient-level predictors of use.

5.3.3. Results

Almost one third (28.0%, 95%CI 26.9-29.1) of the adults in our sample were prescribed at least one antidepressant in the five-year period 2012-16. There was a 36.2% increase in annual prevalence between 2010 and 2016. Incidence was 2.4 (2.1-2.7)% per year. The majority of antidepressant episodes (57.6%) were greater than 9 months duration and adherence was generally high (69.0% with Proportion of Days Covered >80%). Predictors of new antidepressant use included history of affective disorder, being female, physical comorbidities, higher neuroticism scores, and lower cognitive function scores.

5.3.4. Conclusions

Antidepressant prevalence is greater than previously reported but incidence remains relatively stable. We found the majority of antidepressant episodes to be of relatively long duration with good estimated adherence. Our study supports the hypothesis that increased long-term use among existing (and returning) users, along with wider ranges of indications for antidepressants, has significantly increased the prevalence of these medications.

5.4 Introduction

Antidepressants are the most commonly prescribed psychiatric medication and one of the most commonly prescribed medicines (Raymond et al., 2007; Olfson and Marcus, 2009). In the last 30 years, there has been a significant increase in antidepressant usage in high income countries (Ilyas and Moncrieff, 2012; Kendrick et al., 2015; Moore et al., 2009; Meijer et al., 2004; Huijbregts et al., 2017; Lockhart and Guthrie, 2011; Munoz-Arroyo et al., 2006; Petty et al., 2006; Raymond et al., 2007; Exeter et al., 2009; Mojtabai and Olfson, 2014; Olfson and Marcus, 2009; Gonzalez-Lopez et al., 2015; Mars et al., 2017). Antidepressant consumption has reportedly increased 400% in the USA between 1998-2008 (Pratt et al., 2011), while antidepressant prescriptions in the UK increased twofold between 1995-2011 (Spence et al., 2014). Comparison of electronic prescribing records in five European countries suggests that antidepressant prescribing is comparatively high in the UK for adults aged 20-60, especially among females (Abbing-Karahagopian Huerta et al., 2014). In the USA, annual antidepressant prevalence for 2011 was estimated at 14.4% (Zhong et al., 2014) compared to an annual prevalence of depression in 2015 of 6.7% (National Institute of Mental Health, 2017b) and 2.7% for generalized anxiety disorder (National Institute of Mental Health, 2017a).

The extent to which this rising tide of antidepressant prescribing is appropriate to clinical need is an area of ongoing controversy (Cruickshank et al., 2008; Lockhart and Guthrie, 2011; Reid I, 2013; Spence D, 2013). Antidepressant use has risen to a significantly greater degree than any rise in the prevalence of depression (Munoz-Arroyo et al., 2006) or of anxiety disorders (Bandelow and Michaelis, 2015). There is some evidence that illnesses treated by these medications, such as depression and anxiety, are now better recognised and treated at the primary care level (Kessler et

al., 2005) and that GPs and patients are more willing to utilise antidepressant treatment for a wider range of indications (Trifiro et al., 2007; Kessler et al., 2005; Mojtabai and Olfson, 2014). It has also been argued that a greater antidepressant prescription rate does not correspond to an upsurge in incident cases, but rather represents a significant lengthening in the treatment period for existing users (Moore et al., 2009; Raymond et al., 2007; Mojtabai and Olfson, 2014; Mars et al., 2017; Reid I, 2013). Advisory bodies such as NICE and the WHO now recommend a minimum of six to nine months antidepressant treatment for moderate major depressive disorder (MDD) and two years or more treatment for chronic or relapsing illness (Petty et al., 2006; Reid I, 2013; Mars et al., 2017). This can serve to increase prescribing prevalence rates without necessarily increasing incidence.

Nevertheless, concerns have been raised about a medicalisation of ordinary distress with antidepressants (Hollinghurst et al., 2005), and there are ongoing debates about the efficacy of antidepressants in mild-moderate depressive illness (Olfson and Marcus, 2009; Kirsch et al., 2008; Cipriani et al., 2018). There has been increased attention to potential adverse effects of antidepressants (Bet et al., 2013), including discontinuation syndromes (Petty et al., 2006; Bosman et al., 2016), adverse physical outcomes in older adults (Coupland et al., 2011), risk of epilepsy (Hill et al., 2015), increased risk of suicidal thoughts in teens and young adults (Zhong et al., 2014) and increased rates of attempted suicide in the first 28 days after starting and stopping antidepressant treatment (Coupland et al., 2015). There are concerns that antidepressants are insufficiently reviewed by clinicians, leading to unnecessarily long treatment durations (Bosman et al., 2016; Johnson et al., 2012).

Estimating the true prevalence and incidence of antidepressant usage is difficult and there have been few large population-based studies of antidepressant pharmaco-epidemiology. Many research studies of antidepressant use have relatively short follow-up periods (Huijbregts et al., 2017). A number of studies have used survey data (Lewer et al., 2015; Mojtabai and Olfson, 2014; Olfson and Marcus, 2009), although such data is potentially susceptible to recall biases. Other studies have concentrated on use of antidepressants in depressive illness (Kendrick et al., 2015; Moore et al., 2009), which can underestimate the true population prevalence due to the wide range of indications for antidepressants. Record-linking existing population-based cohorts to routinely collected administrative health data presents an opportunity to improve pharmaco-epidemiological estimates of antidepressant use.

Understanding patterns of antidepressant use is important in ensuring appropriate allocation of healthcare resources for patients and in maintaining effective monitoring systems for prescribing and adverse effects. In this study we have used a subset (N=11,052) of Generation Scotland, a large population- and family-based cohort of Scottish adults, with record-linkage to national prescribing data for the period 2009-2016. We aimed to provide a contemporaneous and population-scale quantification of patterns of antidepressant use, in terms of prevalence, incidence, duration of prescribing episodes, adherence to medication, and patient-level predictors of use.

5.5 Method

5.5.1 Study Sample

We used the Generation Scotland: Scottish Family Health Study (GS:SFHS) population- and family-based cohort (N=21,474) of adult volunteers across Scotland, recruited February 2006-March 2011, which has been described elsewhere (Smith et al., 2006; Smith et al., 2013a) (for overview, see Chapter 3).

Recruitment to GS:SFHS began in 2006, but prescribing data was available only from 2009 onwards. We therefore restricted our analysis to those individuals in GS:SFHS recruited from September 2009 to March 2011 (N=11052, 6518 females and 4534 males, see Figure 5.1 and Table 5.1). This ensured that all individuals had at least six months of prescribing data prior to their enrolment in GS:SFHS, with which to ascertain their pre-enrolment medication usage, and at least five years' worth of prescribing data following their enrolment. Of these, 96.5% had medication records available in the prescribing data (the remainder were presumably not using prescribed medication), which compared with 95.6% for the whole GS:SFHS cohort.

Table 5.1 : Demographics of Individuals Used In Current Study Compared to Entire Generation Scotland Cohort And To The Scottish Adult Population

	Individuals in the current study N(%)	GS:SFHS N(%)	Significance (p) of difference in proportion between study sample and GS:SFHS Effect size (Cohen d/h)	Scottish 18+ population N (%)
	(N=11052)	(N=20759) †		(N=4.3M)
Female	6518 (59.0%)	12246 (59.0%)	p=0.98	2.24M (52.1%)
Age 18-24 (Age in 2012)	801 (7.3%)	1194 (5.8%)	p=1.6x10^{-07} *h* = 0.06	501152 (11.7%)
Age 25-34	1460 (13.2%)	2810 (13.5%)	p=0.42	691908 (16.1%)
Age 35-44	1837 (16.6%)	3416 (16.5%)	p=0.70	688418 (16%)
Age 45-54	2246 (20.3%)	4422 (21.3%)	p=0.04 *h*=0.02	800265 (18.6%)
Age 55-64	3022 (27.3%)	5447 (26.2%)	p=0.03 *h*=0.03	663701 (15.5%)
Age 65-74	1295 (11.7%)	2649 (12.8%)	p=0.007 *h*=0.03	522236 (12.2%)
Age 75+	391 (3.5%)	821 (4.0%)	*p*=0.06	424626 (9.9%)
Affective Disorder History				
No MDD on screening	9624 (87.1%)	17998 (86.7%)	p=0.34	
SCID Single episode MDD	729 (6.6%)	1360 (6.6%)	p=0.88	
SCID Recurrent MDD	660 (6.0%)	1327 (6.4%)	p=0.14	
SCID Bipolar disorder	39 (0.4%)	74 (0.4%)	p=0.96	
Recruitment Location				
Aberdeen	1133 (10.3%)	1133 (5.5%)	p=<2.2x10^{-16} *h*=0.18	
Alyth	0 (0%)	14 (0.06%)		
Ayrshire	70 (0.6%)	70 (0.3%)	p=0.0002 *h*=0.04	
Glasgow (BHF)	2235 (20.2%)	4821 (23.2%)	p=8.5x10^{-10} *h*=0.07	
Dundee	3888 (35.2%)	6926 (33.4%)	p=0.001 *h*=0.04	

Perth	1106 10.1%)	3429 (16.5%)	p=<2.2x10^{-16} *h*=0.19
Glasgow (Tennents)	2620 (23.7%)	4214 (20.3%)	p=1.9x10^{-12} *h*=0.08
Dundee/Tayside	0 (0%)	152 (0.7%)	
Deprivation Index			
SIMD 1 – Most Deprived	1325(12.6%)*	2597 (13.3%)*	p=0.11
SIMD 2nd quintile	1576 (15.0%)*	2761 (14.1%)*	p=0.04 *h*=0.03
SIMD 3rd quintile	1693 (16.1%)*	3137 (16.0%)*	p=0.84
SIMD 4th quintile	2604 (24.8%)*	5009 (25.6%)*	p=0.12
SIMD 5 – Least Deprived	3293 (31.4%)*	6043 (30.9%)*	p=0.40
Smoking History			
Never Smoked	5636 (52.8%)*	10604(52.8%)*	p=0.95
Currently Smoke	1834 (17.2%)*	3565 (17.7%)*	p=0.22
Ex- Smoker	3198 (30.0%)*	5918 (29.5%)*	p=0.34

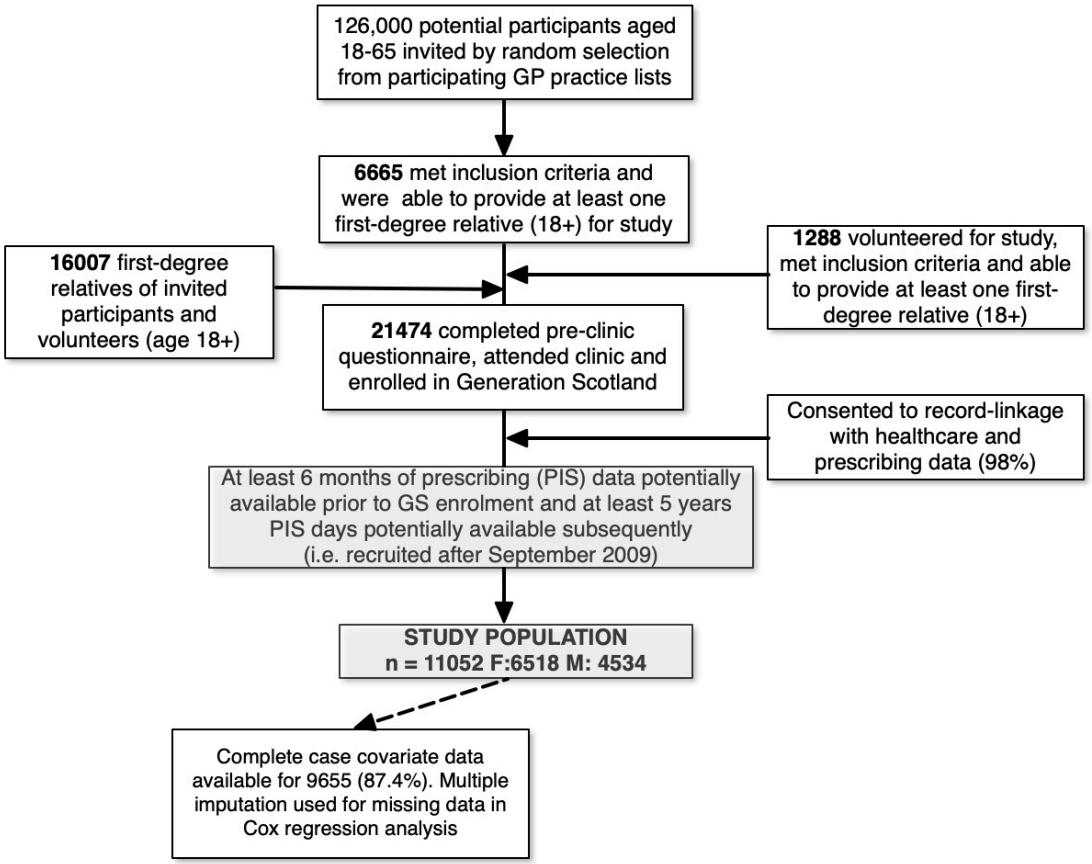
Table 5.1 cont.

	Individuals in the current study N(%)	GS:SFHS N(%)	Significance (p) of difference in proportion between study sample and GS:SFHS Effect size (Cohen d/h)
Other Variables			
GHQ (Likert)	15.8 (8.8)*	16.0 (8.7)*	p=0.09
EPQ Neuroticism	3.7 (3.1)*	3.8 (3.1)*	p=0.0003 *d*=0.04
Mill-Hill Vocabulary Test	30 (4.7) *	30 (4.8)*	p=0.55
Wechsler Digit Symbol Substitution Task	72.0 (17.2)*	72.1 (17.3)*	p=0.02 *d*=0.03
Verbal Fluency Test	39.8 (11.7)*	39.7 (11.7)*	p=0.27
Body mass index	26.8 (5.2)*	26.7 (5.3) *	p=0.05

Abbreviations: MDD = Major Depressive Disorder. SCID = Structured Clinical Interview for DSM-IV Disorders. SIMD = Scottish Index of Multiple Deprivation. GHQ = General Health Questionnaire. EPQ = Eysenck Personality Questionnaire.

* Variable contained missing data which was imputed (see below)
† Total GS:SFHS cohort 21474 but number who had consented to data linkage and where data linkage was possible was 20759

Figure 5.1 : Derivation of Study Population from Generation Scotland cohort



Like GS:SFHS as a whole, the study sample had a higher proportion of females (59%) and was of older age (mean 49 males SD 15.3, 49 females SD 15.2) compared to the Scottish general population (mean 37 males, 39 females, 2001 census) (Smith et al., 2013a). The study sample was typically healthier and more affluent that the general Scottish population, nevertheless 32.9% of individuals lived in areas with socio-economic deprivation worse than the average (median), as measured by the Scottish Index of Multiple Deprivation (Smith et al., 2013a). 99% of the study sample was of white ethnicity (Scottish population 98%).

5.5.2 Phenotyping in Generation Scotland

Sociodemographic information recorded in GS:SFHS included sex, age, smoking status and relationship status, collected by pre-clinic questionnaire at recruitment (see Table 5.1). Lifetime history of affective disorder (major depressive disorder (MDD) and bipolar disorder) was obtained using the Structured Clinical Interview for DSM-IV disorders (SCID) (Smith et al., 2013a). This was operationalised in the pre-clinic questionnaire using two screening questions, with those who answered affirmatively going on be interviewed with the mood sections of the SCID. The screening questions were: "*Have you ever seen anyone for emotional or psychiatric problems?*" and "*Was there ever a time when you, or someone else, thought you should see someone because of the way you were feeling or acting?*".

Cognitive tests included the digit symbol substitution test from the Wechsler Adult Intelligence Scale III (Wechsler D, 1998b), logical memory from the Wechsler Memory

Scale III (Wechsler D, 1998a), and verbal fluency (Lezak, 1995). From these tests, we derived a measure of cognitive ability (*g*) as the first unrotated principal component, explaining 44% of the variance in scores (Marioni et al., 2014). Loadings for processing speed, vocabulary, verbal declarative memory and executive function were -0.41, -0.55, -0.47 and -0.56. The range of *g* was -6.5 to 4.5, with a mean of 0.0 and one standard deviation equating to 1.3.

Psychological distress was measured using the General Health Questionnaire (GHQ-28, Likert scoring) (Goldberg and Hillier, 1979). An overall score of 24 or greater has been used to identify cases of potential psychiatric disorder (Swallow, 2003). Neuroticism was measured using the Eysenck Personality Questionnaire Short Form Revised (EPQ-SF) (Eysenck and Eysenck, 1964). The EPQ-SF is a self-report questionnaire consisting of twelve Yes/No questions which are used to assess neuroticism (on a scale 0-12, with higher scores representing greater neuroticism). The EPQ-SF has been validated with other quantitative measures of neuroticism (Gow et al., 2005) with high reliability (Eysenck et al., 1985). The extraversion scale from the EPQ-SF was not used in this study as it was not found to be significant on model fitting. Schizotypal traits were elicited using the Schizotypy Personality Questionnaire (SPQ) (Raine, 1991). Socioeconomic deprivation was determined using the Scottish Index of Multiple Deprivation 2009 (SIMD) (Scottish Government, 2009).

5.5.3 Prescribing Data and Linkage

All Scottish citizens registered with a General Practitioner are assigned a unique identifier, the Community Health Index (CHI). This was used to deterministically

record-link GS:SFHS participants to the national Prescribing Information System (PIS) administered by NHS Services Scotland Information Services Division(ISD) (Alvarez-Madrazo et al., 2016). PIS is a database of all Scottish NHS medications prescribed by GPs, nurses, dentists, pharmacists, and hospitals, where the medication was dispensed in the community. There is no prescription charge in Scotland since 2011. Hospital-dispensed prescriptions and over-the-counter medications are not included. We obtained PIS prescribing data for April 2009 (the earliest date available) to December 2016.

We additionally linked to the Scottish Morbidity Records (SMR00, SMR01 and SMR04) to obtain information about appointments with outpatient or inpatient secondary mental health services during the period of study. The SMR records Scotland-wide outpatient, day-case and inpatient hospital (including psychiatric hospital) attendances per annum since 1981. We also linked to ISD data on mortality to determine which participants of GS:SFHS had died during the period of follow up and excluded these from our estimates where relevant.

5.5.4 Identification of Psychiatric Medication Usage

The PIS data allows medication to be identified by approved drug name and/or associated British National Formulary (BNF) (Joint Formulary Committee, 2012) paragraph code. Medication indication is not recorded in PIS. PIS records medication name, type and dose. Dosage instructions are not available in standardised, coded, machine-readable form in PIS raw data. However, the Information Services Division(ISD) have developed a Natural Language Processing (NLP) algorithm to

extract dosage instructions from unstructured free text which are part of the PIS records. The algorithm has been verified as accurate although there are issues discerning ‘as required’ from ‘as directed’ in the metadata(Nangle et al., 2017). The number of defined daily doses (DDDs) for each medication are also computed in PIS. DDDs are a measure for standardising drug doses (WHO, 2011). For a small part of the dataset (4.9%) the dosage instructions were missing, and these were imputed (as described below).

We defined antidepressants (drugs for depression) as any drug included in BNF Chapter 4.3, entitled “Antidepressant Drugs”. Selective Serotonin Reuptake Inhibitors (SSRIs) were identified via BNF Section 4.3.3, Tricyclic Antidepressants (TCAs) via Section 4.3.1 and Selective Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) were identified from Section 4.3.4 (venlafaxine and duloxetine). We defined ‘other antidepressants’ as including Monoamine Oxidase Inhibitors (MAOIs), identified via Section 4.3.2, and the remaining drugs within Section 4.3.4. To comply with Neuroscience-based Nomenclature (Worley, 2017), a glossary of the mechanisms of action of each of the medications included in our study is provided in Table 5.2 below.

Table 5.2: Medications that previously antidepressant naïve (n=1250) antidepressant users in GS:SFHS were first commenced on during the entire period studied 2009-2016

	Mechanism of action*	Antidepressant class	Number of individuals	%
Amitriptyline	Reuptake inhibitor (SERT and NET), receptor antagonist (5-HT2)	TCA	37	3.0
Citalopram	Reuptake inhibitor (SERT)	SSRI	499	39.9
Duloxetine	Reuptake inhibitor (SERT and NET)	SNRI	31	2.5
Fluoxetine	Reuptake inhibitor (SERT)	SSRI	270	21.6
Mirtazapine	Receptor antagonist (NE alpha-2, 5-HT2, 5-HT3)	Other	87	7.0
Nortriptyline	Reuptake inhibitor (NET)	TCA	49	3.9
Paroxetine	Reuptake inhibitor (SERT)	SSRI	5	0.4
Sertraline	Reuptake inhibitor (SERT)	SSRI	177	14.2
Tranylcypromine	Enzyme inhibitor (MAO-A and -B), releaser (DA, NE)	MAOI	0	0
Venlafaxine	Reuptake inhibitor (SERT and NET)	SNRI	19	1.5
Lofepramine	Reuptake inhibitor (NET and SERT)	TCA	9	0.7
Trazodone hydrochloride	Reuptake inhibitor (SERT), receptor agonist (5-HT1A), receptor antagonist (5-HT2)	Other	22	1.8
Agomelatine	Receptor agonist (Mel1,Mel2), receptor antagonist (5-HT2B, 5-HT2C)	Other	0	0
Clomipramine hydrochloride	Reuptake inhibitor (SERT, NET (metabolite))	TCA	4	0.3
Dosulepin hydrochloride	Reuptake inhibitor (SERT and NET)	TCA	11	0.9
Doxepin	Reuptake inhibitor (NET and SERT), receptor antagonist (5-HT2)	TCA	4	0.3
Escitalopram	Reuptake inhibitor (SERT)	SSRI	12	1.0
Flupentixol	Receptor antagonist (D2, 5-HT2)	Other	1	0.1
Fluvoxamine maleate	Reuptake inhibitor (SERT)	SSRI	0	0
Imipramine hydrochloride	Reuptake inhibitor (SERT and NET)	TCA	13	1.0
Mianserin hydrochloride	Receptor antagonist (alpha-2), reuptake inhibitor (NET)	TCA	0	0
Moclobemide	Reversible enzyme inhibitor (MAO-A)	MAOI	0	0

Table 5.2 cont.

