Is there an association between cancer and dementia in cohorts with and without T2DM?

A national observational study

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Declaration of Originality

I *(Darina T Bassil)* understand the university's policy on plagiarism, and I declare that the contents of this thesis are my own work, and that I have:

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The work presented in this thesis including the literature review, data preparation, management, analysis and interpretation is entirely my own work. Any contributions from colleagues in terms of algorithms or data preparation has been explicitly acknowledged throughout the thesis. It is important to note that although the work used in this thesis is based on existing data (large primary care database-CPRD), the format of the existing data available is recorded as millions of rows and columns of coded data. As the data collected by CPRD is mainly used for clinical routine practice, the large data recorded requires extensive data management and cleaning to make sure the data needed is readily available for analysis.

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Abstract

Background: Previous studies have suggested an inverse association and a hypothesized mutually protective effect between several forms of cancer and late-onset dementia (LOD). Type 2 diabetes (T2DM) is an established important risk factor for both diseases; however, the precise relationships between T2DM, cancer and LOD still remain poorly understood. This thesis investigates the relationship between different cancers and risk of LOD, and explores the role of prediabetes or T2DM in these associations.

Methodology: Using the Clinical Practice Research Datalink (CPRD), a massive UK primary care database, in years, 1998-2015, a sample of individuals ≥ 65 years old, with and without T2DM were identified. All individuals aged ≥ 65 years old, with and without a T2DM diagnosis were included in this analysis. Individuals with an LOD diagnosis prior to 65 years of age or prior to a T2DM diagnosis, were excluded. All study participants were followed up from the index date to the censor date. Participants were censored at point of LOD diagnosis, death, end of observation period (2015) or last data upload date (last date of follow-up), whichever came first. It was required that participants have been under observation by CPRD for > 1 year prior to cohort entry. Exploratory analyses were performed to investigate the incidence rates of LOD in both non-T2DM and T2DM cohorts. Cox proportional hazard models, with time-dependent covariates, were used to determine the risk of LOD in individuals with and without a cancer diagnosis in both non-T2DM and T2DM cohorts. The cause-specific hazard ratio (csHR) and sub-distribution hazard ratio (sdHR) for overall LOD and death in individuals with cancer were computed, to account for death as a competing risk.

Results: Separate analyses amongst 217,335 individuals with T2DM and 739,061 without T2DM were performed. The mean age (SD) of individuals with T2DM at cohort entry was 71.62 (7.09) years (47.3% females) vs.70.80 (7.66) years (56.9 % females) in the non-T2DM cohort. During follow-up, a total of 165,272 (22 %) and 32,022 (15 %) cancer cases and 51,733 (7 %) and 11,450 (5%) LOD cases were identified in the non-T2DM and T2DM cohorts, respectively. In the non-T2DM cohort, 10,602 (6 %) had both LOD and cancer diagnosis vs. 1,172 (4%) in the T2DM cohort. The incidence rate of LOD was higher in females in both non-T2DM and T2DM cohorts (non-T2DM: 7.15 per 1,000 person years in males and 10.04 per 1,000 person years in females; T2DM: 6.96 per 1,000 person years in males and 10.57 per 1,000 person years in females). There was a higher risk for LOD in cancer individuals in the

non-T2DM cohort [HR 1.16, 95 % CI (1.13-1.20)]. Conversely, in the T2DM cohort, there was a significantly lower risk for developing LOD in lung cancer participants vs. no cancer group [HR 0.52, 95 % CI (0.29-0.94)]. In the presence of death as a competing risk for LOD, lung cancer showed an even more intensified "protective relationship" (sdHR 0.11 (95% CI 0.06, 0.21), when compared to the cause specific hazard ratios (csHR of 1.16 (95% CI 1.13, 1.20). The cumulative incidence function curves showed that in the presence of death, there is a protective effect of cancer on LOD incidence in both cohorts (not observed for csHRs).

Conclusion: Examining the cause-specific and sub distribution hazard models led to the conclusion that the inverse association observed between cancer, lung cancer and LOD, especially in the T2DM cohort, is most likely due to mortality selection. Careful consideration of statistical model specifications is imperative, particularly in older adult population research, where mortality is inevitable.

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List of Abbreviations

AD	Alzheimer's disease
AD-LOD	Dementia attributable to Alzheimer's Design
AP	Amyloid β Plaques
BMI	Body Mass Index
CeVD	Cerebrovascular disease
CI5	Cancer Incidence in Five Continents
CNS	Central Nervous System
CPRD	Clinical Practice Research Datalink
csHR	cause-specific HRs
DSM V	Diagnostic and Statistical Manual of Mental Disorders
FTD	Fronto-temporal Dementia
GP	general practitioners
GPRD	General Practice Research Database
HER	electronic health record
HES	Hospital Episode Statistics
HRs	Hazard ratios
IPW	Inverse Probability Weights (IPW)
IRs	Incidence Rates
LBD	Lewy Body Dementia
LOD	Late-Onset Dementia
MI	Multiple Imputation
NCD	Neurocognitive Disorder
NFTs	Neurofibrillary Tangles
NIAA-AA	National Institute on Aging-Alzheimer's Association
NMSC	Non-melanoma Skin Cancer
ONS	Office of National Statistics
PDD	Parkinson's disease dementia
QOF	Quality and Outcomes Framework
sdHRs	sub-distribution Hazard Ratios
SIRs	Standardized Incidence Ratios
T2DM	Type 2 Diabetes
VaD	Vascular dementia
Wnt	wingless type murine-mammary tumor virus integration site

CHAPTER 1 – INTRODUCTION

1.1 BACKGROUND

The number of elderly individuals (aged ≥65 years old) world-wide is estimated to rise to one billion by 2030, compared to 420 million individuals reported in 2000 (United Nations Report of the Second World Assembly on Aging). As the life expectancy among the elderly continues to increase, so does the rise in the incidence and prevalence of late-onset dementia (LOD) and other chronic diseases, such as Type 2 Diabetes (T2DM) and cancer. All three diseases are known to be associated with advancing age, and largely contribute to the global morbidity and mortality burden in the ageing population.

Previous studies have reported that people with cancer are less likely to develop late-onset dementia (occurs from 65 years old), especially dementia attributable to Alzheimer's disease. The reported protective effect shows a lower risk of cancer among those diagnosed with dementia and vice-versa. The underlying reasons for this relationship remain largely unclear. Some research suggests that factors which increase the risk of cancer, can decrease the risk of dementia. Type 2 diabetes (T2DM) is an important risk factor for both diseases, but it is to date unclear whether it affects the relationship observed between cancer and dementia

This thesis uses a large national database to explore the relationship between cancer and dementia in a primary care population ≥ 65 years in individuals with and without T2DM.

Findings from this study will provide an enhanced understanding of key comorbidities and inter-risk relationships, for these common and increasingly prevalent age-related diseases. In particular, the novel data produced could pave the way for biomarker-enriched observational studies and/or lifestyle interventional studies. Study results could aid the understanding of the mechanisms underlying the relationships between the diseases of interest, and potentially demonstrate opportunities for risk reduction.

This chapter gives brief background information about the main diseases of interest: late-onset dementia and cancer, their relationship and the shared risk factors between the two, importantly T2DM. I then proceed to give an overview of the thesis by presenting my overall and specific aims, as well as the significance and rationale of the study.

1.1.1 Late-onset Dementia (LOD)

(a) Definition and major sub-types of late-onset dementia (LOD)

Late-onset dementia (LOD) is a debilitating, neurodegenerative syndrome typically affecting individuals over the age of 65, with distinct characteristics including the progressive deterioration of cognitive and memory functions (Prince M, 2007).

The DSM V (Diagnostic and Statistical Manual of Mental Disorders) criteria, by the American Psychiatric Association (APA), defines dementia as a neurocognitive disorder (NCD), whereby the cognitive impairment is severe enough to interfere with the activities of daily living, including social and occupational tasks (Simpson JR, 2014). The diagnostic criteria of dementia requires an impairment in at least one or more of the following cognitive domains: aphasia (language), apraxia (motor functions), agnosia (loss of sensory information) or disturbance in executive functions (attention, planning) (Simpson JR, 2014). Additionally, the criteria requires the exclusion of other possible reversible causes of cognitive impairment such as cognitive decline due to depression, psychosis or other mood disorders (Scott KR and Barrett AM, 2007).

Alzheimer's disease (AD) is thought to be the most common form of dementia (AD-LOD) accounting for more than half of dementia cases (VanDerFlier WM and Scheltens P, 2005, Prince M, 2007). The pathological landmark of AD is the presence of progressive brain atrophy associated with extracellular amyloid β plaques (AP) and intracellular neurofibrillary tangles (NFTs), formed of "twisted" hyper- phosphorylated tau protein (Griffin WS, 2006, Selkoe DJ, 2004). Presently, the only method to confirm AD diagnosis is through post-mortem analysis and autopsy (Jellinger KA, 2000). A combination of various tools have been proposed to aid clinicians in identifying and ascertaining tentative cases of AD, including but not limited to: psychiatric and neuropsychological tests, clinical and neurological examinations, structural and functional neuroimaging, measurements of biological markers in the cerebrospinal fluid and other biological samples and genetic testing (Jellinger KA, 2000).
In the clinical setting, differentiating between AD and other forms of LOD still remains a challenge. The most recent to-date diagnostic criteria, and still currently adopted, is the 2011

National Institute on Aging-Alzheimer's Association (NIA-AA) "Research" Criteria for AD (McKhann GM et al., 2011a). The criteria mainly requires evidence of absence of significance of vascular-type lesions as a minimum diagnostic requirement for AD, and biomarker supportive evidence of abnormal brain load of amyloid and tau, using functional and structural imagining, as well as cerebrospinal fluid studies (McKhann GM et al., 2011a).

Vascular dementia (VaD) is thought to be the second most common form of LOD, although VaD pure forms have been reported to be very rare (Perneczky R et al., 2016). VaD is defined as cognitive impairment associated with micro and macro-vascular brain lesions, either ischemic or hemorrhagic and mainly caused by cerebrovascular disease and pathology (Román GC, 2003, Román GC, 2004). Imaging studies on VaD have shown that the cerebrovascular changes are predominantly subcortical in nature (Chui H, 2008). The diagnostic criteria of VaD require the presence of cognitive impairment, vascular brain lesions, a stroke diagnosis preceding dementia, and the exclusion of other types of dementia (Román GC, 2003).

AD-LOD and VaD are followed by Lewy Body Dementia (LBD) and Parkinson's disease with dementia (PDD) (VanDerFlier WM and Scheltens P, 2005). The two types are typically associated to Parkinson's disease (PD). LBD usually affects patients prior to or within a year from the onset of the parkinsonian motor manifestations, whilst PDD usually occurs years after PD- motor disease onset (McKeith IG and Mosimann UP, 2004).

It is key to note that the majority of LOD cases over the age of 75 have mixed pathological abnormalities (Fernando MS and Ince PG, 2004, White L et al., 2005, Aguero-Torres H et al., 2006, Nelson PT et al., 2007, Schneider JA et al., 2007, Sonnen JA et al., 2007, Fotuhi M et al., 2009, Schneider JA et al., 2009).

(b)Prevalence and Incidence of late-onset dementia (LOD)

The prevalence and incidence of LOD increases with age (Fratiglioni L et al., 1999, Fratiglioni L et al., 2000). The prevalence of LOD is known to double every 5 years from the age of 65, ultimately affecting approximately 40% of individuals over the age of 80-85 (Ferri CP et al., 2005, Prince M, 2007) . The incidence rate of LOD has been reported to increase from 1 per 1000 person years in individuals between the ages of 60 and 64, to approximately 70 per 1000

person years in individuals above the age of 90 (Qiu C et al., 2007). Indeed a report by Ferri et al (2005) estimated the annual number of new cases of LOD to exceed 4.6 million patients, worldwide.

In 2010, the global prevalence of LOD in individuals above the age of 60 was estimated to be 4.7 %, with the highest regional prevalence in North America at 6.9 %, followed by 6.2 % in Europe, 4 % in Asia and 2.6 % in Africa (Sosa-Ortiz AL et al., 2012). According to the World Alzheimer's Report, the number of people with LOD will double every 20 years, reaching 65.7 million people in 2030 and 115.4 million in 2050, compared to 35.6 million people in 2009 (Prince M et al., 2013). In 2011, approximately 33.9 million people worldwide had a diagnosis of AD, a statistic which is expected to triple in the next 40 years (Barnes DE and Yaffe K, 2011). An estimate of about 25 million individuals with LOD was reported in 2000, with approximately 52 % from less developed countries (Wimo A et al., 2003).

Furthermore, the socio-economic burden of dementia world-wide is vast and the disease is now being acknowledged as a grand challenge for the world economies. According to the Alzheimer's disease International annual report of 2012, the total cost of dementia worldwide in 2010 was estimated at 604 US billion dollars, rose to $818 billion by 2014 , will exceed the trillion mark by 2018 and is expected to increase by 85 % in 2030 (Wimo A et al., 2017). In the UK, a 2010 report by the Alzheimer's research trust has projected the dementia annual cost at 23 billion pounds, a figure that is almost equivalent to the annual cost of stroke, cancer and heart diseases combined (Wimo A et al., 2013).

1.1.2 Cancer

(a) Definition and major sub-types of cancer

Similar to LOD, the etiology of cancer is also multifactorial, and thought to involve complex interactions between a variety of genetic, lifestyle and environmental factors resulting in an exponential and uncontrolled growth and proliferation of abnormal cells (Wilson S et al., 2002).

There are more than 100 different types of cancers reported (Cancer Research UK) and, with the emerging new biomarker developments providing a more granular characterization of cancer types and sub-types, this number is ever increasing (Cancer Research UK). However investigations within this thesis will only focus on the most common types of cancer. According to the Cancer Registration Statistics England (2015), the most common forms of cancer in the UK are prostate, breast, lung, bowel and colorectal cancers and account for more than 50 % of malignant cancer registrations. Breast and prostate cancers are the most common in females and males, respectively (Risbridger GP et al., 2010). This is followed by lung, bowel and colorectal cancers, which account for the most common causes of cancer-related mortality in the UK (Cancer Research UK). In terms of benign and non-malignant tumors, non-melanoma skin cancer (NMSC) has been shown to be the most frequent form in the UK and world-wide (Lomas A et al., 2012).

(b)Prevalence and Incidence of cancer:

It has been estimated that the prevalence of cancer increases with age; indeed, more than a third of cancers are diagnosed in people over the age of 75 (Cancer Research UK). In 2012 alone, it was estimated that there were 3.45 million new cases of cancer (excluding non-melanoma skin cancer), and more than 8.2 million deaths due to cancer, worldwide (Ferlay J et al., 2013). The most prevalent cancer types worldwide are lung, breast (women), bowel and prostate cancer (men).

The incidence of all cancer forms in males over the age of 65 (2,4682.2 per 100,000) has been reported to be four times that of the incidence in males in the 45-64 age group (56.7 per 100,000 person years) (Baranovsky A and Myers MH, 1986). Similarly, in females above the age of 65 (1,401 per 100,000) the incidence of all cancer forms was reported to be twice that of females in the 45-64 age group (609.7 per 100,000) (Baranovsky A and Myers MH, 1986). In 2011, a total of 139,951 cancer deaths were recorded in England and Wales, as a result of the leading cancer types: lung, colorectal, breast and prostate (Jemal A et al., 2011).

The incidence and prevalence of cancer continue to grow and, by 2030, the number of new cases annually will exceed 22 million, globally. Compared to the 2008 statistics, this will represent an increase of 75% (World Health Organization: Cancer Research UK: World Cancer Fact Sheet).

1.1.3 The relationship between cancer and late-onset dementia

An inverse association and hypothesized mutually protective effect has been proposed, by several authors, between cancer and LOD (Roe CM et al., 2005, Roe CM et al., 2010, Driver JA et al., 2012, White RS et al., 2013, Romero J et al., 2014, Musicco M et al., 2013). Tabares –Seisdedos et al (2009) defined this protective anticancer effect under the concept of "inverse co-morbidity", suggesting that cancer patients seem to have a lower than expected co-occurrence of neuropsychiatric or central nervous system (CNS) disorders (Tabarés-Seisdedos R et al., 2009). Others have questioned the existence of this relationship and suggested that this association may be a "false positive" finding, due to misdiagnosis and selective mortality. Individuals with cognitive impairment are less likely to be screened for other diseases, and individuals with cancer might not live long enough to develop dementia (Scherder E et al., 1999, Marwill SL et al., 1996).

The biological mechanisms and processes underlying LOD forms and cancer are complex and poorly understood. There is significant evidence that the risk of cancer as well as the risk of LOD increases with advancing age. Previous reports have suggested that carcinogenesis and neurodegeneration might be linked to one another, based on some of the shared biological pathways and genetic characteristics evident in both diseases (Lu KP et al., 2003, Migliore L et al., 2005, Staropoli JF, 2008, Behrens MI et al., 2009, Wang W et al., 2009, Driver JA and Lu KP, 2010, West AB et al., 2005). For example, Driver et al (2012) propose deregulation of the cell cycle as a mechanism synonymous to the two conditions.
Epidemiological studies exploring the links between cancer and LOD, particularly AD-LOD have been, initially scarce but have recently been gaining popularity. Earlier studies, based on autopsy material, reported a lower prevalence of cancer in AD patients (Corsellis JAN, 1963, Tirumalasetti F et al., 1991, DeSouky AL, 1992, Beard CM et al., 1996). More recent population-based and case-control studies have investigated the incidence of cancer in AD-LOD cohorts; AD-LOD in cancer cohorts; and finally, cancer and AD-LOD simultaneously (White RS et al., 2013, Romero J et al., 2014, Musicco M et al., 2013).

Having carefully reviewed the literature, I will present, in the next chapter, key findings (and remaining questions) regarding the relationship between AD-LOD and cancer and will attempt

to discuss various biological mechanisms and genetic variables that have been reported to potentially underpin this relationship.

However, both the existence of this inverse association and the putative underlying mechanisms still remain unclear and rather controversial. Various proposals have been put forward, implicating shared genetic pathways (p53 and pin1 genes), common disease processes (e.g. chronic inflammation), and common risk factors with potentially explanatory effects (such as smoking, understood to increase risk of cancer, but protect against Parkinson's disease) (Ganguli M, 2015)). I am particularly interested in evaluating "known" risk factors that may be common for the two conditions, such as obesity and T2DM.

1.1.4 Shared risk factors of cancer and LOD

Like all other common diseases, LOD and cancer seem to result from complex interplays of a variety of biological and lifestyle (over the life-time) factors that have been extensively reported in several review and meta-analyses papers (Bellou V et al., 2017, Vijayvergia N and Denlinger CS, 2015). The main relevant biological, environmental and lifestyle factors as well as vascular risk factors are given below. Systematic reviews on modifiable risk factors include several variables, the most consistent being physical activity, smoking, obesity, and alcohol (Baumgart M et al., 2015, Khan N et al., 2010). Medical conditions that have been identified include cerebrovascular disease, hypertension, diabetes and hypercholesterolemia (Chen JH et al., 2009, Stein CJ and Colditz GA, 2004).

Literature on the diseases of interest suggests a complex intertwining relationship. Although some covariates are clearly associated with LOD and cancer, others show no clear understanding of whether an association exists altogether. The pervasive overlap in risk factors between cancer and LOD and the reported interactions between risk factors themselves, suggests an urgent need to further study and aim to disentangle these complex associations. Accordingly, several studies have begun to explore multi domain approaches for the prevention of LOD and other old-age related diseases. The Australia Diabetes , Obesity and Lifestyle study reported that a 5 to 20 % reduction for each LOD risk factor could decrease the prevalence of LOD by 1.6 and 7.2 % in 2020 (Ashby-Mitchell K et al., 2017). Findings from the Finnish Geriatric Intervention Study to Prevent Cognitive impairment and Disability (FINGER)

suggest that a 2 year multidomain intervention including diet, cognitive training and vascular risk monitoring could improve cognitive function and decrease risk of dementia later in life (Kivipelto M et al., 2015). Furthermore, the European Dementia Prevention Initiative (EDPI) has recently been established as a collaboration between the FINGER study and two other large randomized controlled trials (RCTs) (PreDIVA, MAPT). EDPI's main objective is to combine the knowledge and findings of the three studies to determine the optimal design and future directions for multidomain studies targeting the prevention of LOD.

(a) Biological factors:

LOD is a disease of old age and its incidence increases exponentially with age, with some preponderance in woman and is most prevalent among black ethnic groups (Gao S et al., 1998). Similarly, advancing age is a risk factor for overall and specific cancer types (White MC et al., 2014). In cancer, incidence and mortality rates seem to be higher in males for the majority of cancers, even when disregarding sex-specific cancers such as prostate, testicular and ovarian cancer (Dorak MT and Karpuzoglu E, 2012). In the UK, cancer also seems to be more common in blacks and whites than in Asians (Garte S, 1998).

(b) Shared Lifestyle and Environmental factors:

Smoking

Systematic reviews and meta-analysis that aimed to evaluate the risk of dementia in relation to smoking have reported an increased risk for dementia among smokers (Lee Y et al., 2009, Flicker L, 2009, Reitz C et al., 2007, Cataldo JK et al., 2010) . Findings from the Rotterdam study have shown that the risk of dementia doubles in smokers, with a genotype-dependent effect, since significance was only noted in non-carriers of the APOEε4 allele – the major genetic determinant of AD (Ott A et al., 1998, Kivipelto M et al., 2008). Despite the growing evidence of smoking being a risk factor for dementia, especially in longitudinal studies, a number of older studies (mainly case-control) have reported an inverse relationship between smoking and dementia (Duijn CMv and Hofman A, 1991) or no association at all (Tyas SL et

al., 2000). These conflicting results in the literature have been attributed to differing methods across studies, as well as issues of confounding and bias (Kukull WA, 2001).

On the other hand, cancer has consistently been shown to be associated with smoking. Specifically, smokers have an increased risk for cancers of the lung, mouth, throat, larynx, esophagus, liver, pancreas stomach, kidney, bowel, ovary, bladder and cervix (Cancer research UK). A study on approximately 34,000 male British Doctors followed up for 50 years revealed a decrease in mortality rate in non-smokers (due to prevention and cessation strategies) and a threefold increase in age specific mortality rate, for individuals with prolonged cigarette smoking (Doll R et al., 2004).

Alcohol

Alcohol consumption is another factor that has been widely investigated in both the dementia and cancer domains. Several studies suggest that excessive alcohol consumption increases the risk of dementia (Anttila T et al., 2004, Sabia S et al., 2009), with suggestions of a dose dependent relationship, particularly with vascular dementia (O'Keefe JH et al., 2007).

At the same time, other studies have reported a beneficial effect of moderate drinking on dementia risk (Peters R et al., 2008, Luchsinger JA et al., 2004a, Ganguli M et al., 2005, Simons LA et al., 2006). One of the first studies to look into this relationship is the PAQID (Personnes Agess Quid), which reported that the risk of dementia was reduced by 5.3 in mild drinkers, compared to none drinkers (Orgogozo JM et al., 1997). The Copenhagen City heart study has also found a beneficial association in individuals with monthly and weekly intake of wine, compared to individuals who never or hardly drink (Truelsen T et al., 2002). Additional reviews and meta-analysis suggest that the different findings found between various studies should be interpreted with caution, to account for varying methodologies and the lack of standardized definitions for alcohol consumption (Xu W, 2017).

In cancer, current epidemiological evidence suggests a causal association between heavy alcohol consumption and the following cancers: liver, colon, oropharynx, larynx, esophagus, rectum and female breast (Bagnardi V et al., 2001). Further research has also emerged to

support this association by showing that cancer risk can be reversed, by terminating alcohol consumption (Ahmad-Kiadaliri A et al., 2013). The UK based Million Women Study investigated the effect of moderate intake of alcohol on cancer risk in women and found that low to moderate alcohol consumption increased the incidence of cancer (Allen N et al., 2009). Moreover, a meta-analysis that investigated the effect of alcohol and smoking on cancer risk in a total of 19 body sites, found that concurrent smoking has a modifying additive effect and substantially increases the risk of cancer (Bagnardi V et al., 2001).

To summarize, more accurately defining the relatively complex role of modifiable risk factors, such as smoking and alcohol, on dementia risk still remains a scientific challenge. Evaluating the effect of each of these variables independently may not be appropriate as many of them interact with each other. The question remains whether each of those modifiable risk factors solely predisposes individuals to dementia (and some cancers), or whether an individual's susceptibility to disease results from the confounding effect of several or all of interlinked covariates.

Physical Activity

Several systematic reviews and randomized controlled trials (RCTs) have illustrated the importance of physical activity as a protective factor, for both cancer and LOD (Barreto PdS et al., 2015, Sabia S et al., 2017, Moore SC et al., 2016). A recent systematic review examined the association between different physical activity frequencies and cognitive function for over 100,000 individuals, from 20 different countries. Results showed a dose response association, where individuals who exercised at least once a week were positively associated with cognitive function, compared to individuals who did not exercise (β coefficients reported for: moderate intensity physical activity: 0.52-0.75, and vigorous intensity physical activity: 0.26-0.33)(Barreto PdS et al., 2015). Conversely, a recent prospective study, the Whitehall II cohort study, examined the effect of physical activity on cognitive decline and dementia, over a period of 27 years. The authors reported no association between physical activity, cognitive decline and risk of dementia. In fact, they suggested that previous studies reporting a protective

association of physical activity may be due to reversible causation, whereby individuals in the preclinical stages of dementia had lower physical activity levels (Sabia S et al., 2017).

Studies exploring the effect of physical activity and several types of cancer have also been extensively examined. A recent meta-analysis with pooled results for over 1 million participants from 12 prospective US and European populations, showed a positive association between low physical activity levels and the following types of cancer: esophageal adenocarcinoma, liver, lung, kidney, gastric endometrial, myeloid leukemia, myeloma, colon, head and neck and breast (Moore SC et al., 2016). Additionally, low levels of physical activity were associated with an increased risk for malignant melanoma and prostate cancer (Moore SC et al., 2016). Similarly, the National Health and Nutrition Examination Survey (NHANES I) cohort explored the physical activity and cancer relationship in over 12,000 individuals (Albanes D et al., 1989). An increased risk of cancer was reported among individuals who were physically inactive, compared to very active individuals (RR 1.7, 95% CI 1.4-2.4 for men, RR 1.6, 95% CI 1.2-3.5 for women). Upon stratifying by sex and different cancer types, this relationship was stronger, specifically among men, for colorectal (RR 1.6, 95% CI 0.7, 3.5) and lung cancer (RR 1.6; 95% CI = 1.2, 3.5) (Albanes DBlair A and Taylor PR, 1989).

(c) Vascular factors:

Cardiovascular risk factors such as BMI, hypertension, hypercholesterolemia, as well as cerebrovascular diseases are thought to be linked to dementia risk, especially the vascular dementia (VaD) form. With that being said, recent literature suggests that the majority of dementia cases are due to mixed pathology, over the age of 75 (Kuller LH et al., 2012). There is mounting evidence that vascular risk factors especially in midlife might have an effect on dementia risk later in life. However, understanding the relationship between various cardiovascular risk factors is rather complex and needs to be carefully managed since relationships are heavily intertwined. Although the majority of LOD pathophysiological studies propose that vascular risk factors undeniably have an effect on brain function and structure, it is to date unclear how these pathological changes effect cognition and dementia risk (Iadecola C et al., 2016). Other important clinical covariates include depression and brain injury, which are both majorly implicated in dementia and cancer research.

BMI

Several reviews have suggested that increasing BMI is independently associated with a higher risk for dementia, even after adjusting for common confounders such as smoking, age and medical comorbidities (Gorospe EC and Dave JK, 2007, Whitmer RA et al., 2005, Rosengren A et al., 2005). An age and gender-dependent effect was observed in a study by Gustafson et al (2003) with 18 year follow -up of overweight individuals. The authors reported that being overweight in older age is a risk factor for dementia and is more significant in women. Evidently, it is likely that being overweight in midlife increases the risk for dementia (Hassing LB et al., 2009). A population based prospective Mayo clinic study on aging emphasized the importance of detecting changes in weight from mid-life to late-life, and how this could serve as a marker for identifying individuals with increased risk for mild cognitive impairment (MCI) and dementia (Alhurani RE et al., 2017). Other studies have shown that this observed increase in dementia risk is not statistically significant and further studies are needed to clearly validate the relationship between dementia and obesity, independent of other confounders (Kivipelto M et al., 2005). By contrast, a recent longitudinal study conducted by the Louisiana State University Hospital on about 45,000 patients from 30 to 96 years old, found that higher BMI at baseline was associated with lower risk of dementia amongst diabetic patients and that this relationship is stronger in African Americans (Hu G et al., 2012). Similarly, a recent prospective longitudinal cohort by Bell and colleagues (2017) showed that higher BMI in later life decreases the risk of incident MCI and AD. Furthermore, a recent CPRD-based retrospective study on 2 million patients revealed that being underweight in middle and old age actually increases the risk of dementia over two decades (Qizilbash N et al., 2015) .

In the cancer field, approximately 20 percent of all cancers are thought to be related to obesity (Wolin KY et al., 2010). Pooled results from a recent systematic review and meta-analysis of prospective observational studies on about 280, 000 incident cases of cancer, have demonstrated that the association between cancer and obesity varies within different sex and ethnic groups (Renehan AG et al., 2008). In the UK Million women study, increasing BMI was correlated with specific types of cancer: colorectal, malignant melanoma, breast and endometrial cancer. Equally, 5 percent of all cancers in post-menopausal women was associated with being overweight (Reeves GK et al., 2007). Likewise, Bhaskaran (2014) used

CPRD data to investigate the association between BMI and 22 of the most common cancers, and found that BMI was linked to 17 cancer types. In particular, higher BMI was found to increase the risk of kidney, gallbladder, uterine, cervical and thyroid cancer, and a positive relationship was additionally seen for BMI and diagnosis of colon, liver, ovarian and breast cancer (for post-menopausal women) (Bhaskaran K et al., 2014).

Hypertension

An abundant number of studies have shown that hypertension in midlife is associated with a higher risk for dementia in later life (Yamada M et al., 2003, Launer LJ, 2000) .The Honolulu Aging Study found that high blood pressure in middle age increases the risk of dementia in older age, particularly among men never treated with antihypertensive medication (Launer LJ, 2000). Further post-mortem analysis of the study concluded that high blood pressure is directly related to brain atrophy and accumulation of neurofibrillary tangles and neurotic plaques (Petrovitch H, 2000) .In fact, few studies suggest that antihypertensive treatments could reduce the risk of dementia (Khachaturian AS et al., 2006, Tully PJ et al., 2016, Ruitenberg A et al., 2001). Other studies attempted to predominantly evaluate the effect of raised blood pressure across different age spectrums and investigate whether the risk for dementia varies as well. The 90 + population study in the US found that participants with a hypertension age of onset between 80 and 89 had a lower risk for dementia, compared to those without hypertension (Corrada MM et al., 2017) . Similarly, another prospective cohort study in Washington on 2,356 participants found that high systolic blood pressure was associated with greater risk for dementia in those below 75, but not in older subjects (Li G et al., 2007).

In a recent retrospective cohort study using the National Insurance Research Database of about 10,000 patients with diabetes and 50,000 age and sex matched non-diabetic patients, researchers found that dementia risk was higher in diabetics and the risk did not significantly increase in the presence of hypertension and hyperlipidemia. However, in the non-diabetes cohort, patients who had both hypertension and hyperlipidemia had a higher risk of dementia compared to those without (Fan Y-C et al., 2017). This study sheds light on the complexity of vascular risk factors and whether they are perhaps meditated through one main mechanism (ex: insulin resistance) without really having an independent effect on dementia risk. A recent prospective cohort study of four US communities, ARIC (Atherosclerosis Risk in

communities), revealed that the risk of dementia was highest among individuals with hypertension, diabetes and who were of black race, smokers, APOEε4 allele carriers and with a lower educational attainment (Gottesman RF et al., 2014).

Although studies on the effects of hypertension on the risk of cancer is not as profuse as it is in dementia research, there have been some systematic reviews that summarized studies on hypertension and specific types of cancers. In prostate cancer, a recent meta-analysis revealed an increase in the risk of prostate cancer among individuals with hypertension (Liang Z et al., 2016). Similar results were seen in a systematic review that focused on breast cancer. In a further subgroup analysis, it was found that this association between hypertension and breast cancer was only significant among post-menopausal women (Han H et al., 2017). The risk for renal cancer has also been shown to be associated with hypertension, with the risk being 2 to 4 times for renal cancer among hypertensive individuals (Radišauskas R et al., 2016).

Hypercholesterolemia

Elevated cholesterol levels during mid-life have been reported to be associated with an increased risk for dementia (Helzner EP et al., 2009, Alonso A et al., 2009). A recent meta-analysis that investigated the relationship between total levels of cholesterol and risk for dementia in 18 prospective studies, found that only mid-life total cholesterol level was related to dementia risk; and there was no risk observed when examining late-life total cholesterol (Anstey KJ et al., 2008) .Similarly, a Finnish population study reported that mid-life elevated cholesterol level (≥ 6.5 mmol/L) was a significant risk for MCI, which consequently might convert to dementia, even after adjusting for possible confounders (Kivipelto M et al., 2001). The Norwegian Countries study (NCS) included approximately 5,000 participants with a follow up of 35 years, and also found an association between increased total cholesterol level (≥ 7.8 mmol/L) and risk of dying from or with dementia in later life , even after adjusting for all other vascular risk factors (Strand BH et al., 2012) .On the other hand, several reports have suggested that there is no association between hypercholesterolemia and cognitive decline or dementia at any point in life (Mielke MM et al., 2010, Blom K et al., 2014). In addition, few studies have investigated the effect of statin use on dementia risk and confounding results have been observed. A meta-analysis of prospective cohort studies reported that there was a reduced risk of dementia among statin users (Song Y et al., 2013), while results from an earlier pooled

analysis by Zhou et al (2007) was unsuccessful in detecting any association between statins and incidence of dementia.

Hypercholesterolemia has also been extensively investigated in the cancer domain with evidence suggesting an inverse association between hypercholesterolemia and cancer (Knekt P et al., 1988, Ahn J et al., 2009). The US NHANES epidemiologic study revealed that both men and women in the lowest cholesterol quintiles had nearly double and 1.2 times the risk for cancer incidence and mortality, respectively (Schatzkin A et al., 1987) . A more recent population study involving about a million Korean adults reported different associations for varying cholesterol levels with different cancer types. It appeared that higher cholesterol levels were positively associated with risk for prostate and colon cancer in men and breast cancer in women, while lower cholesterol levels were inversely associated with liver, stomach and lung cancer (Kitahara CM et al., 2011). Statins were also investigated in relation to cancer risk. In a recent meta-analysis that included 6663 incident and 2000 death cancer cases, it was found that statins had no effect on reducing the incidence of cancer (Dale KM et al., 2006). Similar results were reported by Murtola et al (2007), were any sign of statins being protective for prostate cancer has disappeared after adjusting for potential confounders.

Cerebrovascular disease (CeVD)

Traditionally, a diagnosis of dementia in a patient with a history of cerebrovascular disease is thought to be defined as vascular dementia. However, the majority of dementia cases in the elderly are of mixed pathologies. Kuller et al (2005) reported that 44 percent of incident dementia cases in those above 65, had vascular disease. Stroke, a common type of cerebrovascular disease, has been consistently found to be associated with a higher dementia risk (Leys D et al., 2005, Vermeer SE et al., 2003, Troncoso JC et al., 2009). Similarly, atrial fibrillation (AF) has also been shown to increase the risk for dementia (Ott A et al., 1997, Dublin S et al., 2012, Bunch TJ et al., 2010). It is important to note that AF is a known cause of embolic stroke and, therefore, the relationship between AF and dementia may be driven by stroke.

Similarly, cerebrovascular diseases has also been found to share common risk factors with cancer (Koene RJ et al., 2016). Nonetheless, studies on the effect of CeVD as a specific risk factor for cancer is rather scarce. Research in this area has focused more on the incidence and prevalence of CeVD among cancer survivors as a consequence of cancer treatment (Saynak M et al., 2008). However, due to the immense sum of studies emphasizing its importance as a comorbidity for both dementia and cancer as well as the strong commonality of risk factors among the all three, it was of particular importance to include this as a covariate in my analysis models.

(d) Other factors:

Depression

Depression has also been extensively evaluated in relation to risk of dementia. Systematic reviews and meta- analysis on the relation of depression and dementia reported a positive effect of depression on risk of dementia due to Alzheimer's disease (AD) in later life, indicating that depression might be an independent risk factor for AD (Ownby RL et al., 2006, Jorm AF, 2001). In a retrospective cohort study on 13,535 individuals of the Kaiser Medical Care Program of Northern California, the risk of developing dementia was approximately double in individuals with mid-life or late life depression (Barnes DE et al., 2012). These results are consistent with findings reported from the Framingham Heart study, where depressed participants had more than a 50 % increased risk for dementia over a course of 17 years of follow up (Saczynski JS et al., 2010). Similarly, the Baltimore Longitudinal study of Aging found that this positive association between depression and dementia is even stronger among recurrent depression cases (Dotson VM et al., 2010). Also, the Diabetes and Aging study that investigated an ethnically random sample of 19,239 T2DM patients found that patients with concurrent depression had a 100 % increase in dementia risk compared to diabetics without depression (Katon WJ, 2011). Other studies argued that depression follows the incidence of dementia (Chen P et al., 1999) or happens concurrently with it (Heun R et al., 2002, Ganguli M et al., 2006). A 2012 review by Possel and colleagues investigated the relationship between depression and dementia in different studies and found that the results varied greatly in context of the time to diagnosis and the variety of depression scales used. Subsequently, it remains unclear whether depression is actually a risk factor or a prodromal feature of dementia and

further studies are needed to help better understand the true nature of associations between the two diseases.

Determining whether or not depression is a risk factor for cancer has been argued in research for a long time. Several large-scale studies have explored the relationship between depression and cancer. The Baltimore Epidemiologic population- based study with a follow- up of 24 years reported a higher risk of overall cancer and specifically breast cancer among those with depression (Gross AL et al., 2010). Another prospective cohort study, the Established Populations for Epidemiologic Studies of the Elderly, found that even after adjusting for all possible confounders the hazard ratio for cancer among the chronically depressed was higher than those without depression (Penninx BW et al., 1998). Other studies have reported no association between depression and cancer. In a large register- based study in Denmark there was no evidence to support that depression is an independent risk factor for dementia, but it showed that depression plays an important role in modifying lifestyle factors that could ultimately have an effect on cancer risk (Dalton SO et al., 2002). The perplexing results reported in the depression and cancer connection could be attributed to the varying nature of sample size, follow- up time and depression psychometric scales used across different studies.

Brain Injury

It comes as no surprise that brain injury has been reported in some studies as a risk factor of dementia. A recent meta-analysis summarizing results from over 32 studies found that head injury significantly increased the risk of dementia and AD (LI Y et al., 2017) . Another meta-analysis by Fleminger et al (2003) explored the relationship between head injury and dementia and found that the relationship was only significant in males, after controlling for possible confounders. In the MIRAGE study, the risk of dementia was reported to be higher among those with head injury and loss of consciousness compared to those with head injury and without loss of consciousness (Guo Z et al., 2000). Furthermore, a study on 548 US Navy and Marine veterans found that veterans with severe and moderate traumatic brain injury were 4 and 2 times more likely to have dementia compared to those without, respectively (Plassman BL et al., 2000).

The relationship between brain injury and cancer, especially brain tumors, have also been investigated. A population based study in Taiwan, using the Traumatic Brain Injury Registry and the National Health Insurance Research Database, showed that individuals with traumatic brain injury had a higher incidence for malignant brain tumor diagnosis compared to those without (Chen YH et al., 2012). On the other hand, a population based study in Sweden by Nygren et al (2001), found no association between brain injury and brain tumors in a cohort of about 311,000 individuals even after stratification of the analysis by age and other important covariates (Nygren C et al., 2001).

1.1.5 T2DM as a risk factor for late-onset dementia and cancer

T2DM is a common and "complex" chronic illness, accounting for more than 90 % of diabetes cases, worldwide; its risk (like cancer and LOD) increases with age (American Diabetes Association). A combination of genetic and environmental factors is responsible for such global proliferation (Neel JV, 1962, Tuomilehto J et al., 2001, Langenberg C et al., 2011) . Almost 27% of individuals aged over 65 currently have a diagnosis of diabetes (American diabetes Association). The prevalence of T2DM in this age group is anticipated to rise to 366 million people by 2030 (Wild S et al., 2004). In 2005, diabetes accounted for 1.1 million deaths globally and diabetes related deaths are predicted to double between 2005 and 2030 (World Health Organization, Diabetes fact sheet 2010) warranting international concern about the increasing economic and public health burden of the disease (Wild S et al., 2004, Shaw JE et al., 2010).

There is growing evidence for an increased risk of LOD in individuals with T2DM (Ott A et al., 1999, Peila R et al., 2002, Haan MN, 2006, Lu F-P et al., 2009, Crane PK et al., 2013). Several systematic reviews and meta-analyses indicate that T2DM is an important risk factor for LOD (Xu WL et al., 2004, Lu F-PLin K-P and Kuo H-K, 2009, Kopf D and Frölich L, 2009, Cheng G et al., 2012, Biessels GJ et al., 2014, Vagelatos N and Eslick G, 2013) . Numerous meta-analysis report that the risk of LOD appears to increase in individuals with T2DM, specifically when investigating AD-LOD (RR range: 1.46-1.56) and VaD (RR range: 2.27-2.48 (Cheng G et al., 2012, Gudala K et al., 2013). Similarly, the population based "Honolulu-Asia Aging" Study with 2574 male participants found that diabetes was associated with LOD in general (RR 1.5) and more specifically with AD-LOD (RR 1.8) (Peila RRodriguez BL and Launer LJ, 2002). A two-fold increase in the risk for AD-LOD has also been reported

in individuals with T2DM (Ott A et al., 1999). Research conducted by Larsson et al (2005) suggested that this risk seems to be higher in men compared to women (RR 2.27 and 1.37 respectively). The retrospective "Cardiovascular Health Cognition" Study evaluated 2574 individuals without LOD over a period of 8 years, during which 411 new cases of LOD were identified (Irie F et al., 2008). The authors reported an increased risk for both AD-LOD and mixed AD-LOD in the presence of T2DM. Additional analysis revealed the APOEε4 allele responsible for a further increased risk for AD-LOD and mixed AD-LOD (Irie F et al., 2008). Furthermore, individuals with T2DM have been shown to have an earlier age of LOD diagnosis, compared to those without T2DM (Zilkens RR et al., 2013), as well as an increased mortality rate in individuals diagnosed with both T2DM and LOD (Murthy SB et al., 2010, Helzner EP et al., 2008).

However, the precise mechanisms underpinning links between T2DM and LOD (including AD) are still unresolved; plausible explanations include hyperglycaemia and insulin resistance (Biessels GJ and Kappelle LJ, 2005, Qiu WQ and Folstein MF, 2006, Cukierman-Yaffee T, 2009). Insulin resistance is regarded as a characteristic of T2DM defined by the failure of body cells to respond to insulin, resulting in increased production of insulin (hyperinsulinemia) (DeFronzo RA, 2004). At the same time, insulin resistance and impaired insulin signaling decrease glucose uptake in regions that are known to have a significant impact on AD progression(Matsuzaki T et al., 2010, O'Neill C et al., 2012) affecting the synaptic plasticity, as well as β-amyloid and tau metabolic regulations in the brain (Schiöth HB et al., 2012). Studies have shown an increased β-amyloid accumulation in insulin resistant mice (Park S et al., 2013). Similarly, in human studies there was an increase in the incidence of AD in individuals with hyperinsulemia (Qiu WQ and Folstein MF, 2006, Luchsinger JA et al., 2004b, Schrijvers EMC, 2010). Moreover, these disruptions in insulin signaling pathways play a significant role in cognitive and psychomotor functioning (Cosway R et al., 2001, Ryan CM and Geckle MO, 2000).

Interestingly, findings that confirm insulin insufficiency and resistance in AD patients have led to the belief that AD is merely a "Type 3 Diabetes"(Steen E et al., 2005). Type 3 diabetes and the notion of AD being a neuroendocrine disease, was first introduced by Suzanne de la Monte and Jack Wands(Monte SMdl and Wands JR, 2008). The authors reported that, in both human and animal studies, several molecular and biochemical factors may be common to AD and T2DM. In particular, impaired insulin signaling and deficiency cause disturbances in brain

insulin, leading to biochemical lesions in AD. Furthermore, studies have investigated the effect of intranasal insulin, commonly used for the treatment of T2DM, on cognitive impairment and reported an improvement in cognitive functions, in support of the Type 3 diabetes theory (Haan MN, 2006, Reger MA and Craft S, 2006).

Similarly, the role of T2DM as a risk factor for cancer has been extensively examined (Hemminki K et al., 2010, Shikata K et al., 2013). Numerous studies have shown that individuals with T2DM are at increased risk of developing cancer, compared to individuals without T2MD(Czyżyk A and Szczepanik Z, 2000). The cellular imbalances caused by T2DM create a biological environment which is vulnerable for random genetic faults, possibly leading to carcinogenesis(Orgel E and Mittelman S, 2013) . Hyperinsulinemia and hyperglycemia are the current proposed mechanisms that link T2DM and cancer, with insulin resistance playing the leading role in this association (Orgel E and Mittelman S, 2013).

Positive associations between T2DM and liver cancer, pancreatic cancer (Hemminki K et al., 2010, Czyżyk A and Szczepanik Z, 2000, Grote VA, 2011, Chari ST et al., 2005, Huxley R et al., 2005), bladder cancer (Larsson SC, 2006), breast cancer (Larsson SC et al., 2007, Xue F and Michels KB, 2007, Gorin SS et al., 2005, Weiderpass E et al., 1997), colorectal cancer(Larsson SC et al., 2005, Stocks T et al., 2009, Khaw KT et al., 2004, Nilsen TIL and Vatten LJ, 2001, Wideroff L et al., 1997), lung cancer(Tseng CH, 2013) and gastric cancer(Shimoyama S, 2013) have been well studied. Conversely, there appears to be an inverse association between T2DM and prostate cancer (Tsilidis KK et al., 2014, Gong Z et al., 2006, Kasper JS and Giovannucci E, 2006, Giovannucci E and Michaud D, 2007). Individuals with T2DM have a 25-40 % reduction in risk of developing prostate cancer, compared to individuals without T2DM(Wotton CJ et al., 2010).

A number of genome wide association studies propose an increased risk of LOD and cancer, mainly due to genetic predisposition, metabolic imbalances and dysregulation of pathological pathways(Abbatecola A et al., 2011, McCarthy M and Zeggini E, 2009). T2DM is a complex metabolic illness that is linked to pathological changes in the cerebral, membrane and amyloid setting as well as small degree of cortical and subcortical atrophy (Cosway R et al., 2001). Additionally, common mechanisms in T2DM such as insulin resistance and hyper-insulinemia have been associated with cancer risk and progression (McCarthy M and Zeggini E, 2009).

The figure below represents the interrelationships between T2DM, cancer and dementia.

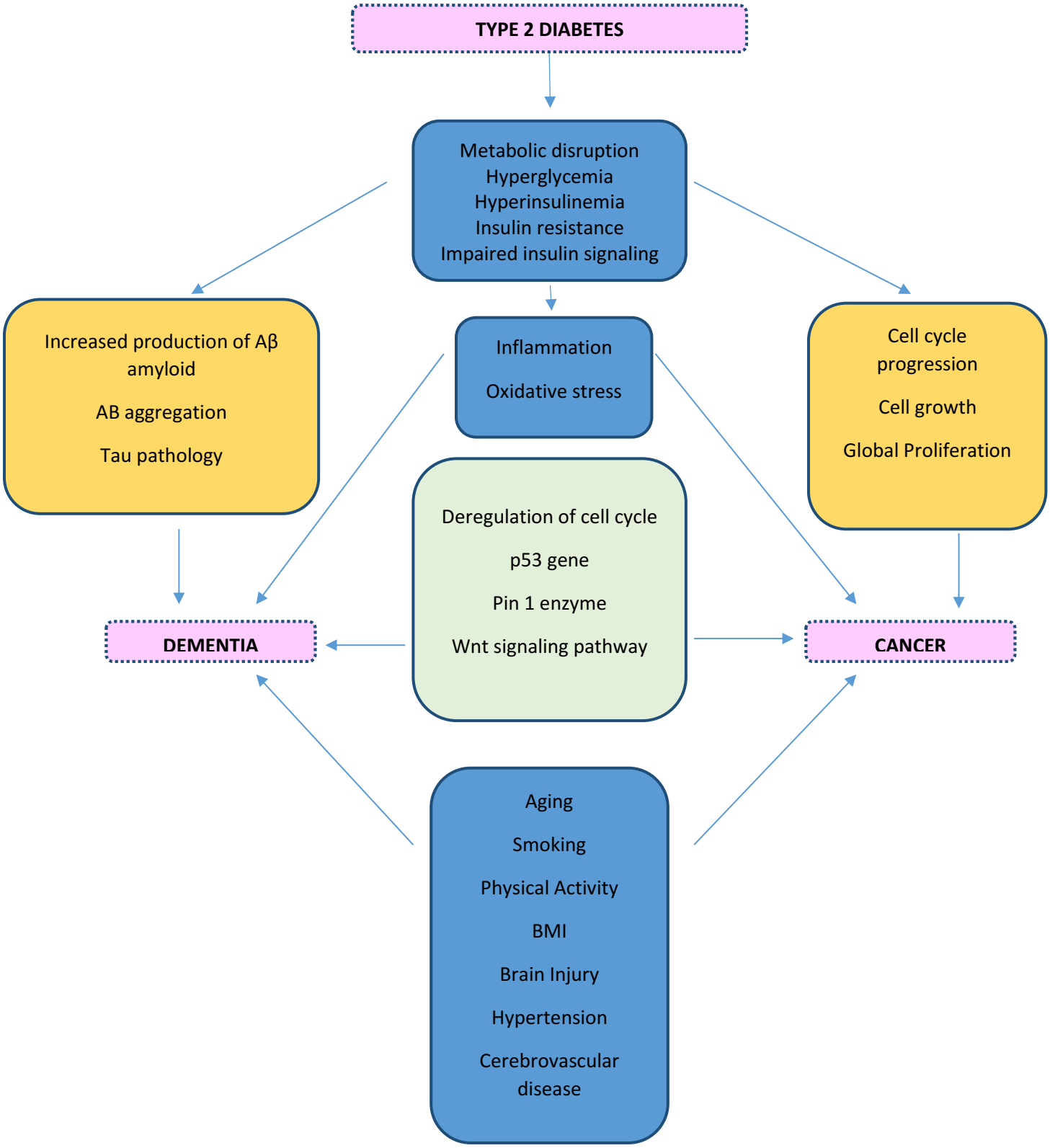


Figure 1: The interrelationships between T2DM, cancer and dementia.

1.2 THESIS OVERVIEW

1.2.1 Overall aim

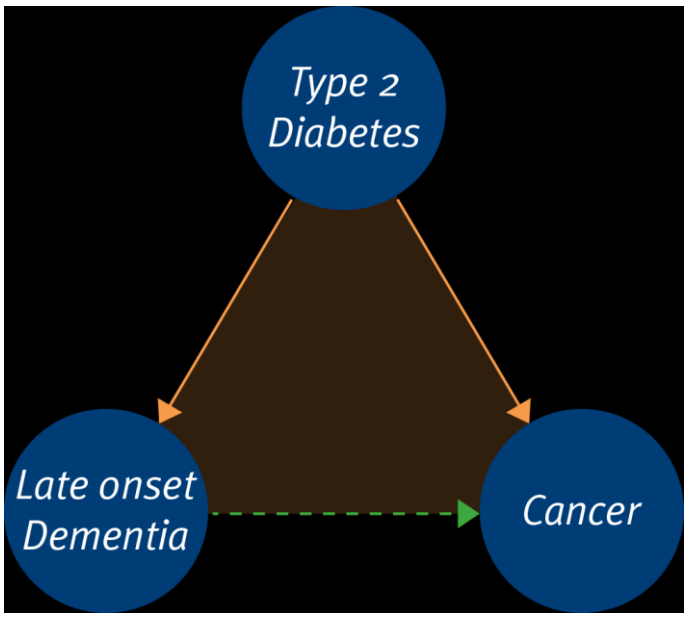
An inverse association has been reported between LOD, especially dementia attributable to Alzheimer's disease (AD-LOD) and cancer. A better understanding of the precise role of common risk factors that increase the risk of *both* cancer and LOD is of particular importance, given the high and increasing prevalence of such shared risk factors, including T2DM. T2DM is an important risk factor for both cancer and LOD, but it is to-date unclear whether it is relevant to the observed inverse relationship observed between cancer and LOD.

In light of the established complex relationship between cancer and LOD, and the known relationship between these two comorbidities and T2DM, it is possible that T2DM may play a significant role in this relationship. The landmark biological processes of T2DM i.e. insulin resistance, altered glucose levels and inflammatory imbalances are likely to facilitate an unrelenting constant destruction of cellular cycles; thus encouraging both carcinogenic and neurodegenerative processes.

To my knowledge, there have been no reports of studies exploring the relationship between all three diseases in a comprehensive and scientifically rigorous manner. The lack of clarity between the factors and the associations across these diseases, highlights the need for an in-depth exploration on what might be an essential gap or missing parameter in this field of research. Studies investigating the relationship between T2DM, cancer and LOD/AD-LOD can have significant implications on future therapeutic discoveries, biological mechanisms and genetic pathways that these three diseases share.

The overall aim of the study is to use a large national database to explore the relationship between cancer, LOD and AD-LOD in a primary care population aged ≥ 65 years old, in individuals with and without T2DM.

The directed acyclic graph (DAG) for the study below represents the relationship between the study variables, as well as the relationship under investigation. Solid lines indicate the associations that are assumed to be present based on previous literature. The dotted line indicates the association that is being examined in the current analysis.



1.2.2 Objectives

The primary aim of my thesis is to investigate the relationship between different types of cancer and LOD/AD-LOD separately in individuals with and without T2DM, using a large UK primary care database (CPRD). This study will thus attempt to investigate the conundrum of a hypothesized inverse relationship between several forms of cancer and LOD, in view of their shared risk factor of insulin resistance and T2DM. Incidence of death will also be investigated to consider the issue of mortality selection.

The objectives involve examining data from the CPRD UK primary care populations in order to:

1. Examine the incidence of LOD, and AD-LOD in individuals with and without T2DM
2. Examine the incidence of any cancer, and major cancer subgroups, in individuals with and without T2DM

3. Examine the incidence of LOD, and AD-LOD among groups with and without a cancer diagnosis, separately for individuals with and without T2DM diagnosis
4. Estimate the risk of developing LOD diagnosis and AD-LOD, among individuals with versus without a previous or existing diagnosis of any cancer and specific types of cancer (e.g. lung, breast, prostate, bowel, non-melanomatous skin or melanomatous skin cancer) for individuals with and without a T2DM diagnosis
5. Investigate death as a competing risk in the cancer and LOD/AD-LOD relationship

1.2.3 Study Significance and Rationale

"To draw a distinction between disease and normal aging is to attempt to separate the undefined from the undefinable" (Evans et al 1988). With an ageing population reaching unprecedented proportions world-wide, the number of individuals with age-related diseases and comorbid illnesses is on the rise. According to Feinstein et al (1970), comorbidities are defined as "clinical disorders that exist additionally to an index disease".

Valders et al (2009) suggest that "patients with several medical disorders is rather a rule than an exception". Comorbidities are prevalent, especially amongst the elderly(Akker Mvd et al., 1998, Barnett K et al., 2012). In a US report, it has been estimated that the prevalence of comorbidities is expected to increase to more than 157 million Americans, with approximately 81 million citizens having multiple conditions by 2020 (Lancet 2009). With this increasing prevalence of comorbidities, it remains imperative to examine cohorts with specific comorbidities rather than to adjust for these comorbidities in data analysis. It is also pivotal to research these comorbid diseases concurrently, ultimately making results more generalizable and applicable to the general population.

Several epidemiological studies have suggested an inverse association between cancer and LOD, whilst basic research studies highlight potential shared biological mechanisms between these two diseases. A potential inverse association between the two diseases might provide insight into disease pathophysiology and prevention. Current evidence stems from a limited number of studies with small sample sizes, inappropriately partial and incomplete evaluation of potential confounders, limited examination of sensitivity analyses and failure to investigate different subgroups of LOD and cancer.

In this study, CPRD data will shed light into the aforementioned question using a robust design and methodology, whilst capitalizing on the richness of available data using statistical approaches. This study aims to investigate the association between cancer diagnosis and incident LOD among individuals with and without T2DM. The ability to use primary care – derived longitudinal data in this study, will allow me to investigate a larger number of confounding factors (compared to previous studies) and stratify the population into cancer survivors and none survivors to examine the effect of survival bias. More importantly, as the overall cancer incidence represents a heterogeneous group of diseases, I will be able to test the association looking at different major cancer subgroups to investigate whether the observed association is different in relation to different cancer endpoints. Findings from this study may contribute to the understanding of the etiology of these important diseases and could form the basis of further studies aimed at exploring the potential effects of different treatments (e.g. cancer treatment) in relation to LOD and vice versa.

1.2.4 Thesis Structure

The chapter consequent to this introductory chapter provides a detailed literature review of all the studies on the relationship between cancer and LOD (AD-LOD), including their strengths and limitations. I also propose some of the possible biological mechanisms underlying the inverse relationship observed in some studies, while also discussing probable reasons for studies that report a nil relationship between cancer and LOD (AD-LOD).

Chapter three presents the data source, the data and coding system, including the strengths and limitations of the main data source used. I additionally discuss the study design and the eligibility criteria for both non-T2DM and T2DM cohorts. Importantly, I explain how the main variables of interest were extracted and how the data was cleaned and managed to readily be available for data analysis. Furthermore, the data management and cleaning steps required the development of an algorithm for identifying additional cases of LOD as well as an algorithm to classify different LOD cases into the correct sub groups. Chapter three concludes by giving an overview of the statistical analysis plan. Consequently, chapter four aims to present the results for the main research question, by addressing each of the statistical aims. The results

chapter is separated into a presentation of the demographic characteristics, the identification of cancer and LOD cases as well as their incidence rate in both cohorts. The results then expand to specifically investigate the association between LOD and cancer and assess the role of death as a competing risk in the association found. Following the results chapter, chapter five discusses and compares my findings in light of similar studies in the literature as well as presents the main strengths and limitations of this study. The final chapter, chapter six, summarizes and concludes the work done in this thesis and provides directions for future work.

CHAPTER 2 – LOD (AD-LOD) AND CANCER RELATIONSHIP

LITERATURE REVIEW

This chapter presents the key literature on the relationship between AD-LOD and cancer, summarizing: (1) studies on the incidence of cancer in individuals with LOD (AD),(2) studies on the incidence of LOD (AD) in individuals with cancer and (3) studies that have explored this relationship in a bidirectional manner. The final section of the chapter discusses the various biological mechanisms and gene variations that have been reported to play a role in the cancer/LOD (AD) relationship.

