Population Health Sciences Institute

Mild Cognitive Impairment (MCI) in the Population: New Criteria and Cohort Effects

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Dedication

I dedicate my thesis to my family

My mother, Beverley

For being the best mam and dad I could ask for, for always believing in me, giving me resilience and humour. Thank you for your support in everything I have done.

My friend, Laura

For being there at my highest, lowest and everything in between, the best friend I could have.

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For your love and support. You have done far more for me than I can begin to thank you for.

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ABSTRACT

Much work on identifying individuals at high risk of dementia has focused on the clinical concept of MCI, which is considered to be an intermediate state between normal cognitive ageing and dementia. Many definitions for this state exist, including for example amnestic-MCI and Other Cognitive Impairment no Dementia (OCIND). This study utilises the Cognitive Function and Ageing Studies (CFAS) I & II, to explore the concept of MCI in the UK population.

The first study focused on updating the definition of MCI and established a cognitive spectrum to capture participants of CFAS with no cognitive impairment through to dementia. The definitions were then used to estimate the UK population prevalence of MCI. A natural progression was to use the follow-up (wave II) of CFAS II to determine the incidence and progression of MCI and OCIND. The final study focused on risk factors associated with prevalent MCI, OCIND and dementia, as well as incident cognitive impairment. The link between cognitive function and both socio-demographic factors (i.e. education, deprivation and loneliness) and medical co-morbidities (i.e. Parkinson's disease, heart attack and diabetes) were investigated.

Mild dementia has, along with CFAS defined dementia, declined, (5.7%, 95% CI: 3.8, 8·1) in 1991 to 315,142 (3.0%, 95% CI: 2.4, 3.8) in 2011. There is a clear increase in the prevalence of OCIND with MCI remaining stable. In CFAS II the overall incidence rate for RMCI, is 138.5 per 1000-person years (95% CI: 131.5, 145.5) and 233.5 per 1000-person years (95% CI: 228.4, 238.6) for OCIND. Key risk factors for incident MCI and transition to dementia were smoking status, loneliness and poor self-reported health.

The analysis highlights the need to move beyond the current narrow dementia criteria which exclude large proportions of older people with cognitive impairment. Findings suggest that the increase in OCIND and stability of MCI could reflect "normal cognitive ageing" among a population which is substantially older. Evidence suggests it is through healthy lifestyle behaviours, better educational attainment, minimizing risks from comorbidities in the wider population which should be further encouraged to reduce risk of cognitive impairment.

LIST OF ABBREVIATIONS

AACD - age-associated cognitive decline

AAMI - age-associated memory impairment

AD – Alzheimer's disease

ADL – Activities of daily living

AGECAT - Automated geriatric examination for computer assisted taxonomy

AMCI – Amnestic Mild Cognitive Impairment

ARCD - age-related cognitive decline

CAMCOG – Cambridge Cognitive Examination

CDR – clinical dementia rating scale

CFAS – Cognitive function and ageing studies

CI – Confidence interval

CIND - cognitive impairment no dementia

C-PIB C-labelled Pittsburgh Compound-B

DEM - dementia

DSM – Diagnostic and statistical manual

DSM – III – R – Diagnostic and statistical manual 3rd edition (revised)

DSM – V – Diagnostic and statistical manual 5th edition

FHSA - The Family Health Service Authorities

FI – Functional Impairment

IADL – Instrumental activities of daily living

IPW – Inverse probability weighting

IR – Incidence Rate

IRR – Incidence rate ratio

LCD - limited cognitive disturbance

MCD - (ICD-10), mild cognitive disorder (International Classification of Diseases 10th Revision)

MCDi - (GDS3), mild cognitive decline (Global Deterioration Scale Stage 3)

MCDo - (GDS4), moderate cognitive decline (Global Deterioration Scale Stage 4)

MCI – Mild Cognitive Impairment

MD - minimal dementia

MI – Multiple imputation

MICE – Multiple imputation by chained equations

MMCI – Multiple Mild Cognitive Impairment

MMSE – Mini mental state examination

MNCD - mild neurocognitive disorder

MRC – Medical Research Council

NaMCI – Non-amnestic Mild Cognitive Impairment

NCI – No Cognitive Impairment

NIA-AA - National Institute on Aging and the Alzheimer's Association

N-MCI - non-amnestic mild cognitive impairment

OCIND – Other Cognitive Impairment not Dementia

OR – Odds ratio

PD – Parkinson's disease

PET - positron emission tomography

QD - questionable dementia

RMCI – Revised Mild Cognitive Impairment

SCI – Severe cognitive impairment

SD – Standard Deviation

SMC - self-reported memory complaint

SRH – Self reported health

VRF – Vascular risk factors

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1 POPULATION AGEING & DEMENTIA

Chapter Overview

In this chapter I will introduce the concepts of population ageing and dementia. It will discuss not only the medical and health perspectives of the ageing population, but also the impact on society as a whole, particularly in light of the current dementia epidemic. The chapter will also touch on the importance of Newcastle as both a university and a city as a global centre for research into the health and wellbeing of older people. Finally, I will introduce the cohort of people on which this thesis is based and give an outline of the thesis going forward.

1.1 The ageing population

In order to understand why ageing has emerged as such a key area of policy in both the UK and the world. Population ageing describes the changing age demographics across an entire population, be that a country, continent or indeed the global population. Over the last century the gradual increase in the age of populations has become rapid, both proportionally and in absolute terms. In relative terms, the World Health Organization estimated in 2012 that only one country, Japan, had a population where more than 30% of people were aged 65 years or over (World Health Organization, 2015). Projections to 2050, on the other hand, estimate that this will be the case for many more countries including countries in Europe and North America, but also in areas less associated with population ageing from the developing world such as Chile, China, The Islamic Republic of Iran, the Republic of Korea, the Russian Federation, Thailand and Viet Nam (World Health Organization, 2015).

The ageing demographic of the UK is clear, the UK government reported that in mid-2014 for the first time in its history the median age of the population exceeded 40 years. This was a rise from 33.9 years in 1974. Although the increase in longevity for the UK has been gradual relative to those in the developing nations, the trend that has been developing throughout the entire 20th century shows no sign of slowing down. It is projected that between the years 2014 and 2019 the absolute number of people aged 60 years and over will increase from 14.9 million to 21.9 million people. In proportional terms this represents over 70% of the UK population (ONS, 2012).

Epidemiological changes that have led to population ageing in the UK and around the world include falling rates of fertility and mortality; that is younger people entering the population along with less old-aged people leaving it (Smallwood and Chamberlain, 2005). In the UK falling fertility can be traced as far back as 1964; at this time the estimated total fertility rate in England and Wales was 2.93 children per woman, in comparison the estimates in 2014 were 1.83 children per woman. In other words, the UK has experienced over 40 years of fertility rates below the replacement level of 2.1 children per woman (Smallwood and Chamberlain, 2005). In addition to falling fertility, population ageing is compounded by a decline in mortality; long- term epidemiological shifts have meant that changing age structure in the UK is mostly attributable to the long-term decline in mortality of those in the older age groups. In 1950 it was estimated that the mortality rate for men and women in their early 80s was around 160 (men) and 120 (women) per thousand population; over time this reduced to 120 (men) and 75 (women) per thousand population in the 1990's (Smallwood and Chamberlain, 2005).

Increased life expectancy due to low mortality has historically been related to the increased likelihood in surviving childhood and early life as interventions for previously fatal infectious disease have come to light (Bloom, 2011). Today the dominant factor is the decline in mortality rates for those aged years over 65. Although it is positive news that more people are living longer, historically high fertility rates contributed to slowing ageing demographics. For example, after World War II the UK experienced a high birth rate, which continued into the 1960's `baby boom' period. The result of this was increased numbers of people of similar ages in the UK population. Consequently, those born in the aftermath of the Second World War are currently in their late 60's / early 70's, and will be in their 90's by 2040. Additionally, the baby boom generation currently in their late 50's/ early 60's will be aged over 70 by 2040. (Government Office for Science, 2016).

1.2 Ageing and society

The impact of ageing populations will be and indeed has already been felt across the breadth of society within the UK and many other nations. The biggest issue that ageing populations contribute to be the number of people paying taxes is decreasing, resulting in a strain on public services, at a time when for the same

reason the numbers of people relying on them is on the rise. This outlines the fundamental difference of growing old in a society that is ageing as a whole, compared to one where the majority remains young. The disparity between the tax paying young and the service reliant old has been quantified via the old age support ratio (number of working age people divided by number of people eligible for the state pension), setting a baseline figure for this balance which can if needed be altered to reflect extensions in working life (Government Office for Science, 2016). In 2012 the ratio was measured at 3.21:1, 3.21 working age for every one person of state pension age. The ratio has since been adjusted to account for changes in pension age, in 2020 the ratio will be 3.47:1 based on current pension age. In any case, as the numbers of people reaching state pension age is rising faster than the number of working age people, by 2041 the ratio will have fallen back to a level of 2.65:1. Percentage growth of people of pension age is predicted to be 37% (to 16.8 million) from 2012 to 2041, in comparison to only 13% (to 44.6 million) working aged people over the same period (Government Office for Science, 2016).

The increase in UK life expectancy is for the most part a product of its own success. Evidence suggests that people are not only living longer, but more of their years are being spent in better health, shown by healthy life expectancies (HLE) at birth rising comparatively faster than life expectancy (LE). These figures for HLE at birth, when looking at HLE measured specifically at 65 and 85 are not meeting the pace of LE improvements. The combination of this evidence suggests that healthy life years are primarily being gained in the younger age groups, as a consequence, people over 65 are living longer with more years being spent in ill-health. This identifies the issues in which this thesis shall address; unless this trend can be reversed a major challenge for nations dealing with ageing populations will be the increasing prevalence of long term chronic health conditions associated increasing age, specifically in terms of this thesis, dementia (Government Office for Science, 2016).

For the UK, changing ageing structures and increases in longevity will continue to have fundamental impact. Both health outcomes and economics are intertwined by the effects of these changes, historically the UK has relied on a predominantly young population has enabled resources to be allocated to a relatively smaller older population. The demand for resources will be increasingly strained by a growing number of older people fuelled by increasing life expectancy. If improvements are

not made in improving healthy life expectancy, there will be unprecedented demand for resources to support the increasing numbers of those living with age-related health, care and social requirements. To make matters more complicated, these changes are taking place in the context of bellow-replacement birth rate, therefore the capacity for workforces to provide the financial and practical support for an increasing number of older dependents is reduced (Government Office for Science, 2016).

1.3 Ageing & health services

As discussed in previous sections, the disparity between life expectancy and healthy life expectancy for the older UK population is gathering pace. Evidence suggests that if this trend cannot be reversed the strain of the ageing population on public services will be felt most severely on health and care services. Indeed, the Personal Social Services Research Unit (PSSRU) projects that users of publicly funded home care services will grow by 86% to 393, 300 in 2035(Wittenberg and Hu, 2015).

In addition to the growing numbers of those living in ill health, the natural consequence of population ageing is the increasing prevalence of age-related health conditions. For example, as the population ages more people are at increased risk of developing conditions such as cardiovascular disease, musculoskeletal disease and dementia. Regarding dementia, the risk of dementia almost doubles with each 5 years of age after 65 years (ONS, 2012) and dementia prevalence projections predict the number of cases of dementia will rise from 822, 000 to 940, 000 by 2021 and over 1.7 million in 2051 (Matthews et al., 2013a). This is despite age-specific incidence of dementia falling since 1991 (Matthews et al., 2016b).

As the pressures on health and care services increase so does the pressure on the public purse, indeed the UK Office for Budget Responsibility identified health and long-term care as two of the main drivers of increase in non-interest spending due to the ageing population. The OBR went further to project that government spending on health care would have to rise from 7.6% in the period 2022-23 to 13.8% of Gross Domestic Product (GDP) in 2067-68, as well as costs of adult social care rising from 1.3% in 2022-23 to 1.9% of GDP by 2067-68 (OBR, 2018).

Specifically, in the case of dementia, costs in the UK for 2013 were estimated at £26.3 billion (39% of this cost estimated to be due to social care, and 44% to unpaid care). This is predicted to rise from what was 0.6% of GDP in 2002, to 0.82-0.96% by 2031 (Comas-Herrera et al., 2011). The costs of dementia care are becoming increasingly complex as patients are more likely to have long hospital stays and are often less likely to be able to return to their homes. Additional complexity is derived from the increasing multi-morbidity associated with advancing age, compounding already existing conditions and increasing healthcare costs associated with each condition (Lehnert et al., 2011).

Although much of the observations of an ageing society appear negative, there is positive evidence that life course interventions can reduce the time spent in ill-health. Indeed, a number of key lifestyle factors have been associated with improved long-term health outcomes for example, not smoking, moderate alcohol consumption, good nutrition and physical activity. Further evidence has suggested that smoking and alcohol consumption has reduced in the UK, however physical inactivity has become more prevalent (Fried et al., 2001). Behavioural risk factors are often intertwined with wider socio-demographics such that there is a strong association between these behaviours, socio-economic status and health in later life. In those aged 65 years and over lower socio-economic status is associated with poorer physical, psychological, cognitive health and overall frailty (Fried et al., 2001) . Some evidence suggests that reducing smoking and obesity have a more significant impact on HLE than LE, affecting the proportion of life spent in ill-health (Jagger, 2015), although there is an overall lack of evidence of how lifestyle impacts on HLE (Jagger, 2015).

1.4 Dementia

Dementia is not a part of normal ageing, it is a neurological condition, the main symptoms of which are cognitive and functional impairment. There is a great deal of complexity involved in research into dementia partly due to the many forms in which the disease manifests such as vascular dementia, Alzheimer’s disease, Lewy body dementia and mixed dementia (World Health Organization, 2015). As the pathology of these subtypes vary this makes research more complex. Dementia mainly affects people over the age of 65 years and doubles approximately every 5 years. Dementia

is most prevalent in populations over the age of 85 years. The estimated prevalence of dementia in England was 6.5% (670, 000 cases) in 2015 (Matthews et al., 2013a).

1.4.1 Global Dementia Epidemiology

Since the 1980's there has been a push in the epidemiological research into how prevalent dementia is in the population, both national and global. In 2013 a meta-analysis was conducted on previous dementia prevalence estimates to shed light on how many people over 60 years of age are affected by dementia in 21 global burden of disease regions. Data from the 21 regions included showed that in 2010 age-standardized prevalence of dementia for those aged over 60 years varied largely between global regions. For example, prevalence for west sub-Saharan Africa was 2.07% whereas Latin America had the highest prevalence of 8.50%. Although the variation seems initially very wide, most of the variation was accounted for by the very low prevalence in African regions; with the prevalence of African regions excluded variation in dementia prevalence was found to range from 5% to 7% (Prince et al., 2013).

When applying these prevalence estimates to the 2010 United Nations (UN) population estimates it was estimated that around 35.6 million people were living with dementia worldwide. Western Europe was found to have the highest number of people living with dementia (7.0 million), followed by East Asia, south Asia and North America (5.5, 4.4 & 4.4 million). The study also highlighted a number of nations in 2010 where the number of people living with dementia was over 1 million. These countries included: China (5.4 million); USA (3.9 million); India (3.7 million); Japan (2.5 million); Germany (1.5 million); Russia (1.2 million); France (1.1 million); Italy (1.1 million); and Brazil (1.0 million). A number of projections were made including that the number of people living with dementia was predicted to double every 20 years, increasing the numbers from 35.6 million in 2010 to 65.7 million in 2030 and 115.4 million in 2050. It is important to highlight that whereas most of the growth in the prevalence of dementia has been in seen in high income countries, the majority of the growth in dementia in the future will come from low and middle income countries (LMICs). In 2010, 57.7% of the global dementia population resided in LMIC's, whereas by 2030 this will rise to 63.4% and 70.5% by 2050 (Prince et al., 2013).

1.4.2 Changes in dementia epidemiology

There are several reasons to hypothesise that the prevalence of dementia is likely to change over time. Indeed, populations and lifestyles have changed hugely over the generations for good or ill. For example, a number of risk factors related to dementia have been on the increase over the past few decades such as: rising prevalence of sedentary lifestyles, the epidemic in obesity and increasing numbers of people with diabetes combined with an increase in the number of people living over the age of 80 shifting the distribution of average age of death (disease, 2010). Factors such as languishing inequalities in health outcomes, a greater number of people surviving and living after a stroke and with heart disease are all contributing factors to higher risk of dementia and have all been increasing over recent decades (M., 2010). However, there are also a number of societal changes that could be attributed to a reduction in the risk of dementia. For example, there has been a marked decrease in vascular mortality in recent decades, around half of this decrease is due to the improvements made in primary prevention of heart disease (Jones and Greene, 2012). Education, particularly in the early ages, has gone through drastic intergenerational change for the better, such that a much greater number of people have access to more years of education, which has consistently been shown to reduce the risk of dementia (Meng and D'Arcy, 2012a).