	Mechanism of action*	Antidepressant class	Number of individuals	%
Phenelzine	Enzyme inhibitor (MAO-A and -B)	MAOI	0	0
Reboxetine	Reuptake inhibitor (NET)	Other	0	0
Trimipramine	Receptor antagonist (5-HT2 and D2)	TCA	0	0
Tryptophan	Essential amino acid, precursor to 5-HT and Me	Other	0	0

* = source: Neuroscience-Based nomenclature http://www.nbn2.org/ [Accessed 26-10-18]
Abbreviations: SERT = serotonin transporter. 5-HT = 5-hydroxytryptamine/serotonin. NE=noradrenaline. NET = noradrenaline transporter. DA/D=dopamine. Me=Melatonin. MAO=monoamine oxidase. SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressant. MAOI=monoamine reuptake inhibitor. SNRI=selective serotonin and noradrenaline reuptake inhibitor.

We recorded antidepressant medication use as any dispensed prescription during the period analysed (which was the defined 5 year period 2012-2016 in some analyses and 1-5 years following individual GS:SFHS recruitment in others, as specified). We also applied additional thresholds : in the majority of our analyses, and unless otherwise stated, we repeated our analyses excluding low dose (<75mg) amitriptyline prescriptions, as this medication and dosage is most commonly prescribed for non-psychiatric purposes (such as neuropathic pain, migraine and tension headache) and frequently for very short periods (Mars et al., 2017). With regard to antidepressant dosage, we produced estimates for antidepressants of all dosages, and separate estimates for antidepressants prescriptions which met at least minimum BNF dose recommendations for MDD (for adult or older adults as appropriate).

5.5.5 Prevalence and Incidence

For each one-year period, we calculated the number of patients receiving any antidepressant prescription. Annual prevalence was calculated as the number of living cohort members using at least one antidepressant prescription that year, as a proportion of the reference sample. We also calculated the period prevalence for 2012-16 and the period prevalence for antidepressant use in the five years following each individual's enrolment in GS:SFHS.

To calculate incidence, we defined antidepressant naïve individuals as those who (a)were not on any antidepressant at the time of enrolment to GS:SFHS, or the 6 months preceding, and (b) did not report antidepressant use on the medication self-report questionnaire included in GS:SFHS, and (c) did not have a history of MDD or bipolar disorder on the SCID (which would indicate likely, although not definite, previous antidepressant use) (d) did not have a previous diagnosis of affective or anxiety disorders in the Scottish Morbidity Record (SMR) prior to GS:SFHS recruitment. We calculated incidence on the basis of the number of new users from the antidepressant naïve group, divided by the number of cohort members without antidepressant use in the preceding year.

The antidepressant naïve group were used solely in the calculation of incidence. In the Cox analysis of time to antidepressant use (see below), those currently on antidepressants were excluded, but the subset included those who had likely previously been on antidepressants. This is because a history of Major Depressive Disorder is known to be an important risk factor in antidepressant use and excluding

those with a history of MDD from the analysis would significantly bias the results regarding predictors of use.

5.5.6 Identification of Antidepressant Episodes and Adherence

We defined a drug treatment "episode" as consecutively dispensed prescriptions with a maximum interval between prescribing events of 90 days after the expected end date of the previous prescription, based on the dosage instructions (Gardarsdottir et al., 2010). We used 90 days as the cut-off point as it is unusual in the UK to be given more than three months medication per prescribing event (for sensitivity analyses with alternative cut-off points see Table 5.3). The end of a prescribing episode is therefore the duration from the final prescription to the time when the prescription ends based on dosage instructions, up to a maximum of 90 days.

We did not include new episodes which began in the second half of 2016, as it was not possible to estimate their duration. We defined "long-term" antidepressant use as a consecutive antidepressant episode of at least 15 months (based on three months for acute treatment, nine months for continuation-phase treatment, and three months for discontinuation, following the approach of Keyloun et al. (2017)).

Table 5.3

Part A : Sensitivity Analysis of Medication Possession Ratio (MPR) per Antidepressant Episodes During 5 Year Period 2012-2016 With Cut-Off Point Between Episodes Varying Between 60 and 360 Days

Cut-Off Point Between Episodes	Individuals	Prescribing Episodes (2012-2016)	Mean Duration (days)	Median Duration (days)	Min MPR (%)	MPR 1Q (%)	MPR Median (%)	MPR Mean (%)	MPR 3Q (%)	Max MPR (%)
60	2385	4370	526	231	10.9	90.3	100	99.3	103.4	411.8
90	2385	3595	679	307	10.6	86.5	99.1	96.3	100.5	411.8
120	2385	3280	777	372	11.7	84.9	98.1	95	101.1	411.8
150	2385	3117	839	411	11.7	83.5	97.4	94	100.7	411.8
180	2385	3008	891	452	11.7	82.2	96.6	93.2	100.7	411.8
270	2385	2813	997	557	11.7	79.9	95.7	91.4	100.4	283.7
360	2385	2707	1064	654	11.7	77.8	94.7	90	100	283.7

Part B : Sensitivity Analysis of Proportion of Days Covered (PDC) per Antidepressant Episode During 5 Year Period 2012-2016 With Cut-Off Point Between Episodes Varying Between 60 and 360 Days

Cut-Off Point Between Episodes	Individuals	Prescribing Episodes (2012-16)	Mean Duration (days)	Median Duration (days)	Min PDC (%)	PDC 1Q (%)	PDC Median (%)	PDC Mean (%)	PDC 3Q (%)	PDC Max (%)	% Adherent PDC
60	2385	4370	526	231	10.7	80.3	88.9	87.4	100	100	76
90	2385	3595	679	307	10.6	77	86.3	84.9	99.3	100	69
120	2385	3280	777	372	5.8	74.4	85.1	82.7	96.9	100	64.6
150	2385	3117	839	411	3.1	72.3	84.5	81.4	96.3	100	61.7
180	2385	3008	891	452	3.1	70.4	83.6	80.1	95.5	100	59.3
270	2385	2813	997	557	3.1	65.9	82.2	77.6	94.5	100	55.5
360	2385	2707	1064	654	3.1	62.3	81.1	75.9	93.3	100	52.8

Part C : Comparison of Proportion of Days Covered for Antidepressant Episodes involving Different Medication Classes (SSRI, TCA, SNRI, MAOI, Other) and Different Previous Histories of Affective Disorder on GS:SFHS Recruitment

Group	Cut-Off Point Between Episodes	Individuals	Mean Duration (days)	Median Duration (days)	Min PDC (%)	PDC 1Q (%)	PDC Median (%)	PDC Mean (%)	PDC 3Q (%)	PDC Max (%)	% Adherent PDC (>= 80% PDC)
SSRI	90	1924	672	326	1	76.7	85.8	84.5	96.8	100	68.1
TCA*	90	422	937	488	1	76.8	85.5	84.3	100	100	67.8
SNRI	90	310	1120	931	25.7	76.3	84.2	83.2	90.8	100	67.3
MAOI	90	14	1251	1110	52.4	71	77.1	77.3	82.7	100	31.3
Other	90	414	908	522	28.5	76.8	85	83.9	94.1	100	65.9
MDD history:											
Bipolar disorder	90	29	813	568	62.9	72.9	81.8	83.5	94.2	100	56.3
Recurrent MDD	90	421	968	576	23.2	76.1	84.7	83.3	92.3	100	66.1
No MDD history	90	1611	578.9	265.5	10.6	77.7	87.4	85.5	100	100	70.3

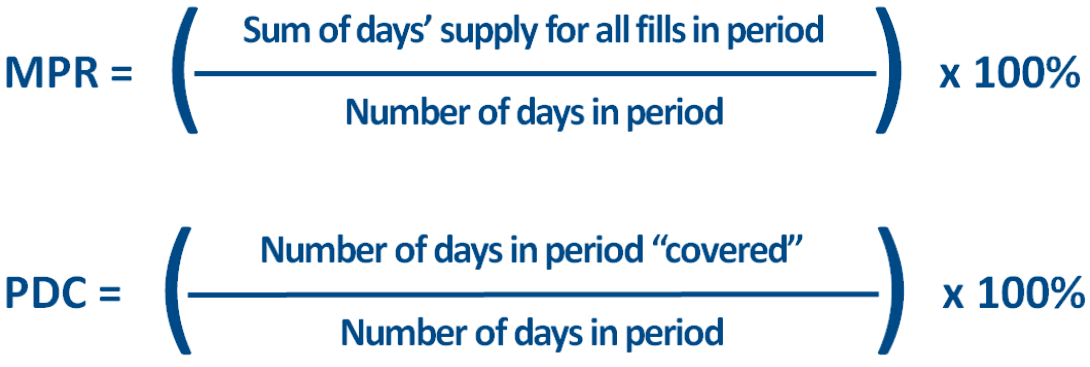
*** = TCA - excluding low dose amitriptyline**

Abbreviations : MPR = Medication Possession Ratio. 1Q=1st quartile. 3Q=third quartile. MDD = major depressive disorder. MPR=medication possession ratio. PDC=proportion of days covered.

We calculated medication adherence (Figure 5.2) using the Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) metrics (Keyloun et al., 2017). MPR is defined as the sum of the day's supply for all dispensed medication in the episode divided by the number of days in the period, expressed as a percentage. PDC is defined as the number of days in a prescribing episode that are adequately "covered" by the preceding prescribing event, divided by the number of days in the episode, expressed as a percentage.

Compared to MPR, PDC is generally regarded as a more conservative and preferred measure and is the primary method utilised in the study. Satisfactory adherence was defined as MPR or PDC >80% for the antidepressant episode (Keyloun et al., 2017). Sensitivity analyses (Table 5.3 Part A and Part B) indicated that PDC was the more discriminatory measure compared to MPR, although both measures are reported (see Results section).

Figure 5.2 Calculation of Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC)



Source: https://www.pharmacytimes.com/contributor/michael-crowe-pharmd-mba-csp-fmpa/2015/07/do-you-know-the-difference-between-these-adherence-measures [*Pharmacy Times,* July 05, 2015, Accessed 9th July 2019]

5.5.7 Statistical Analysis

All analyses were carried out using R version 3.2.3 (R Core Team, 2015). Prevalence and incidence rates were expressed as percentages, together with 95% confidence intervals. These estimates were reweighted by age and sex to reflect the Scottish population, using the 2011 Scottish census (Scottish Government, 2011). Age-sex reweighting was performed using the direct standardisation method using the R package “epitools”.

As GS:SFHS is a family based cohort, which could lead to biases due to the hierarchical structure of the data, we used a mixed model implementation of Cox regression (with inter-relatedness controlled using pedigree as a random effect), using the R package “coxme”. We controlled for potential confounding related to the recruitment area from which each participant was enrolled using a categorical variable in the model.

There was some (range 0.8-5.1%) missing data for some of the variables collected in Generation Scotland (see below and Table 5.4) and this missing data was imputed using the Multiple Imputation by Chained Equations method implemented in the R package “mice” (van Buuren, 2012). The final estimates were the result of pooling n=100 imputed datasets, using Rubin’s rules (van Buuren, 2012). P values were corrected for multiple testing using the False Discovery Rate (FDR) method.

5.5.8 Imputation method for missing drug dosage data

There were 8048 records in the antidepressant data with missing prescription instructions (out of 134290 records in total, or 6.0% missing data). A five-step imputation strategy was employed for these missing records.

(1) If a missing data prescribing record could be matched to one with the same user (unique ID), the same antidepressant medication, at the same dose, and the same dispensed quantity, then these prescribing instructions were used to impute for that individual. This reduced the missing data from 8048 records to 814 records.

(2) If a prescribing record has the same user (unique ID), the same antidepressant, and the same strength as another prescription for the same users, then these prescribing instructions were used. This step did not reduce the count (did not improve upon the step above).

(3) If a missing data prescribing record could be matched to one with the same user (unique ID) and the same antidepressant, then these prescribing instructions were used to impute. This reduced missing data from 814 to 553 records.

(4) For the remaining 553 records (0.4% of the total dataset) the median dosage instructions for that specific antidepressant in the cohort were used.

5.5.9 Missing Data and Imputation of Generation Scotland phenotypic variables

As shown in Table 5.4, there was some missing data in the phenotypic variables used in the analyses of this study. The amount of missing data was <5% for every variable apart from SIMD quintile (5.1%) with the proportion of individuals with missing data in at least one field being 12.6%.

Imputation of these variables was performed using Multiple Imputation by Chained Equations in the R package “mice”. An assumption of multiple imputation is that the missing data is not Not Missing At Random (NMAR) and can credibly be defined as Missing At Random (MAR) or Missing Completely At Random (MCAR).

As shown in Table 5.4, when stratified against the affective disorder status of GS:SFHS participants, there are no significant differences in the total missingness between those with a history of affective disorder and those without. We imputed the missing data on the basis of the hypothesis that the missingness was MAR type.

Table 5.4 : Missing Data in GS:SFHS Variables

Variable name	Missing records (N=11052)	% missing data (which was imputed)	% missingness in individuals with no history of affective disorder	% missingness in individuals with history of affective disorder (p= p value of two sample test for equality of proportions)
Sex	0	-		
Age	0	-		
SCID affective disorder status	0	-		
SIMD Quintile	561	5.1%	5.0%	5.7%(p=0.3)
BMI	91	0.8%	0.8%	0.8% (p=0.9)
SPQ	261	2.4%	2.3%	2.7%(p=0.05)
Neuroticism	254	2.3%	2.4%	1.9%(=0.3)
Smoking	384	3.5%	3.5%	3.4%(p=0.9)
Alcohol	535	4.8%	4.7%	5.5% (p=0.2)
Physical Health	254	2.3%	2.3%	2.6%(p=0.05)
Appointment location	0	-		
Cognitive function (g)	203	1.8%	1.9%	0.9%(p=0.007)
Individuals with missing data in at least one field	1397	12.6%	12.7%	12.5%(p=0.9)

5.6 Results

5.6.1 Sample

The basic demographics of the sample compared to the Scottish population are presented in Table 5.1. An antidepressant was prescribed at least once to 3742 individuals (33.9(95%CI 33.0-34.8)%) of the 11,052 in our study between April 2009 and December 2016. There was a 36.2% increase in the annual prevalence of antidepressant prescribing between 2010 (age-sex reweighted prevalence 12.7(95%CI 12.0-13.5)%) and 2016 (17.3(16.5-18.3)%). During the seven year period 2010-16, 79,857 antidepressant prescriptions were dispensed (22 for every antidepressant user in GS:SFHS).

Low dose amitriptyline prescriptions (<75mg) accounted for 18.3% of prescriptions and 943 individuals (25%) were only prescribed low dose amitriptyline. Discounting low dose amitriptyline, there were 2624 antidepressant users with a mean of 1.8 antidepressant episodes (range 1-9, S.D. 1.1) during the period 2010-16. Although we had no data on specific indication, 84.2% of these episodes reached a dosage equivalent to at least the required BNF minimum for the treatment of Major Depressive Disorder.

The most commonly prescribed class of antidepressants was Selective Serotonin Reuptake Inhibitors (SSRIs), accounting for 54% of prescriptions in 2010 and 52.7% in 2016 (65.6% and 64% respectively if low dose amitriptyline excluded). The proportion of Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) prescribed increased from 9.1% in 2010 to 10.9% in 2016, and the proportion of other antidepressants (such as mirtazapine) increased from 6.7% to 8.3% during the same

period. The proportion of Tricyclic Antidepressants (TCAs) was 27.8% in 2016, or 12.3% if low dose amitriptyline excluded.

5.6.2 Period Prevalence 2012-16

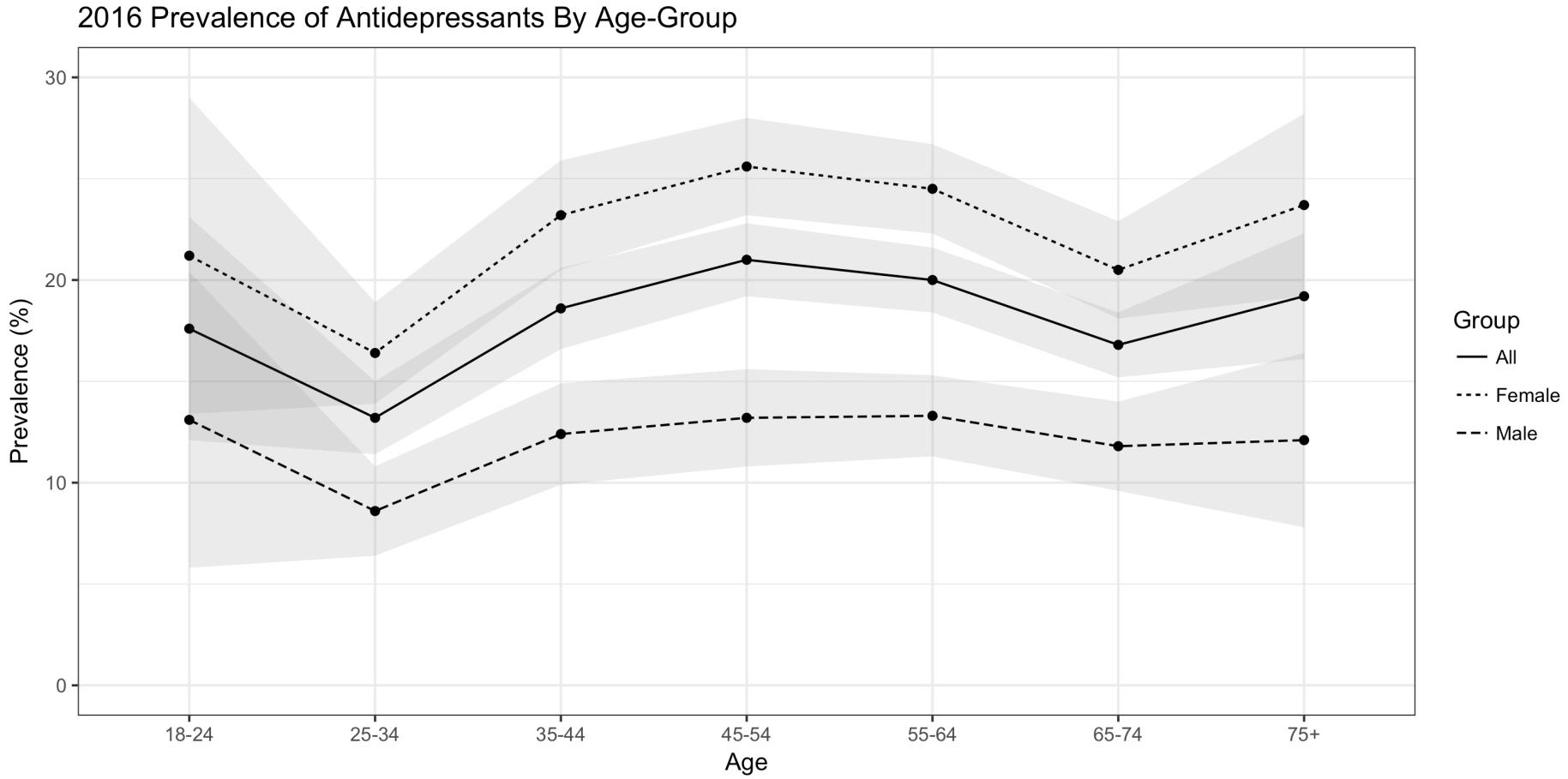
The 5-year 2012-2016 age-sex reweighted period prevalence of antidepressant use was 28.0 (95%CI 26.9-29.1)% for the cohort. With low dose amitriptyline excluded, the prevalence was 20.8 (19.9-21.8)% (see Table 5.5). The five-year prevalence was considerably higher among females, 34.9 (33.3-36.6)%, than males, 20.4 (19.0-22.0)%. There was a bimodal distribution of antidepressant use by age, with 2012-16 period prevalence highest in the 45-54 age group for all antidepressants (33.3 (31.3-35.3%)) and a second peak in the 75+ age group (33.3(28.8-38.8)%) (Figure 5.3).