2.1 BACKGROUND

Dementia and cancer are leading causes of morbidity and mortality in the UK (Murray CJ et al., 2013). Their incidence has increased rapidly over recent years and projections suggest that these trends are set to continue (Prince M et al., 2013). Some recent observational studies have suggested a lower risk of cancer among those diagnosed with dementia vs. without, and vice versa (Ganguli M, 2015). In some studies, this relationship is observed for particular types of cancer or dementia only, indicative that survival bias cannot fully explain these observed associations (Ganguli M, 2015) ; while an autopsy study and consideration of alternative neurological outcomes, have limited potential explanation by ascertainment bias (Tirumalasetti F HL, Birkett DP, 1991, Driver JA BA, Au R, et al 2012).

Several studies have explored the relationship between cancer and central nervous system (CNS) disorders such as Parkinson's disease (Becker C et al., 2010, Driver JA et al., 2007, Inzelberg R and Jankovic J, 2007), Huntington's disease (Ji J et al., 2012) and Multiple Sclerosis (Kingwell E et al., 2012). These studies have all shown a reduced incidence of cancer in individuals with the aforementioned CNS disorders. A meta-analysis of cancer incidence in 577,013 participants of 50 observational studies, reported a lower co-occurrence of cancer in patients in the presence of CNS and neurodegenerative disorders (Catalá-López F et al., 2014).

Conversely, only a limited number of studies have explored the link between cancer and AD-LOD (Beard CM et al., 1996, DeSouky AL, 1992, Romero J et al., 2014). None of those studies stratified their results by risk factors/diseases. Instead, they adopted an explorative approach to obtain a preliminary understanding of the relationship between cancer and AD. Other studies have questioned the existence of this relationship and suggested that this association may be

due to misdiagnosis, whereby individuals with cognitive impairment are less likely to be screened for cancer (Scherder E et al., 1999, Marwill SLFreund KM and Barry PP, 1996).

Early examples of studies that explored this association were based on autopsy data. These studies showed lower prevalence of cancer in participants that had AD-LOD (Beard CM et al., 1996, DeSouky AL, 1992, Tirumalasetti FHan L and Birkett DP, 1991). More recent population-based and case-control studies have investigated the incidence of cancer in AD-LOD cohorts; AD-LOD in cancer cohorts; and, finally, cancer and AD-LOD simultaneously. Research has shown that AD accounts for more than 80 % of dementia cases (Reitz C et al., 2007, Fratiglioni L et al., 2000), but it has also been found that the majority of individuals with dementia after the age of 80 present with mixed pathologies (Fotuhi MHachinski V and Whitehouse PJ, 2009, Schneider JA et al., 2009, Schneider JA et al., 2007). Furthermore, AD-like pathology has been reported in significant numbers of asymptomatic individuals, over the age of 65 (Sonnen JA et al., 2007, Knopman DS, 2001). Hence, the need to employ more specific language and to differentiate between AD and LOD both in the clinical and research settings. As per the NIA-AA 2011 criteria, the term AD-LOD must be documented with imaging/ biomarker based evidence of amyloid and tau pathological involvement and of exclusion of all other possible causes of dementia, such as MRI- findings suggestive of vascular lesions (McKhann GM et al., 2011b, Dubois B et al., 2010).

Additionally, autopsy studies have found that the brains of the majority of LOD sufferers present with a combination of mixed pathologies, rather than a single neuropathological disease (Schneider JA et al., 2009, Nelson PT et al., 2007, Schneider JA et al., 2007, Sonnen JA et al., 2007, Aguero-Torres HKivipelto M and VonStrauss E, 2006). Several authors have also argued that the "last century" dogma that all LODs are mainly vascular in their etiology, is still valid today for dementia occurring after the age of 75(Graham NL et al., 2004, Groves W et al., 2000, Breteler MM, 2000, Hulette C et al., 1997).

In this review, the term LOD will be employed and will include all forms under this heading. Dementia associated to PD (LBD and PD-dementia) and cases with earlier onset such as familial cases and Fronto-temporal Dementia (FTD) will be excluded. This review will be undertaken with a special focus on dementia attributable to Alzheimer's disease (AD-LOD)

2.2 METHODS

A comprehensive search was conducted using OVID MEDLINE and PubMed on published literature on the relationship of LOD, AD and Cancer, up until April 2017. Initially, keywords used were AD and Cancer and were limited to human studies (Appendix 1). Due to the paucity of literature on this topic, the review was inclusive of all types of studies published on this association. The search initially resulted in 10,688 articles, with 10,502 remaining after duplicate removal. A total of 10,382 articles were excluded when screened by title and abstract and only 120 articles were screened by full text. Ninety six articles were specific to the AD-LOD/ LOD and cancer relationship, fifteen of which were studies on AD-LOD/LOD and cancer. The remaining 81 were review and opinion papers, which centered on the possible genetic associations between cancer and AD-LOD and their biological plausibility (Figure 2).

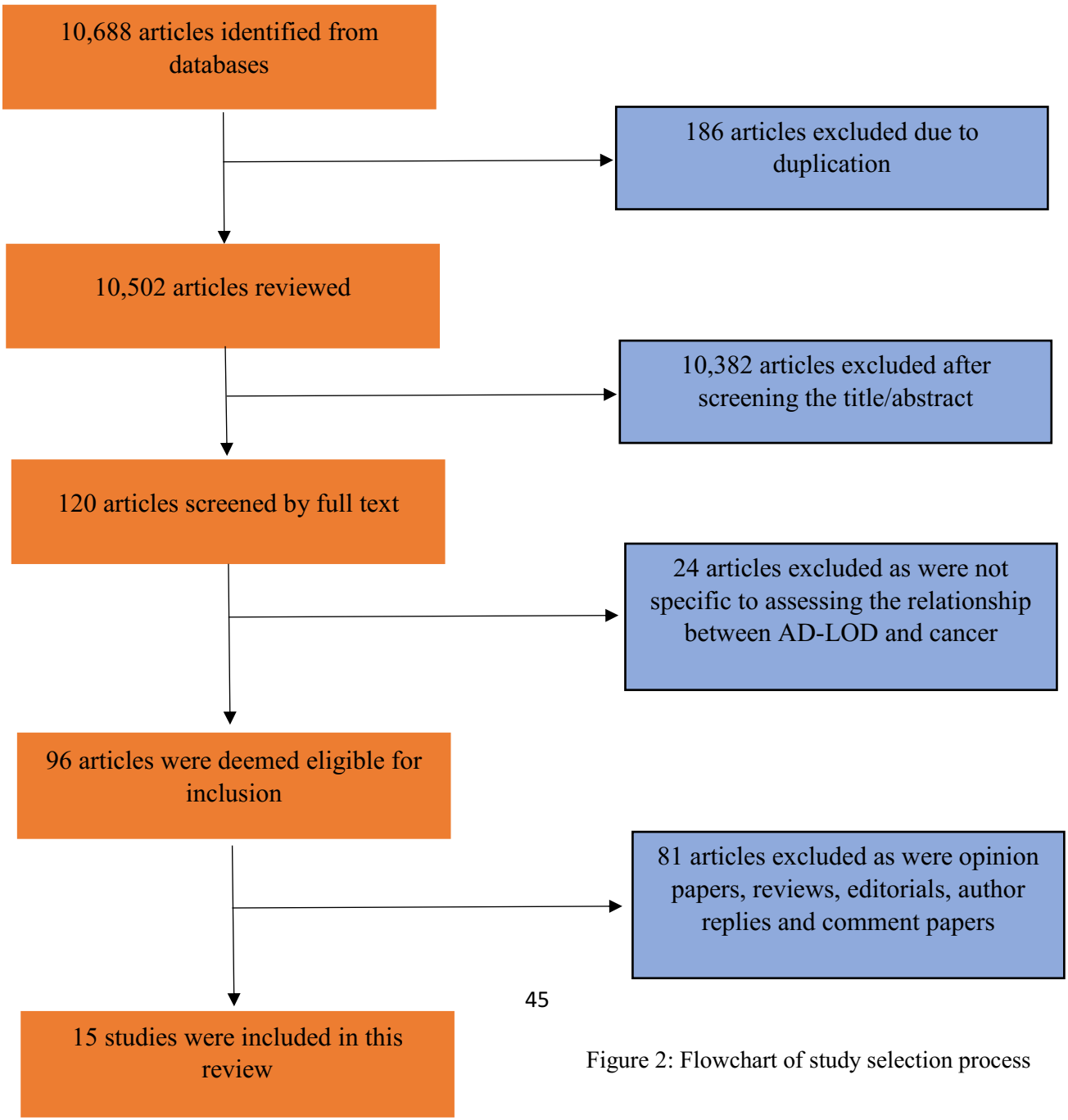


Figure 2: Flowchart of study selection process

2.3 RESULTS

2.3.1 Characteristics of Studies included

Fifteen studies met the eligibility criteria and were included in this review. Four of the studies were on cancer incidence following LOD/AD-LOD diagnosis, six of the studies were on the incidence of LOD/AD-LOD in individuals with cancer and five studies assessed this relationship in a bidirectional manner. The following data was extracted for each of the studies of interest: (1) name of the author, year and country (2) study design (3) study population (4) cancer cases identification method (5) LOD/AD-LOD cases identification method (6) confounders that were adjusted for in the analysis (if any) (6) the outcome of interest represented as RR, HR or OR along with the 95% CIs.

2.3.2 Studies on incidence of cancer in individuals with LOD (AD)

An age and sex matched case–control study researched the frequency of cancerous tumors diagnosed, prior to the onset of AD-LOD and excluding individuals with other LOD forms (Realmuto S et al., 2012). The study included 126 individuals with AD-LOD matched with 252 controls. The mean age of AD-LOD onset was 71.1±7.5 years and the average MMSE score was 12.9±8.3, with an AD-LOD duration of 5.8±2.8 yrs. Results showed that an inverse association was only statistically significant in women with an adjusted OR of 0.5 (95% CI 0.3, 0.9). In addition, individuals with AD-LOD showed a significantly reduced risk of endocrine related neoplasms, with an adjusted OR of 0.5 (95% CI 0.2-1.0) (Realmuto S et al., 2012). With regards to tumor grading, no significant differences were identified. Researchers further stratified data by sex and endocrine/non-endocrine tumors in both cases and controls. In female participants, 14.4% cases vs. 25% of endocrine related tumors were reported in individuals with AD-LOD and controls, respectively. These findings led the authors to conclude a plausible protective effect of estrogen (Realmuto S et al., 2012).

Ou et al (2013) utilized Taiwan's National Health Insurance database to retrospectively evaluate 6,960 individuals with AD-LOD. Standardized incidence ratios (SIRs) were used for calculating the incidence of cancer in individuals with AD-LOD. Participants with AD-LOD had a lower risk for developing cancer (SIR=0.88, 95%CI 0.80, 0.97) compared to the general

population. However, when stratified by gender, the relationship remained significant only in women with AD-LOD (SIR=0.81, 95% CI 0.70, 0.93) and more specifically in individuals between the ages of 60 and 79 (SIR=0.76, 95% CI 0.69, 0.92). This lower risk of cancer in women was mostly found for cancers of the genitourinary system, stomach, central nervous system, colon and rectum, liver and biliary tract, hematologic malignancies, head and neck. An exception to this finding was lung cancer, for which only men with AD-LOD had a decreased risk (SIR=0.75, 95% CI=0.57-0.98) (Ou SM et al., 2013). The authors suggested that the difference in significance between men and women may be due to a protective estrogen effect. Lower levels of estrogen may stimulate the death of tumor cells, thus protecting women with AD-LOD from cancer. Furthermore, the significant results found between lung cancer and AD-LOD, specifically in men, could be due to tobacco smoking. Previous studies found a risk reduction in PD in those who smoke. However, studies on AD and smoking are still controversial and confounding (Ou SM et al., 2013).This study included a large database with SIRs adjusted for age, sex and calendar year. The authors found that being a male, > 80 years old with chronic obstructive pulmonary disease and cirrhosis, are the greatest risk factors for a comorbid diagnosis of cancer and AD-LOD. However, they have also proposed that the age risk factor (>80 years old) could be a result of misdiagnosis, given that the elderly are less likely to undergo invasive procedures for cancer detection (Ou SM et al., 2013).

In addition to the study conducted by Ou et al (2013), Lin et al (2016) also used a large database in Taiwan (National Health Insurance Research Dataset and the National Cancer Registry) to investigate the effect of LOD diagnosis on risk reduction in cancer. A total of 3282 individuals with LOD, along with 13,128 controls were examined for a period of 7 years. Results have shown a protective association between LOD and cancer (HR=0.77, 95 % CI 0.65-0.91), specifically for colon (HR=0.54, 95 % CI 0.29-0.99) and prostate (HR=0.44, 95% CI 0.20-0.98) cancers (Lin HL et al., 2016).

Another prospective population based study investigated the relationship between the symptoms of LOD and cancer specific mortality (Romero JP et al., 2014). The study was based on the Neurological Diseases in Central Spain (NEDICES) survey, which included a final cohort of 4,197 elderly participants (467 LOD cases and 3,730 free of LOD). The participants were followed up for an average of 7.1 years, after which 403 participants with LOD (277 with possible or probable AD-LOD, 126 non –AD-LOD) and 1,573 participants without LOD died. Results have shown that after adjusting for possible confounders (demographics and

comorbidities), a decreased occurrence of cancer was observed in those with possible or probable AD-LOD (HR=0.53 95%CI 0.29-0.95) compared to non-AD-LOD and LOD-free individuals (Romero JP et al., 2014).

The above studies are summarized in table 1.

Table 1: Characteristics of studies on incidence of cancer in individuals with LOD (AD)

Study (Country)	Study Design	Study Population Age (years)	Definition of LOD/AD-LOD	Definition of Ca	Adjusted for	Incidence of Ca
Romero et al 2014 (Spain)	Population based survey	467 dementia (155 M, 312 F) 3,730 free of dementia. (1607 M, 2,123 F) ≥ 65	Questionnaire, face to face interview, MMSE, Pfeffer Functional Activities Questionnaire, neurological evaluation, neuropsychological battery	Death certificates	Age Gender, Education Smoking Alcohol Depression	**Possible or Probable AD:** HR 0.53 (95% CI 0.29,0.95)* **Non-ADD:** HR 0.97 (95% CI 0.48 ,1.98) The free dementia group was used as the reference category
Ou et al 2013 (Taiwan)	Population based (Retrospective)	6960 AD (2762 M,4198 F) ≥ 40	Registry based	Registry based	Gender Age Duration of AD diagnosis	**Overall**: SIR 0.88 (95% CI 0.80,0.97)* F :SIR 0.81 (95% CI 0.70,0.93)* M: SIR 0.95 (95% CI 0.83,1.08) For F: Head, Neck, skin, hematological malignancies, liver, biliary tract, genitourinary system, stomach.* For M:Lung and mediastinum*
Lin et al 2016 (Taiwan)	Population based (Retrospective)	3282 dementia (1650 M, 1632 F) 13,128 controls (1650 M, 1632 F) ≥ 40	Registry based	Registry based	Age Sex Hypertension Diabetes Stroke	**Overall**: HR 0.77 (95% CI 0.65, 0.91)* **Colon** : HR 0.54 (95% CI 0.29-0.99)* **Prostate:** HR 0.44(95% CI 0.20-0.98)*
Realmuto et al 2012 (Italy)	Case-control paired matched study (age and sex)	126 AD (36 M,90 F) 252 controls (72 M,180 F) AD onset (years) 71.1 ± 7.5	Neurological Examination, neuropsychological battery, medical history, and brain computed tomography or MRI	Semi-structured questionnaire (For AD: caregivers) Review of medical records.	Smoking Education Age Gender	**Overall**: OR 0.6 (95% CI 0.4, 1.1) F:OR 0.5 (95% CI 0.3, 0.9)* M:OR 2.1 (95% CI 0.5,8.5) **Endocrine related**: OR 0.5 (95% CI 0.2,1) F: OR 0.4 (95% CI 0.2,0.8)* M: OR 4.9 (95% CI 0.4,67.2) **Not Endocrine related**: OR 1.3 (95% CI 0.6,2.9) F:OR 0.8 (95% CI 0.2,2.5) M:OR 1.5 (95% CI 0.3,7.7)

M: Male, F: Female, SIR: Standardized Incidence Ratios, HR: Hazard Ratio, OR: Odds Ratio, RR: Relative Risk, CI: Confidence Interval *All Significant results (p<0.05)

2.3.3 Studies on the incidence of LOD (AD) in individuals with cancer

A population based study examined 19,756 cases of 18 different types of cancer, along with their matched age and sex controls (8 controls per one case of cancer) (Attner B1 LT, Noreen D, Olsson H, 2010). The overall risk for an LOD diagnosis in individuals with cancer was low compared to controls (RR=0.60, 95% CI=0.52-0.69) and markedly increased in individuals who were older than 70 (RR=0.59, 95% CI=0.52-0.68)(Attner B1 LT, Noreen D, Olsson H, 2010). When stratifying data by cancer types, the lower rate of LOD was statistically significant in individuals with colon cancer (RR=0.60, 95% CI=0.40-0.91) followed by lung cancer (RR=0.53, 95% CI= 0.31-0.90), melanoma (RR=0.44, 95% CI=0.20-0.97), prostate carcinoma (RR=0.49, 95 % CI=0.33-0.72) and urinary bladder/tract cancer (RR=0.40,95% CI=0.22-0.73). There was no statistical significance amongst individuals with cervical cancer, brain tumors and leukemia. The authors concluded that this inverse association was mainly due to the underdiagnoses of cancer (Attner B1 LT, Noreen D, Olsson H, 2010). All cancer types showed a reduced relative risk; tumors that were within deep body structures had a lower risk compared to malignancies that are closer to the body surface. Therefore, it is possible that participants were not able to explain symptoms to their physicians, or that physicians may have omitted to further explore cancer diagnosis in individuals with LOD. Thus, cancer care may be adversely affected in individuals with LOD, leading to high cancer related mortality (Rozzini R and Trabucchi M, 2009).

Other studies investigated the association of specific cancer types with AD-LOD. For instance, one population based study explored the relationship between non melanoma skin cancer (NMSC) and AD in a longitudinal study of aging in New York (White RS et al., 2013). A total of 1102 participants were included in the study, of whom 109 had prevalent NMSC diagnosis, 32 developed NMSC during the study and 993 had no NMSC at baseline. Researchers used four models in the statistical analysis to adjust for confounders, all of which included age as the basic time measure. All models showed that the protective effect between NMSC and AD-LOD was further diminished, when looking at only AD-LOD diagnosis compared to any AD diagnosis and all-cause LOD. Upon examining AD-LOD diagnoses only, there was a statistically significant protective effect, even after adjusting for demographic data and vascular risk factors (HR= 0.21, 95% CI= 0.051-0.87). The significance is, however, lost when the number of APOE4 alleles is adjusted for (in addition to other confounders). The authors

concluded that individuals with NMSC and over the age of 70 have a reduced risk of developing AD-LOD, specifically when compared to other LOD types. The main limitations of this study were that NMSC cases were self-reported (potentially resulting in erroneous clinical data) and the data provided on APOE4 genotype was limited (thus reducing the value of their power calculations) (White RS et al., 2013).

Similarly, a nationwide cohort study in Denmark investigated the association between NMSC and AD-LOD, as well as overall LOD (Schmidt SA et al., 2017). A total of 216,221 individuals with NMSC and 1,081,097 controls matched by age and sex were included. The study showed a slight inverse relationship between cancer, AD-LOD (HR=0.95, 95% CI 0.92-0.98) and overall LOD (HR=0.92, 95% CI 0.90-0.94). However, the association only appeared at the beginning of the follow –up period and disappeared after 5-10 years. The authors indicated that the observed inverse association is most likely due to ascertainment bias, where individuals with underdiagnosed early cognitive impairment could be less aware of NMSC symptoms (Schmidt SA et al., 2017).

In Taiwan, a case control study was conducted on 3281 newly diagnosed cases of hepatocellular carcinoma (HCC) along with 13,124 controls, using the Taiwan National Health Insurance Program (Lai SW et al., 2014). No association was found between HCC and AD-LOD after controlling for possible confounders (OR=0.51, 95%CI=0.19-1.42).

Although the majority of studies investigating the cancer and LOD association have been population-based, a very recent study by Yarchoan et al (2017) has investigated this association from a neuropathological perspective. The authors used data from the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP) to analyze the pathologic data and history of cancer in individuals with AD-LOD. Specifically, they have explored the AD pathology (neurofibrillary tangles and amyloid-β load) post-mortem in a cohort of 1,289 individuals. Results have shown that individuals with a history of cancer had a lower risk for developing AD [OR 0.70, 95% CI 0.55-0.89] and a decreased load of neurofibrillary tangles; however the amyloid-β load was similar in those with and without a history of cancer (Yarchoan M et al., 2017).

Finally, a retrospective study, using the UTAH population database, examined several different statistical techniques to explore the association between cancer and AD-LOD in 94,435

individuals (Hanson HA et al., 2016). The authors found that different model specifications can change the direction of the results majorly. In this study, the authors perform several statistical models, with cancer as the exposure variable, and explore the effect of cancer as a time-varying and non-time varying covariate. In the time-varying covariate scenario, it is assumed that individuals with cancer contribute person years to the no-cancer group until the diagnosis of cancer, after which they contribute person years to the cancer group. On the other hand, in the non-time varying covariate scenario, it is assumed that individuals with a cancer diagnosis, will contribute person years to the cancer group only, regardless of when they were diagnosed with cancer (never/ever). Results showed that upon accounting for cancer as a non-time-varying covariate, an inverse association between cancer and AD-LOD was observed. However, when cancer was specified as a time varying covariate, no inverse association between cancer and AD-LOD was found. Additionally the authors used several statistical methodologies to account for death as a competing risk, and described mortality selection as the main reason behind the inverse association observed (Hanson HA et al., 2016).

The above studies are summarized in Tables 2 and 3.

Table 2: Characteristics of studies on incidence LOD (AD) in individuals with cancer

Study (Country)	Study Design	Study Population Age (years)	Definition of LOD/AD-LOD	Definition of Ca	Adjusted for	Incidence of LOD/AD-LOD
Attner et al 2010 (Sweden)	Population based study	19,756 Ca 147,324 controls Age of entry not specified	Registry based	Registry based Looked at 18 different types of Ca (Only sig presented)	None	**Overall**: RR 0.60 (95% CI 0.52,0.69)* **≤70 yrs**: RR 0.73 (95% CI 0.45,1.19) **>70 yrs**: RR 0.59 (95% CI 0.52,0.68)* **Cancer types(Significant only presented)*** **Colon :** RR 0.60 (95% CI 0.40,0.91)* **Lung:** RR 0.53 (95% CI 0.31,0.90)* **Melanoma:** RR 0.44 (95% CI 0.20,0.97) * **Prostate:** RR 0.49 (95% CI 0.33,0.72)* **Urinary/Bladder:** RR 0.40 (95% CI 0.22,0.73)*
White el al 2013 (USA)	Population based Longitudinal study	At baseline: 109 NMSC (50 M,59 F) 961 NMSC free (368 M ,593 F) ≥68	Memory impairment plus impairment in at least one additional cognitive domain	By asking the participants	Model 1 : (Gender) Model 2: (Gender+ Education) Model 3: (Demographic +Vascular risk factors) Model 4: (Demographic +Vascular risk factors+ number of APOE4 alleles)	**Overall LOD (all-cause):** Model 1: HR 0.64 (95% CI 0.34,1.23) Model 2: HR 0.66 (95% CI 0.34,1.27) Model 3: HR 0.68 (95% CI 0.35,1.31) Model 4: HR 0.75 (95% CI 0.32,1.76) **Any AD** Model 1: HR 0.47 (95% CI 0.21,1.09) Model 2: HR 0.49 (95% CI 0.21,1.13) Model 3: HR 0.50 (95% CI 0.22,1.17) Model 4: HR 0.60 (95% CI 0.21,1.72) **Only AD** Model 1: HR 0.20 (95% CI 0.048,0.81)* Model 2: HR 0.21 (95% CI 0.051,0.85)* Model 3: HR 0.21 (95% CI 0.051,0.87)* Model 4: HR 0.18 (95% CI 0.024,1.34)
Lai et al 2014 (Taiwan)	Case-control study	3281 Hepatocellular carcinoma (2044 M , 1237 F) 13,214 controls (8176 M , 4948 F) ≥65	Registry based	Registry based	Diabetes mellitus, cirrhosis, alcoholic liver damage, other chronic hepatitis, hepatitis B and C infection	**Overall :** OR 0.51 (95% CI 0.19,1.42)

M: male, F: female, SIR: Standardized Incidence Ratios, NMSC: Non-melanoma skin cancer HR: Hazard Ratio, OR: Odds Ratio, RR: Relative Risk, CI: Confidence Interval

***All Significant results (p<0.05)**

Table 3: Continuation - characteristics of studies on incidence LOD (AD) in individuals with cancer

Study (Country)	Study Design	Study Population Age (years)	Definition of LOD/AD-LOD	Definition of Ca	Adjusted for	Incidence of LOD/AD-LOD
Schmidt et al 2017 (Denmark)	Nationwide cohort study	216,221 cancer (110,235 F, 105.986 M) 1,081,097 controls (551,173 F, 529,924 M) ≥ 18	Registry based	Registry based	Age, sex, calendar period of NMSC diagnosis, alcohol related diagnosis, hospital diagnosed obesity, hypertension, ischemic heart disease, congestive heart failure, diabetes, multiple sclerosis	**Overall**: HR 0.92 (95% CI 0.90, 0.94)* **AD-LOD:** HR 0.95 (95% CI 0.92, 0.98)*
Yarchoan et al 2017 (USA)	Longitudinal study	401 cancer (139 M,262 F) 888 no cancer (308 M,580 F) Age of entry not specified	Cognitive testing Autopsy	Self-reported	Age at death, sex, race, education, APOE4	**Overall**: OR 0.75 (95% CI 0.58, 0.97)* **AD-LOD:** OR 0.73 (95% CI 0.56, 0.94)*
Hanson et al 2016 (USA)	Population based (Retrospective) cohort study	92,425 (44,552 M,47,873 F) 65-79	Registry based Death certificates	Registry based	Age Sex	**AD- LOD:** HR 0.96 (95% CI 0.84, 1.09) (cancer as time-varying covariate) **AD- LOD:** HR 0.73 (95% CI 0.67, 0.85)* (cancer as non time-varying covariate)

M: male, F: female, SIR: Standardized Incidence Ratios, HR: Hazard Ratio, OR: Odds Ratio, RR: Relative Risk, CI: Confidence Interval ***All Significant results (p<0.05)**

2.3.4 Studies on the incidence of both cancer and LOD (AD) among individuals with LOD(AD) and cancer, respectively

A longitudinal study researching the association and incidence risk between cancer and AD-LOD was conducted in the US using archival data from a variation of longitudinal studies conducted by the Washington University Alzheimer's Disease Research Center (Roe CM et al., 2005). At the time of cohort entry, 594 participants without LOD and no history of cancer were followed up , of which 45 participants developed one or more cancer during follow-up. Cox proportional hazard models adjusted individually for sex, age at cohort entry and education as well as adjusted in different combinations of models were considered in the final analysis. Findings suggested that the AD-LOD cohort had a slower rate for developing cancer compared to the no dementia group even after adjustment for demographic confounders (HR= 0.391, 95% CI=0.207, 0.739). The rates were faster for males and older aged participants, respectively. Similarly, the cancer cohort had a slower rate for developing AD-LOD compared to the cancer free group. The findings showed that AD-LOD diagnosis was faster for older age and slower for Caucasians.

The authors further explored this relationship in a population-based study in 2010 (thus prior to the NIAA-AA criteria for AD) using the cardiovascular health study cohort (Roe CM et al., 2010). Data analysis were conducted on two levels. The first was to examine whether prevalent dementia was associated with future hospitalization for cancer and the second was to look at whether history of cancer at baseline is linked to a possible future diagnosis of dementia. Results showed that individuals with AD had a lower likelihood of being hospitalized for cancer diagnosis, compared to dementia free individuals, especially in Caucasians. However, no significant relationship was observed with regards to VaD and mixed dementia (VaD and AD). This study emphasizes the importance of ethnicity and socio-economic factors. A main limitation of the study was the non- availability of out-patient care data. Thus, benign and untreated tumors as well as those treated on an outpatient basis were not represented in this study. The authors advocated to specifically look at cancer survival rates to improve our understanding on the relationship between cancer and AD (Roe CM et al., 2010).

A prospective/retrospective cohort study using a computerized health information system (Local Health Authority of Milano) studied the risk of developing AD-LOD and cancer

regardless of the chronological manifestation of the diseases (Musicco M et al., 2013). This study included participants who were above the age of 60 and diagnosed with both cancer and AD-LOD. There were 21,451 newly diagnosed cancer cases and 2832 AD-LOD cases. A total of 1616 participants had both diagnoses concurrently, 68 of which had AD-LOD preceding the diagnosis of cancer. Data was stratified for each participant to control for confounding biases such as underdiagnoses and controlled life expectancy.
Each participant had two follow-up periods (1) preceding the diagnosis of cancer or AD- LOD (the index date being the date of cohort entry until censor date) (2) following the diagnosis of cancer or AD-LOD (the index date being the diagnosis of cancer or AD until censor date). Person years at risk were used to calculate the incidence of cancer and AD-LOD and relative risks were assessed as observed time-expected occurrences to estimate the expected cancer cases in the AD-LOD cohort and vice-versa.

Results showed that in individuals with cancer, there was a statistically significant decreased risk for AD-LOD (RR=0.65, 95% CI=0.56, 0.76) and in individuals with AD-LOD the risk for cancer was approximately halved compared to age and sex matched controls. These findings seemed to be characteristic of older age (>70 years)(Musicco M et al., 2013).

Furthermore, researchers proceeded to calculate the risk reductions for the incidence of AD-LOD in individuals with cancer, which was found to be similar, before cancer diagnosis (RR=0.66, 95% CI= 0.54, 0.81) and after (RR=0.64, 95% CI=0.50-0.81). The risk of cancer incidence in individuals with AD-LOD was significantly higher before AD-LOD diagnosis (RR= 0.42, 95% CI= 0.32, 0.53) compared to after (RR=0.79, 95% CI= 0.64, 0.97)(Musicco M et al., 2013). Additionally, researchers studied individuals surviving or dying during the follow up period in the AD-LOD cohort. It appeared that the RR for this association was always lower in survivors (RR=0.42, 95 % CI= 0.33, 0.53) compared to non-survivors showing a border line significance of RR= 0.86 (95 % CI= 0.68-1.06). Different origins of cancer tissues in the AD-LOD cohort were also analyzed. They found a significantly lower risk for AD-LOD incidence for lung and colorectal cancer in comparison to tumors of other origin (Musicco M et al., 2013).

A case control study using the Framingham Heart study was conducted to establish the relationship between cancer and AD-LOD (Driver JA BA, Au R, et al 2012). A total of 1268 dementia free individuals and 323 dementia cases (probable 221 AD-LOD, 36 possible AD-

LOD, 66 other types of dementia) were identified. Results showed that participants with a history of cancer had a significantly lower risk of probable AD-LOD (HR =0.67, 95% CI=0.47-0.97) after adjusting for age, sex and smoking. Additionally, a lower risk of AD-LOD was found amongst more participants with a history of smoking related cancers (oral, pharynx, larynx, esophagus, stomach, pancreas, lung, cervix, bladder and kidney) compared to non-smoking related cancers. However, this relationship was specific only to AD-LOD cases, as there was no significant relationship with cancer in AD and other types of dementia (Driver JA BA, Au R, et al 2012). The incidence of cancer was also compared in individuals with any dementia and controls. Findings indicated a lower risk of cancer for probable AD-LOD cases (HR=0.39, 95% CI=0.26-0.58), possible AD (HR=0.38, 95 % CI= 0.25-0.56) as well as any dementia cases (HR=0.44, 95 % CI=0.32, 0.61) .Upon excluding deceased participants from the analyses, results were no longer significant. Thus, revealing that the initially observed inverse association was not a result of diminished survival in individuals with cancer (Driver JA BA, Au R, et al 2012).

Similar to Roe et al (2005), researchers in this study suggest that some of the decreased risk could be due to underdiagnosis. Dementia cases are less likely to be diagnosed with cancers, detected from screening, compared to individuals free of dementia. The underdiagnosis may partially account for this decreased risk (Driver JA BA, Au R, et al 2012).

A US study using the Surveillance, Epidemiology, and End Results (SEER) data also evaluated the relationship between cancer and AD-LOD for 836,947 individuals with cancer and 142,869 controls (Freedman DM et al., 2016) . Results showed a lower prevalence of AD-LOD in individuals with cancer compared to without (OR 0.86; 95% CI = 0.81–0.92). Upon investigating the incidence of AD-LOD in 742,809 individuals with cancer and 420,518 without cancer, a lower risk of AD-LOD was observed in individuals with cancer (HR 0.87 (95% CI = 0.84–0.90). Additionally, the authors used injuries from automobile accidents as a secondary outcome to account for ascertainment bias. There was no association observed between cancer diagnosis and a later diagnosis for an automobile accident injury (HR = 1.03; 95% CI = 0.98-1.07). The authors conclude that the originally lower risk for AD-LOD found in individuals with cancer , was most likely due to the underdiagnosis of AD-LOD in individuals with cancer (Freedman DM et al., 2016).

The above studies are summarized in Tables 4 and 5.

Table 4: Characteristics of studies on incidence of both cancer and LOD (AD) among individuals with LOD (AD) and cancer, respectively

Study (Country)	Study Design	Study Population Age (years)	Definition of LOD/AD-LOD	Definition of Ca	Adjusted for	Incidence of cancer	Incidence of LOD/AD-LOD
Driver et al 2012 (USA)	Nested age and sex matched case- control study	1278 total 176 Cancer (72 M , 104 F) 1102 No Cancer (424 M , 678 F) ≥65	MMSE, neuropsychological examinations, CDR, hospital records, tomography and MRI, autopsy.	Routine examinations, postal survey, telephone interview, death records, pathology reports	Age Sex Smoking For Incidence of AD: Model 1 (age, sex, smoking and incident cancer)	**Any Cancer** **Any dementia :** HR 0.44 (95%CI 0.32,0.61)* **Possible AD:** HR 0.38(95% CI 0.25,0.56)* **Probable AD:** HR 0.39(95%CI 0.26,0.58)* **Smoking related cancer** **Any dementia :** HR 0.45 (95%CI 0.26,0.77)* **Possible AD:** HR 0.45(95% CI 0.24,0.84)* **Probable AD:** HR 0.45(95%CI 0.24,0.88)* **Non-Smoking related cancer** **Any dementia :** HR 0.45 (95%CI 0.31,0.65)* **Possible AD:** HR 0.36(95% CI 0.22,0.58)* **Probable AD:** HR 0.36 (95%CI 0.21,0.59)*	**Any Dementia** **All :** HR 0.83 (95%CI 0.63,1.10) **Smoking related:** HR 0.79(95% CI 0.45,1.39) **Non- Smoking related:** HR 0.84(95%CI 0.62,1.13) **Possible AD** **All :** HR 0.81 (95%CI 0.59,1.11) **Smoking related:** HR 0.62(95% CI 0.31,1.26) **Non- Smoking related:** HR 0.87(95%CI 0.62,1.21) **Probable AD** **All :** HR 0.67 (95%CI 0.47,0.97)* **Smoking related:** HR 0.26(95% CI 0.08,0.82)* **Non- Smoking related:** HR 0.82(95%CI 0.57,1.19)
Musicco et al 2013 (Italy)	Prospective/ Retrospective Cohort study	2832 ADD (947 M , 1885 F) 21,451 Cancer (12,225 M , 9226 F) ≥60	Antidementia drug or had a hospital discharge or payment exemption for AD dementia	Registry based	Age Sex Calendar year of follow up	**Total:** HR 0.57(95% CI 0.49,0.67)* **Before Diagnosis:** HR 0.42(95% CI 0.32,0.53)* **After Diagnosis:** HR 0.79(95% CI 0.64,0.97)* **In Survivors:** HR 0.42(95% CI 0.33,0.53)* **In non-survivors:** HR 0.86(95% CI 0.68,1.06)**	**Total:** HR 0.65(95% CI 0.56,0.76)* **Before Diagnosis:** HR 0.66 (95% CI 0.54,0.81)* **After Diagnosis:** HR 0.64(95%CI 0.50,0.81)* **In Survivors:** HR 0.58(95%CI 0.46,0.72)* **In non-survivors:** HR 0.75(95% CI 0.60,0.93)*
Roe et al 2009 (USA)	Prospective Cohort study	**Prevalent:** Dementia 227 (116 M , 111 F) Cancer 522 (216 M, 306 F) **Incident:** Dementia 478 (192 M, 286 F) Cancer 376 (204 M, 172 F) **No history:** Dementia 2315 (951 M ,1364 F) Cancer 2122 (839 M, 1283 F) ≥65	Clinical visits , informant/proxy interviews, physician questionnaires, MRI, medical records	Interview questionnaire, hospitalization for cancer	Demographic factors, smoking, obesity and physical activity	**Pure AD :** HR 0.31 (95% CI 0.12,0.86)* **Any AD (Pure AD + mixed AD/VaD):** HR 0.41 (95% CI 0.20,0.84)* **Mixed AD/VaD:** HR 0.58 (95% CI 0.21,1.56) **Any VaD(Pure VaD + mixed AD/VaD):** HR 0.89 (95% CI 0.45,1.77) **Pure VaD:** HR 1.64 (95% CI 0.66,4.11) **Any dementia diagnosis:** HR 0.70 (95% CI 0.42,1.17)	**In Whites** **Pure AD:** HR 0.57 (95% CI 0.36,0.90)* **Any AD (Pure AD + mixed AD/VaD):** HR 0.72 (95% CI 0.52,0.97)* **Mixed AD/VaD:** HR 1.06 (95% CI 0.68,1.65) **Any VaD(Pure VaD + mixed AD/VaD):** HR 1.01 (95% CI 0.69,1.48) **Pure VaD:** HR 0.78 (95% CI 0.36,1.66) **Any dementia diagnosis:** HR 0.79 (95% CI 0.59,1.06)

M: male, F: female, HR: Hazard Ratio, CI: Confidence Interval ***All Significant results (p<0.05)**

Table 5: Continuation - Characteristics of studies on incidence of both cancer and LOD (AD) among individuals with LOD (AD) and cancer, respectively

Study (Country)	Study Design	Study Population Age (years)	Definition of LOD/AD-LOD	Definition of Ca	Adjusted for	Incidence of cancer	Incidence of LOD/AD-LOD
Roe et al 2005 (USA)	Prospective Longitudinal Study	395 ADD (2044 M, 1237 F) 594 no dementia diagnosis (69 M , 130 F) 50 Cancer (24 M , 26 F) 199 No Cancer (69 M , 130 F) ≥47	Semi structural interview , physical and neurologic exam, histopathology exam , clinical dementia rating	Self-reported	Model 1 : (Male gender) Model 2: (Age at first assessment) Model 3: (Years of Education) Model 4: (Male gender +Age at first assessment +Education) For incidence of AD in cancer Model 2 was white race, Model 3 was age, Model 4 was education and Model 5 included white race	**Model 1:** ADD diagnosis HR 0.39 (95% CI 0.207,0.739) * M HR 2.13 (95% CI 1.187,3.833)* **Model 2:** ADD diagnosis HR 0.37 (95% CI 0.200,0.688)* Age HR 1.05 (95% CI 1.014,1.081)* **Model 3:** ADD diagnosis HR 0.36 (95% CI 0.193,0.685)* Education HR 1.03 (95% CI 0.935,1.125) **Model 4:** ADD diagnosis HR 0.39 (95% CI 0.21,0.74)* M HR 2.33(95% CI 1.28,4.23)* Age HR 1.05 (95% CI 1.02,1.09)* Education HR 1.03 (95% CI 0.94,1.12) ADD: Alzheimer's due to dementia.	**Model 1:** Cancer diagnosis HR 0.34 (95% CI 0.10,1.11) M HR 0.99 (95% CI 0.51,1.91) **Model 2:** Cancer diagnosis HR 0.39 (95% CI 0.12,1.30) White HR 0.20 (95% CI 0.08,0.49)* **Model 3:** Cancer diagnosis HR 0.35 (95% CI 0.108,1.14) Age HR 1.05 (95% CI 1.018,1.09)* **Model 4:** Cancer diagnosis HR 0.35 (95% CI 0.107,1.13) Education HR 0.94 (95% CI 0.849,1.04) **Model 5:** Cancer diagnosis HR 0.40 (95% CI 0.122,0.13)* M HR 1.33 (95% CI 0.663,2.67) White HR 1.18 (95% CI 0.072,0.47)* Age HR 1.05 (95% CI 1.018,1.09)* Education HR 0.99 (95% CI 0.895,1.10)
Freedman et al 2016 (USA)	Case-control study/ Prospective cohort study	Cancer cases for case-control study: 836,947 Controls: 200,000 Cancer for population study: 742,809 Controls for population:420,518 66-85	Registry based using ICD-9 in medicare if there was one hospital or two outpatient AD claims	Cancer cases were patients in SEER who had been diagnosed with a first primary malignancy registry based data?	Sex, race/ethnicity, age, cancer registry(because background incidence varies) Frequency of physician visits	**Any cancer** **AD**: OR 0.86; 95% CI = 0.81–0.92)*	**AD-LOD** HR 0.87 (95% CI = 0.84-0.90)*

M: male, F: female, HR: Hazard Ratio, OR: Odds Ration CI: Confidence Interval ***All Significant results (p<0.05)**

2.4 POSSIBLE BIOLOGICAL MECHANISMS

A total of 15 studies examined the relationship between LOD / AD-LOD and cancer. Studies have reported conflicting findings, with the majority (11 studies) reporting an inverse association between the two diseases. One of the plausible explanations suggested for the inverse association observed, are the shared biological mechanisms reported between LOD and cancer. The risk of both AD and cancer increases with older age and have contradictory cellular mechanisms. Research has shown that it is likely for carcinogenesis and neurodegeneration to be linked to one another based on the biological pathways and genetic characteristics that they share (Driver JA and Lu KP, 2010, Behrens MILendon C and Roe CM, 2009, Wang W et al., 2009, Staropoli JF, 2008, West ABDawson VL and Dawson TM, 2005, Lu KP, 2004, Migliore L et al., 2005).

A number of common mechanisms may link cancer to AD. Driver et al (2012) suggest that the main mechanism is the one that incorrectly regulates the cell cycle, where on the one hand it causes the unrestrained spread of the cells and on the other, apoptosis (Driver JA et al., 2012). A study by Plun-Favreau et al (2010) summarizes the genes responsible in cancer and neurodegeneration pathways (Plun-Favreau H et al., 2010). The p53 gene has regularly been identified as a tumor suppressor which, when inactivated, causes cancer (Murray-Zmijewski F et al., 2008). The gene is usually inactivated in approximately 50 percent of cancer cases (Plun-Favreau H et al., 2010). Additionally, the gene has been reported to appear in individuals with AD-LOD, where elevated levels of p53 are activated due to the presence of Aβ proteins (Cenini G et al., 2008, Hooper C et al., 2007, Ohyagi Y et al., 2005, Blalock EM et al., 2004). Accordingly, individuals with increased levels of p53 are at a lower risk of developing cancer yet remain at a higher risk for developing AD-LOD.

Another molecule that is pivotal in understanding cancer and AD is the Pin1 enzyme. Pin1 plays a neuroprotective role in AD, by altering proteins (Tau and AP) that are fundamental to AD pathology. Therefore, in the absence of Pin1, accumulation of NFTs and APs are more likely to be reported (Driver JA et al., 2014). Pin1 also inactivates tumor suppressor genes resulting in cancer. The overexpression of Pin1 has been identified in both cancer and individuals with AD (Bao L et al., 2004, Ayala G et al., 2003, Sultana R et al., 2006). The Wnt (wingless type murine-mammary tumor virus integration site) signaling pathway has also been reported in both cancer and LOD(Coombs GS et al., 2008). A number of various mechanisms

in the Wnt pathway have been linked to carcinogenesis and tumor development , especially in colorectal , lung, prostate and breast cancer (Buongiorno P et al., 2008, Firestein R et al., 2008, Karim RZ et al., 2004, Fiorentino M et al., 2008). Similarly, Wnt signaling activity has been shown to cause Aβ-induced neurotoxicity and neuronal death(Ferrari GVD and Moon RT, 2006, Caricasole A et al., 2005). Consequently, a deregulation of the Wnt signaling pathway could possibly explain the inverse association observed between the cancer and LOD.

It is important to note, studies that have reported an inverse association between cancer and LOD/ AD-LOD have several statistical limitations, such as notwithstanding the specificity of diagnostic criteria used, small sample sizes, limited follow-up time, and failure to account for multiple relevant confounders, selective mortality and ascertainment bias. In fact, the four studies that have acknowledged some of the aforementioned limitations in their analysis, found no association between LOD/AD-LOD and cancer (1 study accounted for selective mortality, 2 accounted for ascertainment bias and 1 adjusted for multiple relevant confounders).

2.5 CONCLUSION

The inconsistent findings reported in studies on LOD/AD-LOD and cancer makes it difficult to draw any conclusions on this association. Although the majority of studies support an inverse association, these studies have several limitations. Recent studies that used additional statistical methodologies to account for selective mortality and ascertainment bias, found no association between cancer and LOD/AD-LOD.

This review has led to a better understanding of the current literature on the association between LOD/AD-LOD and cancer, and importantly helped identify the current research gaps to address in future studies. Further epidemiologic studies are needed to investigate the risk of LOD/AD-LOD and different types of cancer in large cohorts. Furthermore, consideration of multiple confounders in the analysis, as well as an investigation into this relationship in the presence of comorbidities, could shed some light onto the nature of the cancer and LOD/AD-LOD relationship. Importantly, the implementation of accurate and careful statistical methodologies to account for selective mortality and ascertainment bias, is crucial, as it may provide further clarification on whether an inverse association truly exists.

CHAPTER 3 – METHODOLOGY

Chapter three introduces the main data source used for this thesis, along with the study design, population and the variables of interest. This chapter clearly describes the data extraction, cleaning and management process and how the data was prepared for analysis. The last section summarizes the statistical analysis plan and the statistical aims, which are targeted in the following chapter.

3.1 Data source: Clinical practice Research Datalink (CPRD)

3.1.1 Overview

The Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database (GPRD), is an ongoing primary care database of anonymized electronic medical health records (Herrett E et al., 2015, Williams T, 2012). Originally established in 1987 as part of the value added medical products (VAMP) in London, it has now become one of the largest and leading longitudinal primary care medical record databases in the UK and world-wide (Herrett E et al., 2015, Williams T, 2012, Tate AR, 2014). Participating countries include England, Wales, Scotland and Northern Ireland. CPRD is jointly funded by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the NHS National Institute for Health Research (NIHR) (CPRD n.d).

In the UK, general practitioners (GPs) are the primary point of contact for any health-related matters; thus, allowing primary care data to be a rich storehouse for ethically approved medical and public health research opportunities. Over 98 % of the UK population are registered with a GP, with data existing from as early as 1987 and updated from follow up visits and routine consultations (Herrett E et al., 2015). Participating practices collect and upload patient information as part of their daily clinical care practice. Hence all general practice consultations are recorded and captured onto the CPRD server. These uploads then serve as the foundation for general practice data and a portal for longitudinal electronic health records now available for research. Patients registered with these participating practices are notified about the data extraction process and are given the chance to withdraw (Williams T, 2012).

3.1.2 Data and Coding System

CPRD encompasses over 11.3 million patients from 674 practices in the UK, who are active patients (4.4 million) or were registered with participating GPs (Rodríguez LAG and Gutthann SP, 1998, Khan NF et al., 2010). It is representative of the general population in terms of age, sex and ethnicity (Martinez C et al., 2013). The CPRD database divides the information into patient, practice, staff, consultation, clinical, therapy, test, immunisations and referral data files (Herrett E et al., 2015). Data on these subjects include information such as demographics, medical diagnoses, symptoms, tests, immunisations, prescriptions (date, daily dose, and drug substance), health related behaviors, hospitalisations and referrals to secondary care (Parkinson J et al., 2006) (Figure 3).

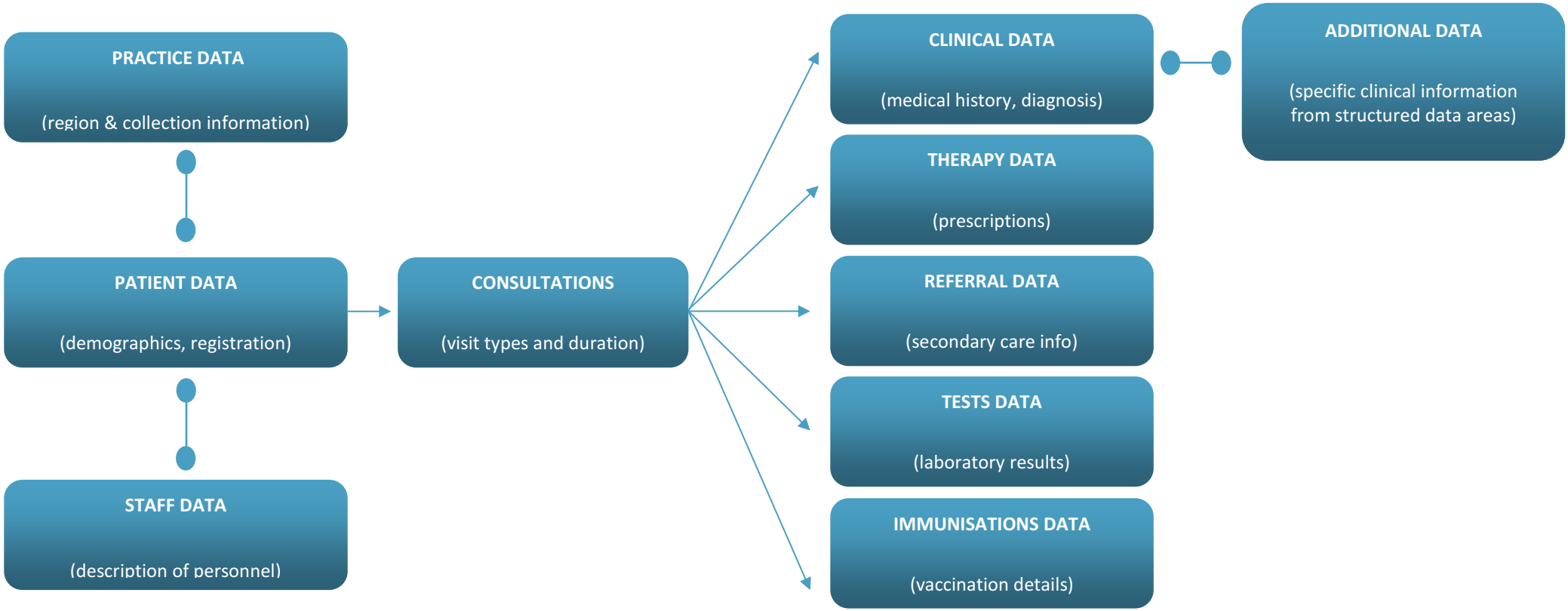


Figure 3: Schematic diagram for data held in CPRD

All medical events in the database are recorded electronically by general practice staff, using version 2 READ medical codes (Chisholm J, 1990). READ codes are a hierarchical clinical coding system of over 96,000 codes and is a medical thesaurus for reporting clinical findings and procedures (Chisholm J, 1990). The codes follow a graded structure arrangement, where you can record a finding starting from a main chapter heading (example code: Eu00. Dementia in Alzheimer's disease) and gradually move to a more detailed subheading (example code: Eu001 Dementia in Alzheimer's disease with late onset). Prescriptions issued by GPs are recorded using the "prodcode", a CPRD unique code that follows the British National Formulary (BNF) classification for information on selection, prescribing, dispensing and administration of drugs (Springate DA et al., 2014).

The value and significance of CPRD is further enhanced, by allowing a secure anonymized linkage to secondary data such as Hospital Episode Statistics (HES) and mortality data, through the Office of National Statistics (ONS). HES is a national dataset with information on hospitalisation data including all admissions, outpatient and emergency appointments to the National Health Service (NHS) hospitals in the UK (CPRD n.d). Diagnoses are recorded using the International Statistical Classification of Diseases and Health Related Problems, 10th revision (ICD-10) and for recording the procedures the Office of Population Censuses and Survey Classifications of Interventions and Procedure, Version 4 (OPCS-4) is used (Herrett E et al., 2015). The ONS is another linkage dataset which captures mortality specific data including the cause of death, and is recorded using ICD-10 (Herrett E et al., 2015). Other linkages include the Index of Multiple Deprivation and Townsend scores (small- area measure of social deprivation) and disease registries (e.g. the National Cancer Intelligence Network, the Myocardial Ischaemia National Audit Project). Almost half of the UK CPRD practices have agreed to participate in the CPRD linkage scheme (CPRD n.d). The linkage process involves linking the patient level data from participating practices to other data sources, via a secure third party (Herrett E et al., 2015) (Table 6).

CPRD has a broad approval from the National Information Governance Board Ethics and Confidentiality Committee (NRES) for observational studies using anonymized primary care data and linkage datasets (CPRD n.d). Access to the data is reliant on approval from the Independent Scientific Advisory Committee (ISAC) for MHRA database research. This committee is responsible for reviewing protocols for scientific value, and providing guidance

for access for research-related requests to access CPRD dataset (CPRD n.d). This study has been approved by ISAC (protocol number: 16_219R2)

Table 6: Patient information available in CPRD and other linkage dataset

Database / Linkage dataset	GP Registration	Medical Information	Death Information
CPRD (Primary Care Database)	Demographics Medical History	Medical History, symptoms, signs and diagnosis, prescriptions, immunisations, referrals and tests	Death Date
HES (Hospital Episode Statistics)		Hospital admission and discharge dates, imaging data, operations and surgical procedures	
ONS (Death and Census Data)			Cause and date of death
IMD (Index of Multiple Deprivation)	Proxy to socio-demographic and socio-economic data		

3.1.3 Strengths

CPRD research has proven its value through numerous peer-reviewed publications in the fields of epidemiology, public health and pharmacoepidemiology (Herrett E et al., 2015). The power of CPRD resides in the quality of its data, size and representativeness.

The quality of research in CPRD is monitored at both patient and practice level. The "Acceptable Research Quality" (ARQ) flags any inconsistencies in individual patient data such as validity of age and sex, registration status, transfer out of practice date and clinical event dates (Herrett E et al., 2010). Practice level data is audited using the "Up to Standard" (UTS) marker which monitors the practice mortality rates and continuity of data recordings through gap analysis (Herrett E et al., 2010). These internal checks ensure the logical consistency of patient registration data, complete longitudinal records and continuous plausible practice level data.

In 2004, the quality of data collected in English practices was further enriched with the introduction of the Quality and Outcomes Framework (QOF), an incentive payment scheme to motivate GPs to record main key data information such as smoking status, BMI, ethnicity, etc (Kendrick T, 2015). Studies that have investigated the influence of QOF on data quality have shown a significant improvement in the recording of many variables (Mathur R et al., 2014, Quint JK et al., 2014, Kontopantelis E et al., 2015). Of note, participating GPs are required to undergo training on how to record medical information and meet quality standards before they can be part of the CPRD, to ensure consistency and standardization (CPRD n.d).

In addition to the prominent data quality that CPRD offers, the size of the database and the follow up time available is another key asset (Herrett E et al., 2010, Herrett E et al., 2015). Research investigations in CPRD can give limitless possibilities for identifying subclinical populations and rare diseases, whilst maintaining sufficient statistical power and precision (Carrington JM and Effken JA, 2011). Furthermore, CPRD data are broadly representative of the UK population, which further enhances the validity and reliability of the data and ensures generalizability of research findings (Herrett E et al., 2010).

The CPRD has been validated in previous studies (Lawrenson R et al., 1999, Seshadri S et al., 2001, Jick SS et al., 2003, Herrett E et al., 2010) and extensively used in studies on many diseases, including diabetes, cancer and dementia (Dunn N et al., 2005, Parkinson JDavis S and Staa Tv, 2006, Martinez CJones RW and Rietbrock S, 2013) all of which have had shown a significant impact in the public health and therapeutic sectors. Research from CPRD had significant effect on our knowledge and approach for various therapeutic and preventive strategies. One of the most prominent studies that resulted from CPRD is that on measles-mumps-rubella (MMR) vaccination, that showed no association with autism or other developmental disorders in children (Smeeth L et al., 2004). In the field of neurodegenerative diseases, CPRD has generated numerous reports with novel findings. A recent study on LOD and BMI in about two million people, has shown that being underweight in middle and old age is, indeed, a risk factor for LOD (Qizilbash N et al., 2015). Furthermore, there have been numerous CPRD-based publications on cancer epidemiology, disease management and pharmacoepidemiology. A CPRD – based large retrospective cohort study investigating the association between the use of metformin compared with other anti-diabetic medications and cancer risk, found no evidence that metformin users had a reduced risk of cancer compared to individuals prescribed with other antidiabetic drugs (Tsilidis KK et al., 2014).

To conclude, CPRD provides an advanced information infrastructure with reliable research data and sufficient qualitative and statistical power for data analysis; therefore, allowing for informed improvements in health care and clinical decisions in a variety of diseases.

3.1.4 Challenges and Limitations

The issue of missing data represents one of the major challenges of the use of CPRD and other large-scale electronic health record (EHR) databases (Marston L et al., 2010, Herrett E et al., 2015). Incomplete data could result in biased analyses and may thus reduce the validity and reliability of the study. For instance, individuals with certain chronic diseases are more likely to visit the GP and will have more consultation data, compared to healthy individuals. This could lead to ascertainment bias, where individuals are more likely to have common risk factor data recorded (BMI, smoking, physical activity, etc.), as well as records of other complex diseases (such as LOD) (Thiru K et al., 2003, Chan KS et al., 2010).

Furthermore, differentiating between missing data and absent data may add another layer of complexity (Hogan WR and Wagner MM, 1997, Thiru KHassey A and Sullivan F, 2003). In EHR databases, an absence of a certain record for a disease is interpreted as the individual not having that disease. However, it might be the case that the GP has simply not recorded the disease or that the patient has not approached the GP in the first place with the disease. Unfortunately, the extensive range of variables recorded into CPRD poses a higher risk for biases due to missing data.

Another issue in CPRD is the definition of variables and their use in different studies. Each study is responsible for developing its own list of definitions and algorithms for identifying specific variables of interest, as there are no standard case definition and code lists. This may result in varying data from different studies using the same data and variables (Springate DA et al., 2014).

Lastly, there is no way of capturing a broader range of data such as over the counter medication use, prescription in secondary care and adherence to treatments (Herrett E et al., 2015). There is also no method for monitoring that the information received by GPs from secondary care is

manually entered onto CPRD in a consistent manner (Kousoulis AA et al., 2015). Also, certain patient subgroups are not captured effectively in CPRD such as prisoners, refugees, etc.(Herrett E et al., 2015); although CPRD operates with accordance to the Data Protection Act, confidentiality and informed consent issues in EHR databases are still regarded as challenging (Herrett E et al., 2010).