Although the number of studies which examine the changing patterns of dementia over time are relatively rare, a small number of studies from the US have indicated that the prevalence of dementia and severe cognitive impairment has reduced over the past two decades. Data from the US in the Health and Retirement Study found decreases in cognitive impairment from 12.2% to 8.7% between 1993 and 2002 (Rocca et al., 2011a). These findings combined with reductions in ischemic cerebrovascular disease and other cardio-metabolic risk factors discussed previously, suggest cautious optimism for the changes risk of cognitive impairment and dementia in current cohorts of older aged people (Rocca et al., 2011b). Further evidence from the US (Langa et al., 2008), again using national data from the Health and Retirement Study, found evidence that the changes in cognitive impairment between 1993 and 2004 can be described as a ‘compression’, meaning that fewer older Americans were described as having significant cognitive impairment. However, those who did meet criteria for significant cognitive impairment showed a

more rapid decline toward death than those who are cognitively healthy. Importantly, this study rather than pointing to a reduction in risk factors, alluded to an investment in cognitive reserve, through formal education in childhood and continued cognitive stimulation during work and leisure in adulthood, as contributing to the reduction in cognitive impairment and dementia (Langa et al., 2008).

Some studies from Europe have also found a reduction in the prevalence of severe cognitive impairment and dementia over time; although results have been mixed and not always statistically significant. Results from the Netherlands (Rotterdam study) showed a trend, though not a statistically significant trend, of a fall in dementia incidence between 1990 and 2005 (Incident Rate Ratio (IRR): 0.75, 95% confidence interval (CI): 0.56, 1.02) (Schrijvers et al., 2012). Results from Sweden in the Kungsholm Project (KP) and Swedish National Study on Ageing and Care in Kungsholm (SNAC-KP) indicated that dementia prevalence in the time period between the late 1980's and early 2000's had remained stable, while the number of people dying with the condition had decreased (Qiu et al., 2013). A Spanish study using data from the ZARADEMP Project found that there was no significant change in global prevalence of dementia but, dementia prevalence was found to be significantly lower in men, particularly between the ages of 70 and 84 (Lobo et al., 2007). Finally, a study of people over the age of 90 born 10 years apart (1905 vs 1915) had their cognitive test scores analysed and it was found that those born 10 years later in the 1915 cohort scored consistently better in terms of both cognition and activities of daily living, suggesting that people were living longer with better cognitive functioning (Christensen et al., 2013). Although there is a range of good news, optimism has been restrained due to a number of factors such as the variation in study methods (e.g. for identifying the study population), access to health care in different populations and in some cases the often understated changes in diagnostic and sampling methods and limitations of analytical approaches. Additionally, not all studies show the same trend, for example the Hisayama Study in Japan studied both all-cause dementia in 1985, 1992, 1998 and 2005 and showed that over these time points both all-cause dementia and AD significantly increased significantly over time (Sekita et al., 2010).

1.4.3 Dementia epidemiology in the UK

Dementia and cognitive impairment epidemiology have primarily been studied in the UK using the Cognitive Function and Ageing Studies (CFAS). These studies use a multi-centre approach including a wide range in demographics of the UK population in both 1991 and 2008. By using inverse probability weighting techniques the studies have been able to provide generalizable two decade comparisons in dementia prevalence and incidence in the UK. CFAS found that between 1991 and 2011 the estimated number of individuals with dementia grew from 664,000 to 670,000; this was in fact a 24% reduction in the amount that would be expected due to population ageing alone (Matthews et al., 2013a), which predicted the number of dementia cases in 2011 to be 884, 000. However, there was another aspect of the study which looked at the prevalence of dementia within care settings and in contrast to the wider population the prevalence of dementia in care homes has increased from 56% to 70% between 1991 and 2011 (Matthews et al., 2013a).

Although prevalence is an important measure of the trends, a stronger comparison is that of incidence. Incidence is considered a better measure as it takes into account mortality; the prevalence of dementia is a result of both mortality and dementia incidence. Measuring incidence across time and geographical locations is more informative as it takes into account the changing mortality between those living with dementia and those who aren't (Matthews et al., 2016a). In 2016 CFAS produced the first two decade comparison in dementia incidence across time in the UK. Much like the findings in dementia prevalence there was also found to be a decrease in incidence between 1991 and 2011. Incidence was observed to have declined by around 20% (95% CI: 0-40%), this was understood to be driven by a marked decrease in dementia incidence in men in every measured age group (Matthews et al., 2016a). In terms of number of cases, there are an estimated 210, 000 incident cases per year, this is made up of around 74,000 men and 135,000 women. These findings offer more evidence that the trends in dementia for whole populations is subject to change over time, given that age and sex specific incidence rates and the number of people developing dementia per year has remained stable even in the face of an ageing population (Matthews et al., 2016a).

This study shows that trends in dementia in the UK have changed significantly over the last few decades, indeed they fit in the context of previously discussed studies

from the US and studies from Europe which infer a reduction in dementia risk in developed countries (Manton et al., 2005, Lobo et al., 2007, Qiu et al., 2013, Schrijvers et al., 2012, Langa et al., 2008, Rocca et al., 2011b).

1.4.4 Risk Factors for dementia and cognitive impairment

Most theories that attempt to explain the changing trends in brain and cognitive health have focused on cardio-metabolic and societal risk factors. In the UK, like many developed countries, risk factors associated with dementia have changed drastically over the generations including risks such as diabetes, metabolic syndrome and poor cardiovascular health (Capewell et al., 2009). Education has long been the focus of dementia risk reduction and, like cardio-metabolic risk factors, has seen significant changes between the two generations measured in CFAS namely, a change in the minimum statutory requirement and greater numbers of individuals staying in formal education longer. A recent study into the Population Attributable Risk (PAR) of potential risk factors for dementia (Norton et al., 2014) found that, around the world, low educational attainment represented the highest PAR (19.1% 95% CI: 12.3-25.6).For the UK specifically the highest PAR was being physically inactive (21.8% 95% CI: 6.1-37.7%); this was also the highest PAR for comparable populations such as the US, and Europe. Crucially in this study it was shown that when PAR factors for the USA, Europe and the UK were combined modifiable risk factors including diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment accounted for around 30% of dementia cases. Furthermore, the authors calculated that under the assumptions that risk factors had a causal relationship with dementia and preventative intervention could be made at the appropriate age that the prevalence of dementia globally could be reduced by 8.3%. These calculations assume that risk factor prevalence can be reduced by 10% per decade (Norton et al., 2014).

In addition to the effect of health and societal factors associated with the increased risk of cognitive impairment, there is increasing evidence that lifestyle factors such as increased educational attainment, physical activity and social engagement can have a substantial effect on the reducing dementia risk. This is referred to as the theory of cognitive reserve or cognitive lifestyles and is often given credit for providing a “protective effect” for cognitive impairment and dementia. Indeed, most

theories describe an increased cognitive reserve as being responsible for increasing the brains ability compensate for the neuropathological damage associated with cognitive impairment and dementia, and therefore enable an individual to maintain a higher level of cognitive function into older age before being affected by an often more rapid decline in neurodegenerative cognitive impairment (Valenzuela et al., 2011, Valenzuela et al., 2012, Marioni et al., 2012b). There is no doubt that cognitive decline and impairment has been changing and indeed improving within Caucasian populations (Schaie et al., 2005, Llewellyn and Matthews, 2009, Salthouse, 2005), given the vast amount of societal change that has occurred in many western and developed nations in areas associated with cognitive impairment, it is therefore not surprising that so many studies are now showing declining prevalence and incidence of dementia in these populations.

1.4.5 Treatments

Presently there is no cure for dementia and only a limited amount of treatment options to manage the disease. Treatment for dementia is usually effective for specific subtypes, such as those that cause brain tumours or hydrocephalus (excess brain fluid), which can be treated with surgery (Barrett and Burns, 2014). For dementia, as a consequence of neural degeneration, most treatment options focus on reducing risk factors such as high blood pressure and cholesterol, type 1 diabetes and smoking (Barrett and Burns, 2014). The limited number of pharmaceutical treatment options are usually reserved for the more severe symptoms. Acetylcholinesterase inhibitors such as Aricept (donepezil) can be used to treat mild Alzheimer's disease and combating hallucinations in dementia with Lewy bodies, however they carry side effects such as nausea. In the most severe cases antipsychotic drugs can be used, however they remain prescribed as a last resort. Although they can combat disruptive behaviour they also carry side effects such as rigidity, immobility and disrupt communication skills. They can also have unpleasant side effects such as vomiting and loss of appetite (Barrett and Burns, 2014). Psychological treatment options are also available such as cognitive stimulation and behavioural therapy, although the reality remains that the majority of cases of dementia cannot be cured, and symptoms will gradually progress and become more severe over time (Barrett and Burns, 2014). As a result, research effort is being focused on prevention including a better understanding of risk and protective factors.

1.5 Ageing research in Newcastle

Newcastle University has been at the forefront of ageing research stretching back over the last 60 years. Currently ageing research occurs across the whole University but is recognised under the Newcastle University Institute for Ageing, which is based at the heart of Europe's largest multidisciplinary site into ageing – the Newcastle Campus for Ageing and Vitality. It comprises research excellence across the following institutes:

- Agri-Food Research and Innovation
- Cell and Molecular Biosciences
- Cellular Medicine
- Health and Society
- Neuroscience

Newcastle focuses its learning and studies on three main ageing research areas: **How we age**, **living better** and **environmental aspects of ageing.** We look at **how we age** in order to have a full understanding of the biological and cellular processes involved in the ageing process. Examining the ageing process throughout the life course in order to learn new ways about **living better** with chronic, age-related illnesses. Finally, the psychosocial, economic and **environmental aspects of ageing** involves looking at the challenges that a growing older population brings, as well as opportunities.

In the field of epidemiology Newcastle has been a leader in the development of population cohort studies, particularly to investigate health throughout the life course and specifically the older population. Including:

1.5.1 The cognitive function and ageing studies I & II

The Cognitive Function and Ageing Studies (CFAS) are large, multi-centre, population based studies of individuals aged 65 years and over living in the community, including institutions. There are three main studies within the CFAS group; MRC CFAS, the original study which began in 1989, the comparison study CFAS II (2008 onward) and CFAS Wales (2011).

The initial aims of CFAS were to investigate dementia and cognitive decline in a representative sample of the UK population including a discretion of the service

needs of dementia sufferers and the degree of disability they suffered. Additional aims were to find out which factors increase the risk of someone developing dementia, to investigate the different diseases that cause dementia and determine how quickly dementia progresses.

Since 1989 life expectancy in the UK and across the globe has increased with dramatic changes in some major chronic diseases. Symptomatic treatments for dementia, specifically its most commonly diagnosed form, Alzheimer's disease, has been adopted and there is major research in the area of early detection and novel disease modifying therapies.

Having provided estimations of dementia occurrence for the UK from its first studies CFAS was increasingly asked to provide evidence on generational change in dementia, cognition and life expectancy by the government and the public, leading to the new CFAS II study. The use of CFAS in public policy decisions and in long term projections is now well established. In addition, CFAS research is investigating emerging issues such as cognitive screening, mild cognitive impairment (MCI) and early detection. Importantly, the two CFAS studies share similar methodology allowing for comparison across the two cohorts.

1.6 Thesis structure

The second chapter of this thesis will introduce the concept of MCI, it will describe how MCI has evolved as a diagnosis and a concept. Discussion will focus on how MCI has been historically and is currently operationalized in the literature, how it has risen to the forefront of how we think about cognitive impairment and controversial issues around MCI.

The third chapter will give a comprehensive outline of CFAS including the study setting, recruitment protocol, response rates and baseline findings. Full details of how MCI was operationalized in the CFAS population are also presented.

The next three chapters will follow the structure of the three sub-studies described in the abstract. Chapter four will introduce the prevalence of MCI within CFAS and the UK, the fifth chapter will include incidence rates for MCI, while the sixth will focus on risk factors for both prevalent and incident MCI as well as transition rates from MCI to dementia. All findings will be discussed in the context of the existing literature.

The seventh and final chapter discusses the conclusions of the thesis as a whole, the implications of findings in the context of the exiting literature in addition to the strengths and limitations of this work and future directions.

2 MILD COGNITIVE IMPAIRMENT (MCI): A LITERATURE REVIEW

Chapter Overview

The focus of this chapter is on the concept of MCI in the context of scientific literature, including its evolution from a concept to a clinical diagnosis and research entity. I will discuss issues surrounding the operationalization of MCI, how definitions are continuously updated over time and controversial areas of MCI being debated to this day. Finally, I will end on the previous body of MCI work from the MRC CFAS (1991), identify the gaps in the research which have led to the aims and research questions this thesis will address. (Petersen, 2016b)

2.1 Introduction

In the last decade medical research has been dominated by investigation into the concept of healthy ageing and its implications for chronic disease in old age. A key research focus has been to identify early signs and predictors of age-related disease such as dementia, which could then be translated into successful intervention and preventative strategies. To date there have been many attempts at identifying and defining these early preclinical cognitive changes (Flicker et al., 1991, Petersen et al., 2009, Stephan et al., 2010, Unverzagt et al., 2001b). The most widely accepted and enduring has been the definition of Mild Cognitive Impairment (MCI) (Stephan et al., 2010). The concept of MCI has evolved over the past 20 years and has been intensely studied from many perspectives including clinical, genetic, imaging, pathological and epidemiological.

However, this emerging concept, regardless of definition, remains controversial. Many definitions for this state exist, including amnestic-MCI (Petersen, 2004) and Cognitive Impairment no Dementia (CIND) (Graham et al., 1997). When diagnosed in clinical settings, individuals with amnestic-MCI have an annual dementia progression rate of approximately 9.6% (95%CI: 6.3-13.4%), with about 39.2% progressing to dementia over five years (Mitchell and Shiri-Feshki, 2009). In population-based studies progression rates vary across the different MCI definitions (12) and are generally found to be lower than the rates reported in clinical samples (amnestic-MCI: 4.9%; 95%CI: 1.6-9.9%) (Matthews et al., 2008). Further, results from the first Medical Research Council Cognitive Function and Ageing Study (CFAS I) MCI programme of work found that most individuals at high risk of dementia are excluded from a MCI diagnosis (e.g., defined as Other Cognitive Impairment no

Dementia: OCIND) (Stephan et al., 2010, Unverzagt et al., 2001a, Petersen, 2004, Graham et al., 1997, Mitchell and Shiri-Feshki, 2009, Matthews et al., 2008, Stephan et al., 2008a). This raises questions regarding the utility of MCI in population-based settings (Stephan et al., 2010, Unverzagt et al., 2001a, Petersen, 2004, Graham et al., 1997, Mitchell and Shiri-Feshki, 2009, Matthews et al., 2008, Stephan et al., 2008a).

2.2 Cognitive Impairment

The progression of normal cognitive function to dementia has become a topic of great interest in ageing research. Dementia itself has been defined as not being a normal part of the ageing process, therefore it has become important to understand the progression from normal cognitive function to pathological functioning or dementia. Cognitive function develops and improves for individuals over their life course, however cognitive decline has been a difficult subject for researchers and clinicians to define; the International Classification of Diseases (ICD) and Diagnostic and Statistical Manual (DSM) criteria describes a point in time at which a declining in cognitive function of a gradual onset which is present for at least 6 months. Cognitive decline as a disorder is measured by difficulties in a number of cognitive domains, such as memory and learning, attention and concentration, problem solving, language and visuospatial function (Levy, 1994). An age restriction has not been set for diagnostic criteria for cognitive decline, this is due to evidence that, although the disorder is more prevalent in elderly populations, onset may be much earlier in life with varying degrees of progression (Levy, 1994). The age at which cognitive decline begins, or first becomes evident is a widely debated topic. Studies into the development of dementia have shown the disease to have a long gestational period, with individuals affected by cognitive decline at different ages, and with differing rates of progression (Stern, 2002). There is also emerging evidence that suggests the individuals may be experiencing age related cognitive decline under the age of 60 (Singh-Manoux et al., 2012).

As cognitive decline progresses some individuals may progress past a threshold to cognitive impairment. This refers to having problems with cognitive functioning and often results in difficulties with day to day life, but the individual has not yet reached a stage to be classified as having dementia (Petersen et al., 1999). Interest has been

focused on defining this cognitive threshold, but there has been a lack of consensus around a set definition. Mild cognitive impairment (MCI), incipient dementia and isolated memory impairment have all been used to describe the condition of cognitive impairment (Flicker et al., 1991). A number of reviews suggest being classified as cognitively impaired carries an increased risk of developing dementia, between 1% and 25% per year (Dawe et al., 1992). However, the wide variation in risk has been attributed to differing opinions on diagnostic criteria, measurement instruments and the use of small samples (Dawe et al., 1992).