Table 5.5 : Prevalence of Antidepressant Medications, by Class, 2012-2016

	All antidepressant		SSRI		TCA		Other antidepressants		Antidepressants excluding low dose amitriptyline	
	2012-16	n	2012-16	n	2012-16	n	2012-16	n	2012-16	n
Crude Rate	**29.5(28.6-30.4)**	3167	**17.4(16.7-18.2)**	1883	**15.0(14.3-15.7)**	1619	**5.8(5.4-6.3)**	630	**21.9(21.1-22.7)**	2366
Reweighted Rate	**28.0(26.9-29.1)**		**16.5(15.7-17.4)**		**14.1(13.4-15.0)**		**5.6(5.1-6.2)**		**20.8(19.9-21.8)**	
Sex -Male (crude)	**20.4(19.2-21.7)**	900	**11.1(10.2-12.1)**	489	**10.0(9.1-11.0)**	440	**4.4(3.8-5.1)**	195	**14.7(13.7-15.8)**	647
(RW)	**20.4(19.0-22.0)**		**11.1(10.1-12.3)**		**9.9(8.7-11.1)**		**4.4(3.8-5.2)**		**14.7(13.5-16.1)**	
Sex – Female (crude)	**35.4(34.3-36.6)**	2267	**21.8(20.8-22.8)**	1394	**18.4(17.4-19.4)**	1179	**6.8(6.2-7.5)**	435	**26.9(25.8-28.0)**	1719
(RW)	**34.9 (33.3-36.6)**		**21.4(20.2-22.7)**		**18.1(16.9-19.3)**		**6.7(6.0-7.5)**		**26.4(25.0-27.9)**	
Age – 18-24	**22.6(19.8-25.7)**	181	**18.4(15.8-21.3)**	147	**6.6(5.0-8.6)**	53	**4.0(2.8-5.7)**	32	**19.5(16.8-22.4)**	156
25-34	**23.0(20.9-25.3)**	335	**17.5(15.6-19.5)**	255	**8.5(7.1-10.0)**	123	**4.7(3.7-6.0)**	71	**19.5(17.5-21.7)**	284
35-44	**32.9(30.7-35.1)**	601	**22.5(20.6-24.5)**	411	**14.1(12.5-15.8)**	257	**7.3(6.2-8.7)**	134	**26.6(24.6-28.7)**	487
45-54	**33.3(31.3-35.3)**	739	**20.6(19.0-22.4)**	458	**16.8(15.3-18.4)**	373	**6.1(5.1-7.2)**	136	**25.2(23.4-27.1)**	560
55-64	**29.1(27.4-30.7)**	858	**14.9(13.6-16.3)**	440	**17.0(15.7-18.4)**	503	**6.0(5.2-6.9)**	177	**20.6(19.1-22.1)**	607
65-74	**28.3(25.8-30.9)**	346	**10.6(9.0-12.5)**	130	**19.5(17.4-21.9)**	239	**4.6(3.5-5.9)**	57	**16.4(14.4-18.7)**	201
75+	**33.3(28.3-38.8)**	107	**13.1(9.7-17.4)**	42	**22.1(17.8-27.1)**	71	**7.2(4.7-10.7)**	23	**22.1(17.8-27.1)**	71

Abbreviations : RW=age-sex reweighted. SSRI=Selective Serotonin Reuptake Inhibitors. TCA=Tricyclic Antidepressants. n = total number within grouping with prescription records of at least one antidepressant usage.

Figure 5.3 : 2016 Age and sex specific period prevalence of antidepressant for all antidepressant types and indications



5.6.3 Prevalence of Antidepressant Prescribing in One to Five Years Follow-Up

In the first year following each individual's GS:SFHS enrolment, 11.2 (95%CI 10.6-11.8)% of the cohort had at least one antidepressant prescription (excluding low dose amitriptyline, as does all analysis in this section), which increased to 20.8 (20.0-21.6)% after five years.

Among those with a history of recurrent MDD on recruitment, 52.4 (48.5-56.2)% were prescribed at least one antidepressant within one year following GS recruitment and for bipolar disorder the proportion was 46.2 (30.4-62.6)%. For those with no history of MDD on recruitment, 6.9 (6.5-7.5)% were prescribed at least one antidepressant within one year – or 2.5 (2.2-2.9)% if those already on antidepressants at recruitment were excluded.

Among those with a GHQ-28 Likert score of 24 or above at the time of GS:SFHS recruitment, 31.7 (95% CI 29.4-34.1)% had at least one antidepressant prescription within 1 year.

Among the antidepressant naïve subgroup at the time of GS:SFHS recruitment, 6.6 (5.1-8.6)% of those with a GHQ-28 Likert score of >=24 were prescribed antidepressants within one year and 9.2 (4.1-18.6)% of those scoring over three standard deviations above the mean on the GHQ depression subscale (subscale D) were prescribed an antidepressant within 1 year.

5.6.4 Incidence of Antidepressant Prescribing 2012-16

The age-sex reweighted incidence of antidepressant prescribing was 2.4 (2.1-2.7)% per year for all antidepressants and 1.6 (1.4-1.9)% if low dose amitriptyline was excluded. Incidence was greater in females 2.7 (2.4-3.2)% than males 2.0 (1.6-2.5)%.

77.1% of incident antidepressant users were commenced on an SSRI, with 11.9% on a TCA (low dose amitriptyline excluded), 4.0% on a serotonin and noradrenaline reuptake inhibitor (SNRI) and 7.0% on other antidepressants (especially mirtazapine). The most common individual medication for new users was citalopram (39.9%), followed by fluoxetine (21.6%) and sertraline (14.2%). Less than 1% were commenced on paroxetine and none on reboxetine or MAOIs. The most common tricyclic antidepressant for new users was nortriptyline (3.9%) followed by higher dose amitriptyline (3.0%).

5.6.5 Antidepressant Episodes

In the five years period 2012-16, 2385 individuals used antidepressants and we determined 3595 antidepressant episodes (low dose amitriptyline excluded). Some 86.6% (n=3112) of episodes reached at least minimum dose required for treatment of MDD (although actual indication was not available). We allowed antidepressant switching or combination during episodes, with the majority of episodes (79.3%) having just one antidepressant, 13.6% having two and 7.1% having three or more (range 3-6).

Over half (57.6%) of antidepressant episodes were of 9 months or greater and 44.8% met our 15-month criteria for long term use, with the majority of antidepressant users (57.7%) having a least one episode of long-term duration. Nevertheless, approximately one tenth (10.6%) of episodes were of less than 30 days duration and a further 12.6% were of 31-90 days, meaning that approximately one quarter of episodes were less than three months duration.

5.6.6 Adherence

For the 3595 antidepressant episodes between 2012-16 (n=2385 individuals), the mean Medication Possession Ratio (MPR) per antidepressant episode was 96.0% (range 11-412) and the mean Proportion of Days Covered (PDC) was 84.9% (range 11-100). Using PDC >= 80% as defining adherence, 69.0% of antidepressant episodes were adherent, when using 90 days as the cut-off point between antidepressant episodes (for sensitivity analysis see Table 5.3). Mean PDC was similar across medication classes (SSRI 84.5%, TCA 84.3%, SNRI 83.2%, MAOI 77.3%, other 83.9%, see Table 5.3).

5.6.7 Polypharmacy

Other medications that were also prescribed with antidepressants during an antidepressant episode were determined, with simultaneous use on at least three occasions being classed as “regular” use.

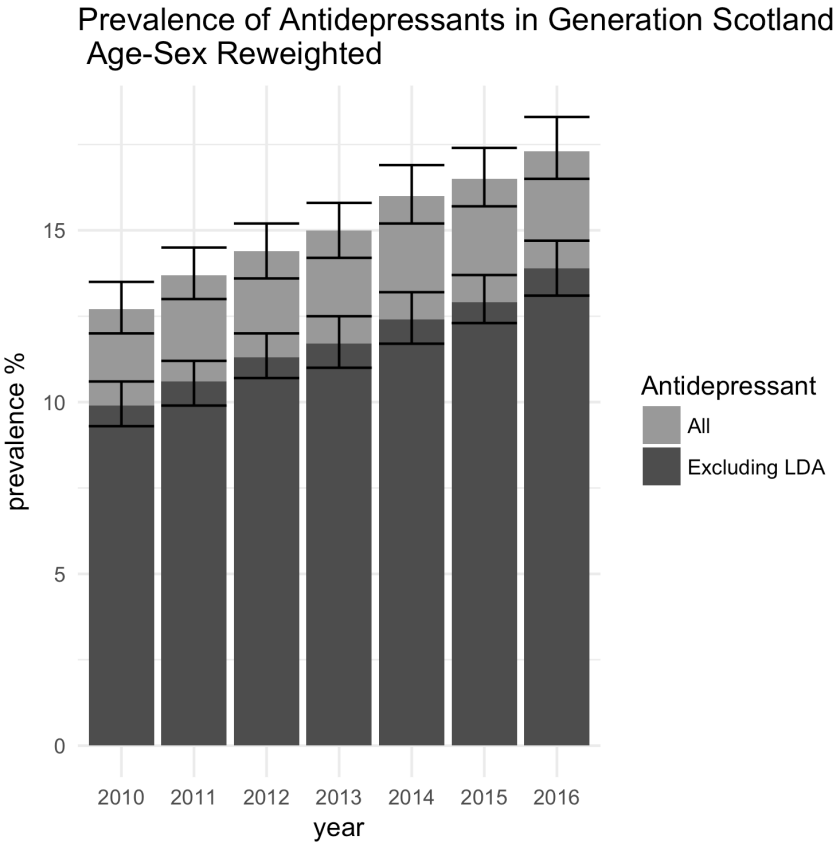
Anxiolytics (medicines for anxiety) were also prescribed to 34.1% of antidepressant users (16.4% regularly), including benzodiazepines 23.6% (10.7% regularly) and “Z-

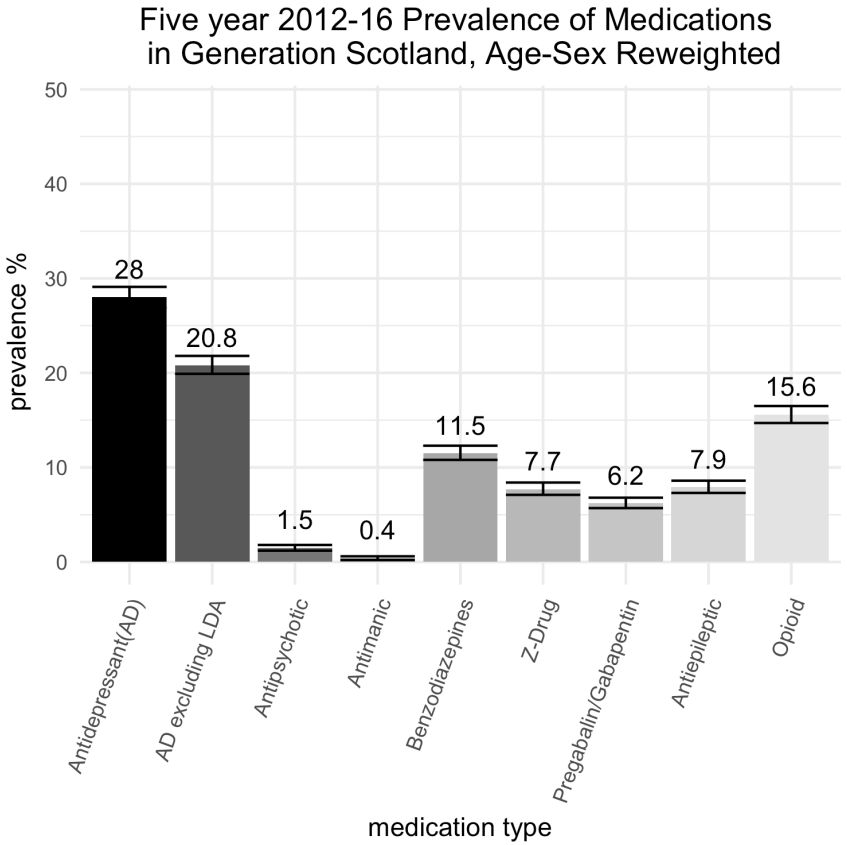
drugs" (the benzodiazepine-receptor agonists zopiclone, zolpidem and zaleplon) 18.9% (7.6% regularly).

Pregabalin or gabapentin (alpha-2 delta calcium channel blockers often used to treat anxiety and neuropathic pain as well as epilepsy) were also prescribed to 12.8% of users (8.9% regularly). Antipsychotics (medicines to treat psychosis) were also prescribed to 6.8% antidepressant users (5.1% regularly). Lithium compounds or sodium valproate, which are also used to treat mood disorders, were also prescribed to 1.6% (1.4% regularly).

Opiate-based analgesic (pain relieving) medications were also prescribed to 22% of antidepressant users (13.3% regularly), compared to a general five-year prevalence of 15.6% (Figure 5.4). Opioid use was also higher in those with a history of bipolar disorder (33.3%,regular 18.5%) and recurrent MDD (27.8%, regular 17.3%) on GS:SFHS recruitment, compared to those with no affective disorder history (20.5%, regular 12.3%).

Figure 5.4: Age-Sex Reweighted Prevalence of Antidepressants And Other Medications In GS:SFHS





Abbreviations: LDA= low dose amitriptyline.

5.6.8 Use of Psychiatric Services

Using record linkage to hospital data, 10.0 (8.9-11.2)% of antidepressant users in the five years following GS:SFHS enrolment, who were prescribed at least the minimum BNF recommended dosage for MDD, had a psychiatric outpatient appointment during at least one of their antidepressant treatment episodes. Some 1.8(1.4-2.5)% of antidepressant users were admitted to psychiatric hospital during at least one episode of antidepressant treatment.

5.6.9 Predictors of Antidepressant Use : Time to Event Analysis

We performed time-to-antidepressant-use Cox regression analysis for the five years following individual GS:SFHS enrolment, excluding those individuals already on antidepressants (Figure 5.5 and Table 5.6).

Female gender was predictive of commencing antidepressants in the multivariable model (Hazard Ratio (HR)=1.74, 95% CI 1.53-1.98, p_{FDR}<0.0001). Greater levels of deprivation (lower SIMD score) were associated with increased likelihood of antidepressant prescriptions in univariate analysis (and in complete case analysis, see Table 5.7) although this was not significant in the multivariable model.

Neuroticism (HR 1.12,1.09-1.14 per unit, p_{FDR}<0.0001), previous history of unemployment (HR=1.24, 1.06-1.45, p_{FDR}=0.02) and smoking status (current smokers HR 1.57 (1.34-1.84, p_{FDR} <0.0001) were also positively associated with antidepressant use, whereas cognitive function (g) scores were negatively associated (HR 0.89, 0.85-0.93, p_{FDR} 0.001). Multiple physical comorbidities (3+) were positively

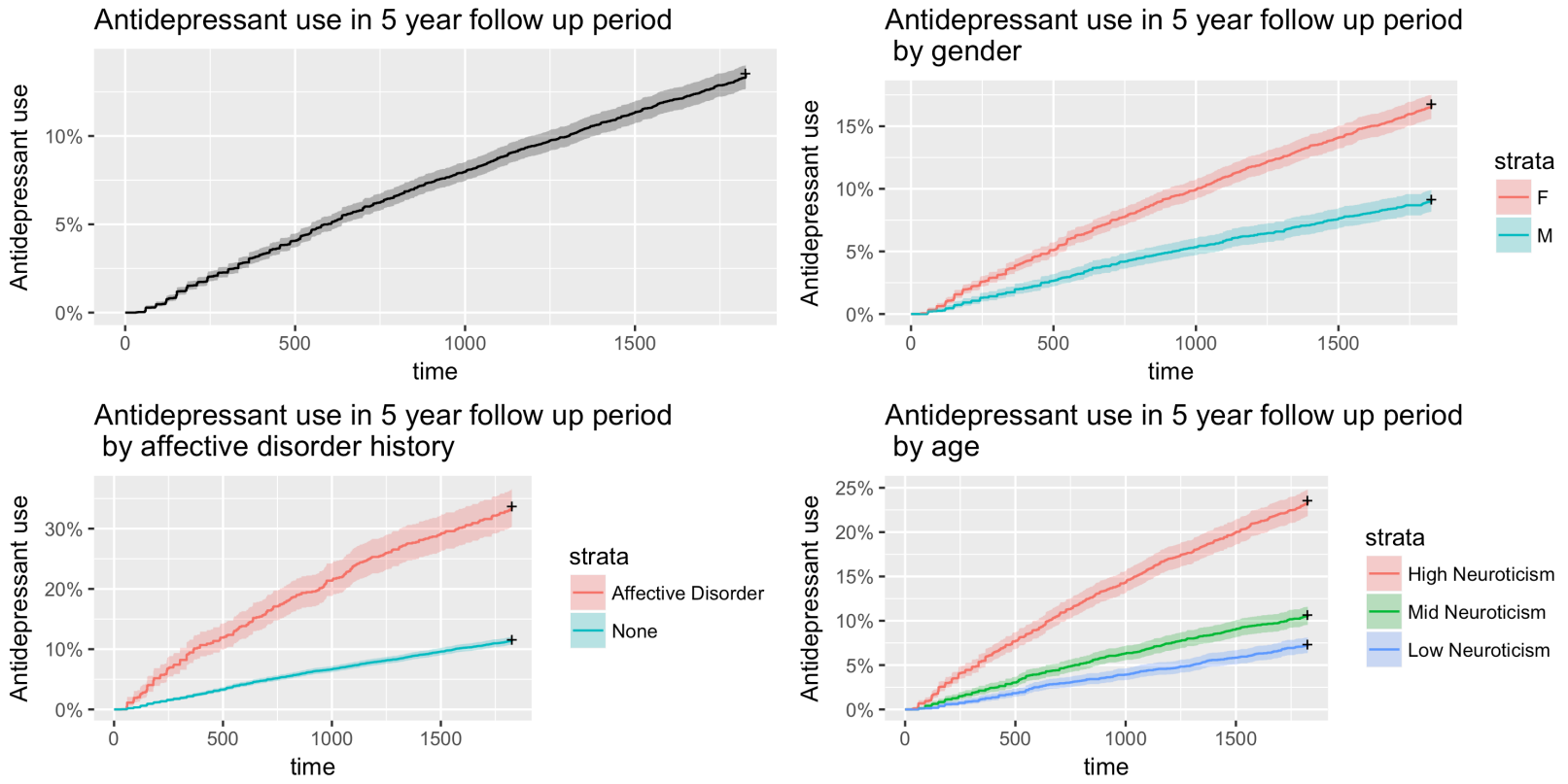
associated with antidepressant use (HR 1.85,1.33-2.57, p_{FDR} 0.002). The most predictive factor for antidepressant use was previous history of affective disorder on GS:SFHS recruitment, with history of a single episode of MDD having a hazard ratio of 2.22 (1.85-2.67, p_{FDR}<0.0001).

Table 5.6 : Cox Regression of Time-To-Antidepressant-Use in GS:SFHS (Excluding those Already Using Antidepressants At Time Of Recruitment), N=9953 of whom n=1347 went on to use antidepressants within 5 years

	Univariate		**Multivariable**		
	Hazard Ratio	p	Hazard Ratio	p(FDR)	Sig
Intercept					
Sex – male	Ref	Ref	Ref	Ref	
– female	1.94(1.72-2.19)	<0.0001	1.74(1.53-1.98)	<0.0001	***
Age :18-24	Ref	Ref	Ref	Ref	Ref
:25-34	0.81(0.64-1.03)	0.16	0.79(0.62-1.01)	0.119	
: 35-44	1.03(0.83-1.28)	0.92	0.95(0.75-1.21)	0.787	
: 45-54	0.99(0.80-1.22)	0.92	1.00(0.79-1.26)	0.993	
: 55-64	0.72(0.58-0.89)	0.007	0.72(0.57-0.92)	0.021	*
:65-74	0.49(0.37-0.64)	<0.0001	0.48(0.35-0.64)	<0.0001	***
:75+	0.93(0.67-1.29)	0.92	0.74(0.52-1.07)	0.193	
No MDD on Screening	Ref	Ref	Ref	Ref	Ref
MDD – Single Episode	3.17(2.69-3.76)	<0.0001	2.22(1.85-2.67)	<0.0001	***
MDD – Recurrent	4.33(3.54-5.30)	<0.0001	2.10(1.68-2.62)	<0.0001	***
MDD – Bipolar	4.84(2.38-9.85)	<0.0001	2.11(0.99-4.47)	0.109	
Never Smoked	Ref	Ref	Ref	Ref	Ref
Currently Smoke	2.05(1.78-2.37)	<0.0001	1.57(1.34-1.84)	<0.0001	***
Ex-Smoker	1.30(1.14-1.48)	<0.0001	1.33(1.15-1.53)	0.001	*
Neuroticism	1.20(1.18-1.22)	<0.0001	1.12(1.09-1.14)	<0.0001	***
SPQ	1.11(1.09-1.12)	<0.0001	1.03(1.01-1.05)	0.003	*
Cognitive function (g)	0.85(0.81-0.89)	<0.0001	0.89(0.85-0.93)	<0.0001	***
No physical health complaints	Ref	Ref	Ref	Ref	Ref
1-2 physical health complaints	1.22(1.08-1.38)	<0.0001	1.27(1.11-1.44)	0.003	*
3+ physical health complaints	1.79(1.34-2.41)	<0.0001	1.85(1.33-2.57)	0.002	*
Unemployment history			1.24(1.06-1.45)	0.021	*
SIMD – Most Deprived quintile	2.03(1.70-2.42)	<0.0001	1.23(1.01-1.49)	0.086	.
SIMD – 2nd quintile	1.47(1.23-1.76)	<0.001	1.07(0.88-1.29)	0.64	
SIMD – 3rd quintile	1.27(1.06-1.52)	0.013	1.06(0.88-1.28)	0.64	
SIMD – 4th quintile	1.02(0.87-1.21)	0.79	0.93(0.78-1.10)	0.54	
SIMD – Least Deprived quintile	Ref	Ref	Ref	Ref	Ref

N.B. The following covariates were in the model but not shown as not significant in multivariable analysis: Location of GS:SFHS enrolment(not significant in univariate or multivariable analyses), self-reported alcohol use, body mass index (bmi).
Abbreviations: Sig=significance level *p<0.05, **p=<0.001, ***p<0.0001 Ref=reference level g = cognitive function score. GHQ = General Health Questionnaire. MDD = Major Depressive Disorder. SIMD = Scottish Index of Multiple Deprivation. SPQ = Schizotypal Personality Questionnaire.