Notably, it is important to remember that the data captured in EHR databases is primarily aimed at improving patient diagnosis and management in clinical practice, rather than for research purposes. Hence, using EHR for research requires extensive efforts and expertise in data management and quantitative scientific methodologies to effectively compensate for its limitations.

Although CPRD, like all EHR databases, presents several challenges; it still remains a powerful and attractive resource due to the wealth of data, population coverage, representativeness and longitudinal nature of the data. Moreover, various statistical and analytical approaches have proven their value in minimizing bias and managing the above challenges and limitations, such as the use of multiple imputation to deal with missing data.

In summary, CPRD provides a unique opportunity to investigate the research questions attempted in this thesis. The large sample size available allows for a reliable investigation into the relationship between multiple disease presentations, such as cancer and LOD, in the presence of various clinical events and risk factors, such as type 2 diabetes, hypertension, smoking, stroke, etc. Also, the availability of linkage databases enriches the quality of the study data, through filling in the gaps with regards to hospitalization and mortality.

3.2 METHODS

3.2.1 Study Design

An open cohort study design was used to investigate the association between cancer and LOD separately in individuals ≥ 65 years, with and without T2DM, identified using the longitudinal routine English primary care data, as described above (Figure 4).

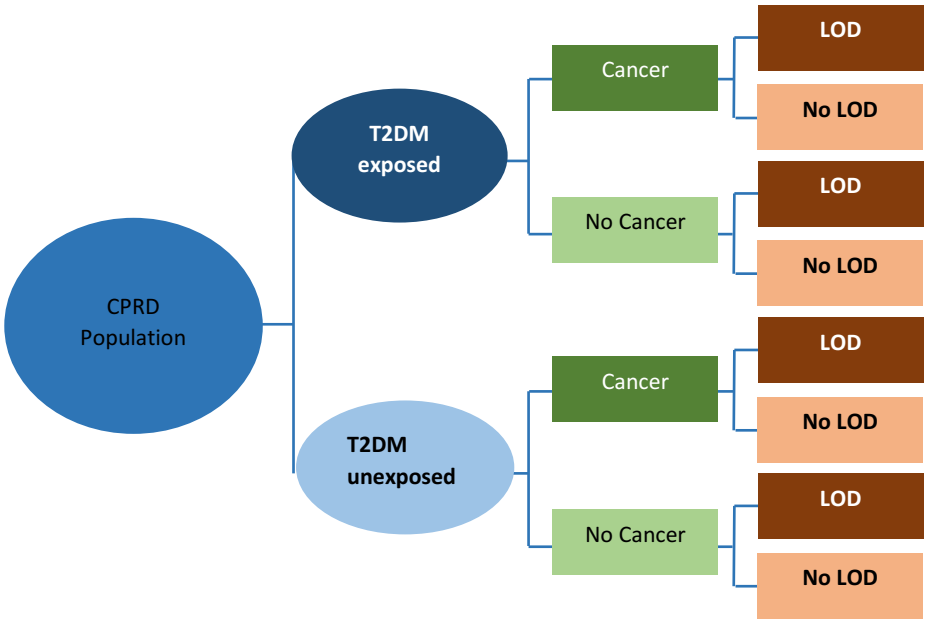


Figure 4: Study Design Schematic (T2DM: Type II diabetes, LOD: Late onset dementia)

3.2.2 Study Population

Populations with and without a diagnosis of T2DM, were separately investigated. In view of the linked data coverage periods, the observation period extended from 1998-2015, with cohort entry permitted until 01 January 2014. All study participants were followed up from the index date to the censor date. Participants were censored at point of LOD diagnosis, death, end of observation period (2015) or last data upload date (last date of follow-up). It was required that participants have been under observation by CPRD for ≥1 year prior to cohort entry. The cohorts were restricted to patients with linked data. Thus, the cohort included individuals registered with participating English practices at the time of transfer of identifiers for matching, with a valid NHS number or postcode, who did not opt out of matching.

(a) Eligibility criteria for the T2DM cohort

All individuals aged ≥65 years old with a T2DM diagnosis were included in the analysis. The index date was identified as the year of cohort entry: 1998 if participant was ≥65 years old with a T2DM diagnosis. For individuals who turned 65 after 1998, the index year was the year they

turned 65 (if T2DM diagnosis happened prior to the age of 65) or the index year was the year of the first record of their T2DM diagnosis (if T2DM diagnosis happened after the age of 65) and they were observed until the failure event. Individuals with an LOD diagnosis prior to the age of 65 were excluded, as they may have represented individuals with early onset dementia. Participants with an LOD diagnosis prior to T2DM diagnosis were also excluded

(b) Eligibility criteria for the non-T2DM cohort

All individuals aged ≥65 years old and without a T2DM diagnosis in 1998 were included in this analysis. The index year was identified as the year of cohort entry: 1998 if participant was ≥ 65 years old in 1998. For individuals who turned 65 after 1998, the index year was the year they turned 65 and they were observed until the failure event. Individuals with an LOD diagnosis prior to the age of 65 were excluded, as they may have represented individuals with early onset dementia.

3.2.3 Study Variables:

(a) Exposure variable:

Individuals with and without T2DM were considered for the occurrence of cancer (prior to LOD diagnosis), which was measured as the first medical diagnosis for cancer in CPRD based on READ codes.

Based on current statistics outlining the most common forms of cancer in the UK (Cancer Research UK) the following cancer types were used: lung cancer, breast cancer, prostate cancer, bowel cancer and skin cancer (including non-melanoma skin cancer). An additional group called “other cancers” was formed to include all other less common types of cancer.

(b) Outcome Variable:

The primary outcome was LOD. Clarity on the nosology of AD and LODs is still lacking. Several committee-based diagnostic criteria for AD have been proposed, in the last two decades; the most recent and currently adopted being the 2011 NIA-AA Criteria for AD for research (McKhann GM et al., 2011a). These research criteria require evidence of absence of significant vascular-type lesions (as a minimum diagnostic requirement for AD) and biomarker supportive evidence of abnormal brain load of amyloid and tau, based on positron emission tomography (PET) and/or CSF studies, as well as evidence of neurodegeneration, based on magnetic resonance imaging (MRI), high tau and/or FDG-PET. The NIA/AA criteria are currently being revised to now define the disease stages based on the biomarker evidence for amyloid & tau load and neurodegeneration, as part of the diagnostic criteria. Furthermore, several phases of AD stages are being proposed, from the asymptomatic stage I to various stages based on the degree and extent of memory and cognitive decline. Asymptomatic individuals with evidence of neurodegeneration but with normal amyloid and tau are defined as "Suspected Non-Alzheimer's disease Pathophysiology" (SNAP) (Jack CR et al., 2016). However, the required biomarker studies have not been (and still are not) part of the clinical practice diagnostic armamentarium in the UK and most (if not all) countries. Furthermore, the co-occurrence of mixed pathologies (amyloid, tau, micro and other vascular pathological features and Lewy bodies) in the majority of LOD patients over the age of 75 has been well documented (Fotuhi MHachinski V and Whitehouse PJ, 2009, Schneider JA et al., 2009, Nelson PT et al., 2007, Schneider JA et al., 2007, Sonnen JA et al., 2007, Aguero-Torres H,Kivipelto M and VonStrauss E, 2006, White L et al., 2005, Fernando MS and Ince PG, 2004). Based on these considerations and the information available in CPRD, I classified LOD as per the following: (1) probable AD (READ and product codes indicating a diagnosis for AD only); (2) possible AD (reported diagnosis of AD was preceded by a code referring to another LOD form, such as VaD) and (3) other LOD (READ and product codes indicating a diagnosis for other types of LOD or LOD without specification of the type).

(c)Demographic, lifestyle and clinical covariates:

Several demographic and lifestyle covariates have been reported to affect the risk for LOD (reviewed by Bellou et al 2016) and cancer. Based on the literature on the shared risk factors between LOD and cancer, and the available information in CPRD, the following covariates were considered: age, sex, ethnicity, smoking, alcohol, BMI, hypertension, hypercholesterolemia, cerebrovascular disease, depression and brain injury.

3.3 DATA PREPARATION AND EXTRACTION

CPRD contains millions of rows and columns of longitudinal data and requires extensive data processing and management. The data preparation stage involved defining the variables of interest, through generating operational definitions and building code lists. This step is critical in CPRD as it helps ensure the reproducibility and credibility of the study. Subsequently, I extracted the data and cleaned it to create a customized dataset that would be readily available for analysis.

3.3.1 Operational definitions and Code lists

Variables of interest were identified in accordance with the main research question, and the operational definitions were generated for the corresponding demographic, lifestyle, clinical, exposure and outcome variables. Code lists were built using searchable data and coding dictionaries provided by CPRD, encompassing all diagnostic and prescription terms along with their corresponding descriptive terms. As mentioned previously, CPRD uses READ and product codes for diagnostic and drug prescription events, respectively. Additionally, QOF codes and code lists from published CPRD papers were used to create a more exhaustive and accurate code list. The code lists were then used to extract a customized cohort of individuals from CPRD, with electronic health records containing the codes of interest during any point in time. A summary of the operational definitions, code list references for all the variables of interest is presented in Tables 7-9.

Main Covariates	Operational definition	Code list	Data File used
Late-Onset Dementia (LOD)	Determined using READ or product codes primarily, or HES ICD10 or ONS ICD9/10 codes. The 2011 NIA-AA Criteria for Alzheimer's Disease was used for a more accurate diagnosis: Dementia possibly attributable to Alzheimer's disease, dementia probably attributable to Alzheimer's disease and other late-onset dementias.	Appendix 2&3	Clinical Therapy HES linkage data
Cancer	Determined using READ codes indicating cancer diagnosis. Additionally used READ codes from specific code lists indicating the cancer types of interest.	Appendix 4-10	Clinical
Type II Diabetes (T2DM)	Determined using READ codes indicating T2DM diagnosis.	Appendix 11	Clinical

Table 7: Main covariates operational definitions, code lists and data files used

Demographic and lifestyle Covariates	Operational definition	Code list	Data File used
Sex	First recorded patient sex in database	N/A	Patient
Age	Age at cohort entry	N/A	Patient
Ethnicity	Determined using READ codes primarily and HES-recorded ethnicity (where a READ code is unavailable). Any remaining missing data was assumed to be White. The data was collapsed into a categorical variable based on the five Level 1 ONS ethnic group classifications derived for the 2001 Census. The latest ethnic category recorded for a patient was used if >1 was entered.	Appendix 12	Clinical HES linkage data
Smoking use	Smoking status was categorised as current-, ex- or never- smoker using READ codes. The latest value was carried forward at date of cohort entry. Smoking status was preferentially assessed using the 'additional' data file (enttype=4), and the relatively vague smoking READ codes were used, where this was absent.	Appendix 13	Clinical Additional
Alcohol consumption	A categorical variable describing weekly consumption (categories: no alcohol use, <14 units/week, 15-42 units/week, and 43+ units/week) was used. The most recent relevant READ code available at date of cohort entry was used. Alcohol use status was preferentially assessed using the 'additional' data file (enttype=5), and the relatively vague alcohol READ codes were used, if this was absent.	Appendix 14	Clinical Additional

Table 8: Demographic and lifestyle covariates operational definitions, code lists and data files used

Clinical Covariates	Operational definition	Code list	Data File used
BMI	The most recent BMI category recorded using READ codes , or category within which a continuous BMI measurement falls at the date of cohort entry, and then using the additional data file (enttype= 13 and 14), where this was absent.	Appendix 15	Clinical Additional
Hypertension	Binary variable describing presence or absence of hypertension diagnosis prior to censor date, based on a set of identified READ codes.	Appendix 16	Clinical
Hypercholesterolemia	Binary variable describing presence or absence of hypertension diagnosis prior to censor date, based on a set of identified READ codes.	Appendix 17	Clinical
Depression	Binary variable describing presence or absence of history of depression prior to censor date, based on a set of identified READ codes.	Appendix 18	Clinical
Brain Injury	Binary variable describing presence or absence of brain injury prior to censor date, based on a set of identified READ codes.	Appendix 19	Clinical
Cerebrovascular disease	Binary variable describing presence or absence of cerebrovascular disease prior to censor date, based on a set of identified READ codes.	Appendix 20	Clinical

Table 9: Clinical covariates operational definitions, code lists and data files used

3.3.2 Data extraction

Two separate extractions were done to achieve the cohorts of interest. The first extraction was done using the T2DM code list (Appendix 11), which resulted in a sample of all individuals in CPRD who were ≥ 65 and had a diagnosis of T2DM at any point in their life. The second extraction was based on extracting a random sample of individuals who were ≥ 65 without a diagnosis of T2DM i.e. never had a code from the T2DM code list. After cleaning the data by removing inconsistencies, individuals with erroneous demographic data and applying the observation criteria, there was a total of 217,335 T2DM individuals and 739,061 individuals without T2DM, included in the study for analysis (Figure 5).

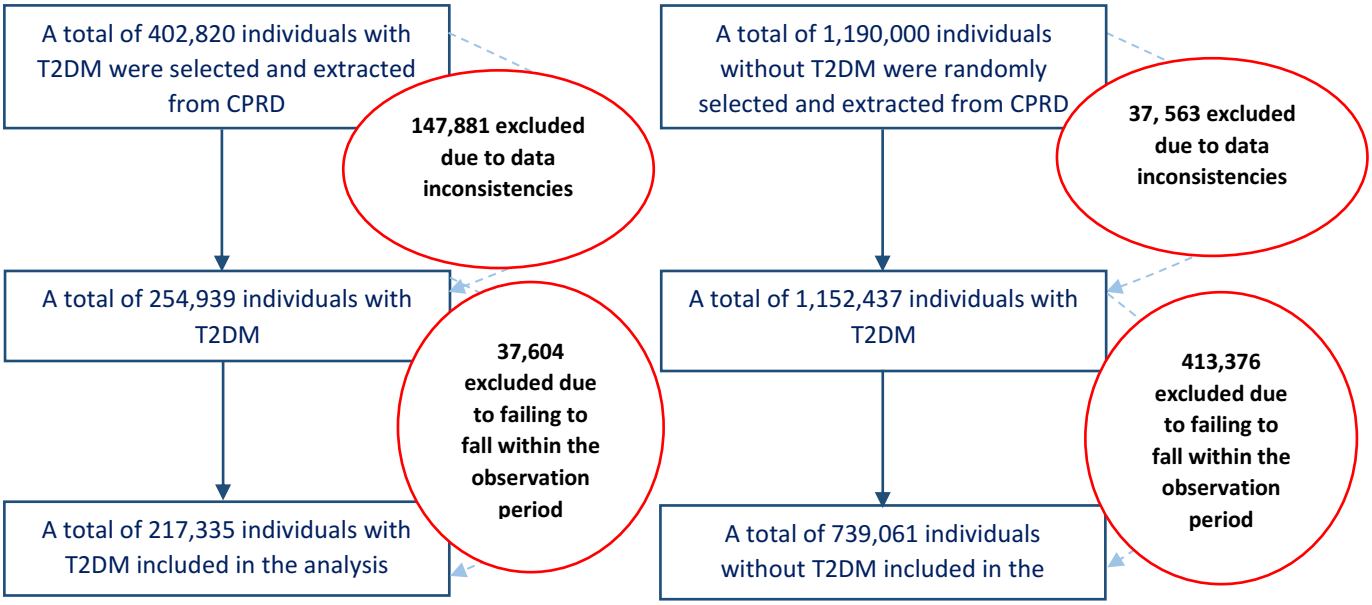


Figure 5: T2DM and Non-T2DM cohorts' extraction from CPRD

Following the extractions, both cohorts generated a number of files with different types of data available (Figure 3). The various data files can be linked together using the anonymized patient identifier (patid) variable, which is consistent throughout the files and monthly database build updates. For the purpose of this thesis, the following data files were used: patient, clinical, therapy and additional data files. The files were then filtered by the code lists to illustrate information that is relevant to the variables of interest. The following data file information was extracted for both of the cohorts: LOD, cancer, demographic, lifestyle and clinical variables.

Additionally, HES and ONS linkage data was used for some variables in order to fill in the missing gaps and ensure that all possible clinical events have been captured.

Tables 7-9 include guidance on the data files that were used to extract different data variables. The following data cleaning section will expand on the data files used and how they were managed and cleaned in relation to the variables of interest.

3.3.3 Data Cleaning

There were multiple cases of observations per patient record, as any kind of interaction with the GP or health personnel was recorded as one observation. For the demographic covariates, the only two readily available variables used were age and sex. The remaining set of demographic, lifestyle and clinical variables, required further exploration and categorization. I primarily used the READ codes in the clinical file extracts to filter the data for the demographic, lifestyle and clinical variables. The absence of a READ code was interpreted as the absence of the event of interest.

(a) Demographic and lifestyle covariates

For the ethnicity variable, HES-recorded data proved helpful in cases where ethnicity was missing from the original clinical file extracts. Ethnicity was categorized using the Level 1 ONS 2001 census group classifications into White, Asian, Mixed, Black and other. Individuals with missing ethnicities were assumed to be White by default.

Smoking and alcohol were also initially extracted using READ codes from the clinical file extract. However, due to the large amount of missing data, the additional file data was also used to fill in the gaps, as well as to capture the most updated information for individuals of interest. The additional files for smoking and alcohol had detailed information available for predefined events, through specially designed data fields, such as alcohol consumption/ week, number of cigarettes/ week. Consequently, I was able to classify alcohol and smoking as accurately as possible according to the most up to date information. Smoking was categorised to current smoker, ex-smoker and never smoker. Alcohol consumption was categorised into no alcohol use, (0-14] units/week, (14-42] units/week and 42+ units/week.

(b) Clinical Covariates

The same rational was followed for the classification of BMI, where both clinical and additional file extracts were used. The most recent READ code for a BMI category recorded at the date of cohort entry was used. In cases where the BMI was absent in the clinical file, the additional file was used to look into distinct fields for height and weight and the BMI was calculated. Finally, BMI was categorized into the following categories: underweight (<18.5), normal (18.5-25), overweight (25-30) and obese (>30). The remaining clinical covariates, i.e. hypertension, hypercholesterolemia, depression, brain injury and CeVD were all cleaned and organized. READ codes were used from the clinical file extracts to form binary variables representing history/no history of the covariate. Individuals within CPRD had multiple records per clinical event. However, for the purpose of this work, I kept the first occurrence only of the event as a proxy of the history of any of those covariates. The first clinical event date for the covariate of interest was used to calculate the age of onset for the covariate. This has enabled me to capture whether the covariates occurred before, during or after cohort entry.

(c) Exposure Variable

A code list was developed for overall cancer as well as separate code lists for the specific cancer types of interest: lung cancer, breast cancer, prostate cancer, bowel and skin cancer (including non-melanoma skin cancer). The code list was based on READ codes from the data dictionary and QOF cancer codes, representing only malignant disease and tumours. Additionally, I tried to capture all other cancer types in this study under a separate variable group "Other cancers". The first ever record for a cancer diagnosis was used to indicate the presence of cancer and calculate the age of cancer onset. Some individuals had different types of cancers in their records, either reported within the same day or recorded during a different visit to the GP. As it was practically impossible to know whether the second type of cancer was entered by the GP in error or a co-morbid second cancer form or a cancer metastasis of the pre-existing malignant tumour into another region or organ, I decided to include such occurrence as part of the "other cancer" group. Similarly, several individuals did not have a code indicating a specific type of cancer but rather a code indicating cancer of NOS or a metastatic cancer. These individuals were also considered as part of the "other cancer group", due to the difficulty in identifying the origin of the cancer.

(d) Outcome Variable

Due to the high levels of underdiagnoses of LOD in primary care (Connolly A et al., 2011a) , a combination of methods were used to create a comprehensive code list for LOD. READ codes from the data dictionary and the QOF LOD code list were primarily used, along with code lists from previous CPRD publications in dementia. Additionally, the PRIMIS dementia audit codes were used to capture non-QOF diagnoses such as LOD monitoring codes and other mental health codes (Table 10).

READCODES	DESCRIPTION
6AB..	Dementia annual review
3AD..00	Dementia test
66h..00	Dementia monitoring
9Ou..%	Dementia monitoring administration
8BPa.	Antipsychotic drug therapy for dementia
8Hla.00	Referral to dementia care advisor
8HTY.	Referral to memory clinic
38C1000	Assessment for dementia
38C1300	Assessment of psychotic and behavioral symptoms of dementia
8CSA.	Dementia advance care plan agreed
8CMG2	Review of dementia advance care plan
8IAe0	Dementia advance care plan declined
9Ou2.00	Dementia monitoring second letter
9Ou1.00	Dementia monitoring first letter
9Ou3.00	Dementia monitoring third letter
9Ou4.00	Dementia monitoring verbal invite
9Ou5.00	Dementia monitoring telephone invite

Table 10: PRIMIS dementia audit

Upon capturing all possible LOD cases, three additional data management steps were applied to properly identify and classify the LOD cases. The first step involved using HES/ONS mortality linkage data to detect additional LOD cases using ICD-10 codes. Two recent studies of the concordance between primary care and HES diagnoses of coronary heart disease (CHD) found that using HES diagnoses increased the incidence of CHD over and above diagnoses in primary care EHRs by about 17%.(Payne RA et al., 2012, Herrett E et al., 2013). I was able to supplement diagnoses in primary care data with HES, in those practices who have consented to participate in the linkage scheme (approximately 70% of the contributing practices in England, or roughly 55% of all practices in the database).

Secondly, the therapy file extract from CPRD was used to identify individuals on dementia drugs that did not have a code specifying an LOD diagnosis otherwise. Dementia drugs mainly included acetylcholinesterase inhibitors (Rivastigmine, Donepezil and Galantamine) and memantine (Casey DA et al., 2010). According to the European Medicine Agency Committee, both classes of drugs are solely used for the treatment of AD and other LODs. Thirdly, in an effort to not miss any LOD cases, I made use of parts of an LOD algorithm developed by a fellow researcher, Dr. Anita Kulatilake, working on a different CPRD-based research project, within my department. Specifically, I have used the steps involved in identifying underdiagnosed cases of LOD using eight cognitive function neurocognitive tests, commonly used in clinical practice in the UK for dementia diagnosis. In these cases, the cut-off points for the dementia tests were used to test and validate the scores in CPRD (Table 11).

Med Codes	Read Terms	Cognitive Function Test	Score range	Score for dementia diagnosis
83484	MMSE score	MMSE	0-30	<24
82481	Mini-mental state examination	MMSE	0-30	<24
11862	Mini mental state score	MMSE	0-30	<24
10493	MMSE - Mini-mental state examination	MMSE	0-30	<24
10503	Mini-mental state examination	MMSE	0-30	<24
11862	Modified mini-mental state 3MS examination	MMSE	0-30	<24
49674	Mini-mental state examination	MMSE	0-30	<24
89036	Modified mini-mental state 3MS examination	MMSE	0-30	<24
98742	Modified mini-mental state examination	MMSE	0-30	<24
36637	Modified mini-mental state examination	MMSE	0-30	<24
95796	Mini mental state score	MMSE	0-30	<24
108416	Mini-Cog	Mini-Cog	0-5	<3
35203	Mini-Cog	Mini-Cog	0-5	<3
55882	Six item cognitive impairment test	6-Item Cog	0-28	>8
35305	Six item cognitive impairment test	6 -item Cog	0-28	>8
3530	Six item cognitive impairment test	6 -item Cog	0-28	>8
9794	AMT - Abbreviated mental test	AMT	0-10	<=7
19037	Abbreviated mental test	AMT	0-10	<=7
26819	Abbreviated mental test	AMT	0-10	<=7
35203	DRS - Clinical dementia rating scale	CDR	0-3	>0.5
44880	Clinical dementia rating scale	CDR	0-3	>0.5
39471	Dementia rating scale	CDR	0-3	>0.5
101074	GPCOG - general practitioner assessment of cognition	GPCog	0-9	0-4
103076	GPCOG patient examination	GPCog	0-9	0-4
101710	GPCOG informant interview	GPCog	0-9	0-4
100140	Addenbrooke's cognitive examination revised	ACER	0-100	<82
11862	Addenbrooke's cognitive examination revised - attention and orientation subscale	ACER	0-100	<82
103076	Addenbrooke's cognitive examination revised - fluency subscale	ACER	0-100	<82
19037	Addenbrooke's cognitive examination revised - memory subscale	ACER	0-100	<82
26142	Addenbrooke's cognitive examination revised - language subscale	ACER	0-100	<82
26326	Addenbrooke's cognitive examination revised - visuospatial subscale	ACER	0-100	<82

Table 11: Cognitive tests used for identification of dementia (Medcodes, read terms, cognitive function test, score range, and scores for dementia diagnosis)

(d-1) Algorithm for identifying additional LOD cases

Consequently, an overall algorithm for reporting all possible LOD cases was comprised of the following: (1) READ and PRIMIS codes identified from the clinical file extracts, (2) product codes for dementia drugs from the therapy file extract, (3) cases identified from the HES/ONS linkage data, and (4) additional cases identified from valid tests scores for the most common dementia cognitive tests (Figure 6)

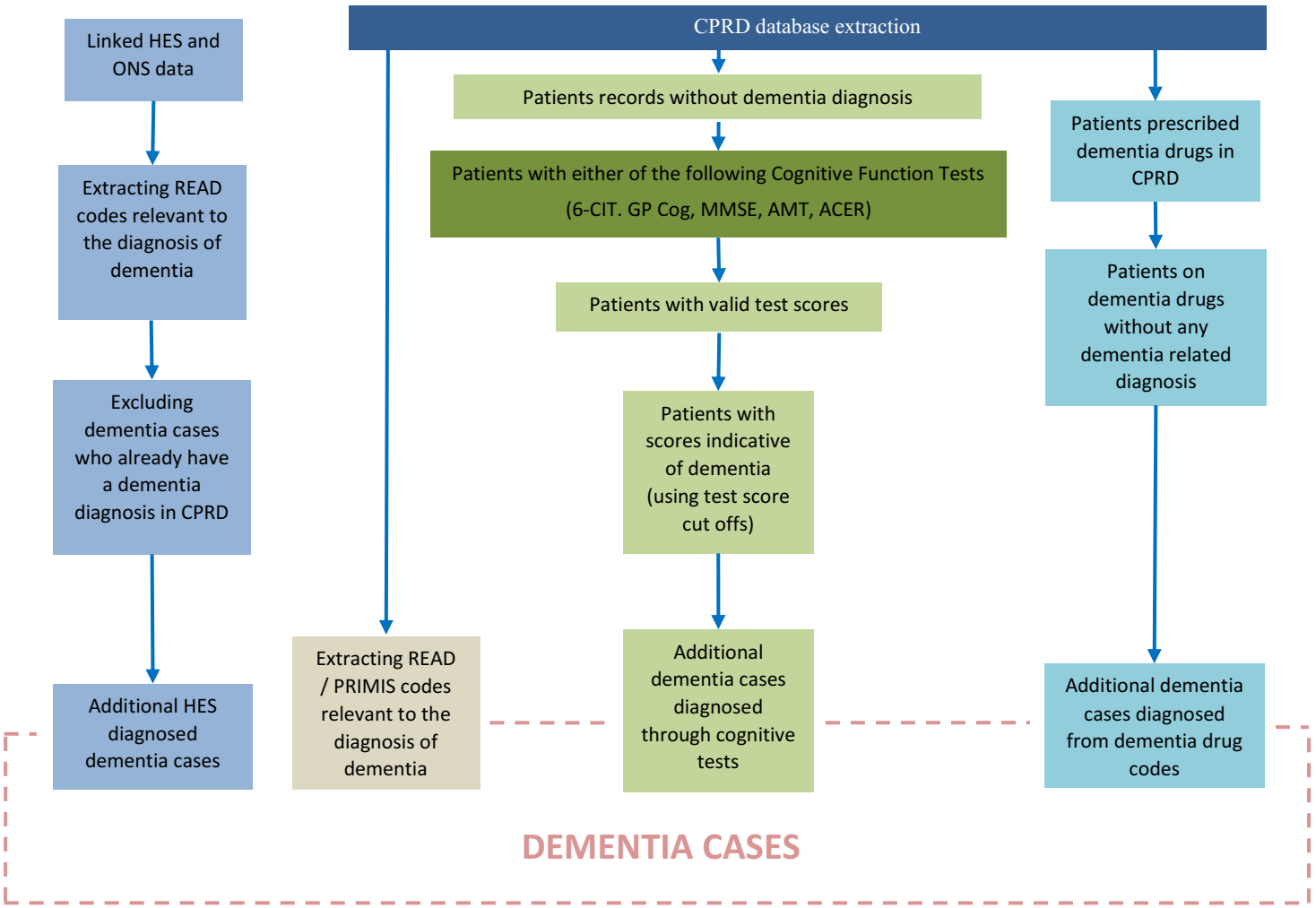


Figure 6: Algorithm for identifying dementia cases

(d-2) Algorithm for classifying LOD types

Once the maximum number of possible LOD cases was achieved, I proceeded to classify the LOD cases into different sub-types. As previously mentioned, differentiating between AD and other LOD forms, in both clinical and research setting is quite challenging. Based on the key gaps in our understanding of the nosology of LOD and AD, as well as the limited availability of clinical tools for the evaluation of brain amyloid, tau load, and neurodegeneration, I decided to use the term of LOD throughout all chapters and results to include all forms (excluding earlier onset such as familial cases and Fronto-temporal Dementia (FTD)) with a special focus on dementia attributable to Alzheimer's disease (AD-LOD). As per the NIA-AA 2011 criteria, LOD was classified as probable AD (codes corresponding to a physician recorded diagnosis for AD only) , possible AD (codes indicating a diagnosis for AD preceded with evidence of an earlier diagnosis of another LOD form, such as VaD) and other LOD (codes indicating a diagnosis of LOD other than AD) (Figure 7). The other LOD group consisted of vascular dementia (VaD), Lewy body dementia (LBD), Parkinson's disease dementia (PDD), and unspecified dementia. The unspecified dementia code list was based on a combination of a) individuals who had a READ code indicating LOD without any indication of the specific type b) individuals who had a code for dementia drugs without a dementia diagnosis code, hence making it impossible to identify the specific type of dementia c) individuals identified through the PRIMIS code (Table 10) without an indication of a specific type of dementia.

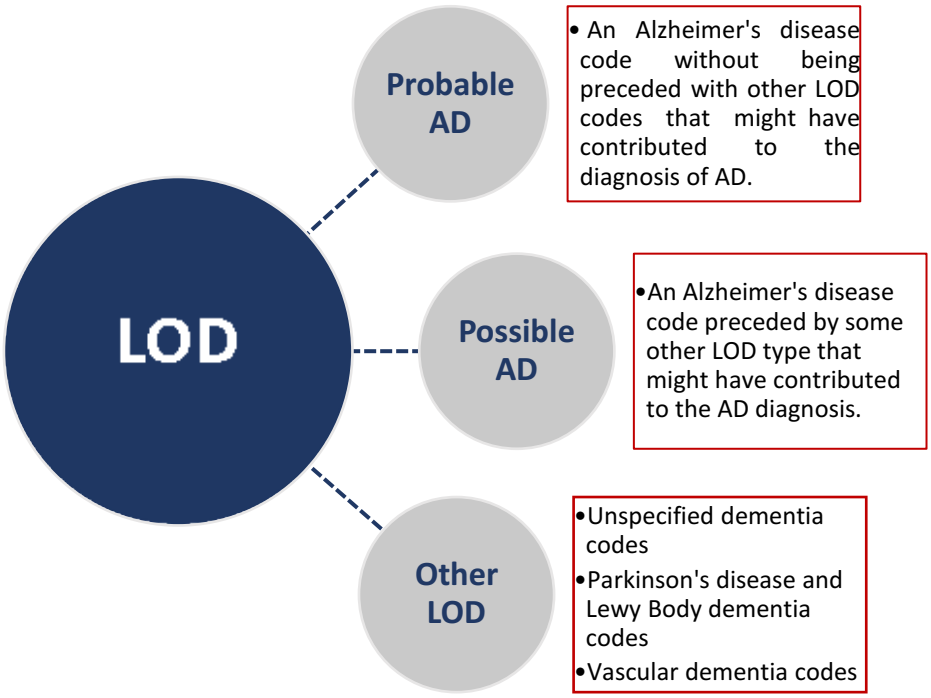
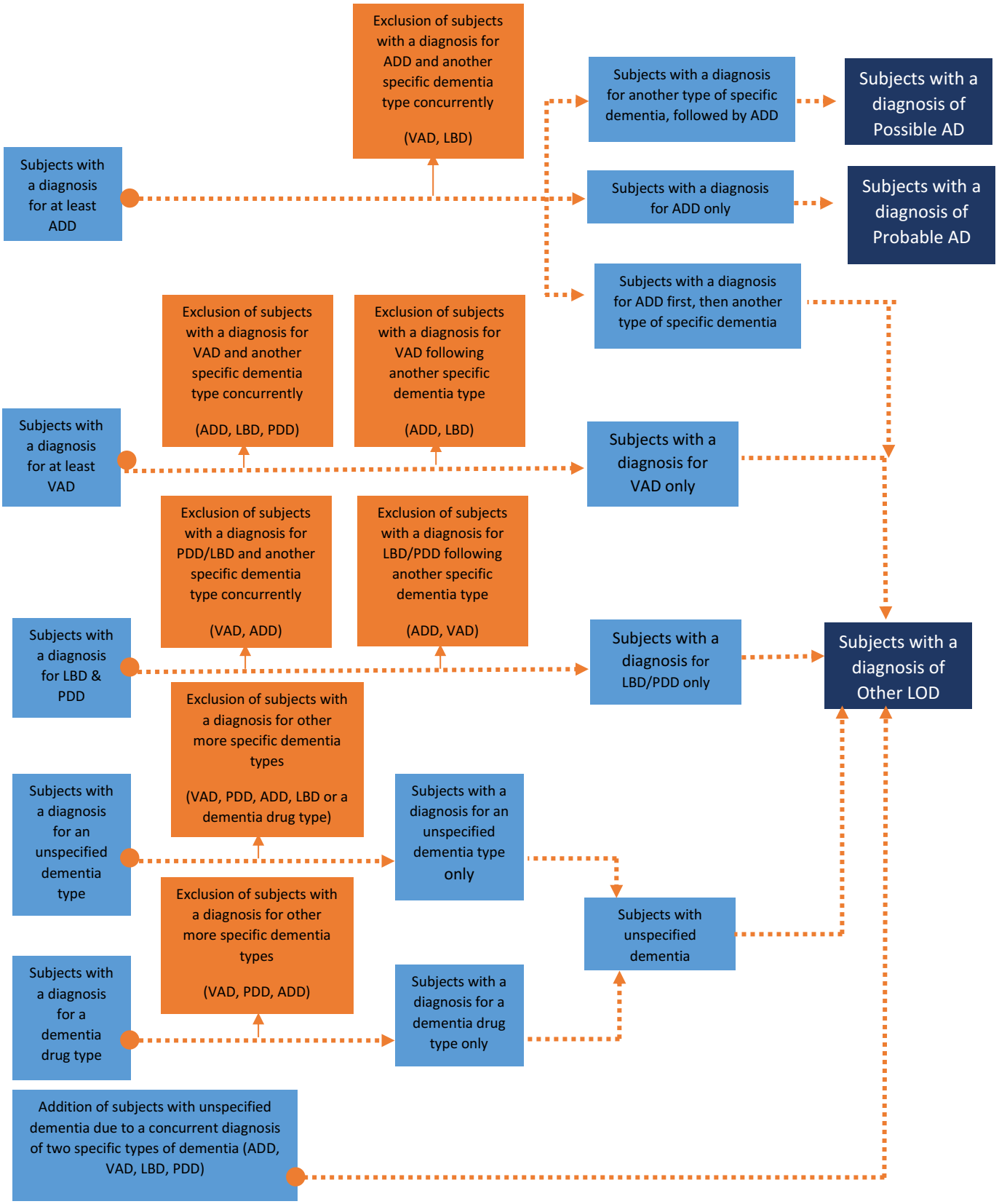


Figure 7: Different LOD sub-types and their classification

A specific algorithm was then created to distribute individuals into the specific LOD categories: probable AD, possible AD and other LOD. Individuals who had multiple LOD diagnosis codes recorded concurrently, were assumed to be ambiguous and were included, as a result, in the unspecified dementia group. For individuals who had a combination of LOD codes recorded followed by each other (ex: PDD diagnosed in 2000 and VaD diagnosed in 2010), the date of the first code for LOD diagnosis was used to indicate the age of onset of LOD. However, the later code for LOD diagnosis was used to categorize the individual into the proper LOD category. The rationale was that the later LOD diagnosis would be expected to be more informed and accurate, as the GP would have received more information with regards to the type of LOD, and would be in a position to update the diagnosis. On the case of AD, individuals who had a diagnosis of AD solely, were classified as "probable AD" and individuals with an earlier diagnosis of a non- AD form of LOD were subsequently re-classified as "possible AD". An algorithm illustrating a step by step decision approach to the final dementia categorizations is presented below (Figure 8).



ADD: Alzheimer's disease dementia, AD: Alzheimer's disease, PDD: Parkinson's disease dementia, LBD: Lewy-Body dementia, VAD: Vascular disease dementia, LOD: Late-onset dementia

Figure 8: Algorithm for classifying dementia types

3.4 DATA ANALYSIS

3.4.1 Statistical Analysis Plan

In order to adequately investigate the association between cancer and LOD separately in individuals with and without T2DM, I have opted to apply an open cohort study design. The incidence rates (IRs) of cancer and LOD were computed separately, in subpopulations with and without T2DM. The IRs were adjusted by sex and 4- year age categories (60-64, 65-69, 70-74, 75-79, and 80+ years) using a person-year analysis. Individuals were considered at risk and contributed person years from date of cohort entry to diagnosis of LOD/cancer, death date, transfer out data, or end of observation period, whichever came first. A number of individuals had a diagnosis date of LOD/ cancer that was identical to their date of cohort entry. In order to allow for these individuals to contribute person years to the IRs of LOD/cancer, I have set the data so that they contributed 0.5 years of follow-up time (between cohort entry and diagnosis of LOD/cancer) to the person-year analysis. The calculation of IRs for specific types of LOD/ cancer involved censoring for other types of LOD/cancer, to allow for an accurate comparison of IRs between different types. For instance, if calculating IR of probable AD, individuals with possible AD and other LOD diagnosis were censored, to ensure that they did not incorrectly contribute to the non LOD group.

For overall and different types of cancer, I have additionally calculated the standardized incidence ratios, using the Cancer Incidence in Five Continents volume X (CI5 X) (Forman D et al 2014), as a reference. The standardized incidence ratio was calculated by dividing the observed cases of cancer in the study by the expected number of cases (CI5 UK incidence rate multiplied by the number of individuals in the study) x 100.

In order to evaluate the risk of LOD in individuals with and without cancer, I treated cancer as a time-varying covariate. The data was split to allow for participants with cancer to contribute person-years to the no cancer group up until cancer diagnosis, and then contribute person years to

the cancer group. Individuals who were diagnosed with cancer prior to cohort entry contributed person years only to the cancer group. Individuals who had a diagnosis date of cancer that was identical to their date of cohort entry or to the date of LOD diagnosis, contributed 0.5 years of follow-up time to the person-year analysis. The cumulative incidence of LOD and different LOD sub-types was further examined in individuals with vs. without cancer, using Kaplan Meier estimates with age as the time scale.

Cox proportional hazard models, with time-dependent covariates and age as the time-scale, were applied to determine the risk of overall LOD and specific LOD types in individuals with and without a cancer diagnosis. Crude hazard ratios (HRs) and 95 % CIs were calculated and adjusted to account for various possible confounders, identified from the literature. Confounders included sex, BMI (underweight (<18.5), normal (18.5-25), overweight (25-30) and obese (>30)) and smoking status (never smokers, ex-smokers and current smokers).

To investigate whether or not any associations observed between LOD and cancer were due to selective mortality, the Fine and Gray competing risk models with cause specific (csHRs) and sub-distribution Hazard Ratios (sdHRs) for overall LOD and specific types were used. This model accounted for death as a competing risk by allowing individuals to contribute person years after their death. The sdHRs were then compared to the cause-specific HRs (csHR) for LOD (where individuals who had the competing risk are removed from the risk analysis). Cumulative incidence risk plots of LOD were calculated to better understand the difference in mortality rate between individuals with cancer vs. without.

STATA 14 package (StataCorp, College Station, Texas, USA) was used for the analysis.

3.4.2 Statistical analysis aims overview

The below stated aims were completed in duplicate for the cohorts with and without T2DM

1. Age - and sex- stratified incidence were calculated for both any LOD, and AD-LOD, per person-year at risk, for each cohort.

2. Crude and age- and sex- standardized cancer incidence rates were computed (overall and for each cancer type of interest) for each cohort.

3. Age- and sex- stratified incidence of any LOD, and AD-LOD, for those with each cancer diagnosis, and without any cancer diagnosis, for each cohort were also calculated. Kaplan-Meier curves were produced to demonstrate time-to-any LOD and time-to-AD-LOD, for each cohort, and associated summary time-to-diagnosis measures.

4. Cox proportional hazards models were used to obtain estimated unadjusted and adjusted hazard ratios, denoting risk of any LOD among individuals with versus without an existing or previous cancer diagnosis, for each cohort. This analysis was repeated for AD-LOD specifically.

5. As per Aim 4, for the more specific cancer diagnoses. NB. The analyses relating to breast and prostate cancer was limited to females and males, respectively.

6. Cox proportional HRs and cumulative incidence risk plots for death were calculated. Additionally, the sub-distribution Hazard Ratios (sdHRs) and cause specific Hazard (csHRs) for overall LOD and specific types were computed, along with cumulative incidence risk plots of LOD, to account for death as a competing risk.

3.4.3 Handling of missing data

With regards to the outcome and exposure variables and diagnosis – based covariates, the absence of a record of a diagnosis (as per definitions above) was considered to be equivalent to the absence of a diagnosis. Missing data on ethnicity was supplemented using HES ethnicity data, or otherwise was assumed to be White by default, as recommend by previous studies on missing ethnicity data in CPRD (Mathur R et al., 2014, Hippisley-Cox J, et al 2010, Hippisley-Cox J, et al 2008 Collins GS, et al 2011, Collins GS, et al 2010). The white ethnic group was combined with the group where ethnicity was not recorded since based on the study population, which is comparable to the

UK population, 93% or more of people without ethnicity recorded would be expected to be from a white ethnic group.

In this study, missing mainly involved smoking status, alcohol use and BMI .In order to be able to handle missing data in a statistically valid manner, it is imperative to firstly explore and understand the nature, mechanisms and caused of data missingness. Sterne et al (2009) suggests three different possible mechanisms for consideration of missing data: missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR). In an MCAR scenario, there is no difference between the missing and observed values. For instance, it is not possible to collect the blood pressure measurements for some individuals, due to the blood pressure machine being broken. The MAR scenario, assumes that the missingness is dependent on the observed values. For example, there are missing blood pressure measurement because younger people are less likely to have their blood pressure measurement taken. Finally, in the MNAR scenario, the missing values depend on the unobserved values or on the reason why it's missing. For instance, BMI data is more likely to be measured in individuals who are obese compared to those who look like they have normal BMI. MNAR is usually more likely to arise with mental health data, where individuals who are depressed are less likely to report their mental status to the GP. Studies accounting for MNAR are very scarce, as it is quite challenging and complicated to analyze (Schafer JL and Graham JW, 2002, Groenwold RHH et al., 2014). In this study, the MAR mechanism best illustrated the missing scenario for smoking, BMI and alcohol values. Specifically, since the introduction of the QOF incentive scheme in 2004, the measurement of these values and other important diseases and lifestyle behaviors have been recorded more frequently (Kontopantelis E et al., 2017). It is important to acknowledge that these values are better reported in patients with chronic conditions, such as diabetes and cardiovascular disease (Delaney JAC et al., 2009). Conversely, life-style data for patients without chronic diseases is more likely to be missing, especially before 2004.

There are several methods that can be used to deal with missing data in large databases, including complete case analysis and imputation based approaches (Green J et al., 2010, Silva APD et al., 2017) . Unfortunately, not all of these approaches offer reliable data and selection bias free results, such as simple imputation of missing values and complete cases analysis (Carpenter JR and

Kenward MG, 2007). Multiple imputation (MI) and Inverse Probability Weights (IPW) have been very commonly used in primary care databases as methods for dealing with missing data (Carpenter JRKenward MG and Vans S, 2006) . In fact, MI is more commonly used than IPW, but it is much more computationally complex and, thus, less rigorous (Sterne JAC et al., 2009a, Rezvan PH et al., 2015) . Thus, computational errors are very likely and can result in inaccurate estimates due to the various stages of model building in MI (Rezvan PHLee KJ and Simpson JA, 2015). In comparison, IPW is a simpler method for dealing with missing data which assumes a missingness model (probability that an individual is a complete case) rather than an imputation model (missing values are replaced by values randomly generated) (Carpenter JRKenward MG and Vans S, 2006). The IPW method basically rebuilds the study population by upweighting the data based on subjects who have complete data. Consequently, each participant in the study with missing data was weighted by the inverse probability of a complete case. Given the technical complications of MI and the computational intensity required, I have opted to use the IPW method as a reliable technique to correct for missing data in this study.

CHAPTER 4 – RESULTS

This chapter presents the results of this study, including the case identification and baseline characteristics of LOD and cancer in the non-T2DM and T2DM cohorts. Cancer was evaluated both as cancer overall and for the following specific types: lung, breast, prostate, bowel, non-melanoma and melanoma skin cancer, were under examination. LOD was ascertained as overall LOD, probable AD, possible AD and other LOD forms. Firstly, the incidence rate for each of LOD and cancer was calculated, along with their specific sub-types, using the person-years at risk as the denominator. Individuals were followed up from cohort entry to diagnosis of LOD/cancer, death date, transfer out data, or end of observation period, whichever came first. I also censored for other types of LOD and cancers, when calculating the IRs for specific types of cancer and LOD. In an effort to compare the cancer results of my study with the reported UK general population data, I also calculated the standardized incidence ratios, using the Cancer Incidence in Five Continents volume X (CI5 X) data as a reference.

Next, I identified the LOD cases in individuals with and without cancer. The history of cancer in individuals with LOD, and sub-types of LOD, was summarized in Kaplan Meier graphs. Preliminary analysis for both LOD and cancer were done to explore the distribution of demographic data (age, sex, ethnicity), lifestyle variables (BMI, smoking status, alcohol status) and relevant co-morbid diseases (hypertension, hypercholesterolemia, CeVD, depression and brain injury). Based on the literature and theory on the shared risk factors between LOD and cancer, the following possible confounders were included: age, sex, BMI and smoking status. Cox regression models were used, with age as the time scale, to calculate the hazard ratios and 95 % CIs of LOD and different types of LOD, in individuals with cancer vs. without. The crude hazard ratios for LOD as well as the adjusted hazard ratios for age, sex, BMI and smoking status were presented in tables. Given that 30 % of BMI, alcohol and smoking data were missing, I used the Inverse Probability Weights (IPW) methods to account for missing data in the final models. Cancer, the exposure variable, was treated as a time-varying covariate. In other words, participants with cancer contributed person-years to the no cancer group up until cancer diagnosis, and then contributed person years to the cancer group. The last section in the chapter examines the incidence rate of death in both non-T2DM and T2DM cohorts. Additionally, to account for death as a competing risk in the study, the Fine and Gray competing risk models with cause-specific HR (csHR) and

sub-distribution HR (sdHR) for LOD were calculated, along with the cumulative incidence risk plots of LOD.

4.1 Demographic Characteristics

At baseline, a total of 217,335 individuals with T2DM and 739,061 without T2DM were included in the study. The mean age (SD) of individuals with T2DM at cohort entry was 71.62 (7.09) years (47.3% females) vs.70.80 (7.66) years (56.9 % females) in the non-T2DM cohort. Table 12 illustrates the distribution of individuals with T2DM and without T2DM, by age and sex at cohort entry.

Table 12: Distribution of individuals in the T2DM and non-T2DM cohorts, by age and sex at cohort entry

	Non-T2DM cohort		***T2DM cohort***	
Age groups /Sex	**Males n (%)**	**Females n (%)**	**Males n (%)**	**Females n (%)**
65- 69 years old	208,298 (28)	230,242 (31)	63,537 (29)	44,598(20)
70-74 years old	41,525(6)	55,384(7)	22,497(10)	19,882(9)
75-79 years old	34,878(5)	56,178(7)	15,499(7)	17,165(8)
80 and above	34,224(5)	79,317(11)	12,967(6)	21,190(10)
Total	739,061		217,335	

In the T2DM cohort, the mean age of T2DM diagnosis was 69.9 (8.96) years, with the majority of individuals in the cohort having an onset of T2DM diagnosis aged ≥65 years old (n=154,835) (71%) and only 29% of the individuals in the T2DM cohort had a T2DM onset age < 65 years (n=25,412).

The majority of individuals in both cohorts were white and never smokers. Compared to the non-T2DM cohort, participants with T2DM were more likely to be obese (47 %) and have no history of alcohol consumption (Table 13). Data on BMI, alcohol and smoking were missing at baseline in both cohorts for approximately 30 % of the individuals. There was no information on smoking status in 101,233 (14 %) individuals in the non-T2DM and in 35,563 (16 %) individuals in the T2DM cohorts; BMI data were missing in 178,273 (24 %) and 80,737 (37 %) individuals, in the non-T2DM and T2DM cohorts, respectively; and alcohol consumption data were not available in 212,371 (28 %) in the non-T2DM cohort and in 59,404 (27 %) individuals in the T2DM cohort. As expected, the prevalent and incident number of individuals with hypertension, hypercholesterolemia, depression and CeVD were higher in the T2DM cohort, compared to the non-T2DM cohort (Table 14).

Table 13: Distribution of demographic and lifestyle characteristics for the T2DM and non-T2DM cohorts

Demographic and lifestyle Characteristics (%)	*Non-T2DM cohort*	*T2DM cohort*
Ethnicity	n=739,061	n=217,335
White	730,677 (99)	204,823(94)
Mixed	365(<1)	612(<1)
Asian	3,437(<1)	6,626(3)
Black	1,903(<1)	3,128(1)
Other	2,679(<1)	2,146(1)
Region	n=739,061	n=217,335
North East	11,916 (2)	3,322(1)
North West	77,441 (10)	25,795(12)
Yorkshire & The Humber	32,077(4)	7,825(4)
East Midlands	29,101(4)	8,550(4)
West Midlands	63,587(9)	19,571(9)
East of England	70,329(10)	19,220(9)
South West	69,566(9)	20,076(9)
South Central	81,954(11)	21,595(10)
London	77,836(11)	23,119(11)
South East Coast	79,204(11)	21,789(10)
Northern Ireland	18,709(2)	5,796(2)
Scotland	64,191(9)	19,199(9)
Wales	63,150(8)	21,478(10)
Smoking Status [a]	n=638,724	n=181,772
Never	398,131 (63)	92,206(51)
Ex	118,534 (18)	61,780(34)
Current	122,059 (19)	27,786(15)
BMI Category [b]	n=561,956	n=136,598
Underweight (<18.5)	31,494 (6)	922(1)
Normal (18.5- 25)	261,155(47)	22,583(17)
Overweight(25-30)	194,392(34)	48,556(35)
Obese (>30)	74,915(13)	64,537(47)
Alcohol Consumption Categories [c]	n=527,785	n=157,931
0	107,710 (20)	70,574(45)
(0,14] units /week	277,534(53)	69,026(43)
(14,42] units/week	38,701(7)	15,353(10)
42+ units/ week	103,840(20)	2,978(2)

a) 101,233 (14 %) and 35,563 (16%) individuals did not have the smoking status available in the non- T2DM and T2DM cohorts, respectively.

b) 178,273 (24%) and 80,737 (37 %) individuals did not have the BMI data available in the non-T2DM and T2DM cohorts, respectively.

c) 212,371(28%) and 59,404(27%) individuals did not have alcohol data available in the T2DM and non-T2DM cohorts, respectively.

History of Relevant Diseases	*Non-T2DM cohort n (%)*	*T2DM cohort n (%)*
Brain Injury		
Yes	7,854 (1)	2,671(1)
Prevalent	2,272	1,464
Incident	5,582	1,207
No	731,207 (99)	214,664(99)
Hypertension		
Yes	335,568(45)	161,877(66)
Prevalent	210,699	143,076
Incident	124,869	74,259
No	403,493 (55)	55,458(25)
Hypercholesterolemia		
Yes	105,263(14)	60,527(28)
Prevalent	55,041	49,116
Incident	50,222	11,411
No	633,798 (86)	156,808(72)
Depression		
Yes	142,267(19)	55,586 (25)
Prevalent	99,859	35,640
Incident	42,408	19.508
No	596,794 (81)	161,749 (74)
Cerebrovascular Disease (CeVD)		
Yes	213,461(29)	96,307(44)
Prevalent	118,996	42,120
Incident	94,465	13,466
No	525,600 (71)	121,028(56)

Table 14: Distribution of various relevant diseases in both T2DM and non-T2DM cohorts.

4.2 Cancer in non-T2DM and T2DM cohorts

4.2.1 Cases identified

Overall, 32,022 (15 %) and 165,272 (22 %) cancer cases were identified in the T2DM and non-T2DM cohorts, respectively. In the T2DM cohort, the majority of cancers were diagnosed in males (60 %) and in participants above the age of 60 (69 %). In the non-T2DM cohort, there were 52% of cancer female cases, whilst 61% of cancer cases were aged 60 and above.

Table 15 summarizes the characteristics of the cancer participants included in the study sample. The observations between the cancer groups in both non-T2DM and T2DM cohorts showed similar distribution of demographics and lifestyle variables, except for smoking, BMI and alcohol data. However, these variables should be interpreted with caution, in view of the missing data in both cohorts, although their distribution was relatively non dissimilar. Smoking data were missing in 87,633 (15 %) individuals without cancer and 12,704 (7 %) with cancer in the non T2DM cohort and in 31,177 (16 %) individuals without cancer and 4,386 (14 %) with cancer in the T2DM cohort; 148,420 (25 %) individuals without cancer and 28,685 (17 %) with cancer did not have BMI data available in the non-T2DM cohort and in 69,417 (38 %) individuals without cancer and 11,320 (35 %) with cancer in the T2DM cohort. Finally, 170,043 (30 %) individuals without cancer and 41,233 (25 %) with cancer did not have alcohol consumption data available in the non T2DM cohort, whilst the corresponding numbers in the T2DM cohort were: 51,420 (28 %) individuals without cancer and 7,984 (25 %) with cancer, respectively.

The most common type of cancer in the T2DM and non-T2DM cohorts was non-melanoma skin cancer (N=6639 and 50,214). The most common sites were breast for females and prostate for males, in both cohorts (Figure 9). At cohort entry, 70,704 participants had a history of cancer and 94,568 additional cancer cases were diagnosed during follow-up in the non-T2DM cohort, which represents 22 % of the total cohort. In comparison, 7,364 prevalent and 24,658 incident cancer

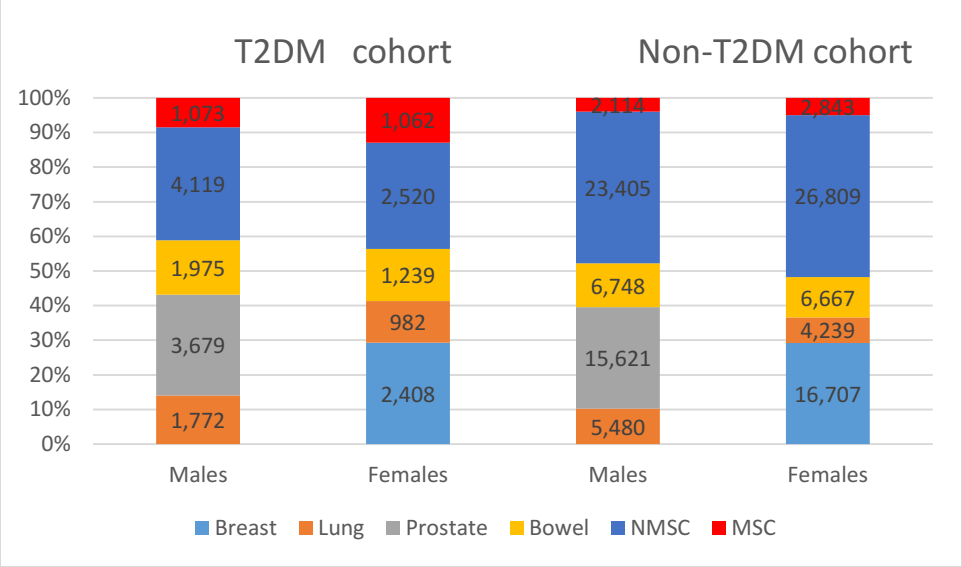
cases were identified in the T2DM cohort, which represents 3 % and 11 %, respectively such as lung and bowel cancers in both non-T2DM (29 %) (Table 16).

Table 15: Demographic and lifestyle characteristics of study participants by cancer status in both T2DM and non-T2DM cohorts.

Cohort	Non-T2DM cohort				T2DM cohort			
	No Cancer (N=573,789)		Cancer (N=165,272)		No Cancer (N=185,313)		Cancer (N=32,022)	
	No. or mean	% or (SD)	No. or mean	% or (SD)	No. or mean	% or (SD)	No. or mean	% or(SD)
Sex								
Males	239,670	42	79,255	48	95,265	51	19,235	60
Females	334,104	58	86,017	52	90,048	49	12,787	40
Ethnicity								
White	566,751	99	163,926	99	173,653	94	31,170	97
Black	1,524	<1	379	<1	2,856	1	272	<1
Mixed	315	<1	50	<1	559	1	53	<1
Asian	3,055	<1	382	<1	6,273	3	353	1
Other	2,144	<1	535	<1	1,972	1	174	<1
Age at diagnosis	71	(7.8)	71	(11.5)	72	(7.2)	75	(7.8)
Smoking status[a]								
Never smokers	305,605	53	92,526	56	79,039	59	13,167	41
Current smokers	94,914	16	27,145	16	23,140	12	4,646	14
Ex-smokers	85,637	15	32,897	20	51,957	28	9,823	31
BMI category[b]								
Underweight	22,810	4	8,684	5	806	<1	116	<1
Normal	195,170	34	65,985	40	18,846	10	3,737	12
Overweight	148,260	26	46,132	28	40,603	22	7,953	25
Obese	59,129	10	15,786	9	55,641	30	8,896	28
Alcohol consumption[c]								
0	82,554	20	25,156	20	60,301	32	10,273	32
(0,14] units /week	207,900	51	69,634	56	58,281	31	10,745	33
(14,42]	28,898	7	9,803	8	12,788	7	2,565	8
units/week	84,394	21	19,446	16	2,523	1	455	1
42+ units/ week								

a)87,633 (15 %) individuals without cancer and 12,704 (7 %) with cancer in the non- T2DM cohort and 31,177 (16%) without cancer and 4,386 (14%) individuals with cancer in the T2DM cohort, did not have smoking status . b) 148,420 (25%) individuals without cancer and 28,685 (17 %) with cancer in the non-T2DM cohort and 69,417 (38 %) individuals without cancer and 11,320 (35 %) with cancer in the T2DM cohort did not have BMI data available . c) 170,043(30%) individuals without cancer and 41,233(25%) with cancer in the non-T2DM cohort and 51,420 (28 %) individuals without cancer and 7,984 (25 %) with cancer in the T2DM cohort did not have alcohol consumption data.