2.3 History of Mild Cognitive Impairment

The first definition of MCI was derived in the 1980s where Reisenberg described an intermediate state of cognitive function based on the Global Deterioration Scale (GDS)(Reisberg et al., 1988). Following this, the study of MCI gathered considerable pace, when in 1999 Peterson et al. investigated MCI in the context of observational studies of ageing and proposed the definition of amnestic MCI (Petersen et al., 1999). By 2003 there was growing evidence that the standing definition of amnestic MCI as proposed by Petersen and colleagues was not fit for purpose, particularly within population-based settings. The definition was considered too narrow due to the fact that it relied on memory impairment rather than a multi-domain approach. Therefore in 2004, new international criteria which attempted to broaden the concept of MCI and included a variety of aetiologies and clinical profiles was proposed (Winblad et al., 2004, Petersen, 2004). Although the redefinition of MCI allowed for an expansion in its research base, there still remains a degree of controversy around the subject. It is often stated that MCI research is too heterogeneous, and the concept is unstable. Many factors have been identified which influence MCI including: (i) settings in which the criteria are used; (ii) age of subjects; (iii) operational criteria; (iv) implementation of the diagnostic criteria; (v) retrospective versus prospective data collection; (vi) algorithmic versus clinical application of the criteria; (vii) blindness with respect to previous diagnoses; (viii) length of follow-up of subjects when assessing outcome; and, (iv) stability of the construct (Petersen et al., 2014b).

2.4 Updated Criteria

MCI as a concept and diagnostic entity has evolved over time; table 2.1 describes a number of attempts to redefine MCI to increase its utility. Recently, the National Institute on Ageing and the Alzheimer's Association (NIA-AA), proposed new criteria designed to capture MCI due to AD (Table 2.1) (Albert et al., 2011). Also, with the introduction of the recent 5th edition of the DSM (American Psychiatric Association, 2013), significant changes to the definition and classification of dementia and MCI were made with the appearance of the new terms including 'Mild Neurocognitive Disorder' (NCD), and Major NCD (analogous with MCI and dementia, respectively) (American Psychiatric Association, 2013). Mild NCD describes subtle stages of cognitive impairment which are not serious enough to warrant a diagnosis of major NCD. The criteria for mild NCD include: (i) clinical concern raised by the patient or an informant, or observations made by the clinician; (ii) cognitive impairment in one or more cognitive domains preferably relative to appropriate normative data for that individual; (iii) preservation of functional independence; and (iv) no dementia (American Psychiatric Association, 2013). The DSM advocates that the use of neuropsychological testing is helpful in making a diagnosis of mild NCD, however it does not state which test batteries are appropriate, or indeed cut-off scores. It also suggests that the initial stage of diagnosis should be identifying mild or major NCD and subsequently determining aetiology (Petersen et al., 2014b).

Table 2-1: Four main MCI definitions and corresponding diagnostic criteria including: Original Mayo Clinic, IWG / Expanded Mayo, NIA-AA and DSM-5 criteria (Petersen et al., 2014b)

MCI Definitions	Original Mayo Clinic	Expanded Mayo / 2004 Consensus	NIA-AA	DSM-5
Criteria				
Self or informant-reported memory complaint	X			
Self or informant-reported cognitive complaint		X	X	X
Objective Memory Complaint	X			
Objective Cognitive Complaint		X	X	X
Essentially Preserved General Cognitive Function	X			
Preserved Independence in Functional Abilities	X	X	X	X
No Dementia	X	X	X	X

2.5 MCI Subtypes

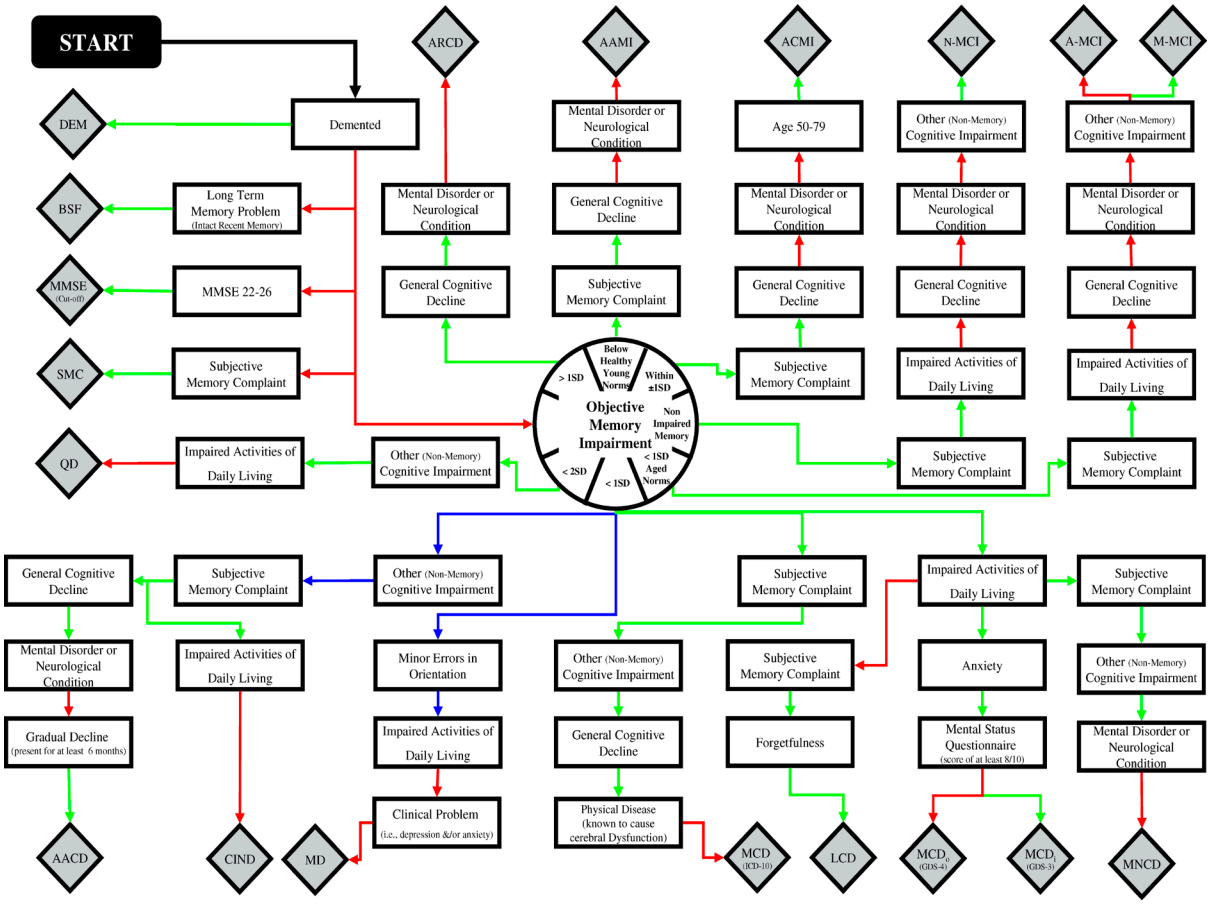
The first subtyping of MCI was reported by Peterson in 2004 based on the cognitive profile of clinical patients. Two subtypes were defined including: amnestic (aMCI), where performance in neuropsychological tests regarding memory were poor, or non-amnestic (naMCI) where performance in other cognitive domains outside of memory, such as language, visual spatial or executive function, were poor (Petersen, 2004). MCI can then be further subcategorized into single or multiple domains (Petersen, 2004).

MCI can be subtyped based on aetiology. The NIA-AA work group have redefined the criteria for MCI which is due specifically to AD based on the use of biomarkers (Albert et al., 2011). However, they clarify that biomarkers are recommended only for research purposes (Winblad et al., 2004, Petersen, 2004, American Psychiatric Association, 2013, Albert et al., 2011). Two main sets of biomarkers have been proposed including amyloid-beta (Aβ) and neuronal injury's shown in Table 1 (Albert et al., 2011). In addition, the DSM-5 considers multiple possible aetiologies including: AD, frontotemporal dementia, vascular cognitive impairment, and dementia with Lewy bodies, Parkinson's disease, Huntington's disease, HIV/AIDS, traumatic brain injury and substance abuse.

2.6 Operationalization of MCI

No single method for operationalizing MCI has been developed or adopted across clinical or research settings (Winblad et al., 2004, Petersen, 2004, American Psychiatric Association, 2013, Albert et al., 2011). In 2007 a review was conducted to operationalize the many different definitions of MCI. This resulted in operational criteria for 18 possible definitions of MCI as shown in Figure 2.1 (Matthews et al., 2007).

Figure 2-1: Schematic Overview of the Approach Used to Classify MCI across Different Definitions in the Medical Research Council Cognitive Function and Ageing Study (Matthews et al., 2007).



Key: AACD, age-associated cognitive decline; AAMI, age-associated memory impairment; ACMI, age-consistent memory impairment; ARCD, age-related cognitive decline; CIND, cognitive impairment no dementia; DEM, dementia; LCD, limited cognitive disturbance; MCD (ICD-10), mild cognitive disorder (International Classification of Diseases 10th Revision); MCD_i (GDS3), mild cognitive decline (Global Deterioration Scale Stage 3); MCD_o(GDS4), moderate cognitive decline (Global Deterioration Scale Stage 4); MD, minimal dementia; M-MCI, multiple mild cognitive impairment; MMSE, Mini Mental State Examination Cut-off Scores; MNCD, mild neurocognitive disorder; N-MCI, non-amnestic mild cognitive impairment; QD, questionable dementia; SD, standard deviation; SMC, self-reported memory complaint.

Ultimately the definitions state that a clinical change in cognitive function must be identified in order to warrant a diagnosis of MCI. This information is collected in a couple ways: (i) there is a subjective memory complaint by the individual or a reliable informant; and, (ii) this complaint is then confirmed by an objective measure, such as neuropsychological test batteries. Objective cognitive impairment is then defined by poor performance in one or more domain. It is not specified which tests are a gold standard however it is widely excepted that the test must include all main areas of

cognitive function, such as executive functions, memory, attention, visual spatial skills and language (Petersen et al., 2014b).

In order for an individual to be diagnosed with MCI they must also show that they have generally preserved independence in functional abilities. This is usually identified through in-depth interviews with the individual and next of kin and measured using Activities of Daily Living scores (ADL's) or Instrumental Activities of Daily Living scores (IADL's) scales. Mild deficits in ADL's are often accepted in the classification of MCI, however basic function must be retained. Finally, individuals who meet cognitive and functional criteria must not be diagnosed with dementia (Petersen et al., 2014b).

2.7 Prevalence of MCI

How studies characterise people within their population with MCI depends largely on how cognitive function is measured in these studies. Indeed, this can vary in aspects such as norms used for assessments, age and education as well as cultural contexts. Because of this we see heterogeneity in the estimated prevalence, incidence and rates of progression to dementia in MCI cases (Petersen et al., 2014b). Table 2.2 shows a review on MCI prevalence according to the expanded Mayo Clinic criteria. As shown, there are substantial variations in prevalence estimates ranging from 3% to 42% (Ward et al., 2012). This makes the planning for public health and health services increasingly difficult. There is some evidence that suggests that a degree of this variation can be explained by ethnic and cultural difference.

Table 2-2: Prevalence estimates of mild cognitive impairment (MCI) defined according to expanded Mayo Clinic criteria in major population-based studies (Petersen et al., 2014b).

Study	Location	References	n	Age (years)	Prevalence %
CHS	USA	(Lopez et al., 2003)	1690	≥75	22.0
EPESE	USA	(Purser et al., 2005)	3673	≥65	24.7
LEILA 75+	Germany	(Busse et al., 2006)	980	75–79	19.3
Kolkata	India	(Das et al., 2007b)	745	≥50	14.9
ILSA	Italy	(Di Carlo et al., 2007)	2830	65–84	16.1
KP	Sweden	(Caracciolo et al., 2008)	379	≥75	11.1
3C	France	(Artero et al., 2008b)	6892	≥65	42.0
Manhattan	USA	(Manly et al., 2008b)	2364	≥65	21.8
ADAMS	USA	(Plassman et al., 2008)	856	≥71	22.2
Mayo	USA	(Petersen et al., 2010)	1969	70–89	14.8
CSBA	Italy	(Ravaglia et al., 2008a)	1016	≥65	7.7
Tone Town	Japan	(Sasaki et al., 2009)	1888	≥65	18.9
MYHAT	USA	(Ganguli et al., 2010)	2036	≥65	16.6
HNR	Germany	(Dlugaj et al., 2010)	4145	50–80	7.8
South Korea	Korea	(Kim et al., 2011)	1673	≥65	24.1
MemoVie	Luxemburg	(Perquin et al., 2012)	1377	65–70	20.0

A number of country and study specific factors may affect prevalence. AMCI has been shown to be 5 times more prevalent in India than in China, even when standardized to age, sex and educational differences (Sosa et al., 2012). NaMCI has also been shown to be more prevalent in a black compared to white population, again after controlling for geographical location, age, sex and education (Katz et al., 2012). Other studies have also suggested that the prevalence of MCI increases with age (Petersen et al., 2010, O'Bryant et al., 2013), and that it is more prevalent in men (Petersen et al., 2010) (Ganguli et al., 2004). Education has also been highlighted as influencing the prevalence of MCI (OR: 0.92, 95% CI: 0.86–0.98) (O'Bryant et al., 2013). These findings suggest that some of the heterogeneity in prevalence can be attributed to demographic and cultural variances, however methodological differences and varying definitions of MCI are also thought to have a significant impact on prevalence studies (Ward et al., 2012).

When operationalising MCI there is large variability in the measurement of objective cognitive decline. Investigators have pointed out that even small changes to aspects of this can have a significant impact on MCI prevalence including cross-study differences in the thresholds used to classify someone as cognitively impaired or the number of cognitive test results required (Kochan et al., 2010). There are also issues around studies opting to rely heavily on global scales with only limited forms of neuropsychological testing, when more comprehensive test batteries have greater reliability when identifying MCI (Bondi and Smith, 2014).

Attempts have been made to account for these issues and operationalize MCI in a harmonized way across a number of populations from the U.S., Australia, Europe and Asia in the Cohort Studies of Memory in and International Consortium (COSMIC) Consortium (Sachdev et al., 2013). The aim of this is to apply uniform diagnostic criteria and give a reliable global estimate of MCI across geographical and ethno-cultural regions. The study identified three definitions of cognitive impairment: A Clinical Dementia Rating (CDR) score of 0.5.; A Mini Mental State Examination (MMSE) score of 24-27 and scoring in the bottom 6.681% of the population on cognitive testing, this equated to the 1.5 SD cut off applied to MCI from original Petersen (Petersen et al., 1999) and revised (Petersen, 2004) criteria.

The study found that across the 11 studies included MCI prevalence ranged from 5.0% - 36.7%. When harmonized diagnostic criteria were applied the range of

prevalence decreased in all three MCI definitions including, performing in the lowest 6.681% in cognitive domain testing (3.2%–10.8%); CDR of 0.5 (1.8% – 14.9%); MMSE score of 24–27 (2.1%–20.7%) (Sachdev et al., 2015). This evidence highlights the effect that using different methods of operationalizing MCI across studies has on overall prevalence estimates.

Prevalence for impairment by lowest percentile of the population, and most attributed to Petersen clinic criteria for MCI showed a prevalence of 5.9% (3.2 – 10.8%) overall. This definition also increased with age ($p = 0.001$) but were unaffected by sex or the main races / ethnicities investigated (White and Chinese). The likelihood of having MCI also increased by not having completed high school ($p = < 0.01$) (Sachdev et al., 2013).

Projections estimate that low and middle income countries will see much of the increase in the prevalence of dementia due to their rapidly ageing populations. As MCI is frequently implemented to capture those at higher risk of developing dementia, investigating the proportion of the older age population in low and middle income countries with MCI is of growing importance. This information will be needed to support governments as they plan the future of their country's health and social care needs.

The 10/66 study attempted to address this research gap. The study mapped aMCI in a cross-sectional cohort carried out in urban and rural sites from eight low and middle income countries, including Peru, Mexico, China, and India; and 3 urban sites in Cuba, the Dominican Republic, and Venezuela between 2003 and 2007. Participants were over the age of 65 years and approximately 2000 participants were sampled from each country (Sosa et al., 2012). In this study it was found that the prevalence of aMCI varied widely, much like high income countries, ranging from 0.8% in China to 4.3% in India. In terms of risk factors aMCI was associated with disability and with neuropsychiatric symptoms (including anxiety, apathy and irritability), but not with sociodemographic factors (age and education) (Sosa et al., 2012). On the whole, although this was not a longitudinal study so risk of developing dementia could not be studied, the absolute numbers and proportion of older aged individuals with MCI revealed the potential implications for health and social care service planning in these rapidly ageing and populous regions.

2.8 Risk Factors

Two main risk factors for MCI include increasing age and lower levels of education. However, there are issues surrounding these associations (Petersen et al., 2014b). First is the fact that neuropsychological tests used in the classification of MCI are often corrected for age and education. Second, MCI by definition is often a transitory state in which the setting of data collection can have an impact on risk profiles.