Figure 5.5 : Kaplan-Meier Time To Event Curves For Incident Antidepressant Prescriptions In 5 Years Following Recruitment To GS:SFHS



History of affective disorder is defined as previous history of single or recurrent episode MDD or bipolar disorder on the SCID interview. 'High' neuroticism is defined as a neuroticism score occurring in the upper tertile of Eysenck Personality Questionnaire-Short Form neuroticism scores, and 'low' is defined as occurring in the lower tertile. Abbreviations : "F" = Female. "M"=Male.

For comparison with Table 5.6, a complete case analysis (N=6855) for the time-to-event Cox regression is shown below in Table 5.7.

Table 5.7 : Complete Case Analysis Cox Regression of Time to Antidepressant Use in Generation Scotland Cohort (Excluding those Already Using Antidepressants At Time Of Recruitment), n=6855

	Multivariable		
	Hazard Ratio	p(FDR)	Sig
Intercept			
Sex: Male	Ref	Ref	
Sex: Female	1.83(1.59-2.10)	<0.001	***
Age 18-24	Ref	Ref	Ref
Age 25-34	0.77(0.59-1.01)	0.126	
Age 35-44	1.00(0.78-1.28)	1.00	
Age 45-54	1.02(0.80-1.31)	0.919	
Age 55-64	0.77(0.60-0.99)	0.093	.
Age 65-74	0.48(0.35-0.66)	<0.0001	***
Age 75+	0.77(0.51-1.15)	0.30	
No MDD on Screening	Ref	Ref	Ref
MDD – Single Episode	2.13(1.76-2.58)	<0.001	***
MDD – Recurrent	1.99(1.57-2.51)	<0.001	***
MDD – Bipolar	1.49(0.62-3.60)	0.491	
Never Smoked	Ref	Ref	Ref
Currently Smoke	1.54(1.31-1.82)	<0.0001	***
Ex-Smoker	1.38(1.19-1.59)	<0.0001	***
SIMD – Most deprived quintile	1.30(1.06-1.60)	0.026	*
SIMD – 2nd quintile	1.15(0.95-1.40)	0.245	
SIMD – 3rd quintile	1.10(0.90-1.34)	0.458	
SIMD – 4th quintile	0.99(0.83-1.19)	0.951	
SIMD – Least deprived quintile	Ref	Ref	Ref
Neuroticism	1.12(1.10-1.15)	<0.0001	***
SPQ	1.03(1.01-1.05)	0.002	*
g	0.90(0.85-0.94)	<0.0001	***
No physical health complaints	Ref	Ref	Ref
1-2 physical health complaints	1.25(1.09-1.44)	0.004	*
3+ physical health complaints	2.05(1.45-2.89)	<0.0001	***

Table 5.8: Crude and Age-Sex Reweighted Prevalence of Antidepressants in Generation Scotland 2010-2016

Antidepressant Prevalence	2010	2011	2012	2013	2014	2015	2016
All antidepressants							
Crude	13.9(13.3-14.6)	14.8(14.2-15.5)	15.7(15.0-16.4)	16.3(15.6-17.0)	17.1(16.4-17.9)	17.8(17.1-18.5)	18.3(17.6-19.1)
Age-Sex Reweighted	12.7(12.0-13.5)	13.7(13.0-14.5)	14.4(13.6-15.2)	15.0(14.2-15.8)	16.0(15.2-16.9)	16.5(15.7-17.4)	17.3(16.5-18.3)
Exc. Low dose amitriptyline							
Crude	11.0(10.5-11.6)	11.7(11.1-12.3(	12.5(11.8-13.1)	12.7(12.1-13.4)	13.4(12.8-14.1)	14.1(13.5-14.8)	14.7(14.0-15.4)
Age-Sex Reweighted	9.9(9.3-10.6)	10.6(9.9-11.2)	11.3(10.7-12.0)	11.7(11.0-12.5)	12.4(11.7-13.2)	12.9(12.3-13.7)	13.9(13.1-14.7)

5.7 Discussion

5.7.1 Summary of Main Results

In this study, we demonstrate an increase in antidepressant usage in this UK cohort, with an estimated 17.3% of the adult population using antidepressants in 2016, an increase of nearly one third (36.2%) on 2010 (see Table 5.8 above). We have found that, even if low dose amitriptyline use is discounted, one fifth of our sample (20.8%) has been prescribed an antidepressant at least once between 2012-16. The prescribing of antidepressants continues to be dominated by the SSRI class, but we observed a rise in the proportion of SNRIs, and other antidepressants such as mirtazapine, prescribed. This is an interesting trend and may be further stimulated by future revisions of clinical guidance, which may recategorize mirtazapine as a first-line treatment in psychiatric disorders such as major depression, leading to further increases in prevalence of use and interest in the efficacy and safety profile of mirtazapine and other non-SSRI antidepressants (Coupland et al., 2015; Cipriani et al., 2018).

Our findings accord with recent UK data which has found that antidepressant prescribing is the highest ever at 64.7m prescriptions for England in 2016 (NHS Digital, 2017). However, in this study we also found a reweighted incidence for new antidepressant users of just 2.4%, and a duration for antidepressant episodes of in excess of 15 months in nearly half of episodes identified. This supports the hypothesis of increased longer-term use by regular antidepressant users driving much of the increased prevalence of antidepressants we report. Our study also found that

adherence to antidepressants was relatively high, meeting the more conservative PDC threshold adherence of 80% in 69.0% of cases.

We found that history of affective disorder, multiple physical comorbidities, and being female, were the most predictive of antidepressant use. We also report an interesting association between neuroticism and antidepressant use, with considerably greater incident antidepressant use in the upper tertile of EPQ-SF neuroticism scores (Figure 4.4). Neuroticism is a personality trait with significant clinical overlap with psychiatric disorder (Smith et al., 2016), which is relatively straightforward to measure prospectively, and our results suggest that it could be a useful predictor of future antidepressant usage. A recent study in older adults (Steffens et al., 2018)has found that neuroticism may be also associated with lower remission rates of antidepressant-treated depression. As discussed in the methods, extraversion was not found to be significant on model fitting and was not included in this analysis.

We also found that cognitive function had an inverse association with antidepressant use, in line with previous research indicating an association between cognitive impairment and MDD (Marazziti et al., 2010). Evidence is accumulating of the presence of cognitive impairment with depressive disorder(Sumiyoshi et al., 2019). It has also been shown that lower baseline cognitive performance (by the measure of lower IQ) carries increased risk of later depression(Zammit et al., 2004). It is therefore possible that greater antidepressant prescribing is associated with worsened cognitive function scores because lower cognitive function is associated with depression. In addition, depressive illness could be associated with cognitive impairment although evidence for this is mixed and studies in mild cognitive impairment (MCI) and dementia suggests that depression accompanies MCI but does

not preceed it(Richard et al., 2013). Antidepressant use is associated with improvement in some measures of cognitive function(Rosenblat et al., 2015).

With this study methodology we cannot judge definitely whether the increasing antidepressant prevalence we found is appropriate to clinical indication. The prevalence of prescribing we report should be seen in the context of not only the prevalence of MDD, but the prevalence of anxiety disorders, eating disorders, sexual disorders, sleep disorders and other indications for antidepressant medication.

Nevertheless, it has also been argued that current rates of antidepressant treatment may still not identify all those most likely to benefit (Kendrick et al., 2005). The National Health and Nutrition Examination Surveys 2005-08 (Pratt et al., 2011) found that only one third of those with severe depressive symptoms were on antidepressant therapy, and less than half of those taking multiple antidepressants had seen a mental health professional in the past year. In our study, we found that, among those antidepressant naïve individuals with the highest psychiatric 'caseness' according to GHQ scores in Generation Scotland, just 6.6% were prescribed an antidepressant within one year of follow-up, and less than 10% of those with the highest severe depression caseness (three standard deviations on the GHQ-28 D subscale) were prescribed an antidepressant within one year. This might indicate potential unmet clinical need for antidepressants, although such a conclusion should be approached with caution as GHQ is a measure of psychiatric distress at one timepoint, and higher GHQ scores do not necessarily indicate requirement for antidepressants.

It has also been previously argued that antidepressants are insufficiently reviewed by clinicians, leading to unnecessarily long treatment durations (Bosman et al., 2016;

Johnson et al., 2012). The European Study of the Epidemiology of Mental Disorders (ESEMed) demonstrated that 63.5% of those with mood disorders had not consulted health services in the previous 12 months (Alonso J, 2004), with similar findings in the US National Comorbidity Survey Replication (Wang et al., 2005). We found that only a small minority of antidepressant users are being reviewed in outpatient psychiatry, suggesting that the majority of antidepressant monitoring takes place in primary care. The high prevalence of antidepressant use we report suggests that there may be scope for increasing the rate of medication reviews for long-term antidepressant users in primary (and secondary) care, with consideration of managed discontinuation of treatment. This can help manage the risks associated with prolonged antidepressant exposure when a sustained recovery from illness has been achieved.

Indeed, in recent years there has been a drive by government in both the UK and Scotland to reduce the prevalence of antidepressants. The Chief Medical Officer of Scotland has convened a working group of experts (Short Life Working Group On Prescription Medicine Dependence And Withdrawal) to examine prescribing trends, including for antidepressants. This has made recommendations for further research to isolate withdrawal effects of antidepressants from the original disorder and its return; optimal recommended withdrawal regimes and prevention or treatment of dependence or withdrawal(Scottish Government, 2021). The Royal College of Psychiatrists has released a position statement on antidepressants and depression (Royal College of Psychiatrists, 2019). This document expresses concerns about long-term use of antidepressants (beyond 2 years) and withdrawal management. It recommends that all antidepressants are tapered prior to discontinuation to minimise withdrawal reactions and failed discontinuation. This study has identified that there is

increased antidepressant prevalence associated with long prescription cycles and that the vast majority is being managed, it would seem, in primary care. Regular reviews of the usefulness of continuing antidepressant medication in general practice would appear therefore to be the most tractable approach to meeting government objectives.

Among medications frequently also prescribed with antidepressants, the most common psychiatric class was anxiolytics, especially benzodiazepines and “Z-drugs”. We found that prescribing of analgesic and opiate medication was appreciably higher in antidepressant users, especially those with a history of recurrent depression and bipolar disorder. An association between depression and pain has been previously described (McIntosh et al., 2016a) and could be related to altered pain sensitivity in depressed states and comorbidity of depression with painful conditions.

5.7.2 Comparison with Previous Studies

A previous prescribing database study of the Tayside population of Scotland (n=325,000) (Lockhart and Guthrie, 2011) found an increase in prevalence from 8.0% in 1995/96 to 13.4% in 2006/07. The standardised rate for 2006-07 antidepressants was 13.1% (SSRIs 7.9%, TCAs 5.2%, other antidepressants 1.9%) compared to the reweighted 2016 rates of 17.3% (10.5%, 5.8%, 3.2%) found in our study. Analysis of the UK Clinical Practice Research Datalink (CPRD, N=1,524,201) found that 23% of individuals were prescribed at least one antidepressant between 1995 and 2001 (Mars et al., 2017).

Results from the US National Health and Nutrition Examination Survey (NHANES) found a 2009-10 annual prevalence of 10.4% (Mojtabai and Olfson, 2014), with 67.4% reporting use for 24 months or longer, and 17.1% for <6 months. Incidence was estimated at 2.55% (per 100 individuals per year) in comparison with our estimated incidence of 2.4%. In this US study, 32.5% of antidepressant users had visited a mental health professional in the previous year, compared with 10.0% in our UK-based study.

A prescription database study in British Columbia conducted in 2004 (Raymond et al., 2007) found a prevalence of 7.2% and found that lower socioeconomic groupings and lowest income groupings had higher prevalence of antidepressant use. In our time-to-event analysis we found the lowest SIMD quintiles were associated with antidepressant use in univariate analysis but not in the multivariable model.

A recent study of routine general practice care data in a cohort based in Amsterdam (n=156,620) found 43.7% of antidepressant users were long-term users (Huijbregts et al., 2017), which is similar to our own finding of 44.8%.

5.7.3 Strengths and Limitations

This study benefitted from the relatively large population-based GS:SFHS cohort and the availability of structured clinical interview data alongside quantitative measures of non-specific psychiatric morbidity and numerous demographic, socio-economic and psychological variables. The national prescribing and morbidity data to which it was linked was of high fidelity (with a capture rate in excess of 95%) and, being nationally

based, reduced the chance of individuals being lost to follow up during the study period due to, for example, moving their GP practice.

We were also able to record the date of dispensing as well as prescribing, and whether the medication was collected. By applying a longitudinal retrospective design rather than a cross-sectional approach, this study increased the potential for accurate measurement of the pharmaco-epidemiological variables.

However, by using a cohort study as its basis, this analysis is also susceptible to selection and confounding biases. Another significant limitation is the lack of details of the indication of medication use in the PIS prescribing data (as with many other prescribing databases based on routinely collected administrative data). In GS:SFHS, previous history of affective disorder was collected via screening using the SCID, but we were not able to determine ongoing and subsequent psychiatric diagnoses in the period studied following GS:SFHS recruitment. It is likely that a proportion of those individuals with no previous history of affective disorder were subsequently diagnosed with such, or that other psychiatric disorders such as anxiety disorders were the indication for later antidepressant treatment. GS:SFHS did not provide data on baseline history of anxiety disorders to complement the SCID-derived history of affective disorders. We were also not able to determine the extent to which severity of psychiatric symptoms or level of functional impairment determines antidepressant usage.

Prescribing data is also an imperfect proxy for medication use, given that the medication may not be taken (primary noncompliance) or may not be used as directed (secondary noncompliance). Noncompliance to antidepressant medication has been

previously estimated at 50% (Haynes et al., 2008). The PIS prescribing data only covered prescriptions issued in the community, and therefore may underestimate true prevalence and treatment duration, although it would be expected that most antidepressant users commenced in hospital would continue medication in the community. A further limitation of our study being based on routinely collected administrative prescribing data is that it is also not possible to determine the extent to which the antidepressant prescribing we recorded was appropriate to clinical need or consistent with treatment guidelines.

Although we attempted to apply stringent criteria for incident use of antidepressants – using prescription data, linked morbidity data, self-report and objectively measured history of affective disorder to screen antidepressant naïve cohort members – we may still have falsely identified some previous antidepressant users as incident cases, particularly as we did not have data preceding April 2009.

Our Cox regression analysis of predictors of antidepressant use within 5 years was necessarily restricted by the variables available to us in GS:SFHS. We were able to derive effect sizes for numerous variables previously associated with antidepressant use, such as history of affective disorder, medical comorbidities and female gender. However, due to the limited diagnostic information available in GS:SFHS we were not able to quantify the association between non-affective psychiatric disorders such as anxiety disorders (which are likely to be significantly predictive) and antidepressant use. The conclusions of our time-to-event analysis need to be placed in the context of the variables available in our model.

The cohort was also for adults only, thereby not including antidepressant use among the under 18s, and the overall population prevalence and incidence would be expected to be lower than our figures since children are prescribed antidepressants less frequently.

5.7.4 Future Directions and Clinical Implications

We found that antidepressant prevalence was higher than previously reported for the UK, but that incidence remains relatively stable. This suggests that increased antidepressant prevalence is driven by longer treatment durations and good levels of adherence, and previous users returning to medication for a wider range of indications, rather than an upsurge in incident cases.

Our study also demonstrates the utility of record-linking administrative health data to population-based cohorts to provide enhanced pharmaco-epidemiological estimates of prevalence, incidence and adherence. We also found significant relationships between neuroticism and cognitive function for antidepressant use, even when affective disorder was controlled for. These tests are relatively easy to administer and could prove useful to clinicians in constructing predictive models of clinical risk.

More research is required to investigate the clinical appropriateness of antidepressant prescribing. Our research suggests that the vast majority of antidepressant prescribing, and medication review, takes place in the primary care setting in the UK. Primary care will necessarily therefore remain the focal point for future efforts to improve antidepressant prescribing practices, monitoring of adherence and adverse effects, and managed discontinuation of treatment when clinically appropriate.

5.8 Concluding Remarks

In this chapter I have demonstrated using the example of antidepressant pharmaco-epidemiology how linked data can be used to enhance a cross-sectional cohort study to address a longitudinal research question.

The implications of this are potentially profound for existing population-based and selective cohorts, and also for biobanks. Increasingly, we can speculate that researchers will incorporate into the study design of cohorts the ability to link to administrative health data and also to regularly update this data. Further effort should be made by funding bodies, research ethics and governance administrations, and the research community to simplify the process of obtaining regular releases of new data to improve the quality of longitudinal analyses.

However, it is important to remember that a data-linked cohort study is not the same as a true longitudinal study. When choosing appropriate statistical tools for analysis, researchers need to pay close attention to the time points at which predictor and outcome variables were measured. For example, in the cohort phenotypic data there is often only one time of measurement, at recruitment, whereas in linked data there are potentially far more available timepoints. The applicability of certain statistical techniques, such as structural equation modelling, depends on the temporal sequence of measurement of predictor and outcome variables.

Nevertheless, the linkage of administrative data to existing cohort data breathes new life into these datasets and offers researchers a range of potential new avenues for research. As I shall explore in the next chapter, as well as allowing the adoption of a

more longitudinal approach to cohort data, record-linkage also enables the defining of entirely new cases and phenotypes within the research population, allowing study of phenotypes that are less predisposed to accurate self-report and which researchers may not have considered when designing the original cohort.

Chapter 6: The Identification and Study of a New Self-harm Phenotype within a Population-based Cohort through Record-Linkage

6.1 Introductory Remarks

In Chapter 1, we saw that self-harm is a significantly prevalent behaviour which, given its emotive nature, is particularly likely to be affected by self-reporting and follow-up issues which constrain the ability of classical cohort studies to effectively study it.

Record-linkage to administrative health data offers the potential to augment existing cohort data with information on self-harm (at least that which appears in healthcare records) which the individuals involved may not otherwise feel comfortable to disclose. Thus, in the following chapter I demonstrate how linked data has allowed the GS:SFHS cohort, which did not at the time of recruitment take much information regarding self-harm (outside of what was collected in tools like the SCID and GHQ), to be used for a highly scaled, replicated, study of self-harm and the stress-response associated psychological trait neuroticism. The ability to *identify new phenotypes for study* is one of the core features of record-linkage to administrative health data that I have argued for in this thesis.

In the preceding chapter, I demonstrated that neuroticism is independently associated with antidepressant use, even when MDD status is included as a covariate. In this chapter I shall investigate whether neuroticism is also independently predictive of self-harm, another major MDD-associated outcome.

The following chapter has been published in the journal *Social Psychiatry and Psychiatric Epidemiology* (Hafferty et al., 2019a). As the first author of the publication I jointly conceived the study, performed the analysis, wrote the manuscript and prepared all the tables and figures. To acknowledge the contribution of the co-authors (see also Publications section of this thesis for breakdown of author contributions) the term “we” rather than “I” is used throughout this chapter.

6.2 Paper: The Role of Neuroticism in Self-Harm and Suicidal Ideation – Results from Two UK Population-Based Cohorts

6.3 Abstract

6.3.1 Background

Self-harm is common, debilitating and associated with completed suicide and increased all-cause mortality, but there is uncertainty about its causal risk factors, limiting risk assessment and effective management. Neuroticism is a stable personality trait associated with self-harm and suicidal ideation, and correlated with coping styles, but its value as an independent predictor of these outcomes is disputed.

6.3.2 Methods

Prior history of hospital-treated self-harm was obtained by record-linkage to administrative health data in Generation Scotland:Scottish Family Health Study (N=15,798; self-harm cases=339) and by a self-report variable in UK Biobank (N=35,227; self-harm cases=772). Neuroticism in both cohorts was measured using

the Eysenck Personality Questionnaire-Short Form (EPQ-SF). Associations of neuroticism with self-harm were tested using multivariable regression following adjustment for age, sex, cognitive ability, educational attainment, socioeconomic deprivation and relationship status. A subset of GS:SFHS was followed-up with suicidal ideation elicited by self-report (n=3342, suicidal ideation cases=158) and coping styles measured by the Coping Inventory for Stressful Situations. The relationship of neuroticism to suicidal ideation, and the role of coping style, was then investigated using multivariable logistic regression.

6.3.3 Results

Neuroticism was positively associated with hospital-associated self-harm in GS:SFHS (per EPQ-SF unit Odds Ratio 1.2 95% Credible Interval 1.1-1.2, p_{FDR} 0.0003) and UKB (per EPQ-SF unit Odds Ratio 1.1 95%Confidence Interval 1.1-1.2, p_{FDR} 9.8 $x10^{-17}$). Neuroticism, and the neuroticism-correlated coping style, emotion-oriented coping (EoC), were also associated with suicidal ideation in multivariable models.

6.3.4 Conclusions

Neuroticism is an independent predictor of hospital-treated self-harm risk. Neuroticism, and emotion-oriented coping styles, are also predictive of suicidal ideation.

6.4 Introduction

Suicide is a major global health challenge and is the leading cause of death among young people aged 20-34 years in the UK (Office of National Statistics, 2017). A variety of sociodemographic, biological and psychological risk factors have been proposed for completed suicide (for review, see (Turecki and Brent, 2016)). Among the most predictive, and potentially amenable to clinical intervention, are (1) history of self-harm, which is associated with 37.2 times increased risk of completed suicide within the first year following an act of self-harm(Olfson et al., 2017), and (2) suicidal ideation, which in a recent meta-analysis is associated with increased risk ratios for competed suicide of 2.35-8.00 (Hubers et al., 2018).