Figure 9: Distribution of specific cancer types by sex in both T2DM and non-T2DM cohorts.



T2DM cohort

Total Breast:	2,408
Total Lung:	2,754
Total Prostate:	3,679
Total Bowel:	3,214
Total NMSC:	6,639

Non-T2DM cohort

Total Breast:	16,707
Total Lung:	9,719
Total Prostate:	15,621
Total Bowel:	13,415
Total NMSC:	50,214

NMSC: Non-Melanoma skin cancer, MSC: Melanoma skin cancer

Table 16: Distribution of specific cancer types in both T2DM and non-T2DM cohorts.

	Non-T2DM cohort			*T2DM cohort*		
Cancer Types	Total No (N=165,272)	No (%) of cancers Prevalent (N=70,704)	Incident (N=94,568)	Total No (N=32,022)	No (%) of cancers Prevalent (N=7,364)	Incident (N=24,658)
Lung	9,719(7)	1,528 (2)	8,191 (9)	2,754(9)	319 (4)	2,435 (10)
Breast	16,707(10)	9,569 (13)	7,138 (7)	2,408(7)	744 (10)	1,664 (7)
Prostate	15,621(9)	4,907 (7)	10,714 (11)	3,679(11)	1011 (14)	2,668 (11)
Bowel	13,415(8)	5,270(7)	8,145 (9)	3,214(10)	701 (9)	2,513 (10)
NMSC	50,214(30)	22,478 (32)	27,736 (29)	6,639(21)	1,697 (23)	4,942 (20)
MSC	4,957 (3)	3,572 (5)	1,385 (2)	2,136(7)	384 (5)	1,752 (7)
Other	54,639(32)	23,380 (33)	31,259(33)	11,192(35)	2,508 (34)	8,684 (35)

NMSC: Non-Melanoma skin cancer, MSC: Melanoma skin cancer

4.2.2 Incidence rate of cancer in non-T2DM and T2DM cohorts

There were a total of 94,568 and 24,658 incident cases of cancer in the non-T2DM and T2DM cohorts, respectively. In the non-T2DM cohort, the overall incidence rate of cancer was 25.54 per 1,000 person years in males and 16.55 per 1,000 person years in females, and increased by age. The highest overall incidence rate was for non- melanoma skin cancer (5.88 per 1,000 person years), prostate cancer in males (5.63 per 1,000 person years) and breast cancer in females (2.61 per 1,000 person years). The incidence rate for cancer was higher in males, compared to females. As expected, the incidence rate for different cancer categories increased with age, up until the age of 80, after which the incidence of cancer dropped for the majority of cancers (Tables 17 and 18).

The incidence rate of overall cancer was higher in the T2DM cohort (23.69 per 1,000 person years) compared to the non-T2DM cohort (20.21 per 1,000 person years). In the T2DM cohort, the overall incidence rate of cancer was 27.80 per 1,000 person years in males and 19.35 per 1,000 person years in females. Upon stratification by specific cancer types, lung, breast, bowel and melanoma skin cancer showed a higher incidence rate in the T2DM cohort, compared to the non-T2DM cohort. However, there was a lower incidence rate of non-melanoma skin cancer and prostate cancer in individuals with T2DM. Similar to the non-T2DM cohort, the highest overall incidence rate was for non- melanoma skin cancer (4.75 per 1,000 person years), prostate cancer in males (5.33 per 1,000 person years) and breast cancer in females (3.42 per 1,000 person years), and there was a higher incidence for overall cancer and different cancer types (non-sex specific) in males compared to females (Table 18).

Table 17: Incidence rates (95%CI) of different cancer types, stratified by sex and age of cancer diagnosis, in the non-T2DM cohort.

CANCER TYPE AGE (YEARS)	*NON-T2DM COHORT*					
	MALES		FEMALES		TOTAL	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
OVERALL	**25.54**	**25.34-25.78**	**16.55**	**16.41-16.69**	**20.21**	**20.08-20.33**
65-69	20.72	20.35-21.10	15.15	14.85-15.46	17.80	17.57-18.04
70-74	22.99	22.59-23.39	14.76	14.47-15.05	18.46	18.22-18.70
75-79	28.61	28.11-29.13	17.01	16.68-17.34	21.75	21.47-22.04
80 and above	31.13	30.66-31.62	18.20	17.95-18.45	22.33	22.11-22.57
LUNG	**2.37**	**2.30-2.43**	**1.28**	**1.24-1.32**	**1.72**	**1.68-1.76**
65-69	1.86	1.75-1.97	1.17	1.09-1.26	1.50	1.43-1.57
70-74	2.28	2.16-2.41	1.34	1.26-1.43	1.77	1.69-1.84
75-79	2.87	2.71-3.03	1.44	1.35-1.54	2.03	1.94-2.11
80 and above	2.61	2.48-2.76	1.21	1.14-1.27	1.66	1.59-1.72
BREAST		-	**2.61**	**2.55-2.67**	**1.55**	**1.51-1.58**
65-69			3.40	3.25-3.54	1.78	1.70-1.85
70-74		-	2.38	2.27-2.50	1.31	1.25-1.37
75-79		-	2.34	2.23-2.47	1.39	1.32-1.46
80 and above		-	2.44	2.35-2.53	1.66	1.60-1.72
PROSTATE	**5.63**	**5.53-5.73**		-	**2.29**	**2.25-2.33**
65-69	4.94	4.76-5.13			2.35	2.27-2.44
70-74	5.09	4.91-5.28		-	2.29	2.21-2.38
75-79	6.43	6.19-6.67		-	2.63	2.53-2.73
80 and above	6.31	6.10-6.53		-	2.02	1.95-2.09
BOWEL	**2.17**	**2.11-2.24**	**1.43**	**1.39-1.47**	**1.73**	**1.70-1.77**
65-69	1.70	1.60-1.81	1.03	0.95-1.11	1.35	1.29-1.42
70-74	1.92	1.81-2.04	1.21	1.13-1.29	1.53	1.46-1.60
75-79	2.49	2.35-2.65	1.53	1.44-1.63	1.93	1.84-2.01
80 and above	2.69	2.56-2.84	1.74	1.66-1.82	2.04	1.98-2.12
NMSC	**6.75**	**6.63-6.86**	**5.29**	**5.21-5.37**	**5.88**	**5.82-5.95**
65-69	5.21	5.03-5.40	4.24	4.09-4.41	4.71	4.58-4.83
70-74	5.93	5.73-6.14	4.51	4.35-4.67	5.15	5.03-5.28
75-79	7.30	7.05-7.56	5.45	5.27-5.64	6.21	6.06-6.36
80 and above	8.86	8.61-9.12	6.28	6.14-6.43	7.11	6.98-7.24
MSC	**0.35**	**0.33-0.38**	**0.29**	**0.28-0.31**	**0.32**	**0.30-0.33**
65-69	0.27	0.23-0.31	0.21	0.18-0.25	0.24	0.21-0.27
70-74	0.29	0.25-0.34	0.21	0.18-0.25	0.25	0.22-0.28
75-79	0.40	0.34-0.46	0.34	0.29-0.39	0.36	0.33-0.40
80 and above	0.47	0.42-0.54	0.37	0.33-0.41	0.40	0.37-0.43

NMSC: Non-Melanoma skin cancer, MSC: Melanoma skin cancer

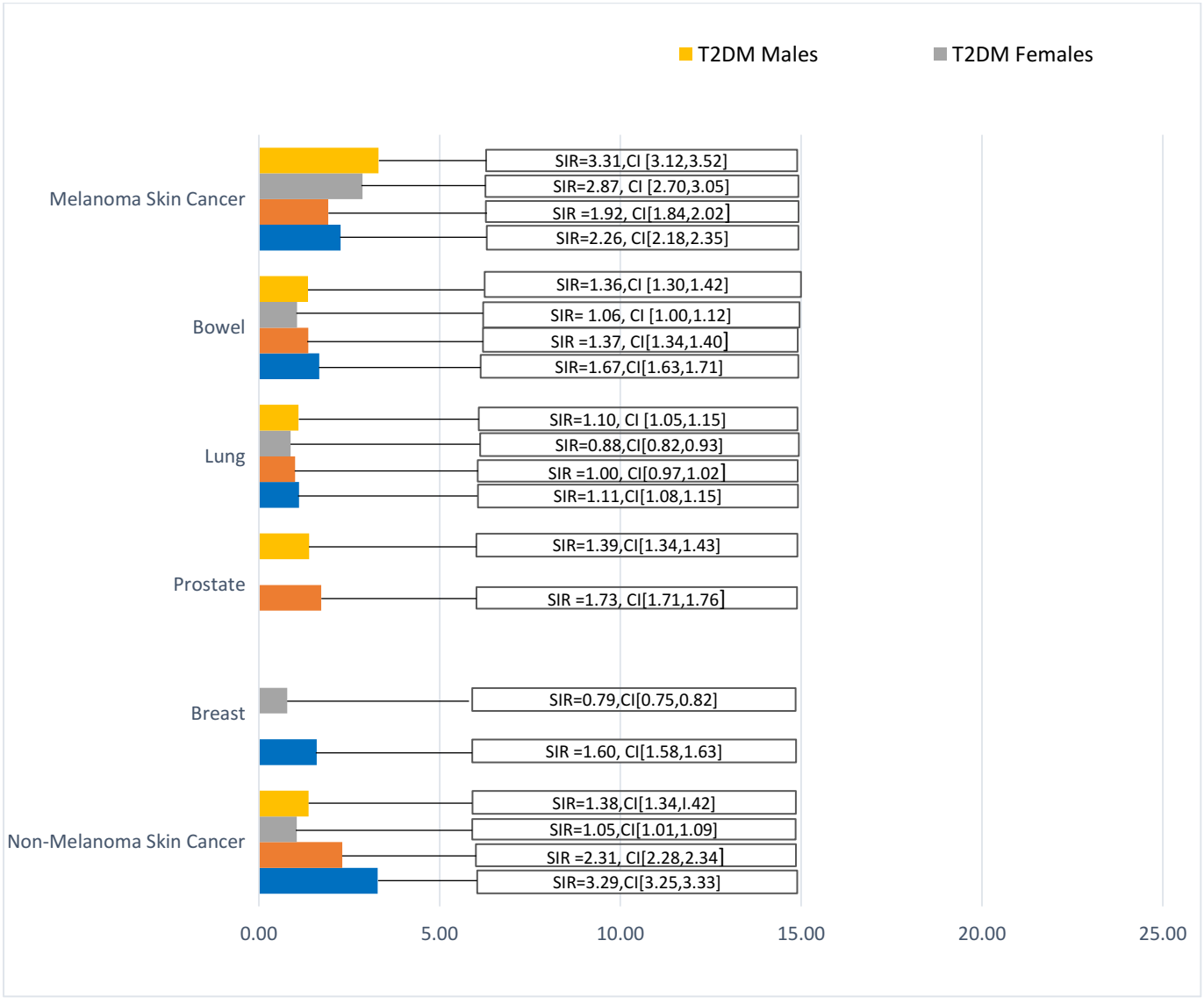
Table 18: Incidence rates (95%CI) of different cancer types, stratified by sex and age of cancer diagnosis, in the T2DM cohort.

CANCER AGE (YEARS)	T2DM COHORT					
	MALES		FEMALES		TOTAL	
	RATE	95% CI	RATE	95% CI	RATE	95% CI
OVERALL	**27.80**	**27.39-28.22**	**19.35**	**19.00-19.71**	**23.69**	**23.42-23.97**
65-69	22.16	21.44-22.91	17.08	16.32-17.87	20.08	19.55-20.62
70-74	25.22	24.49-25.97	17.56	16.89-18.26	21.82	21.31-22.33
75-79	31.37	30.47-32.30	20.85	20.10-21.63	26.25	25.66-26.85
80 and above	33.38	32.46-34.31	20.80	20.19-21.43	26.06	25.54-26.60
LUNG	**2.77**	**2.64-2.90**	**1.62**	**1.52-1.72**	**2.21**	**2.13-2.94**
65-69	2.07	1.86-2.31	1.35	1.15-1.59	1.78	1.62-1.94
70-74	2.73	2.50-2.99	1.70	1.50-1.93	2.28	2.12-2.45
75-79	3.18	2.90-3.48	1.84	1.63-2.08	2.53	2.35-2.72
80 and above	3.15	2.88-3.45	1.55	1.39-1.73	2.22	2.07-2.38
BREAST		-	**3.42**	**3.23-3.58**	**1.67**	**1.62-1.80**
65-69			4.18	3.81-4.58	1.71	1.56-1.88
70-74		-	2.89	2.62-3.18	1.28	1.16-1.41
75-79		-	3.31	3.02-3.63	1.61	1.47-1.77
80 and above		-	3.47	3.23-3.74	2.02	1.87-2.17
PROSTATE	**5.33**	**5.15-5.51**		-	**2.74**	**2.65-2.83**
65-69	4.37	4.05-4.71			2.58	2.39-2.78
70-74	5.04	4.72-5.38		-	2.80	2.62-2.99
75-79	6.23	5.84-6.65		-	3.20	3.00-3.41
80 and above	5.81	5.44-6.21		-	2.43	2.28-2.61
BOWEL	**2.82**	**2.69-2.96**	**1.94**	**1.83-2.05**	**2.39**	**2.31-2.48**
65-69	2.32	2.09-2.57	1.55	1.34-1.80	2.00	1.84-2.18
70-74	2.63	2.40-2.87	1.74	1.54-1.97	2.23	2.07-2.40
75-79	3.18	2.90-3.48	2.37	2.13-2.65	2.79	2.60-2.99
80 and above	3.25	2.97-3.55	1.99	1.81-2.19	2.52	2.36-2.69
NMSC	**5.70**	**5.51-5.89**	**3.74**	**3.59-3.90**	**4.75**	**4.63-4.87**
65-69	4.74	4.41-5.09	3.00	2.69-3.34	4.02	3.79-4.27
70-74	4.77	4.46-5.11	3.05	2.78-3.53	4.01	3.80-4.23
75-79	6.13	5.74-6.55	3.86	3.55-4.20	5.03	4.77-5.30
80 and above	7.39	6.97-7.84	4.53	4.25-4.83	5.73	5.48-5.98
MSC	**1.63**	**1.53-1.73**	**1.71**	**1.61-1.82**	**1.70**	**1.60-1.74**
65-69	0.56	0.45-0.69	0.63	0.50-0.80	0.59	0.50-0.69
70-74	1.23	1.08-1.40	1.09	0.93-1.28	1.17	1.06-1.29
75-79	2.04	1.82-2.29	2.03	1.81-2.29	2.04	1.88-2.21
80 and above	2.84	2.58-3.12	2.49	2.29-2.72	2.64	2.47-2.81

NMSC: Non-Melanoma skin cancer, MSC: Melanoma skin cancer

The incidence rate of cancer in this population was compared to that of the general UK population. The Cancer Incidence in Five Continents volume X (CI5 X) was used to compute the Standardized Incidence Ratios (SIRs) and their corresponding 95 % CIs for cancer, in both T2DM and non-T2DM cohorts. The SIRs for specific cancer types were calculated using the observed/expected ratios. Figure 10 represent the SIRs for both T2DM and non-T2DM cohorts, compared to the CI5 X. Results in this study illustrate similar patterns, for both T2DM and non-T2DM cohorts, as that in the CI5 X incidence rate reports (Figure 10).

Figure 10: SIRs for specific cancer types by sex in the non-T2DM cohort & T2DM cohort, with CI5 X data as a reference group.



4.3 Late-Onset Dementia (LOD) in non-T2DM and T2DM cohorts

4.3.1 Ascertained LOD Cases

Overall, 11,450 (5 %) and 51,733 (7 %) LOD cases were identified during follow-up in the T2DM and non-T2DM cohorts, respectively. In both cohorts, the majority of LOD cases were identified in individuals above the age of 80 (62 % in T2DM cohort and 66 % in non-T2DM cohort) with a preponderance of women (58 % in T2DM cohort and 69 % in non-T2DM cohort). The mean age (SD) at diagnosis was 81.4(6.9) years and 82.7(7.1) years in the T2DM and non-T2DM cohorts, respectively. Table 19 summarizes the characteristics of the LOD participants included in the study sample. There was a similar distribution of demographics and lifestyle variables for the LOD group in both cohorts, except for smoking, BMI and alcohol. However, the data regarding these variables should be interpreted with caution because of missing data. In the non-T2DM cohort, smoking status was not reported in: 95,339 (14 %) individuals without LOD and 4,998 (10 %) with LOD; 61,269 (23 %) individuals without LOD and 15,836 (31 %) with LOD did not have BMI data available, and 193,044(28 %) individuals without LOD and 18,232 (35 %) with LOD did not have data on alcohol consumption. In the T2DM cohort, 32,619 (16 %) individuals without LOD and 2,944 (25 %) with LOD did not have smoking status data, 75,509 (37 %) individuals without LOD and 5,228 (46 %) with LOD did not have BMI data available, and 55,225 (27 %) individuals without LOD and 4,179 (36 %) with LOD did not have alcohol consumption data.

In general, compared to the non-T2DM cohort, the T2DM cohort had a higher prevalence of relevant co-morbid diseases (hypertension, hypercholesterolemia, CeVD, depression) (Figure 11). In the T2DM cohort vs. non-T2DM cohort, individuals with incident LOD displayed the following distribution of relevant diseases: 73 % vs. 51 % had hypertension, 25 % vs. 13 % had hypercholesterolemia, 50 % vs. 40 % had CeVD and 33 % vs. 29 % had depression, respectively. Brain injury did not differ substantially between both cohorts. However, individuals with incident LOD, regardless of diabetes status, had a slightly higher prevalence of brain injury compared to individuals without (Figure 11).

Figure 11: Prevalence (%) of various relevant diseases in both T2DM and non-T2DM cohorts, by LOD status.

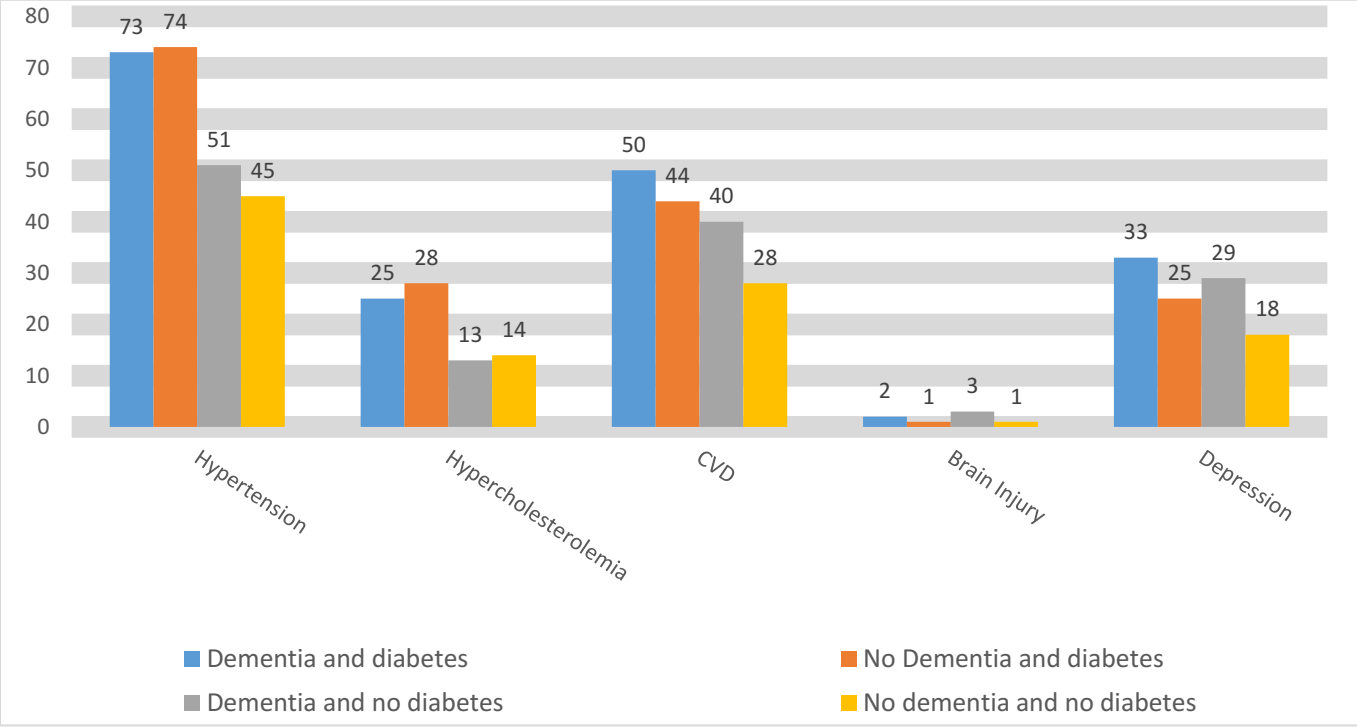


Table 19: Demographic and lifestyle variables of study participants by LOD status in both T2DM and non-T2DM cohorts.

Cohort	Non-T2DM cohort				T2DM cohort			
	No LOD (N=687,328)		LOD(N=51,733)		No LOD(N=205,885)		LOD(N=11,450)	
	No. or mean	% or (SD)	No. or mean	% or (SD)	No. or mean	% or (SD)	No. or mean	% or (SD)
Sex								
Males	301,551	44	17,374	33	109,705	53	4,795	42
Females	385,777	56	34,359	66	96,180	47	6,655	58
Ethnicity								
White	679,481	99	51,196	99	193,945	94	10,878	95
Black	1,733	<1	170	<1	2,914	1	214	2
Mixed	340	<1	25	<1	577	1	35	<1
Asian	3,265	<1	172	<1	6,378	3	248	2
Other	2,509	<1	170	<1	2,071	1	75	<1
Age at diagnosis	70	(7.7)	82.7	(7.1)	71	(7.0)	81.4	(6.9)
Smoking status[a]								
Never smokers	365,334	53	32,797	63	87,325	42	4,881	43
Current smokers	117,116	17	4,943	9	26,814	13	972	8
Ex-smokers	109,539	16	8,995	17	51,127	29	2,653	23
BMI category[b]								
Underweight	26,587	4	4,907	9	842	<1	80	<1
Normal	242,055	35	19,100	37	21,112	10	1,471	13
Overweight	185,401	27	8,991	17	46,183	22	2,373	21
Obese	72,016	10	2,899	6	62,239	30	2,298	20
Alcohol consumption[c]								
0	99,633	20	8,077	24	66,918	32	3,656	32
(0,14] units /week	262,107	53	15,427	46	65,994	32	3,032	26
(14,42]units/week	37,447	7	1,254	3	14,923	7	430	4
42+ units/ week	95,097	19	8,743	26	2,825	1	153	1

LOD: Late-onset dementia a) 95,339 (14 %) individuals without LOD and 4,998 (10 %) with LOD in the non- T2DM and 32,619 (16%) individuals without LOD and 2,944 (25%) with LOD in the T2DM cohort, did not have smoking status .b) 161,269 (23%) individuals without LOD and 15,836 (31 %) with LOD in the non-T2DM and 75,509 (37 %) individuals without LOD and 5,228 (46 %) with LOD in the T2DM cohort did not have BMI data available .c) 193,044(28%) individuals without LOD and 18,232(35%) with LOD in the non-T2DM and 55,225 (27 %) individuals without LOD and 4,179 (36 %) with LOD in the T2DM cohort did not have alcohol consumption data.

In the T2DM cohort, 2,341 (20 %) met the criteria for probable AD, 48 (1 %) for possible AD and 9,061 (79 %) for other LODs. Of the 9,061 individuals in the other LOD group, 3,201 (35 %) were reported as vascular dementia (VaD), 191(2 %) had Parkinson's disease dementia (PDD) and Lewy body dementia (LBD) and 5,669 (63 %) were classified as having "unspecified dementia".

The unspecified dementia group consisted of 1,540 (27 %) individuals who had codes for a dementia drug and 4,129 (73 %) with dementia monitoring codes and codes for senile dementia of unspecified type. In the non-T2DM cohort, 14,033 (27 %) cases were classified as probable AD, 1,937 (4 %) as possible AD and 35,763 (69 %) as other LODs. Similar to the T2DM cohort, the majority of cases (29,614 (83 %)) were reported as cases of "unspecified dementia". The diagnosis of VaD was made in 5,503 (15 %) individuals and 646 (2 %) were reported as PDD and LBD. The unspecified dementia group consisted of 2,730 (9 %) individuals who had codes for a dementia drug and 26,884 (91 %) had codes for dementia monitoring and codes for senile dementia of unspecified type. Table 20 summarizes the distribution of overall LOD and specific LOD types by age and sex.

Table 20: Distribution of LOD type by age and sex in both T2DM and non-T2DM cohorts.

	NON-T2DM cohort					T2DM cohort				
LOD types	N (%)	65 to 69 yrs old	70 to 74 yrs old	75 to 79 yrs old	80 and above	N (%)	65 to 69 yrs old	70 to 74 yrs old	75 to 79 yrs old	80 and above
Probable AD	**14,033(27)**	**698**	**1,630**	**2,917**	**8,788**	**2,341(20)**	**120**	**268**	**559**	**1,394**
Male	4,301(40)	292	601	1,027	2,381	937(40)	65	134	253	485
Female	9,732(70)	406	1,029	1,890	6,407	1,404(60)	55	134	306	909
Possible AD	**1,937(4)**	**56**	**196**	**363**	**1,322**	**48 (<1)**	**4**	**8**	**16**	**20**
Male	621(22)	21	71	148	381	23(48)	2	4	8	9
Female	1,316(68)	35	125	215	9415	25(52)	2	4	8	11
Other LOD	**35,763(69)**	**1,539**	**3,079**	**5,672**	**25,473**	**9,061(79)**	**474**	**1,044**	**1,868**	**5,675**
Male	12,452(42)	809	1,471	2,409	7,763	3,835(42)	278	581	923	2,053
Female	23,311(58)	730	1,608	3,263	17,710	5,226(58)	196	463	945	3,622
VaD	**5,503(15)**	**152**	**434**	**972**	**3,945**	**3,201(35)**	**136**	**369**	**745**	**1,951**
Male	2,150(39)	92	249	436	1,373	1,470(46)	80	214	381	795
Female	3,353(61)	60	185	536	2,572	1,731(54)	56	155	364	1,156
LBD AND PDD	**646(2)**	**37**	**108**	**148**	**353**	**191(2)**	**12**	**34**	**60**	**85**
Male	373(55)	28	72	90	183	125(65)	10	28	38	49
Female	273(42)	9	36	58	170	46(35)	2	6	22	36
Unspecified dementia	**29,614(83)**	**1,350**	**2,537**	**4,552**	**21,175**	**5,669(62)**	**326**	**641**	**1,063**	**3,639**
Male	9,929(33)	689	1,150	1,883	6,207	2,240	188	339	504	1,209
Female	19,685(65)	661	1,387	2,669	14,968	3,429	138	302	559	2,430
Overall LOD	**51,733**	**2,291**	**4,892**	**8,943**	**35,607**	**11,450**	**598**	**1,320**	**2,443**	**7,089**
Male	17,374	1,122	2,137	3,584	10,531	4,795	345	719	1,184	2,547
Female	34,359	1,169	2,755	5,359	25,076	6,655	253	601	1,259	4,542

LOD: Late-onset dementia AD: Alzheimer's disease, VaD: Vascular disease dementia, LBD: Lewy body disease dementia, PDD: Parkinson's disease dementia

4.3.2 Incidence rate of LOD in non-T2DM and T2DM cohorts

There were a total of 51,733 and 11,450 incident cases of LOD during follow up in the non-T2DM and T2DM cohorts, respectively. In the non-T2DM cohort, the overall incidence rate of LOD was 7.15 per 1,000 person years in males and 10.04 per 1,000 person years in females. The incidence increased with age, with the highest overall incidence rate observed among females aged 80 and above (19.99 per 1,000 person years). Females evidently had a higher incidence rate when compared to males, in both non-T2DM and T2DM cohorts (Table 21). The incidence rate of overall LOD in the T2DM cohort did not differ substantially from the non-T2DM cohort. In the T2DM cohort, the overall LOD incidence rate was 6.96 per 1,000 person years in males and 10.57 per 1,000 person years in females. Similar to the non-T2DM cohort, the highest overall incidence rate was among females in the 80 years and above age group (21.06 per 1,000 person years) (Table 21).

Upon investigating the different LOD categories, similar patterns of incidence to that of the overall LOD were observed. There was a higher incidence of different LOD types with increasing age, particularly among females. The incidence for probable AD in the non-T2DM and T2DM cohorts was 2.40 and 1.77 per 1,000 person years, respectively; for possible AD, the incidence was 0.33 and 0.04 per 1,000 years respectively and for, other LOD forms, the incidence was 6.11 and 6.87 respectively. Further exploration of the "other LOD" group was conducted, to unravel variations in incidence among the other types of LOD. As expected, the incidence rate of VaD was higher in the T2DM cohort (2.43 per 1,000 person years) compared to the non-T2DM cohort (0.94 per 1,000 person years). Similarly, the incidence rate of PDD and LBD was slightly higher in the T2DM cohort (0.14 per 1,000 person years) compared to the non-T2DM cohort (0.11 per 1,000 person years), with higher rates observed among males. With regards to unspecified dementia, the incidence rate was higher among the non-T2DM cohort group (5.06 per 1,000 person years), particularly among females (11.93 per 1,000 person years). However, the unspecified dementia group represents LOD patients for whom the GPs did not specify a dementia type. Therefore, they may well correspond to either possible AD or VaD or, indeed, cases of mixed pathologies. A summary of the incidence rates for overall LOD and specific LOD types can be found in Tables 21 and 22.

Table 21: Incidence rate (95%CI) of overall LOD stratified by age and sex in both T2DM and non-T2DM cohorts.

	NON-T2DM COHORT		T2DM COHORT	
	Rate	95% CI	Rate	95% CI
Males (age yrs)				
65-69	1.76	(1.66-1.86)	2.04	(1.83-2.27)
70-74	3.35	(3.21-3.49)	3.67	(3.41-3.95)
75-79	7.10	(6.87-7.33)	7.36	(6.95-7.79)
80 and above	16.11	(15.81-16.42)	15.16	(14.58-15.76)
Females (age yrs)				
65-69	1.65	(1.56-1.75)	2.10	(1.86-2.39)
70-74	3.58	(3.45-3.72)	3.97	(3.66-4.30)
75-79	7.71	(7.50-7.92)	8.41	(7.96-8.90)
80 and above	19.99	(19.75-20.24)	21.06	(20.46-21.68)
Overall	8.84	(8.77-8.92)	8.68	(8.53-8.85)

Table 22: Incidence rates (95%CI) of possible AD, probable AD and other LODs stratified by age and sex in both T2DM and non-T2DM cohorts.

		NON-T2DM COHORT		T2DM COHORT	
POSSIBLE AD	Age (YRS)	Rate	95% CI	Rate	95% CI
Males	65-69	0.03	(0.02-0.05)	0.01	(0.00-0.04)
	70-74	0.10	(0.08-0.13)	0.02	(0.00-0.03)
	75-79	0.29	(0.25-0.34)	0.05	(0.01-0.04)
	80 and above	0.59	(0.53-0.65)	0.05	(0.00-0.00)
Females	65-69	0.05	(0.03-0.06)	0.02	(0.00-0.06)
	70-74	0.15	(0.13-0.18)	0.03	(0.01-0.07)
	75-79	0.30	(0.30-0.34)	0.05	(0.03-0.11)
	80 and above	0.76	(0.71-0.81)	0.05	(0.03-0.09)
Overall		0.33	(0.32-0.35)	0.04	(0.03-0.05)
PROBABLE AD					
Males	65-69	0.45	(0.40-0.51)	0.38	(0.30-0.49)
	70-74	0.95	(0.88-1.03)	0.68	(0.58-0.81)
	75-79	2.03	(1.91-2.15)	1.57	(1.39-1.78)
	80 and above	3.65	(3.50-3.80)	2.88	(2.63-3.15)
Females	65-69	0.57	(0.52-0.63)	0.47	(0.36-0.61)
	70-74	1.34	(1.26-1.42)	0.87	(0.74-1.04)
	75-79	2.72	(2.60-2.85)	2.06	(1.84-2.30)
	80 and above	5.11	(4.99-5.24)	4.21	(3.94-4.49)
Overall		2.40	(2.36-2.44)	1.77	(1.70-1.85)
OTHER LOD					
Males	65-69	1.27	(1.19-1.36)	1.64	(1.46-1.85)
	70-74	2.30	(2.18-2.42)	2.96	(2.73-3.21)
	75-79	4.78	(4.59-4.97)	5.73	(5.37-6.11)
	80 and above	11.88	(11.61-12.14)	12.23	(11.71-12.76)
Females	65-69	1.03	(0.96-1.11)	1.62	(1.40-1.87)
	70-74	2.09	(1.99-2.20)	3.07	(2.80-3.36)
	75-79	4.69	(4.53-4.85)	6.30	(5.91-6.72)
	80 and above	14.11	(13.91-14.33)	16.80	(16.26-17.35)
Overall		6.11	(6.05-6.18)	6.87	(6.73-7.02)

LOD: Late-onset Dementia, AD: Alzheimer's disease

4.4 Cancer and risk of LOD in non-T2DM and T2DM cohorts

4.4.1 LOD Cases identified by cancer status

Tables 23 and 24 summarize the distribution of different cancer types by LOD sub-groups in non-T2DM and T2DM cohorts. To investigate the risk of LOD in individuals with and without cancer, 1,535 individuals who had cancer post LOD diagnosis in the non-T2DM cohort, were excluded. In the T2DM cohort, there were no individuals with a diagnosis of cancer following a diagnosis of LOD.

In the T2DM cohort, among 32,022 individuals with cancer, there was a diagnosis of LOD in 1,172 (4 %), compared to 10,278 LOD cases (6 %) in 185,313 individuals without cancer. In the non-T2DM cohort, 10,602 (6 %) individuals were diagnosed with LOD among 163,737 cancer participants; compared to 39,596 (7 %) LOD cases identified in 573,789 individuals without cancer. In the majority of cases, cancer diagnosis was made in individuals aged ≥65 years old; the highest number of LOD cases involved the non-melanoma skin (40 %) and breast (12 %) cancer groups, and the lowest number of LOD cases observed in the lung cancer group (1 %). In comparison, the highest number of LOD cases in the T2DM cohort group were in the melanoma skin cancer group (7%) and the lowest number of LOD cases identified was, again, in the lung cancer group (<1%).

Table 23: Distribution of different cancer types by LOD categories, in the non-T2DM cohort.

Non-T2DM	No. (%)	Diagnosis of LOD (%)			
		All LODs	Probable AD	Possible AD	Other LOD
Lung Cancer	9,599 (6)	166(1)	34(1)	3(1)	129(2)
Breast Cancer	16,534(10)	1,219(12)	330(12)	42(10)	847(11)
Prostate Cancer	15,520(9)	905(8)	206(9)	32(8)	667(9)
NMS Cancer	49,726(30)	4,267(40)	1,100(42)	183(45)	2,984(39)
MS Cancer	4,927(4)	409(4)	112(4)	13(3)	284(4)
Bowel Cancer	13,309(8)	829(8)	188(7)	33(9)	608(8)
Other Cancers	54,122(33)	2,807(27)	674(25)	99(24)	2034(27)
Total	163,737	10,602	2,644	405	7,553

LOD: Late-onset dementia AD: Alzheimer's disease, NMS cancer: Non-melanoma skin cancer, MS cancer: melanoma skin cancer

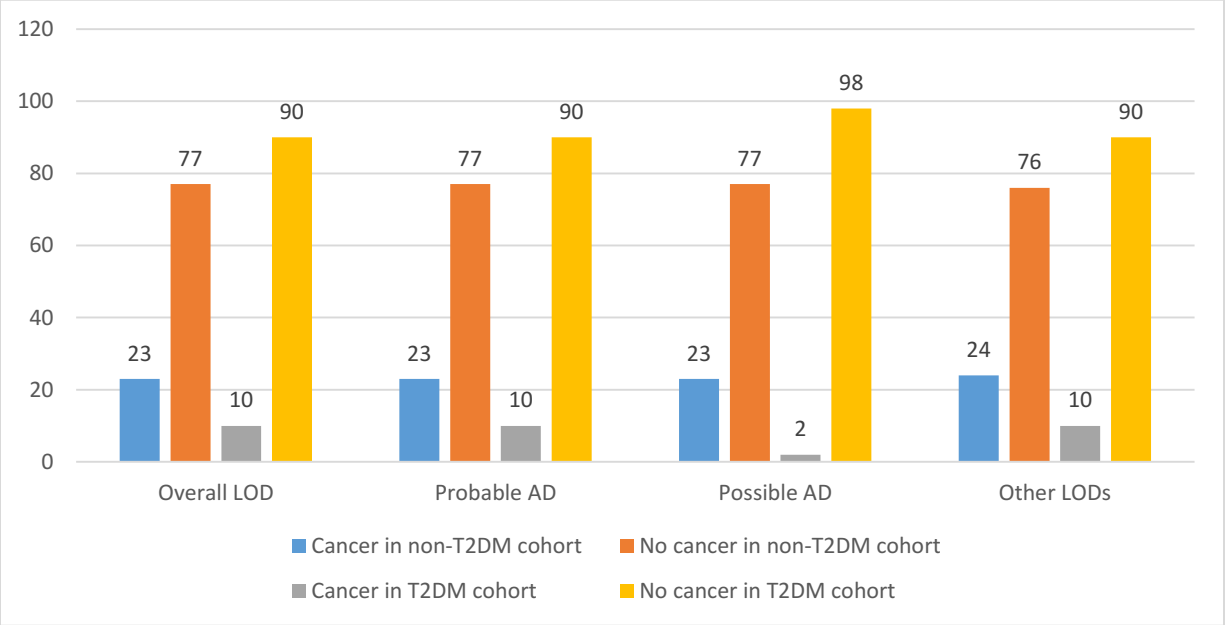
Table 24: Distribution of different cancer types by LOD categories, in the T2DM cohort.

T2DM	No. (%)	Diagnosis of LOD (%)			
		All LOD	Probable AD	Possible AD	Other LOD
Lung Cancer	2,754(8)	23(2)	3(1)	0	20(2)
Breast Cancer	2,408(7)	111(9)	17(7)	0	94(10)
Prostate Cancer	3,679(11)	161(14)	42(18)	0	119(13)
NMS Cancer	6,639(21)	348(30)	74(31)	0	274(29)
MS Cancer	2,135(7)	142(12)	21(9)	1	120(13)
Bowel Cancer	3,214(10)	98(8)	25(10)	0	73(8)
Other Cancers	11,193(36)	289(25)	55(23)	0	234(25)
Total	32,022	1,172	237	1	934

LOD: Late-onset dementia, AD: Alzheimer's disease, NMS cancer: Non-melanoma skin cancer, MS cancer: melanoma skin cancer

Figure 12 illustrates the distribution of overall LOD and LOD types by cancer status. There were fewer individuals identified as having both LOD and cancer, compared to LOD diagnosis in individuals without cancer, in both non-T2DM and T2DM cohorts. In the T2DM cohort, 10 % of the 11,450 LOD cases vs. 23 % of the 51,733 LOD cases in the non-T2DM cohort, had a history of cancer.

Figure 12: Distribution (%) of overall LOD and LOD types by cancer status in T2DM and non-T2DM cohorts.



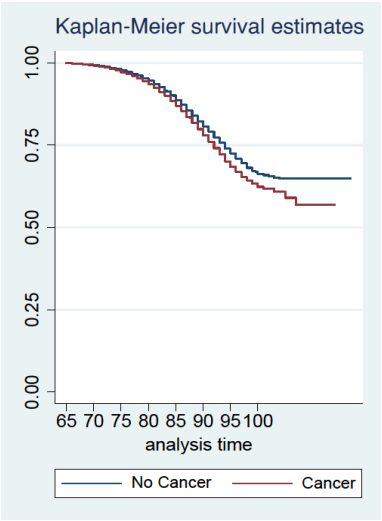
LOD: Late-onset dementia, AD: Alzheimer's disease,

4.4.2 Kaplan-Meier estimates of time to LOD by cancer status

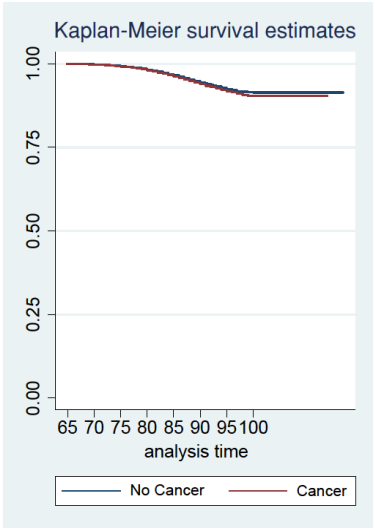
The Kaplan-Meier estimates revealed somewhat conflicting findings in both non-T2DM and T2DM cohorts. In the non-T2DM cohort, the cancer group showed a higher rate for overall LOD and probable AD. Conversely, in the T2DM cohort, it appeared that the non- cancer group had a higher rate for LOD and probable AD, compared to the cancer group. On the other hand, the number of individuals with incident diagnosis of possible AD was too small (1,937 and 48 individuals in the non-T2DM and T2DM cohorts, respectively) to allow for any inferences to be made from their inconclusive Kaplan-Meier survival estimate plots (Figure 13).

Figure 13: A. Kaplan Meier estimate plots for overall LOD in non-T2DM (A1) and T2DM (A2) cohorts. B. Kaplan Meier estimate plots for probable AD in non-T2DM (B1) and T2DM (B2) cohorts C. Kaplan Meier estimate plots for possible AD in non-T2DM (C1) and T2DM (C2) cohorts

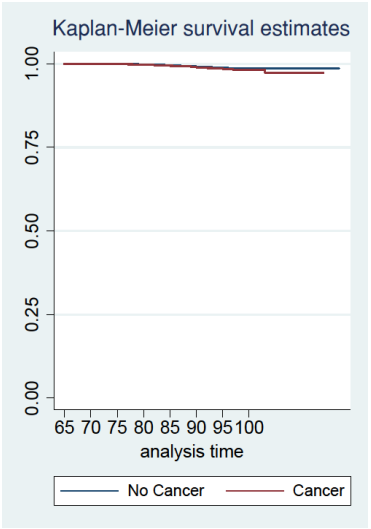
A1.



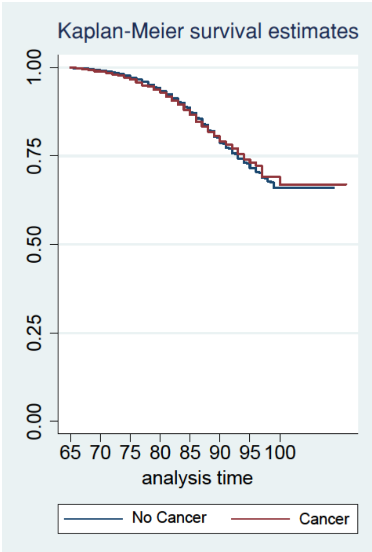
B1.



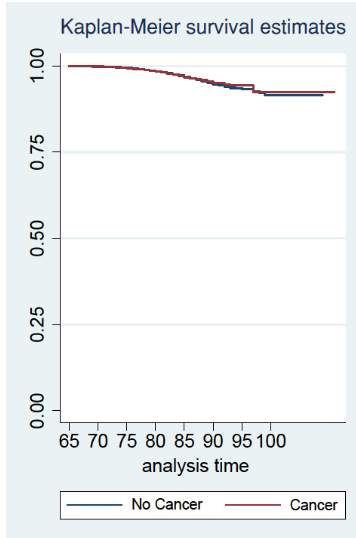
C1.



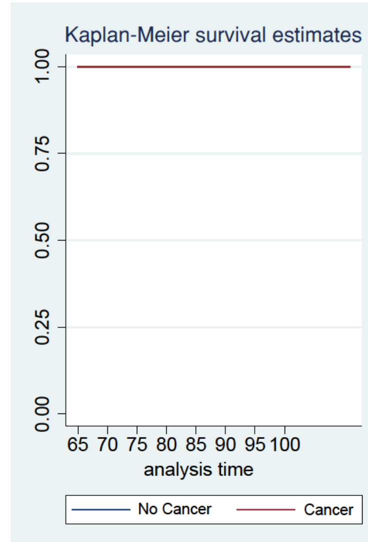
A2.



B2.



C2.



4.4.3 Hazard ratios of LOD and cancer in relation to clinical and demographic factors

Cox proportional hazard models, with age as the time- scale, were used to investigate the HR and 95 % CIs for overall LOD was first investigated with relation to various clinical and demographic factors. Participants who were females [non-T2DM: HR 1.16, 95 % CI (1.13-1.18), T2DM: HR 1.17, 95 % CI (1.11-1.24)], of black ethnicity [non-T2DM: HR 1.85 , 95 % CI (1.54-2.22), T2DM: HR 1.60 ,95 % CI (1.29-1.98)] and underweight [non-T2DM: HR 1.53, 95 % CI (1.48-1.58), T2DM: HR 1.39 ,95 % CI (1.07-1.80)] at baseline were at higher risk for overall LOD in both cohorts (Table 25). Furthermore, participants with a history of depression [non-T2DM: HR 1.79, 95 % CI (1.74-1.83), T2DM: HR 1.64 , 95 % CI (1.55-1.73)], brain injury [non-T2DM: HR 2.12, 95 % CI (1.97-2.27), T2DM: HR 2.10, 95 % CI (1.78-2.49)], hypercholesterolemia [non-T2DM: HR 1.11, 95 % CI (1.07-1.14), T2DM: HR 1.09 , 95 % CI (1.03-1.15)] and CeVD[non-T2DM: HR 1.10, 95 % CI (1.08-1.13), T2DM: HR 1.03 , 95 % CI (0.98-1.09)] were at a higher risk of overall LOD (Table 25). Individuals with a history of hypertension had a 12 % and 17 % lower risk for overall LOD in the non-T2DM [HR 0.88, 95 % CI (0.85-0.90)] and T2DM [HR 0.83, 95 % CI (0.78-0.89)] cohorts, respectively (Table 25). The models were repeated for probable AD categorized individuals. Different findings to that of overall LOD were observed, however, this could be attributed to the low incidence found in this group. I have omitted presenting the results for the possible AD group and only presented the probable AD group, as there were only 1,937 and 48 individuals identified with incident diagnoses of possible AD in the non-T2DM and T2DM cohorts,

respectively (Table 26).The results for VaD and unspecified dementia were additionally tabulated, as they made up the majority of the overall LOD cases (Tables 27 and 28).

Table 25: Hazard ratios (95% CI) of overall LOD stratified by different demographic and lifestyle variables in the T2DM and non-T2DM cohorts.

	T2DM COHORT N= 217, 335 (11,450 with overall LOD)		NON-T2DM COHORT N=739,061 (51,733 with overall LOD)	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Sex				
Male	Ref		Ref	
Female	1.17(1.11-1.24)	P<0.0001	1.15 (1.12-1.18)	P<0.0001
Ethnicity				
White	Ref		Ref	
Mixed	1.59(0.98-2.58)	0.058	1.25(0.77-2.03)	0.371
Asian	1.18(0.98-1.43)	0.071	0.90(0.73-1.10)	0.311
Black	1.60(1.29-1.98)	P<0.0001	1.88(1.54-2.30)	P<0.0001
Other	1.00(0.71-1.39)	0.982	1.03(0.83-1.27)	0.797
BMI				
Underweight	1.39 (1.07-1.80)	0.013	1.49 (1.44-1.55)	P<0.0001
Normal	Ref		Ref	
Overweight	0.86 (0.80-0.92)	P<0.0001	0.78 (0.76-0.80)	P<0.0001
Obese	0.83 (0.78-0.90)	P<0.0001	0.74 (0.71-0.78)	P<0.0001
Smoking				
Never	Ref		Ref	
Current	1.05(0.96-1.15)	0.262	1.04 (1.00-1.08)	0.024
Ex	0.96(0.91-1.02)	0.220	1.05 (1.00-1.10)	0.044
Alcohol consumption				
0	Ref		Ref	
(0,14] units /week	0.91(0.86-0.96)	0.001	0.83(0.80-0.85)	P<0.0001
(14,42] units/week	0.81(0.72-0.91)	P<0.0001	0.74(0.69-0.79)	P<0.0001
42+ units/ week	1.15(0.86-1.55)	0.332	1.08(1.04-1.12)	P<0.0001
Depression				
No	Ref		Ref	
Yes	1.64(1.55-1.73)	P<0.0001	1.79(1.74-1.83)	P<0.0001
Brain Injury				
No	Ref		Ref	
Yes	2.10(1.78-2.49)	P<0.0001	2.12(1.97-2.27)	P<0.0001
Hypertension				
No	Ref		Ref	
Yes	0.83(0.78-0.89)	P<0.0001	0.88(0.85-0.90)	P<0.0001
CeVD				
No	Ref		Ref	
Yes	1.03(0.98-1.09)	0.216	1.10(1.08-1.13)	P<0.0001
Hypercholesterolemia				
No	Ref		Ref	
Yes	1.09(1.03-1.15)	0.004	1.11(1.07-1.14)	P<0.0001

CeVD: Cerebrovascular disease

Table 26: Hazard ratios (95 %CI) of probable AD stratified by different demographic ad lifestyle variables in the T2DM and non-T2DM cohorts.

	T2DM COHORT N= 217, 335 (2,341 with probable AD)		NON-T2DM COHORT N=739,061 (14,033 with probable AD)	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Sex				
Male	Ref		Ref	
Female	1.42(1.27-1.60)	P<0.0001	1.37 (1.30-1.45)	P<0.0001
Ethnicity				
White	Ref		Ref	
Mixed	0.77(0.19-3.08)	0.713	1.13(0.42-3.05)	0.803
Asian	0.91(0.58-1.43)	0.682	0.84(0.56-1.26)	0.396
Black	1.48(0.94-2.34)	0.092	1.57(1.03-2.39)	0.034
Other	0.98(0.49-1.95)	0.949	1.02(0.67-1.56)	0.917
BMI				
Underweight	1.08 (0.60-1.94)	0.790	1.42 (1.32-1.54)	P<0.0001
Normal	Ref		Ref	
Overweight	0.75 (0.65-0.87)	P<0.0001	0.67 (0.63-0.71)	P<0.0001
Obese	0.69 (0.59-0.80)	P<0.0001	0.60 (0.55-0.67)	P<0.0001
Smoking				
Never	Ref		Ref	
Current	0.89(0.78-1.00)	0.061	0.77(0.71-0.83)	P<0.0001
Ex	0.82(0.67-1.00)	0.056	0.88(0.83-0.94)	P<0.0001
Alcohol consumption				
0	Ref		Ref	
(0,14] units /week	0.90(0.80-1.02)	0.099	0.87(0.82-0.93)	P<0.0001
(14,42] units/week	0.73(0.56-0.94)	0.015	0.73(0.64-0.84)	P<0.0001
42+ units/ week	0.44(0.16-1.19)	0.107	1.09(1.01-1.13)	0.025
Depression				
No	Ref		Ref	
Yes	1.49(1.322-1.68)	P<0.0001	1.65(1.56-1.73)	P<0.0001
Brain Injury				
No	Ref		Ref	
Yes	1.27(0.81-2.00)	0.297	1.74(1.50-2.03)	P<0.0001
Hypertension				
No	Ref		Ref	
Yes	0.80(0.70-0.92)	0.001	0.73(0.70-0.77)	P<0.0001
CeVD				
No	Ref		Ref	
Yes	0.68(0.60-0.76)	P<0.0001	0.73(0.69-0.77)	P<0.0001
Hypercholesterolemia				
No	Ref		Ref	
Yes	1.22(1.08-1.38)	0.001	1.06(0.99-1.13)	0.069

CeVD: Cerebrovascular disease

Participants in the non-T2DM cohort were at a higher risk for vascular dementia (VaD) if they were males [HR 1.11, 95 % CI (1.02-1.20)], underweight [HR 1.22, 95 % CI (1.07-1.39)], current smokers [HR 1.44, 95 % CI (1.30-1.61)] or ex-smokers [HR 1.24, 95 % CI (1.13-1.47)] at baseline. History of depression [HR 1.74, 95 % CI (1.60-1.89)], hypertension [HR 1.15, 95 % CI (1.06-1.25)] and hypercholesterolemia [HR 1.16, 95 % CI (1.05-1.29)] also increased the risk for VaD. History of brain injury [HR 3.16, 95 % CI (2.63-3.80)] and CeVD [HR 2.37, 95 % CI (2.18-2.57)], showed a 2 to 3 fold increase on the risk of VaD (Table 27). Conversely, in the T2DM cohort there were no sex, ethnicity and BMI differences for risk of VaD. However, smokers [HR 1.28, 95 % CI (1.09-1.50)] and individuals who consumed 42+ units of alcohol/ week [HR 1.71, 95 % CI (1.09-2.68)] (at baseline) were at a higher risk for VaD. Similar to the non-T2DM cohort, the T2DM cohort showed an increased risk for VaD in individuals with a history of depression [HR 1.62, 95 % CI (1.46-1.79)], brain injury [HR 3.14, 95 % CI (2.44-4.04)] and CeVD [HR 1.66, 95 % CI (1.50-1.85)] but there were no differences observed for risk of VaD in individuals with hypertension and hypercholesterolemia, compared to individuals without (Table 27).

Patients with unspecified dementia showed similar results to the overall LOD group. Individuals who were females [non-T2DM: HR 1.13, 95 % CI (1.09-1.17), T2DM: HR 1.23, 95 % CI (1.13-1.33)], of black ethnicity [non-T2DM: HR 2.27 ,95 % CI (1.78-2.90), T2DM: HR 1.77 ,95 % CI (1.30-2.41)] and underweight [non-T2DM: HR 1.58, 95 % CI (1.50-1.66), T2DM: HR 1.56 ,95 % CI (1.09-2.25)] at baseline were at higher risk for overall LOD in both cohorts (Table 28). Participants with a history of depression [non-T2DM: HR 1.86, 95 % CI (1.79-1.82), T2DM: HR 1.74, 95 % CI (1.60-1.89)] and brain injury [non-T2DM: HR 2.10, 95 % CI (1.92-2.31), T2DM: HR 1.82, 95 % CI (1.38-2.38)] were also at a higher risk for overall LOD. Increased risk of unspecified dementia in the presence of hypercholesterolemia [HR 1.11, 95 % CI (1.06-1.15)] and CeVD [HR 1.17, 95 % CI (1.13-1.21)] was only observed in the non-T2DM cohort. Individuals with a history of hypertension had a 9 % and 21 % lower risk for overall LOD in the non-T2DM [HR 0.91, 95 % CI (0.88-0.94)] and T2DM [HR 0.79, 95 % CI (0.72-0.87)] cohorts, respectively (Table 28).

Table 27: Hazard ratios (95%CI) of vascular dementia (VaD) stratified by different demographic and lifestyle variables in the T2DM and non-T2DM cohorts.

	T2DM COHORT N= 217, 335 (3,201 with VaD)		NON-T2DM COHORT N=739,061 (5,503 with VaD)	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Sex				
Male	Ref		Ref	
Female	1.00(0.91-1.11)	0.946	0.90 (0.83-0.98)	0.012
Ethnicity				
White	Ref		Ref	
Mixed	1.77(0.72-4.30)	0.210	1.96(0.48-7.96)	0.346
Asian	1.13(0.79-1.62)	0.493	0.56(0.25-1.27)	0.170
Black	1.45(0.97-2.18)	0.070	0.67(0.25-1.79)	0.422
Other	0.85(0.44-1.65)	0.643	0.44(0.18-1.06)	0.068
BMI				
Underweight	1.39 (0.85-2.28)	0.186	1.22 (1.07-1.39)	0.003
Normal	Ref		Ref	
Overweight	0.93 (0.81-1.06)	0.276	0.82 (0.75-0.90)	P<0.0001
Obese	0.95 (0.59-0.80)	0.510	0.78 (0.67-0.90)	0.001
Smoking				
Never	Ref		Ref	
Current	1.28(1.09-1.50)	0.002	1.44(1.30-1.61)	P<0.0001
Ex	1.00(0.90-1.50)	0.950	1.24(1.13-1.37)	P<0.0001
Alcohol consumption				
0	Ref		Ref	
(0,14] units /week	0.92(0.83-1.02)	0.126	0.78(0.71-0.86)	P<0.0001
(14,42] units/week	0.85(0.68-1.05)	0.138	0.90(0.74-1.09)	0.273
42+ units/ week	1.71(1.09-2.68)	0.019	0.93(0.83-1.04)	0.227
Depression				
No	Ref		Ref	
Yes	1.62 (1.46-1.79)	P<0.0001	1.74(1.60-1.89)	P<0.0001
Brain Injury				
No	Ref		Ref	
Yes	3.14(2.44-4.04)	P<0.0001	3.16(2.63-3.80)	P<0.0001
Hypertension				
No	Ref		Ref	
Yes	0.98(0.86-1.11)	0.771	1.15(1.06-1.25)	0.001
CeVD				
No	Ref		Ref	
Yes	1.66(1.50-1.85)	P<0.0001	2.37(2.18-2.57)	P<0.0001
Hypercholesterolemia				
No	Ref		Ref	
Yes	1.03(0.92-1.15)	0.579	1.16(1.05-1.29)	0.003

CeVD: Cerebrovascular disease

Table 28: Hazard ratios (95 %CI) of unspecified dementia stratified by different demographic and lifestyle variables in the T2DM and non-T2DM cohorts.

	T2DM COHORT N= 217, 335 (5,669 with unspecified dementia)		NON-T2DM COHORT N=739,061 (29,614 with unspecified dementia)	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Sex				
Male	Ref		Ref	
Female	1.23(1.13-1.33)	P<0.0001	1.13 (1.09-1.17)	P<0.0001
Ethnicity				
White	Ref		Ref	
Mixed	2.00(1.06-3.78)	0.032	1.29(0.68-2.43)	0.431
Asian	1.42(1.10-1.83)	0.008	0.90(0.69-1.18)	0.461
Black	1.77(1.30-2.41)	P<0.0001	2.27(1.78-2.90)	P<0.0001
Other	1.09(0.67-1.76)	0.734	1.15(0.89-1.49)	0.288
BMI				
Underweight	1.56 (1.09-2.25)	0.016	1.58 (1.50-1.66)	P<0.0001
Normal	Ref		Ref	
Overweight	0.86 (0.77-0.96)	0.007	0.82 (0.79-0.85)	P<0.0001
Obese	0.85 (0.76-0.95)	0.003	0.81 (0.77-0.86)	P<0.0001
Smoking				
Never	Ref		Ref	
Current	1.05(0.92-1.20)	0.447	0.98(0.93-1.03)	0.393
Ex	0.98(0.89-1.07)	0.634	1.02(0.97-1.06)	0.410
Alcohol consumption				
0	Ref		Ref	
(0,14] units /week	0.89(0.82-0.97)	0.008	0.81(0.78-0.85)	P<0.0001
(14,42] units/week	0.81(0.68-0.97)	0.019	0.69(0.63-0.76)	P<0.0001
42+ units/ week	1.23(0.81-1.87)	0.329	1.11(1.06-1.16)	P<0.0001
Depression				
No	Ref		Ref	
Yes	1.74(1.60-1.89)	P<0.0001	1.86(1.79-1.92)	P<0.0001
Brain Injury				
No	Ref		Ref	
Yes	1.82(1.39-2.38)	P<0.0001	2.10(1.92-2.31)	P<0.0001
Hypertension				
No	Ref		Ref	
Yes	0.79(0.72-0.87)	P<0.0001	0.91(0.88-0.94)	P<0.0001
CeVD				
No	Ref		Ref	
Yes	0.93(0.86-1.01)	0.105	1.17(1.13-1.21)	P<0.0001
Hypercholesterolemia				
No	Ref		Ref	
Yes	1.06(0.97-1.16)	0.206	1.11(1.06-1.15)	P<0.0001

CeVD: Cerebrovascular disease

I have additionally applied hazard ratios to evaluate the potential role of several variables on cancer risk before embarking on evaluating the risk of LOD based on cancer types. Variables included demographic data (age, sex, ethnicity), lifestyle variables (BMI, smoking status, alcohol status) and relevant co-morbid diseases, such as hypertension, hypercholesterolemia, CeVD, depression and brain injury. The unadjusted and adjusted HRs and 95 % CIs for the risk of cancer in the presence of various relevant diseases and demographics were computed.