Other risk factors include gender, where males are generally found to be more at risk of developing MCI (Roberts et al., 2012a, Caracciolo et al., 2008), APOE E4 gene in some but not all studies (Boyle et al., 2010, Tervo et al., 2004, Caracciolo et al., 2012), anaemia (Stephan et al., 2011), neuropsychiatric symptoms such as depression (Enache et al., 2011, van der Linde et al., 2013), environmental and lifestyle factors such as physical inactivity (Ahlskog et al., 2011) and vascular disease where findings have also been mixed. In a number of cross-sectional studies MCI has been associated with stroke (Artero et al., 2008b, Atti et al., 2010) and heart disease (Di Carlo et al., 2007, Roberts et al., 2010); however, in terms of prospective studies, no such associations have been found (Monastero et al., 2007, Luck et al., 2010a). Similar patterns can be seen in other diseases such as diabetes where associations appear in cross-sectional (Roberts et al., 2008, Atti et al., 2010), but not prospective studies (Luck et al., 2010a, Xu et al., 2010b). Discrepancies in results may be due to competing outcomes such as increased risk of death or progression to dementia during follow-up amongst patients with vascular disease, before MCI can be detected (Petersen et al., 2014b).

2.9 Implementation of MCI Criteria

Lack of consensus around how criteria for MCI is operationalized within studies is influencing MCI research, with an even greater impact in clinical settings. Recent reviews have proposed that although it may be unrealistic to expect a standard test battery to be used across all settings and populations, it is reasonable to aim for guidelines around which cognitive domains these batteries should test, how many tests should be used per domain, the cut-off scores for the tests and the norms applied to them. It has also been pointed out that similar efforts should be made regarding the assessment of functional impairment (Petersen et al., 2014b). A major

effort should be made to establish agreement between researchers and clinicians to identify a core, culturally generalizable, set of specific criteria with further standardization and norm generation for particular populations and population subgroups (Petersen et al., 2014b).

2.10 MCI in practice: a clinical evaluation

2.10.1 Establishing MCI Diagnosis

In order to initiate a clinical evaluation of MCI there must be a subjective cognitive concern. The next stage for the clinician is to evaluate the concern; primarily this is done by obtaining a patient history from either the patient themselves or someone who knows the patient very well, for example a family member. Particular emphasis is placed on obtaining the cognitive concern being raised subjectively at first by the patient, informant or the clinician (Petersen, 2016b). When evaluating the cognitive concern, it is important to understand that the cognitive concern is not to reflect general low cognitive function, which could be lifelong. Indeed, MCI is rather a reflection of the change in individual cognitive performance. It is for this reason that clinical history is so important to the clinical evaluation, since in this situation there can be no reliance on formal longitudinal data for the individual's cognition. It is at this point of the evaluation where the type of cognitive concern should be taken into account. The nature of the cognitive concern can determine the way the evaluation proceeds for example, if the patient is concerned primarily with changes in their memory the clinician will therefore focus investigation, such a following up by focussing on recent incidences of forgetfulness which may have appeared in the previous 6 – 12 months (Petersen, 2016b). In practise the clinician can assess an individual's recent instances of forgetfulness such as the ability to remember appointments such as visits with friends. Individuals repeating themselves in conversation can be assessed as cues of an evolving memory deficit, highlighting the need for clinicians to understand the changes in cognition for the individual (Petersen, 2016b).

The next phase of the clinical evaluation is to establish the breadth of cognitive concern for the individual. For example, it is important to establish the domains involved, whether memory is the only domain of concerned or whether other

domains like attention and concentration are also involved, or indeed whether it is a combination of domains. It has been highlighted that in a number of cases individuals may believe there is only a problem in memory, but domains such as attention and concentration can often be misinterpreted as problems with memory. At this stage the evaluation moves onto establishing a more objective measure of cognitive impairment. The clinician can implement a number of tools to characterize the impairment, for example cognitive testing which can differentiate between cognitive domains such as the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) or the Cambridge Cognition Examination (CAMCOG) (Matthews et al., 2008, Stephan et al., 2008b). Clinicians are advised to take care when using these tools and they should not be relied on alone for an individual diagnosis (Petersen, 2016b). One of the biggest issues at this stage of a diagnosis is the clinical differentiation between genuine cognitive impairment and changes in cognition which could be a part of normal cognitive ageing. In this situation the literature points to neuropsychological testing being particularly helpful (Petersen, 2016b). It is advised that cognitive function can be characterized by a neuropsychologist and a judgement can be made on whether cognitive function is normal for the patient's age, sex and education level. However, the literature can also be vague on this front. For example, if this neuropsychological assessment is not available clinicians are advised to make a judgement about a patient's cognitive function based on their own estimations (Petersen, 2016b).

As well as assessing impairments in cognitive domains, there are other aspects to the MCI diagnosis such as the preserved physical function. In clinical terms this is largely a subjective assessment to identify whether the individual is capable of carrying out tasks while maintaining their independence. It is at this point where clinicians are advised that a reliable informant can be useful, for example if the individual is able to carry out activities of daily living without assistance such as paying the bills, driving, bathing and shopping. This information can also be interpreted in a way that can rule out dementia from the diagnosis. Indeed, if cognitive impairment has not reached a stage where daily living is impeded then the MCI criteria for ruling out dementia can be accepted. (Petersen, 2016b).

The last important stage of diagnosis is identifying the more specific subtype of MCI the individual is experiencing. This stage is important for understanding the cognitive

impairment as well as further understanding any underlying aetiologies. For example, if the only cognitive impairments found are memory deficits the patient can be diagnosed as having amnestic MCI (typically associated with an increased risk of AD), or if the deficits are in non-memory domains, they can be diagnosed with non-amnestic MCI subtypes (typically associated with non-AD type dementia).

2.10.2 Investigation of aetiology and biomarkers

Establishing the initial diagnosis of MCI is often only the first half of the clinical evaluation. The second phase is to establish the cause(s) of the cognitive impairment. There can be a number of possible explanations for instances of cognitive decline. If the changes in cognition are seen to be gradual over a longer period of time, then the most likely cause is thought to be due to an underlying neurodegenerative disease. However, there are several other explanations that must be explored, if the individual in question is known to have a history of cardiovascular risk factors then it is possible that vascular events could be the cause of the cognitive impairment. A wide range of medical factors could also contribute to cognitive decline including major episodes of anxiety and depression, poorly controlled diabetes, chronic obstructive pulmonary disease and heart failure.

Emphasis is also growing on the role neuroimaging and biomarkers in the diagnosis of MCI. For example, clinicians may implement further testing such as a MRI scan, fluorodeoxyglucose positron emission tomography (FDG-PET) or positron emission tomography (PET) for amyloid imaging along with a CSF analysis. Additional insights into the aetiology may be found with further testing, however it has been argued that in many cases these tests are often invasive and very expensive, and therefore the utility of implementing such tests should be considered.

In terms of treatment, like with dementia, there are currently no pharmacological treatments approved by the US Food and Drug Administration (FDA) for MCI due to AD. However, due to the increasing evidence for the role that modifiable lifestyle factors play in the risk for dementia and cognitive impairments, lifestyle modifications and cognitive and behavioural therapies can be useful. Also, counselling patients on expectations can be an important option. The contribution of medical comorbidities, as outlined previously, including sleep disorders such as sleep apnoea, also need to be considered since some of these have treatable components (Petersen, 2016b).

As well as MCI patients may be diagnosed with functional cognitive disorder. The core clinical criteria for the disorder include (1) one or more persistent cognitive symptoms that are distressing and/ or cause significant impairment in day-to-day functioning, inconsistencies between self-reported symptoms and everyday function / neuropsychological test results, (2) symptoms are not better explained by another neurodegenerative, (3) neurological, general medical or mental health condition. And finally (4) symptoms do not objectively progress over time, although they may fluctuate (Pennington et al., 2015).

2.11 Issues surrounding Operationalisation of MCI

2.11.1 Which cognitive domains are implicated?

In the first conceptions of MCI, the state was defined by presentation of deficits in memory in isolation. However, although isolated memory disorders do exist, they are rare and some researchers have concluded that impairment specifically in memory is more often due to the inadequacy of cognitive tests to measure other cognitive domains (Petersen et al., 1999, Richards et al., 1999). To adequately detect this the cognitive tests would require a high level of specificity and tests used to assess MCI often fall short of this; for example memory tests often involve measures of attention and verbal ability. Rather than the concept of MCI being considered as too vague to operationalise, it is thought that different tests applied yield different observations, the most common conclusion is that the measures rather than the concept are inadequate (Ritchie and Ritchie, 2012).

2.11.2 What is impairment?

Defining what constitutes as impairment is a key feature of operationalizing MCI. MCI refers to a process of cognitive decline, although it is assessed at one point in time. The decline of function necessary to be considered as MCI has been described as “beyond that expected for education and age” (Petersen et al., 1997). Measuring what is “beyond” this expected level is one of the most debated aspects of MCI. A common measure has been set as being 1.5-2 SD’s below what is expected. However, this is contested as the 1.5-2 SD’s is criticised of being set in light of little empirical evidence and often compared within population groups which are highly variable (Ritchie and Ritchie, 2012). Further, cognitive tests for which the 1.5-2 SD

cut-off applies often give highly skewed distributions where SD's would be an inappropriate measure (Ritchie and Ritchie, 2012). An alternative definition of cognitive impairment has been suggested with impairment defined as early stage dementia with reference to dementia scale scores and this has been argued to conceptually allow the syndrome to drift between a non-specific form of poor memory performance and early dementia (Zaudig, 1992, Kluger et al., 1997).

2.11.3 Absence of functional loss as a diagnostic criterion

Another aspect of operationalizing MCI is the need for identifying cognitive impairment in the absence of general functional impairment. Most definitions require there to be no functional impairment present to meet MCI criteria, however evidence has been presented that in many cases functional impairment is compromised in cases of MCI (Aretouli and Brandt, 2010). Furthermore, functional impairments in cases with MCI have been associated with MCI biomarkers including cerebrospinal fluid abnormalities and APOE genotype. (Ritchie et al., 2001, Touchon and Ritchie, 1999, Okonkwo et al., 2010, Aretouli and Brandt, 2010).

2.11.4 Is MCI a prodromal form of all dementias?

There have been a number of studies intended to determine what type of dementia MCI is a prodromal form of. Most of these studies have been clinical and make reference to Alzheimer's disease alone, and vascular dementia or all forms of dementia (Ritchie and Ritchie, 2011). Population studies on the other hand tend to refer to MCI being due to all causes (Mariani et al., 2007). The lack of a clear definition for which of the dementias is the eventual endpoint has inevitably added to the variation seen across studies of prevalence and risk factors. The absence of agreement on which type of dementia MCI is a prodromal of also makes it difficult to validate the concept retrospectively.

The spectrum of MCI subtypes was arguably broadened to take into account varying dementias as outcomes, however this did not solve outstanding problems such as having no standard measurement criteria, definitions of impairment or specifying control groups. The issue of functional impairment has already been touched on, both clinical and population studies have shown compromised functional activity to be a feature of prodromal dementia, however criteria for MCI contradict this, as everyday functioning is required to be intact (Ritchie and Ritchie 2011). In

longitudinal studies, cases of MCI can progress to dementia, remain stable or revert to a normal state of cognitive function (Petersen et al., 2001). This can make it confusing about which clinical end-points MCI is referring.

2.12 Research Leading up to this Project (context, Theory & Gaps)

MCI has previously been investigated within the CFAS study. The CFAS MCI program of research began almost a decade ago in 2007.

2.12.1 How Different Definitions of Early Cognitive Change Work in the CFAS Population.

In 2007 the CFAS I population was used to investigate the existing classifications of MCI and its associated stages of cognitive decline. Eighteen different definitions of cognitive decline were mapped in the baseline sample and a very high degree of variability in the prevalence of MCI across the different definitions was found (range 0.1 to 42%). (Stephan et al., 2007). Variability in prevalence reflected the differences in the focus and content of each definition. An overlap was found between definitions such that many individuals were concurrently classified as both normal and impaired (Stephan et al., 2007). The paper concluded that classification of cognitively impaired individuals was highly dependent on how criteria for impairment are defined and operationalized. Given the importance of early detection of dementia and the calls for screening, and recruitment into pharmacological trials of cognitively impaired individuals, there is an urgent need for an agreed-upon standard MCI case definition (Stephan et al., 2007).

2.12.2 Missed diagnosis in MCI definitions

Further work aimed to understand the impact of missed diagnosis (Stephan et al., 2008a). It was found that the prevalence of cognitive decline which was not classified from current MCI definitions at the time, was extremely variable (3.7-30%). This reflected the heterogeneity in MCI classification requirements (Stephan et al., 2008a). It was concluded that in terms of the narrower MCI criteria initially designed for the clinical setting when applied to a population-based cohort resulted in many people who would progress to dementia being excluded from an MCI diagnosis. Therefore, in population-based settings a broader definition of MCI is more effective at selecting individuals at risk of developing dementia, albeit with a higher rate of

false positives. While exclusion may be a good thing in the population since most people are presumably ‘normal’, over-inclusion is more likely to be harmful. Further work needs to investigate the best classification system for application in the population (Stephan et al., 2008a).

2.12.3 Two year progression from MCI to dementia

In 2008 a study was conducted to determine the 2-year outcome from 16 different classifications of MCI (Matthews et al., 2008). It was found that the most likely outcome across the different definitions of MCI was cognitive impairment which could not be classified or a return to normal cognitive function. There was generally a poor and varied progression to dementia; of those who did progress to dementia most were from MCI criteria which included both memory and non-memory domains. Further, for some classifications of MCI progression to dementia was dependant on age (Matthews et al., 2008). The paper concluded that current classifications of MCI have variable outcomes in population-based samples. Progression to dementia is relatively rare and is dependent on age and definition. Selection criteria developed for the clinic are based on a “high risk” approach that leads to exclusion of a large percentage of the impaired population who are neither normal nor demented and for whom no intervention options are currently available (Matthews et al., 2008).

2.12.4 Optimizing MCI for discriminating dementia risk

The criteria set out for MCI have been shown to predict dementia risk in a clinical setting. A 2010 study showed that risk of dementia in the population is different, and that set out to determine whether there is an optimal MCI-derived threshold for discriminating at-risk from not-at-risk cases (Stephan et al., 2010). To do this, two risk thresholds were derived from each of seven different concepts of MCI including: Mayo Clinic-defined amnestic, non-amnestic, multiple, and revised MCI, MCI based on MMSE derived categories, and the definitions of Cognitive Impairment No Dementia (CIND) and Age-Related Cognitive Decline (ARCD). Receiver operating characteristic analysis were used to compare the predictive validity of 2-year incident dementia for each risk threshold across the different MCI definitions (Stephan et al., 2010).

It was found that MCI-derived risk thresholds varied in their ability to predict dementia. MCI thresholds were accurate in identifying individuals not at-risk of

dementia progression (false-negative range: 0–3.4%). No MCI-derived threshold accurately identified an at-risk group with a 2-year progression rate greater than 20%. Criteria for ARCD defined the threshold with the highest sensitivity and specificity for dementia conversion (Stephan et al., 2010). It also showed that MCI-derived thresholds do not reliably identify individuals at-risk of incident dementia at 2 years when applied in the general population. A large subpopulation of individuals not at-risk was more reliably identified. What is considered a sufficient level of accuracy for identification of individuals at increased risk of dementia depends on the motivation for screening and on the safety and efficacy of available interventions (Stephan et al., 2010).

2.12.5 Medical co-morbidity in MCI

In 2011 health related co-morbidity was explored in MCI cases to determine the best criteria for MCI in order to capture a representative study sample for the future possibilities of MCI screening methods (Ritchie and Ritchie, 2012). The study also examined the role of health-related co-morbidity as a risk factor for progression from MCI to dementia.

Participants were classified into: No Cognitive Impairment (NCI), MCI, OCIND or dementia. The paper found that over 50% of the individuals in each group reported at least one medical condition. Patterns of disease prevalence were similar in NCI, MCI and OCIND groups. Only anaemia was shown to be associated with an increased risk of progressing from MCI to dementia (Stephan et al., 2011).

This study shows that excluding individuals with medical conditions in the classification of MCI diagnosis would exclude the majority of the population. In terms of clinical trials, these exclusions make recruitment more difficult as well as reducing the generalisability of the results. It also shows that medical co-morbidity does not help to distinguish progressive from non-progressive MCI (Stephan et al., 2011).

2.13 Research Gaps

Updated population prevalence figures for dementia and cognitive impairment in some Western countries (e.g., USA, Denmark and the UK), have hinted at reductions in severe cognitive impairment and dementia (Christensen et al., Matthews et al., 2013a). This has been suggested to be possibly due to

improvements in health and lifestyle factors. Whether cohort effects are seen in the prevalence of MCI and risk of progression to dementia is not known, but has important public health implications (e.g., population burden of disease). Further, determining how best to identify individuals at high risk of dementia will have important implications for intervention trials (e.g., clinical trial recruitment protocols), treatment (where available e.g., personalised medicine), public health surveillance (e.g., monitoring) and education (e.g., prevention programmes) (Matthews et al., 2013a)

2.14 Aims of the project

The aim is to undertake a detailed investigation of the state of MCI in a current cohort of individuals aged 65 years and over including: prevalence, dementia progression and risk factors for future cognitive decline and determine whether there are cohort effects in these measures.