Self-harm is a common and debilitating behaviour characterised by self-injury or self-poisoning, irrespective of the apparent purpose of the act (National Collaborating Centre for Mental Health, 2004). Estimated lifetime prevalence of self-harm is 1-6%, with the UK reportedly having the highest self-harm rate in Europe (Horrocks, 2002). Incidence is estimated at 400/100,000 population per year (University of York, 1998). However, many people who self-harm do not attend clinical services, and thus true prevalence may be considerably greater (Hawton et al., 2002).

Self-harm is aetiologically associated with childhood maltreatment (Fergusson et al., 2000; Statham et al., 1998) and physical illness (De Leo et al., 2001). In addition, a number of demographic factors are predictive of self-harm, including being female (Schmidtke et al., 1996); young adulthood (Schmidtke et al., 1996); being unmarried (Schmidtke et al., 1996); or separated/divorced (Petronis et al., 1990); being

socioeconomically disadvantaged (Taylor et al., 2004); unemployed (Platt S., 2000); or low educational attainment (Rappaport et al., 2017).

Psychiatric illness also has well-known associations with self-harm (Skegg, 2005). One systematic review of non-fatal self-injury presenting to hospital reported a pooled prevalence for psychiatric disorder of 83.9%, with mood disorders the most common category (58.5%) (Hawton et al., 2013). The association between depressive disorder and self-harm has been found in numerous other studies (Colman et al., 2004; Beautrais, 2000).

6.4.1 Types of Self-Harm

Self-harm is performed with a variety of motivations, including attempted suicide, self-mutilation, seeking psychological relief, and the communication of distress. Often, there is not a single readily definable motivation, but multiple factors occurring simultaneously (Kapur et al., 2013). In the majority of cases, the intention is not to die (Skegg, 2005).

Given the difficulties encountered clinically in ascertaining intent and motivation, it has been argued that the terms ‘deliberate self-harm’, ‘self-harm’, ‘attempted suicide’ and ‘suicidality’ are imprecise for research purposes (Nock, 2010). Recently, the Fifth Edition of the Diagnostic and Statistical Manual for Mental Disorders (American Psychiatric Association, 2013) has proposed a distinction between ‘nonsuicidal self-injury’ (NSSI) and ‘suicidal behaviour disorder’ as ‘Conditions For Further Study’. However, it remains controversial whether such discrete categorizations can be confidently made in clinical practice, or demonstrate differentiable suicidal outcomes,

given the biases inherent in self-report, and the close association of NSSI with suicidal behaviour (Kapur et al., 2013) (Cooper et al., 2005). Broadly defined 'self-harm' therefore remains an important clinical outcome in current suicidology literature (Kapur et al., 2013; Hawton et al., 2015).

Another approach to subcategorising self-harm is on the basis of whether it has received hospital treatment. Hospital-treated self-harm is recognised as an important intervention point in suicide prevention (Carroll et al., 2014). Approximately one seventh to one fifth of those with hospital-treated self-harm will repeat their self-harm within one year (Olfson et al., 2015). Self-harm that requires medical attention significantly increases the future risk of suicide (Cooper et al., 2005), particularly if admission to hospital is required (Gibb et al., 2005). Within the UK, up to one fifth of those who die by suicide have attended hospital for self-harm in the preceding year (Gairin et al., 2003).

6.4.2 Suicidal Ideation

Suicidal ideation, additionally, is an important antecedent to progression to significant self-harm and suicide attempts (Kessler et al., 1999; Fergusson et al., 2000). Individuals who express suicidal ideation have significantly greater 12 month prevalence of self-harm and completed suicide, especially if there is associated planning (Turecki and Brent, 2016). Nevertheless, the relationship between self-harm and suicidal ideation is complex, with suicidal ideation having reportedly more than three times greater prevalence than suicide attempts (Nock et al., 2008).

6.4.3 Self-Harm and Psychological Characteristics

Both self-harm and suicidal ideation are associated with personality, including personality disorders (Haw et al., 2001) and normally-distributed personality traits. In particular, neuroticism is associated with suicidal ideation (Rappaport et al., 2017; Cox et al., 2004), suicide attempts (Pickles et al., 2010; Sharif et al., 2014), and suicide (Draper et al., 2014; Tanji et al., 2015). A systematic review of personality traits and suicidality (Brezo et al., 2006) found that neuroticism (and hopelessness) were the most predictive traits in risk screening.

Neuroticism is a partially-heritable personality trait which incorporates negative affectivity (McCrae and Costa, 1987; Eysenck, 1975) and increased sensitivity to stress (for review see(Lahey, 2009)). An important aspect of neuroticism is that individual differences in the trait are moderately to highly stable over many years (Conley, 1985; Gale et al., 2010) and thus might be useful as a patient level predictor for future self-harm risk. However, the link between neuroticism and self-harm is not wholly consistent and one large study did not find an association between neuroticism and lifetime history of prior suicide attempts (Cox et al., 2004).

Neuroticism is also highly correlated with affective disorder and both conditions show evidence of substantially overlapping genetic architecture (Navrady et al., 2017a; Kendler et al., 1993; Jardine et al., 1984). There is uncertainty about whether neuroticism is a significant predictor of self-harm irrespective of depressive disorder history (Farmer et al., 2001; Rappaport et al., 2017) or whether it is insignificant when comorbid depression is controlled for (Batterham and Christensen, 2012; Bi et al., 2012). A recent study (Rappaport et al., 2017) in Chinese females concluded that

neuroticism was significantly associated with suicide attempts even after controlling for comorbid depression and also stressful life events. Stressful life events are an additional posited factor in suicidal behaviour and it is hypothesised that neuroticism may serve to increase negative perceptions of these events (Kendler et al., 2003; Pickles et al., 2010).

6.4.4 Protective Factors and Coping Styles

While considerable work has been undertaken at elucidating risk factors for self-harm and suicidal ideation, less is known about protective factors, which are not merely the absence of risk (Skegg, 2005). One component of managing adversity is coping styles, the behavioural and cognitive strategies adopted in response to stressful life events. These are not only situational but may be environmentally and genetically conditioned (Folkman and Moskowitz, 2004). They are of particular interest because they are potentially modifiable and might be impacted by treatment (Chou, 2017; Eggert et al., 1995).

Coping strategies are elicited by questionnaires like the Coping Inventory for Stressful Situations (Endler, 1990) which yields three main groups of coping strategies. The first is a “task-“ or problem-oriented coping style (ToC), which is characterised by purposeful efforts aimed at problem solving. “Avoidance-orientated” (AoC) coping, by contrast, is defined by behaviours aimed at avoiding difficult circumstances (Cosway, 2000). Finally, “emotion-orientated” coping (EoC) is characterised by attempts to regulate difficult emotions as a means of coping.

While ToC is generally seen as positively related to health and psychological adaptation, AoC and EoC are generally seen as less psychologically adaptive, and have been associated with negative mental health outcomes(Higgins, 1995). Task-oriented coping is thought to be negatively correlated with neuroticism (Connor-Smith and Flachsbart, 2007) while emotion-oriented coping is positively correlated (Endler and Parker, 1990). Moreover, emotion- and avoidance- oriented coping are thought to be associated with greater risk of suicidal ideation, while task-oriented coping is associated with lower risk (Chou, 2017).

6.4.5 Outline of Study

In the first part of the study, we aimed to investigate the relationship between neuroticism and hospital-treated self-harm. We employed two large UK population-based cohorts with neuroticism quantified by the same Eysenck Personality Questionnaire-Revised Short Form (EPQ-SF) scale. In one cohort, Generation Scotland (GS:SFHS), we used record-linkage to administrative health data to identify individuals with previous hospital-treated self-harm (generally defined and including all types of intentional self-injury requiring admission to medical or psychiatric hospital, N=15,798; self-harm cases=339). In the second cohort, UK Biobank (UKB), we used self-reported intentional self-harm (whether or not with intention to end life) requiring hospital treatment (including emergency department) and/or review by psychiatric services (N=35,227; self-harm cases=772). We hypothesised that neuroticism would be positively associated with self-harm, even after adjustment for depressive disorder and other significant sociodemographic factors.

In the second part of the study, we employed a follow-up sample of GS:SFHS with contemporaneous self-reported measures of suicidal ideation (n=3356, suicidal ideation cases=161). This follow-up group also had self-reported questionnaire data on significant life events and coping styles in response to stress. We hypothesised that neuroticism would also be independently predictive of suicidal ideation in this group, when adjusted for depressive disorder, significant life events and other significant demographic factors. We also aimed to ascertain the relationships on suicidal ideation of coping styles, particularly those correlated with neuroticism.

6.5 Methods

6.5.1 Cohorts

Generation Scotland:Scottish Family Health Study (GS:SFHS) was a population- and family-based epidemiological adult (age 18+) cohort recruited February 2006-March 2011, which has been described elsewhere (Smith et al., 2006; Smith et al., 2013a). GS:SFHS had a higher proportion of females (59%) and was of older age (mean 49 males, 49 females) compared to the Scottish population (mean 37 males, 39 females, 2001 census) (Smith et al., 2013a). GS:SFHS participants were typically healthier and more affluent than the general Scottish population, nevertheless 32.9% of individuals lived in areas with worse than average socioeconomic deprivation (Smith et al., 2013a). 99% of the study group was of white ethnicity (Scottish population 98%). Sociodemographic information on age, sex, educational attainment and relationship status were collected by questionnaire on enrolment.

Neuroticism was measured using the Eysenck Personality Questionnaire-Revised Short Form (EPQ-SF) (Eysenck, 1985). The neuroticism subsection of the EPQ-SF consists of 12 'Yes/No' questions (e.g. 'Are you a worrier?'). Scores range from 0 to 12, with higher scores indicating greater neuroticism. This scale has been concurrently validated with other quantitative measures of neuroticism (Gow, 2005) and has high reported reliability (α-coefficients 0.85-0.88) (Eysenck, 1985).

Trained researchers elicited lifetime history of major depressive disorder (MDD) by using the screening questions from the Structured Clinical Interview for DSM-IV Disorders (Smith et al., 2013a) and, if either screening question was positive, going on to administer the mood sections of the SCID. The screening questions were: "*Have you ever seen anyone for emotional or psychiatric problems?*" and "*Was there ever a time when you, or someone else, thought you should see someone because of the way you were feeling or acting?*". A diagnosis of MDD was made according to DSM-IV criteria and all interviews were conducted by a trained researcher (2011 cases identified, 12.7% of cohort). Individuals with a history of bipolar disorder were excluded.

Cognitive testing included the digit symbol substitution test from the Wechsler Adult Intelligence Scale III (Wechsler D, 1998a), logical memory from the Wechsler Memory Scale III (Wechsler D, 1998b) and verbal fluency (Lezak MD, 1995). From these tests, a measure of cognitive function (*g*) was derived as the first unrotated principal component, explaining 44% of the variance in scores (Marioni et al., 2014). Loadings for processing speed, vocabulary, verbal declarative memory and executive function were 0.43, 0.53, 0.49 and 0.54 respectively. The range of *g* was -4.48 to 8.96, mean 0.00, one standard deviation 1.3. Socioeconomic deprivation was determined using

the Scottish Index of Multiple Deprivation 2009 (SIMD) (Scottish Government, 2009). This measure employs 6976 geographical area-based data-zones across Scotland which are then ranked in order of deprivation, ascertained through weighted scores in seven domains including employment, education, health, housing and crime, with data-zone 1 the most deprived and 6976 the least deprived.

6.5.2 Identification of Self-Harm in GS:SFHS

All Scottish citizens registered with a General Practitioner are assigned an unique identifier, the Community Health Index (CHI). This was used to deterministically record-link GS:SFHS participants to the Scottish Morbidity Records to obtain information about hospital admissions (SMR01) and psychiatric hospital admissions (SMR04) associated with self-harm. Written informed consent was obtained from 98% of GS:SFHS and only those who consented were linked. Self-harm cases were identified by matching to admissions codes with E950-E959 (ICD-9) or X60-X84, Z915, E98 and Y1-Y3 (ICD-10) (Batty et al., 2010). Scottish NHS data on mortality was also linked, to exclude any GS:SFHS participants who died during follow-up.

6.5.3 Recontact Group and Identification of Suicidal Ideation in GS:SFHS

In 2014, GS:SFHS participants were re-contacted for a follow up assessment of mental health (Navrady et al., 2018). Suicidal Ideation was elicited using two questions from the General Health Questionnaire-28 (Goldberg and Hillier, 1979). Participants were asked *"During the past few weeks…Have you thought of the possibility you might make away with yourself?"* and *"Have you found the idea of taking your own life kept coming into your mind?"*. Participants who answered

'Definitely have' or 'Has crossed my mind' to either question were defined as suicidal ideation cases (n=3503, cases=158 (4.7%)).

Stressful life events were ascertained using the List of Threatening Experiences (LTE), whereby respondents self-reported their experiences from a list of 12 common threatening life events, occurring in the preceding six months (Brugha et al., 1985; Brugha and Cragg, 1990). Examples of LTE include "*Serious injury or assault to yourself*", "*Made redundant or sacked from job*" and "*marital difficulties or break off of a steady relationship*" (for full list see Figure 6.1 below). For each event endorsed, contextual threat was rated on a scale from 3 ("*very bad*") to 1 ("*not too bad"*). The LTE has demonstrated high test-retest reliability and good agreement with informant information (Cohen's κ 0.63-0.90) (Brugha and Cragg, 1990).

Figure 6.1 - The List of Threatening Experiences

List of Threatening Experiences (LTE)

1. Serious injury or assault to yourself
2. Serious injury or assault to a close relative
3. Death of a parent, spouse, child or sibling
4. Death of a close family friend or other relative
5. Separation due to marital difficulties or break up of a steady relationship
6. Serious problem(s) with close friend, neighbour or relative
7. Made redundant or sacked from job
8. Seeking work unsuccessfully for more than one month
9. Major financial crisis (such as losing three month's income)
10. Problems with the police involving court appearance
11. Something of value lost or stolen
12. Yourself or your partner give birth

Source: Brugha, T., Bebbington, P., Tennant, C., & Hurry, J. (1985). The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychological Medicine*, 15(1), 189-194.

Coping styles were elicited using the Coping Inventory for Stressful Situations (CISS) (Endler, 1990; Cosway, 2000), a 48 item self-report questionnaire enabling responders to rate on a 5-point scale their engagement in coping styles in response to stress, including task-, avoidance- and emotion-oriented coping. The CISS shows robust validity and reliability (alpha reliability coefficients (Cronbach's alpha) of 0.82-0.90 for the main factors) (Cosway, 2000). History of MDD was re-ascertained using the Composite International Diagnostic Interview – Short Form (CIDI-SF) self-report questionnaire (Kessler, 1998), with 605 cases identified (18.1% of sample). Bipolar disorder cases were excluded. Unlike the main GS:SFHS cohort, only one member from each family was analysed (i.e. unrelated sample).

6.5.4 Identification of Self-Harm in UK Biobank

UK Biobank is a population-based cohort of adults aged 40-69 recruited across the UK from 2006-2010, which has been described elsewhere (Sudlow et al., 2015). During baseline assessment (Smith et al., 2013b) participants provided socio-demographic information via a touch-screen questionnaire, including educational attainment and whether they lived as a singleton or couple. This study included a subset of 35227 (7.0%) of UKB with complete case information for the variables of interest. Individuals in UKB who were also present in GS:SFHS (n=201) were excluded.

Self-harm was ascertained through the touch-screen questionnaire. Participants were asked "*Have you deliberately harmed yourself, whether or not you meant to end your life?*". A follow-up question enquired "*Following any time when you took an overdose*

or deliberately tried to harm yourself did you (tick all that apply)". Participants who ticked "*see anyone from psychiatric or mental health services, including liaison services*" and/or "*need hospital treatment (e.g. A&E)*" were included as cases in this study (772 cases, 2.2% of sample). The other answers, which were not included as cases, were "*use a helpline*", "*see own GP*", "*receive help from friends/family*" and "*prefer not to answer*".

Neuroticism was assessed using the EPQ-SF(Eysenck, 1985), administered via the touch-screen questionnaire. Lifetime history of depression was ascertained by touch screen questionnaire relating to lifetime experience of depressive symptoms and contact with mental health services (Smith et al., 2013b).

Cognitive testing was administered via three touch-screen tests: (1) a symbol matching task over 12 trials (reaction time) (2) 13 logic/reasoning questions over two minutes (verbal-numerical reasoning) (3) card pair matching task (visuo-spatial memory). From these tests a single measure of cognitive ability (*g*) was extracted as the first unrotated principal component, explaining 42% of the variance. Loadings for visuo-spatial memory, verbal-numerical reasoning and reaction time were 0.58, -0.62 and 0.53 respectively. The range of *g was* -4.35 to 5.6, with a mean of 0.0 and one standard deviation equating to 1.12.

Socio-economic deprivation was measured via the Townsend Deprivation Index, a census-based measure incorporating unemployment, non-home ownership, household overcrowding and non-car ownership (Jarman et al., 1991). Each small postcode-based geographical area is assigned a Townsend Score, with zero

indicating mean deprivation, negative scores indicating relative affluence, and positive scores indicating relative deprivation.

6.5.5 Statistical Analysis

All analyses were carried out using R version 3.2.3 (R Core Team, 2015). Complete case analysis was employed in both cohorts (see Table 6.1 for analysis of complete case versus whole-cohort variables). Generalised linear models with logit-link function (logistic regression) were used to identify predictors of self-harm in UK Biobank. In the GS:SFHS self-harm study, additional adjustment for inter-relatedness of the family-based cohort was performed using a Bayesian mixed model approach, with pedigree fitted as a random effect, using an inverse pedigree matrix within the R package MCMCglmm. This implements a Markov Chain Monto Carlo estimator, with a "threshold" family probit link function which produces similar results to a logit function, optimised to pedigree based mixed effects models.

In the GS:SFHS and UKB multivariable analyses of hospital-treated self-harm, predictor variables are reported unstandardized.

TABLE 6.1.A - Complete Case versus Whole Sample Proportions and Missing Data for GS:SFHS and UKB Analysis of Predictors of History of Self-harm requiring Hospital Attendance

GS:SFHS	15798		20685		χ^2 **test**	**UKB**						**Cohens h**
	Complete Cases	%	**Whole Sample**	**%**	**p**		**Complete Cases**	**%**	**Whole Cohort**	**%**	**p**	**Effect size**
Male	6544	41.4	8489	41.0	0.46	Male	16092	45.7	22498	46.2	0.11	
Female	9254	58.6	12196	59.0		Female	19135	54.3	26164	53.8		
18-24	1506	9.5	1963	9.5	0.89	18-24	N/A		N/A			
25-34	2115	13.4	2711	13.1	0.43	25-34	N/A		N/A			
35-44	2965	18.8	3836	18.5	0.59	35-44	3328	9.4	4601	9.5	0.97	
45-54	3448	21.8	4603	22.3	0.33	45-54	9899	28.1	13623	28.0	0.74	
55-64	4184	26.5	5313	25.7	0.09	55-64	16325	46.3	22972	47.2	0.013	0.02
65-74	1255	7.9	1713	8.3	0.24	65-74	5675	16.1	7466	15.3	0.0026	0.02
75+	325	2.1	546	2.6	0.0003	75+			0			
No MDD	13787	87.3	17998	87.0	0.46	No MDD	23054	65.4	30840	63.4		
History MDD	2011	12.7	2687	13.0		History MDD	12173	34.6	17822	36.6	$6.5x10^{-10}$	0.04

Missing Data						**Missing Data**						
SIMD/Townsend			1208	5.8		SIMD/Townsend			66	0.1		
EPQ Neuroticism			1758	8.5		EPQ Neuroticism			0	0.0		
Living as couple			839	4.1		Living as couple			0	0.0		
Education			2097	10.1		Education			101	0.2		
Cognitive ability(g)			475	2.3		Cognitive ability(g)			6086	12.5		

Abbreviations: χ^2 = Chi-squared test p = p-value MDD = Major Depressive Disorder SIMD = Scottish Index of Multiple Deprivation EPQ = Eysenck Personality Questionnaire

TABLE 6.1.B – Analysis of Complete Case versus Whole Sample proportions and missing data for GS:SFHS follow-up analysis of predictors of suicidal ideation

Follow up study on suicidal ideation					χ^2 test
	Complete Cases	%	Whole Cohort	%	p value
Male	1399	39.9	1534	38.7	0.27
Female	2104	60.1	2432	61.3	
18-24	23	0.7	23	0.6	0.67
25-34	232	6.6	247	6.2	0.49
35-44	355	10.1	385	9.7	0.54
45-54	785	22.4	871	22.0	0.64
55-64	1221	34.9	1391	35.1	0.84
65-74	780	22.3	913	23.0	0.44
75+	107	3.1	136	3.4	0.36
No MDD	2829	80.8	3200	80.7	0.94
History MDD	674	19.2	766	19.3	
No SH	3410	97.3	3842	96.9	0.23
History SH	93	2.7	124	3.1	

Missing Data				%	
SIMD/Townsend			0	0.0	
EPQ Neuroticism			0	0.0	
List of threatening experiences			10	0.3	
CISS Emotion oriented coping			144	3.6	
CISS Task oriented coping			204	5.1	
CISS Avoidance oriented coping			172	4.3	

Abbreviations: χ^2 = Chi-squared test p = p-value MDD = Major Depressive Disorder SIMD = Scottish Index of Multiple Deprivation EPQ = Eysenck Personality Questionnaire SH = Self-harm CISS = Coping Inventory for Stressful Situations

In the GS:SFHS suicidal ideation follow-up study, an unrelated sample was used and multivariable logistic regression was employed. In this analysis, continuous variables were scaled to have a mean of zero and standard deviation of one, to facilitate interpretation of the CISS and LTE predictor variables. During fitting of models, interaction terms for neuroticism and depression, and neuroticism and coping styles, were tested to investigate potential moderation on neuroticism.