Brain injury [non-T2DM: HR 1.01, 95 % CI (0.94-1.08), p-value:0.823, T2DM: HR 1.05, 95 % CI (0.91-1.21), p-value: 0.522] and depression [non-T2DM: HR 1.03, 95 % CI (1.00-1.05), p-value <0.0001,T2DM: HR 1.00, 95 % CI (0.96-1.03), p-value:0.860] did not have any association with cancer in both cohorts. Similarly, history of hypertension [HR 1.01, 95 % CI (0.99-1.02), p-value: 0.294] and hypercholesterolemia [HR 0.99, 95 % CI (0.97-1.01), p-value: 0.377] had no association with cancer in the non-T2DM cohort. However, in the T2DM cohort hypertension [HR 0.91, 95 % CI (0.88-0.95), p-value <0.05] and hypercholesterolemia [HR 0.90, 95 % CI (0.87-0.93), p-value <0.05] have shown a slight association. Having said that, T2DM is associated with both hypertension and hypercholesterolemia, possibly indicating that the relationship observed is mainly driven by T2DM, rather than by a causal relationship between cancer and hypertension and or hypercholesterolemia.

History of CeVD was found to increase the risk of cancer [non-T2DM: HR 1.15, 95 % CI (1.13-1.17), p-value < 0.05, T2DM: HR 1.09, 95 % CI (1.06-1.13), p-value < 0.05]. Nonetheless, it would be sensible to assume that the association observed is based on shared risk factors rather than a causal relationship between CeVD and cancer. Based on the known associations and shared risk factors between CeVD and diabetes, it is plausible that the conflicting results observed for these variables in relation to cancer, are mainly driven by differences in the distribution of risk factors between the two cohorts.

Based on my literature review and reported hypotheses on shared risk factors between LOD and cancer, the following possible confounders were included in my analysis: age, sex, BMI and smoking status. The final analyses were carried out controlling for age, sex, smoking and BMI.

The unadjusted and adjusted HRs, along with their 95 % CIs, for overall LOD in individuals without and with cancer were computed.

4.4.4 Hazard ratios investigating the incidence of LOD by cancer status

(a) Hazard ratio for overall LOD by cancer status

During a mean observation period of 7.91 (5.32) years, the crude hazard of LOD in individuals with cancer was 1.16 [95 % CI (1.13-1.20)] fold higher than for individuals with no cancer diagnosis, in the non-T2DM cohort. Similar results were observed when investigating specific types of cancers. The highest risk for overall LOD was observed in individuals with breast cancer [HR of 1.30, 95 % CI (1.20-1.41)]. There was no observed association between risk for overall LOD and lung cancer, as well as melanoma skin cancer (Table 29). After adjusting for sex, BMI and smoking, the cox proportional hazard regression showed similar results to that of the unadjusted HR models. Individuals with overall cancer (and specific types of cancer except for lung and melanoma skin cancer) had a higher risk for overall LOD compared to individuals without cancer. In the adjusted model, the highest risk for LOD was now observed among individuals with prostate cancer [HR 1.32, 95 % CI (1.20-1.43)] in addition to breast cancer [HR 1.25 , 95 % CI (1.15-1.35)] (Tables 29 and 30).

In the T2DM cohort, 11,450 individuals were diagnosed with overall LOD during a mean observation period of 6.06 (4.17) years. No association was observed between cancer, the majority of cancer types and the risk for subsequent overall LOD. However, individuals with lung cancer had a significantly lower risk for developing overall LOD, even after adjusting for possible confounders, compared to individuals without cancer [HR 0.52, 95 % CI (0.29-0.94)] (Table 29) and other types of cancer [HR 0.50 , 95 % CI (0.28-0.91)] (Table 30).

Table 29: Hazard ratios (95 %CI) of overall LOD in individuals with different types of cancer in T2DM and non-T2DM cohorts (compared to no cancer)

	T2DM COHORT		NON-T2DM COHORT	
	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value
Overall Cancer	1.00 (0.92-1.08) 0.993	1.03(0.95-1.11) 0.517	1.16(1.13-1.20) P<0.0001	1.17(1.14-1.21) P<0.0001
Breast Cancer	0.93(0.70-1.22) 0.587	0.94(0.71-1.23) 0.643	1.30(1.20-1.41) P<0.0001	1.25(1.15-1.35) P<0.0001
Lung Cancer	0.52 (0.29-0.94) 0.030	0.52(0.29-0.94) 0.032	1.05(0.85-1.29) 0.634	1.05(0.86-1.30) 0.600
Prostate Cancer	1.17(0.96-1.44) 0.107	1.17(0.96-1.43) 0.119	1.18(1.08-1.29) P<0.0001	1.31(1.20-1.43) P<0.0001
NMS Cancer	1.07(0.93-1.23) 0.308	1.11(0.97-1.28) 0.127	1.19(1.14-1.95) P<0.0001	1.19(1.14-1.24) P<0.0001
MS Cancer	1.05(0.84-1.30) 0.662	1.06(0.86-1.32) 0.573	1.03(0.91-1.17) 0.605	1.05(0.92-1.18) 0.471
Bowel Cancer	0.91(0.70-1.17) 0.451	0.92(0.71-1.19) 0.538	1.13(1.03-1.24) 0.010	1.14(1.04-1.25) 0.006

† Computed using stratified Cox proportion Hazard regression adjusted by age. NMS: Non-melanoma skin cancer, MS: Melanoma skin cancer

ǂ Adjusted additionally for sex (excluding breast and prostate cancers), BMI and smoking

Table 30: Hazard ratios (95 %CI) of overall LOD in individuals with different types of cancer in T2DM and non-T2DM cohorts (compared to other cancers)

	T2DM COHORT		NON-T2DM COHORT	
	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value
Breast Cancer	0.92(0.69-1.22) 0.571	0.92(0.69-1.23) 0.594	1.13 (1.04-1.23) 0.003	1.07(0.98-1.16) 0.110
Lung Cancer	0.51(0.28-0.93) 0.028	0.50(0.28-0.91) 0.023	0.90(0.73-1.11) 0.328	0.90(0.73-1.11) 0.314
Prostate Cancer	1.21(0.98-1.50) 0.080	1.19(0.96-1.48) 0.104	1.01(0.93-1.11) 0.765	1.12(1.03-1.23) 0.011
NMS Cancer	1.11(0.94-1.30) 0.218	1.12(0.95-1.32) 0.166	1.03(0.98-1.08) 0.268	1.02(0.97-1.08) 0.346
MS Cancer	1.06(0.84-1.33) 0.639	1.04(0.83-1.31) 0.729	0.88(0.78-1.00) 0.047	0.88(0.78-1.00) 0.057
Bowel Cancer	0.90(0.69-1.17) 0.428	0.89(0.68-1.16) 0.387	0.97(0.88-1.06) 0.481	0.96(0.88-1.06) 0.464

† Computed using stratified Cox proportion Hazard regression adjusted by age. NMS: Non-melanoma skin cancer, MS: Melanoma skin cancer

ǂ Adjusted additionally for sex (excluding breast and prostate cancers), BMI and smoking

(b) Hazard ratio for probable AD by cancer status

Similar to overall LOD, individuals with cancer in the non-T2DM cohort had a higher risk for developing probable AD [HR 1.12, 95 % CI (1.06-1.19)]. The highest risk for probable AD was observed in individuals with breast cancer [HR 1.37, 95 % CI (1.18-1.59)] and prostate cancer [HR 1.25, 95 % CI (1.04-1.49)]. After adjusting for possible confounders, there was no significant difference in risk for probable AD between the lung cancer [HR 0.62, 95 % CI (0.36-1.05)], melanoma skin cancer [HR 1.10, 95 % CI (0.87-1.39)], bowel cancer groups [HR 0.94, 95 % CI (0.77-1.14)] and the no cancer group (Table 31).

In the T2DM cohort, there was no significant difference in the risk for probable AD between cancer (and specific types of cancer) and the no cancer group, with one exception; participants in the prostate cancer group appeared to have a higher risk for developing probable AD compared to individuals with other types of cancers [HR 1.74, 95 % CI (1.13-2.67)] and the no cancer group [HR 1.52,95 % CI (1.03-2.25)] (Tables 31 and 32).

As mentioned previously, the incidence of possible AD was too low to calculate separate estimates and, therefore, results will not be presented.

Table 31: Hazard ratios (95 %CI) of probable AD in individuals with different types of cancer in T2DM and non-T2DM cohorts (compared to no cancer)

	T2DM COHORT		NON-T2DM COHORT	
	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ‡ p-value	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ‡ p-value
Overall Cancer	0.96 (0.80-1.15) 0.659	1.00(0.83-1.20) 0.973	1.10(1.37-1.66) 0.002	1.12(1.06-1.19) P<0.0001
Breast Cancer	0.54(0.24-1.21) 0.136	0.54(0.24-1.22) 0.139	1.39(1.20-1.62) P<0.0001	1.37(1.18-1.59) P<0.0001
Lung Cancer	0.46 (0.11-1.84) 0.270	0.48(0.12-1.95) 0.308	0.57(0.34-0.97) 0.040	0.62(0.36-1.05) 0.076
Prostate Cancer	1.54(1.04-2.28) 0.030	1.52(1.03-2.25) 0.034	1.00(0.84-1.19) 0.996	1.25(1.04-1.49) 0.017
NMS Cancer	1.11(0.81-1.52) 0.501	1.17(0.85-1.60) 0.332	1.14(1.04-1.24) 0.003	1.15(1.06-1.25) 0.001
MS Cancer	0.94(0.56-1.57) 0.810	0.95(0.57-1.58) 0.835	1.08(0.85-1.37) 0.501	1.10(0.87-1.39) 0.439
Bowel Cancer	0.83(0.46-1.51) 0.551	0.87(0.48-1.57) 0.643	0.92(0.75-1.12) 0.396	0.94(0.77-1.14) 0.525

† Computed using stratified Cox proportion Hazard regression adjusted by age. NMS: Non-melanoma skin cancer, MS: Melanoma skin cancer ‡ Adjusted additionally for sex (excluding breast and prostate cancers), BMI and smoking

Table 32: Hazard ratios (95 %CI) of probable AD in individuals with different types of cancer in T2DM and non-T2DM cohorts (compared to other cancers)

	T2DM COHORT		NON-T2DM COHORT	
	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value
Breast Cancer	0.54(0.24-1.24) 0.147	0.54(0.24-1.24) 0.146	1.31 (1.12-1.53) 0.001	1.28(1.10-1.50) 0.002
Lung Cancer	0.47(0.11-1.90) 0.289	0.47(0.12-1.93) 0.299	0.52(0.30-0.88) 0.015	0.55(0.32-0.93) 0.026
Prostate Cancer	1.77(1.15-2.72) 0.009	1.74(1.13-2.67) 0.012	0.90(0.75-1.08) 0.267	0.94(0.79-1.13) 0.011
NMS Cancer	1.23(0.85-1.79) 0.265	1.24(0.85-1.79) 0.256	1.06(0.95-1.17) 0.298	1.04(0.94-1.16) 0.424
MS Cancer	0.98(0.57-1.67) 0.931	0.94(0.55-1.60) 0.813	0.99(0.77-1.25) 0.911	0.98(0.77-1.25) 0.862
Bowel Cancer	0.86(0.46-1.59) 0.628	0.89(0.68-1.16) 0.387	0.82(0.67-1.01) 0.061	0.82(0.67-1.01) 0.064

† Computed using stratified Cox proportion Hazard regression adjusted by age. NMS: Non-melanoma skin cancer, MS: Melanoma skin cancer

ǂ Adjusted additionally for sex (excluding breast and prostate cancers), BMI and smoking

(c) Hazard ratio for vascular dementia (VaD) by cancer status

Compared to participants without cancer, individuals with cancer showed no significant associations with VaD in the T2DM cohort (Table 33). In the non-T2DM cohort, individuals with non-melanoma skin cancer had a higher risk for VaD diagnosis, even after adjusting for all confounders [HR 1.25,95 % CI (1.10-1.42)]. However, when compared to other cancer types, there was no strong evidence that lung [HR 1.19,95 % CI (0.70-2.02)], bowel [HR 1.06,95 % CI (0.80-1.41)], prostate [HR 1.04,95 % CI (0.80-1.35)], or NMSC [HR 1.08,95 % CI (0.92-1.26)] estimates differed from the estimates of other cancer types, indicating that the observed high risk may not be specific to NMSC (Table 34).

Table 33: Hazard ratios (95 %CI) of VaD in individuals with different types of cancer in T2DM and non-T2DM cohorts (compared to no cancer)

	T2DM COHORT		NON-T2DM COHORT	
	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value
Overall Cancer	0.96 (0.82-1.12) 0.602	0.96(0.82-1.13) 0.634	1.20(1.10-1.32) P<0.0001	1.19(1.09-1.31) P<0.0001
Breast Cancer	1.08(0.66-1.77) 0.762	1.08(0.66-1.78) 0.748	1.12(0.87-1.45) 0.388	1.14(0.89-1.48) 0.300
Lung Cancer	0.39 (0.10-1.56) 0.186	0.38(0.09-1.50) 0.167	1.59(0.94-2.70) 0.083	1.42(0.84-2.40) 0.196
Prostate Cancer	0.88(0.56-1.37) 0.573	0.88(0.56-1.37) 0.573	1.24(0.96-1.61) 0.093	1.24(0.96-1.61) 0.094
NMS Cancer	0.96(0.72-1.28) 0.788	0.97(0.73-1.29) 0.848	1.26(1.10-1.43) 0.001	1.25(1.10-1.42) 0.001
MS Cancer	1.01(0.66-1.56) 0.946	1.02(0.66-1.57) 0.916	0.80(0.53-1.21) 0.299	0.80(0.53-1.22) 0.308
Bowel Cancer	0.94(0.57-1.55) 0.821	0.95(0.58-1.56) 0.837	1.27(0.97-1.68) 0.081	1.26(0.96-1.66) 0.096

† Computed using stratified Cox proportion Hazard regression adjusted by age. NMS: Non-melanoma skin cancer, MS: Melanoma skin cancer

ǂ Adjusted additionally for sex (excluding breast and prostate cancers), BMI and smoking

Table 34: Hazard ratios (95 %CI) of VaD in individuals with different types of cancer in T2DM and non-T2DM cohorts (compared to other cancers)

	T2DM COHORT		NON-T2DM COHORT	
	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value
Breast Cancer	1.14(0.68-1.91) 0.622	1.14(0.68-1.91) 0.618	0.92 (0.71-1.20) 0.548	0.95(0.73-1.24) 0.701
Lung Cancer	0.40(0.10-1.61) 0.200	0.38(0.09-1.54) 0.177	1.33(0.78-2.26) 0.294	1.19(0.70-2.02) 0.519
Prostate Cancer	0.91 (0.57-1.45) 0.683	0.90(0.57-1.44) 0.673	1.03(0.79-1.35) 0.792	1.04(0.80-1.35) 0.771
NMS Cancer	1.00(0.72-1.40) 0.983	1.01(0.73-1.41) 0.933	1.07(0.92-1.25) 0.368	1.08(0.92-1.26) 0.342
MS Cancer	1.07(0.68-1.68) 0.783	1.07(0.68-1.69) 0.765	0.65(0.43-1.00) 0.048	0.66(0.44-1.01) 0.056
Bowel Cancer	0.98(0.59-1.65) 0.950	0.98(0.59-1.65) 0.954	1.06(0.80-1.41) 0.666	1.06(0.80-1.41) 0.670

† Computed using stratified Cox proportion Hazard regression adjusted by age. NMS: Non-melanoma skin cancer, MS: Melanoma skin cancer

ǂ Adjusted additionally for sex (excluding breast and prostate cancers), BMI and smoking

(d) Hazard ratio for unspecified dementia by cancer status

In the non-T2DM cohort, the risk for unspecified dementia was higher among individuals with overall cancer compared to individuals without [HR 1.19,95 % CI (1.14-1.23)]. Upon investigating specific cancer types, an increased risk for unspecified dementia was observed among individuals with breast cancer [HR 1.31, 95 % CI (1.18-1.45)], prostate cancer [HR 1.24 ,95 % CI (1.11-1.39)], NMSC [HR 1.18 ,95 % CI (1.12-1.25)] and bowel cancer [HR 1.21, 95 % CI (1.08-1.36)](Table 35). However, there was no difference observed in the risk for unspecified dementia between individuals with lung cancer, melanoma skin cancer vs. individuals without cancer (Table 36). Furthermore, when comparing the risk of unspecified dementia in specific cancer types: prostate [HR 1.06,95 % CI (0.94-1.19)], breast [HR 1.12,95 % CI (1.01-1.25)], bowel [HR 1.02,95 % CI (0.90-1.15)] and NMSC [HR 0.99,95 % CI (0.93-1.06)], the estimates did not differ by cancer type (Table 36).

In contrast to the observed slightly higher risk for unspecified dementia among individuals with cancer in the non-T2DM cohort, individuals in the T2DM cohort showed no difference in relation to the rate of unspecified dementia between individuals with cancer vs. without (Tables 35 and 36).

Table 35: Hazard ratios (95 %CI) of unspecified dementia in individuals with different types of cancer in T2DM and non-T2DM cohorts (compared to no cancer)

	T2DM COHORT		NON-T2DM COHORT	
	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ǂ p-value
Overall Cancer	1.04 (0.91-1.18) 0.569	1.08(0.95-1.22) 0.250	1.18(1.13-1.22) P<0.0001	1.19(1.14-1.23) P<0.0001
Breast Cancer	1.05(0.69-1.58) 0.827	1.06(0.70-1.61) 0.771	1.31(1.18-1.46) P<0.0001	1.31(1.18-1.45) P<0.0001
Lung Cancer	0.70 (0.31-1.57) 0.390	0.71(0.32-1.59) 0.408	1.22(0.95-1.58) 0.116	1.22(0.95-1.58) 0.117
Prostate Cancer	1.16(0.84-1.60) 0.373	1.15(0.84-1.59) 0.382	1.211(1.08-1.36) 0.001	1.24(1.11-1.39) P<0.0001
NMS Cancer	1.12(0.90-1.39) 0.326	1.17(0.94-1.46) 0.153	1.18(1.11-1.24) P<0.0001	1.18(1.12-1.25) P<0.0001
MS Cancer	1.21(0.87-1.67) 0.255	1.24(0.89-1.71) 0.201	1.07(0.91-1.25) 0.437	1.08(0.92-1.27) 0.335
Bowel Cancer	0.83(0.54-1.29) 0.415	0.86(0.55-1.33) 0.494	1.20(1.07-1.36) 0.002	1.21(1.08-1.36) 0.002

† Computed using stratified Cox proportion Hazard regression adjusted by age. NMS: Non-melanoma skin cancer, MS: Melanoma skin cancer ǂ Adjusted additionally for sex (excluding breast and prostate cancers), BMI and smoking

Table 36: Hazard ratios (95 %CI) of unspecified dementia in individuals with different types of cancer in T2DM and non-T2DM cohorts (compared to other cancers)

	T2DM COHORT		NON-T2DM COHORT	
	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ‡ p-value	Unadjusted HR (95 % CI) † p-value	Adjusted HR (95 % CI) ‡ p-value
Breast Cancer	1.01(0.66-1.55) 0.962	1.01(0.66-1.56) 0.951	1.13 (1.01-1.26) 0.030	1.12(1.01-1.25) 0.037
Lung Cancer	0.67(0.30-1.51) 0.335	0.65(0.29-1.47) 0.305	1.04(0.80-1.34) 0.768	1.04(0.80-1.33) 0.816
Prostate Cancer	1.13 (0.80-1.60) 0.468	1.11(0.79-1.57) 0.531	1.03(0.91-1.16) 0.628	1.06(0.94-1.19) 0.322
NMS Cancer	1.11(0.86-1.43) 0.429	1.13(0.87-1.46) 0.357	1.00(0.93-1.07) 0.914	0.99(0.93-1.06) 0.869
MS Cancer	1.19(0.84-1.68) 0.328	1.17(0.83-1.65) 0.374	0.90(0.76-1.06) 0.206	0.91(0.77-1.07) 0.242
Bowel Cancer	0.79(0.50-1.24) 0.301	0.78(0.50-1.23) 0.283	1.02(0.91-1.16) 0.698	1.02(0.90-1.15) 0.731

† Computed using stratified Cox proportion Hazard regression adjusted by age. NMS: Non-melanoma skin cancer, MS: Melanoma skin cancer

‡ Adjusted additionally for sex (excluding breast and prostate cancers), BMI and smoking

4.4.5 Incidence rate of Death in non-T2DM and T2DM cohorts

To further investigate the observed inverse relationship for overall LOD and lung cancer in the T2DM cohort, the probability of death as a competing risk was investigated. Initially, the incidence rate of death among individuals with T2DM and non-T2DM was examined, to gain a better understanding of the distribution of death in both cohorts.

In the non-T2DM cohort, a total of 227,473 (31 %) individuals have died, of which 72,585 (32 %) had a diagnosis of cancer in the course of follow up of 7.91 (5.32) years. In comparison, 54,921 (25 %) individuals have died during 6.06 (4.17) years of follow up in the T2DM cohort, of which 14,278 (26 %) had a diagnosis of cancer. The mean age of death was 82.95 (8.32) years and 80.77 (7.72) years in the non-T2DM and T2DM cohort, respectively. As expected, the incidence rate of death was slightly higher in the T2DM cohort (41.66 per 1,000 person years) compared to the non-T2DM cohort (38.90 per 1,000 person years) (Table 37)

Table 37: Incidence rate (95% CI) of death in T2DM and non-T2DM cohorts

	Non-T2DM Cohort			T2DM cohort		
	Total	Males	Females	Total	Males	Females
No. of deaths	227,473	99,995	127,478	54,921	28,685	26,236
Age at death, years						
Mean (SD)	82.95(8.32)	80.86(7.89)	84.59(8.29)	80.77(7.72)	79.38(7.31)	82.30(7.87)
Median (range)	83(65-114)	81(65-114)	85(65-113)	81(65-111)	79(65-111)	83(66-109)
Length of follow-up, years (SD)		7.91 (5.32)			6.06(4.17)	
Incidence rate (95 % CI) cases per 1,000 person year	38.90(38.74-39.05)	41.17(40.91-41.42)	37.28(37.08-37.49)	41.66(41.31-42.01)	41.65(41.17-42.14)	41.67(41.17-42.18)

4.4.6 Death as a competing risk in the T2DM and non-T2DM cohorts

Death as competing risk was examined to better characterise the observed inverse association between lung cancer and overall LOD in the T2DM cohort. The results were also obtained in the non-T2DM cohort for comparison.

The cause-specific HR (csHR) and sub-distribution HR (sdHR) for overall LOD and death in individuals with cancer and lung cancer are presented in Tables 38 and 39. Using the cause-specific hazard approach, I used cox regression models to investigate the hazard of dementia while censoring for death and vice-versa. In the T2DM cohort, overall cancer was not associated with overall LOD with a csHR of 1.00 (95% CI 0.92, 1.08). Additionally, the hazard of dementia among individuals with lung cancer was 50 % lower compared to individuals without cancer and the hazard of death was 3.34 and 16.72 times higher in individuals with overall cancer and lung cancer respectively, compared to individuals without cancer. Conversely, in the non-T2DM cohort, overall cancer was associated with a csHR of 1.16 (95% CI 1.13, 1.20) for overall LOD and lung

cancer was not associated with overall LOD (Table 38). The csHR associated with lung cancer for death in both cohorts was similar [non-T2DM: csHR of 16.30 (95% CI 15.26-17.42) and T2DM: csHR of 16.72 (95% CI 15.57-17.96)]. There was a slightly higher csHR associated with overall cancer for death in the T2DM cohort [csHR of 3.34 (95% CI 3.25, 3.44)] compared to the non-T2DM cohort [csHR of 2.32 (95% CI 2.28, 2.35)] (Table 38).

I repeated the same analysis using the sub distribution proportional hazard model approach. In the T2DM cohort, the hazard of dementia was 30 % lower for overall cancer and 90 % lower in individuals with lung cancer compared to individuals without. In the non-T2DM cohort, the sdHR associated with overall cancer was 0.91 (95% CI 0.89, 0.94) for overall LOD and 0.21 (95% CI 0.17, 0.26) for overall LOD in association with lung cancer (Table 39). The sdHR approach model showed lower values compared to the csHR model, as the risk set in both approaches is different. As the sdHR model assumes that individuals who have experienced dementia or death remain in the risk set, this results in a higher number of individuals with cancer at risk of dementia or death which portrays an even stronger protective relationship between cancer and dementia compared to the csHR model.

Table 38: Cause specific hazard ratios (95 %CI) of overall LOD and death in T2DM and non-T2DM cohorts

	T2DM Cohort		Non-T2DM Cohort	
Cause- specific Hazard model (95 % CI) P-value	**Death**	**Overall LOD**	**Death**	**Overall LOD**
Overall Cancer	3.34(3.25-3.44) P<0.0001	1.00(0.92-1.08) 0.993	2.32(2.28-2.35) P<0.0001	1.16(1.13-1.20) P<0.0001
Lung Cancer	16.72(15.57-17.96) P<0.0001	0.52(0.29-0.94) 0.030	16.30(15.26-17.42) P<0.0001	1.05(0.85-1.29) 0.634

Table 39: Sub distribution hazard ratios (95 %CI) of overall LOD and death in T2DM and non-T2DM cohorts

	T2DM Cohort		Non-T2DM Cohort	
Sub distribution Hazard model (95 % CI) P-value	**Death (LOD as a competing risk)**	**Overall LOD (Death as a competing risk)**	**Death (LOD as a competing risk)**	**Overall LOD (Death as a competing risk)**
Overall Cancer	3.38(3.29-3.48) P<0.0001	0.70(0.64-0.75) P<0.0001	2.32(2.28-2.35) P<0.0001	0.91(0.89-0.94) P<0.0001
Lung Cancer	17.26(16.06-18.54)	0.11(0.06-0.21) P<0.0001	15.86(14.97-16.81) P<0.0001	0.21(0.17-0.26) P<0.0001

The cumulative incidence functions for LOD and death among individuals with cancer, lung cancer vs. without are illustrated in Figure 14.

In the T2DM cohort, in the presence of death, the analysis of the LOD cumulative incidence curve showed a protective effect of cancer on LOD incidence, which did not appear with the csHRs. With lung cancer, the protective association seen for LOD was further intensified in the presence of death as a competing event (Figure 14A1). Upon exploring LOD as a competing risk, individuals with cancer and lung cancer had a higher cumulative incidence rate of death compared to individuals without cancer (Figure 14B1).

In the non-T2DM cohort, in the presence of death, the cumulative incidence curve showed a protective effect of lung cancer on LOD incidence (Figure 14A2). Similar to the T2DM cohort, in the presence of LOD as a competing risk, individuals with cancer, and especially lung cancer, had a higher cumulative incidence rate of death compared to individuals without cancer (Figure 14B2).

Figure 14: Cumulative incidence function plots for overall LOD, in the presence of death as a competing risk in T2DM (A1) and non- T2DM (A2) cohorts. B. Cumulative incidence function plots for death, in the presence of LOD as a competing risk in T2DM (B1) and non- T2DM (B2) cohorts

Figure 14.A1

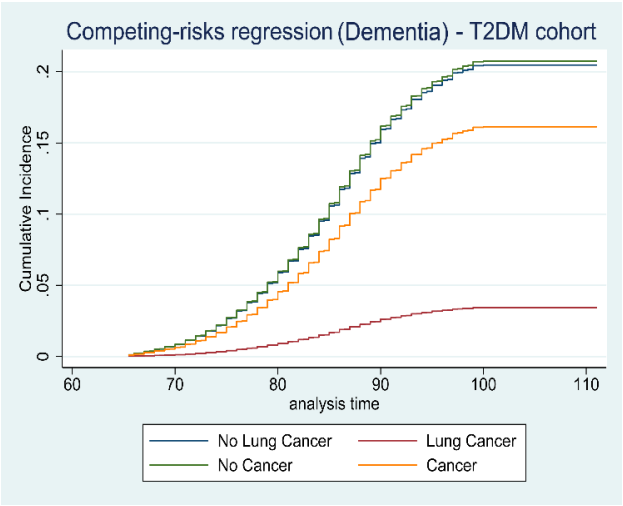


Figure 14.B1

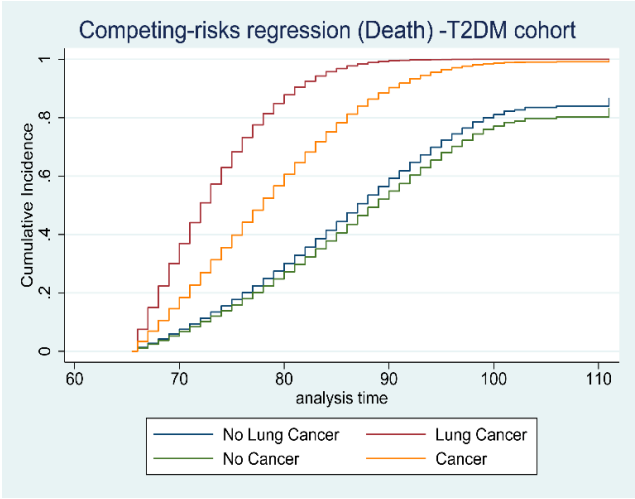


Figure 14.A2

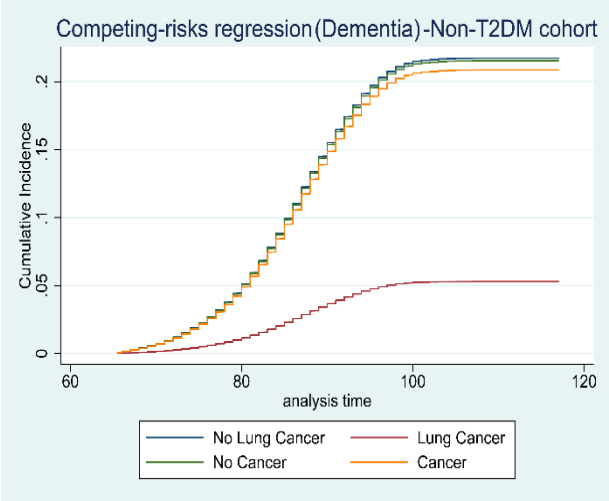
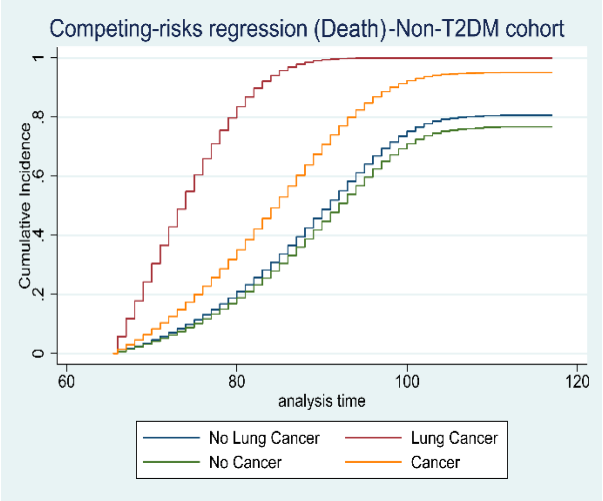


Figure 14.B2



4.5 SUMMARY

My sample included a total of 739,061 individuals without T2DM and 217,335 with T2DM. The mean (SD) age of individuals without T2DM at cohort entry was 70.80 (7.66) years (56.9% females) and 71.62 (7.09) years in the T2DM cohort (47.3 % females). The majority of individuals in both cohorts were white and never smokers. Compared with the non-T2DM cohort, individuals with T2DM were more likely to be obese (47 %) and have a higher distribution of clinical relevant diseases such as hypertension, hypercholesterolemia, depression and CeVD. Data on BMI, alcohol and smoking was missing at baseline in both cohorts for approximately 30 % of the individuals.

During follow-up, a total of 165,272 (22 %) and 32,022 (15 %) cancer cases were identified in the non-T2DM and T2DM cohorts, respectively. In the non-T2DM cohort, 52 % of the cancer cases were females aged over 60 years old (61 %). The overall incidence rate of cancer was 25.54 per 1,000 person years in males and 16.55 per 1,000 person years in females and increased with age. The highest overall incidence rate was for non- melanoma skin cancer (5.88 per 1,000 person years), prostate cancer in males (5.63 per 1,000 person years) and breast cancer in females (2.61 per 1,000 person years). In the T2DM cohort, the majority of cancers were diagnosed in males (60 %) and individuals above the age of 60 (69 %). The incidence rate of overall and different cancer types was higher in the T2DM cohort compared to the non-T2DM cohort. The overall incidence rate of cancer was 27.80 per 1,000 person years in males and 19.35 per 1,000 person years in females. The most common type of cancer in the both cohorts were non-melanoma skin cancer (4.75 per 1,000 person years), breast cancer (3.42 per 1,000 person years) for females and prostate cancer (5.33 per 1,000 person years) for males, with males clearly showing a higher overall cancer incidence rate when compared to females. Standardized Incidence Ratios (SIRs) and their corresponding 95 % CIs for cancer in both cohorts were computed using the Cancer Incidence in Five Continents volume X (CI5 X) as a reference and the results were comparable to that of the UK population.

A total of 11,450 (5 %) and 51,733 (7%) LOD cases were identified during follow-up in the T2DM and non-T2DM cohorts, respectively. In both cohorts, the majority of LOD cases were identified in individuals above the age of 80 (62 % T2DM cohort and 66 % non-T2DM cohort) with a

preponderance of women (58 % T2DM cohort and 69 % non-T2DM cohort). The mean age at diagnosis was 81.4 years (6.9) and 82.7 years (7.1) in the T2DM and non-T2DM cohorts, respectively. In the T2DM cohort vs. non-T2DM cohort, individuals with incident LOD displayed the following distribution of relevant diseases: 73 % vs. 51 % had hypertension, 25 % vs. 13 % had hypercholesterolemia, 50 % vs. 40 % had CeVD and 33 % vs. 29 % had depression, respectively. Brain injury did not differ substantially between both cohorts. However, individuals with a diagnosis of incident LOD, regardless of diabetes status, had a slightly higher prevalence of brain injury compared to individuals without.

In the T2DM cohort, a total of 2,341(20%) met the criteria for probable AD, 48 (1%) for possible AD and 9,061 (79 %) for other LODs. Of the 9,061 in the other LOD group, 3,201 (35%) had VaD, 191(2%) had PDD and LBD and 5,669 (63%) were classified as having "unspecified dementia". The unspecified dementia group consisted of 1,540 (27%) individuals who had no codes for specific LOD types but codes for a dementia drug and 4,129 (73%) with codes for dementia monitoring and codes for senile dementia of unspecified type. The overall incidence rate of LOD was 8.68 per 1,000 person years, 1.77 per 1,000 person years for probable AD, 0.04 per 1,000 years for possible AD and 6.87 for other LODs. The incidence of overall LOD increased with age with the highest overall incidence rate among females in the 80 and above age group (19.99 per 1,000 person years).

In the non-T2DM cohort, 14,033 (27%) cases were classified as probable AD, 1,937(4%) as possible AD and 35,763 (69 %) as other LODs. The majority of LOD cases belonged to the "unspecified dementia" group comprising of 29,614(83%) cases, followed by 5,503 (15 %) individuals with VaD and 646 (2%) with Parkinson's disease and Lewy-Body disease dementia. The unspecified dementia group consisted of 2,730 (9%) individuals who had codes for a dementia drug and 26,884 (91%) with codes for dementia monitoring and codes for senile dementia of unspecified type. The overall LOD incidence rate was 8.84 per 1,000 person years, 2.40 per 1,000 person years for probable AD, 0.33 per 1,000 years for possible AD and 6.11 per 1,000 person years for other LODs. Similar to the non-T2DM cohort, the highest overall incidence rate was among females in the 80 and above age group. In both T2DM and non-T2DM cohorts, females

evidently had a higher incidence rate when compared to males. The incidence rate of overall LOD did not differ substantially between both cohorts.

In the T2DM cohort, among 32,022 individuals with cancer 1,172 (4%) were diagnosed with LOD compared to 10,278 LOD cases in the 185,313 (6%) individuals without cancer. In the non-T2DM cohort, 10,602 (6%) individuals were diagnosed with LOD among 163,737 cancer participants compared to 39,596 (7%) LOD cases in 573,789 individuals without cancer. The majority of cancers occurred in individuals aged ≥65 years with the highest LOD cases appearing to be in the non-melanoma skin (40%) and breast (12%) cancer groups and lowest number of LOD cases in the lung cancer group (1 %) for the non-T2DM cohort. In comparison, the highest LOD cases in the T2DM cohort group were in the melanoma skin cancer group (7%) and lowest number of LOD cases was in the lung cancer group (<1%). Kaplan –Meier curves in the non-T2DM cohort, showed a higher rate for overall LOD and probable AD among individuals with cancer. However, in the T2DM cohort, it appeared that individuals without cancer showed a higher rate for LOD and probable AD compared to the cancer group. The incidence in the possible AD group was too small in both cohorts to allow us to make any inferences.

Overall there was a higher risk for overall LOD [HR 1.16, 95 % CI (1.13-1.20)] and probable AD [HR 1.12, 95 % CI (1.06-1.19)] in individuals with cancer, in the non-T2DM cohort. However, there was no significant association between risk for overall LOD, probable AD and lung cancer as well as melanoma skin cancer. Additionally, the risk for unspecified dementia was higher among individuals with cancer compared to without [HR 1.19, 95 % CI (1.14-1.23)]. Upon investigating specific cancer types, an increased risk for unspecified dementia was observed among the breast cancer [HR 1.31, 95 % CI (1.18-1.45)], prostate cancer [HR 1.24, 95 % CI (1.11-1.39)], non-melanoma skin cancer [HR 1.18, 95 % CI (1.12-1.25)] and bowel cancer [HR 1.21, 95 % CI (1.08-1.36)]. Conversely, in the T2DM cohort , individuals with lung cancer had a significantly lower risk for developing overall LOD, even after adjusting for possible confounders, when compared to individuals without cancer [HR 0.52, 95 % CI (0.29-0.94)] and other types of cancer [HR 0.50, 95 % CI (0.28-0.91)]. There was also no difference in the risk of probable AD between individuals with cancer and without. However, participants in the prostate cancer group appeared to have a higher risk for developing probable AD compared to individuals in the other

cancer group [HR 1.74, 95 % CI (1.13-2.67)] and individuals without cancer [HR 1.52, 95 % CI (1.03-2.25)] . The risk for subsequent VaD did not differ substantially between individuals with cancer and without in both cohorts.

The cause-specific hazard ratio (csHR) and sub-distribution hazard ratio (sdHR) for overall LOD and death in individuals with cancer and lung cancer were computed. There was a slightly higher csHR associated with overall cancer for death in the T2DM cohort (csHR of 3.34 (95% CI 3.25, 3.44) compared to the non-T2DM cohort (csHR of 2.32 (95% CI 2.28, 2.35). The csHR associated with lung cancer for death in both cohorts was similar [non-T2DM: csHR of 16.30 (95% CI 15.26-17.42) and T2DM: csHR of 16.72 (95% CI 15.57-17.96)].

In the T2DM cohort, lung cancer was associated with a decreased risk of overall LOD with a csHR of 0.52 (95% CI 0.29, 0.94). On the other hand, overall cancer was not associated with LOD. With the sub-distribution hazard model, lung cancer showed a further decreased risk with sdHR of 0.11 (95% CI 0.06, 0.21) compared to the csHR. Conversely, in the non-T2DM cohort, only overall cancer was associated with a csHR of 1.16 (95% CI 1.13, 1.20) for overall LOD and there was no association with lung cancer. The sdHR associated with overall cancer was 0.91 (95% CI 0.89, 0.94) and 0.21 (95% CI 0.17, 0.26) with lung cancer, for overall LOD.

Cumulative incidence function curves showed that in the presence of death, there is a protective effect of cancer on LOD incidence in both cohorts. This protective effect does not appear in the analysis of cause specific hazards. The protective association seen for LOD in individuals with lung cancer is further strengthened in the presence of death as a competing event, in both cohorts, but especially in the T2DM cohort. Upon exploring LOD as a competing risk, individuals with cancer and lung cancer had a higher cumulative incidence rate of death compared to individuals without cancer.

In summary, investigating the cause-specific and sub distribution hazard models helped to conclude that the inverse association observed between cancer, lung cancer and overall LOD, especially in the T2DM cohort, is most likely due to mortality selection.

CHAPTER 5 – DISCUSSION

Scientific reports on the relationship between cancer and AD, as well as of other LOD forms have been varied and somewhat conflicting. Indeed, the epidemiological evidence for a positive versus negative effect of cancer on the incidence of LOD are abound in the scientific literature. Hence, the need for a robust evaluation of the cancer-LOD-T2DM relationship given the potential public health impact of a positive finding. To this end, I have sought to address the T2DM, cancer-LOD conundrum in a population of patients with T2DM vs a population with no T2DM, with the aid of UK's largest population- based database, the CPRD. By statistically evaluating the relationship between cancer and LOD incidence in 956,396 individuals with and without T2DM, I was able to shed light on the relationships between cancer, LOD and T2DM using incidence rates of the two former comorbidities in individuals with or without T2DM.

Results revealed nil significant association observed between cancer and LOD. No evidence of a protective effect of cancer vis a vis overall LOD and dementia attributable to AD (AD-LOD) in both non-T2DM and T2DM cohorts was noted. This finding is in line with reports from recent population-based studies, who similarly observed nil significant associations (Hanson HA et al., 2016, Schmidt SA et al., 2017, Freedman DM et al., 2016). Upon examining the cause-specific and sub distribution hazard models, my findings suggest that the inverse association observed between cancer, lung cancer and LOD, especially in the T2DM cohort, is most likely due to mortality selection. Indeed, this finding, observed in the T2DM cohort only, was specific for lung cancer, a form of cancer with known high mortality. The implication is that individuals with lethal forms of cancer do not live long enough to reach a stage of clinically significant cognitive decline and LOD diagnosis, the risk of which in known to exponentially increase with age, from the age of 65.

In fact, in the non-T2DM cohort, there was an increased risk of overall LOD among individuals with cancer. It is true that I have not observed the same increased risk in the T2DM cohort, however it is important to note that the incidence rate of death was higher among the T2DM cohort compared to that of the non-T2DM cohort. In view of that, it is plausible that individuals in the T2DM cohort might have died before developing symptoms of cognitive decline and subsequent LOD, thus concealing any relationship between LOD and cancer. This finding is critical in view of the fact that majority of the reports highlighting conflicting associations between cancer and

LOD incidence, have not accounted for survival bias (Roe CM et al., 2005, Musicco M et al., 2013).

In the subsequent sections, I will discuss and compare my findings in light of similar studies in the literature. I will address the incidence of LOD and cancer, followed by an in-depth exploration of the following topics: LOD and cancer, cancer and diabetes, and diabetes and LOD.

5.1 Incidence of LOD

My investigation into the incidence of LOD in the two cohorts revealed rates that are comparable to the vast majority of published related studies. As expected, the incidence of LOD increased with age, with the highest incidence reported in individuals aged ≥80, which was sex-specific (increased incidence noted in females compared to males). The Framingham study found similar results, showing a doubling of incidence of LOD and probable AD every 5 years, for both men and women combined (Bachman DL et al., 1993). These findings were replicated by Paykel et al in 1994, where the incidence of LOD in individuals aged >75 years, seemed to approximately double every 5 years. A later population-based cohort, which included only individuals aged > 90 years, found that the prevalence of LOD was higher amongst women compared to men, with the doubling effect (every 5 years) noted specifically in women (Corrada MM et al., 2008).

Additional studies have investigated this sex specific incidence of LOD in different LOD types, mainly in the very old, where the risk of LOD is the highest. Results from my analysis of the CPRD cohort, found a pronounced increase in LOD incidence in individuals above the age of 80 for both men and women, with an apparent bias towards females. My findings are in line with the afore-mentioned studies that have reported an increased incidence of LOD in women, particularly of AD-LOD, whilst the incidence of vascular dementia (VaD) was higher in men. In the Rotterdam study, there were no sex specific differences reported for overall LOD, but upon examining data from individuals above the age of 90, the incidence of AD-LOD was higher for women (Ruitenberg A et al., 2001). Similarly, the Kungsholmen project, which involved 1,473 participants aged 75 and above, reported a higher incidence rate of LOD and AD-LOD for women as compared to men

(19.6 vs. 12.4 per 1,000 person years) (Fratiglioni L et al., 1997). A more recent study incorporating several European countries, with pooled results from 8 population-based studies, found that the incidence of LOD and AD-LOD increased up to the age of 85. However, in individuals above the age of 85, the incidence seemed to increase only in women (Fratiglioni L et al., 2000). These studies, along with mine thus allude to an age-dependent effect of the female-sex specificity for increased incidence of LOD.

Several theories have been proposed to explain the observed sex differences in LOD incidence. One such rationale is that women have a longer life expectancy than men. Since the risk of LOD increases with older age and doubles every 5 years, after the age of 65, women are at a greater risk for LOD due to being alive for a longer time (Mangialasche F et al., 2012, Solomon A et al., 2013, Rocca WA et al., 2014). Furthermore, a number of studies reported that the prevalence of possible LOD risk factors such as hypertension, diabetes, and hyperlipidemia is more common in women as compared to men of the same age, particularly in individuals aged > 75 years old (Carlo AD et al., 2007, Azad NA et al., 2007, Chêne G et al., 2015) . Subsequently, this high risk profile places older-aged women at a higher risk for LOD compared to age-matched men.

Another putative theorem proposes the protective impact of education on LOD risk. It has been consistently reported that education plays an important role in neuroprotection (Sharp ES and Gatz M, 2011, Mortamais M et al., 2014, Xu W et al., 2016). Although education is now accessible to both men and women, this was not the case in the early decades of the 20th century (Rocca WA et al., 2014, Mielke MM et al., 2014). Access to education was more challenging for women worldwide, particularly for women who are now above the age of 70, and from countries with strong traditional ideals (Mielke MMVemuri P and Rocca WA, 2014). Educational attainment has also been reported as a key element in the cognitive reserve hypothesis, whereby individuals with a higher degree of education contribute more points to their cognitive reserve, and as a result, are more resilient to neurodegeneration and LOD (Meng X and D'Arcy C, 2012, Stern Y, 2013, Wang HX et al., 2017). Other studies suggest that women who are concerned about their memory, are more likely to visit memory clinics or a GP, as opposed to men (Cutler DM and McClellan M, 2001). Thus, it is possible that women receive an earlier diagnosis of LOD, while a lower incidence

appears in men may merely reflect later or underdiagnosis of LOD (Knopman DS, 2001, Wilson RS et al., 2011).

An additional widely held assumption is the relationship between oestrogen and LOD. Oestrogen has been reported to have a neuroprotective effect; hence the loss of this hormone could lead to several metabolic malfunctions, including expression of cerebral factors leading to neurodegeneration (Brann DW, 2007). Earlier studies in post-menopausal women have shown an increased risk of LOD and AD, triggered by the decline of oestrogen levels with age (Fillit H et al., 1986). Consequently, reports on the possible role of hormone replacement therapy (HRT) and its effect on LOD risk began to emerge (Hogervorst E et al., 2009, Dye RV et al., 2012). However, over the years, research into the relationship between HRT and LOD has shown somewhat conflicting results. One of the largest clinical trials in post-menopausal women, the Women Health Initiative Memory study (WHIMS), investigated the effect of HRT usage in approximately 4,500 post-menopausal women (Shumaker SA, 1998). The study concluded that HRT increased the risk of cognitive impairment and LOD, in women above the age of 65. Conversely, two other clinical trials, the KEEPS and ELITE studies, found no relationship between HRT and LOD (Gleason CE et al., 2015, Kantarci K, 2016). Similarly, a recent large observational study "Kuopio Osteoporosis risk factor and prevention study" in approximately 8,000 post-menopausal women found no protective relationship between HRT and LOD. More recently, a small decrease in AD-LOD risk has been reported in women who have self-reported long-term use of HRT (Imtiaz B et al., 2017).

Lastly, researchers have explored the differences in the neuroanatomical structure and brain dimensions in men and women. Particularly, several studies have reported that women seem to have a lower gray matter volume, cortical thickness and brain volume than men (Lüders E et al., 2002, Zaidi ZF, 2010); all of which potentially confer an increased risk for LOD (Smith CD et al., 2007, Ikram MA et al., 2010). Furthermore, genetic studies investigating the effect of the APOE4 allele , showed a correlation with hippocampal atrophy, especially in women (Farrer LA et al., 1997, Fleisher A et al., 2005). All these theories combined, point towards a range of potential explanations for the sex-specific differences reported in LOD prevalence. Interestingly, a recent report from the Cambridge group, based on the "Cognitive Function and Ageing Study" I and II (CFAS I and II) in the UK, found a decline of LOD incidence by 20 %, mainly in men but not in

women (Matthews FE et al., 2013). Nevertheless, there is still lack of clarity on the precise mechanisms underpinning the observed sex-specific differences, and further research, based on well-designed prospective longitudinal studies, is warranted.

5.2 Incidence of Cancer

In this study, a total of 32,022 (15 %) and 165,272 (22 %) cancer cases were identified in the T2DM and non-T2DM cohorts, respectively. The incidence of cancer increased with age, with the majority of cancers occurring after the age of 60 years old. The highest incidence rate of cancer was reported in individuals above the age of 80, with an overall incidence rate of 22.33 (95 % CI 22.11-22.57) and 26.06 (95 % CI 25.54-26.61) in the non-T2DM and T2DM cohorts, respectively. This is consistent with previous reports, showing a higher distribution of cancer (nearly 65.3 %) among the elderly (ONS.GOV). A report on the effect of age on cancer incidence, indicated a 4 and 2 fold increase in incidence of cancer in individuals above the age of 65 (compared to those in the 45 to 64 age group category) for males and females, respectively (Baranovsky A and Myers MH, 1986). In the UK, the incidence of cancer has increased between the years of 1995 and 2015 from 648.8 to 667.4 per 100,000 in males and 469.6 to 542.8 per 100,000 in females (ONS.GOV). Nonetheless, medical advancements in early detection, screening and novel therapies for several forms of cancer have led to a reduction in mortality rates in cancer cases (ONS.GOV). The mortality rates have been reported to have declined from 427.8 to 329.5 per 100,000 in males and 268.4 to 226.6 per 100,000 in females (ONS.GOV).

Similarly to previous sex-specific studies on cancer incidence and prevalence, this study has observed a higher incidence of cancer in men compared to women for overall cancer (Non-T2DM cohort: 25.54 vs 16.55 per 1,000 person years, T2DM cohort: 27.80 vs 19.35 per 1,000 person years) and the majority of cancers of interest, in both cohorts. It has been consistently reported that men, compared to women, are more likely to develop cancer (Ashley DJ, 1969, Pearce MS and Parker L, 2001, Cartwright RA et al., 2002, Cook MB et al., 2009, Edgren G, 2012) . A report from the CI5 has revealed a higher incidence of cancer in men for about 32 out of 35 cancer sites

(Edgren G, 2012). Additionally, figures from Cancer Research UK (CRUK) have illustrated a higher cancer death rate in men compared to women (202 vs 147 per 100,000) (CRUK report on excess cancer burden in men). In fact, upon excluding sex- specific cancers such as prostate and ovarian cancer, the authors reported an even stronger burden of cancer risk for men, with 67 % of men more likely to die due to cancer (CRUK report on excess cancer burden in men).

Several factors have been proposed to account for the sex differences in cancer incidence. The most consistent ones involve sex hormones, genetic predisposition and family history, occupational exposure and importantly environmental factors such as smoking, diet, alcohol consumption and exposure to sunlight (Zahm SH and Fraumeni JF, 1995, Klein SL, 2000, Cook MB et al., 2009, Gabory A et al., 2009, Dorak MT and Karpuzoglu E, 2012).

The most common type of cancer in my study was NMSC for both cohorts, and it accounted for 30 % and 21 % of the cancer cases in the non-T2DM and T2DM cohorts, respectively. NMSC has been shown to be the most frequent cancer in the UK and Europe (Lomas ALeonardi-Bee J and Bath-Hextall F, 2012). Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common types of NMSC, with BCC constituting 80 % of all NMSC cases (Katalinic A et al., 2003). In the UK, many cancer time-trend reports exclude NMSC from their statistical analysis, mainly due to its benign nature, as well as the underdiagnosis of NMSC in cancer registries (Public Health England). In fact, this was originally led by the recommendation to only report the first BCC or SCC detected in patients, given by the United Kingdom Association of Cancer Registries (UKACR, 2013), the European Network of Cancer Registries (ENCR, 2000) and the International Agency for Research on Cancer (IARC, 2004). The rationale for this recording methodology is to allow the standardization of cancer incidence rates across geographic regions. Additionally, some NMSC cases are not recorded when treated topically, such as small or isolated BCC. Studies from East Scotland, Netherlands, Finland and Malta have shown underreporting of NMSC to range between 30 to 50% (Brewster DH et al., 2007, Vries Ed et al., 2012).

Following NMSC, the most common cancer sites found in both cohorts were breast and prostate cancer for females and males, respectively. Breast cancer incidence rate was 2.61 (95 % CI 2.55-2.67) and 3.42 (95 % CI 3.23-3.58) in the non-T2DM and T2DM cohorts, respectively. This is in line with previous studies reporting breast cancer as the most common cancer in females,

accounting for 23 % of cancer cases and 14 % of total cancer deaths in 2008 (Jemal A et al., 2011). In England, the incidence rate of breast cancer has increased from 163.6 in 2005 to 170.2 per 100,000 in 2015 (Cancer registration statistics England, 2015). The rise in breast cancer incidence has been reported worldwide, and the advanced screening and detection of breast cancer has been suggested as the main driver for this observed increased incidence (Jemal A et al., 2011, Jemal A et al., 2010, Coleman MP et al., 2011).

In this study, prostate cancer appeared to be the most common type among males, with an incidence rate of 5.63 (95% CI 5.53-5.73) and 5.33 (95 % CI 5.15-5.51) in the non-T2DM and T2DM cohorts, respectively. Congruently, the cancer registration statistics of England in 2015 have shown prostate cancer to be the most common in males, the incidence of which increased from 174.6 in 2005 to 266.5 per 100,000 in 2015. Furthermore, reports on cancer statistics in 2004 have presented a 3 fold increase in incidence of prostate cancer in individuals between the ages of 45 and 70 , as well as a 50 % increase in the 70-79 age group, compared to rates in 1992 (Farmer R, 2008) . Like breast cancer, there has been a decrease in mortality rates in prostate cancer over the years, mainly due to the early detection of prostate cancer and the introduction and wide use of the prostate-specific antibody test (PSA)(Cary KC and Cooperberg MR, 2013). According to the "Excess cancer burden in men" report by Cancer Research UK, the rate of mortality has declined by 17 % compared to rates in the early 1900s. A study comparing the cancer mortality statistics for USA and UK, using the cancer research UK and the SEER program between 1975 and 2004, found that the mortality rate in the US declined by -4.17 % each year compared to -1.14 % in the UK. The authors attributed the rationale for the differential findings to an increase in prostate cancer screening and PSA in the US compared to the UK, between 1994 and 2004 (Collin SM et al., 2008).

In England, prostate, breast, lung, bowel and colorectal cancers have been found to be the most common forms of cancer, and account for more than 50 % of malignant cancer registrations (Cancer Registration Statistics England, 2015). This distribution has also been portrayed in my results, with lung and bowel cancers being the most common cancers for both sexes combined, following NMSC. The incidence rate of lung cancer was higher in males compared to females

(non-T2DM cohort: 2.37 vs 1.28 per 1,000 person years, T2DM cohort: 2.77 vs 1.62 per 1,000 person years). Furthermore, cancer statistics reports show lung cancer to be the leading cause of cancer death in males and the second leading cause of cancer death in females (Jemal A et al., 2011). Nevertheless, the incidence rate for lung cancer has been reported to have decreased from 127.9 (in 1994) to 89.4 per 100,000 cases, with a mortality rate drop of 4.02 in 2015 (Cancer Registration Statistics England, 2015). This has mainly been attributed to the drop in smoking prevalence rates amongst men (Moolgavkar SH, 2012). In contrast, the incidence rate of lung cancer in females has increased from 51.4 to 65.6 per 100,000 cases in 2015 (Cancer Registration Statistics England, 2015).

Bowel cancer is the third most common cancer, after lung cancer, in both females and males (Cancer Research UK). In this study, higher incidence of bowel cancer was observed in males compared to females, in both cohorts (Non-T2DM cohort: 2.17 vs 1.43 per 1,000 person years, T2DM cohort: 2.82 vs 1.94 per 1,000 person years). Previous reports on the incidence of bowel cancer indicated a rather stable rate between 1995 and 2015, with approximately 84.6 cases per 100,000 in males and 56.8 cases per 100,000 in females (Cancer registration Statistics England, 2015). There is a variation in incidence rates reported between various countries in Europe and worldwide, with some unfolding a decrease in mortality rates (Cancer registration Statistics England, 2015). The differences in rates reported could be due to variations in prevalence of risk factors, diagnostic techniques and bowel cancer screening methods (Westlake S and Cooper N, 2008).

5.3 LOD and cancer: a conundrum

In contrast to my findings with regards to selective mortality, several previous studies have reported an inverse association between cancer and LOD, specifically AD-LOD (Driver JA et al., 2012, Roe CM et al., 2005, Musicco M et al., 2013). The majority of these studies have attributed their findings to the biological pathways and genetic characteristics shared among both diseases. At the same time, it is prudent to highlight the potential limitations of these studies. Some of these include small sample size (Roe CM et al., 2005, Roe CM et al., 2010, Driver JA et al., 2012,

Musicco M et al., 2013, White RS et al., 2013), ascertainment bias (Ou SM et al., 2013) and limited follow-up period (Roe CM et al., 2005, Roe CM et al., 2010, Musicco M et al., 2013, White RS et al., 2013). Several systematic reviews and meta-analyses that aimed at summarizing the pooled results between studies, also reported an inverse relationship between cancer and LOD in both directions (Ma LL et al., 2014, Zhang Q et al., 2015, Shi HB et al., 2015). However, the authors suggested caution in interpreting these results, emphasizing the limitations of these studies, such as survival bias considerations, statistical model misspecifications, time varying nature of cancer diagnosis specifications (prevalent vs. incident), heterogeneity in the diagnostic criteria for LOD and AD, as well as different confounding variable considerations.