2.15 Objectives:

I. Operationalise MCI in CFAS and investigate changes in prevalence over two decades.

II. Undertake a longitudinal analysis to investigate progression of the condition

III. Determine the risk factors associated with future cognitive decline in MCI cases

IV. Compare prevalence and risk of dementia of the different definitions of MCI in CFAS II

2.16 Research Questions

The PhD project will address three research questions:

I. What is the population prevalence of MCI (across the different definitions and any new definitions identified by the updated systematic review e.g., International Working Group Diagnostic Criteria and NIA-AA Core Clinical Criteria for MCI (Albert et al., 2011)) in individuals from the CFAS II Study?

II. What is the longitudinal course of MCI (e.g., risk of two year incident dementia) and what are the risk factors (e.g., health, social, demographic) associated with progression of cognitive symptoms?

III. Are cohort effects observed in the prevalence of MCI?

2.17 Chapter Summary

The concept of MCI has been in a state of evolution since its inception, indeed perhaps the only constant factor in this diagnosis has been the controversy surrounding it. The initial attempt to identify a state of cognitive function that is mild enough not to interfere with everyday functioning, while also with the severity necessary to predict progression to dementia was undoubtedly ambitious and is still a growing area of research today. Arguably however the push and pull between the definitions sensitivity and specificity is at the heart of its controversy. The future of defining pre-dementia states appear to be in the field of biomarker development. However as it currently stands the evidence for current MCI diagnosis must be treated critically, and indeed there are still many questions surrounding the utility of MCI and whether as a concept it has any clinical or indeed research value at all.

3 METHODS

Chapter Overview

The aim of this chapter is to give an overview of the work undertaken to map MCI criteria, the conceptualization of which discussed in earlier chapters, into population-based cohort studies, describing in detail the mapping process of MCI, as well as other states within the cognitive spectrum. This will be achieved by the following objectives:

i. Identifying the components of MCI and cognitive impairment discussed in *Chapter II: Conceptualisation of Mild Cognitive Impairment.*

ii. *Introducing and describing the Cognitive Function and Ageing Studies (CFAS I & II).*

iii. Developing a cognitive spectrum which encapsulates MCI, along with other definitions of impairment less severe than dementia.

iv. Description of variables that are used in the analysis of risk factors

v. How missing data was handled in the analysis by Multiple Imputation.

3.1 Introduction

This current chapter maps components of MCI that were most readily identified in the operational definitions and reviews into longitudinal population-based cohort studies.

The aim of reviewing the literature was to capture the definition of MCI, which could be appropriately mapped in datasets of population-based cohort studies. This was done by producing a model of cognitive impairment which could categorise every participant in the CFAS studies into a category representing their level of cognitive impairment. Participants with MCI were identified using Petersen's revised MCI criteria. Once identified using this criteria population prevalence could be assessed using agreed statistical modelling. This chapter lays the foundation for the subsequent quantitative addressing population prevalence, cohort effects and longitudinal course.

3.2 Population-based Cohort Studies

Work in this thesis is carried out in CFAS, at its core they are longitudinal cohorts by design. Longitudinal studies are designed to allow continuous or repeated measures, following participants to the study for a period of time, which in many cases can be years or decades. In general, longitudinal studies are observational, that is they do not apply any influence on the participants within the study, data can be collected on a wide range of exposures and outcomes, in quantitative or qualitative in nature. Longitudinal studies can offer great insights into the study of specific risk factors and how they influence the development of disease, or indeed how treatment can effect disease outcomes over varying lengths of time. Cohorts are designed with pre-determined populations in mind, older aged population in CFAS for example, which means appropriate statistical analyses can be performed to investigate changes over time for either the group as a whole, or specific groups within the population (Van Belle et al., 2004).

Longitudinal studies are often seen as an extension to cross-sectional analyses, cross-sectional studies are similar in that they offer the opportunity to study a number of variables at any given time, critically though they do not consider the influence time. Therefore the crucial difference between the two study types is that cross-sectional studies are less valid when it comes to looking at cause and effect relationships. Cross sectional studies are often considered as preliminary investigations as they require less time and resource to set up, while longitudinal data is richer, longitudinal studies require significant resource and cumbersome to manage. Cognitive Function and Ageing Studies (CFAS) I & II

3.3 CFAS I

Title of Study

MRC multicentre study of cognitive function and ageing (MRC-CFAS)

3.3.1 Aims of MRC CFAS

I. The main aims of the multicentre study are:

II. To estimate the prevalence and incidence of cognitive decline, dementia, and the range of variation of those two measures throughout England and Wales.

The study should be capable of identifying a two-fold or greater difference between localities in these rates.

III. To determine the natural history of dementia, in particular the rate of progression of cognitive decline including the distribution of the interval between the identification of cognitive impairment and death.

IV. To evaluate the degree of disability associated with cognitive decline and the service needs this disability generates.

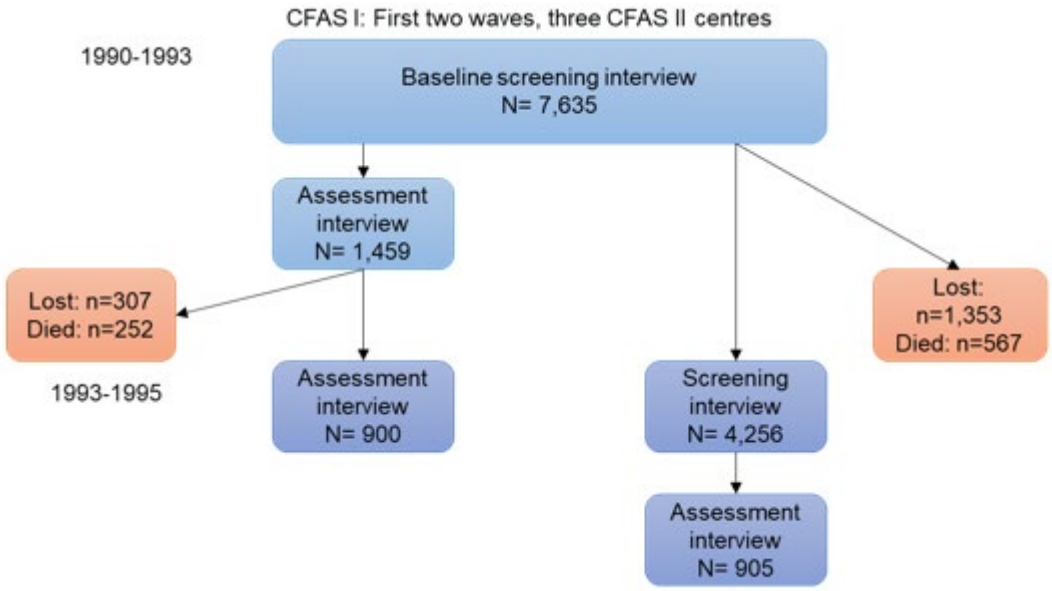
3.3.2 Study Population and Sample

The medical Research Council Cognitive Function and Ageing Study (CFAS) is a multidisciplinary, multiphase longitudinal population-based cohort study founded in 1990 (Brayne et al., 2006) (figure 3.1). Five sites in the UK were chosen to recruit participants for MRC CFAS including Cambridgeshire, Gwynedd, Newcastle-Upon-Tyne, Nottingham and Oxford; participants were recruited using identical data collection methodologies for each site. Liverpool was also included as an additional study site, however, recruitment methods were not identical to the remaining sites. Eligibility for inclusion to the study included individuals who were over the age of 65 living within the specified geographical location. The Family Health Service Authorities (FHSA) supplied population information for all sites except Gwynedd, identifying all individuals aged 65 years and older. Population-based sampling, stratified to the ages 65-74 and >75, was implemented until 2500 interviews were achieved at each centre. Due to the inability to release the FHSA information in Gwynedd, GP surgery records were searched with ascertainment based on surgery size (Matthews et al., 2004).

Structured, computer assisted interviews were administered by trained interviewers in the respondents' homes. Information was collected regarding: demography, i.e. marital status, education, socioeconomic status; social support; cognitive impairment via the MMSE and augmented cognitive tests as recommended by MRC guidance (Folstein et al., 1983); functional ability via ADL/IADL measured using a modified Townsend ADL score (Townsend and Ryan, 1991, Townsend et al., 1988); mental state using the standardised Geriatric Mental State Examination to which the algorithmic diagnostic system Automated geriatric examination for computer assisted taxonomy (AGECAT) was applied for a range of mental disorders, most notably

dementia (organicity) and depression (Copeland et al., 1976); self-reported chronic diseases, including heart disease, cerebrovascular disease, Rose angina scale and intermittent claudication; depression; anxiety; endocrine disorders; self-perceived health and psychological functioning.

Figure 3-1: Figure shows flow of 7,635 individuals from CFAS I, including baseline screening and assessment stages and 2 year follow up screening and assessment stages.



3.3.3 Key Findings

3.3.3.1 Prevalence of Dementia in England and Wales

The MRC CFAS study in 1991 published the results of the first CFAS dementia prevalence study for England and wales. The sample population was recruited initially using general practitioner (GP) registers (Family Health Service Authorities lists), resulting in around 2500 individuals were randomly selected for each CFAS centre. Cases of prevalent dementia were identified using two stages, firstly the whole study population was subject to a screening interview which identified potential cases, leading to those potential cases undergoing a more detailed prevalence assessment (Brayne et al., 1998).

The combined prevalence estimates across the centres, standardised to the England and wales over 65 population, showed overall population prevalence of dementia to be 6.6% (95% CI: 5.9, 7.3). These estimates suggested that around half a million (543,000) people in England and Wales would be expected to be suffering from

dementia of mild or greater severity. The combined prevalence results from all centres were found to be successfully generalizable to the national population due to the small degree of variability in prevalence across CFAS centres (Brayne et al., 1998).

3.3.3.2 Prevalence of Dementia in Institutional Care

CFAS collected information from 13,004 participants regarding housing status, including 571 (4.4%) living in residential or nursing homes. Using this data CFAS could estimate that the standardised prevalence of dementia for those living in institutional care was 62% (95% CI: 52, 71), this also included cases of dementia where the main diagnosis was of depression or anxiety. The results also showed no variation in prevalence by the type of care homes, however, dementia in care homes was more prevalent in women than in men, with no increase in prevalence by age. Overall 326 of the 571 individuals in care homes previously had a diagnosis of dementia, those accounted for 34% (95% CI 30-39) of all dementia cases identified by CFAS (Matthews and Dening, 2002).

3.3.3.3 Incidence of Dementia

Using CFAS' follow-up waves, incidence of dementia could be estimated across the five original CFAS sites. It was estimated that around 163,000 new cases of dementia occur in England and Wales each year (95% CI: 96,000, 272,000). Results of this study also showed a marked increase in dementia incidence with age in men and in women.

Table 1 presents the incidence rates for dementia found by the CFAS study. The results show that the increase in incidence with age is marked for both sexes and continues into the oldest age groups with no tailing off. Similar to the results in prevalence there was no convincing evidence of variation across the different centres and the incidence rates did not reflect the variations in the prevalence of possible risk factors in these sites.

From the CFAS results it can be estimated that approximately 163,000 new cases of dementia occur in England and Wales each year (95% CI: 96,000, 272,000) (Matthews et al., 2005).

3.3.3.4 Risk Factors for Dementia

The longitudinal follow-up waves of CFAS were also used to investigate possible risk factors associated with dementia. Information on possible risk factors could be collected at baseline and associations with dementia could be analysed after 2 and 6 years of follow-up. The results of these analysis showed that women and increasing age were both strongly associated with dementia. A number of other socio-demographic factors were found to be associated with dementia including: having fewer years spent in education (P trend = 0.02), poor self-perceived health, stroke, Parkinson's disease. This study argued that the association between increasing age and dementia was far greater than others studied (OR: 25.6), highlighting the significance of population ageing on the likelihood of people dying with dementia in the coming years (Yip et al., 2006).

3.3.4 The Burden of Diseases on Disability-Free Life Expectancy in Later Life

Although the main aims of CFAS were to primarily investigate dementia and cognition it has also led to significant research in wider areas of ageing epidemiology, including that of disability and life expectancy. These analyses showed that more disability-free years were gained than total life years in persons free of stroke, cognitive impairment, arthritis, and/or visual impairment at baseline. This finding suggests that elimination of these conditions would result in a compression of disability (Jagger et al., 2007).

3.4 CFAS II

Title of Study

Cognitive Function and Ageing Study II

3.4.1 Aims of CFAS I and CFAS II:

I. Estimate the prevalence and incidence of cognitive impairment and dementia nearly 20 years after the first CFAS cohorts were established and to quantify differences seen between 1991-2 and 2008-2010.

II. Investigate whether the measures that characterize the intermediate stage (Mild Cognitive Impairment) best within original CFAS are stable across generations.

III. Measure population differences over time and to assess differences between urban and rural settings, and the new relationships between health, social factors and service receipt.

IV. Compare healthy active life expectancy over time for the whole group and within social groups and assess whether over the last 20 years educational and occupational social groups have experienced differential change and whether there has been a trade-off between physical and mental health expectancy.

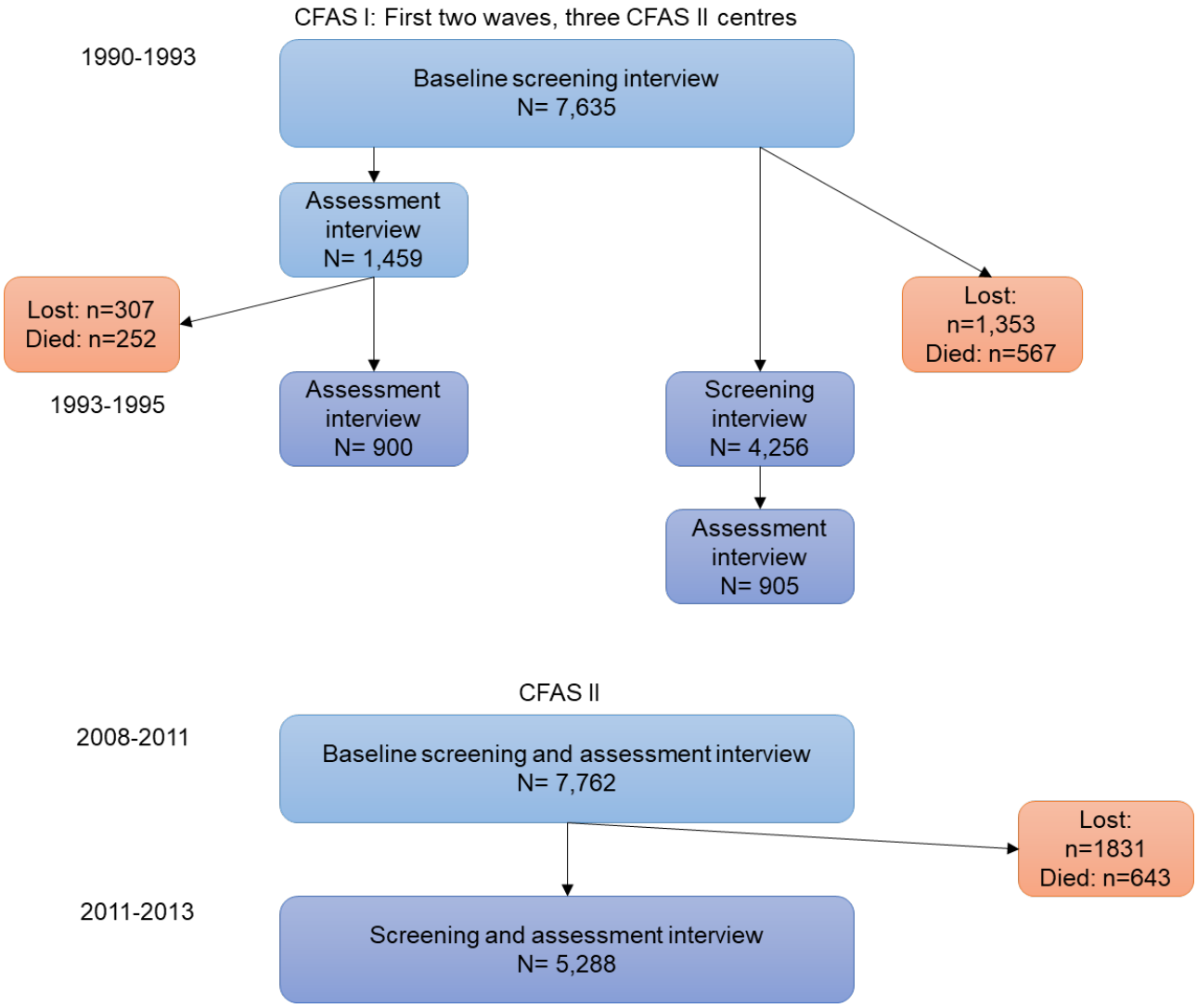
The Cognitive Function and Ageing Study II is a separate population-based cohort study designed to build on the findings of MRC CFAS. The design of the study allows for a cross generational two-decade comparison of cognition and older age in the UK.