Coefficients were expressed as odds ratios with 95% credible intervals and 95% confidence intervals as applicable. P values were reported after False Discovery Rate adjustment (Benjamini, 1995). Group differences between numeric variables were ascertained using Cohen's t-test and Cohen's *d* measure of effect size, and differences between proportions were assessed using z-test and Cohen's *h*. For all analyses, we have reported all measures, conditions, data exclusions and the determination of sample sizes and further information is available in Table 6.1.

6.6 Results

6.6.1 GS:SFHS

As presented in Table 6.2, there were 339 (2.1%) GS:SFHS individuals identified with previous self-harm requiring hospital admission. Self-harm cases were slightly younger (mean age 44.7 versus 47.1, p=<0.001, Cohen's *d*=0.16), predominantly female (66.7% versus 58.4%, p0.002, Cohen's *h*=0.17), with lower mean cognitive ability scores, greater prevalence of depression history (47.5% versus 12%, p<0.001, *h*=0.81)and with higher mean neuroticism (mean 6.4 versus 3.7, p<0.001, *d*=0.89).

Self-harm cases were more likely to be from more deprived areas as measured by SIMD (mean 1964 versus 1823, p<0.001, *d*=0.58). The proportion of graduates was lower in self-harm cases (17.1% versus 33.9%, p<0.001, *h*=0.39).

A greater proportion of self-harm cases reporting being single (51.9% versus 31.7%, p<0.001, *h*=0.31).

Table 6.2: Socio-demographic, clinical and cognitive characteristics of GS:SFHS (N=15798) and UK Biobank (N=35227) cohorts used in this study

	GS:SFHS (N=15798)			UKB (N=35227)		
	Self-Harm (%/s.d.)	Controls (%/s.d.)	p value (effect size)	Self-Harm (%/s.d.)	Controls (%/s.d.)	p value (effect size)
Total	339(2.1)	15459		772(2.2)	34455	
Female	226(66.7)	9028(58.4)	0.002 (0.17)	544(70.5)	18591(54.0)	<0.001 (0.34)
Age	44.7 (12.3)	47.1(15.0)	0.0005 (0.16)	53.3(7.6)	56.6(7.7)	<0.001(0.43)
Age categories :						
18-24	18(5.3)	1488(9.6)				
25-34	57(16.8)	2058(13.3)				
35-44 (GS:SFHS) / 40-44 (UKB)	94(27.7)	2871(18.6)		113(14.6)	3215(9.3)	
45-54	87(25.7)	3361(21.7)		311(40.3)	9588(27.8)	
55-64	71(20.9)	4113(26.6)		300(38.9)	16025(46.5)	
65-74	10(2.9)	1245(8.1)		48(6.2)	5627(16.3)	
75+	2(0.6)	323(2.1)				
History of depression	161(47.5)	1850(12.0)	<0.001 (0.81)	699(90.5)	11474(33.3)	<0.001 (1.3)
EPQ Neuroticism (mean)	6.4(3.5)	3.7(3.1)	<0.001 (0.89)	5.6(3.1)	3.3(2.8)	<0.001 (0.83)

Continued on next page…

Table 6.2 cont.

	Self-Harm (%/s.d.)	Controls (%/s.d.)	p value (effect size)	Self-Harm (%/s.d.)	Controls (%/s.d.)	p value (effect size)
Cognitive ability scores (mean):						
Verbal Declarative	15.5(4.4)	16.3(3.9)	0.003 (0.19)			
Vocabulary	28.4(4.8)	30.3(4.7)	<0.001 (0.40)			
Processing Speed	67.3(16.9)	73.1(16.9)	<0.001 (0.34)			
Executive Function	23.8(8.2)	25.9(8.1)	<0.001(0.26)			
Visual Memory				1.4(0.6)	1.4(0.6)	0.20
Verbal-Numerical Reasoning				6.8(2.1)	6.7(2.1)	0.25
Reaction Time				6.3(0.2)	6.3(0.2)	0.10
SIMD rank (mean, most deprived rank 1, least deprived rank 6976)	2918(1964)	3993(1823)	<0.001 (0.58)			
Townsend score (mean)				-0.5(3.1)	-1.7(2.6)	<0.001 (0.44)
Education : No qualification or other	83(24.5)	1897(12.3)	<0.001 (0.32)	34(4.4)	2082(6.0)	0.06
O-levels/GCSEs	52(15.3)	1882(12.2)		155(20.1)	6907(20.1)	
CSE or equivalent				37(4.8)	1330(3.9)	
A-levels or equivalent	29(8.6)	1808(11.7)		116(15.0)	4712(13.7)	
NVQ or equivalent	117(34.5)	4636(30.0)		39(5.1)	1773(5.2)	
Other professional				33(4.3)	1802(5.2)	
College or university degree	58(17.1)	5236(33.9)	<0.001 (0.39)	358(46.4)	15849(46.0)	0.83
Living as single	176(51.9)	4906(31.7)	<0.001 (0.31)	306(39.6)	7930(23.0)	<0.001 (0.36)

Percentages are shown in brackets for categorical variables and standard deviations for continuous variables. Probability (p) values are derived from Cohen's t-tests for continuous variables and z-tests for proportions. Effect sizes are derived from Cohen's *d* for numeric variables and Cohen's *h* for categorical variables. Townsend scores are standardised – positive values of the index indicate areas of high material deprivation, negative values indicate relative affluences, and score 0 indicates mean values. Abbreviations: GS:SFHS = Generation Scotland, UKB = UK Biobank, SIMD = Scottish Index of Multiple Deprivation; s.d. = standard deviation. O-levels/GCSEs = ordinary level (Year 11) school certificate. CSE=Certificate of Secondary Education (Year 11). A-levels = Advanced level (Year 13) school certificate.

The most predictive factor for previous self-harm (Table 5.3) was history of major depressive disorder (OR 5.6 95% Credible Interval (CI) 3.5-8.9, p_{FDR} 0.0004). Neuroticism was positively associated with self-harm risk by an odds ratio of 1.2 (95%CI 1.1-1.2, p_{FDR}=0.0003) per EPQ-SF unit. No significant interaction terms were found during model fitting.

The significant effects of neuroticism were found in both male-only and female-only combined models (see Table 6.4). Figure 6.2 displays the increased risk of self-harm per unit of EPQ-SF neuroticism score predicted by our model for both cohorts.

The age groups 25-34, 35-44 and 45-54 were positively associated with self-harm whereas age groups 64-74 and 75+ were negatively associated, compared to the reference category of 55-64. Gender did not show a significant association in the combined model. Having a higher SIMD score (less deprived) was associated with decreased risk of self-harm (per quintile unit OR 0.8 95%CI 0.7-0.9, p_{FDR}=0.0004). Having no qualifications and being single increased risk. Cognitive ability showed an inverse association with self-harm (per unit OR 0.8; 95%CI 0.7-0.9, p_{FDR} =0.0005).

Table 6.3: Multivariable analysis of predictors of history of self-harm involving hospital/psychiatric treatment in GS:SFHS and UKB (comparison made to any reported history of self-harm in UKB (*))

	GS:SFHS	Self-harm with hospital attendance	UKB	Self-harm with hospital attendance	UKB(*)	*Any reported self-harm
Cases (%)	339(2.1%)		772(2.2%)		1578(4.4%)	
	Odds Ratios	**p_{FDR}**	**Odds Ratios**	**p_{FDR}**	**Odds Ratios**	**p_{FDR}**
Gender : Male	Ref		Ref		Ref	
Female	1.1(0.8-1.4)	0.67	1.3(1.1-1.5)	0.005(*)	1.3(1.1-1.4)	0.0001(***)
Age : 18-24	0.5(0.3-1.0)	0.07(.)	-	-	-	-
25-34	2.0(1.2-3.3)	0.01(*)	-	-	-	-
35-44	2.2(1.4-3.5)	<0.001 (**)	1.4(1.1-1.7)	0.03(*)	2.1(1.8-2.4)	<0.001(***)
45-54	1.6(1.1-2.5)	0.03(*)	1.4(1.2-1.7)	<0.001 (**)	1.7(1.5-1.9)	<0.001(***)
55-64	Ref		Ref		Ref	
64-74	0.4(0.2-0.8)	0.02(*)	0.6(0.5-0.9)	0.01(*)	0.7(0.5-0.8)	<0.001 (**)
75+	0.2(0.04-0.97)	0.04(*)	-	-	-	-
No history of depression	Ref		Ref		Ref	
History of Depression	5.6(3.5-8.9)	<0.001 (**)	12.7(9.9-16.4)	<0.001 (***)	6.4(5.5-7.3)	<0.001(***)
EPQ Neuroticism	1.2(1.1-1.2)	<0.001 (**)	1.1(1.1-1.2)	<0.001(***)	1.1(1.1-1.2)	<0.001[1](***)
Cognitive function (g)	0.8(0.7-0.9)	<0.001 (**)	1.1(1.0-1.2)	0.051(.)	1.1(1.0-1.1)	0.004(*)
Education : No qualification or other	2.2(1.2-4.1)	0.02(*)	1.0(0.6-1.4)	0.96	0.9(0.6-1.2)	0.47
O levels	1.1(0.7-2.1)	0.67	1.0(0.8-1.3)	0.97	1.0(0.8-1.2)	0.94
CSE or equivalent			1.0(0.7-1.5)	0.98	0.9(0.7-1.2)	0.56
A-levels or equivalent	Ref		Ref		Ref	
NVQ or equivalent	1.4(0.8-2.4)	0.23	1.1(0.8-1.6)	0.77	1.0(0.7-1.3)	0.99
Other professional			0.9(0.6-1.4)	0.96	1.0(0.8-1.4)	0.94
College or university degree	0.7(0.4-1.2)	0.20	1.0(0.8-1.2)	0.96	1.1(1.0-1.3)	0.20
SIMD quintile (increased score, less socioeconomically deprived)	0.8(0.7-0.9)	<0.001 (**)				
Townsend score (increased score, more socioeconomically deprived)			1.1(1.1-1.1)	<0.001 (***)	1.1(1.1-1.1)	<0.001 (***)
Living as couple	Ref		Ref		Ref	
Living as single	2.0(1.5-2.8)	<0.001 (**)	1.3(1.1-1.5)	0.005(*)	1.3(1.1-1.4)	<0.001 (***)

95% credible (GS:SFHS) and confidence (UKB) intervals are shown in brackets for odds ratios. Significance indicators are * = p<0.05, **=p<0.001, ***=p<0.0001. Abbreviations: GS:SFHS = Generation Scotland cohort; UKB = UK Biobank cohort; pFDR = p value using False Discovery Rate method; EPQ = Eysenck Personality Questionnaire; SIMD=Scottish Index of Multiple Deprivation; NVQ = National Vocational Qualification; Ref= reference category. O-levels/GCSEs = ordinary level (Year 11) school certificate. CSE=Certificate of Secondary Education (Year 11). A-levels = Advanced level (Year 13) school certificate.

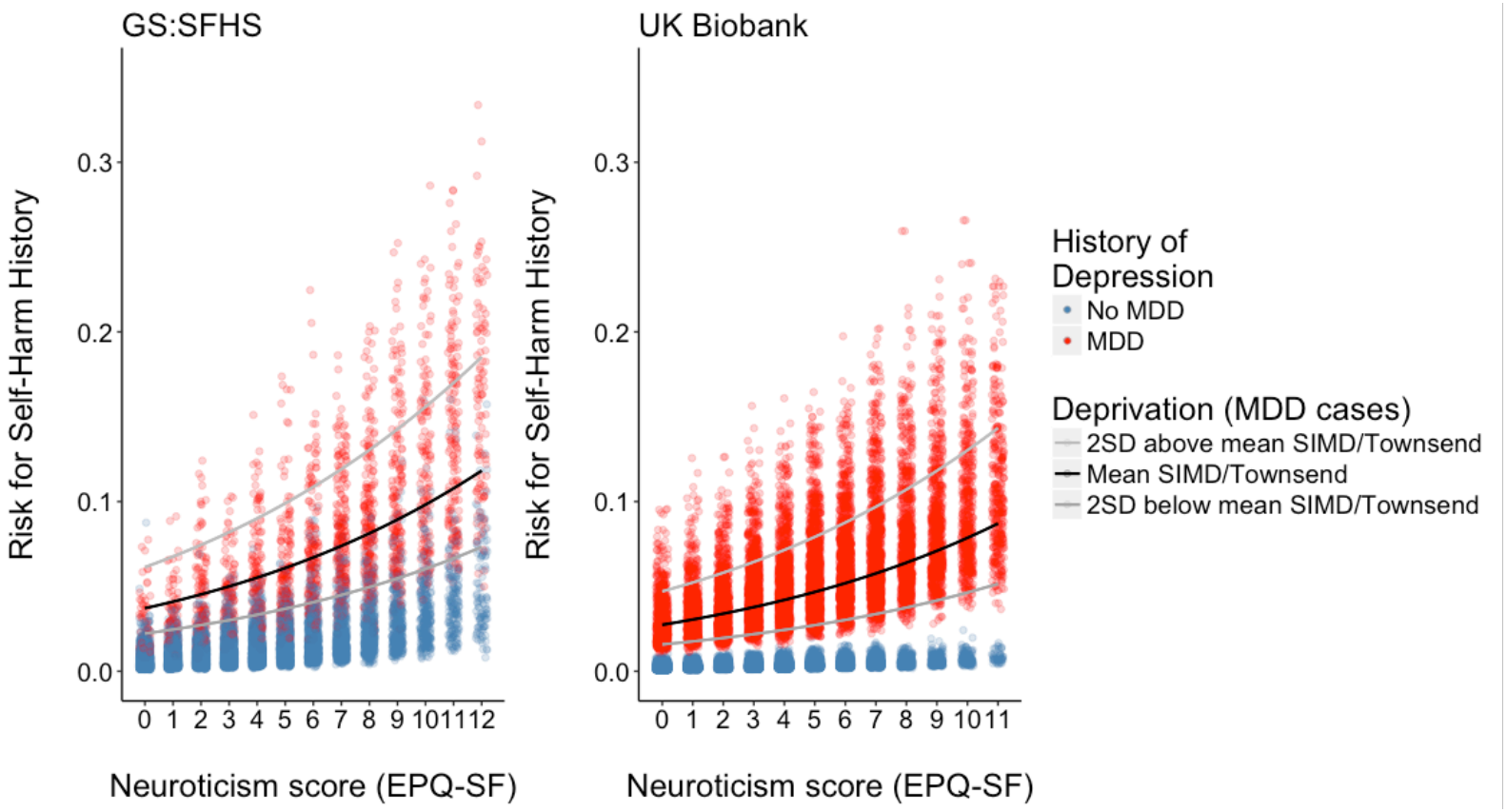
Table 6.4: Male and Female Models from GS:SFHS and UKB

GS:SFHS	OR Male (95% CI)	pFDR	Odds Ratios Female (95% CI)	pFDR	UKB	Odds Ratios Male (95% CI)	pFDR	Odds Ratios Female(95% CI)	pFDR
Age 18-24	0.05(0.01-0.4)	<0.001 (**)	0.9(0.3-2.7)	0.94					
Age 25-34	1.4(0.5-3.6)	0.63	3.1(1.3-7.9)	0.01(*)					
Age 35-44	1.1(0.5-3.0)	0.77	4.3(2.0-10.0)	<0.001 (**)	**Age 35-44**	1.4(0.9-2.2)	0.15	1.3(0.98-1.7)	0.15
Age 45-54	1.2(0.5-2.9)	0.72	2.4(1.2-5.1)	0.02(*)	**Age 45-54**	1.7(1.3-2.4)	0.002(*)	1.3(1.1-1.6)	0.04(*)
Age 55-64	Ref				**Age 55-64**	Ref			
Age 65-74	0.5(0.1-2.0)	0.46	0.2(0.03-0.7)	0.01(*)	**Age 65-74**	0.6(0.3-1.0)	0.10(.)	0.7(0.5-1.0)	0.13
Age 75+	0.03(0.001-1.6)	0.13	0.2(0.02-1.8)	0.22					
No history of depression	Ref				**No history of depression**	Ref			
History of depression (SCID)	8.2(3.0-25.9)	<0.001 (**)	9.8(4.3-26.6)	<0.001 (**)	**History of depression (self-report)**	15.2(10.0-24.0)	$2.9x10^{-33}$(***)	11.3(8.4-15.6)	<0.001 (***)
EPQ-SF Neuroticism	1.3(1.1-1.5)	<0.001 (**)	1.2(1.1-1.4)	<0.001 (**)	**EPQ-SF Neuroticism**	1.1(1.1-1.2)	$6.8x10^{-07}$(***)	1.1(1.1-1.1)	<0.001 (***)
Cognitive function (g)	0.8(0.6-1.0)	0.17	0.7(0.5-0.9)	0.001(*)	**Cognitive function(g)**	1.1(1.0-1.3)	0.08(.)	1.1(1.0-1.2)	0.37
Socioeconomic deprivation quintile (SIMD)	0.7(0.5-0.9)	0.01(*)	0.8(0.6-0.9)	0.003(*)					
					Socioeconomic deprivation (Townsend score)	1.1(1.1-1.2)	$6.8x10^{-7}$	1.1(1.1-1.1)	<0.001 (***)

Table 6.4 cont.

GS:SFHS	OR Male (95% CI)	pFDR	Odds Ratios Female (95% CI)	pFDR	UKB	Odds Ratios Male (95% CI)	pFDR	Odds Ratios Female(95% CI)	pFDR
Educational attainment : No Qualification	2.0(0.5-8.9)	0.49	2.9(1.0-7.6)	0.049(*)	**Educational attainment : None of the above**	0.7(0.4-1.4)	0.41	1.1(0.6-1.8))	0.72
O Levels/GCSEs or equivalent	1.5(0.4-5.0)	0.63	1.0(0.4-2.5)	0.93	**O levels/GCSEs or equivalent**	0.7(0.4-1.1)	0.16	1.1(0.9-1.6)	0.47
					CSEs or equivalent	0.8(0.4-1.6)	0.62	1.1(0.7-1.8)	0.72
A Levels or equivalent	Ref				**A Levels**	Ref			
NVQ or equivalent	1.3(0.5-3.9)	0.68	1.4(0.6-3.3)	0.42	**NVQ or equivalent**	0.7(0.4-1.3)	0.35	1.5(0.9-2.4)	0.22
College or University Degree	0.4(0.1-1.5)	0.32	0.6(0.2-1.4)	0.31	**College or University degree**	0.6(0.4-0.9)	0.02(*)	1.2(0.9-1.6)	0.24
					Other professional qualifications e.g. : nursing, teaching	0.9(0.4-1.8)	0.73	1.0(0.6-1.6)	0.93
Household relationship status: Couple	Ref				**Household relationship status: Couple**	Ref			
Household relationship status :Single	3.2(1.5-7.0)	0.001(**)	2.1(1.3-3.7)	0.004(*)	**Household relationship status :Single**	1.6(1.2-2.1)	0.006(*)	1.2(1.0-1.4)	0.24

Figure 6.2: Predicted risk of self-harm from the multivariable models in GS:SFHS and UKB for different EPQ-SF neuroticism scores.



6.6.2 UK Biobank

There were 772 (2.2%) individuals self-reporting self-harm requiring hospital or psychiatrist review in UKB (Table 6.2). Self-harm cases were slightly younger (UKB's minimum age is 40), predominantly female (70.5% versus 54.0%, p<0.001, *h*=0.34), and with higher mean neuroticism (mean 5.6 versus 3.3, p <0.001,*d*=0.83) and higher prevalence of history of depression (90.5% versus 33.3%, $p<0.001^{-18}$, *h*=1.3). Cognitive ability scores were not significantly different for any of the tests.

Self-harm cases were more likely to be from deprived areas (more positive scores) as measured by the Townsend index (mean -0.5 versus -1.7, p <0.001,d=0.44). Educational attainment was not significantly different between the two groups (χ=7.43, p-value 0.28). The proportion of the self-harm group living as single was 39.6% versus 22.5% for those reporting no history of self-harm.

The most predictive factor in the multivariable logistic model was self-reported history of depression (Table 6.3, OR 12.7 95% Confidence Interval (CI) 9.9-16.4, p_{FDR} <0.001). The odds of self-harm were significantly positively associated with increasing neuroticism scores, OR 1.1 95%CI 1.1-1.2, p_{FDR} <0.001 per EPQ-SF unit. No significant interactions were found during model fitting. The significant effects of neuroticism were found in both the male-only and female-only models (Table 6.4).

Being female was also associated with somewhat higher risk (OR 1.3 95% CI 1.1-1.5, p_{FDR} 0.005), as was being in the 35-44 and 45-54 age groups, whereas the 65-74 age group was protective. No educational factors were significant in the multivariable analysis. Being single and higher Townsend scores (more deprived)

were associated with higher odds of self-harm. Cognitive ability (*g*) was not significant (p_{FDR} = 0.051, OR 1.1, 95%CI 1.0-1.2).

In Table 6.3, comparison is also made to UKB participants who self-reported any self-harm, irrespective of whether hospital attention was sought (1578 cases, 4.4%). In this group self-harm was also positively associated with neuroticism scores (OR 1.1, 95%CI 1.1-1.2, p_{FDR} <0.001 per EPQ-SF unit). Positive association was also found for history of depression, being female, younger age group, increasing Townsend deprivation score and being single. However, in this group increasing cognitive function score increased odds of self-harm (OR 1.1, 95%CI 1.0-1.1, p_{FDR} 0.004 per unit *g*).