More recently, Yarchoan et al (2017) used pathological and clinical data, from the Religious Order Study (ROS) and the Rush Memory Ageing Project (MAP), to investigate the relationship between cancer history and AD pathology observed at autopsy (paired helical filament tau (PHFtau) neurofibrillary tangles and amyloid-β load). The authors reported reduced odds of developing AD and lower density of neurofibrillary tangles, but no effect on amyloid-β load, in individuals with history of cancer.

It is important to also take into account the few studies that have investigated the relationship between cancer and LOD in both directions simultaneously. These studies have mainly reported a lower incidence of AD in individuals with cancer compared to individuals without, and an even further lower incidence of cancer in individuals with AD compared to individuals without (Roe CM et al., 2010, Musicco M et al., 2013, Driver JA et al., 2012). Conversely, a US longitudinal study using the SEER-Medicare data found an inverse relationship between AD and cancer, but only when AD preceded cancer (Akushevich I et al., 2013). The authors highlighted the importance of ascertainment bias in the observed specific inverse relationship, when accounting for cancer after LOD diagnosis. I have only explored the incidence of LOD in individuals with cancer and avoided exploring the incidence of cancer in individuals with LOD. This direction was selected in light of the outcome being investigated in this study i.e. incidence of LOD, and previous studies cautioning the limitations and the uncontrolled effect of ascertainment bias, when exploring the risk of cancer after LOD diagnosis.

The variability of findings regarding the potential effect of one of these complex diseases on the risk for the other, underline the importance of taking into account several epidemiological, methodological and statistical considerations. These considerations are pivotal prior to embarking on studies aimed at exploring putative biological mechanisms, underpinning the relationship between LOD and cancer. In the below sub-sections, I will outline a few key examples, such as the role of mortality selection and the effect of chemotherapy and comorbidities.

5.3.1 Mortality Selection

Upon examining the cause-specific and sub-distribution hazard models, I found no inverse relationship between cancer and LOD in both non-T2DM and T2DM cohorts. The cumulative incidence function curves illustrated a lower hazard ratio in the presence of death, which was not observed in the cause specific hazards. The presence of a "protective effect" was initially illustrated in the T2DM cohort, when examining lung cancer specifically. However, competing risk analysis showed that it was actually death that was driving this effect, whereby the reduction in survival of cancer patients limited the likelihood of LOD diagnosis later in life. Similar results were observed following cohort-stratification using 'LOD-type'.

Compared to participants without cancer, individuals with cancer showed no inverse associations with probable AD, VaD and unspecified dementia in both non-T2DM and T2DM cohorts. Furthermore, the mean age of death in both cohorts ranged between 80 and 83 years. As mentioned previously, the incidence of LOD was highest in individuals aged 80+; lending credence to the possibility that selective mortality may drive the observed decrease in LOD incidence.

In studies on elderly populations aimed at evaluating complex (multifactorial) diseases, comorbidities and their inter-relationships, the selection of the appropriate statistical methodologies is of paramount importance. In this study, I used the cox regression methods with age as the time-scale and cancer as a time-varying covariate, as well as the Fine and Gray model, to account for death as a competing risk. The treatment of cancer as a time-varying covariate,

assumes that individuals with cancer contribute person years to the no-cancer group until the diagnosis of cancer, after which they contribute person years to the cancer group. Similarly, a recent retrospective study using the Utah population database examined over 100,000 individuals for the relationship between LOD and cancer (Hanson HA et al., 2016). Interestingly, this study used several different statistical approaches (for the same data) to illustrate the sensitivity of the models to the effect of competing risks of death. The authors found that there was no inverse association between cancer and LOD, when accounting for cancer as a time varying covariate. However, when investigating cancer as non-time varying covariate, an inverse relationship between cancer and LOD was found. The authors commented that, in their latter model, individuals with cancer incorrectly contribute person years only to the cancer group, by assuming they have had a cancer diagnosis at all times since cohort entry (never/ever). Understandably, when using cancer as a non-time varying covariate it appears as though there are more cancer survivors, leading to a lower risk for LOD. Additionally, the authors explored two different methods to account for death as a competing risk: the Kalbfleisch and Prentice method (KP) and the Fine and Gray method (FG). Both of these approaches showed a lower sub-distribution hazard in the cancer group, due to higher mortality and an artificial increase in the persons at risk in that group. This report is an exemplar on the need for careful selection of the appropriate statistical methodologies in studies involving diseases of high mortality (Hanson HA et al., 2016).

One of the initial studies that accounted for cancer as a non-time varying covariate was by Driver et al (2012), based on data from the Framingham Heart Study cohort. This has been one of the most sited reports on an inverse association between cancer and LOD and vice versa. However, the statistical methodology employed by these authors clearly has the potential of introducing bias, as it assumes that cancer exposure is present throughout the whole observation period. In addition to using cancer as a time-varying covariate to correct for this bias, it is important to account for LOD and cancer exposure timelines appropriately. For instance, in this study I excluded individuals with a cancer diagnosis post LOD diagnosis, to ensure that these individuals do not incorrectly contribute person years to the cancer exposure group.

Another important issue to account for is the difference between prevalent and incident cancer cases. A population-based observational study using the Adult Changes on Thought cohort (ACT)

showed different associations with AD by cancer status, i.e. prevalent vs. incident cases (Bowles EJA et al., 2017). The authors found an inverse association with incident but not prevalent cancer compared to individuals without cancer, attributing their findings to the frequency of late-stage and aggressive cancers in incident cancers cases, as well the importance of mortality selection. In my study, I found a greater number of incident cancer cases compared to prevalent cases in both T2DM and non-T2DM cohorts. In line with the findings from the ACT cohort, the majority of incident cancers in my study were more likely to be associated with a higher mortality risk such as lung and bowel cancers in both cohorts. This is expected as individuals with prevalent cancers are most likely cancer survivors.

5.3.2 Comorbidities, multi-morbidities and LOD

A key study result features an increased risk of overall LOD in individuals with cancer compared to individuals without, in the non-T2DM cohort. One possible explanation for this finding is the prolonged survival time period in individuals without T2DM, resulting in an increased life expectancy and thus potential increase in LOD incidence rate (that is for individuals presenting with presence of other LOD risk factors). There have been several reports on the high prevalence of comorbidities and multi-morbidities among individuals with LOD (Schubert CC et al., 2006, Sanderson M et al., 2002). Similarly, studies on individuals with cancer have shown a poorer survival in individuals with comorbidities, compared to individuals without (Braithwaite D et al., 2012). A Danish study on 237,938 breast cancer patients, between the ages of 45 and 84, and their matched controls found that individuals with concomitant LOD had the strongest interaction with breast cancer and death rates (Ording AG et al., 2013). Thus, it is reasonable to assume that the shared comorbidities between cancer and LOD (the onset of which much likely preceded recording of the clinical diagnosis), could have caused the increase in risk of LOD among individuals with cancer compared to without.

Conversely, in the T2DM cohort, there was no observed relationship between overall LOD and cancer. The frequency of comorbidities is especially common in individuals with T2DM and

vascular diseases, possibly leading to an increase in the risk of progression to LOD (Biessels GJ, 2006). In fact, numerous studies have showed diabetes to be the most frequent comorbidity for LOD (Poblador-Plou B et al., 2014, Götz J et al., 2013). A nationwide study in Taiwan, including 8,456 individuals either with MCI, LOD or cognitively normal, showed a much higher frequency of comorbidities in individuals with MCI (20.9 %) and LOD (27.3 %) compared to individuals who were cognitively unaffected (15%). Furthermore, there was a higher risk of diabetes (OR 1.24, CI 1.07, 1.44) associated with LOD and cognitive deterioration in the elderly (Chen T-B et al., 2017). Interestingly, another Taiwanese study specifically investigated the effect of comorbidities on LOD in individuals with diabetes. The study included 33,709 individuals with diabetes and 67,077 randomly selected controls. The authors reported a higher prevalence of comorbidities among individuals with diabetes, compared to individuals without. The HR for LOD in individuals with diabetes increased from 1.41 in individuals without comorbidities to 2.49 in individuals who had 4 or more comorbidities (Kuo SC et al., 2015).

Consequently, it is not surprising that individuals with cancer in the T2DM cohort had an intensified effect for disease progression and an accelerated effect in mortality. Additionally, an increase in the number of comorbid diseases may lead to faster cognitive deterioration, whilst inadvertently resulting in the under-diagnosis of LOD itself (Solomon A et al., 2011).

Finally, it is worth noting that individuals in the non-T2DM cohort might have developed diabetes after an LOD diagnosis. However, this might have not been recorded in a timely manner possibly due to the individuals with early/ mild cognitive decline not recognizing their symptoms and seeking medical advice (Piette J and Kerr E, 2006) ; or that GPs might be disinclined to investigate diseases in individuals with LOD (Kerr E et al., 2007, Piette J and Kerr E, 2006). Quite a few studies suggest that there is a difference in treatment between individuals with LOD and individuals without, in the medical settings (Bunn F et al., 2014). On the other hand, it is possible that individuals with LOD might have had T2DM, before their LOD diagnosis that had not been noted by the GP due to the delay between the pre-diagnostic prodromal and early disease stages and the actual diagnosis.

Finally, it is important to remember that both LOD and AD-LOD, as well as T2DM have long periods of a pre-clinical stage, progressing for many years (even decades) prior to symptoms and signs becoming noticeable, leading to their diagnosis.

5.3.3 Chemotherapy and LOD

Chemotherapy is another essential factor that should be taken into account when exploring the relationship between LOD and cancer. Patients undergoing different chemotherapy procedures have been known to suffer from cognitive impairment, also known as "chemo-brain" (Janelsins MC et al., 2014). A number of studies, often reporting rather inconclusive or conflicting results, have been published on this phenomenon, mainly involving breast cancer patients (Hermelink K, 2015, Moore HCF, 2014). Several studies have found that chemotherapy may result in cognitive decline and impairment (Seigers R and Fardell JE, 2011, Bender CM et al., 2006, Ahles TA et al., 2002). A study by Heck et al (2008) using the Surveillance, Epidemiology and End Results (SEER) Medicare database, examined 18,360 women diagnosed with breast cancer and the incidence of LOD and other cognitive impairment among individuals who have had chemotherapy vs. no chemotherapy. Results have shown that women who have undergone chemotherapy for breast cancer are at an increased risk of developing LOD [HR 1.20, 95 % CI (1.08-1.33)]. In another study, non-central nervous system cancer patients, who have survived for at least 5 years, were compared to their cancer-free twins. Results showed that cancer survivors were more likely to have cognitive impairment (OR=2.10, 95 % CI 1.36-3.24, p-value <0.001) and twice as likely to have LOD. However, this observed relationship with LOD did not reach statistical significance (Heflin LH et al., 2005). In Taiwan, Chen et al (2016) investigated the relationship between LOD and head and neck cancer diagnosis using the Taiwanese National Insurance Health database. The study included approximately 20,000 participants and found that in individuals <65 years old, who have received radiotherapy with or without chemotherapy at a younger age, had almost a 3 fold higher risk of LOD compared to individuals who have undergone surgery for the treatment of cancer (YinyuanChen W et al., 2016).

In this study, I found that individuals with cancer in the non-T2DM cohort were at a higher risk for overall LOD [HR 1.16, 95 % CI (1.13-1.20)]. Particularly, the risk for unspecified dementia was higher among individuals with cancer compared to without [HR 1.19, 95 % CI (1.14-1.23)]. One limitation of my study is the lack of 'cancer treatment' as a potential confounder. Nevertheless, it is prudent to consider that in the non-T2DM cohort, the observed increased risk of LOD among individuals with cancer could be attributed to the abundance of cancer treatments used among cancer survivors in this cohort specifically, compared to the T2DM cohort.

It is also important to take note of other studies that have argued for invalidity of the "chemo brain" hypothesis, as a risk factor for LOD incidence in later life. Using the SEER database, Baxter et al (2009) reported nil significant association for individuals who received chemotherapy and LOD progression, after controlling for possible confounders. Another study on 62,565 women, followed up for 16 years, found that there was no significant association between chemotherapy and the risk for LOD or cognitive impairment (Du XL et al., 2010). Other studies conversely allude to the protective effect of a cancer diagnosis on LOD incidence (Driver JA et al., 2012). A recent study on 5209 veterans utilizing the Framingham study cohort, explored the effect of participants' cancer treatments i.e. chemotherapy and radiation, on the inverse association between cancer and AD-LOD (Driver JA et al., 2012). Results showed that chemotherapy lowered the risk for developing AD-LOD by almost 17% to 23% in specific types of cancer, in addition to the decreased risk seen from cancer itself. Hence, it is not possible to conclude that the reduced risk between cancer and AD is fully explained by chemotherapy. Conversely, non-significant results were seen with regards to the effect of radiotherapy. Further analysis on cancer patients (plus or minus chemotherapy), showed a 25% to 45% decrease of AD-LOD in individuals who had undergone chemotherapy (Driver JA et al., 2012).

A few notable studies that aimed to further explore the reported protective effect of chemotherapy, examined the effect of repurposing cancer drugs for the treatment of LOD in animal studies (Habchi J et al., 2016). This approach stemmed from earlier molecular studies which reported a marked decrease in neurotoxicity by the cancer drug, Nilotinib, where an increase in brain dopamine levels post treatment was proposed to halt neurodegeneration. This research avenue is

being explored even further given recent phase-II clinical trials investigating the effect of Nilotinib in Parkinson's disease (Georgetown University, USA 2017).

It is important to consider several limitations when examining the results from chemotherapy and LOD studies as well as understanding their implications. Evidently, studies on the risk of LOD in cancer patients are too few to make any direct inferences. Importantly, the limited studies available have mainly focused on cognitive impairment rather than progression to LOD. Furthermore, several studies on chemotherapy and cognitive impairment have shown that cognitive impairment could in fact start before chemotherapy as a result of other factors such as stress, depression or anxiety (Hermelink K, 2015). Additional concerns emanate from research showing that patients with LOD, concurrently diagnosed with cancer, are less likely to undergo invasive procedures or chemotherapy (Koppelmans V et al., 2013, Blustein J and Weiss L, 1998). Moreover, misdiagnosis of AD-LOD in individuals with cancer due to misinterpretation for a chemotherapy side effect, remains a notable limitation (Hutchinson AD et al., 2012). It is also important to remember, that the majority of studies have mainly involved breast cancer patients and their findings may not be applicable to other cancer forms.

5.4 LOD and Diabetes

The widely-reported finding of an increased risk of LOD in individuals with T2DM was not replicated in my study. Indeed, I found incidence rates of LOD in both cohorts to be comparable (overall incidence rate of LOD - 8.84 per 1,000 years in non-T2DM cohort, and 8.68 per 1000 in the T2DM cohort). In line with existing reports, the incidence rate of VaD was higher in the T2DM cohort (2.43 per 1,000 person years) compared to the non-T2DM cohort (0.94 per 1,000 person years).

It is important to note that the incidence of death was higher in the T2DM cohort (41.66 per 1,000 person years) compared to the non-T2DM cohort (38.90 per 1,000 person years). As a result, individuals in the T2DM cohort had a shorter follow-up period to develop LOD later in life.

Furthermore, upon the investigation of the age of T2DM diagnosis among individuals with LOD vs. without, only 10 % of the 11,450 individuals with LOD had an onset of T2DM diagnosis aged<65 years old. These numbers are in line with findings from the study by Muliner et al (2005), using the GPRD database, which reported only 30 % of the 44,230 individuals with T2DM, to have had an age of T2DM onset <65 years old. Interestingly, a study by Xu et al (2009) investigated the association between T2DM diagnosis (midlife vs. late-life) and risk of LOD. Authors showed that the diagnosis of diabetes during midlife (age of onset < 65 years old) revealed a stronger risk for LOD, compared to risk of LOD in individuals diagnosed with T2DM later in life (age of onset ≥65 years). Consequently, the high prevalence of late-life T2DM age of onset in my sample, could explain the comparable risk of LOD between individuals with and without T2DM, and the failure to observe the previously reported higher incidence of LOD in individuals with T2DM. Again, it is important to note the long pre-clinical (potentially slowly progressive) stages of both LOD and T2DM that is a generic limitation of all epidemiological studies attempting to explore mutual effects and or interactions and interdependencies between these disorder.

In the sections below, I discuss a few critical theories that provide some rationale for my observations of the comparable overall LOD incidence rates in both cohorts.

5.4.1 Antidiabetic drugs and LOD

An essential factor to consider in the LOD and diabetes relationship is the use of antidiabetic drugs, and its effect on the incidence of LOD and AD-LOD. Although research findings in this area still remain rather unclear and sometimes conflicting, a number of reports suggest a reduced risk of LOD in relation to the choice of antidiabetic medication. Consequently, the use of antidiabetic drugs could be one of the potential explanations for the somewhat similar incidence of LOD observed between the T2DM and non-T2DM cohorts in this study, thus a potential confounder of the associations observed in the T2DM group.

Reports on insulin resistance and its potential role in the complex aetiopathology of LOD and AD-LOD have encouraged researchers to explore the use of antidiabetic drugs for the treatment of

LOD and AD-LOD. A study by Beeri et al (2008) suggested that a combination of insulin and anti-diabetic drugs can significantly lower the neurofibrillary plaques in specific brain areas. Another study examined the effect of oral antidiabetic drug, solely and in conjunction with insulin in 104 mild to moderate AD patients, followed up for 12 months (Plastino M et al., 2010). Results revealed anti-cognate effects for sole use of oral antidiabetic medication: 56.5% worsening of cognitive functions in the antidiabetic drugs only group compared to a 23.2 % worsening in the group randomized to both antidiabetic drugs and insulin (Plastino M et al., 2010). Similar results were reported in a recent double-blind randomized-controlled trial on 104 adults with MCI randomized to either a low dose (20 IU) or high dose (40 IU) of intranasal insulin for 4 months (Craft S et al., 2012). The authors showed that an increase in insulin dosage leads to a significant improvement in the memory component of the Alzheimer disease assessment cognitive (ADAS-Cog) scale. Additionally, lumbar spinal fluid and brain PET scans obtained from a subset of the randomized participants confirmed changes in CSF biomarkers and metabolic dysfunction in both low and high dose groups (Craft S et al., 2012).

Several reviews have summarized the results from in vitro animal studies and clinical studies which examined the effect of different classes of antidiabetic drugs on AD and cognition (Yarchoan M and Arnold SE, 2014, Alagiakrishnan K et al., 2013) . Metformin is (and has been) the first choice treatment for T2DM, and acts via the regulation of glucose metabolism in the liver, brain and systemic tissues (American Diabetes Association). Interestingly, a recent population-based matched case control study in the UK used the CPRD database, for an in-depth study on the use of antidiabetic medication, including metformin in relation to AD (Imfeld P et al., 2012). Researchers in this study found that long term users of metformin (60 or more prescriptions) were in fact at greater risk for developing AD (OR =1.71, 96% CI 1.12-2.60) while other antidiabetic drugs did not have a significant effect on the risk for developing AD (Imfeld P et al., 2012). Similarly, a recent Australian study found that AD and cognitively impaired subjects, who are metformin users, performed worse on cognitive assessments compared to their non-metformin user-counterpart (OR 2.23, 95 % CI 1.05-4.75). Interestingly, subjects who were metformin users with additional intake of calcium supplementation had better cognitive performance (OR 0.41, 95 % CI 0.91-0.92) (Moore E et al., 2013). Conversely, a Taiwanese study found that the use of metformin significantly lowered the risk for LOD, even after adjusting for confounders such as

cerebrovascular disease (Hsu CC et al., 2011), alluding to a location-specific association for metformin use and LOD risk.

Thiazolidinedione (examples of which include rosiglitazone and pioglitazone) is another class of antidiabetic drugs, whose use has been explored in relation to LOD/AD-LOD. Animal studies have revealed a positive effect of thiazolidinediones on expression of AD-related biomarkers (Nicolakakis N and Hamel E, 2010). A study by Pederson et al (2006), showed that the administration of rosiglitazone to study animals (mice) elicited improved spatial learning and memory abilities, in comparison to the non-treated control animals.

Another study by Escribano et al (2010) showed that mice with prolonged treatment of rosiglitazone had a lower αβ burden in the brain and reduction of amyloid plaques. Human studies have also shown improved memory and changes in CSF amyloid β levels after 6 months, in subjects treated with rosiglitazone compared to placebo (Watson GS and Craft S, 2004). Conversely, a few studies found no effect of rosiglitazone on memory (Harrington C et al., 2011). Interestingly, a clinical trial on 511 participants randomized to either 4 or 8 mg of rosiglitazone showed no differences in cognitive and memory performance between both arms. However, further stratification by APOE genotype showed cognitive and functional improvement (only in APOE4 negative carriers who were on 8 mg of rosiglitazone) Risner ME et al. (2006).

Similar to rosiglitazone, pioglitazone has also been used in research for potential treatment of LOD/AD. Studies in mice transgenic models showed that pioglitazone treatment reversed learning deficits in the Morris water maze test (Papadopoulos P et al., 2013). Another study showed that pioglitazone presented improved cognitive effects only in female mice, inferring that the effect of pioglitazone on cognitive enhancement is gender related (Masciopinto F et al., 2012). Studies in humans have showed opposing findings on pioglitazone and its effect on cognition. A study on 67,731 non-demented and non-diabetic participants, followed up for a median of 2.4 years, was done to compare the risk of LOD with intake of select antidiabetic medications (Cheng C et al., 2014). Results showed that diabetes is associated with an increased risk for LOD, and this risk becomes weaker when participants use sulfonylureas and metformin, rather than thiazolidinedione (Cheng C et al., 2014). Another prospective cohort study, using 145,928 individuals above the age

of 60, found a 47 % decrease in incidence of LOD among individuals with long- term use of pioglitazone (Heneka MT et al., 2015). Interestingly, a current ongoing phase III, multicenter, double-blind randomized placebo controlled "prevention" trial, the "TOMMORROW study" is investigating the efficacy of low-dose pioglitazone in cognitively unimpaired elderly individuals, as a treatment to delay the onset of MCI due to AD, in cognitively normal individuals.

Recent research has also focused on the Glucagon like peptide -1 (GLP-1) class of antidiabetics such as exenatide. An animal study on the effect of exenatide showed beneficial effects on both short and long term memory in mice (Bomba M et al., 2013).

Finally, it is important to mention that elderly individuals with T2DM are more likely to also present (mainly vascular) co-morbidities and multi-morbidities, related to vascular or micro-vascular complications and may therefore require multi drug combination therapies (ex: antihypertensive drugs) compared to single drugs (Yurgin N et al., 2007). In the T2DM cohort, there was a higher prevalence of other relevant diseases (ex: hypertension, hypercholesterolemia, CeVD) compared to the non-T2DM cohort. As a result, investigating the specific effect of antidiabetic drug-use on risk of LOD still remains an inadvertently challenging endeavor. .

5.4.2 Lifestyle behavioral changes and LOD

Based on previous studies on LOD and T2DM, I was expecting a higher incidence of LOD in the T2DM cohort. However, I did not find a significant difference in incidence rates for overall LOD among both cohorts. One of the plausible explanations for this observation could be related to the shared risk factors between diabetes and LOD and, importantly, the better management of such lifestyle risk factors today.

Over the past epoch, the improvement of life expectancy has led to an increased prevalence of age-related chronic diseases, such as LOD and diabetes, among the elderly (Kinsella K and Phillips D, 2005). The increased prevalence of diabetes has been reported to increase the incidence of LOD (CDC, National center for Health Statistics). However, in recent years there has been an emerging

emphasis of the importance of lifestyle behaviors (ex: physical activity, smoking, diet, etc...) and their management. Physical activity and diet have been known to impact both T2DM and LOD risk, and have continuously been reported to be a key factor for managing T2DM (Boule NG et al., 2001). In fact, several reviews and meta-analyses have reported an improvement in disease progression and development of comorbidities in individuals with T2DM, as a result of improving lifestyle behaviors (Avery L et al., 2012, Schellenberg ES, 2013, Baker MK et al., 2011). In a 4-year RCT conducted in the US, 4503 overweight individuals with T2DM were randomized to either receive an intensive lifestyle intervention or diabetes support and education sessions. Results showed an 11.5 % and 7 % partial or complete remission of T2DM in the intensive lifestyle intervention arm after the first year and 4 years, respectively (Gregg EW et al., 2012).

Interestingly, over the last few decades, recent findings in Europe and US suggest a reduction in prevalence and incidence of LOD; primarily due to preventative interventions targeting lifestyle risk factors (Matthews FE et al., 2013, Rocca WA et al., 2011, Qiu C et al., 2013, Ahmadi-Abhari S et al., 2017) . In the UK, a decline of LOD incidence by 20 % has been reported over two decades in the cognitive function and ageing study I and II (CFAS I and II), mainly in men but not in women. Additionally, changes to LOD policies and support for early detection of LOD have also played a role in this observed decrease of incidence (Matthews FE et al., 2013).

Furthermore, cardiovascular disease, stroke and vascular risk factors have all been associated with LOD (Leys D et al., 2005, Vermeer SE et al., 2003) . Recent reports allude to a decrease in the incidence of such diseases leading to an overall decline in LOD incidence (Ahmadi-Abhari S et al., 2017, Wu Y-T et al., 2017, Qiu CRonchi DD and Fratiglioni L, 2007) . A very recent modelling study in England and Wales "the English longitudinal study of Ageing (ELSA)" on 17,906 individuals from 2000-2013, showed a decrease in LOD incidence by 2.7 % each year, even after accounting for mortality and dropout (Ahmadi-Abhari S et al., 2017). Similarly, another study examined 1065 individuals, 85-years old and above, and found that the prevalence of LOD decreased from 29.8% to 21.7% in 2008-10, especially for VaD; the authors attributed this finding to higher education, cognitive reserve and better treatment for stroke (Skoog I et al., 2017). The Framingham heart study has also investigated LOD prevalence and included 5202 individuals, 60 years of age and above. They found that the HR for LOD was reduced by 22 % (1980-early 1990)

to 38 % (late 1990s- early 2000s) and further to 44 % (late 2000s-2010), mainly due to better cardiovascular health and education (Satizabal C et al., 2016). Additionally, it is important to note the significance of several new medications introduced for the treatment of cardiovascular disease such as new-generation antihypertensives, anti-inflammatory drugs and statins. The introduction of these drugs and their potential neuroprotective value may have contributed to the decrease in the incidence of micro vascular, cardiovascular disease and stroke and consequently LOD (Rocca WA et al., 2011).

With that being said, we cannot disregard some limitations of several studies assessing LOD-trends not withstanding methodological issues, variation in dementia terminology and in diagnostic criteria, especially in the periods prior to the 1990s (Skoog I et al., 2017, Wu Y-T et al., 2017).

To conclude, it is possible that the comparable incidence of LOD observed in both cohorts of this study, is due to the decreased risk of cardiovascular disease and decline in stroke, as well as the better management of risk factors. The decline in vascular risk over the years could cause the decrease in LOD incidence, while at the same time increasing the life expectancy and increasing number of individual at risks for LOD.

5.5 Cancer and Diabetes

As anticipated, the overall incidence rate of cancer was higher in the T2DM cohort (23.69 per 1,000 person years) compared to the non-T2DM cohort (20.21 per 1,000 person years). Upon further stratification by sex, males had a higher incidence rate of cancer in both cohorts compared to females (Non- T2DM cohort: 25.54 vs 16.55 per 1,000 person years, T2DM cohort: 27.80 vs 19.35 per 1,000 person years).

Several previous studies have suggested an increased incidence of certain types of cancer in the presence of diabetes (Wideroff L et al., 1997, Hemminki K et al., 2010, Shikata KNinomiya T and Kiyohara Y, 2013, Giovannucci E et al., 2010). Particularly, some studies have reported an increased incidence of liver, pancreatic, stomach, colorectal, kidney, bladder and breast cancer in

individuals with T2DM (Larsson SCOrsini N and Wolk A, 2005, Larsson SCMantzoros CS and Wolk A, 2007, Kasper JS and Giovannucci E, 2006, Shimoyama S, 2013). The relative risk for pancreatic and liver cancers has been shown to be 2-fold and between 1.2-1.5 fold for colon, rectum, breast and bladder cancer, in individuals with T2DM (Giovannucci E et al., 2010). Furthermore, a number of meta- analyses investigating the risk of cancer incidence, found a higher risk of overall cancer (RR: 1.14) and a 1.27 fold higher risk of mortality in individuals with T2DM.

Research has shown a strong association between incidence of breast cancer and bowel cancer with T2DM (KM De Bruijn et al., 2013, Jiang Y et al., 2011, Ren X et al., 2009) . A meta-analysis combining over 30 cohort studies, showed a pooled RR of 1.27 for bowel cancer in individuals with T2DM (Jiang Y et al., 2011). Other studies have demonstrated similar associations, though specific for colon cancer, with the exclusion of rectal cancer (Ren X et al., 2009). One of the most widespread held theories for this association lies within the notion that individuals with T2DM are more likely to be exposed to bowel toxins, such as fecal bile acids, encouraging carcinogenesis (C Yao et al., 2014). Similarly, a meta-analysis summarizing over 20 studies, reported a RR of 1.23 for breast cancer in individuals with T2DM (KM De Bruijn et al., 2013). The influence of hyperinsulinemia on eostrogen has been suggested as a plausible reason for the reported increased incidence of breast cancer. Evidently, the bioactive eostrogen secreted in individuals with T2DM seems to encourage the multiplication of breast cancer cells (James R et al., 2011).

Similarly, in this study, the incidence of bowel (T2DM cohort: 2.39 per 1,000 person years vs. Non-T2DM cohort: 1.73 per 1000 person years) and breast cancer (T2DM cohort: 3.42 per 1,000 person years vs. Non-T2DM cohort: 2.61 per 1000 person years) was higher in individuals with T2DM compared to individuals without.

Conversely, prostate cancer has been reported to have an inverse relationship with T2DM (Kasper JS and Giovannucci E, 2006). In this study, there was a negligible association observed between prostate cancer and diabetes (T2DM cohort: 5.33 per 1,000 person years vs. Non-T2DM cohort: 5.63 per 1000 person years). It is important to note that several studies have pointed out the importance of the duration of diabetes on the risk for prostate cancer (Rodriguez C et al., 2005, Giovannucci E et al., 1998). In the cancer prevention II Nutrition Cohort, the authors investigated

5,318 incident prostate cases, and showed that the risk of prostate cancer was higher in the first 3 years post diabetes diagnosis (RR=1.23) with a decline observed 4 years post diabetes diagnosis(RR=0.63) (Rodriguez C et al., 2005). Another study, the "Health professionals Follow up study" found that there was a 24 % increase in risk for prostate cancer in the first 5 years after diabetes diagnosis (RR=1.24) in comparison to 10 years post diagnosis (RR=0.54) (Giovannucci E et al., 1998).

In this study, I was not able to account for the duration of diabetes in the cancer and diabetes relationship. Therefore, it could be that the observed decreased incidence of prostate cancer in individuals with T2DM was nominal, due to the majority of prostate cancers being diagnosed with close proximity, following the diagnosis of T2DM. It is also plausible that individuals diagnosed with T2DM are more likely to be examined for diabetic complications and undergo general health screening, including PSA testing (Rodriguez C et al., 2005); which may well account for the comparable incidence of prostate cancer observed between both non-T2DM and T2DM cohorts.

Finally, the majority of studies investigating the relationship between lung cancer, skin cancer and T2DM, reported nil significant association (Giovannucci E et al., 2010) . Interestingly, in this study I observed an increased risk for lung cancer (T2DM cohort: 2.21 per 1,000 person years vs. Non-T2DM cohort: 1.72 per 1000 person years) and melanoma skin cancer (T2DM cohort: 1.70 per 1,000 person years vs. Non-T2DM cohort: 0.32 per 1000 person years) in individuals with T2DM. To my knowledge, to date there are no documentations of a direct biological underpinning mechanism (such as shared gene pools) link between lung or melanoma skin cancer and T2DM. Nevertheless I hypothesize that the observed increased risk may be driven by the possible shared mechanisms between diabetes and these forms of cancer, such as insulin resistance, hyperinsulinemia and hyperglycemia (Giovannucci E et al., 2010, Heiden MV et al., 2009, Dankner R et al., 2016).

5.6 Limitations and Strengths

In this section, I will present the overall limitations associated with my research project and the key strategies attempted to mitigate such limitations. Some examples include actual study design, issues inherent to fundamental study data from CPRD such as under-diagnosis, misdiagnosis of investigated conditions, and missing data.

5.6.1 Study Design

As this is an observational study, one of the limitations is the inability to infer a causal component to any associations identified. One of the principal challenges in observational studies is related to the issues of precision and validity (Carlson MDA and Morrison RS, 2009). However, these issues can be mitigated by selecting the appropriate methodological approaches and strategies to minimize biases.

Validity is a concern that must be tackled for optimal interpretation of results. This includes both internal and external validity (Carlson MDA and Morrison RS, 2009). Internal validity can be dealt with by having a control or comparison group for the exposure cohort. In this study, individuals without T2DM were selected at random for comparison and stratified by cancer exposure. Furthermore, CPRD is one of the world's largest EHR databases, encompassing all regions within the UK, with more than 11 million patients included. The large sample size and coverage available in CPRD, ensures external validity, thus making the sample generalizable and representative of the whole population.

RCTs are known to be the golden standard in clinical research, as they are thought to contain a more reliant methodology for the identification of causal relationships. However, observational studies offer the advantage of the longitudinal nature of data and extended follow-up periods. This is particularly important in studies of the elderly, where most diseases are more prevalent with increasing age. The key strength of this study resides in its very large sample size, which included

197,294 cancer and 63,183 LOD cases in total, identified in both non-T2DM and T2DM cohorts. Most of the previously reported studies that have explored this relationship did not have such large sample sizes and long follow-up periods in their population based cohorts. The largest sample size used in previous studies was that of the Danish National patient registry (DNPR) with 216,221 cancer patients included and a matched comparison cohort of 1,081,097 individuals. However this study only explored the relationship between NMSC and LOD and did not explore different cancer types (Schmidt SA et al., 2017).

Furthermore, the large sample size available in this study has allowed me to attempt an in-depth exploration of the relationship between LOD and cancer, including stratification of findings by disease-type. Stratification by LOD-type in the analysis revealed a relatively small sample available for the probable and possible AD groups. This was unsurprising given the complexity in definition and case ascertainment of AD in related research. Thus, I have further discussed the challenges typically encountered with accurate definition of AD in research and clinical practice in the section below on definition of AD and LOD. Additionally, it is important to note that the largest LOD group was the unspecified dementia group, and it is difficult to rule out the possibility that some of these cases may have been individuals with AD-LOD. The long pre-clinical stages that are typical of both LOD and T2DM represents another important limitation of epidemiological studies, such as this work, exploring their inter-relationships.

An important feature of EHR databases resides in the extensive medical and clinical information captured in a medical setting, by clinical staff and GPs. This more or less warrants accurate medical data compared to self-reported medical data. The medical diagnoses available in CPRD are further supported by the linkage databases that are also available, providing further information on hospitalization and mortality. Nevertheless, it is also critical to highlight that other relevant information such as lifestyle and behavioral data (physical activity, smoking, alcohol) are poorly captured and, mainly, self-reported.

Finally, one cannot disregard and account for the time-span between the incidence of each study diagnosis (T2DM, LOD and cancer) given the significant variance in pre-diagnostic phases and clinical course, as well as variability with recording of initial clinical manifestations (typically

retrospectively documented) by the GPs. Nevertheless, CPRD provides longitudinal data with long follow-up periods, allowing to characterize and evaluate disease progression to calculate incidence rates.

5.6.2 Underdiagnosis of LOD

In this study, I found that individuals diagnosed with cancer were at a higher risk of LOD in the non-T2DM cohort. In addition to the possibility of chemotherapy and comorbidity playing a role as discussed in the previous sections; another important prospect is the underdiagnosis of LOD.

Underdiagnosis of LOD in primary care is well-documented (Connolly A et al., 2011b). A US study using 200,000 participants >65 years old from the DARTNet institute practice performance registry dataset revealed a deficiency in LOD rate detection and management in general practice. Similarly, a meta-analysis of 15 studies, conducted by Mitchell et al in 2011 found that although GPs were able to identify 75 % of the LOD cases, they recorded this medical finding in only 40 % of individuals with LOD (Mitchell AJ et al., 2011). In the UK, GPs are very cautious about reporting and referring patients with cognitive complaints to secondary care (Bamford C et al., 2007) , especially given the paucity of effective medicines for patients with early symptoms of LOD (Vernooij-Dassen MJ et al., 2005) . Although, there is emerging evidence that the rates for LOD underdiagnosis is decreasing (Borson S et al., 2013), there still remains the common belief among practitioners that changes in cognition are simply due to old age and there is nothing that can be done about it (Harada C et al., 2013). Notably, a financial incentive was introduced in April 2006 in the UK to increase awareness and detection of LOD, especially in the primary care setting (Mukadam N et al., 2015). Several studies have argued that since the implementation of this program, there has been an increase in the detection rates for LOD, among general practices in the UK (Knapp M et al., 2014, Donegan K et al., 2017). In addition to the GP's role in the proper documentation of an LOD diagnosis in medical records, patients may also contribute to the issue of LOD underdiagnosis. This is evident from studies reporting that patients might be reluctant to report their cognitive symptoms to the GP, due to the cultural beliefs about ageing (Valcour V et al., 2000) and the feelings of shame associated with it (Arlt S et al., 2007).

Nevertheless, the issue of underdiagnosis of LOD in this study was mitigated by using a combination of methods to identify as many LOD cases as possible in CPRD; as well as to capture any under- reported cases of LOD. An overall algorithm was built for reporting all possible LOD cases and comprised of: (1) LOD cases identified from CPRD using medical READ and PRIMIS codes (2) LOD cases identified from CPRD using product codes for dementia drugs (3) LOD cases identified from valid tests scores for the most common dementia cognitive tests and (4) LOD cases identified from the HES/ONS linkage data.

5.6.3 Definition and Case Ascertainment of LOD and AD

In addition to the issue of underdiagnosis of LOD in primary care, it is important to acknowledge the ongoing debate on the nosology, diagnosis and aetiological complexity of LOD and AD. Over the decades, there has been a substantial change in the diagnostic criteria and definition of AD and LOD. The diagnostic definition of AD was first reported in 1984 by the National-Institute of Aging-Alzheimer's-Association (NIA-AA) and the Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) (McKhann et al 1984). The criteria were revisited 27 years later (2011 NIA-AA criteria) and updated to include the concept that the diagnosis of AD can only be established postmortem by autopsy or biopsy. Furthermore, the authors recommended the use of the terms of possible and probable AD dementia with evidence of AD pathophysiological process for a more accurate definition of AD in research studies. They have additionally incorporated the importance of investigating biomarkers, such as imaging and cerebrospinal fluid markers, in Alzheimer dementia to increase the likelihood and accuracy of the diagnosis(McKhann GM et al., 2011b). In parallel, the NIA-AA has also attempted to define diagnostic criteria especially developed to cover the preclinical stage of AD and mild cognitive impairment (MCI) (Albert M, 2011). The International working group (IWG), working closely with the NIA-AA group, also highlighted the importance of differentiating between the actual clinical disease-AD and the disease pathology, which can only be established by observing neuronal lesions and plaques on autopsy (Dubois B, 2014).

The NIA-AA criteria are currently being revised to now define the disease state, based on the biomarker evidence for amyloid & tau abnormalities and neurodegeneration, as an integral part of the diagnostic criteria. Furthermore, AD is increasingly seen as a continuum, starting from the asymptomatic stage I to various stages based on the degree and extent of memory and cognitive decline. Asymptomatic individuals with evidence of neurodegeneration but with normal amyloid and tau are now defined as "Suspected Non-Alzheimer's disease Pathophysiology" (SNAP) (Jack CR et al., 2016). However, the required biomarker studies require expensive technology imaging platforms that are scarce outside specialized research centres, and not yet part of the clinical diagnostic armamentarium of clinical practice in the United Kingdom and most (if not all) other industrialized countries.

In this study, the most recent NIA-AA 2011 criteria were used in the form of a diagnostic algorithm to categorize individuals with probable AD, as it was assumed that, in line with these criteria, the physician- made diagnosis of AD (when reported) resided in the presence of progressive decline of memory, cognitive and functional abilities, in the absence of other pathologies or features suggestive of other dementia forms;. Nevertheless, there are several important gaps in our understanding of biological mechanisms and, therefore, in AD nosology that still remain main barriers in defining and differentiating AD and other LOD forms in clinical and research settings, as well as in the discovery and development of disease modifying therapies (Gauthier S et al., 2016). Therefore, it comes as no surprise that the possible and probable AD categories were of relatively small sample size, compared to the size that may have been obtained with a combination of all cases into an 'AD' group. The latter unquestionably introduces bias to the results generated and unfortunately is not uncommon in research studies on LOD and AD.

The diagnosis and classification of AD and LOD has advanced over the years; however, several challenges remain with the diagnosis of LOD in primary care, the primary contact of the patient (Karantzoulis S and Galvin J, 2011). Research suggests that GPs seem to remain reluctant in diagnosing individuals with AD, primarily due to lack of confidence in skillset and knowledge depth for diagnosing LOD types and AD and the lack of specific therapies for the different LOD forms (Boustani M et al., 2003) . This is further reflected by the manner in which GPs compute

LOD medical information into EHR databases. The majority of the medical codes entered are usually non-specific, without any suggestion for the type of LOD. GPs sometimes also provide information on LOD in the form of free text rather than a diagnostic code in electronic records. LOD entered in free medical notes are usually not captured by researches, as they usually rely on diagnostic and accurate coded information (Rait G et al., 2010). To further supplement this issue, this study has found the "unspecified dementia" to be the largest LOD group. This group was mainly comprised of a combination of individuals with an unspecified code for LOD, codes for dementia drugs solely (typically symptomatic for cognitive decline in general but applied to all LOD forms), or something as simple as a code indicating that the individuals are being reviewed for LOD such as dementia annual review, dementia monitoring plan agreed, referral to dementia care advisor, etc.

Furthermore, it is important to note that LOD is a clinical syndrome and therefore is very much reliant on the clinician's clinical judgement and perception of LOD, AD and the diagnostic criteria (Kukull WA et al., 1990). Hence, the ability to differentiate between various subtypes of LOD can be rather challenging for the clinician, especially given the unavailability of biomarker-related technologies and tools in clinical practice. Thus the most reliable and accurate diagnosis is still based on post-mortem pathological findings (McKhann GM et al., 2011a). To complicate this matter even further, the majority of individuals who present with cognitive impairment usually have multiple comorbidities, making it even more difficult for the clinician to decide with precision the specific disease type and any transitional periods from asymptomatic to symptomatic AD (Sperling RA et al., 2011).

Another important issue to consider is the prevalence of mixed pathologies related to LOD and AD on post- mortem studies of LOD (including AD) patients, over the age of 75, i.e. the age group of the vast majority of dementia patients, thus further complicating the definite clinical diagnosis of LOD sub-types (Bennett DA, 2017, Chui HC and Ramirez-Gomez L, 2015). It has been well established that mixed pathologies (amyloid, tau, micro and other vascular pathological features and Lewy bodies) co-occur in the majority of patients with LOD over the age of 75 (Schneider JA et al., 2007). A US study that included 483 autopsied probable AD and MCI individuals from the Religious study and the Rush Memory and Aging Project, found that about 45 % of those

individuals have mixed pathology , the most common being macroscopic infarcts (Schneider JA et al., 2009) . Similarly, the longitudinal Cambridge city over-75s cohort (CC75C) study found that 22 % of the 213 included autopsied participants had mixed dementia mainly consisting of Alzheimer type and cerebrovascular pathology, especially micro infarcts (Brayne C et al., 2009). Matthews et al (2009) used the CFAS prospective longitudinal study with information on 456 autopsied brains, and found that multiple pathologies mainly determine the overall burden of LOD rather one specific pure pathology.

To conclude, there are, still, significant gaps in our understanding of the nosological boundaries and definitions of LOD, VaD and AD. Consequently, this makes the standardization and comparability of studies complicated and even more challenging.

5.6.4 Missing Data

Most primary EHR databases have significant proportions of missing data for pivotal variables of interest (Cooper LA et al., 2011) . Although EHR databases offer large opportunities for research, their primary objective is mainly to improve disease clinical management- diagnosis and treatment. Usually in research studies, one is able to collect the information needed at regular intervals of time as required by the study. In EHR databases, such as CPRD, information is recorded intermittently. In other words, unless the patient visits the GP for a consultation, it is impossible to obtain any updated information for that patient. Accordingly, a missing value in CPRD could primarily indicate that the patient did not visit their GP.

In this study, a significant amount of data on BMI, alcohol and smoking were missing at baseline in both cohorts for approximately 30 % of the individuals. This is not uncommon in EHR databases and has been previously reported in studies assessing missing data in CPRD (Bhaskaran K et al., 2013, Booth HP et al., 2013). A longitudinal study used CPRD to assess records of a random sample of a million patients aged 16 and above, and found that BMI completeness was 37 % in 1994, and then increased to 77 % from 2005 to 2011. Furthermore, the authors reported that this increase seemed to be higher in females and increased with age (Bhaskaran K et al., 2013).

Smoking is another important lifestyle variable that has been under recorded in CPRD. A study investigating smoking records in CPRD in 1996, found that former smoking and current smoking was under recorded, when compared to national health survey data (Lewis JD and Brensinger C, 2004). However, a more recent study by Booth et al 2013, has reported an improvement in smoking records between 2007 and 2011. The authors primarily attributed their findings to the introduction of the QOF incentive, to encourage practices to collect information on smoking and provide cessation advice (Booth HPPrevost AT and Gulliford MC, 2013). Similarly, a GPRD study assessing the prevalence of alcohol use disorders in the UK, found that GPs tend to underreport heavy alcohol drinkers (Cheeta S et al., 2008). Additionally, it was found that approximately 50 % of men, who consume more than 20 units of alcohol per week, underreport their alcohol consumption at registration (Marston L et al., 2010).

The assumption of the MAR mechanism in this study, allowed for a complete powerful statistical analysis, through the use of appropriate methods for handling incomplete data (Carpenter JR and Kenward MG, 2007, Schafer JL and Olsen MK, 1998, Carpenter JR et al., 2006). Several statistical methods have been used to handle missing data in large databases; to avoid the risk of bias. The most commonly used ones are the Multiple Imputation (MI) and the Inverse Probability Weights (IPW). MI of missing data has been applied more widely compared to other techniques, but is fairly complex and demanding in terms of computation and model building; this may well lead to a higher probability of bias and inaccurate results (Sterne JAC et al., 2009b, Seaman SR et al., 2012). On the other hand, IPW is a much simpler technique which assumes the probability of a complete cases model (Seaman SR et al., 2012). Using the IPW method, each participant in the study was weighted by the inverse probability of a complete case; thus allowing the data to be weighted in a way that is representative of the whole sample (Seaman SR et al., 2012). In this study, the IPW was used to account for the missing values of BMI, alcohol consumption and smoking status, taking into consideration that any established confounder effects (on the exposure or outcome) need to be interpreted with caution.

As this study mainly investigated multifactorial diseases of the elderly, one cannot disregard the importance of lifestyle covariates such as BMI, smoking and alcohol in this epidemiological study.

Based on preliminary analysis for cancer and LOD, I have adjusted for these variables in the final cox models and assessed the relationship between LOD and cancer. It is true that due to the proportion of missing data in the sample, I was careful not to make any inferences or establish any confounder effects for these lifestyle variables. However, I consistently observed an interesting association between LOD and BMI for both cohorts in the study. Individuals who were underweight had a higher risk of LOD (T2DM: 1.39 (1.07-1.80), Non-T2DM cohort: 1.49 (1.44-1.55)) compared to individuals with normal BMI, while individuals who were overweight (T2DM: 0.86 (0.80-0.92, Non- T2DM cohort: 0.78 (0.76-0.80)) or obese (T2DM: 0.83 (0.78-0.90, Non-T2DM cohort: 0.74 (0.71-0.78)) had a lower risk of developing LOD. Interestingly, there have been a few studies emerging with similar results (Qizilbash N et al., 2015, Walters K et al., 2016). In a study on BMI and risk of LOD in two million people over two decades using CPRD, it was found that being underweight in middle and old age carries an increased risk of LOD over two decades. These findings oppose the known hypothesis that obesity in middle age could increase the risk of LOD in old age (Qizilbash N et al., 2015). Another study by Walters et al 2016, which predicted the LOD risk in primary care using the THIN database, has also shown a small negative association between increasing BMI and LOD diagnosis in a risk model for a cohort of 60-79 and 80-95 year olds.

In this study, the age of cohort entry was at least 65 years of age; as a result I did not have the opportunity to explore middle-aged individuals. Accordingly, the observed effects of BMI in the elderly could be due to low BMI measurements captured right before diagnosis of LOD. Nonetheless, it is important to note that all the studies that have found similar results on BMI and LOD, have used large primary care EHR databases. Hence, issues of missing data remain a limitation in such studies, given the various methods applied for handling missing and their potential effect on the association between BMI and LOD.

5.7 Summary

In this chapter, I have discussed the findings observed in this study in relation to related and relevant literature on this research topic. Following an in depth exploration of the relationships between T2DM, cancer and LOD using a highly powered study design, my main finding, contrary

to some reports in the literature, is that cancer diagnosis may not have a protective effect on overall LOD, as well as AD-LOD incidence. Importantly, the appropriate use of statistical methods and competing risk analysis needs to be considered when accounting for mortality selection. Furthermore, I have proposed several other important considerations that need to be taken into account when investigating the LOD and cancer relationship, such as chemotherapy and comorbidities.

In this study, I have explored the incidence of LOD and cancer in both non-T2DM and T2DM cohorts. In line with related studies, I have shown that the incidence of LOD and cancer increases with age, with a higher incidence of cancer in males and higher incidence of LOD in females. Interestingly, my data showcases comparable rates for incidence of LOD in both non-T2DM and T2DM cohorts. This is in contrast to the numerous studies suggesting that T2DM increases the risk of LOD. Therefore, I have put forward several possible explanations for my observations, such as the putative effect of anti-diabetic medications and of lifestyle changes on the risk of LOD. Nonetheless, the incidence of cancer was evidently higher for individuals with T2DM compared to non-T2DM.

The limitations and strengths of this study were also presented in this section, along with the use of the highly resourceful CPRD database and issues with study design, under-diagnosis and misdiagnosis of LOD. Moreover, I have further explored the effect of missing data and missing data concepts and why I have opted to use the IPW method. In the next section, I will describe the highlights of my study in view of my perception of the current literature, and provide some insight on future directions and overall importance and translation potential of these findings in the public health space.

CHAPTER 6 – CONCLUSION AND PERSPECTIVES

Previous studies have suggested that individuals with cancer are less likely to develop late-onset dementia, especially dementia attributable to Alzheimer's disease. The reported protective effect purports a lower risk of cancer amongst individuals diagnosed with late-onset dementia. Having conducted a systematic review of the literature around this topic, I found 15 studies that explored associations between late-onset dementia (dementia attributable to Alzheimer's disease) and cancer. The majority of the studies were population-based and reported inverse associations between late-onset dementia (dementia attributable to Alzheimer's disease) and cancer. Several of those studies attributed their findings to the multifaceted biological mechanisms underpinning the investigated diseases. At the same time, other studies have argued that the observed inverse association is a result of statistical and methodological limitations, such as underdiagnosis of dementia, ascertainment bias, and selective mortality.

The true underlying causes for this putative inverse relationship remains largely unclear. There are several biological pathways, such as chronic inflammation and insulin resistance, which have consistently been reported to impact both late-onset dementia and cancer diseases. The multifactorial nature of cancer and late-onset dementia, as well as the shared risk factors between both diseases, could further shed light into the possible links and common pathways. Importantly, T2DM is a risk factor for both cancer and late-onset dementia, and the three diseases have been found to share several biological similarities, in terms of metabolic and mitogenic mechanisms. Given the important role that T2DM has in the cancer and late-onset dementia pathways, it is pivotal to explore the cancer and late-onset dementia relationship in the context of T2DM.

I attempted a robust investigation exploring associations between cancer and late-onset dementia in individuals with and without T2DM, using a large-scale routine English primary care database (CPRD). Upon calculation of the incidence rates of cancer and late-onset dementia, parallel findings with reported literature were observed, whereby the incidence of late-onset dementia and cancer increased with age, with a higher incidence of cancer in males than females. Late-onset dementia incidence rates were noted to be higher in females, a finding in line with existing reports albeit in smaller cohorts. Interestingly, this study did not find a higher incidence of late-onset dementia in individuals with cancer compared to individuals without. For all intents and purposes, I have shown from my large-scale, highly powered study that upon accounting for death as a

competing risk and accurately identifying the exposure variable, there is no inverse association between cancer and late-onset dementia that is T2DM dependent.

It is yet important to note, especially given the findings from this study, that the plausibility of shared biological and genetic mechanisms between the two diseases i.e. cancer and late-onset dementia, cannot be excluded. These mechanisms might not be directly associated with an inverse relationship between cancer and late-onset dementia per se, but they can offer insightful information into mechanistic actions and pathways involved in cancer and late-onset dementia progression. It is well-accepted that cancer, late-onset dementia and T2DM are multifactorial diseases. The prevalence of comorbidities in the elderly further complicates the investigation of drugs and novel compounds targeting these conditions. Nevertheless, exploring new drugs and compounds that could display insulin-like behavior, while also impeding tumor multiplication and facilitating neuroprotective activity, could be promising. Thus, designing longitudinal population-based studies to test such compounds and assess their efficacy on modifying pathologies associated with cancer and late-onset dementia, remains imperative.

This study had several limitations including type of study, underdiagnosis and misdiagnosis of late-onset dementia, as well as missing data. As described in the previous section, I mitigated the complexity in the identification and classification of underdiagnosed dementia attributable to Alzheimer's disease, by developing a combination of sequential algorithms. These algorithms further proved the need for national policies to improve the referral and detection of dementia. The definition of late-onset dementia and dementia attributable to Alzheimer's disease is another complicated issue that puzzles researchers world-wide, and the diagnostic criteria for dementia attributable to Alzheimer's disease is continuously under revision. Furthermore, future studies could capture a larger sample of T2DM individuals by designing algorithms that could include antidiabetic drugs and routine recordings of HBA1C levels, in addition to the standard use of medical codes defining individual with T2DM diagnosis. Lastly, an important limitation in this study and all epidemiological studies remains to be the long pre-clinical stages that are typical of both LOD and T2DM.

Due to time constraints, I was not able to capture other possible significant factors that could play a role in the cancer and late-onset dementia relationship. It would have been particularly interesting to examine the effect of chemotherapy and antidiabetic therapies in this study. Another interesting aspect that I would have liked to cover is a separate analysis for other outcomes, such as incident stroke, which is not known to share an inverse relationship with cancer, 'in addition to', as well as 'instead of' late-onset dementia, as the neurological disease outcome of interest, to further account for mortality bias.

The majority of studies on cancer and late-onset dementia are population-based studies that utilize registry based data. Thus it is crucial to ascertain a uniform strategy for the identification of cases as well as statistical methods. The standardization of these processes will allow the comparability of various studies, and the proper identification of cumulative risks amongst the diseases of interest.

Clinical based research exhaustively targeting T2DM, cancer and late-onset dementia is imperative for disentangling the associations, and molecular mechanisms, underlying these diseases. Further research in this area could strategically inform the development of novel diagnostic and therapeutic drugs, for the treatment of cancer and late-onset dementia. Moreover, it may contribute to the formulation of public health guidelines and prevention strategies. Developing clinical based studies to target these three diseases and investigate various novel treatments is hopeful, but it is important to acknowledge that there is still much more to learn.

In spite of the above limitations, this study was a much needed undertaking to comprehensively explore the relationship between three highly prevalent diseases, and to better delineate the enigmatic associations between them. To my knowledge, this is the first study to explore the late-onset dementia and cancer relationship in the UK with such a large cohort sample, and the first and highest powered globally to investigate this association in individuals with T2DM.

"Dementia and Cancer: It's too complicated", wrote Mary Ganguli, a dementia research expert in this field, in her latest publications. I hope that this study has shed some light into the importance of exploring these relevant diseases concurrently, as well as encouraged future studies to investigate some of the shared biological mechanisms and genetic pathways underpinning these three diseases.