3.4.2 Study Population and Sample

Baseline fieldwork for CFAS II was conducted between 2008 and 2011, including follow-up interviews conducted approximately 2 years after the baseline interview (figure 3.2). The recruitment methodology for CFAS II remained identical to the design implemented for MRC CFAS. Its methods of measuring health, cognitive and functional ability also remained Identical to MRC CFAS. Due to these identical study designs CFAS II offers a unique opportunity to investigate generational differences in the older age population.

The study sample of CFAS II built on the foundations of MRC CFAS, 2500 participants were recruited from three of the original sites including Cambridgeshire, Newcastle-upon-Tyne and Nottingham. Following identical study design across England according to MRC CFAS design. These three sites from the MRC CFAS study were named CFAS I, due to the ability for direct comparison to the CFAS II study sampled two-decades later.

Figure 3-2: Figure shows flow of 7,635 individuals from CFAS I and 7,762 individuals in CFAS II through the baseline and 2 year follow-up, detailing those who are lost to follow-up and those who died between the waves



3.4.3 Key Findings

3.4.3.1 A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II

In the UK CFAS estimated an extra 209,600 new dementia cases per year. A reduction of age-specific incidence means that the numbers of people estimated to develop dementia in any year had remained relatively stable (Matthews et al., 2016a).

3.4.3.2 Prevalence of Dementia in England and Wales – a two decade comparison

This study provided further evidence that a cohort effect exists in dementia prevalence. Later-born populations have a lower risk of prevalent dementia than those born earlier in the past century (Matthews et al., 2013b).

3.4.3.3 Changing non-participation in epidemiological studies of older people: evidence from the Cognitive Function and Ageing Study I and II

Non-participation in epidemiological studies of older people has increased substantially in the past two decades and public willingness to take part in studies of this kind would appear to be declining. As communities become more diverse and older people have increasing commitments on their time, new ways to engage prospective participants are urgently needed (Gao et al., 2015).

3.4.3.4 Dementia in Western Europe: epidemiological evidence and implications for policy making

The evidence from this study suggests that attention to optimum health early in life might benefit cognitive health late in life. Highlighting that policy planning and future research should be balanced across primary (policies reducing risk and increasing cognitive reserve), secondary (early detection and screening), and tertiary (once dementia is present) prevention. Each has their place, but upstream primary prevention has the largest effect on reduction of later dementia occurrence and disability (Wu et al., 2016).

3.5 Selection of Appropriate Variables

3.5.1 Mapping Procedure

In order to measure cognitive impairment across the entire spectrum, definitions were mapped according to case definitions common to the literature. From reviews of the literature it was clear that the most common case definition of MCI is the revise criteria for MCI. Individuals were defined with Petersen's MCI if they were:

I. Did not have dementia

II. Good general cognitive health

III. No impairment in ADL's

IV. Impairment in memory or non-memory cognitive domains for their age.

According to the revised criteria individuals were classified further into MCI subtypes dependant on the nature of their cognitive impairment.

Although MCI could be mapped this way the aims of the project were to map a cognitive spectrum including categories such as OCIND which is a similar concept to MCI but applies less stringent criteria to be met, representing a slightly less severe form of MCI. There are also cognitive spectrum more severe than MCI but less severe than dementia. These categories included OCIND with disability, aiming to represent those individuals which have a mild cognitive impairment but also have an impairment in their ADL's so therefore would not constitute a MCI diagnosis. Moderate / severe cognitive impairment was also mapped to represent those who have clear impairments in their general cognition which would in itself disqualifies individuals from the MCI diagnosis. Similarly, a group with identical cognitive impairment but also had disability making their health outcomes more severe was mapped, which for this dissertation I will identify as mild dementia. Finally dementia was mapped using the DSM-III-R criteria using the AGECAT algorithm.

The reasoning behind these numerous categories was to take into account the prevalence of cognitive states for those individuals who do not meet MCI criteria but arguably could be at similar risk of developing dementia, as well as those who classify as having cognitive impairment alongside inability to conduct ADL's which would not be picked up by the dementia algorithm but arguably have similar care needs to those with dementia.

This section of the chapter will go on to describe in more detail about the mapping of cognitive and functional impairment along with descriptions of the mapping of categories included in the cognitive spectrum.

3.6 Mapping Cognitive Impairment Variables

In order to meet the diagnostic criteria for cognitive impairment variables, a number of variables from the MRC CFAS and CFAS II questionnaires were recorded in STATA. A full description of questions used are included in appendix C and D.

3.6.1 Subjective Memory Complaints SMCs:

SMCs were identified using recoding questions from the CFAS questionnaires including “have you had any problems with your memory?”, “In the past 6 months have you had problems with your memory?” also, an informant was questioned, “Have you noticed a change in the participant’s memory?” These were recoded into a binary yes (1) no (0) variable.

3.6.2 Objective Cognitive Impairment:

CAMCOG Variables: In order to identify objective measures of cognitive impairment 10 variables were used from the CAMCOG test applied in the CFAS interview, a full description of the CAMCOG is included in appendix C. The CAMCOG test is a Neuropsychological test battery covering the following cognitive domains:

I. Orientation
II. Language comprehension
III. Language expression
IV. Remote memory
V. Recent memory
VI. Attention calculation
VII. Praxis
VIII. Abstract thinking
IX. Perception

Age corrected cut off scores for these tests were applied in order to identify cognitive impairment. Age corrected scores were accomplished using 5 age bands, (65-69, 70-74, 75-79, 80-84, and 85+), cut off scores were applied using the 16th percentile for each test which was representative of 1 SD from the mean which is suggested by Petersen / Mayo clinic criteria as most appropriate cut off to determine MCI. The 16th percentile rather than SD was used as it is more appropriate due to the CAMCOG test data being highly skewed (a characteristic of most neuropsychological tests). CAMCOG test scores were also corrected for education which was measured in three bands, (<9 years, 10-11 years and > 12 years)

3.7 Defining cut-points for cognitive impairment

3.7.1 CFAS / MCI definition

Petersen's definition of MCI suggests cut-off points for cognitive impairment should be adjusted for age, sex and education by 1-1.5 SD from normal. However, using a standard deviation cut point suggests data from cognitive testing should follow a normal distribution, this is not the case for the CFAS CAMCOG scores, as many more participants' score between the median and maximum values and this is reflected in most cognitive testing. Therefore, the median was decided as a more appropriate measure for the skewed CAMCOG data.

Previous studies from the CFAS I MCI project showed that the 16th percentile was the best cut off for cognitive impairment. This represents a SD of 1%, this was tested against the more frequently used 1.5%; the 1 SD cut off was chosen as a previous CFAS study found that when compared to the 1.5 SD cut off, the 1 SD had the effect of reducing sensitivity without significantly increasing specificity.

3.7.2 Quantile regression

Quantile regression provides an alternative to ordinary least squares (OLS) regression and related methods, which typically assume that associations between independent and dependent variables are the same at all levels. Quantile regression is ***not*** a regression estimated on a quantile, or subsample of data as the name may suggest. Quantile methods allow the analyst to relax the common regression slope assumption. In OLS regression, the goal is to minimize the distances between the values predicted by the regression line and the observed values. In contrast, quantile regression differentially weights the distances between the values predicted by the regression line and the observed values, then tries to minimize the weighted distances.

The cut points for each individual component of the CAMCOG score were modelled using quantile regression for the 16th percentile. The models were adjusted for age, sex and education. This technique allowed for a more robust estimates of the age sex and education adjusted 1SD cut point for cognitive impairment.

3.7.3 Good general cognitive function

This criterion was measured using the Mini Mental State examination (MMSE), a widely used test of global cognitive function. Cut off scores were applied to the MMSE scores to indicate cognitive impairment, a score of < 24 was deemed to indicate the presence of cognitive impairment. A score of between 21 & 23 was deemed as mild impairment and a score of < 21 was described as severe cognitive impairment.

3.8 Functional Impairment

A key aspect of the MCI criteria is that general functioning must not be impaired, therefore it is important to measure participants function impairment (FI). ADLs are a standard method for measuring FI activities of daily living, the CFAS participant interviews asked a number of questions that were intended to identify people who need assistance at least several times a week based on ADLs.

Individuals in CFAS were identified as having ADL disability based on the answered given to 4 questions. If participants answered that they "need help" with being "able to wash all over to bathe", "being able to prepare and cook a hot meal" or "being able to put on your socks or shoes". An additional question was also asked addressing mobility, if participants were "usually ambulant housebound", "chair-fast permanently" or "bedfast permanently".

In summary this definition identifies those who cannot independently bath, cook a hot meal, put on their socks and shoes or if the participant is immobile, they are classified with ADL-disability and therefore in terms of the definition of MCI have a functional impairment.

3.9 Mapping of Cognitive Impairment Diagnostic Criteria:

Mapping of all cognitive outcomes is shown in figure 3.3. Figure 3.4 shows cognitive outcomes ordered by severity.

3.9.1 No Cognitive Impairment (NCI)

This group was defined as being free of any impairment. They show no memory complaints, and identified by being above the threshold for cognitive impairment on

the MMSE and CAMCOG tests, as well as having no identifiable impairments in incremental activities of daily living (IADL). They also have no dementia as measured by the AGECAT algorithm.

3.9.2 Other Cognitive Impairment No Dementia (OCIND)

OCIND is the most common term to describe the concept of MCI after Petersen's Mayo criteria this, however, is also the loosest definition. OCIND was identified in CFAS as any individual who fell below the cut off for cognitive impairment in the CAMCOG and MMSE tests; they may or may not have a memory complaint and cannot have an MMSE score below the threshold for severe impairment of < 21. They also are free of disability as measured by the IADL scale and no AGECAT dementia diagnosis.

3.9.3 Amnestic MCI (aMCI)

Petersen's aMCI was diagnosed according to published Mayo clinic criteria; to meet these criteria it was necessary for participants to have given a SMC, scoring below the threshold on only the memory components of the CAMCOG assessment and a score of above mild impairment in the MMSE to meet the 'good general cognition' criteria. Participants also had to be free of impairments in disability by IADL scale and have no diagnosis of dementia by the AGECAT.

3.9.4 Non-amnestic MCI (NaMCI)

Petersen's aMCI was diagnosed according to published Mayo clinic criteria, to meet these criteria it was necessary for participants to have given a SMC, scoring below the threshold on only the non-memory components of the CAMCOG assessment and a score of above mild impairment in the MMSE to meet the 'good general cognition' criteria. Participants also had to be free of impairments in disability by IADL scale and have no diagnosis of dementia by the AGECAT.

3.9.5 Multiple MCI (mMCI)

Petersen's mMCI was diagnosed according to published Mayo clinic criteria, to meet these criteria it was necessary for participants to have given a SMC, scoring below the threshold on memory and non-memory components of the CAMCOG assessment and a score of above mild impairment in the MMSE to meet the 'good

general cognition' criteria. Participants also had to be free of impairments in disability by IADL scale and have no diagnosis of dementia by the AGECAT.

3.9.6 OCIND (with Functional Impairment)

This category was created in order to evaluate those that would have fallen into the MCI definition based on their cognitive abilities alone. Therefore, they meet all criteria for mMCI except that they have a disability as measured by the IADL scale.

3.9.7 Revised MCI (RMCI)

This category comprises Petersen's original mayo clinic diagnosis, which was revised in 2004 to be a broader more encompassing definition, anybody who meets aMCI, naMCI or mMCI can be classified as RMCI also.

3.9.8 Moderate/ Severe Cognitive Impairment

In order to meet the SCI criteria participants have to have scored less than 21 on the MMSE test. They must also be free of disability measured by IADL's and be free of dementia diagnosis by the AGECAT. They may or may not have a SMC and the CAMCOG results are not taken into account with this definition.

3.9.9 Mild Dementia

The mild dementia category is identical to the severe cognitive impairment category except they carry disability as measured by the IADL scale to reflect diagnostic criteria of dementia, however, they have not been deemed to meet the DSM-IIIR criteria for dementia.

3.9.10 CFAS Dementia

Dementia was diagnosed using the AGECAT algorithm, which has been described in the literature.

Figure 3-3: Flow chart for mapping cognitive spectrum outcomes.

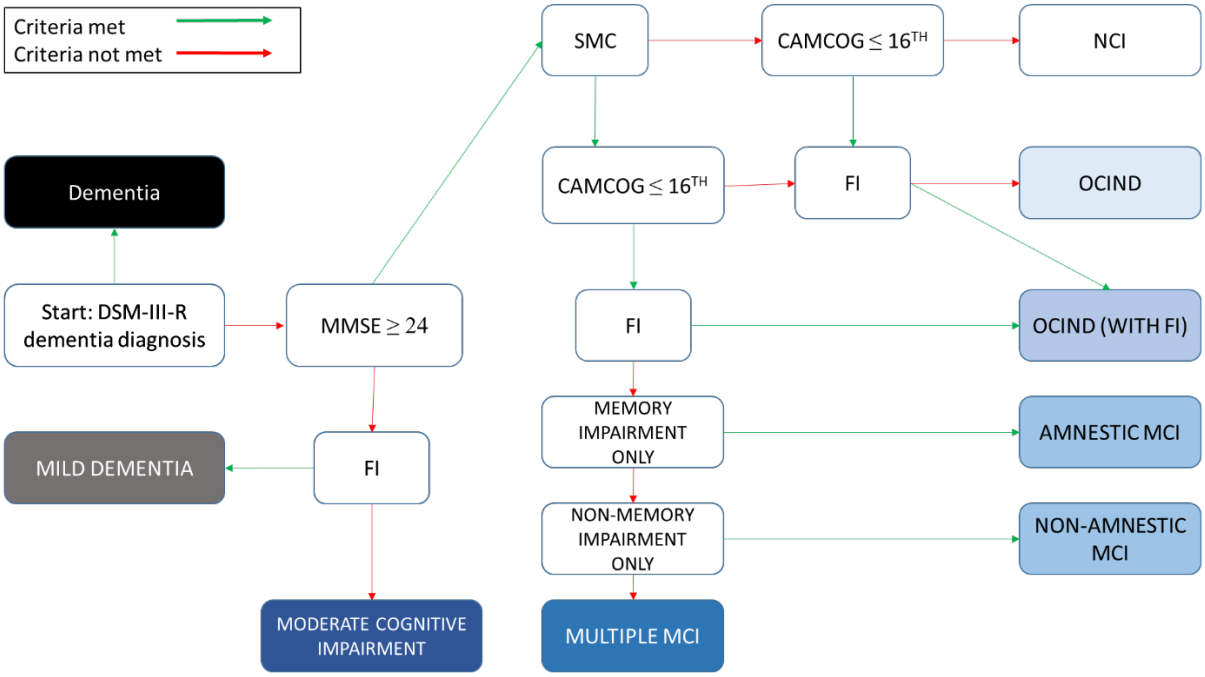
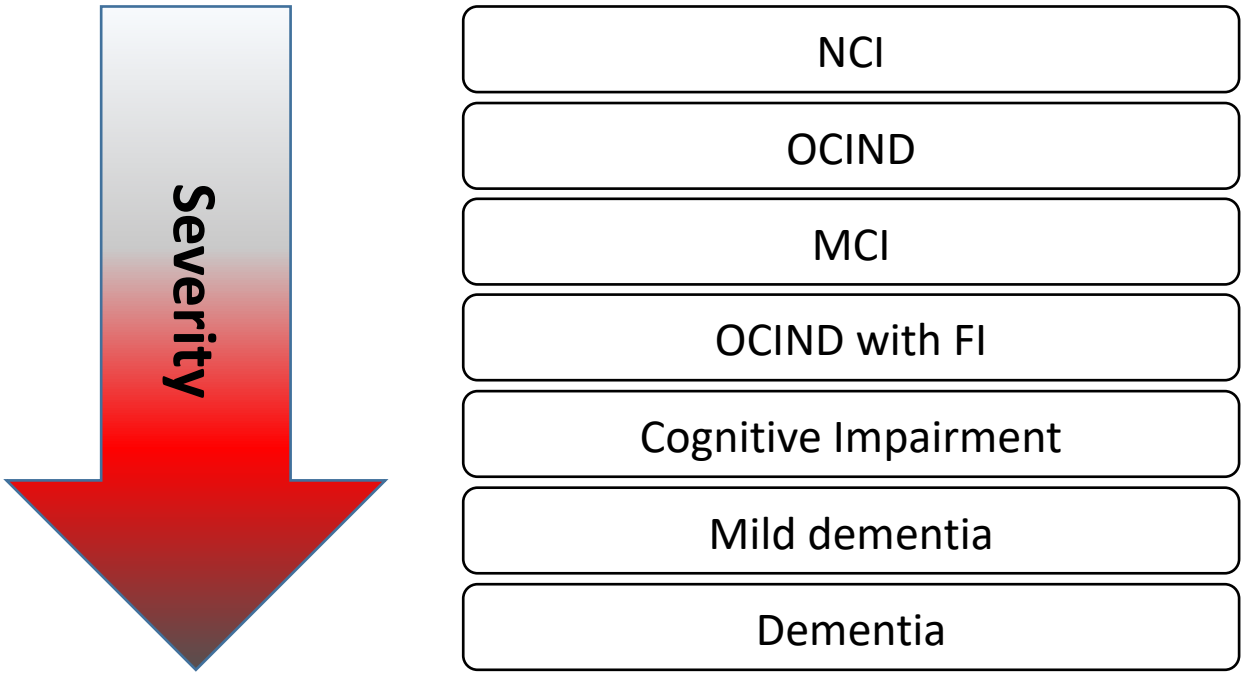


Figure 3-4: Cognitive and functional outcomes for the cognitive spectrum ordered by severity.