6.6.3 GS:SFHS Suicidal Ideation Re-Contact Study

In the GS:SFHS re-contact study (N=3342) there were 158 individuals with self-reported suicidal ideation (4.7%) (Table 5.3). Of these 21 (13.3%) had a record-linkage based history of self-harm compared to 1.9% in the control group. History of self-harm was the most predictive factor for suicidal ideation in the multivariable model (OR 3.5, 95%CI 1.9-6.2, p_{FDR}<0.001) followed by history of depression (OR 3.2, 2.3-4.7, p_{FDR}<0.001). Scores in the List of Threatening Experiences increased odds of suicidal ideation (1.3, 1.2-1.5, p_{FDR}<0.001 per standard deviation unit).

Table 6.5: Multivariable analysis of predictors of history of suicidal ideation in GS:SFHS Re-Contact Study (N=3342)

	Odds Ratios		
	Univariate model	*Multivariable model*	*Multivariable model including coping styles*
	OR(95%CI, p_{FDR} value)	OR(95%CI, p_{FDR} value)	OR(95%CI, p_{FDR} value)
Female gender	0.08(0.5-1.0) p=0.08	**0.5(0.3-0.7) p<0.001**	**0.4(0.3-0.7) p<0.001**
Age	**0.08(0.7-1.0) p=0.01**	0.9(0.8-1.1) p=0.21	1.0(0.9-1.2) p=0.85
History of depression (CIDI)	**4.7(3.4-6.4) p<0.001**	**3.2(2.3-4.7) p<0.001**	**2.3(1.6-3.4) p<0.001**
EPQ Neuroticism score *	**1.9(1.7-2.2) p<0.001**	**1.6(1.3-1.8) p<0.001**	1.1(0.9-1.4) p=0.44
Cognitive ability(g) *	**0.8(0.7-0.9) p=0.002**	0.9(0.7-1.1) p=0.21	0.9(0.7-1.0) p=0.15
Socioeconomic deprivation (SIMD) rank *	**0.7(0.6-0.9) p<0.001**	0.9(0.8-1.1) p=0.26	0.9(0.8-1.1) p=0.36
History of self-harm	**8.1(4.76-13.5) p<0.001**	**3.5(1.9-6.2) p<0.001**	**3.2(1.7-5.8) p<0.001**
List of Threatening Experiences total *	**1.4(1.3-1.6) p<0.001**	**1.3(1.2-1.5) p<0.001**	**1.3(1.1-1.5) p<0.001**
CISS Emotion oriented coping *	**2.9(2.4-3.5) p<0.001**		**2.4(1.9-3.0) p<0.001[2]**
CISS Task oriented coping *	**0.6(0.5-0.7) p<0.001**		**0.8(0.6-0.9) p=0.03**
CISS Avoidance oriented coping *	0.9(0.8-1.1) p=0.33		0.8(0.7-1.0) p=0.15

* = Continuous variables have been scaled to have a mean of zero and standard deviation of one.
95% confidence intervals are shown in brackets for odds ratios. Abbreviations: OR = Odds Ratio. 95%CI = 95% Confidence Interval. EPQ = Eysenck Personality Questionnaire-revised Short Form. SIMD = Scottish Index of Multiple Deprivation.
CISS = Coping Inventory for Stressful Situations CIDI = Composite International Diagnostic Interview

Neuroticism was positively associated with suicidal ideation in the multivariable model (OR 1.6, 1.3-1.8, p_{FDR}<0.001 per standard deviation unit). However, this association attenuated to non-significant OR 1.1 (0.9-1.4, p=0.44) when coping styles were added to the model (Table 6.5). In the full multivariable model including coping styles, EoC was positively associated with suicidal ideation (OR 2.4, 1.9-3.0, p_{FDR}<0.001) and

ToC was negatively associated (OR 0.8, 0.8-0.9, p_{FDR}=0.03), while AoC was not significantly associated. The correlation matrix revealed that EoC and neuroticism were significantly correlated, r=0.50 p <0.001 and task-oriented coping were moderately negatively correlated (r=-0.18 p <0.001, Table 6.6). In moderation analysis no significant ($p \leq 0.05$) interaction terms were found for neuroticism*ToC, neuroticism*AoC or neuroticism*EoC on suicidal ideation, controlled for age, sex and depression status.

Table 6.6 : Correlation Matrix of Variables in Re-Contact Study

Correlation Matrix

	Neuroticism	AoC	EoC	ToC	BLEQ Total
Neuroticism					
AoC	0.13				
EoC	0.50	0.02			
ToC	-0.18	0.20	-0.18		
LTE Total	0.12	0.03	0.08	-0.02	

Abbreviations : AoC = Avoidance Oriented Coping. EoC = Emotion Oriented Coping. ToC = Task Oriented Coping. LTE = List of Threatening Experiences

Table 6.7: Multivariable analysis of predictors of history of suicidal ideation in GS Re-Contact Study (N=3342)

	History of suicidal ideation n=158 (%/s.d.)	**Controls** N=3184 (%/s.d.)	p value (Effect size)
Female gender *n* (%)	84(53.2)	1913(60.1)	0.08
Age *mean*(s.d.)	53.6(12.7)	56.2(12.1)	0.02 (0.21)
History of depression(CIDI) *n* (%)	76(48.1)	529(16.6)	<0.001 (0.69)
EPQ Neuroticism score *mean*(s.d.)	5.7(3.4)	3.3(3.0)	<0.001 (0.80)
Cognitive ability(g) *mean*(s.d.)	0.13(1.3)	0.42(1.2)	0.005 (0.25)
Socioeconomic deprivation (SIMD) rank *mean*(s.d.)	3664(1975)	42198(1743)	0.0007 (0.32)
History of self-harm *n* (%)	21 (13.3)	59 (1.9)	<0.001 (0.47)
List of Threatening Experiences total *mean*(s.d.)	1.6(1.6)	0.9(1.3)	<0.001 (0.55)
CISS Emotion oriented coping *mean*(s.d.)	49.5(12.3)	36.6(11.9)	<0.001 (1.0)
CISS Task oriented coping *mean*(s.d.)	48.5(12.9)	55.5(11.4)	<0.001 (0.61)
CISS Avoidance oriented coping *mean*(s.d.)	38.6(9.2)	39.4(10.3)	0.28

Effect sizes are shown using Cohen's *d* (quantitative) and Cohen's *h* (categorical). Abbreviations : OR = Odds Ratio. 95%CI = 95% Confidence Interval. EPQ = Eysenck Personality Questionnaire-revised Short Form. SIMD = Scottish Index of Multiple Deprivation. CISS = Coping Inventory for Stressful Situations CIDI = Composite International Diagnostic Interview. s.d. = standard deviation.

6.7 Discussion

Here we report a significant independent association between neuroticism and history of self-harm requiring medical attention in two large population-based cohorts, using both self-reported and record-linkage derived measures of self-harm. This finding remained significant when controlling for history of depression, socioeconomic deprivation, educational attainment and relationship status.

In both UKB and GS:SFHS we found that history of depression was the predictor with largest effect size on hospital-treated self-harm risk. In our multivariable models, predicted self-harm risk (Figure 6.2) was relatively low in UKB in non-depressed individuals even at higher neuroticism scores, whereas in GS:SFHS more neurotic non-depressed cases also had significant overall risk. This disparity may be explained by the use of self-reported depression in UKB, with broader inclusion criteria than GS:SFHS (which employed the objectively assessed SCID). Thus 90.5% of self-harm cases reported history of depression in UKB, versus 47.5% in GS:SFHS (Table 6.2).

We found a significant protective relationship for higher cognitive scores against self-harm in GS:SFHS, but not in UKB. Previous studies have found that cognitive impairment is associated with suicide and self-harm (Sorberg et al., 2013; Jiang et al., 1999; Batty et al., 2010; Gunnell et al., 2005; Alati et al., 2009) . However, other studies have found increased cognitive scores may increase self-harm risk (Apter et al., 1993; Chang et al., 2014). One explanation for the discrepancy in our results is that different measures of cognitive ability were used in the two cohorts (Table 6.2). Moreover, previous research on depression and cognitive ability in GS:SFHS and

UKB (Navrady et al., 2017b) has been similarly inconclusive, with an association between *g* and depression being identified in GS:SFHS but not UKB.

For education attainment, we found fewer graduates and more individuals without qualifications in self-harm cases in GS:SFHS, but this difference was not significant in UKB. This might be accounted for in population sampling differences between GS:SFHS and UKB, with the latter having more graduates among controls also (Table 6.2).

We found socioeconomic deprivation was significantly associated with self-harm history in both cohorts, as was living as a singleton. Female gender was not predictive of self-harm in GS:SFHS but was significantly associated in UKB, albeit with modest effect size (Table 6.3). Previous multi-centre studies have shown female rates of self-harm to be significantly higher than male (Schmidtke et al., 1996). However, our GS:SFHS analysis was for hospital inpatient admitted self-harm and it may be that in this subgroup female gender is less predictive of risk, given that hospital-treated self-harm arguably lies on a spectrum between non-serious self-harm and suicide, the latter of which is four times more common in males (Maris, 2002).

In our follow-up analysis of suicidal ideation, we found an independent association between neuroticism and self-reported suicidal ideation, which remained significant when controlled for history of depression, socioeconomic deprivation and significant life events. When coping styles were added to the model, the association with suicidal ideation was no longer significant, implying that neuroticism's effect is not independent of coping style. We showed that emotion-orientated coping is highly positively correlated with neuroticism (r=0.50) and task-orientated coping negatively

correlated (r=-0.18). In addition, we found that emotion-oriented coping was positively associated with suicidal ideation whereas task-oriented coping was negatively associated. This relationship was also found in a study of suicidal ideation in middle-aged workers in Japan, albeit without employing a validated coping style instrument (Sugawara et al., 2012). A further study found emotion-focused coping, but not problem-focused coping, was associated with suicidal ideation in adolescents (Horwitz et al., 2011). “Active” (task-oriented) coping and positive reinterpretation were also associated with lower suicidality, adjusted for depression, in a study of 500 college students (Chou, 2017).

6.7.1 Study Strengths and Limitations

This study had a number of strengths for establishing the association of neuroticism to hospital-treated self-harm. We have employed two large, population-based cohorts which both have phenotypic information for major covariates of self-harm, allowing comparison between the groups while both using the same EPQ-SF measure of neuroticism. By utilising self-report in one cohort, and health-data record-linkage in the other, our study design obviates some of the biases which can arise from utilising either method alone. GS:SFHS encompasses the range of adult age groups, and UKB focuses on middle-age to older adults, thus our findings are a significant contribution to self-harm research where many of the available studies are for teenagers or young adults. By extending our analysis to suicidal ideation, we were also able to demonstrate an association with neuroticism and correlated coping styles (emotion- and task-oriented coping), the latter of which are potentially modifiable by clinical intervention.

There are also some important limitations to our work. The cohorts we use are population-based but are not fully representative, as UKB includes adults of ages 40-69 and GS:SFHS has an older mean age that the Scottish population. Additionally, the use of GP registration as an inclusion criteria for our GS:SFHS study (by enabling record-linkage via CHI number) leads to potential selection bias in our identification of self-harming individuals, although in the UK 96% of individuals are registered with a GP (Smith et al., 2013a) indicating that such biases are likely to be small. The prevalence of self-harm we record should thus be used with caution and should not be taken as a reliable population estimate. Nevertheless, it is sobering that prevalence of hospital-treated self-harm was relatively high (2.1% for GS:SFHS and 2.2% for UKB). Since self-harm is more common in younger people, the true population prevalence is likely to be greater still. We have also adopted a cross-sectional design and thus causality between factors such as neuroticism and self-harm; and neuroticism, coping style and suicidal ideation; is suggested rather than conclusively demonstrated by our models.

The type of self-harm we have studied is self-harm involving hospital care. We used a general definition of self-harm as the data available to us did not allow distinction between non-suicidal self-injury and suicide attempts, as this information is not available in the routinely collected administrative hospital data linked to in GS:SFHS (and was not part of the self-report question in UKB). This could limit the transferability of our results to other studies, although as discussed, the extent to which such distinctions of suicidal intent can be accurately made in practice is controversial.

In GS:SFHS we defined self-harm cases via admission to medical or psychiatric hospital, as ascertained by record-linkage. We therefore have not included a number

of self-harm cases that were managed in the Emergency Department, where available data is incomplete (Marrs, 2016). This represents approximately 50% of self-harm cases presenting to hospital, although there are wide variations between hospitals (Cooper et al., 2013). A recent study has found that routine hospital data underestimates rates of self-harm by approximately 60% compared to combined survey-hospital database methods (Clements et al., 2016), as – for example – self-harm which is assessed in the Emergency Department, but which does not lead to hospital admission, may not be included.

However, hospital-admission self-harm is itself an important variable, as cases that are admitted are likely to be more serious and can therefore be expected to be of greater risk of further self-harm and completed suicide (Gibb et al., 2005). The UKB self-report variable was for self-harm requiring any hospital or psychiatric management (including Emergency Department) and therefore, while highly correlated with the GS:SFHS variable, was more general in its scope. The overall prevalence of self-harm in GS:SFHS and UKB was similar (2.1% and 2.2% respectively). This might seem surprising as one might expect the more general self-harm definition in UKB to return a higher prevalence. This could be explained by the fact that the UKB cohort had no individuals younger than 40 and this has decreased the overall self-harm prevalence, since younger age groups are at relatively higher risk.

We employed a complete-case design in our multivariable analyses in GS:SFHS and UKB. Potentially, this could have biased our results compared to the whole samples, although comparison (Table 6.1) indicated that there were no significant and large-

effect differences in major variables studied through the complete-case approach. Nevertheless, this method could have introduced biases in ways we did not measure.

In summary, our findings must be seen in the context of self-harm with a high propensity to cause physical harm warranting medical attention. However, the UKB cohort did include a variable for any self-harm regardless of hospital attendance and we also included this multivariable analysis (Table 6.3). Neuroticism was found to be associated in this group also, with similar effect size (OR 1.1, 95CI 1.1-1.2, p $=3.4x10^{-41}$ per EPQ-SF unit).

With regard to our analysis of suicidal ideation and coping-style, neuroticism as a trait was measured during GS:SFHS enrolment, which was some years before the recontact when coping style and suicidal ideation were measured. However, as discussed, neuroticism is considered to be a relatively stable trait and would not be expected to change significantly over this time period. We also controlled neuroticism by age at enrolment rather than age at recontact within the models.

Our assumption that neuroticism is a stable trait should be weighed against the possibility that neuroticism is itself affected by a history of self-harm (i.e. that an episode of self-harm increases neuroticism score). This is an area that is relatively under-researched. There is some evidence that environmental influences, including trauma, are associated with increased neuroticism scores but this has only been demonstrated for episodes that occurred in childhood and adolescence(Lahey, 2009). Indeed, studies that have investigated the impact of traumatic events in middle adulthood on neuroticism have found that it does not reliably change(Ogle et al., 2014). As discussed, studies on self-harm have generally concluded that the causal

relationship, such as it exists, is between neuroticism as a risk factor and self-harm as an outcome. Neuroticism is generally understood as a stable trait although neuroticism scores peak in late adolescence and decline moderately through adulthood(Lahey, 2009).

Another important consideration is the extent to which neuroticism and emotion-oriented coping are separate constructs or both emanant from innate responses to stress. While we found the correlation of neuroticism and EoC to be significant (0.5), it was evidently not complete. There is also evidence that coping style is amenable to clinical treatment in prevention of suicide (Ghahramanlou-Holloway et al., 2012), whereas personality traits are understood as more therapeutically static.

6.7.2 Conclusions and Implications For Practice

We have found that a questionnaire which is relatively quick to administer in a clinical setting, the EPQ-SF, is significantly independently predictive of self-harm and suicidal ideation when adjusted for multiple other significant factors, including history of depression. Neuroticism is therefore an important factor which should be included in future studies of self-harm and suicidality risk.

Self-harm is just one of the potential outcomes of high neuroticism. Indeed, there is growing evidence that neuroticism is a psychological trait of profound public health significance(Lahey, 2009). Neuroticism is associated with mental health outcomes including major depressive disorder, anxiety disorders/PTSD and schizophrenia(Gale et al., 2016). It is also associated with physical health outcomes include coronary artery disease, eczema, asthma, smoking, irritable bowel syndrome and elevated body mass index(Gale et al., 2016; Lahey, 2009). Measurement of neuroticism in clinical risk models, particularly given neuroticism's predictive ability in identifying those who will develop disease(Lahey, 2009), arguably has important public health potential in preventative medicine, especially for individuals with high neuroticism who request intervention.

Our research also implies a potential role for cognitive-behavioural therapies focused on decreasing emotion-oriented coping and increasing adaptive task-oriented coping in individuals with suicidal ideation. There is current limited research in this area, although previous studies are encouraging (Eggert et al., 1995; Eggert et al., 2002). The coping styles questionnaires are also relatively straightforward to administer clinically and our study suggests that greater attention to reducing emotion-orientated

coping, and reinforcing task-oriented coping strategies, in individuals presenting with suicidal ideation is likely to have a beneficial effect in protecting against self-harm.

We also demonstrate the utility of record-linkage to health data for examining research variables such as self-harm, where there may be an unwillingness to self-report caseness but a willingness to provide consent for anonymised data linkage. Such record-linked cohort studies provide an important new avenue for future research on self-harm and psychiatric illness.

6.8 Concluding Remarks

In this chapter I have shown that neuroticism is independently predictive of hospital-associated self-harm even when controlling for MDD status. Adding to the information in Chapter 5, the research presented here provides further evidence that neuroticism is a significant predictor variable in studies of MDD-associated outcomes.

As argued in Chapter 1, future studies of self-harm that combine self-report with other sources of data, including linkage to administrative health data, will demonstrate improved ability to correctly identify cases and enable large-scale studies which can also incorporate genetic, epigenetic and imaging data contained within applicable cohort studies.

The ability to link GS:SFHS to Scottish Morbidity Records and the self-harm data within them has enabled one of the largest studies of self-harm and its psychological predisposing factors yet undertaken. As I have argued throughout this thesis, such work has important public health implications in its own right, but also illuminates the potential of linked data to reinvigorate existing psychiatric cohort (and other) studies by the identification of entirely new phenotypes for future analysis.

Chapter 7: General Discussion and Conclusions

7.1 Main Findings

This thesis sets out to quantify psychotropic treatment (especially antidepressant exposure) and illness outcome (especially self-harm) in a population- and family-based cohort featuring a well-defined phenotype of Major Depressive Disorder. Record-linkage to administrative health and prescribing data was employed which – as discussed within this thesis – enabled some of the difficulties and potential biases inherent in classical, self-report based, psychiatric studies of these topics to be overcome.

The introductory chapters provided a review of depressive illness, antidepressant treatment and the aetiology of self-harm. The evolution of record-linkage as a discipline within psychiatric research was also described. The comprehensive psychological and sociodemographic data contained within the Generation Scotland study (and also UK Biobank) was also detailed.

The overall objectives of this thesis were identified in Chapter 1 and considered throughout. These were to address the following questions:

1. Are users of psychiatric medications less likely to accurately self-report their usage in research studies compared to users of other medications?
2. Has exposure to antidepressant medications significantly increased in recent years and, if so, is this due to a change in how antidepressants are used ?
3. Is the psychological trait of neuroticism an independent risk factor for the MDD-associated outcomes of antidepressant use and self-harm ?

I will discuss the applicable research findings of this thesis for each objective in turn.

7.1.1 Are users of psychiatric medications less likely to accurately self-report their usage in research studies compared to users of other medications?

In Chapter 4, the self-reported medication use of a relevant subset of participants in GS:SFHS was validated against Scottish NHS prescriptions data as a gold standard. The hypothesis of this study was that psychiatric medications would be relatively under-reported compared to other medications such as antihypertensives, due to patient-level factors like self-stigma.

What was found was a more complex and nuanced picture. Antidepressant medication self-report was found to demonstrate very good agreement with the prescribing data gold standard, indeed comparable to that found for antihypertensives and cholesterol-lowering medications.

However, the other psychiatric medication type studied, mood stabilizers, showed moderate-poor agreement. While self-stigma could potentially be a factor for mood stabilizers, I considered that a potentially greater causal explanation was the use of the confusing term ‘mood stabilizer’ (which is misunderstood among healthcare professionals as well as the general public), especially given that no representative examples had been provided to users.

In summary, my analysis did not support the hypothesis that there was a simple relationship between psychiatric medication and under-reporting in cohort studies,

but the work justified the use of data-linkage (where possible) to provide greater granularity of medication use, particularly for medication classes that may be less widely recognised by the general public. I found that a relevant past medical history was the strongest predictor for self-report sensitivity, regardless of whether the medication was psychiatric or non-psychiatric.

7.1.2 Has exposure to antidepressant medications significantly increased in recent years and, if so, is this due to a change in how antidepressants are used?

In Chapter 5, the cross-sectional phenotypic data of GS:SFHS was combined with seven years-worth of longitudinal national prescribing data to obtain new and robust estimates of antidepressant exposure prevalence, incidence, adherence and predictors of use. I hypothesised that antidepressant prevalence would have increased, given the recent findings in multiple research studies and national summaries of prescribing data.

However, the levels of increase I found were striking – a prevalence of almost one third of the adults in our sample in the five-year period 2012-16 (over one fifth if amitriptyline is excluded), representing an increase in prevalence of more than 36%. Nevertheless, my analysis found that antidepressant incidence remained stable and that the majority of antidepressant treatment episodes were of long (>9 months) duration. This implies that the significant increase in antidepressant exposure is mainly explained by longer treatment cycles, wider range of indications, and returns to usage by previous users.

I was also able to demonstrate that antidepressant adherence (measured using the Proportion of Days Covered (PDC) system) remained generally high, which is an important finding as psychiatric medication is often associated with poor concordance.