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Appendix01:

Ovid Medline Search:

1. Alzheimer$.ab,ti.
2. Dementi$.ab,ti.
3. (lewy$ adj2 bod$).ab,ti.
4. (chronic adj2 cerebrovascular).ab,ti.
5. ("organic brain disease" or "organic brain syndrome").ab,ti.
6. (cerebr$ adj2 deteriorat$).ab,ti.
7. Alzheimer Disease/
8. Dementia/
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. Neoplas$.ab,ti.
11. Cancer$.ab,ti.
12. Carcinoma$.ab,ti.
13. Tumour$.ab,ti.
14. Tumor$.ab,ti.
15. Adenocarcinoma$.ab,ti.
16. Leukemi$.ab,ti.
17. Leukaemia$.ab,ti.
18. Lymphoma$.ab,ti.
19. Malignan$.ab,ti.
20. Melanoma$.ab,ti.
21. Sarcoma$.ab,ti.
22. exp Neoplasms/
23. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 9 and 23

Appendix02:

MEDCODES	DESCRIPTION
4693	[X] Unspecified dementia
6578	Vascular dementia
7323	Uncomplicated senile dementia
7572	– Lewy body dementia
8934	[X]Subcortical vascular dementia
9509	[X]Dementia in Parkinson's disease
11175	Multi-infarct dementia
12621	Dementia with other diseases
18386	Senile dementia with paranoia
19393	[X]Vascular dementia, unspecified
19477	Arteriosclerotic dementia
21887	Senile dementia with depression
26270	[X]Lewy body dementia
29512	Senile degeneration of brain
31016	[X]Mixed cortical and subcortical vascular dementia
37015	Senile dementia with delirium
41089	Senile dementia with depressive or paranoid features NOS
42279	Arteriosclerotic dementia NOS
43089	Uncomplicated arteriosclerotic dementia
43292	Arteriosclerotic dementia with depression
44674	Senile dementia with depressive or paranoid features
46488	[X]Vascular dementia of acute onset
53446	[X]Delirium superimposed on dementia
55313	Other vascular dementia
55467	Arteriosclerotic dementia with paranoia
56912	Arteriosclerotic dementia with delirium
64267	[X]Dementia in other specified diseases classif elsewhere
5931	H/O: dementia
12710	Dementia annual review
55023	Dementia monitoring
85853	Dementia monitoring administration
103193	Antipsychotic drug therapy for dementia
103445	Referral to dementia care advisor
107389	Assessment of psychotic and behavioural symptoms of dementia
107402	Severe cognitive impairment
108228	Dementia advance care plan agreed
108268	Review of dementia advance care plan
108391	Dementia advance care plan declined
83576	Dementia monitoring second letter
49674	Dementia monitoring first letter
89036	Dementia monitoring third letter

Prodcode	productname
11751	Rivastigmine 3mg capsules
57627	Rivatev 4.6mg/24hours transdermal patches (Teva UK Ltd)
57171	Erastig 9.5mg/24hours transdermal patches (Teva UK Ltd)
55928	Exelon 4.5mg capsules (Waymade Healthcare Plc)
36976	Rivastigmine 4.6mg/24hours transdermal patches
56771	Rivastigmine 3mg capsules (Dr Reddy's Laboratories (UK) Ltd)
11546	Exelon 1.5mg capsules (Novartis Pharmaceuticals UK Ltd)
5616	Exelon 6mg capsules (Novartis Pharmaceuticals UK Ltd)
60723	Rivastigmine 6mg capsules (Waymade Healthcare Plc)
58780	Voleze 9.5mg/24hours transdermal patches (Focus Pharmaceuticals Ltd)
11752	Rivastigmine 4.5mg capsules
53882	Rivastigmine 2mg/ml oral solution
37957	Exelon 9.5mg/24hours transdermal patches (Novartis Pharmaceuticals UK Ltd)
11827	Rivastigmine 2mg/ml oral solution sugar free
37444	Exelon 4.6mg/24hours transdermal patches (Novartis Pharmaceuticals UK Ltd)
11716	Exelon 3mg capsules (Novartis Pharmaceuticals UK Ltd)
4597	Rivastigmine 1.5mg capsules
9786	Rivastigmine 6mg capsules
20404	Exelon 4.5mg capsules (Novartis Pharmaceuticals UK Ltd)
37132	Rivastigmine 9.5mg/24hours transdermal patches
18556	Exelon 2mg/ml oral solution (Novartis Pharmaceuticals UK Ltd)
7329	Galantamine 20mg/5ml oral solution sugar free
5334	Reminyl 12mg tablets (Shire Pharmaceuticals Ltd)
10255	Galantamine 8mg modified-release capsules
61476	Acumor XL 24mg capsules (Generics (UK) Ltd)
24088	Reminyl XL 24mg capsules (Shire Pharmaceuticals Ltd)
11635	Galantamine 12mg tablets
9854	Reminyl 4mg tablets (Shire Pharmaceuticals Ltd)
18587	Reminyl XL 8mg capsules (Shire Pharmaceuticals Ltd)
11654	Galantamine 8mg tablets
48482	Galsya XL 8mg capsules (Consilient Health Ltd)
55720	Gatalin XL 24mg capsules (Aspire Pharma Ltd)
10187	Galantamine 4mg tablets
20140	Reminyl XL 16mg capsules (Shire Pharmaceuticals Ltd)
60493	Galantex XL 24mg capsules (Creo Pharma Ltd)
56709	Gatalin XL 16mg capsules (Aspire Pharma Ltd)
7361	Galantamine 24mg modified-release capsules
29288	Reminyl 4mg/ml oral solution (Shire Pharmaceuticals Ltd)
14309	Galantamine 16mg modified-release capsules
48015	Galsya XL 24mg capsules (Consilient Health Ltd)
18062	Reminyl 8mg tablets (Shire Pharmaceuticals Ltd)
9966	Ebixa 5mg/pump oral solution (Lundbeck Ltd)

38976	Memantine 5mg+10mg+15mg+20mg Tablet
61385	Nemdatine 10mg tablets (Actavis UK Ltd)
6225	Memantine 10mg tablets
39240	Memantine 20mg tablets
57139	Ebixa 10mg tablets (DE Pharmaceuticals)
61618	Nemdatine 20mg tablets (Actavis UK Ltd)
39363	Ebixa 20mg tablets (Lundbeck Ltd)
18800	Ebixa 10mg tablets (Lundbeck Ltd)
39362	Ebixa tablets treatment initiation pack (Lundbeck Ltd)
11837	Memantine 10mg/ml oral solution sugar free
56600	Donepezil 5mg tablets (Zentiva)
37188	Aricept Evess 10mg orodispersible tablets (Eisai Ltd)
2931	Donepezil 10mg tablets
35088	Donepezil 10mg orodispersible tablets sugar free
60107	Donepezil 5mg tablets (Alliance Healthcare (Distribution) Ltd)
53842	Aricept 5mg tablets (Waymade Healthcare Plc)
36848	Aricept Evess 5mg orodispersible tablets (Eisai Ltd)
59871	Donepezil 10mg/5ml oral suspension
2930	Donepezil 5mg tablets
35179	Donepezil 5mg orodispersible tablets sugar free
5247	Aricept 10mg tablets (Eisai Ltd)
5400	Aricept 5mg tablets (Eisai Ltd)
58947	Donepezil 10mg tablets (Accord Healthcare Ltd)
58709	Donepezil 10mg tablets (A A H Pharmaceuticals Ltd)
58937	Exelon 13.3mg/24hours transdermal patches (Novartis Pharmaceuticals UK Ltd)

Appendix03:

MEDCODES	DESCRIPTION
1917	Alzheimer’s disease
7664	[X]Dementia in Alzheimer's disease
16797	Alzheimer's disease with early onset
29386	[X]Dementia in Alzheimer's disease, unspecified
30706	[X]Dementia in Alzheimer's dis, atypical or mixed type
32057	Alzheimer's disease with late onset
38678	[X]Dementia in Alzheimer's disease with late onset
49263	[X]Dementia in Alzheimer's disease with early onset
59122	[X]Other Alzheimer's disease

Appendix04:

Medcode	Description
101095	[M]Grade 1 (Stage pTa) papillary urothelial/transit cell ca
102244	[M]Grade 2 (Stage pTa) papillary urothelial/transit cell ca
101978	[M]Grade 3 (Stage pTa) papillary urothelial/transit cell ca
97091	[X]2ndry malignant neoplasm/bladder+oth+unsp urinary organs
7187	Carcinoma in situ of bladder
41571	Malignant neoplasm of bladder neck
44996	Malignant neoplasm of dome of urinary bladder
36949	Malignant neoplasm of other site of urinary bladder
38862	Malignant neoplasm of trigone of urinary bladder
15644	Malignant neoplasm of urethra
779	Malignant neoplasm of urinary bladder
31102	Malignant neoplasm of urinary bladder NOS
35113	Malignant neoplasm of urinary tract
47801	Malignant neoplasm, overlapping lesion of bladder
9712	Papillary transitional cell carcinoma
22146	Secondary malignant neoplasm of bladder
73213	Secondary malignant neoplasm of other urinary organs
21652	Transitional cell carcinoma in situ
6436	Transitional cell carcinoma NOS
41726	Transitional cell papilloma NOS
33897	Transitional cell papilloma or carcin..
1950	Transitional cell papillomas and carc..
10851	Cerebral tumour - malignant
24235	Malig neopl peripheral nerves and autonomic nervous system
53504	Malig neopl, overlap lesion brain & other part of CNS

18617	Malignant neoplasm cerebrum (excluding lobes and ventricles)
41520	Malignant neoplasm of brain
44089	Malignant neoplasm of brain NOS
68641	Malignant neoplasm of brain stem
45154	Malignant neoplasm of cerebellum
28919	Malignant neoplasm of cerebral meninges
70104	Malignant neoplasm of cerebral meninges NOS
54133	Malignant neoplasm of cerebrum NOS
59170	Malignant neoplasm of corpus callosum
35285	Malignant neoplasm of eye, brain and ..
42426	Malignant neoplasm of frontal lobe
55098	Malignant neoplasm of head NOS
39088	Malignant neoplasm of occipital lobe
71139	Malignant neoplasm of other parts of brain
19226	Malignant neoplasm of parietal lobe
46792	Malignant neoplasm of temporal lobe
47556	Malignant neoplasm of temporal lobe NOS
62126	Malignant neoplasm of thalamus
41515	Malignant neoplasm/central nervous sytem , unspecified
5198	Secondary malignant neoplasm of brain
33843	Secondary malignant neoplasm of brain and spinal cord
44534	[M]Intraepit neop,grade III,of cervix, vulva and vagina
3279	Carcinoma in situ of cervix uteri
24228	Carcinoma in situ of endocervix
4087	CIN III - carcinoma in situ of cervix
46939	Malignant neoplasm of cervical vertebra
2747	Malignant neoplasm of cervix uteri
28311	Malignant neoplasm of cervix uteri NOS
57235	Malignant neoplasm of endocervical canal
48820	Malignant neoplasm of endocervix
50285	Malignant neoplasm of endocervix NOS
32955	Malignant neoplasm of other site of cervix
44627	Secondary and unspec malig neop anterior cervical LN
73616	Secondary malignant neoplasm of cervix uteri
13559	Malig neop of kidney and other unspecified urinary organs
29462	Malignant neoplasm of kidney or urinary organs NOS
1599	Malignant neoplasm of kidney parenchyma
12389	Malignant neoplasm of renal pelvis
54184	Malignant neoplasm of renal pelvis NOS
15223	Malignant neoplasm of ureter
28241	Malignant neoplasm of ureteric orifice
1952	Secondary malignant neoplasm of kidney
4072	Acute leukaemia NOS

4251	Acute lymphoid leukaemia
19974	Acute monocytic leukaemia
4413	Acute myeloid leukaemia
27664	Acute promyelocytic leukaemia
37461	Adult T-cell leukaemia
31701	Chronic granulocytic leukaemia
16416	Chronic leukaemia NOS
27790	Chronic lymphatic leukaemia
8625	Chronic lymphoid leukaemia
27458	Chronic monocytic leukaemia
10726	Chronic myeloid leukaemia
27520	Chronic myeloid leukaemia NOS
22050	Chronic myelomonocytic leukaemia
87335	Hairy cell leukaemia
4250	Leukaemia NOS
25191	Leukaemia of unspecified cell type
5137	Leukaemic reticuloendotheliosis
65122	Leukaemic reticuloendotheliosis of unspecified sites
4222	Lymphatic leukaemia
19372	Lymphoid leukaemia
38914	Lymphoid leukaemia NOS
27416	Lymphosarcoma
35875	Monocytic leukaemia
7176	Myeloid leukaemia
99413	Other and unspecified leukaemia NOS
94174	Other specified leukaemia
30632	Other specified leukaemia NOS
39187	Plasma cell leukaemia
31586	Prolymphocytic leukaemia
46771	[M]Hepatocellular carcinoma, fibrolamellar
25310	Carcinoma in situ of liver
22187	Hepatocellular carcinoma
40240	Hepatocellular carcinoma NOS
20234	Hepatoma NOS
26814	Hepatoma, malignant
25641	Liver cell carcinoma
8918	Malignant neoplasm of liver and intrahepatic bile ducts
38978	Malignant neoplasm of liver and intrahepatic bile ducts NOS
26393	Malignant neoplasm of liver unspecified
43490	Other specified carcinomas of liver
16126	Primary carcinoma of liver
25535	Primary malignant neoplasm of liver
44399	Primary malignant neoplasm of liver NOS

36147	Secondary malignant neoplasm of liver
5179	Nodular lymphoma (Brill - Symmers disease)
65701	Nodular lymphoma NOS
94995	Nodular lymphoma of lymph nodes of inguinal region and leg
66327	Nodular lymphoma of unspecified site
44318	Oth and unspecif peripheral & cutaneous T-cell lymphomas
49814	Malignant melanoma of axilla
43463	Malignant melanoma of back
32768	Malignant melanoma of breast
51209	Malignant melanoma of chest wall
71136	Malignant melanoma of chin
73744	Malignant melanoma of ear and external auricular canal NOS
41278	Malignant melanoma of external surface of cheek
45139	Malignant melanoma of external surface of nose
54632	Malignant melanoma of eyelid including canthus
41490	Malignant melanoma of foot
45755	Malignant melanoma of fore-arm
68133	Malignant melanoma of forehead
34259	Malignant melanoma of groin
61246	Malignant melanoma of heel
37872	Malignant melanoma of lower leg
64327	Malignant melanoma of lower limb or hip NOS
45306	Malignant melanoma of neck
47252	Malignant melanoma of other and unspecified parts of face
42153	Malignant melanoma of other specified skin site
55881	Malignant melanoma of scalp
65625	Malignant melanoma of scalp and neck
50505	Malignant melanoma of shoulder
865	Malignant melanoma of skin
28556	Malignant melanoma of skin NOS
58958	Malignant melanoma of temple
51873	Malignant melanoma of thigh
63997	Malignant melanoma of thumb
36899	Malignant melanoma of toe
38689	Malignant melanoma of trunk (excluding scrotum)
45760	Malignant melanoma of trunk, excluding scrotum, NOS
65164	Malignant melanoma of upper limb and shoulder
54685	Malignant melanoma of upper arm
19144	Melanoma and other malignant neoplasm of skin
71044	Melanoma in situ of back
72032	Melanoma in situ of ear and external auricular canal
47850	Melanoma in situ of lower limb, including hip
97858	Melanoma in situ of scalp and neck

19686	Melanoma in situ of skin
56694	Melanoma in situ of upper limb, including shoulder
54246	Melanoma in situ, unspecified
43450	Immunoproliferative neoplasm or myeloma NOS
43552	Kahler's disease
46042	Lambda light chain myeloma
4944	Multiple myeloma
37182	Multiple myeloma and immunoproliferative neoplasms
43312	Myeloma - solitary
15211	Myelomatosis
20440	Myelomonocytic leukaemia
19028	Solitary myeloma
21402	Burkitt's lymphoma
102594	Diffuse large B-cell lymphoma
101114	Diffuse non-Hodgkin's large cell lymphoma
17460	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
65180	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
39798	Diffuse non-Hodgkin's lymphoma, unspecified
17182	Follicular lymphoma NOS
70842	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma
49262	Follicular non-Hodgkin's large cell lymphoma
21549	Follicular non-Hodgkin's lymphoma
28639	Follicular non-Hodgkin's small cleaved cell lymphoma
95545	Maltoma
95715	Mucosa-associated lymphoma
3604	Non - Hodgkin's lymphoma
7940	Non-Hodgkin's lymphoma NOS
8649	Non-Hodgkin's lymphoma, unspecified type
67518	Other types of follicular non-Hodgkins lymphoma
1481	Reticulosarcoma
31794	Unspecified B-cell non-Hodgkin's lymphoma
64336	[X]Other specified types of non-Hodgkin's lymphoma
63375	[X]Unspecified B-cell non-Hodgkin's lymphoma
52326	[M]Adenocarcinoma in adenomatous polyp
73434	[M]Adenocarcinoma in multiple adenomatous polyps
18255	[M]Adenomatous and adenocarcinomatous polyps
52029	[X]Malignant neoplasm without specification of site
86997	[X]Malignant neoplasm/ill-defined sites within resp system
68027	[X]Malignant neoplasm/other and unspecified cranial nerves
54253	[X]Secondary malignant neoplasm of other specified sites
57481	[X]Secondary malignant neoplasm/oth+unspc respiratory organs
88022	[X]Secondary malignant neoplasm/oth+unspcfd digestive organs
27827	Adenocarcinoma in situ

8930	Adenocarcinoma NOS
2272	Adenocarcinomas
33775	Adenoid cystic carcinoma
31004	Adenoid squamous cell carcinoma
19731	Adenoma or or adenocarcinoma in polyposis coli
19091	Adenomas and adenocarcinomas
7473	Carcinoma in situ
20564	Carcinoma in situ NOS
44166	Carcinoma in situ of other and unspecified digestive organs
29898	Carcinoma in situ of other and unspecified parts of uterus
53349	Carcinoma in situ of other specified site
56640	Carcinoma in situ of other specified site NOS
8695	Carcinoma NOS
8693	Carcinoma of other and unspecified sites
21609	Carcinoma, undifferentiated type, NOS
16692	Carcinomatosis
13569	Disseminated malignancy NOS
56600	Epidermoid carcinoma NOS
26858	Gastrinoma and carcinomas
34096	Granular cell carcinoma
49525	Kaposi's sarcoma, unspecified
25961	Large cell carcinoma NOS
1056	Malignant neoplasm of other and unspecified site NOS
38736	Malignant neoplasm of other and unspecified site OS
10995	Malignant neoplasm of other and unspecified sites
90659	Malignant neoplasm of other specified endocrine gland
95421	Malignant neoplasm of other specified female genital organ
88362	Malignant neoplasm of other specified hypopharyngeal site
88144	Malignant neoplasm of other specified part of nervous system
98104	Malignant neoplasm of other specified pleura
40437	Malignant neoplasm of other specified site of eye
47810	Malignant neoplasm of unspecified site
54267	Malignant neoplasm of unspecified site NOS
51352	Malignant neoplasms of independent (primary) multiple sites
22267	Neoplasm, malig, uncertain whether primary or whether metastatic
21868	Neoplasm, malignant
26034	Other malignant neoplasm NOS
40494	Papillary and squamous cell neoplasms
10541	Papillary carcinoma NOS
11035	Primary malignant neoplasm of unknown site
9366	Secondary carcinoma
54679	Secondary malignant neoplasm of unknown site
10134	Squamous cell carcinoma in situ NOS

1624	Squamous cell carcinoma NOS
33497	Squamous cell carcinoma, microinvasive
8627	Tumour cells, malignant
56077	Carcinoma in situ of lower 1/3 oesophagus
8244	Carcinoma in situ of oesophagus
44228	Carcinoma in situ of oesophagus NOS
63470	Malignant neoplasm of abdominal oesophagus
22894	Malignant neoplasm of cardio-oesophageal junction of stomach
54171	Malignant neoplasm of middle third of oesophagus
1062	Malignant neoplasm of oesophagus
30700	Malignant neoplasm of oesophagus NOS
53591	Malignant neoplasm of other specified part of oesophagus
50789	Malignant neoplasm of upper third of oesophogus
67497	Malignant neoplasm, overlapping lesion of oesophagus
4865	Oesophageal cancer
34823	Carcinoma in situ of cheek
24801	Carcinoma in situ of floor of mouth
37505	Carcinoma in situ of oral cavity
30966	Carcinoma in situ of palate
27944	Carcinoma in situ of tongue
9984	Carcinoma of lip
24374	Carcinoma of lip, oral cavity and pharynx
37549	Kaposi's sarcoma of palate
43431	Malignant neoplasm of base of tongue
30402	Malignant neoplasm of buccal mucosa
31364	Malignant neoplasm of cheek mucosa
41931	Malignant neoplasm of cheek NOS
51926	Malignant neoplasm of faucial pillar
20092	Malignant neoplasm of floor of mouth
43400	Malignant neoplasm of gum
37590	Malignant neoplasm of hard palate
51818	Malignant neoplasm of jaw NOS
14712	Malignant neoplasm of lip
68399	Malignant neoplasm of lip unspecified, mucosa
19415	Malignant neoplasm of lip, oral cavity and pharynx
39430	Malignant neoplasm of lip, oral cavity and pharynx NOS
49360	Malignant neoplasm of lower gum
101707	Malignant neoplasm of lower lip, vermilion border NOS
50475	Malignant neoplasm of major salivary gland NOS
33833	Malignant neoplasm of mandible
55015	Malignant neoplasm of mouth NOS
14792	Malignant neoplasm of other and unspecified parts of mouth
56709	Malignant neoplasm of other sites of floor of mouth

37916 Malignant neoplasm of other specified mouth parts
18882 Malignant neoplasm of overlapping lesion of lip
28559 Malignant neoplasm of palate NOS
70819 Malignant neoplasm of palate unspecified
4388 Malignant neoplasm of parotid gland
37724 Malignant neoplasm of retromolar area
40292 Malignant neoplasm of soft palate
51786 Malignant neoplasm of submandibular g..
10283 Malignant neoplasm of tongue
40557 Malignant neoplasm of tongue NOS
16241 Malignant neoplasm of tonsil
24397 Malignant neoplasm of tonsillar fossa
55066 Malignant neoplasm of tonsillar pillar
99001 Malignant neoplasm of upper lip, fren..
98500 Malignant neoplasm of upper lip, mucosa
90610 Malignant neoplasm of upper lip, oral..
37516 Malignant neoplasm of uvula
53884 Malignant neoplasm tonsil NOS
5116 Mixed parotid tumour
16213 Secondary malignant neoplasm of pleura
45824 Secondary malignant neoplasm of tongue
58973 [X]Malignant neoplasm of lip, oral cavity and pharynx
37137 [M]Adenocarcinoma in situ in tubulovillous adenoma
29170 [M]Adenocarcinoma in situ in villous adenoma
28272 [M]Adenocarcinoma, intestinal type
62256 [M]Adrenal cortical tumours NOS
70516 [M]Biliary tract adenomas and adenocarcinomas
61467 [M]Follicular adenocarcinoma, trabecular type
36031 [M]Hepatobiliary tract adenomas and carcinomas
49399 [M]Papillary or squamous cell neoplasm NOS
60045 [M]Tubular adenocarcinoma
93665 [X]Kaposi's sarcoma, unspecified
45262 [X]Malignant neoplasm of male genital organ, unspecified
63925 [X]Malignant neoplasm of meninges, unspecified
95671 [X]Malignant neoplasm of peritoneum, unspecified
53816 [X]Melanocytic naevi, unspecified
44778 Adenocarcinoma in tubulovillous adenoma
40883 Adrenal cortical tumours
40438 Bile duct carcinoma
41313 Bile duct cystadenocarcinoma
2755 Cancers
21792 Carcinoma in situ of ampulla of Vater
47656 Carcinoma in situ of appendix

51934 Carcinoma in situ of biliary system
64089 Carcinoma in situ of common bile duct
45070 Carcinoma in situ of duodenum
53460 Carcinoma in situ of epiglottis
58124 Carcinoma in situ of eye
59499 Carcinoma in situ of fallopian tube
10375 Carcinoma in situ of glottis
37501 Carcinoma in situ of hepatic duct
44663 Carcinoma in situ of hypopharynx
99580 Carcinoma in situ of intrahepatic bile ducts
11403 Carcinoma in situ of larynx
43380 Carcinoma in situ of maxillary sinus
36104 Carcinoma in situ of nasopharynx
27311 Carcinoma in situ of penis
42129 Carcinoma in situ of pharynx
45909 Carcinoma in situ of pituitary gland
58879 Carcinoma in situ of scrotum
8177 Carcinoma in situ of testis
34946 Carcinoma in situ of vagina
7697 Carcinoma in situ of vocal fold - glottis
9902 Carcinoma of bone, connective tissue, skin and breast
16874 Carcinoma of genitourinary organ
45307 Carcinoma of respiratory tract and intrathoracic organs
12609 Carcinoma, anaplastic type, NOS
8711 Cholangiocarcinoma
17979 Cholangioma
11950 Essential (haemorrhagic) thrombocythaemia
21847 Follicular carcinoma
2462 Hodgkin's disease
53397 Hodgkin's disease NOS
97746 Hodgkin's disease NOS of lymph nodes of multiple sites
38939 Hodgkin's disease, lymphocytic-histiocytic predominance
49605 Hodgkin's disease, mixed cellularity
29178 Hodgkin's disease, nodular sclerosis
41369 Lymphosarcoma and reticulosarcoma
39531 Malig neo, overlapping lesion of heart, mediastinum & pleura
65233 Malig neop connective and soft tissue other specified site
53989 Malig neop connective and soft tissue upper limb/shoulder
41011 Malig neop of bone, connective tissue, skin and breast NOS
19389 Malig neop of bone, connective tissue, skin and breast OS
66088 Malig neop of connective and soft tissue of hip and leg
66088 Malig neop of connective and soft tissue of hip and leg
67324 Malig neop of connective and soft tissue of inguinal region

67324 Malig neop of connective and soft tissue of inguinal region
30542 Malig neop of connective and soft tissue of lower leg
58836 Malig neop of connective and soft tissue of pelvis NOS
98408 Malig neop of connective and soft tissue of thorax NOS
44805 Malig neop of connective and soft tissue thigh and upper leg
44805 Malig neop of connective and soft tissue thigh and upper leg
44805 Malig neop of connective and soft tissue thigh and upper leg
57471 Malig neop of connective and soft tissue trunk unspecified
64195 Malig neop of endocrine gland or rela..
64195 Malig neop of endocrine gland or related structure NOS
30511 Malig neop of other endocrine glands and related structures
100232 Malig neop of other site of heart, thymus and mediastinum
11009 Malig neop oth/ill-defined sites digestive tract/peritoneum
46114 Malig neop other/ill-defined sites lip, oral cavity, pharynx
94272 Malig neoplasm of connective and soft tissues of lumb spine
12335 Malignant lymphoma NOS
72725 Malignant lymphoma NOS of intrathoracic lymph nodes
63105 Malignant lymphoma NOS of lymph node inguinal region and leg
34089 Malignant lymphoma NOS of lymph nodes of axilla and arm
60092 Malignant lymphoma NOS of spleen
57427 Malignant lymphoma NOS of unspecified site
17887 Malignant lymphoma otherwise specified
54103 Malignant neoplasm gallbladder and extrahepatic bile ducts
15907 Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
49301 Malignant neoplasm lymphatic or haematopoietic tissue NOS
30646 Malignant neoplasm lymphatic or haematopoietic tissue OS
15976 Malignant neoplasm of abdomen
28148 Malignant neoplasm of adrenal gland
70824 Malignant neoplasm of adrenal gland NOS
10949 Malignant neoplasm of ampulla of Vater
73439 Malignant neoplasm of anterior epiglottis NOS
100918 Malignant neoplasm of anterior wall of nasopharynx NOS
50035 Malignant neoplasm of aortic body and other paraganglia
18632 Malignant neoplasm of appendix
48743 Malignant neoplasm of body of penis
18314 Malignant neoplasm of bone and articular cartilage
16075 Malignant neoplasm of bone and articular cartilage NOS
36731 Malignant neoplasm of canthus
69104 Malignant neoplasm of carpal bone - lunate
60035 Malignant neoplasm of cartilage of ear
71204 Malignant neoplasm of cartilage of nose
23861 Malignant neoplasm of chest wall NOS
15991 Malignant neoplasm of choroid

59041 Malignant neoplasm of ciliary body
53910 Malignant neoplasm of clitoris
7982 Malignant neoplasm of common bile duct
73718 Malignant neoplasm of connective and soft tissue head, face and neck
45071 Malignant neoplasm of connective and soft tissue of abdomen NOS
39899 Malignant neoplasm of craniopharyngeal duct
19475 Malignant neoplasm of descended testis
54186 Malignant neoplasm of diaphragm
18613 Malignant neoplasm of duodenum
72127 Malignant neoplasm of epididymis
26134 Malignant neoplasm of epiglottis, free border
54636 Malignant neoplasm of ethmoid sinus
23433 Malignant neoplasm of extrahepatic bile ducts
74896 Malignant neoplasm of extrahepatic bile ducts NOS
20160 Malignant neoplasm of eye
56718 Malignant neoplasm of eyeball NOS
43087 Malignant neoplasm of eyelid including canthus
49828 Malignant neoplasm of fallopian tube
20166 Malignant neoplasm of female genital organ NOS
56513 Malignant neoplasm of femur
16105 Malignant neoplasm of gallbladder
52594 Malignant neoplasm of genitourinary organ
38931 Malignant neoplasm of genitourinary organ NOS
17841 Malignant neoplasm of glans penis
99185 Malignant neoplasm of glossopalatine fold
318 Malignant neoplasm of glottis
73556 Malignant neoplasm of hand bones NOS
68236 Malignant neoplasm of head, neck and face
58903 Malignant neoplasm of head, neck and face NOS
52537 Malignant neoplasm of hepatic duct
34012 Malignant neoplasm of hypopharynx
33871 Malignant neoplasm of ileum
17559 Malignant neoplasm of intestinal tract, part unspecified
16915 Malignant neoplasm of intrahepatic bile ducts
61643 Malignant neoplasm of intrahepatic bile ducts NOS
58088 Malignant neoplasm of intrahepatic gall duct
59381 Malignant neoplasm of iris
43479 Malignant neoplasm of jejunum
43761 Malignant neoplasm of labia majora
59362 Malignant neoplasm of labia majora NOS
58061 Malignant neoplasm of labia minora
71584 Malignant neoplasm of lacrimal duct
43111 Malignant neoplasm of laryngeal cartilage

97332 Malignant neoplasm of laryngeal cartilage NOS
39084 Malignant neoplasm of laryngopharynx
319 Malignant neoplasm of larynx
9237 Malignant neoplasm of larynx NOS
26813 Malignant neoplasm of larynx, other specified site
102205 Malignant neoplasm of lateral wall of nasopharynx NOS
41958 Malignant neoplasm of lower eyelid
31399 Malignant neoplasm of lower limb NOS
54691 Malignant neoplasm of lumbar vertebra
12323 Malignant neoplasm of lymphatic and haemopoietic tissue
19423 Malignant neoplasm of male breast
48809 Malignant neoplasm of male breast NOS
95458 Malignant neoplasm of nasal bone
23389 Malignant neoplasm of nasal cavities
24675 Malignant neoplasm of nasopharynx
16280 Malignant neoplasm of neck NOS
12490 Malignant neoplasm of nose NOS
50898 Malignant neoplasm of omentum
45667 Malignant neoplasm of orbit
50298 Malignant neoplasm of orbital bone
22893 Malignant neoplasm of oropharynx
43200 Malignant neoplasm of oropharynx NOS
67323 Malignant neoplasm of oropharynx, other specified sites
45267 Malignant neoplasm of other and ill defined site NOS
9030 Malignant neoplasm of other and ill-defined sites
67949 Malignant neoplasm of other male genital organ
54202 Malignant neoplasm of other site of male breast
93842 Malignant neoplasm of palatopharyngeal arch
46153 Malignant neoplasm of parametrium
54631 Malignant neoplasm of pelvic bones, sacrum and coccyx
39413 Malignant neoplasm of pelvic peritoneum
52316 Malignant neoplasm of pelvis
55101 Malignant neoplasm of pelvis NOS
38938 Malignant neoplasm of pelvis, sacrum or coccyx NOS
63224 Malignant neoplasm of penis and other male genital organ NOS
3541 Malignant neoplasm of penis and other male genital organs
43392 Malignant neoplasm of penis, part unspecified
37940 Malignant neoplasm of pharyngeal recess
16297 Malignant neoplasm of pharynx unspecified
33271 Malignant neoplasm of pinna NEC
8550 Malignant neoplasm of pituitary gland
43548 Malignant neoplasm of postcricoid region
95429 Malignant neoplasm of posterior wall of nasopharynx

96869 Malignant neoplasm of posterior wall of nasopharynx NOS
50681 Malignant neoplasm of prepuce (foreskin)
51921 Malignant neoplasm of pubis
39897 Malignant neoplasm of pyriform sinus
21330 Malignant neoplasm of retroperitoneum
44108 Malignant neoplasm of retroperitoneum and peritoneum
16298 Malignant neoplasm of retroperitoneum and peritoneum NOS
61555 Malignant neoplasm of retroperitoneum NOS
37842 Malignant neoplasm of rib
71810 Malignant neoplasm of scapula and long bones of upper arm
47767 Malignant neoplasm of scrotum
37016 Malignant neoplasm of sebaceous gland
62761 Malignant neoplasm of septum of nose
6806 Malignant neoplasm of small intestine and duodenum
43390 Malignant neoplasm of small intestine NOS
40014 Malignant neoplasm of soft tissue of face
59382 Malignant neoplasm of soft tissue of head
48517 Malignant neoplasm of soft tissue of neck
46613 Malignant neoplasm of specified parts of peritoneum
64106 Malignant neoplasm of specified parts of peritoneum NOS
60052 Malignant neoplasm of specified site NOS
65215 Malignant neoplasm of sphenoidal sinus
51115 Malignant neoplasm of spinal cord
49714 Malignant neoplasm of spinal meninges
67211 Malignant neoplasm of spinal meninges NOS
49491 Malignant neoplasm of sternum
26165 Malignant neoplasm of supraglottis
15148 Malignant neoplasm of testis
38510 Malignant neoplasm of testis NOS
32372 Malignant neoplasm of thoracic vertebra
47286 Malignant neoplasm of thorax
27483 Malignant neoplasm of thymus
62556 Malignant neoplasm of thymus, heart a..
40814 Malignant neoplasm of tibia
55550 Malignant neoplasm of upper eyelid
27449 Malignant neoplasm of upper limb NOS
42023 Malignant neoplasm of urachus
37328 Malignant neoplasm of vagina
60772 Malignant neoplasm of vagina NOS
10698 Malignant neoplasm of vaginal vault
49701 Malignant neoplasm of vertebral colum NOS
16704 Malignant neoplasm of vertebral column
62182 Malignant neoplasm of vestibule of nose

4554	Malignant neoplasm of vulva unspecified
35039	Malignant neoplasm, overlapping lesion of bilary tract
66166	Malignant neoplasm, overlapping lesion of small intestine
22158	Malignant plasma cell neoplasm, extramedullary plasmocytoma
24511	Malignant tumour, giant cell type
49656	Melanocytic naevi of lower limb, including hip
12006	Mycosis fungoides
14927	Myelodysplasia
45285	Myelodysplastic syndrome, unspecified
6115	Myeloproliferative disorder
100900	Neurofibromatosis type 1
19437	Osteosarcoma
33333	Other malignant neoplasm of lymphoid and histiocytic tissue
20807	Papillary squamous cell carcinoma
12464	Peripheral T-cell lymphoma
21329	Plasmacytoma NOS
5542	Polycythaemia rubra vera
2481	Polycythaemia vera
12265	Primary thrombocythaemia
11991	Primary vulval cancer
12539	Sarcoma of bone and connective tissue
25366	Secondary and unspec malig neop ant mediastinal lymph nodes
73538	Secondary and unspec malig neop axilla and upper limb LN NOS
37540	Secondary and unspec malig neop axillary lymph nodes
84368	Secondary and unspec malig neop internal iliac lymph nodes
44931	Secondary and unspec malig neop intra-abdominal LON NOS
52736	Secondary and unspec malig neop intra-abdominal lymph nodes
6701	Secondary and unspec malig neop intra-pelvic lymph nodes
64116	Secondary and unspec malig neop intrathoracic lymph nodes
49214	Secondary and unspec malig neop lymph nodes head/face/neck
15507	Secondary and unspec malig neop lymph nodes NOS
52190	Secondary and unspec malig neop pulmonary lymph nodes
9618	Secondary and unspecified malignant neoplasm of lymph nodes
27651	Secondary carcinoma of other specified sites
67396	Secondary malig neop of retroperitoneum and peritoneum
36401	Secondary malignant neoplasm of adrenal gland
7654	Secondary malignant neoplasm of bone and bone marrow
51551	Secondary malignant neoplasm of mediastinum
56345	Secondary malignant neoplasm of other digestive organ
62584	Secondary malignant neoplasm of other respiratory organs
22524	Secondary malignant neoplasm of other specified site NOS
5842	Secondary malignant neoplasm of other specified sites
49145	Secondary malignant neoplasm of penis

27391	Secondary malignant neoplasm of peritoneum
35364	Secondary malignant neoplasm of retroperitoneum
38918	Secondary malignant neoplasm of spinal cord
70736	Secondary malignant neoplasm of vagina
21786	Seminoma of descended testis
2961	Seminoma of testis
100532	Sezary's disease NOS
98142	Siewert type I adenocarcinoma
97499	Siewert type II adenocarcinoma
96094	Siewert type III adenocarcinoma
6966	Spindle cell carcinoma
9476	Teratoma of descended testis
15989	Teratoma of testis
36325	Teratoma of undescended testis
6746	Tubular adenomas and adenocarcinomas
34395	Verrucous carcinoma NOS
4852	Verrucous squamous cell carcinoma
97096	Vulval intraepithelial neoplasia grade 1
96999	Vulval intraepithelial neoplasia grade 2
97107	Vulval intraepithelial neoplasia grade 3
30542	Malig neop of connective and soft tissue of lower leg
57471	Malig neop of connective and soft tissue trunk unspecified
1986	Cancer of ovary
17137	Carcinoma in situ of ovary
8606	Endometrioid adenomas and carcinomas
7805	Malignant neoplasm of ovary
19141	Malignant neoplasm of ovary and other uterine adnexa
44615	Secondary malignant neoplasm of ovary
16931	Carcinoma in situ of pancreas
40810	Malignant neoplasm of body of pancreas
8771	Malignant neoplasm of head of pancreas
8166	Malignant neoplasm of pancreas
34388	Malignant neoplasm of pancreas NOS
35535	Malignant neoplasm of pancreatic duct
39870	Malignant neoplasm of tail of pancreas
21659	Pancreatic adenoma or carcinoma NOS
8032	Pancreatic adenomas and carcinomas
52266	[M]Grawitz tumour
15419	Hypernephroma
8101	Renal adenoma and carcinoma
10668	Renal cell carcinoma
18712	Renal malignant neoplasm
25940	Renal neoplasm of uncertain behaviour

17258 Carcinoma in situ of cardia of stomach
17093 Carcinoma in situ of stomach
37774 Carcinoma in situ of stomach NOS
3357 Carcinoma of digestive organs and peritoneum
27440 Linitis plastica
8154 Malignant ascites
43572 Malignant neoplasm of body of stomach
32022 Malignant neoplasm of cardia of stomach
37859 Malignant neoplasm of cardia of stomach NOS
35180 Malignant neoplasm of digestive organs
15709 Malignant neoplasm of digestive organs and peritoneum
51255 Malignant neoplasm of digestive tract and peritoneum NOS
32362 Malignant neoplasm of fundus of stomach
55434 Malignant neoplasm of greater curve of stomach unspecified
42193 Malignant neoplasm of lesser curve of stomach unspecified
48237 Malignant neoplasm of prepylorus of stomach
19318 Malignant neoplasm of pyloric antrum of stomach
41215 Malignant neoplasm of pyloric canal of stomach
21620 Malignant neoplasm of pylorus of stomach
59092 Malignant neoplasm of pylorus of stomach NOS
8386 Malignant neoplasm of stomach
14800 Malignant neoplasm of stomach NOS
56918 Malignant neoplasm other spec digestive tract and peritoneum
58016 Carcinoma in situ of parathyroid gland
35772 Carcinoma in situ of thyroid cartilage
8958 Carcinoma in situ of thyroid gland
4218 Malignant neoplasm of parathyroid gland
40608 Malignant neoplasm of thyroid and oth..
47862 Malignant neoplasm of thyroid cartilage
5637 Malignant neoplasm of thyroid gland
19263 Thyroid adenoma and adenocarcinoma
60082 [M]Unspecified epithelial neoplasm
7904 Carcinoma in situ of endometrium
3230 Cervical carcinoma (uterus)s
28003 Choriocarcinoma
9447 Endometrioid carcinoma
21914 Intraepithelial carcinoma NOS
19678 Intraepithelial squamous cell carcinoma
7046 Malignant neoplasm of body of uterus
33617 Malignant neoplasm of body of uterus NOS
72723 Malignant neoplasm of cornu of corpus uteri
45490 Malignant neoplasm of corpus uteri NOS
3213 Malignant neoplasm of corpus uteri, excluding isthmus

49400	Malignant neoplasm of endometrium
2890	Malignant neoplasm of endometrium of corpus uteri
68155	Malignant neoplasm of fundus of corpus uteri
45793	Malignant neoplasm of myometrium of corpus uteri
97996	Malignant neoplasm of other site of uterine adnexa
16967	Malignant neoplasm of overlapping lesion of corpus uteri
65106	Malignant neoplasm of uterine adnexa NOS
2744	Malignant neoplasm of uterus, part unspecified
55090	Secondary malignant neoplasm of uterus
12388	Urothelial carcinoma
102476	Vaginal intraepithelial neoplasia grade 1
36495	Carcinoma common bile duct
31393	Carcinoma gallbladder
46478	Carcinoma in situ of adrenal gland

Appendix05:

Medcode	Description
7833	Carcinoma in situ of breast
18694	Intraductal carcinoma in situ of breast
10387	Lobular carcinoma in situ of breast
12499	Malignant neoplasm of breast
31546	Malignant neoplasm of central part of female breast
3968	Malignant neoplasm of female breast
9470	Malignant neoplasm of female breast NOS
26853	Malignant neoplasm of nipple and areola of female breast
23380	Malignant neoplasm of nipple of femal..
59831	Malignant neoplasm of nipple or areola of female breast NOS
56715	Malignant neoplasm of other site of female breast
38475	Malignant neoplasm of other site of female breast NOS
29826	Malignant neoplasm of upper-inner quadrant of female breast
23399	Malignant neoplasm of upper-outer quadrant of female breast
16760	Secondary malignant neoplasm of breast
45222	Malignant neoplasm of lower-inner quadrant of female breast
42070	Malignant neoplasm of lower-outer quadrant of female breast

Appendix06:

Medcode	Description
35325	[X]Malignant neoplasm of respiratory and intrathoracic orga
22156	]Malignant tumour, small cell type
9267	Carcinoma in situ of bronchus and lung
25372	Carcinoma in situ of bronchus or lung NOS
49159	Carcinoma in situ of carina of bronchus
35058	Carcinoma in situ of main bronchus
47897	Carcinoma in situ of middle lobe bron..
46497	Carcinoma in situ of pleura
62610	Carcinoma in situ of respiratory organ NOS
64050	Carcinoma in situ of respiratory system
37579	Carcinoma in situ of upper lobe bronchus and lung
45307	Carcinoma of respiratory tract and intrathoracic organs
35474	Giant cell carcinoma
2587	Lung cancer
34075	Malig neop of respiratory tract and intrathoracic organs
65793	Malig neop of upper respiratory tract, part unspecified
40595	Malignant neoplasm of bronchus or lung
3903	Malignant neoplasm of bronchus or lung
17391	Malignant neoplasm of carina of bronchus
33444	Malignant neoplasm of hilus of lung
18678	Malignant neoplasm of lower lobe bronchus
12582	Malignant neoplasm of lower lobe of lung
31188	Malignant neoplasm of lower lobe, bronchus or lung
42566	Malignant neoplasm of lower lobe, bronchus or lung NOS

42416	Malignant neoplasm of lower third of oesophagus
12870	Malignant neoplasm of main bronchus
21698	Malignant neoplasm of main bronchus NOS
17475	Malignant neoplasm of maxilla
41523	Malignant neoplasm of middle lobe bronchus
39923	Malignant neoplasm of middle lobe of lung
31268	Malignant neoplasm of middle lobe, bronchus or lung
54134	Malignant neoplasm of middle lobe, bronchus or lung NOS
29283	Malignant neoplasm of other site of respiratory tract
36371	Malignant neoplasm of overlapping lesion of bronchus & lung
31573	Malignant neoplasm of pleura
34742	Malignant neoplasm of pleura NOS
42569	Malignant neoplasm of respiratory tract NOS
15221	Malignant neoplasm of trachea
13243	Malignant neoplasm of trachea, bronchus and lung
31700	Malignant neoplasm of upper lobe bronchus
25886	Malignant neoplasm of upper lobe of lung
10358	Malignant neoplasm of upper lobe, bronchus or lung
44169	Malignant neoplasm of upper lobe, bronchus or lung NOS
7484	Mesothelioma
21715	Mesothelioma of lung
9600	Mesothelioma of pleura
9156	Oat cell carcinoma
20170	Pancoast's syndrome
26413	Pleomorphic carcinoma
35053	Secondary malig neop of respiratory and digestive systems
66083	Secondary malig neop of respiratory or digestive system NOS
4137	Secondary malignant neoplasm of lung
9291	Small cell carcinoma NOS
30988	Small cell carcinoma, intermediate cell
21217	Small cell-large cell carcinoma
41816	Squamous cell carcinoma, small cell, non-keratinising

Appendix07:

Medcode	Description
6328	Carcinoma in situ of prostate
54599	High grade prostatic intraepithelial neoplasia
780	Malignant neoplasm of prostate
21590	Secondary malignant neoplasm of prostate

Appendix08

Medcode	Description
4170	[M]Adenomatous and adenocarcinomatous polyps of colon
9491	Anal carcinoma
11628	Cancer of bowel
51054	Carcinoma in situ of anal canal
12273	Carcinoma in situ of anus NOS
31893	Carcinoma in situ of ascending colon
16916	Carcinoma in situ of caecum
6903	Carcinoma in situ of colon
33561	Carcinoma in situ of colon NOS
47667	Carcinoma in situ of descending colon
37501	Carcinoma in situ of hepatic flexure of colon
39080	Carcinoma in situ of rectosigmoid junction
29975	Carcinoma in situ of rectum
60477	Carcinoma in situ of rectum and rectosigmoid junction
17144	Carcinoma in situ of sigmoid colon

37125	Carcinoma in situ of transverse colon
22163	Carcinoma of caecum
7219	Carcinoma of rectum
9118	Colonic cancer
101700	Hereditary nonpolyposis colon cancer
24370	Malignant neoplasm of anal canal
27897	Malignant neoplasm of anus unspecified
10946	Malignant neoplasm of ascending colon
3811	Malignant neoplasm of caecum
1220	Malignant neoplasm of colon
28163	Malignant neoplasm of colon NOS
10864	Malignant neoplasm of descending colon
9088	Malignant neoplasm of hepatic flexure of colon
27855	Malignant neoplasm of rectosigmoid junction
1800	Malignant neoplasm of rectum
35357	Malignant neoplasm of rectum, rectosigmoid junction and anus
2815	Malignant neoplasm of sigmoid colon
6935	Malignant neoplasm of transverse colon
5901	Rectal carcinoma
28727	Secondary malignant neoplasm of colon
44529	Secondary malignant neoplasm of large intestine and rectum
62909	Secondary malignant neoplasm of rectum
18619	Malignant neoplasm of splenic flexure of colon

Appendix09:

Medcode	Description
29524	[M]Basal cell carcinoma, fibroepithelial type
103178	[M]Basal cell carcinoma, infiltrative
102547	[M]Basal cell carcinoma, nodular
102417	[M]Superficial basal cell carcinoma
876	Basal cell carcinoma
3028	Basal cell carcinoma NOS
9885	Basal cell carcinoma, morphoea type
21156	Basal cell naevus syndrome
30853	Basal cell neoplasm NOS
3516	Basal cell neoplasms
29282	Basal cell tumour
94873	[M]Squamous cell carcinoma of skin NOS
56121	[X]Malignant neoplasm of skin, unspecified
2467	Bowen's disease
32249	Carcinoma in situ of ear

19665 Carcinoma in situ of scalp
69345 Carcinoma in situ of scalp and skin of neck
12084 Carcinoma in situ of skin
63142 Carcinoma in situ of skin NOS
38032 Carcinoma in situ of skin of back
8647 Carcinoma in situ of skin of breast
61103 Carcinoma in situ of skin of cheek
69720 Carcinoma in situ of skin of eyebrow
57550 Carcinoma in situ of skin of eyelid including canthus
47789 Carcinoma in situ of skin of forehead..
65222 Carcinoma in situ of skin of jaw
708 Carcinoma in situ of skin of leg
27542 Carcinoma in situ of skin of lower leg
14815 Carcinoma in situ of skin of lower limb and hip
54140 Carcinoma in situ of skin of neck
49254 Carcinoma in situ of skin of other parts of face
38777 Carcinoma in situ of skin of perineum
31511 Carcinoma in situ of skin of temple
50189 Carcinoma in situ skin of ear and external auricular canal
24375 Dermatofibrosarcoma protuberans
57336 Epithelioma, malignant
19041 Intraepidermal carcinoma NOS
27931 Kaposi's sarcoma of skin
37618 Malignant neoplasm of axilla NOS
20685 Malignant neoplasm of axillary tail of female breast
23480 Malignant neoplasm of perianal skin
37165 Malignant neoplasm of scalp
54234 Malignant neoplasm of scalp and skin of neck
2492 Malignant neoplasm of skin NOS
33997 Malignant neoplasm of skin of auricle of ear
45077 Malignant neoplasm of skin of back
30543 Malignant neoplasm of skin of breast
30645 Malignant neoplasm of skin of cheek, external
37969 Malignant neoplasm of skin of chest, excluding breast
49403 Malignant neoplasm of skin of chin
25245 Malignant neoplasm of skin of finger
70587 Malignant neoplasm of skin of foot
30577 Malignant neoplasm of skin of fore-arm
30576 Malignant neoplasm of skin of forehead
54352 Malignant neoplasm of skin of hand
18245 Malignant neoplasm of skin of lip
33682 Malignant neoplasm of skin of lower leg
57442 Malignant neoplasm of skin of lower limb and hip

43619	Malignant neoplasm of skin of neck
16202	Malignant neoplasm of skin of nose (external)
43122	Malignant neoplasm of skin of shoulder
21327	Malignant neoplasm of skin of temple
57446	Malignant neoplasm of skin of trunk, excluding scrotum
15868	Malignant neoplasm of skin of trunk, excluding scrotum, NOS
67748	Malignant neoplasm of skin of umbilicus
42707	Malignant neoplasm of skin of upper arm
30747	Malignant neoplasm of skin of upper limb and shoulder
60526	Malignant neoplasm of skin of upper limb or shoulder NOS
53515	Malignant neoplasm skin of ear and external suricular canal
27370	Malignant neoplasm skin of other and unspecified parts face
4632	Other malignant neoplasm of skin
1940	Rodent ulcer
19945	Secondary malignant neoplasm of skin
55096	Secondary malignant neoplasm of skin NOS
9505	Secondary malignant neoplasm of skin of Breast
43930	Secondary malignant neoplasm of skin of head
48828	Secondary malignant neoplasm of skin of hip and leg
41144	Secondary malignant neoplasm of skin of trunk
93352	Squamous cell carcinoma of skin
93490	Squamous cell carcinoma of skin NOS
29787	Squamous cell carcinoma, keratinising type NOS
7967	Squamous cell neoplasms
60162	[X]Malignant neoplasm overlapping lesion of skin

Appendix10:

medcode	Description
1684	Diabetic on oral treatment
11047	Conversion to insulin
107331	Conversion to insulin in secondary care
107508	Conversion to insulin by diabetes specialist nurse
83532	Diabetes type 2 review
101801	Type II diabetic dietary review
102611	Type 2 diabetic dietary review
108018	Incretin mimetic treatment started
93657	Referral to DESMOND diabetes structured education programme
95093	Did not complete DESMOND diabetes structured educat program
103543	Referral to DESMOND structured programme declined
95159	Did not attend DESMOND diabetes structured education program
93530	Attended DESMOND structured programme
93529	DESMOND diabetes structured education programme completed
14803	Diabetes mellitus, adult onset, no mention of complication
506	Non-insulin dependent diabetes mellitus
43139	Diabetes mellitus, adult onset, with hyperosmolar coma
35105	Diabetes mellitus, adult onset, with renal manifestation
41389	Diabetes mellitus, adult onset, + ophthalmic manifestation
39317	Diabetes mellitus, adult onset, + neurological manifestation
63357	Diabetes mellitus, adult, + peripheral circulatory disorder
33807	Diabetes mellitus, adult with gangrene
56803	NIDDM with peripheral circulatory disorder
4513	Non-insulin dependent diabetes mellitus
5884	NIDDM - Non-insulin dependent diabetes mellitus

17859	Type 2 diabetes mellitus
18219	Type II diabetes mellitus
52303	Non-insulin-dependent diabetes mellitus with renal comps
50225	Type II diabetes mellitus with renal complications
18209	Type 2 diabetes mellitus with renal complications
50429	Non-insulin-dependent diabetes mellitus with ophthalm comps
59725	Type II diabetes mellitus with ophthalmic complications
70316	Type 2 diabetes mellitus with ophthalmic complications
55842	Non-insulin-dependent diabetes mellitus with neuro comps
67905	Type II diabetes mellitus with neurological complications
45919	Type 2 diabetes mellitus with neurological complications
62146	Non-insulin-dependent diabetes mellitus with multiple comps
108005	Type 2 diabetes mellitus with multiple complications
34912	Non-insulin dependent diabetes mellitus with ulcer
55075	Type II diabetes mellitus with ulcer
65704	Type 2 diabetes mellitus with ulcer
40401	Non-insulin dependent diabetes mellitus with gangrene
62107	Type II diabetes mellitus with gangrene
46150	Type 2 diabetes mellitus with gangrene
17262	Non-insulin-dependent diabetes mellitus with retinopathy
58604	Type II diabetes mellitus with retinopathy
42762	Type 2 diabetes mellitus with retinopathy
8403	Non-insulin dependent diabetes mellitus - poor control
24458	Type II diabetes mellitus - poor control
45913	Type 2 diabetes mellitus - poor control
29979	Non-insulin-dependent diabetes mellitus without complication
105784	Type 2 diabetes mellitus without complication
72320	Non-insulin dependent diabetes mellitus with mononeuropathy
50813	Type II diabetes mellitus with mononeuropathy
45467	Non-insulin dependent diabetes mellitus with polyneuropathy
47409	Type II diabetes mellitus with polyneuropathy
59365	Non-insulin dependent diabetes mellitus with nephropathy
64571	Type II diabetes mellitus with nephropathy
24836	Type 2 diabetes mellitus with nephropathy
43785	Non-insulin dependent diabetes mellitus with hypoglyca coma
56268	Type II diabetes mellitus with hypoglycaemic coma
61071	Type 2 diabetes mellitus with hypoglycaemic coma
69278	Non-insulin depend diabetes mellitus with diabetic cataract
48192	Type II diabetes mellitus with diabetic cataract
44779	Type 2 diabetes mellitus with diabetic cataract
54212	Non-insulin-dependent d m with peripheral angiopath
54899	Type II diabetes mellitus with peripheral angiopathy
60699	Type 2 diabetes mellitus with peripheral angiopathy

24693	Non-insulin dependent diabetes mellitus with arthropathy
18143	Type II diabetes mellitus with arthropathy
49869	Type 2 diabetes mellitus with arthropathy
40962	Non-insulin dependent d m with neuropathic arthropathy
47816	Type II diabetes mellitus with neuropathic arthropathy
66965	Type 2 diabetes mellitus with neuropathic arthropathy
18278	Insulin treated Type 2 diabetes mellitus
37648	Insulin treated non-insulin dependent diabetes mellitus
18264	Insulin treated Type II diabetes mellitus
36633	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
758	Type 2 diabetes mellitus
22884	Type II diabetes mellitus
18777	Type 2 diabetes mellitus with renal complications
57278	Type II diabetes mellitus with renal complications
47321	Type 2 diabetes mellitus with ophthalmic complications
100964	Type II diabetes mellitus with ophthalmic complications
34268	Type 2 diabetes mellitus with neurological complications
98616	Type II diabetes mellitus with neurological complications
65267	Type 2 diabetes mellitus with multiple complications
43227	Type II diabetes mellitus with multiple complications
49074	Type 2 diabetes mellitus with ulcer
91646	Type II diabetes mellitus with ulcer
12736	Type 2 diabetes mellitus with gangrene
104323	Type II diabetes mellitus with gangrene
18496	Type 2 diabetes mellitus with retinopathy
49655	Type II diabetes mellitus with retinopathy
25627	Type 2 diabetes mellitus - poor control
47315	Type II diabetes mellitus - poor control
47954	Type 2 diabetes mellitus without complication
53392	Type II diabetes mellitus without complication
62674	Type 2 diabetes mellitus with mononeuropathy
95351	Type II diabetes mellitus with mononeuropathy
18425	Type 2 diabetes mellitus with polyneuropathy
50527	Type II diabetes mellitus with polyneuropathy
12640	Type 2 diabetes mellitus with nephropathy
102201	Type II diabetes mellitus with nephropathy
46917	Type 2 diabetes mellitus with hypoglycaemic coma
98723	Type II diabetes mellitus with hypoglycaemic coma
44982	Type 2 diabetes mellitus with diabetic cataract
93727	Type II diabetes mellitus with diabetic cataract
37806	Type 2 diabetes mellitus with peripheral angiopathy
104639	Type II diabetes mellitus with peripheral angiopathy
59253	Type 2 diabetes mellitus with arthropathy

103902	Type II diabetes mellitus with arthropathy
35385	Type 2 diabetes mellitus with neuropathic arthropathy
1407	Insulin treated Type 2 diabetes mellitus
64668	Insulin treated Type II diabetes mellitus
34450	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
107701	Hyperosmolar non-ketotic state in type II diabetes mellitus
26054	Type 2 diabetes mellitus with persistent proteinuria
60796	Type II diabetes mellitus with persistent proteinuria
18390	Type 2 diabetes mellitus with persistent microalbuminuria
85991	Type II diabetes mellitus with persistent microalbuminuria
32627	Type 2 diabetes mellitus with ketoacidosis
106528	Type II diabetes mellitus with ketoacidosis
51756	Type 2 diabetes mellitus with ketoacidotic coma
106061	Type II diabetes mellitus with ketoacidotic coma
25591	Type 2 diabetes mellitus with exudative maculopathy
63690	Type 2 diabetes mellitus with gastroparesis
7563	Diabetic on diet only

Appendix11:

Medcode	Description
10196	Ethnic groups (census)
12350	African - ethnic category 2001 census
12351	British or mixed British - ethnic category 2001 census
12352	English - ethnic category 2001 census
12355	Greek - ethnic category 2001 census
12402	Oth White European/European unsp/Mixed European 2001 census
12412	Italian - ethnic category 2001 census
12414	Indian or British Indian - ethnic category 2001 census
12420	Filipino - ethnic category 2001 census
12421	Other White background - ethnic category 2001 census
12429	Ethnic group not given - patient refused
12432	Caribbean - ethnic category 2001 census
12433	Baltic Estonian/Latvian/Lithuanian - ethn categ 2001 census
12434	Other - ethnic category 2001 census
12435	Ethnic category - 2001 census
12436	Scottish - ethnic category 2001 census
12437	White and Black African - ethnic category 2001 census
12443	Somali - ethnic category 2001 census
12444	Other white ethnic group
12452	Black British
12459	Ethnic category not stated - 2001 census
12460	Pakistani or British Pakistani - ethnic category 2001 census

12467 Polish - ethnic category 2001 census
12468 Chinese - ethnic category 2001 census
12473 Japanese - ethnic category 2001 census
12482 Indian
12513 Other Asian background - ethnic category 2001 census
12532 Irish - ethnic category 2001 census
12591 Other White or White unspecified ethnic category 2001 census
12608 Sri Lankan - ethnic category 2001 census
12632 Black Caribbean
12633 Other European (NMO)
12638 White and Asian - ethnic category 2001 census
12653 British Asian - ethnic category 2001 census
12668 Other Asian ethnic group
12681 Welsh - ethnic category 2001 census
12696 Other ethnic, mixed origin
12706 Chinese and White - ethnic category 2001 census
12718 Chinese
12719 Vietnamese - ethnic category 2001 census
12730 Malaysian - ethnic category 2001 census
12742 White and Black Caribbean - ethnic category 2001 census
12746 Turkish - ethnic category 2001 census
12756 South and Central American - ethnic category 2001 census
12757 Other ethnic group
12760 Tamil - ethnic category 2001 census
12769 Greek Cypriot - ethnic category 2001 census
12778 Black African
12795 Black and Asian - ethnic category 2001 census
12873 Other Mixed background - ethnic category 2001 census
12887 Sinhalese - ethnic category 2001 census
22467 White
23955 Ethnicity and other related nationality data
24270 Irish (NMO)
24272 Chinese
24339 Black, other, non-mixed origin
24340 Ethnic group not recorded
24690 Pakistani
24740 Bangladeshi
24962 N African Arab/Iranian (NMO)
25082 Iranian (NMO)
25411 Vietnamese
25422 Albanian - ethnic category 2001 census
25434 Tokelauan
25451 Moroccan - ethnic category 2001 census

25623 Other Black - Black/White orig
25676 Black - other, mixed
25920 Indian
25937 Iranian - ethnic category 2001 census
26246 Latin American - ethnic category 2001 census
26310 Other white British ethnic group
26312 Black Black - other
26341 Kosovan - ethnic category 2001 census
26379 Other Asian (NMO)
26391 Mixed Irish and other White - ethnic category 2001 census
26392 Punjabi - ethnic category 2001 census
26455 Any other group - ethnic category 2001 census
28866 Croatian - ethnic category 2001 census
28887 Cornish - ethnic category 2001 census
28888 Bangladeshi or British Bangladeshi - ethn categ 2001 census
28900 Other mixed White - ethnic category 2001 census
28909 Mid East (excl Israeli, Iranian & Arab) - eth cat 2001 cens
28935 Other Asian or Asian unspecified ethnic category 2001 census
28936 Other republics former Yugoslavia - ethnic categ 2001 census
28973 Commonwealth (Russian) Indep States - ethn categ 2001 census
30280 Other ethnic non-mixed (NMO)
32066 Turkish/Turkish Cypriot (NMO)
32069 Turkish Cypriot (NMO)
32110 Brit. ethnic minor. spec.(NMO)
32126 Turkish (NMO)
32136 Other black ethnic group
32165 Other Black - Black/Asian orig
32382 Mauritian/Seychellois/Maldivian/St Helena eth cat 2001census
32389 Other Black background - ethnic category 2001 census
32396 Other Asian
32399 Caribbean Asian - ethnic category 2001 census
32401 Other ethnic, Asian/White orig
32408 Other Mixed or Mixed unspecified ethnic category 2001 census
32413 Turkish Cypriot - ethnic category 2001 census
32420 Other ethnic, other mixed orig
32425 Black Caribbean and White
32443 Black African and White
32479 New Zealand Maori
32778 Cypriot (part not stated) - ethnic category 2001 census
32781 Traveller - gypsy
32886 Nigerian - ethnic category 2001 census
35350 Black - other Asian
35412 Black - other African country

35459 Other ethnic, mixed white orig
38097 E Afric Asian/Indo-Carib (NMO)
39696 Indian sub-continent (NMO)
40096 Mixed Black - ethnic category 2001 census
40097 Black British - ethnic category 2001 census
40102 Ulster Scots - ethnic category 2001 census
40110 Black and White - ethnic category 2001 census
41214 Other ethnic NEC (NMO)
41329 Black N African/Arab/Iranian
42290 Gypsy/Romany - ethnic category 2001 census
42294 Northern Irish - ethnic category 2001 census
45008 New Zealand ethnic groups
45199 Ethnic groups (census) NOS
45947 Greek/Greek Cypriot (NMO)
45955 Greek (NMO)
45964 Kurdish - ethnic category 2001 census
46047 Other Black or Black unspecified ethnic category 2001 census
46056 Mixed Asian - ethnic category 2001 census
46059 Arab - ethnic category 2001 census
46063 Jewish - ethnic category 2001 census
46649 South East Asian
46752 Other Pacific ethnic group
46812 Black North African
46818 East African Asian (NMO)
46956 Bosnian - ethnic category 2001 census
46964 Israeli - ethnic category 2001 census
47005 Asian and Chinese - ethnic category 2001 census
47028 North African - ethnic category 2001 census
47074 Serbian - ethnic category 2001 census
47077 East African Asian - ethnic category 2001 census
47091 Muslim - ethnic category 2001 census
47285 North African Arab (NMO)
47401 Other ethnic, Black/White orig
47601 Irish traveller
47949 Greek Cypriot (NMO)
47965 Black E Afric Asia/Indo-Caribb
47969 Other African countries (NMO)
48005 Black Indian sub-continent
49658 Sikh - ethnic category 2001 census
49940 Black and Chinese - ethnic category 2001 census
50286 Black Iranian
54593 Caribbean I./W.I./Guyana (NMO)
55113 Traveller - ethnic category 2001 census

55223	Irish Traveller - ethnic category 2001 census
55584	Niuean
56127	Hindu - ethnic category 2001 census
57075	West Indian (NMO)
57094	Caribbean Island (NMO)
57286	New Zealand European
57435	Black Caribbean/W.I./Guyana
57752	Black Arab
57753	Black East African Asian
57763	Black Indo-Caribbean
57764	Brit. ethnic minor. unsp (NMO)
60837	Tongan
63872	Buddhist - ethnic category 2001 census
64133	Kashmiri - ethnic category 2001 census
64609	Fijian
64610	Samoan
71425	New Zealand ethnic group NOS
85505	Other European in New Zealand
89910	Cook Island Maori
93144	Guyana (NMO)
94487	Yemeni
96789	Other New Zealand ethnic group
98111	White British - ethnic category 2001 census
98213	White Irish - ethnic category 2001 census
99316	Indo-Caribbean (NMO)
99788	Bulgarian
99808	Romanian
100143	Czech
101162	Nepali
101219	Portuguese
101787	Slovak

Appendix12:

Medcode	Description
93	Cigarette smoker
1822	Very heavy smoker - 40+cigs/d
1823	Smoker
1878	Moderate smoker - 10-19 cigs/d
2111	Health ed. - smoking
3568	Heavy smoker - 20-39 cigs/day
7622	Smoking cessation advice
10184	Pregnancy smoking advice
10558	Current smoker
10742	Referral to stop-smoking clinic
11356	Seen by smoking cessation advisor
11527	DNA - Did not attend smoking cessation clinic
12240	Trying to give up smoking
12941	Occasional smoker
12942	Smoker - amount smoked
12943	Cigar smoker
12944	Light smoker - 1-9 cigs/day
12945	Rolls own cigarettes
12947	Pipe smoker
12951	Smoking restarted
12952	Smoking started
12953	Attends stop smoking monitor.
12958	Trivial smoker - < 1 cig/day
12960	Tobacco consumption NOS
12963	Cigar consumption
12964	Keeps trying to stop smoking
12965	Cigarette consumption
12966	Smoking reduced
12967	Pipe tobacco consumption
18573	Referral to smoking cessation advisor
18926	Lifestyle advice regarding smoking
30423	Thinking about stopping smoking
30762	Not interested in stopping smoking
31114	Ready to stop smoking
41979	Smoking restarted
46321	Reason for restarting smoking
46654	Admitted tobacco cons untrue ?