3.10 Variables for risk factor analysis

3.10.1 Risk factors

A number of sociodemographic and medical co-morbidities were tested in order to establish possible risk factors for MCI/OCIND both at baseline and longitudinally, as well as risk factors for progression from MCI the dementia.

3.10.2 Education

Education data was collected form each participant in the study and was measured in terms of years spent in any form of full time education. For risk factor analysis education was categorized into three groups: 0-9 years, 10 years and > 11 years.

3.10.3 Deprivation

Townsend Deprivation Index: score is a measure of area-based socio-economic status. It does not include a component that overlaps with the individual indicators of socio-economic status. It is a composite measure that takes into account the proportion of unemployed, yet economically active, individuals aged 16-59/64, the proportion of households who do not possess a car, the proportion of households with more than one person per room, and the proportion of households that are not owner-occupied. The higher the score, the more deprived the area.

For analysis of risk factors deprivation was measured using tertiles of the Townsend index.

3.10.4 Medical co-morbidities

A number of cardiovascular and metabolic conditions were measured in CFAS, a number of these conditions will be investigated as possible risk factors including: Parkinson's disease, heart attack, diabetes mellitus, stroke and intermittent claudication. The data was collected and analysed as binary variables, taken from the CFAS questionnaire where participants were simply asked if they had experienced said condition.

3.10.5 Self-reported health

Individual's perception of their own health being poor will be used in chapter 6 as a possible risk factor for MCI. To measure this participants were asked that "for

someone of your age, your own health in general is:" participants could respond with excellent, good, fair, poor or don't know. This was measured as multi-level variable.

3.10.6 Loneliness

Feelings of loneliness were included as possible risk factors for MCI, the data was collected by asking participants "do you feel lonely?" for which they could respond: no, infrequently, frequently/persistently or don't know.

3.11 Missing data

Missing data is a concern in most observational studies, a lack of data often leads to a lack of statistical power required to make precise estimates of measured outcomes. In most cases researchers have completed analysis where data is missing using only cases where data is complete, however this can lead to bias being introduced to the analysis. In a number cases the exclusion of variables due to missing data can lead to the exclusion of substantial number of the original study sample, producing a biased analysis with the knock on effect of losing statistical power and precision (Sterne et al., 2009).

The nature of missing data is broadly classified into 3 definitions of why data is missing which have an impact on the techniques that can be utilised to address them:

I. ***Missing completely at random (MCAR)***: There are no systematic differences between the missing values and the observed values. For example, blood pressure measurements may be missing because of breakdown of an automatic sphygmomanometer.
II. ***Missing at random (MAR)***: Any systematic difference between the missing values and the observed values can be explained by differences in observed data. For example, missing blood pressure measurements may be lower than measured blood pressures but only because younger people may be more likely to have missing blood pressure measurements.
III. ***Missing not at random (MNAR)***: Even after the observed data is taken into account, systematic differences remain between the missing values and the observed values. For example, people with high blood pressure may be more likely to miss clinic appointments because they have headaches.

These definitions can be helpful when deciding how to appropriately handle cases with missing data, for example, bias may be introduced into any analyses of only the complete cases in situations where data is plausibly missing at random but not completely at random. In these cases, other techniques for handling missing data should be used, multiple imputation would be appropriate, for instance, as it allows for individuals with missing data to be included in the analysis (Sterne et al., 2009). In cases where data is not missing at random, however, should only be addressed using sensitivity analysis, which examines the effect if different assumptions around the nature of the missing data. For the longitudinal analysis in later chapters of this thesis, multiple imputation was chosen as an appropriate method of handling missing data.

3.11.1 Multiple Imputation

Multiple imputation is an approach to handle missing data that is unique in that it aims to allow for an amount of uncertainty around the missing data that is being imputed. This is done by creating a set number of differing but plausible imputed datasets, which in turn can be analysed and results from each of these imputed datasets can then be appropriately combined into a single estimate. The technique of multiple imputation was first introduced in 1987 by Rubin, he designed a set of 3 rules that all multiple imputation methods follow which allow for the averaging of outcomes from multiple imputed datasets, these include (Yuan, 2010, Van Buuren, 2018, Rubin, 2004):

I. ***Imputation:*** Similar to single imputation, missing values are imputed. However, the imputed values are drawn m times from a distribution rather than just once. At the end of this step, there should be m completed datasets.
II. ***Analysis:*** Each of the m datasets is analysed. At the end of this step there should be m analyses.
III. ***Pooling:*** The m results are consolidated into one result by calculating the mean, variance, and confidence interval of the variable of concern.

The first stage of Rubin's rules is based on a Bayesian style of statistics, as multiple copies of the dataset are created, the imputed values are derived from the predictive distribution of the observed data. Part of Rubin's first rule is that the imputation stage must account for all the uncertainty in predicting the missing values, there must be

appropriate variability within the multiple imputed values, and therefore the true value of the missing data cannot be known (Sterne et al., 2009). The second stage of the rules are when the results of these imputed datasets are analysed, this can be done using standard statistical methods to fit a model of interest in each of the imputed datasets individually. It is important to understand that each of these fitted models will differ from each other due to the variation that is introduced when the missing values are imputed. Multiple imputation is useful when each of these independent results are averaged together to give overall estimates, which is determined by Rubin's third stage of pooling. Rubin's (Rubin, 2004) rules are used for calculating the standard errors for these analyses, the rules take into account any variation in the results between the independent imputed datasets meaning that the uncertainty in the missing values is reflected in the variation between datasets. Validity in the overall estimates is obtained as the outcome is ultimately the averaged over the distribution of the missing data given what is known from the observed (Rubin, 2004, Sterne et al., 2009). For the longitudinal analysis of incidence and risk factors for MCI multiple imputation by chained equations (MICE) was used, which is appropriate for data that is "missing at random".

3.12 Summary

In summary, this chapter has outlined the design and methodology for the CFAS studies, the aim was to show the unique setting of CFAS in the study of intergenerational change in cognitive function. This chapter also describes in detail how MCI was operationalized within CFAS, for the first time being able to map cognitive impairment as a full continuum from the loosest of definitions captured within the OCIND categories, the classic examples of MCI based on Petersen's criteria including subtypes, as well the more severe cognitive impairment with and without functional impairment. The operationalization of MCI in this chapter will be vital for the understanding of how the prevalence, incidence and risk factor analysis will be undertaken in subsequent chapters, and indeed I have used this chapter to introduce a range of data that will be included in analysis in later chapters such as how risk factor variables were collected and treated in the analysis.

In this chapter issues around missing data were also discussed, this is often a stumbling block for many quantitative analysis, however, in this chapter I have

addressed how by using appropriate and up to date techniques including, inverse probability weighting and multiple imputation, the most robust and generalizable results could be obtained in light of missing data.

4 PREVALENCE OF MILD COGNITIVE IMPAIRMENT (MCI)

Chapter Overview

In this chapter I will outline the first sub-study in the thesis which focuses on the prevalence of MCI in the CFAS study and wider UK. This chapter will introduce findings from previous prevalence studies and discuss the controversies in establishing MCI prevalence. The results in this chapter will cover:

I. Two-decade comparison in prevalence of MCI.
II. Comparison of MCI subtype prevalence.
III. Global predictions of MCI prevalence

4.1 Introduction

MCI represents an intermediate state of cognitive functioning between changes expected as a normal part of ageing and dementia (Petersen et al., 2014b). MCI prevalence has been estimated to range between <1% to 42% in older populations depending on the classification criteria used and setting (e.g. clinical vs. population based) (Petersen, 2016a) (Ward et al., 2012, Sachdev et al., 2015). Reported rates of progression of MCI to dementia also vary and range from around 8% to 15% per year (Petersen, 2016a). However, not all individuals with MCI experience decline; there is evidence that cognitive performance can remain stable or even improve in some cases (Ganguli et al., 2011, Matthews et al., 2008, Aretouli et al., 2011)

Defining MCI is complex and challenging due to lack of standardised diagnostic criteria. Although the MCI criteria developed by Petersen and colleagues are an attempt to standardise MCI, concerns have emerged that the criteria are too restrictive (Ritchie et al., 2001, Rasquin et al., 2005). Population based studies have repeatedly shown that definitions of cognitive decline which cover a broader range of dysfunction, such as other cognitive impairment no dementia (OCIND) are more prevalent than more restrictive definitions of MCI and also have a high progression rate to dementia (Stephan et al., 2007). There is also disagreement about the cut points used to define deficits in cognitive and physical performance to distinguish MCI from minimal or questionable dementia (Roth et al., 1986, American Psychiatric Association, 2000). The longstanding approach of excluding individuals with medical comorbidities has also been challenged, with evidence suggesting that excluding this group could result in insufficient or biased MCI diagnosis, especially for clinical

trials, thus restricting generalizability of results (Stephan et al., 2011). Consensus criteria proposed by the International Working Group on Mild Cognitive Impairment, in 2004, broadened the concept proposed by Petersen and colleagues to include impairment in any cognitive domain as well as relax criteria focused on functional impairment (Winblad et al., 2004). In 2011, the National Institute on Aging and the Alzheimer's Association (NIA-AA) refined the definition of MCI to account for possible aetiologies, including amnestic MCI (aMCI) thought to be associated with AD and non-amnestic MCI (naMCI) with vascular dementia (Albert et al., 2011). In 2013 the new Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) was released and included the diagnosis of mild neurocognitive disorder, a pre-dementia state based on MCI criteria (table 1) (American Psychiatric Association, 2013). Few community based populations have investigated DSM-V mild neurocognitive disorder, however a prevalence of 20% (95% CI: 17.8-23.0) was reported in the LIFE-Adult-Study(Luck et al., 2017). This study also found a 98.6% diagnostic overlap between the DSM-V and consensus MCI criteria.

Whether cohort effects are seen in the prevalence of MCI and risk of progression to dementia is not known, but has important public health implications (e.g., calculating population burden of disease). Further, determining how best to identify individuals at high risk of dementia will have important implications for intervention trials (e.g., clinical trial recruitment protocols), treatment (e.g., personalised medicine), public health surveillance (e.g., monitoring) and education (e.g., prevention programmes). Therefore, in this study, MCI (defined using consensus criteria) (Winblad et al., 2004), in addition to other states of the entire cognitive spectrum, are investigated in the Cognitive Function and Ageing Studies (CFAS) to determine whether similar trends are seen for these states in the last two decades as those seen in dementia.

4.2 Statistical methods for prevalence estimation

4.2.1 Introduction to Logistic Regression

Logistic regression is a statistical modelling technique that is frequently used to analyse population-based cohort studies, as well as the wider health research literature. Procedurally the technique is similar to multiple linear regression analysis, however, logistic regression assumes that the response variable in question is

dichotomous rather than continuous, as is the case in linear regression. The outcome of logistic regression describes impact that variables have on the odds ratio of an observed event of interest. Logistic regression analyses the effect of all variables included, this has the advantage of eliminating the danger of confounding variables on the result (Sedgwick, 2013).

4.2.2 Description of Logistic Regression

In practise logistic regression is implemented similarly to linear regression. Other statistical techniques can be implemented to account for confounding, such as the Mantel-Haenzel OR, although logistic regression has the additional advantage of modelling continuous variables. It is also easier to handle more than two explanatory variables simultaneously using logistic regression. This crucial aspect of the technique allows for the evaluation of impact of multiple explanatory variables on a response variable; when these explanatory variables are modelled individually the effect of covariance among variables is ignored, this leaves the analysis open to confounding effects (Sedgwick, 2013).

4.2.3 Introduction Multinomial Logistic Regression

Multinomial logistic regression models (mlogit) fits maximum likelihood models with discrete dependent (response) variables when the dependent variable takes on more than two outcomes, and those outcomes have no natural ordering. If the dependent variable takes on only two outcomes, estimates are identical to those produced by logit, similarly if the outcomes do have a natural order an ordinal logistic regression model (ologit) would be appropriate (Long et al., 2006).

4.2.4 Description of Multinomial Logistic Regression

Multinomial logistic regression is essentially an extension of the binomial logistic regression described above. To understand the difference between the two, in multinomial regression we must consider the outcomes 1, 2, 3…*m* (e.g. aMCI, naMCI & mMCI) recorded in *y*, and the explanatory variables *X* (e.g. age, sex & education). Under the assumption that there are *m* = 3 outcomes: “aMCI”, “naMCI” and “mMCI”. The values of *y* are then said to be “unordered”, this can often be confused due to the coding of the variables as 1, 2 and 3. These are merely arbitrary due to the assumption that 1 < 2 < 3 does not imply that the outcome 1 (aMCI) is any

less than the outcome 2 (naMCI) is less than outcome 3 (mMCI). This unordered nature of the variables differentiates the use of mlogit from other regression modelling such as linear regression (which assumes continuous dependant variables), ologit (appropriate for ordinal dependant variables) and logit (appropriate for dichotomous dependant variable, which can be thought of as ordered) (Long et al., 2006).

4.2.5 Binary or Multinomial regression?

When modelling for the estimated prevalence of cognitive impairment in CFAS the main decision was to model the predicted probability of belonging to a certain category of the cognitive spectrum. There were two choices which could accomplish this task, those being the modelling techniques described above, binary logistic regression and multinomial logistic regression. Both could be argued as statistically appropriate methods, however both techniques come with their own strengths and weaknesses.

Binary logistic regression was considered, this method involved creating either seven or nine models depending on whether the cognitive spectrum was being modelled with the RMCI or MCI subtype definitions. As the outcome variable for this method is required to be binary 9 categories would be for example 1=aMCI 0=not aMCI, 1=naMCI 0=not naMCI and so on. Conversely, the alternative would be a multinomial model where the whole spectrum is modelled as one variable with 9 outcomes, for example cognitive spectrum: 1=no impairment, 2=OCIND, 3=aMCI… and so on.

Using 9 separate logistic regression models has two main strengths, firstly, it is a relatively simple procedure, this is because of the second strength; high statistical power. As described above as the outcome being modelled is binary there is only one degree of freedom, this in turn means the model is highly stable and has a great deal of statistical power, due to the high number of participants in the CFAS populations. However, it has one particular weakness. Binary regression analysis may have high statistical power for each individual model, but when looking at the predicted probability of belonging to each category of the cognitive spectrum as whole, the spectrum does not represent the entire CFAS population; this is due to the separation of each model. As there is a certain degree of error within each

model, naturally there is a small amount of over or under estimation; even if the confidence intervals around the estimate are within a reliable range, these slight over and under estimations still exist. The result being the when the probability of belonging to each group is summed together, they do not equal 1.

The alternative would be to use the multinomial regression analysis, which finds the strengths and weaknesses are reversed. As binary regression presents a high degree of statistical power with a more stable model, while over or under estimating with each model; the multinomial model has much more degrees of freedom due to the greater number of outcomes. Indeed, with each category added to the model, the model itself becomes more unstable. However, as all outcomes are predicted from one single model the probability of belonging to each category sums to 1, or 100% of the population. The decision therefore was whether to lose statistical power to represent 100% of the population. The problem being, with low statistical power confidence intervals around the estimate could not be predicted.

4.2.6 Calculating Confidence intervals

As mentioned above after the decision to gain prevalence estimates through the route of multinomial logistic regression there was the outstanding issues surrounding appropriate ways to estimate confidence intervals around the estimates. Means of calculating confidence intervals were investigated through a number of routes described below, including: the delta method and bootstrapping.

4.2.7 The delta method

The delta method, in its essence, expands a function of a random variable about its mean, usually with a one-step Taylor approximation, and then takes the variance.

4.2.8 Bootstrapping

Bootstrapping is a process of resampling in a population. It can be used in any test that relies on random sampling with replacement. It is often used to assign a measure of accuracy such as prediction and confidence intervals, to estimates from the population sample. (Efron and Tibshirani, 1994, Efron, 2003).

4.2.9 Confidence intervals summary

Due to the number of categories included in the multinomial model and the relatively small population samples in some of the cognitive groups, a-MCI in particular, the delta method did not offer sufficient statistical power to provide confidence intervals for all prevalence estimates falling between 0 and 1. Therefore, bootstrapping with replacement was chosen as the method for calculating confidence intervals. The accelerated bias-corrected method was chosen as it has the advantage of correcting bias in confidence intervals caused by skewness in the distribution of bootstrapped estimates. 1000 repetitions were used to resample data. This number was chosen as it is advised that repetitions of 50-200 are adequate for estimating standard error and thus normal-approximation confidence intervals, however for the accelerated bias corrected method advises the use of 1000 repetitions.