The choice of a 90 day maximum gap in prescribing events between respective prescribing episodes deserves mention. As discussed in Chapter 5, it is based on NHS prescribing practices of a maximum drug dispensation cycle of 3 months. The 90-day standard employed here has since been adopted by the Scottish Government when measuring treatment course from PIS prescribing data(Scottish Government, 2021). Table 5.3 shows the sensitivity analysis performed with different gap lengths between prescribing episodes of between 60 and 360 days. At 60 days MPR was 100% and PDC 87.4% with a mean treatment episode duration of 526 days. At 120 days MPR was 98.1% and PDC 82.7% with a mean duration of 777 days. A 90 day treatment episode length, as ultimately selected for this analysis, gave a mean treatment duration of 679 days (or approximately two years) and a MPR of 99.1% and PDC of 84.9%. It can be seen that, as expected, PDC is the more discriminating measure of adherence in this context and it was thus preferred.

Another consideration is the extent to which adherence to medication can be gleaned from prescribing data. Adherence can be measured by directly observed therapy or measurement of concentrations of a drug or metabolite in blood or urine. These direct approaches are, however, expensive, burdensome to the health provider, and susceptible to distortion by the patient(Osterberg and Blaschke, 2005). Ascertaining the rate of refilling prescriptions is an established indirect method of measuring adherence, especially in - as discussed in Chapter 5 - a ‘closed’ pharmacy system

such as PIS. However, as discussed in Chapter 5, such measures of adherence as can be made from prescribing data are not able to account for primary or secondary noncompliance. In the case of psychiatric medications a number of interventions have been tried to improve compliance to medication. These include education interventions, cognitive-supportive interventions and the periodic use of reinforcement techniques such as personalised reminders and healthcare worker visits(Osterberg and Blaschke, 2005). However, even these measures cannot sustain adherence unless they are repeated at intervals.

7.1.3 Is the psychological trait of neuroticism an independent risk factor for the MDD-associated outcomes of antidepressant use and self-harm ?

In Chapter 5, my analysis of the predictors of antidepressant use also demonstrated that psychological factors, including higher neuroticism scores (and also lower cognitive function scores), were also evidently associated with antidepressant use, even when controlled for major depression and other major potential confounders.

In Chapter 6, prior history of hospital-treated self-harm was obtained for participants of GS:SFHS using record linkage to the Scottish Morbidity Records. This, combined with a replication sample drawn from UK Biobank, enabled the largest study yet performed on the relationship between neuroticism and self-harm and an additional study of suicidal ideation, neuroticism and coping styles against adversity.

The study hypothesised that neuroticism was independently associated with self-harm, when controlling for major depression and other significant potential confounders. The positive association between neuroticism and self-harm was

demonstrated in both the GS:SFHS and UKB cohorts. The study also demonstrated that the Emotion-oriented Coping style (EoC), itself correlated with neuroticism, was an independent predictor of suicidal ideation risk in multivariable models.

7.2 Implications of Findings

This thesis has investigated psychotropic treatment (especially antidepressants) and illness outcome (especially self-harm) in a population- and family-based cohort where Major Depressive Disorder was well phenotyped. By employing a record-linkage based design in investigating antidepressant exposure and hospital-associated self-harm the work contained here has been able to overcome some of the problems of more classically designed psychiatric studies, such as those based on self-report alone.

The work contained here also provides further evidence for the transformational potential of record-linkage based studies in mental health research. In Chapter 2, I have previously identified four major areas where psychiatric data science, based on record-linkage, can enhance longitudinal cohort studies.

Firstly, by *improved signal and power for discoveries and the reduction of false associations.* As well as being evidenced in all three research Chapters 4-6, this is discussed in Chapter 2 referencing the genetic studies of MDD in GS:SFHS, where the case and control arms were validated using record-linked data as part of this research project(Howard et al., 2017).

Secondly, by *validation of research data and the identification of inaccuracies*, which is specifically addressed in Chapter 4. Thirdly, the *transformation of cross-sectional studies into longitudinal studies,* which is demonstrated in Chapter 5 in the longitudinal study of antidepressant exposure.

Finally, the *identification of new phenotypes for study*, which is particularly demonstrated in Chapter 6, where record-linked data allows GS:SFHS to be used to study self-harm and suicidal ideation, despite these behaviours not being specifically phenotyped during GS:SFHS enrolment.

Taken together, these findings provide new insights into mental illness and major depression-related research, but also clearly demonstrate the utility of record-linkage to administrative health data for addressing modern mental health research questions. Excitingly, the record-linkage studies presented here provide answers to research questions that were potentially unforeseen at the time of GS:SFHS recruitment or that were too difficult to study at scale using conventional population-based cohort phenotyping methods.

7.3 Methodological Considerations and Limitations

The specific limitations associated with each individual study within this thesis have been appropriately addressed within their respective Chapter. Here I shall look at the more all-encompassing limitations applicable to the methodologies used within this thesis.

7.3.1 Study design

Subjects included in this work were drawn from the Generation Scotland cohort (and UK Biobank in Chapter 6). The first limitation that any study employing a population-based (and family-based) cohort must consider is the appropriateness and representativeness of that population for the research questions addressed. GS:SFHS was recruited initially from lists provided by General Practices in Scotland and there was potential for selection bias in that the participants were generally healthier, wealthier, better educated and potentially more likely to be engaged with healthcare services. Also, there was further potential for selection bias given that the population being studied was based in Scotland and this could potentially make conclusions unrepresentative for the UK as a whole. Ethnic minorities, in particular, are relatively less a proportion of population in Scotland compared to the rest of the UK (some 98% of the Scottish population and 99% of the Generation Scotland population are white)(Smith et al., 2013a). However, on the point of representativeness, it can be said that comparison with UKB – a more diversely recruited sample across the UK - as the replication sample in Chapter 6 did not indicate that a Scotland-related selection bias was in evidence, at least for that study.

Regarding further potential selection biases, it is possible that those agreeing to be recruited to GS:SFHS, and/or remaining in the cohort for the follow-up STRADL recontact study, had particular health concerns, or were more health conscious, than the general population. Furthermore, it is possible that those refusing permission for record-linkage were more likely to have significant psychiatric illness or significant self-harm history (thereby refusing permission due to factors such as self-stigma). The number involved in refusing permission for linkage was small (less than 2% of

the Generation Scotland) but still potentially significant. Nevertheless, the prevalences of psychiatric illness and self-harm found in this research is comparable with other large published studies, as discussed in Chapters 5 and 6.

A further major limitation for studies using administrative health data, as discussed throughout this thesis, is that the data was not originally recorded or stored for research purposes. This inevitably means that significant variables, that would almost certainly have been collected in a research study, are missing. For example, the prescribing data had no information on indication of medication use, or any precise information about when (or whether) the medication was taken. Furthermore, in the determination of history of self-harm, I relied on ICD coding which may have been erroneous and did not contain further clinical information I could use to cross-validate diagnoses.

Not having access to primary healthcare records was a potentially significant omission in the administrative dataset available to this study. Primary care/GP data could have provided additional information about diagnoses, indications for treatment, self-harm not presenting to hospital, and also medications not listed in PIS (such as medications dispensed in hospitals). However, primary care data is – at least at present – notoriously unstructured and requires highly sophisticated data mining techniques to extract useful research data from, so it is not certain that having access to primary care data would have realistically improved the methodologies of the included studies.

The studies presented here are, for the research questions undertaken, among the largest yet attempted. Nevertheless, greater sample sizes would improve predictive

power, particularly for large multivariable analyses, and provide further opportunity for replication of the results found.

7.3.2 Statistical analyses

As ever with research studies, it is important to remember that correlation does not equal causation. This study has been able to demonstrate that (1) self-report of mood stabilisers is significantly less accurate than antidepressants and antihypertensives, when validated with prescribing data; and that (2) antidepressant prevalence has significantly increased while incidence has remained stable; and that (3) neuroticism is significantly associated with self-harm presenting to hospitals and with antidepressant use. Our inferences about why this may be the case, presented within the research Chapters, while evidence-based, are far more speculative and provide motivation for further research studies rather than being themselves conclusive.

It is also important to remember that phenotypes derived by record-linkage studies often differ in significant ways from related phenotypes commonly studied in other psychiatric research. Thus, within this thesis I have studied individuals exposed to antidepressants (or at least dispensed medication), rather than individuals with depression taking antidepressants. Similarly, I have analysed individuals presenting to hospital with self-harm, rather than all types of self-harm. It is very important, when assessing the implications and quality of record-linkage based science, to remember that the phenotypes under study often emanate from what is possible to define using available administratively collected data.

7.3.3 Methodological Considerations for Future Studies

The studies presented here provide a foundation upon which further research can be built. For example, through identifying within GS:SFHS those exposed to antidepressants (or other medications) and those with a history of hospital-associated self-harm, these newly defined phenotypes can be further studied using the wealth of sociodemographic, psychological, genetic, epigenetic and imaging data contained within GS:SFHS. A considerable proportion of the variance in the outcomes of antidepressant exposure and self-harm remain unexplained by the multivariable models employed in this study. As more data becomes available, the incorporation of the dataset defined here with further genetic data (such as single nucleotide polymorphisms (SNPs), epigenetic methylation patterns, and whole-genome sequencing); and with additional clinical data (such as from primary care records); and additional sociodemographic data (such as educational and social service data), will improve the predictive and explanatory power of the models.

Furthermore, as UK Biobank (and other large biobanks) continue to improve the quality of their linkage to prescribing, morbidity and general practice related data, the research chapters presented here can be used as a basis for further replication, validation, prevalence and association studies of psychiatric medication and self-harm, taking advantage of even greater statistical power and potentially even more diverse multivariable methodologies.

Future studies may also benefit from a more simplified approval process to gain access to regular updates of administrative data. In particular, future researchers

using Generation Scotland data will benefit from more regular updates of SMR and PIS linked data without having to initiate a new research proposals/requests.

7.4 Future Directions and Strategic Vision

Interest in data science and record-linkage continues to grow apace within psychiatric research and medical research more generally. Future studies of psychiatric pharmaco-epidemiology and self-harm will benefit from ongoing improvements to available datasets and methodologies in the near future. A number of potential future directions for the research work outlined here can be envisaged.

7.4.1 Antidepressant Exposure Studies

With the increased availability of prescribing data and primary care data within UK Biobank over the next few years, it will be possible to replicate the prevalence and adherence measures utilised in this study on a larger population. A critical variable to be defined (most probably using data mining techniques in primary care data) will be the indication of use for medication. It would also be advised for the research community to lobby the administrators of prescribing data in Scotland and the UK to add this variable to future iterations of prescribing data so that within a few years it will be straightforward to stratify antidepressant medication use according to indication.

It is important to remember that an antidepressant user phenotype, derived from linked data as described in this thesis, indicates antidepressant exposure, rather than antidepressant response. The definition and identification of outcome variables which measure antidepressant response (made possible for example through data mining of primary healthcare records) will enable more sophisticated studies. Surrogate measures have been utilised to date in other published studies, such as inferring antidepressant treatment resistance in those individuals who have switched medication multiple times(Wigmore et al., 2019). In future, with more robust linkage-derived measures of treatment response, it should be possible to develop highly powered real-world studies of medication response and resistance, medication switching and medication dropout, which have similarities to clinical trials but which employ record-linkage to administrative data.

The antidepressant exposure phenotype defined in this thesis offers interesting potential avenues for genetic studies aimed at understanding medication response and the development of tailored, precision medicine. Given the numerous adverse effects that are associated with antidepressant discontinuation, the epigenetic and genetic attributes of long-term antidepressant users compared to short-term antidepressant users, and controls, is an intriguing research area. It may for example be possible to use machine-learning techniques to identify SNPs or epigenetic methylation patterns which are associated with antidepressant exposure and/or discontinuation. Study of the epigenetic disparities of those exposed to antidepressants may offer clues to antidepressant mechanism of action, the mechanisms underlying adverse effects and discontinuation, and potentially enabling a clinically usable test for medication usage.

7.4.2 Self-Harm Studies

With regard to the self-harm phenotype derived in this study, it is fairly easy to envision how a relatively simple data mining exercise utilising primary care records and hospital electronic health records could help improve and validate both the case and control groups of the study. With a larger powered study over an even longer time course than has been possible here, it should also be possible to identify dynamic risk factors associated with self-harm and potentially those that are related to completed suicide. Another advantage of more regular uploads of healthcare data, particularly if it is possible to measure suicidal ideation and self-harm at multiple timepoints, is that it will become possible to further investigate the causal processes that may underlie the relationship between self-harming behaviour, neuroticism and coping styles using mediation analysis and structural equation modelling.

7.4.3 Advances in Psychiatric Data Science

I have commented on the absence of General Practice linked data in GS:SFHS at the time of the present study. Efforts are underway to provide such linkage in future, for both GS:SFHS and UKB. Despite the highly unstructured nature of much primary care data, improved data mining techniques should make such data more tractable in future. There is good evidence that diagnostic accuracy derived from codified data in electronic health records can be improved by access to unstructured data of this kind (Ford et al., 2016; McIntosh et al., 2019). However, one of the potential pitfalls of data mining in primary health records is that the clinical information is missing from the unstructured data (i.e. it was never inputted in the first place) or that it is inputted in

such an inconsistent or idiosyncratic manner among GPs as to be inadequate for diagnostic purposes when compiled. Once again, we return to the theme of the potential disconnect between what a data source was designed for (in this case, brief clinical notes) and what we might be intending to use it for (research-grade objective diagnosis and treatment).

In addition to primary care records, it is envisioned that future data linkage exercises will be able to add non-health datasets to mental health cohort studies. As discussed in Chapter 2, the Secure Anonymised Information Linkage (SAIL) project in Wales is already making progress in combining health and other social administrative data. Future access to educational, social service, police, judicial and employment data, to name some examples, could significantly improve the ability of the multivariable models employed in this thesis to more appropriately factor the biopsychosocial basis of mental illness. Such work shows great potential for an improved understanding of the aetiology of conditions such as major depression and self-harm, as well as pharmaco-epidemiology and the study of psychological traits such as neuroticism.

Looking further to the future, it is possible that repositories of personal (and increasingly biosensor- and health-related) data collected by commercial companies such as Amazon, Google and Apple may be available for linkage to health datasets. Tentative steps towards this have been made through collaborations between the NHS, university researchers and enterprises such as Google DeepMind, but the ethical and governance frameworks that must be in place to make such collaborations successful are considerable.

Indeed, the use of commercial databases for these purposes raises several ethical and risk-related concerns(Mittelstadt and Floridi, 2016), most importantly: (1) the risk that consent to use of data was not sufficiently informed; (2) that data privacy is not reliable, such that anonymisation and data protection is incomplete; (3) who has ultimate ownership of the data, and is there a right to be forgotten (4) the so-called 'Big Data divide' between those who can access sophisticated data mining technology and commercial databases, and those who cannot; (5) the monetisation of data provided by patients for altruistic reasons. Greater clarification on these issues is required before commercial databases can be widely utilised for health related research.

One of the constraints of the use of administrative health data commented on in this thesis is precisely that it is collated for administrative purposes rather than the interests of research. In the future, it is hoped that there will be more collaboration between healthcare organisations and the research community so that the information obtained during patient contacts is more useful for the needs of both. One of the benefits of initiatives like the Clinical Record Interactive Search (CRIS) discussed in Chapter 2 is that by its nature it involves the collaboration between NHS Hospital Trusts and the university research community. Increasingly, NHS Trusts are adding research directors and informatics directors to their management teams and it can be envisioned that this will increase the availability of high-quality research data from administrative output. Essential to this process will be the continued consultation and support from patient groups and those involved in ethical oversight and clinical governance.

Many of the techniques utilised in this thesis, such as the derivation of antidepressant episodes and the measurement of adherence, required custom computer coding and testing. Such work is useful, but potentially limits replicability and accessibility of results. Over time, it is envisioned that many processes of data mining, machine learning, Bayesian analysis and pharmaco-epidemiological measurement can be standardised by the widespread adoption of statistical computing packages customised for healthcare use. The widespread adoption of particular software approaches in genetics (such as GCTA, Plink, LD Hub and polygenic risk scoring) and in data science (such as the use of dplyr, ggplot2 and tidyr within the R language) demonstrates the utility to the research community of widespread adoption of standardised approaches. It is hoped that over time similar systems will be available for the record-linkage and pharmaco-epidemiological techniques discussed in this thesis.

7.5 Translation to Improve Clinical Insight and Patient Care

This thesis has emphasised the importance of the personality trait of neuroticism, which is relatively easy to measure using a simple questionnaire (which can be performed online or on a touchscreen) and which is a significant risk factor in antidepressant usage and self-harm, as well as a variety of other psychiatric and medical morbidities. As clinical care becomes further data driven, including more comprehensive EHR systems accessible to patients and clinicians, the quantitative measure of a patient's neuroticism should be seen as a potentially important variable to include.

As has been discussed above, the identification of an antidepressant user phenotype within Generation Scotland allows the development of genetic and epigenetic models which may enable clinical tests of antidepressant usage and/or adverse effect susceptibility. The research within Chapter 5 also has important implications for current clinical practice, including providing evidence supporting the need for more regular review of antidepressant usage at the primary care level (where the vast majority of prescribing is occurring) and the review of medications which appear to be widely also prescribed with antidepressants, including opiate analgesics, anxiolytics and pregabalin/gabapentin. This research provides an evidence base for future clinical guidelines on medication review.

In order to measure adherence in Chapter 5, this thesis involved the generation of computing code that formatted administrative prescribing data into discrete prescribing episodes in which adherence could be analysed using the MPR and PDC methodologies. As prescribing and dispensing becomes increasingly computerised, such a tool more widely applied would be useful to prescribers in both the primary and secondary healthcare sectors in providing an indication as to whether medication concordance was being achieved (at least prompting timely medication review if these simple analytic indicators suggested that it was not).

Finally, this thesis provides evidence of the potential for discovery science emanating from secure, anonymised data linkage of administrative collected healthcare data. Alongside other initiatives discussed here like the CRIS data pipeline, this research can be used in the education of both patients and clinicians about the benefits of enabling anonymised access to their healthcare data, for the improvement of their own clinical care and that of society.

7.6 General Conclusions

This thesis has demonstrated the potential of record-linkage to administrative data for mental health research but also to an extent its current limitations. As with other forms of research, the questions which can be addressed are to a large extent determined by the data which is available for analysis. The availability of large quantities of well-structured data in morbidity and prescribing records has enabled transformative analyses of antidepressant usage and hospital-associated self-harm, which can be relatively well defined with the methods available. However, the potential of record-linkage for more complex questions such as the aetiology of major depression and self-harm, or the basis of antidepressant treatment response and precision medicine, remains more elusive.

As discussed in this chapter, future developments in joint working between academics and healthcare administrators in database design, wider linkage to datasets in primary care and also beyond healthcare, and the adoption of standardised new technologies for data mining and analysis, will progress the data science revolution in psychiatric research which has begun. We can anticipate with confidence the future tangible benefits to sufferers of mental illness which such data-driven approaches will deliver.

List of Publications

First Author :

Hafferty, JD., Smith, DJ., McIntosh, AM. (2017)
"Invited Commentary on Stewart and Davis " 'Big data' in mental health research – current status and emerging possibilities"
Soc Psychiatry Psychiatr Epidemiol. Feb; 52(2): 127-129

Hafferty, JD., Campbell, AI., Navrady, LB., Adams, MJ., MacIntyre, D., Lawrie, SM., Nicodemus, KK., Porteous, DJ., McIntosh, AM. (2018)
"Self-reported medication use validated through record linkage to national prescribing data"
J Clin Epidemiol. 94. 132-142.

Hafferty, JD., Wigmore, EM., Howard, DM., Adams, MJ., Clarke, TK., Campbell, AI., MacIntyre, DJ., Nicodemus, KK., Lawrie, SM., Porteous, DJ., McIntosh, AM. (2019)
"Pharmaco-epidemiology of antidepressant exposure in a UK cohort record-linkage study"
J Psychopharmacol. 33(4)482-493

Hafferty, JD., Navrady, LB., Adams, MJ., Howard, DM., Campbell, AI., Whalley, HC., Lawrie, SM., Nicodemus, KK., Porteous, DJ., Deary, IJ., McIntosh, AM. (2019)
"The role of neuroticism in self-harm and suicidal ideation: results from two UK population-based cohorts"
Soc Psychiatry Psychiatr Epidemiol. doi. 10.1007/s00127-019-01725-7. Epub ahead of print.

Co-author :

Zeng, Y., Navarro, P., Xia, C., Amador, C., Fernandez-Pujals, AM., Thomson, PA., Campbell, A., Nagy, R., Clarke, TK., Hafferty, JD., Smith, BH., Hocking, LJ., Padmanabhan, S., Hayward, C., MacIntyre, DJ., Porteous, DJ., Haley, CS., McIntosh, AM. (2016)
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Howard, DM., Adams, MJ., Clarke, TK., Hafferty, JD., Gibson, J., Shirali, M., Coleman, JRI., Hagenaars, SP., Ward, J., Wigmore, EM., Alloza, C., Shen, X., Barbu, MC., Xu, EY., Whalley, HC., Marioni, RE., Porteous, DJ., Davies, G., Deary, IJ., Hemani, G., Berger, K., Teismann, H., Rawal, R., Arolt, V., Baune, BT., Dannlowski, U., Domschke, K., Tian, C., Hinds, DA., 23andMe Research Team, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Trzaskowski, M., Byrne, EM., Ripke, S., Smith, DJ., Sullivan, PF., Wray, NR., Breen, G., Lewis, CM., McIntosh, AM (2019)
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