62686	Minutes from waking to first tobacco consumption
74907	Smoking cessation therapy
81440	Nicotine replacement therapy using nicotine patches
85247	Nicotine replacement therapy using nicotine inhalator
85975	Nicotine replacement therapy using nicotine gum
89464	Nicotine replacement therapy using nicotine lozenges
90522	Smoking cessation therapy NOS
91708	Other specified smoking cessation therapy
94958	Smoking cessation drug therapy
96992	Smoking cessation - enhanced services administration
98137	Brief intervention for smoking cessation
98154	Referral to NHS stop smoking service
98283	COPD structured smoking assessment declined - enh serv admin
98284	Refer COPD structured smoking assessment - enhanc serv admin
98347	Current smoker annual review - enhanced services admin
98493	Smoking cessatn monitor template complet - enhanc serv admin
100099	Smoking cessation advice declined
101325	Declin cons follow-up evaluation after smoking cess interven
101338	Failed attempt to stop smoking
101385	Consent given for follow-up by smoking cessation team
101634	Consent given follow-up after smoking cessation intervention
101851	Declined consent for follow-up by smoking cessation team
102361	Referral for smoking cessation service offered
103400	Referred for COPD structured smoking assessment
103507	Stop smoking service opportunity signposted
103760	COPD structured smoking assessment declined
104185	Smoking cessation drug therapy declined
104230	Smoking cessation programme declined
104310	Current smoker annual review
105501	Waterpipe tobacco consumption
106359	Referral to smoking cessation service
106391	Referral to smoking cessation service declined
90	Ex smoker
776	Stopped smoking
12878	Date ceased smoking
12946	Ex-smoker - amount unknown
12955	Ex-moderate smoker (10-19/day)
12956	Ex-heavy smoker (20-39/day)
12957	Ex-light smoker (1-9/day)
12959	Ex-very heavy smoker (40+/day)
12961	Ex-trivial smoker (<1/day)
19488	Ex cigar smoker

26470	Ex pipe smoker
97210	Ex-cigarette smoker
98447	Ex-smoker annual review - enhanced services administration
99838	Recently stopped smoking
100495	Ex roll-up cigarette smoker
100963	Ex-smoker annual review
33	Never smoked tobacco

Appendix13

medcode	Description
322	Moderate drinker - 3-6u/day
385	Drinks rarely
669	Nondependent alcohol abuse, unspecified
1399	Alcohol problem drinking
1476	Delirium tremens
1618	Heavy drinker - 7-9u/day
2081	Alcoholism
2082	Alcohol withdrawal syndrome
2083	Alcohol detoxification
2084	Alcohol dependence syndrome
2925	Alcoholic polyneuropathy
3216	Acute alcoholic hepatitis
4447	Non-drinker alcohol
4500	Korsakov's alcoholic psychosis
4506	Alcoholic gastritis
4743	Alcoholic cirrhosis of liver
4915	Alcoholic cardiomyopathy
5740	Acute alcoholic intoxication in alcoholism
5758	[X]Chronic alcoholism
6169	Alcohol dependence syndrome NOS
6467	[X]Alcoholic hallucinosis
7123	[V]Personal history of alcoholism
7602	Chronic alcoholic hepatitis
7746	Nondependent alcohol abuse
7885	Alcoholic liver damage unspecified
7943	Alcoholic hepatitis
8030	[V]Alcohol abuse counselling and surveillance
8363	Oesophageal varices in alcoholic cirrhosis of the liver
8388	[V]Alcohol rehabilitation
8430	H/O: alcoholism
8999	Heavy drinker
9489	Under care of community alcohol team
9849	Referral to community alcohol team
10691	Alcoholic fatty liver
11106	Korsakov's alcoholic psychosis with peripheral neuritis
11670	[X]Korsakov's psychosis, alcohol induced

12353	[X]Mental & behav dis due to use alcohol: psychotic disorder
12442	Alcohol disorder monitoring
12496	Community detoxification registered
12554	Referral to community drug and alcohol team
12970	Non drinker alcohol
12972	Light drinker - 1-2u/day
12974	Nondependent alcohol abuse, episodic
12975	Trivial drinker - <1u/day
12976	Suspect alcohol abuse - denied
12977	Very heavy drinker - >9u/day
12979	Current non drinker
12980	Light drinker
12982	Alcohol intake above recommended sensible limits
12984	Very heavy drinker
12985	Moderate drinker
16225	Alcohol withdrawal delirium
17259	[X]Delirium tremens, alcohol induced
17330	Alcoholic hepatic failure
17607	[X]Alcoholic psychosis NOS
18156	Alcoholics anonymous
18636	Wernicke-Korsakov syndrome
19401	Binge drinker
19494	Hazardous alcohol use
20514	[X]Mental and behav dis due to use alcohol: withdrawal state
20762	Alcohol amnestic syndrome
21412	Adverse reaction to alcohol deterrents
21624	Episodic acute alcoholic intoxication in alcoholism
21650	Admitted to alcohol detoxification centre
21713	Alcoholic fibrosis and sclerosis of liver
21879	[X]Mental and behav dis due to use of alcohol: harmful use
22277	DTs - delirium tremens
24064	Continuous chronic alcoholism
24984	Alcohol-induced chronic pancreatitis
25110	Alcohol withdrawal hallucinosis
26106	Episodic chronic alcoholism
26323	[X]Alcoholic dementia NOS
26472	Alcohol intake within recommended sensible limits
27342	Alcoholic dementia NOS
28150	Nondependent alcohol abuse NOS
28780	[X]Alcohol addiction
29691	Aversion therapy - alcoholism
30162	[X]Alcoholic paranoia
30404	Alcoholic paranoia
30604	Alcohol-induced epilepsy
30695	Harmful alcohol use
31443	Chronic alcoholism
32927	[X]Alcohol withdrawal-induced seizure
32964	Alcohol abuse monitoring

33635	Chronic alcoholism NOS
33670	Other alcoholic psychosis
33839	Cerebellar ataxia due to alcoholism
35330	Alcohol consumption counselling
36296	Acute alcoholic intoxication in alcoholism NOS
36748	Alcoholic encephalopathy
37605	Dipsomania
37691	[X]Chronic alcoholic brain syndrome
37946	Chronic alcoholic brain syndrome
38061	Alcohol induced hallucinations
39327	[X]Mental and behav dis due to use alcohol: dependence syndr
39799	[X]Mental and behav dis due to use alcohol: amnesic syndrome
40530	Acute alcoholic intoxication, unspecified, in alcoholism
41920	Alcohol amnestic syndrome NOS
43193	Unspecified chronic alcoholism
47123	Alcohol counselling by other agencies
47555	Cerebral degeneration due to alcoholism
48241	[X] Adverse reaction to alcohol deterrents
54505	Other alcoholic dementia
56410	Delivery of rehabilitation for alcohol addiction
56947	Continuous acute alcoholic intoxication in alcoholism
57714	Alcohol dependence with acute alcoholic intoxication
59574	Acute alcoholic intoxication in remission, in alcoholism
62000	[X]Men & behav dis due alcoh: resid & late-onset psychot dis
64101	[X]Men & behav dis due alcohl: withdrawl state with delirium
65754	Alcohol-induced pseudo-Cushing's syndrome
65932	[X]Alcoholic jealousy
67651	Alcoholic psychosis NOS
68111	Other alcoholic psychosis NOS
69691	[X]Dipsomania
73876	[X]Alcohol deterrents caus adverse effects in therapeut use
94553	Referral to specialist alcohol treatment service
94670	Alcohol misuse
96053	Brief intervention for excessive alcohol consumptn completed
96054	Extended intervention for excessive alcohol consumptn complt
97261	Brief intervention for excessive alcohol consumptn declined
97680	Declined referral to specialist alcohol treatment service
100474	Laennec's cirrhosis
101718	Drinks in morning to get rid of hangover
102247	Extended interven for excessive alcohol consumption declined
102448	Higher risk drinking
102665	Increasing risk drinking
103459	Referral to community alcohol team declined
104611	Alcohol-induced acute pancreatitis

Appendix14

medcode	Description
2	O/E - weight
3	O/E - height
126	O/E - Underweight
430	Obesity
2839	O/E - overweight
3176	Has seen dietician - obesity
7984	O/E - obese
8105	Body Mass Index
8854	Morbid obesity
9015	Body mass index index 25-29 - overweight
11401	Simple obesity NOS
12530	[D]Underweight
13278	Body mass index 30+ - obesity
16196	H/O: obesity
16404	O/E - weight 10-20% over ideal
17444	Reason for obesity therapy - occupational
17477	[V]Dietary counselling in obesity
17949	Weight screen
21520	O/E - weight NOS
21744	Obesity clinic administration
22556	Body mass index 40+ - severely obese
22695	Central obesity
23376	O/E - weight within 10% ideal
24496	Body mass index less than 20
24755	Pickwickian syndrome
25061	Ideal weight
25968	Generalised obesity
26473	O/E - weight > 20% below ideal
27570	Treatment of obesity stopped
28946	Body Mass Index normal K/M2
29029	O/E -weight 10-20% below ideal
29538	Follow-up obesity assessment
32843	Obesity monitoring admin.
32914	Body Mass Index low K/M2
32974	O/E - weight > 20% over ideal
38059	Extreme obesity with alveolar hypoventilation
38294	Pickwickian syndrome
38632	Treatment of obesity started
38658	Initial obesity assessment
38799	Obesity due to excess calories
40153	Obesity monitoring NOS
41045	O/E - height NOS

42309	Baseline weight
44291	Body mass index 20-24 - normal
47439	Obesity monitoring check done
49250	Drug-induced obesity
49409	Obesity monitoring 1st letter
52034	Attends obesity monitoring
52036	Obesity monitoring default
52735	Obesity monitoring admin.NOS
55585	Obesity monitoring 3rd letter
55586	Obesity monitoring 2nd letter
57111	Height and Weight
59780	O/E - obese
64712	Treatment of obesity changed
66406	Obesity and other hyperalimentation
67516	Refuses obesity monitoring
67517	Obesity monitor phone invite
69757	[X]Other obesity
70898	Obesity and other hyperalimentation NOS
70950	Obesity monitoring verbal inv.
73304	Obesity monitoring deleted
101047	Body mass index centile
103499	Overweight
103574	Obesity hypoventilation syndrome
104129	Adult-onset obesity
104421	Lifelong obesity
105800	Baseline body mass index

Appendix15

Medcode	Description
676	[D]Raised blood pressure reading
97533	[X]Hypertension secondary to other renal disorders
69753	[X]Hypertensive diseases
102458	[X]Other secondary hypertension
18057	Antihypertensive therapy
45149	Attends hypertension monitor.
1894	Benign essential hypertension
63000	Benign hypertensive heart and renal disease
52427	Benign hypertensive heart disease
52127	Benign hypertensive heart disease with CCF
61660	Benign hypertensive heart disease without CCF
43935	Benign hypertensive renal disease
37086	Blind hypertensive eye
11726	Blood pressure procedure refused
8732	BP - hypertensive disease
8857	Cardiomegaly - hypertensive
83473	Diastolic hypertension
799	Essential hypertension
10818	Essential hypertension NOS
21526	Gestational hypertension
16565	Good hypertension control
2666	H/O: hypertension
351	High blood pressure
102406	Hypertension 9 month review
19070	Hypertension annual review
12680	Hypertension clinical management plan
36305	Hypertension monitor.chck done
24127	Hypertension monitored
4444	Hypertension monitoring
13186	Hypertension monitoring
5215	Hypertension monitoring admin.
3712	Hypertension NOS
105480	Hypertension resistant to drug therapy
18482	Hypertension six month review
21826	Hypertension treatm. started
12948	Hypertension treatm.stopped
22333	Hypertension treatment refused
30776	Hypertension:follow-up default

204	Hypertensive disease
7057	Hypertensive disease NOS
63466	Hypertensive heart and renal disease
68659	Hypertensive heart and renal disease NOS
28684	Hypertensive heart and renal disease with renal failure
16292	Hypertensive heart disease
31464	Hypertensive heart disease NOS
16173	Hypertensive heart disease NOS
62718	Hypertensive heart disease NOS with CCF
61166	Hypertensive heart disease NOS without CCF
21837	Hypertensive heart&renal dis wth (congestive) heart failure
4668	Hypertensive renal disease
15106	Hypertensive renal disease NOS
32423	Hypertensive renal disease with renal failure
6702	Hypertensive retinopathy
13188	Hypertensive treatm.changed
15377	Malignant essential hypertension
67232	Malignant hypertensive heart and renal disease
50157	Malignant hypertensive heart disease
72668	Malignant hypertensive heart disease with CCF
95334	Malignant hypertensive heart disease without CCF
39649	Malignant hypertensive renal disease
18590	Moderate hypertension control
3425	On treatment for hypertension
18765	Other specified hypertensive disease
11056	Patient on maximal tolerated antihypertensive therapy
27511	Poor hypertension control
107704	Primary hypertension
245	Primary pulmonary hypertension
5513	Referral to hypertension clinic
29310	Renal hypertension
57288	Secondary benign hypertension
51635	Secondary benign hypertension NOS
25371	Secondary benign renovascular hypertension
7329	Secondary hypertension
16059	Secondary hypertension NOS
42229	Secondary hypertension NOS
31755	Secondary malignant hypertension
73293	Secondary malignant hypertension NOS
59383	Secondary malignant renovascular hypertension
34065	Secondary pulmonary hypertension
31387	Secondary renovascular hypertension NOS
105487	Severe hypertension

105989	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
105316	Stage 1 hypertension
105371	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
105274	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
37243	Standing diastolic blood pressure
4372	Systolic hypertension
102444	Thromboembolic pulmonary hypertension
10632	White coat hypertension

Appendix16

Medcode	Description
13254	Family history of familial hypercholesterolaemia
12596	FH: Hypercholesterolaemia in first degree relative
26915	Plasma random HDL cholesterol level
13762	Plasma fasting HDL cholesterol level
33304	Plasma random LDL cholesterol level
29699	Plasma fasting LDL cholesterol level
34548	Plasma HDL cholesterol level
19764	Plasma LDL cholesterol level
14105	Cholesterol/HDL ratio
14371	Serum cholesterol/HDL ratio
40935	Plasma cholesterol/HDL ratio
35583	Serum cholesterol/LDL ratio
50393	Plasma cholesterol/LDL ratio
63314	Serum cholesterol/VLDL ratio
18040	Plasma total cholesterol level
12	Serum cholesterol
29202	Serum cholesterol borderline
2493	Serum cholesterol raised
35720	Serum cholesterol very high
44	Serum HDL cholesterol level
65	Serum LDL cholesterol level
13816	Serum VLDL cholesterol level
14370	Serum HDL:non-HDL cholesterol ratio
37206	Serum cholesterol studies
13760	Serum fasting HDL cholesterol level
13761	Serum random HDL cholesterol level
13765	Serum fasting LDL cholesterol level
46224	Serum random LDL cholesterol level

14372	Total cholesterol:HDL ratio
14108	HDL : total cholesterol ratio
18147	Total cholesterol measurement
13766	Calculated LDL cholesterol level
13733	Serum total cholesterol level
12821	Serum fasting total cholesterol
26902	Serum cholesterol NOS
61996	O/E: cholesterol gall stone
106626	Calculus cholesterol content
99677	Calculus = cholesterol
14136	Fluid sample cholesterol level
10783	Cholesterol reduction programme
39147	Cholesterol reduction programme - invited
51023	Cholesterol reduction program - attended
10899	Cholesterol reduction program - declined
6243	Patient advised re low cholesterol diet
71747	Hyperlipidaemia clinical management plan
2091	Seen in cholesterol clinic
30335	DNA - Did not attend cholesterol clinic
18708	Disorder of cholesterol metabolism
339	Pure hypercholesterolaemia
3484	Familial hypercholesterolaemia
3386	Familial hypercholesterolaemia
26019	Hyperlipidaemia, group A
102958	Polygenic hypercholesterolaemia
53091	Other specified pure hypercholesterolaemia
7447	Pure hypercholesterolaemia NOS
5791	Mixed hyperlipidaemia
102390	Familial combined hyperlipidaemia
637	Hyperlipidaemia NOS
107252	Hypercholesterolaemia
66240	[X]Other hyperlipidaemia
37905	Cholesterol granuloma
23089	Cholesterolosis of gallbladder
105492	Cholesterol embolus syndrome
50923	[X]Antihyperlipidaem/antiarterioscl drg caus adv ef ther use
33694	Dietary advice for hyperlipidaemia
12569	[V]Dietary surveillance in hypercholesterolaemia
34825	Hyperbetalipoproteinaemia
34224	LDL hyperlipoproteinaemia
37272	Fredrickson type IIa lipidaem

Appendix17

medcode	Description
7011	Single major depressive episode NOS
34390	Single major depressive episode, unspecified
15219	Single major depressive episode, severe, without psychosis
10610	Single major depressive episode
15155	Single major depressive episode, moderate
6950	Endogenous depression first episode
5879	Agitated depression
595	Endogenous depression
6546	Endogenous depression first episode
32159	Single major depressive episode, severe, with psychosis
43324	Single major depressive episode, partial or unspec remission
16506	Single major depressive episode, mild
57409	Single major depressive episode, in full remission
24171	Recurrent major depressive episodes, severe, with psychosis
56273	Recurrent major depressive episodes,partial/unspec remission
6932	Endogenous depression - recurrent
14709	Recurrent major depressive episodes, moderate
15099	Recurrent major depressive episode
25697	Recurrent major depressive episodes, severe, no psychosis
35671	Recurrent major depressive episodes, unspecified
25563	Recurrent major depressive episode NOS
6482	Recurrent depression
55384	Recurrent major depressive episodes, in full remission
29342	Recurrent major depressive episodes, mild
10825	Seasonal affective disorder
27491	Atypical depressive disorder
9183	Masked depression
8478	Reactive depressive psychosis
17770	Psychotic reactive depression
1055	Agitated depression
655	Anxiety with depression
16632	Prolonged depressive reaction
324	Depressive disorder NEC
4323	Chronic depression
20785	[X]Post-schizophrenic depression
11055	[X]Schizoaffective disorder, depressive type
41022	[X]Schizophreniform psychosis, depressive type
35274	[X]Schizoaffective psychosis, depressive type

98414 [X]Major depression, severe without psychotic symptoms
11717 [X]Mild depressive episode
2970 [X]Depressive episode, unspecified
98252 [X]Major depression, moderately severe
98346 [X]Major depression, mild
24117 [X]Single episode of major depression and psychotic symptoms
52678 [X]Single episode of psychogenic depressive psychosis
10667 [X]Mild depression
3291 [X]Depressive disorder NOS
4639 [X]Depressive episode
12099 [X]Severe depressive episode with psychotic symptoms
28863 [X]Single episode of reactive depressive psychosis
9055 [X]Single episode of depressive reaction
7604 [X]Single episode of reactive depression
18510 [X]Single episode of psychogenic depression
56609 [X]Single episode of masked depression NOS
10720 [X]Atypical depression
5987 [X] Reactive depression NOS
543 [X]Depression NOS
28248 [X]Prolonged single episode of reactive depression
9667 [X]Severe depressive episode without psychotic symptoms
22806 [X]Single episode major depression w'out psychotic symptoms
98417 [X]Major depression, severe with psychotic symptoms
6854 [X]Other depressive episodes
9211 [X]Moderate depressive episode
24112 [X]Single episode of psychotic depression
41989 [X]Single episode agitated depressn w'out psychotic symptoms
59386 [X]Single episode vital depression w'out psychotic symptoms
33469 [X]Recurr depress disorder cur epi severe without psyc sympt
22116 [X]Recurrent depressive disorder, currently in remission
47009 [X]Recurrent depress disorder cur epi severe with psyc symp
44300 [X]Recurrent depressive disorder, unspecified
47731 [X]Other recurrent depressive disorders
32941 [X]Recurr severe episodes/major depression+psychotic symptom
28677 [X]Manic-depress psychosis,depressed type+psychotic symptoms
37764 [X]Recurrent severe episodes/reactive depressive psychosis
16861 [X]Recurrent severe episodes of psychotic depression
31757 [X]Recurr severe episodes/psychogenic depressive psychosis
36616 [X]Monopolar depression NOS
19696 [X]Recurrent episodes of psychogenic depression
8902 [X]Recurrent episodes of reactive depression
8851 [X]Recurrent episodes of depressive reaction
28756 [X]Seasonal depressive disorder

8826	[X]SAD - Seasonal affective disorder
23731	[X]Endogenous depression with psychotic symptoms
29784	[X]Recurrent depressive disorder, current episode mild
3292	[X]Recurrent depressive disorder
73991	[X]Vital depression, recurrent without psychotic symptoms
11252	[X]Major depression, recurrent without psychotic symptoms
29451	[X]Manic-depress psychosis,depressd,no psychotic symptoms
29520	[X]Recurrent depressive disorder, current episode moderate
11329	[X]Endogenous depression without psychotic symptoms
15220	[X]Persistant anxiety depression
8584	[X]Depressive neurosis
10290	[X]Depressive personality disorder
7737	[X]Neurotic depression
7953	[X]Dysthymia
7749	[X]Mild anxiety depression
11913	[X]Mixed anxiety and depressive disorder
101153	[X]Recurr major depr ep, severe with psych, psych in remiss
101054	[X]Single major depr ep, severe with psych, psych in remiss
103677	[X]Antenatal depression
48349	Dysphoric mood
1908	O/E - depressed
29424	Morbid thoughts
4067	Suicidal plans
1712	Suicidal ideation
37194	Moderate suicide risk
47022	Plans for deliberate self harm without intent
18671	At risk of DSH - deliberate self harm
106853	Suicide risk unchanged from previous level
11753	Intent of deliberate self harm with detailed plans
12694	Thoughts of deliberate self harm
104485	Suicide risk increased from previous level
10015	Depressed mood
100977	Suspected depression
37948	Psychomotor retardation
2639	Postnatal depression
42000	Other neurotic disorders
3361	Neurasthenia - nervous debility
4659	Generalised anxiety disorder
4634	Recurrent anxiety
43050	Other neurotic disorder NOS
6939	Anxiety state unspecified
2030	Obsessional neurosis
4534	Anxiety state NOS

5249	Neurotic disorders
1758	Chronic anxiety
36246	Brief depressive reaction NOS
1533	Brief depressive reaction
28008	[X]Other mood affective disorders
19054	[X]Recurrent brief depressive episodes
29579	[X]Other specified mood affective disorders
39767	[X]Persistent mood affective disorder, unspecified
5726	[X]Mood - affective disorders
42857	[X]Persistent mood affective disorders
50998	[X]Other single mood affective disorders
29921	[X]Other recurrent mood affective disorders
37090	[X]Unspecified mood affective disorder
50243	[X]Other persistent mood affective disorders
5385	[X]Other anxiety disorders
28090	[X]Other neurotic disorders
101725	[X]Chron post-traumatic stress disorder follow military comb
10344	[X]Generalized anxiety disorder
21431	[X]Neurosis NOS
101785	[X]Acute post-traumatic stress disorder follow military comb
44331	[X]Other specified neurotic disorders
24066	[X]Other specified anxiety disorders
42788	[X]Social neurosis
32182	[X]Traumatic neurosis
49628	[X]Neurotic disorder, unspecified
44321	[X]Other mixed anxiety disorders
23838	[X]Anxiety disorder, unspecified
4979	[X]Postpartum depression NOS
43239	Excepted from depression quality indicators: Informed dissen
48970	Exception reporting: depression quality indicators
28970	Excepted from depression quality indicators: Patient unsuita
19439	Depression resolved
30405	Depression interim review
12122	Depression medication review
12399	Depression annual review
32589	Mental health annual physical examination done

Appendix18

medcode	Description
2864	Intracranial injury NOS no open intracranial wound
2883	Closed traumatic subdural haemorrhage
3535	Intracerebral haemorrhage NOS
4088	Late effect of intracranial injury without skull fracture
5051	Intracerebral haemorrhage
5682	Cerebral haemorrhage following injury
6139	Chronic post-traumatic headache
6196	Late effect of head injury
6569	Subdural haemorrhage following injury
6960	CVA - cerebrovascular accid due to intracerebral haemorrhage
7862	Traumatic subdural haematoma
7912	Pontine haemorrhage
8181	Traumatic subdural haemorrhage
10201	Brain injury NOS
17958	Closed #skull vlt + intracranial injury, unspec state consc
18430	Late effect of contusion
18604	Stroke due to intracerebral haemorrhage
20284	Intracranial haemorrhage NOS
20582	[X]Post-traumatic brain syndrome
27492	Closed fracture of skull NOS with intracranial injury
27632	Diffuse brain injury
27657	Closed fracture vault of skull with intracranial injury
27661	Extradural haemorrhage following injury
28077	Traumatic cerebral haemorrhage
28314	Left sided intracerebral haemorrhage, unspecified
28807	Subarachnoid haemorrhage following injury
30202	Intracerebral haemorrhage, intraventricular
31466	Subdural intracranial abscess
31595	Cortical haemorrhage
31805	Other and unspecified intracranial haemorrhage
32214	Focal brain injury
33455	Closed cerebral contusion
38304	Closed traumatic subarachnoid haemorrhage
38330	Brain injury due to birth trauma NOS
40338	Internal capsule haemorrhage
40659	Crush injury of head
42283	Other cerebral haemorrhage following injury NOS
42692	Cerebral laceration and contusion NOS

42704	Post-head injury syndrome
43882	Discharge from head injury rehabilitation
45421	Closed traumatic extradural haemorrhage
45875	Otogenic intracranial abscess
45956	Closed #skull bse + intracranial injury, LOC unspec duration
46545	Cerebral haemorrhage following injury NOS
48149	Sequelae of intracerebral haemorrhage
48651	Crushing injuries involving head with neck
49715	Phlebitis and thrombophlebitis of intracranial sinuses
49912	Post-traumatic brain syndrome
50687	Closed #skull/face, mult + intracranial inj, 1-24hrs LOC
51299	Open fracture vault of skull with intracranial injury
51308	Intracranial injury NOS + open intracranial wound
52391	Intracranial inj NOS + open intracranial wound+no loss consc
52968	Other cerebral haemorrhage following injury
53980	Traumatic subdural haematoma without open intracranial wound
54085	Post-traumatic hydrocephalus, unspecified
54980	Subdural intracranial abscess
56262	[D]Skull or head x-ray or scan abnormal
56638	Other cerebral h'ge after injury no open intracranial wound
56831	Late effect of intracranial injury NOS
57315	Intracerebral haemorrhage, multiple localized
57529	Cerebral intracranial abscess
58545	Traumatic subarachnoid haemorrhage
59959	Closed #skull vlt with intracranial injury+concussion unspec
60627	Open hindbrain contusion
61140	Intracranial inj NOS + open intracranial wnd+<1hr loss consc
61318	Cortex lacn + open intracranial wound + >24hr LOC + recovery
61357	Open #skull vlt + intracranial injury, LOC unspec duration
62743	Open #skull vlt with intracranial injury + concussion unspec
62835	Open #skull/face, mult + intracranial inj, unspec consc
62841	Closed #skull vlt + intracranial injury, LOC unspec duration
62858	Cortex cont no open intracranial wnd + 1-24hrs loss of consc
63679	Closed fracture base of skull with intracranial injury
64167	Open #skull vlt + intracranial injury, unspec state of consc
64550	Closed #skull NOS + intracranial inj, LOC unspec duration
67603	Open fracture of skull NOS with intracranial injury
67971	Cerebellar intracranial abscess
68560	Brain cont no open intracranial wound + unspec state consc
68800	Subdural h'ge inj no open intracranial wnd + unspec consc
69209	Open cerebral contusion
69491	Closed #skull NOS + intracranial inj, 1-24hrs loss of consc
71725	Closed #skull bse + intracranial injury, >24hr LOC+recovery

71866	Closed #skull/face,mult + intracran inj, concussion unspec
71963	Traumatic cerebral oedema without open intracranial wound
72412	Closed #skull vlt + intracranial injury, >24hr LOC+recovery
72754	Intracranial inj NOS + open intracranial wnd + unspec consc
73206	Mult #skull/face+other bones, closed + intracranial injury
73441	Open #skull vlt + intracranial injury, no loss of consc
73451	Open #skull bse + intracranial injury, >24hr LOC + recovery
73471	Open traumatic extradural haemorrhage
73541	Extradural h'ge inj no open intracranial wnd + unspec consc
91907	Late effects of intracranial abscess or pyogenic infection
93200	Discharge from head injury rehabilitation service
93804	Closed #skull/face, mult + intracranial inj, unspec consc
93851	Closed #skull vlt + intracranial injury, 1-24hr loss consc
94076	Cortex laceration with open intracranial wound
94351	Open traumatic subdural haemorrhage
94409	Cortex cont no open intracranial wnd + concussion unspec
96630	[X]Intracerebral haemorrhage in hemisphere, unspecified
96677	Traumatic subdural haematoma with open intracranial wound
96717	Open traumatic subarachnoid haemorrhage
97064	Open fracture base of skull with intracranial injury
97911	Traumatic extradural haemat without open intracranial wound
98078	Cortex cont no open intracranial wnd + LOC unspec duration
98520	[X]Other intracranial injuries
98776	Closed #skull vlt + intracranial injury, <1hr loss of consc
99018	Closed #skull vlt + intracranial injury, no loss of consc
99019	Closed #skull bse + intracranial inj, unspec state of consc
99072	Traumatic cerebral oedema with open intracranial wound
99282	Open #skull bse + intracranial injury, LOC unspec duration
99505	Open #skull bse + intracranial injury, <1hr loss of consc
100875	Brain cont no open intracranial wound + LOC unspec duration
102718	Open #skull bse + intracranial injury + concussion unspec
104057	Cortex cont no open intracranial wnd + >24 hr LOC + recovery
104726	Open #skull vlt + intracranial injury, >24hr LOC + recovery
104820	Brain cont no open intracranial wound + concussion unspec
105137	Closed #skull bse + intracranial injury, 1-24hr loss consc
105699	Brain cont + open intracranial wound + concussion unspec
106486	Subarach h'ge inj no open intracran wnd + concussion unspec
107041	Mult #skull/face + other bones, open + intracranial injury
107337	Acquired brain injury
107440	Lobar cerebral haemorrhage
108089	Cortex lacn no open intracranial wound + unspec state consc
28353	Congenital hydrocephalus NOS
50565	Thoracic spina bifida with hydrocephalus

103284	Lumbar spina bifida with hydrocephalus - open
46790	Spina bifida with hydrocephalus
72928	Sacral spina bifida with hydrocephalus - closed
105767	Lumbar spina bifida with hydrocephalus - closed
47288	Spina bifida with hydrocephalus - open NOS
9611	Congenital hydrocephalus
45734	Infantile posthaemorrhagic hydrocephalus
98298	Spina bifida with hydrocephalus NOS
5306	Spina bifida with hydrocephalus, unspecified
100957	[X]Post-traumatic hydrocephalus, unspecified
57243	Thoracic spina bifida with hydrocephalus - open
102628	Spina bifida with hydrocephalus of late onset
64717	Spina bifida with hydrocephalus NOS
100673	[X]Other congenital hydrocephalus
4675	Acquired communicating hydrocephalus
60623	Sacral spina bifida with hydrocephalus - open
107917	Congenital hydrocephalus due to toxoplasmosis
107207	X-linked hydrocephalus
98811	Spina bifida with hydrocephalus - open
73085	Other specified spina bifida with hydrocephalus
106579	[X]Unspecified spina bifida with hydrocephalus
93902	Spina bifida with hydrocephalus - closed
42497	Unspecified spina bifida with hydrocephalus
52683	Myelocele with hydrocephalus
104943	Fissured spine with hydrocephalus
2731	Cerebral atrophy
10288	Normal pressure hydrocephalus
63360	Subarachnoid haemorrhage due to birth injury

Appendix19

medcode	Description
52246	Stroke group member
34135	H/O: CVA/stroke
6305	H/O: CVA
5871	H/O: stroke
66873	H/O: Stroke in last year
100639	Central post-stroke pain
107195	Stroke self-management plan agreed
18686	Stroke/CVA annual review
107886	Stroke annual review
10792	Stroke monitoring
105100	Stroke 6 month review
104505	Stroke initial post discharge review
28914	Haemorrhagic stroke monitoring
17960	Carotid, cerebral and subclavian artery operations
94115	Other open operations on cerebral artery or circle of Willis
59604	Anastomosis of cerebral artery
104517	Open embolectomy of cerebral artery
71022	Transluminal operations on cerebral artery/ circle of Willis
26094	Embolisation of cerebral artery NEC
93770	Percutaneous transluminal insertion of stent cerebral artery
66933	Transluminal operation on cerebral art/circle of Willis OS
104715	Transluminal operation on cerebral art/circle of Willis NOS
71127	Carotid, cerebral and subclavian artery operations NOS
23086	[SO]Cerebral artery
34824	[SO]Posterior cerebral artery
55351	Delivery of rehabilitation for stroke
100015	Transient ischaemic attack clinical management plan
13707	Stroke / transient ischaemic attack referral
56458	Ref to multidisciplinary stroke function improvement service
18804	Referral to stroke clinic
104638	Ref multidisciplinary stroke function improvement declined
32959	Seen in Stroke Clinic
31218	Stroke/transient ischaemic attack monitoring administration
28753	Stroke/transient ischaemic attack monitoring first letter
34245	Stroke/transient ischaemic attack monitoring second letter
34375	Stroke/transient ischaemic attack monitoring third letter
51465	Stroke/transient ischaemic attack monitoring verbal invitati
89913	Stroke/transient ischaemic attack monitoring telephone invte

36568	Embolism of central nervous system venous sinus
55885	Embolism cavernous sinus
64467	Embolism superior longitudinal sinus
84404	Embolism transverse sinus
54744	Cerebral degeneration due to cerebrovascular disease
5644	Anoxic - ischaemic encephalopathy
63746	[X]Other transnt cerebral ischaemic attacks+related syndroms
19412	Subarachnoid haemorrhage from middle cerebral artery
5051	Intracerebral haemorrhage
6960	CVA - cerebrovascular accid due to intracerebral haemorrhage
18604	Stroke due to intracerebral haemorrhage
31595	Cortical haemorrhage
40338	Internal capsule haemorrhage
46316	Basal nucleus haemorrhage
13564	Cerebellar haemorrhage
7912	Pontine haemorrhage
62342	Bulbar haemorrhage
30045	External capsule haemorrhage
30202	Intracerebral haemorrhage, intraventricular
57315	Intracerebral haemorrhage, multiple localized
107440	Lobar cerebral haemorrhage
31060	Intracerebral haemorrhage in hemisphere, unspecified
28314	Left sided intracerebral haemorrhage, unspecified
19201	Right sided intracerebral haemorrhage, unspecified
3535	Intracerebral haemorrhage NOS
45781	Precerebral arterial occlusion
63830	Stenosis of precerebral arteries
4152	Thrombosis, carotid artery
98642	Multiple and bilateral precerebral arterial occlusion
51326	Other precerebral artery occlusion
23671	Cerebral infarct due to thrombosis of precerebral arteries
24446	Cerebral infarction due to embolism of precerebral arteries
71585	Precerebral artery occlusion NOS
8837	Cerebral arterial occlusion
5363	CVA - cerebral artery occlusion
6155	Stroke due to cerebral arterial occlusion
16517	Cerebral thrombosis
36717	Cerebral infarction due to thrombosis of cerebral arteries
15019	Cerebral embolism
34758	Cerebral embolus
27975	Cerebral infarction due to embolism of cerebral arteries
3149	Cerebral infarction NOS
25615	Brainstem Infarction

47642	Wallenberg syndrome
9985	Left sided cerebral infarction
10504	Right sided cerebral infarction
26424	Infarction of basal ganglia
504	Transient cerebral ischaemia
1433	Transient ischaemic attack
23942	Basilar artery syndrome
33377	Vertebral artery syndrome
21118	Vertebro-basilar artery syndrome
23465	Subclavian steal syndrome
44765	Carotid artery syndrome hemispheric
50594	Multiple and bilateral precerebral artery syndromes
105738	Carotid territory transient ischaemic attack
19354	Other transient cerebral ischaemia
1895	Transient cerebral ischaemia NOS
55247	Impending cerebral ischaemia
16507	Intermittent cerebral ischaemia
15788	Transient cerebral ischaemia NOS
1469	Stroke and cerebrovascular accident unspecified
1298	CVA unspecified
6253	Stroke unspecified
6116	CVA - Cerebrovascular accident unspecified
18689	Middle cerebral artery syndrome
19280	Anterior cerebral artery syndrome
19260	Posterior cerebral artery syndrome
8443	Brain stem stroke syndrome
17322	Cerebellar stroke syndrome
33499	Pure motor lacunar syndrome
51767	Pure sensory lacunar syndrome
7780	Left sided CVA
12833	Right sided CVA
11171	Cerebral atherosclerosis
40053	Generalised ischaemic cerebrovascular disease NOS
24385	Chronic cerebral ischaemia
39344	Cereb infarct due cerebral venous thrombosis, nonpyogenic
31704	Occlusion/stenosis cerebral arts not result cerebral infarct
51759	Occlusion and stenosis of middle cerebral artery
57527	Occlusion and stenosis of anterior cerebral artery
65770	Occlusion and stenosis of posterior cerebral artery
71274	Occlusion+stenosis of multiple and bilat cerebral arteries
101733	Cerebral vein thrombosis
48149	Sequelae of intracerebral haemorrhage
39403	Sequelae of cerebral infarction

6228	Sequelae of stroke,not specfd as h'morrhage or infarction
40758	Cereb infarct due unsp occlus/stenos precerebr arteries
33543	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
53810	[X]Oth intracerebrl h'morrhage
91627	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
53745	[X]Other cerebral infarction
90572	[X]Occlusion and stenosis of other precerebral arteries
92036	[X]Occlusion and stenosis of other cerebral arteries
96630	[X]Intracerebral haemorrhage in hemisphere, unspecified
94482	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
55974	Cerebral venous thrombosis in the puerperium
47607	CVA - cerebrovascular accident in the puerperium
56279	Stroke in the puerperium
19688	Cerebral anoxia complication
42248	Discharge from stroke serv
19348	[V]Personal history of stroke
7138	[V]Personal history of cerebrovascular accident (CVA)
101251	[V]Personal history of transient ischaemic attack
13567	H/O: TIA
43451	Sequelae of other nontraumatic intracranial haemorrhage
44740	Sequelae of subarachnoid haemorrhage
15788	Transient cerebral ischaem.NOS
240	Ischaemic heart disease
241	Acute myocardial infarction
569	Infarction - cerebral
732	Transluminal balloon angioplasty of coronary artery NOS
1204	Heart attack
1344	Coronary artery disease
1414	Angina on effort
1430	Angina pectoris
1431	Unstable angina
1655	Triple vessel disease of the heart
1676	Ischaemic heart disease NOS
1677	MI - acute myocardial infarction
1678	Inferior myocardial infarction NOS
1792	IHD - Ischaemic heart disease
2155	Ventricular cardiac aneurysm
2156	Stenosis, carotid artery
2417	Vertebro-basilar insufficiency
2491	Coronary thrombosis
2652	Carotid artery stenosis
2654	Endarterectomy of carotid artery NEC
2901	Transluminal balloon angioplasty of coronary artery

3132 Drop attack
3159 Other specified other bypass of coronary artery
3704 Acute subendocardial infarction
3999 Single coronary vessel disease
4017 Old myocardial infarction
4240 Carotid artery occlusion
4635 Cerebral aneurysm, nonruptured
4656 Crescendo angina
5185 Lateral medullary syndrome
5254 Double coronary vessel disease
5268 Insufficiency - basilar artery
5387 Other specified anterior myocardial infarction
5413 Coronary atherosclerosis
5602 Cerebellar infarction
5703 Percutaneous balloon coronary angioplasty
5744 Open angioplasty of coronary artery
5904 Coronary artery operations
6182 Other therapeutic transluminal op on coronary artery OS
6331 Aneurysm of heart
6336 H/O: angina pectoris
6489 Transient global amnesia
7134 Other autograft bypass of coronary artery
7137 Saphenous vein graft replacement of coronary artery OS
7320 Ischaemic cardiomyopathy
7347 Unstable angina
7442 Saphenous vein graft replacement of three coronary arteries
7609 Other autograft replacement of coronary artery NOS
7634 Saphenous vein graft replacement of two coronary arteries
7696 Syncope anginosa
7783 ECG: myocardial infarction
8312 Saphenous vein graft bypass of coronary artery
8679 Saphenous vein graft replacement of one coronary artery
8935 Acute inferolateral infarction
8942 Insertion of coronary artery stent
9276 Acute coronary insufficiency
9413 Other acute and subacute ischaemic heart disease
9414 Other autograft replacement of coronary artery
9507 Acute non-Q wave infarction
9555 Post infarct angina
10209 Autograft replacement of three coronary arteries NEC
10260 Coronary heart disease review
10562 Acute non-ST segment elevation myocardial infarction
10603 Coronary artery operations NOS

10794 Vertebrobasilar insufficiency
11048 Variant angina pectoris
11610 Saphenous vein graft replacement of four+ coronary arteries
11983 Acute coronary syndrome
12139 Acute anterolateral infarction
12229 Acute ST segment elevation myocardial infarction
12733 Carotid endarterectomy and patch
12804 Stable angina
12986 Prinzmetal's angina
13185 Angina control
13187 CHD monitoring
13566 Attack - heart
13571 Thrombosis - coronary
14658 Acute myocardial infarction NOS
14782 Angina control - improving
14897 Anterior myocardial infarction NOS
14898 Lateral myocardial infarction NOS
15252 Brainstem infarction NOS
15349 Angina control NOS
15373 Angina control - poor
15661 Dressler's syndrome
15754 Other chronic ischaemic heart disease NOS
16408 Healed myocardial infarction
16956 Cerebral palsy, not congenital or infantile, acute
17054 [SO]Coronary artery
17133 Mural thrombosis
17307 Angina at rest
17464 Personal history of myocardial infarction
17689 Silent myocardial infarction
17872 Acute anteroseptal infarction
18118 Worsening angina
18125 Nocturnal angina
18135 Coronary heart disease annual review
18249 Saphenous vein graft replacement of coronary artery
18670 Percut transluminal balloon angioplasty one coronary artery
18842 Subsequent myocardial infarction
18889 Asymptomatic coronary heart disease
19046 Rotary blade coronary angioplasty
19164 Repair of aneurysm of coronary artery
19193 Prosthetic replacement of coronary artery NOS
19298 Cardiac event recording
19402 Prosthetic replacement of coronary artery
19413 Autograft replacement of two coronary arteries NEC

19542 Angina control - good
19655 Angina at rest
20095 Angina decubitus
20416 Atherosclerotic heart disease
21844 Transient myocardial ischaemia
22020 Endarterectomy of coronary artery NEC
22383 Other specified ischaemic heart disease
22647 LIMA single anastomosis
22828 Percutaneous transluminal laser coronary angioplasty
23078 Chronic myocardial ischaemia
23579 Postmyocardial infarction syndrome
23708 Atrial septal defect/curr comp folow acut myocardal infarct
23892 Posterior myocardial infarction NOS
24126 Haemopericardium/current comp folow acut myocard infarct
24540 Chronic coronary insufficiency
24783 Arteriosclerotic heart disease
24888 Other therapeutic transluminal operations on coronary artery
25842 Angina pectoris NOS
26863 New onset angina
26966 ECG: S-T elevation
26972 ECG:posterior/inferior infarct
26973 ECG:shows myocardial ischaemia
26975 ECG: antero-septal infarct.
27484 Cardiac aneurysm
27951 Other acute and subacute ischaemic heart disease
27977 Other acute and subacute ischaemic heart disease NOS
28138 Other chronic ischaemic heart disease
28554 Angina pectoris NOS
28736 Acute atrial infarction
28837 Creation of bypass from mammary artery to coronary artery
29300 Angina control - worsening
29421 Silent myocardial ischaemia
29553 Thrombosis atrium,auric append&vent/curr comp foll acute MI
29643 Acute inferoposterior infarction
29758 Acute transmural myocardial infarction of unspecif site
29902 Angina decubitus NOS
29973 Percutaneous transluminal angioplasty of carotid artery
30330 Acute Q-wave infarct
30421 Cardiac rupture following myocardial infarction (MI)
30963 Suspected ischaemic heart disease
31519 Double implant of mammary arteries into coronary arteries
31540 Revision of bypass for three coronary arteries
31556 Allograft replacement of coronary artery

31571 Other specified operations on coronary artery
31679 Other therapeutic transluminal op on coronary artery NOS
32272 Postoperative myocardial infarction
32447 Basilar artery occlusion
32450 Ischaemic chest pain
32651 Allograft bypass of coronary artery
32854 Acute posterolateral myocardial infarction
33461 Revision of bypass for coronary artery
33471 Other bypass of coronary artery NOS
33620 Repair of coronary artery NEC
33650 Percut transluminal coronary thrombolysis with streptokinase
33718 Double anastomosis of mammary arteries to coronary arteries
33735 Percut translum balloon angioplasty mult coronary arteries
34328 Refractory angina
34633 Other specified chronic ischaemic heart disease
34803 Other acute myocardial infarction
34963 Other bypass of coronary artery
34965 Diagnostic transluminal operations on coronary artery
35287 ECG: myocardial ischaemia NOS
35713 Other specified chronic ischaemic heart disease NOS
36011 Prosthetic bypass of coronary artery
36423 Certain current complication follow acute myocardial infarct
36523 Preinfarction syndrome
36609 Atherosclerotic cardiovascular disease
36854 Coronary artery spasm
37657 Ventric septal defect/curr comp fol acut myocardal infarctn
37682 Connection of mammary artery to coronary artery
37719 Connection of mammary artery to coronary artery OS
38609 Subsequent myocardial infarction of inferior wall
39449 Coronary thrombosis not resulting in myocardial infarction
39546 [X]Other forms of angina pectoris
39655 Impending infarction
39693 Subendocardial ischaemia
39904 ECG: old myocardial infarction
40399 H/O: myocardial infarct >60
40429 Acute anteroapical infarction
40847 Vertebral artery occlusion
40996 Percut translum coronary thrombolytic therapy- streptokinase
41221 Acute septal infarction
41547 Transluminal balloon angioplasty of coronary artery OS
41677 Aneurysm of heart NOS
41757 Other open operation on coronary artery NOS
41762 H/O: CVS disease NOS

41835 Postoperative subendocardial myocardial infarction
42104 ECG: S-T depression
42304 Insertion of drug-eluting coronary artery stent
42462 Percut translum balloon angioplasty bypass graft coronary a
42708 Autograft replacement of four of more coronary arteries NEC
43939 Perc translumin balloon angioplasty stenting coronary artery
44561 Autograft replacement of one coronary artery NEC
44585 Repair of coronary artery NOS
44723 Single anast mammary art to left ant descend coronary art
45370 Allograft replacement of four or more coronary arteries
45476 H/O: Treatment for ischaemic heart disease
45809 Subsequent myocardial infarction of anterior wall
45886 Allograft replacement of three coronary arteries
45960 Antianginal therapy
46017 Other acute myocardial infarction NOS
46112 Postoperative transmural myocardial infarction anterior wall
46166 Subsequent myocardial infarction of unspecified site
46276 Postoperative transmural myocardial infarction inferior wall
47580 Percutaneous transluminal insertion stent carotid artery
47637 [X]Other forms of chronic ischaemic heart disease
47788 Other open operations on coronary artery
48767 Allograft replacement of coronary artery NOS
48822 LIMA sequential anastomosis
50372 H/O: Myocardial infarction in last year
51043 Duke's coronary artery disease score
51507 Single anastomosis of mammary artery to coronary artery NEC
51515 Saphenous vein graft replacement coronary artery NOS
51702 Exploration of coronary artery
52517 [X]Ischaemic heart diseases
52615 Myocardial bridge of coronary artery
52637 Canadian Cardiovascular Society classification of angina
52705 ECG: lateral infarction
52938 Revision of bypass for one coronary artery
54251 Preinfarction syndrome NOS
54535 Stenocardia
55074 Percutaneous transluminal angioplasty of vertebral artery
55092 Replacement of coronary arteries using multiple methods
55137 MI - myocardial infarction aborted
55401 ECG: subendocardial infarct
55598 Other replacement of coronary artery
56905 Diagnostic transluminal operation on coronary artery OS
56990 Connection of mammary artery to coronary artery NOS
57062 H/O: Angina in last year

57241 Allograft replacement of two coronary arteries
57495 Infarction - precerebral
57634 Revision of bypass for coronary artery NOS
59032 ECG: myocardial infarct NOS
59189 Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59193 Aneurysm of coronary vessels
59423 Other specified allograft replacement of coronary artery
59940 Ruptur chordae tendinae/curr comp fol acute myocard infarct
60067 Perc translum ball angio insert 1-2 drug elut stents cor art
60753 Single implantation thoracic artery into coronary artery NEC
61072 Myocardial infarction aborted
61208 Perc translum balloon angioplasty stenting coronary art NOS
61248 Diagnostic transluminal operation on coronary artery NOS
61310 Other autograft replacement of coronary artery OS
61592 Transection of muscle bridge of coronary artery
62270 ECG: Q wave pathological
62608 Double anastom thoracic arteries to coronary arteries NEC
62626 Acute papillary muscle infarction
63153 Revision of implantation of thoracic artery into heart
63467 True posterior myocardial infarction
66236 Prosthetic replacement of three coronary arteries
66388 Status anginosus
66583 Percut translum inject therap subst to coronary artery NEC
66664 Prosthetic replacement of two coronary arteries
67087 Other cardiac wall aneurysm
67554 Revision of bypass for two coronary arteries
67591 Single anastomosis of thoracic artery to coronary artery NEC
67761 Prosthetic replacement of four or more coronary arteries
68069 Endovascular repair of carotid artery
68123 RIMA single anastomosis
68139 Single implantation of mammary artery into coronary artery
68357 Microinfarction of heart
68401 [X]Other forms of acute ischaemic heart disease
68748 Postoperative myocardial infarction, unspecified
69247 Other specified repair of coronary artery
69474 Rupture papillary muscle/curr comp fol acute myocard infarct
70111 Allograft replacement of one coronary artery
70755 Replacement of coronary artery NOS
72562 Subsequent myocardial infarction of other sites
72780 Connection of other thoracic artery to coronary artery NOS
85947 Perc translum balloon angioplasty insert 1-2 stents cor art
86071 Percut translum cutting balloon angioplasty coronary artery
87849 Perc tran ball angio ins 3 or more drug elut stents cor art

91737	Transluminal operations on cardiac conduit
92233	RIMA sequential anastomosis
92419	Prosthetic replacement of one coronary artery
92927	Percutaneous cor balloon angiop 3 more stents cor art NEC
93516	Other specified transluminal operations on cardiac conduit
93618	Percutaneous transluminal atherectomy of coronary artery
93706	Percutaneous transluminal balloon dilation cardiac conduit
93828	Other specified replacement of coronary artery
94783	Repair of rupture of coronary artery
95382	Other specified other open operation on coronary artery
96537	OS perc translumina balloon angioplast stenting coronary art
96804	Connection of other thoracic artery to coronary artery
96838	[X]Acute transmural myocardial infarction of unspecif site
97953	Other specified revision of bypass for coronary artery
99434	Transluminal operations on cardiac conduit NOS
99991	[X]Subsequent myocardial infarction of unspecified site
100139	History of myocardial infarction
101121	Coronary artery bypass graft operation planned
101373	Coronary angioplasty planned
101569	Revision of bypass for four or more coronary arteries
102326	Suspected transient ischaemic attack
103655	Frequency of angina
105184	Percutaneous coronary intervention
105202	H/O amaurosis fugax
105216	H/O acute coronary syndrome
105250	Mural cardiac aneurysm
105479	Coronary microvascular disease
105520	Admission to stroke unit
106812	Postoperative transmural myocardial infarction unspec site
107406	Emergency percutaneous coronary intervention
107574	Referral to Angina Plan self-management programme
92036	[X]Oc+sten/o cerebral arteries
90572	[X]Oc+steno/o precerebral artr
73961	[X]Oth spcf periph vasculr dis
29463	Acute inferoposterior infarct
19280	Anterior cerebral artery syn
27975	Cerebr infct/embol/cerebrl art
24446	Cerebr infct/embol/precere art
36717	Cerebr infct/throm/cerebrl art
23671	Cerebr infct/throm/precere art
55247	Impending CVA
1517	Intermittent claudication
16507	Intermittent CVA

18689	Middle cerebral artery syndrm
50594	Multi&bilat precerebrl art syn
5943	Other peripheral vascular dis.
38907	Other spec.periph.vasc.disease
105317	Peripheral arterial disease
2760	Peripheral vasc.disease NOS
3530	Peripheral vascular dis. NOS
19260	Posterior cerebral artery syn