4.2.10 Calculating prevalence

Multinomial logistic regression was used to estimate the age (by 5-year age bands) and sex specific predicted probability of CFAS I & II baseline participants falling into each category of the defined cognitive spectrum, adjusted for age and sex. Bootstrapping with replacement was used to estimate 95% confidence intervals around point estimated of predicted probability, via the bias corrected and accelerated method. These estimates were then applied to the UK population age and sex structure, using data from the office of national statistics UK population estimates from 1991 for CAS I baseline and 2011 for CFAS II baseline. Prevalence could then be reported for both time points (n=cases and proportion).

In addition to observed prevalence estimates for 1991 and 2011, prevalence using age-based projections were also included in the analysis to show differences between expected and observed 2011 estimates. These were calculated using observed 1991 prevalence estimates applied to UK population data for 2011.

4.3 Results

4.3.1 Sample Demographics

In CFAS I 7635 individuals took part in the baseline wave (80% response), with 1459 taking part in the wave 1 assessment interview (82% of those still alive), giving an overall response rate of 66% to the assessment interview. In CFAS II screen and assessment was undertaken in one stage and had a response rate of 56%. Figure 4.1 shows the number of individuals included in the baseline interviews in CFAS I and II. Demographic characteristics including age, sex, location, education and dementia status are shown in table 4.1.

Figure 4-1: CFAS I and CFAS II Study Design Shows flow of 7,635 individuals from CFAS I and 7,762 individuals in CFAS II at baseline

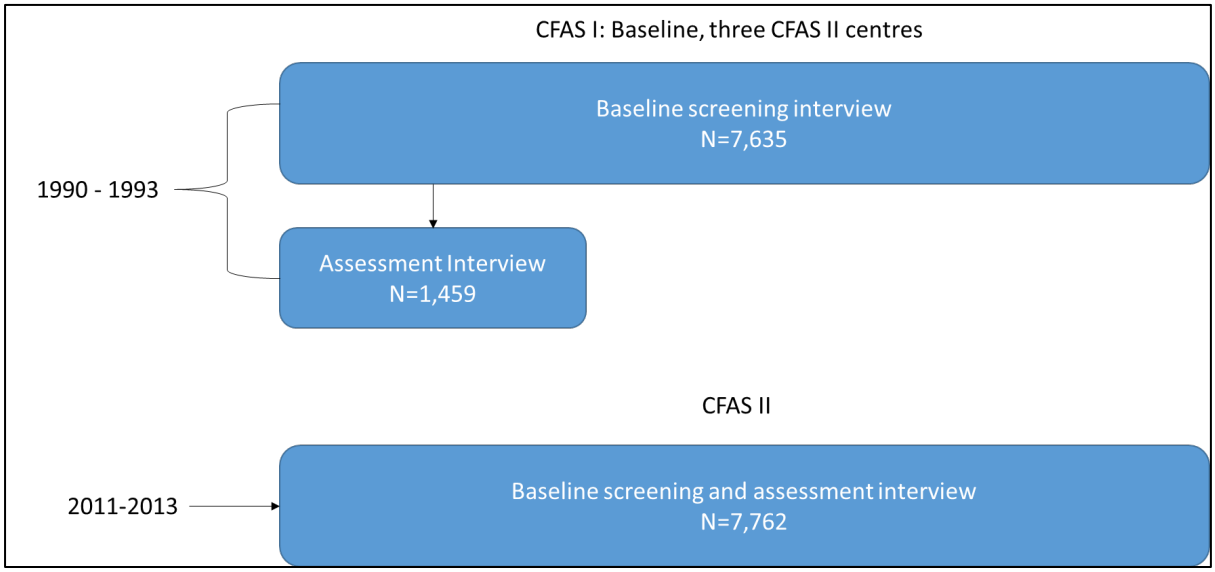


Table 4-1: Baseline sociodemographic characteristics of CFAS I & II. Characteristics (n (%) including sex, age group, education (years full time), geographical area, residential status and dementia status. Percentages are backed weighted for initial non-response (CFAS I screen and CFAS II) and study design (CFAS I assessment).

	CFAS I		CFAS II
	Screening (%) *	Assessment (%) †	N (%) ‡
Sex			
Men	3045 (39)	531 (38)	3550 (44)
Women	4590 (61)	926 (62)	4246 (56)
Age group			
65-69	1981 (25)	310 (23)	1939 (23)
70-74	1776 (23)	320 (22)	1874 (23)
75-79	1725 (22)	263 (23)	1623 (21)
80-84	1308 (18)	291 (20)	1289 (17)
85-89	615 (9)	186 (9)	769 (11)
> 90	230 (4)	87 (3)	302 (6)
Education			
0-9	5529 (74)	1074 (80)	1976 (26)
10	644 (9)	106 (8)	2734 (36)
> 10	1286 (17)	172 (12)	2909 (38)
Geographical Area			
Cambridgeshire	2601 (34)	465 (37)	2558 (30)
Newcastle	2522 (33)	499 (31)	2616 (34)
Nottingham	2512 (33)	493 (32)	2622 (35)
Dementia	na	329 (9)	461 (6)

Key: Data are n (%). CFAS=Cognitive Function and Ageing Study.

** Percentages back-weighted for non-response.*

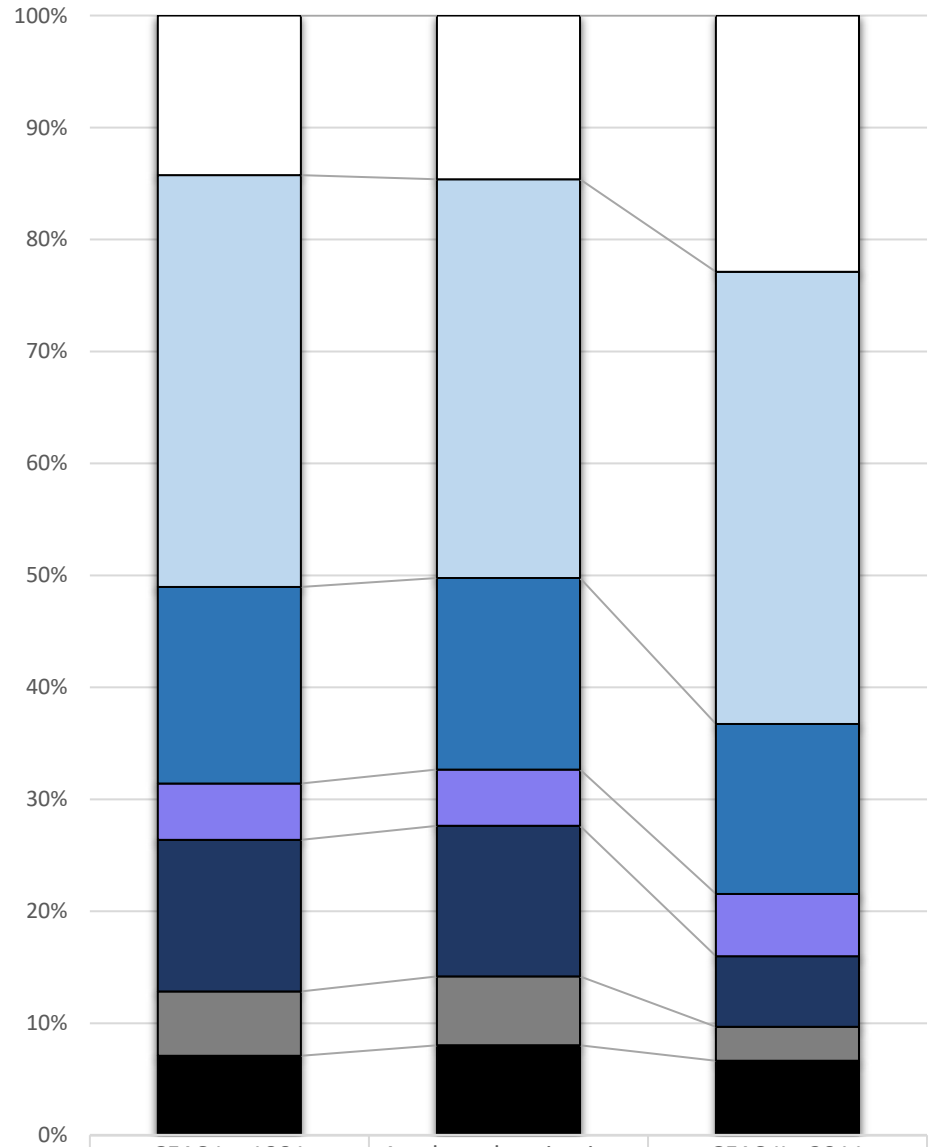
†Percentages back-weighted for sampling design and non-response.

‡Residential status missing for seven individuals for CFAS I (of whom five were also assessed).

4.3.2 UK Population prevalence of each cognitive group

Figure 4.2 shows the cumulative prevalence of each cognitive group standardized to the age and sex structure of the UK in 1991 and 2011. The figure also shows estimated prevalence for 2011 from age and sex-based predictions from the 1991 data. Cohort effects were observed in the definitions of mild dementia and cognitive impairment. Over the two decades, mild dementia has almost halved from 520,704 cases (5.7%, 95% CI: 3.8, 8.) in 1991 to 315,142 cases (3.0%, 95% CI: 2.4, 3.8) in 2011 (Table 4.2). There has been a larger decrease in cognitive impairment, which has proportionally fallen by more than half from 1,225,984 (13.5%, 95% CI: 10.1, 17.5) to 654,436 cases (6.3%, 95% CI: 5.4, 7.3) (Table 4.2). This contrasts with the age-based projections which predicted that the prevalence of mild dementia and cognitive impairment would have remained relatively stable at 6.2% (95% CI: 4.1, 8·7) and 13.4% (95% CI: 9.9, 17·5), respectively (Table 2). The reduction in MCI prevalence over the two decades was small (2.4%) suggesting stable case numbers: 1,590,481 cases (17.6%, 95% CI: 12.5, 22.9) versus 1,575,577 cases (15.2%, 95% CI: 13.8, 16.6). In contrast between 1991 and 2011, OCIND (without FI) prevalence appeared to increase from 3,331,809 (36.8%, 95% CI: 30.3, 43.6) to 4,191,265 cases (40.4%, 95% CI: 38.5, 42.3) while prevalence of OCIND (with FI) remained stable (5.0%, 95% CI: 2.6, 8.1 in 1991 vs. 5.6%, 95% CI: 4.6, 6.5 in 2011) (Table 4.2). An increase in the numbers of people with NCI increased, rising from 1,291,396 cases (14.3%, 95% CI: 9.3, 19.4) in 1991, to an estimated 2,376,070 cases (22.9%, 95% CI: 21.3, 24.5), this result was also higher than predicted age-based projections for 2011 of 1,518,700 cases (14.6%, 95% CI: 9.6, 19.9).

Figure 4-2: Cumulative prevalence of cognitive impairment standardized to UK population age and sex structure (%). *Estimates were obtained using multiple regression modelling, age-based projections for 2011 were obtained using 1991 estimates applied to 2011 population.*



	CFAS I - 1991	Age based projections	CFAS II - 2011
No Impairment	14.3%	14.6%	22.9%
OCIND	36.8%	35.6%	40.4%
MCI	17.6%	17.1%	15.2%
OCIND (with FI)	5.0%	5.0%	5.6%
Cognitive Impairment	13.5%	13.4%	6.3%
Mild dementia	5.7%	6.2%	3.0%
Dementia	7.1%	8.0%	6.6%

NCI = No cognitive impairment, OCIND = Other Cognitive Impairment no Dementia, MCI = Mild Cognitive Impairment, FI=Functional impairment

Table 4-2 Cumulative prevalence of cognitive impairment standardized to UK population age and sex structure. Estimates were obtained using multiple regression modelling, with 95% CI's obtained by bootstrap with 1000 replications via the percentile method. Age based projections for 2011 were obtained using 1991 estimates applied to 2011 population.

	CFAS I		2011 Age based Projections		CFAS II	
Cognitive Group	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
NCI	1,291,396	14.3 (9.3, 19.4)	1,518,700	14.6 (9.6, 19.9)	2,376,070	22.9 (21.3, 24.5)
OCIND	3,331,809	36.8 (30.3, 43.6)	3,695,737	35.6 (29.2, 42.5)	4,191,265	40.4 (38.5, 42.3)
MCI	1,590,481	17.6 (12.5, 22.9)	1,775,397	17.1 (12.1, 22.4)	1,575,577	15.2 (13.5, 16.6)
OCIND (with FI)	456,253	5.0 (2.6, 8.1)	522,149	5.0 (2.6, 8.1)	577,559	5.6 (4.6, 6.5)
Cognitive Impairment	1,225,984	13.5 (10.1, 17.5)	1,395,954	13.4 (9.9, 17.5)	654,436	6.3 (5.4, 7.3)
Mild Dementia	520,704	5.7 (3.8, 8.1)	638,522	6.2 (4.1, 8.7)	315,142	3.0 (2.4, 3.8)
Dementia	642,238	7.1 (5.3, 9.2)	833,426	8.0 (6.1, 10.4)	690,051	6.6 (5.6, 7.8)

4.3.3 Cognitive Spectrum Prevalence by Age & sex

Table 4.4 shows the cumulative prevalence of cognitive impairment and dementia stratified by sex & 5-year age bands based on estimates from the CFAS I study and standardized to UK 1991 population structure, table 4.5 shows the same estimates from the CFAS II study and standardised to the 2011 population structure. This section will compare the prevalence trends with age for the components of the cognitive spectrum.

Table 4-3: Prevalence of cognitive impairment stratified by 5 year age bands and sex based on CFAS I estimates applied to 1991 UK population estimates.

	CFAS I - 1991																			
	65 - 69				70 - 74				75 - 79				80 - 84				85 +			
	n	%	95% CI		n	%	95% CI		n	%	95% CI		n	%	95% CI		n	%	95% CI	
Men																				
NCI	152,574	11.8	(7.1,	16.9)	156,958	16	(11.1,	21.2)	144,631	19.9	(13.9,	26.1)	92,172	22.0	(14.8,	29.4)	44,320	20.9	(12.5,	30.0)
OCIND	627,189	48.6	(40.6,	56.6)	411,254	41.9	(35.4,	48.8)	241,610	33.2	(26.2,	40.6)	98,076	23.4	(16.3,	31.6)	30,049	14.2	(8.2,	22.0)
RMCI	339,969	26.4	(19.2,	33.6)	218,543	22.3	(17.1,	27.9)	125,861	17.3	(12.2,	22.9)	50,127	12.0	(7.4,	17.5)	15,056	7.1	(3.7,	11.7)
OCIND + FI	37,789	2.9	(1.2,	5.6)	38,896	4.0	(1.9,	6.5)	35,794	4.9	(2.5,	7.5)	22,781	5.4	(2.7,	8.6)	10,963	5.2	(2.2,	9.3
SCI	100,340	7.8	(5.3,	10.7)	101,266	10.3	(7.5,	13.6)	91,740	12.6	(9.4,	17.0)	57,372	13.7	(9.6,	19.0)	27,080	12.8	(8.0,	19.3)
Mild dementia	19,475	1.5	(0.7,	2.6)	29,958	3.1	(1.6,	5.0)	41,469	5.7	(3.3,	9.0)	39,658	9.5	(5.5,	14.4)	28,607	13.5	(7.6,	20.5)
Dementia	12,381	1.0	(0.6,	1.5)	25,341	2.6	(1.8,	3.6)	46,343	6.4	(4.7,	8.4)	58,628	14	(10.5,	18.7)	55,962	26.4	(19.3,	35.4)
Women																				
NCI	139,609	9.3	(5.6,	13.6)	159,951	12.3	(8.3,	16.3)	170,122	15.0	(10.4,	19.3)	133,658	16	(10.6,	21.2)	97,401	14.7	(8.8,	21.1)
OCIND	743,281	49.6	(42.1,	58.3)	542,898	41.9	(36.0,	47.8)	367,669	32.3	(27.0,	37.5)	184,218	22.1	(16.8,	27.6)	85,565	12.9	(8.4,	18.1)
RMCI	332,095	22.2	(15.6,	28.4)	237,915	18.3	(13.9,	23.2)	157,946	13.9	(9.9,	18.3)	77,592	9.3	(5.7,	13.3)	35,377	5.4	(2.7,	8.6)
OCIND + FI	61,865	4.1	(1.8,	7.0)	70,830	5.5	(3.2,	8.0)	75,218	6.6	(4.1,	9.4)	59,070	7.1	(4.1,	10.8)	43,047	6.5	(3.1,	11.5)
SCI	174,661	11.7	(8.1,	15.9)	196,663	15.2	(11.7,	19.1)	205,171	18.0	(14.,6,	21.9)	158,354	19	(15.0,	23.2)	113,337	17.1	(12.4,	21.9)
Mild dementia	29,510	2.0	(1.1,	3.1)	50,852	3.9	(2.6,	5.2()	81,021	7.1	(5.4,	9.1)	95,613	11.5	(8.7,	14.8)	104,543	15.8	(11.4,	21.1)
Dementia	16,777	1.1	(0.6,	1.9)	38,269	3.0	(1.9,	4.3)	80,680	7.1	(5.3,	9.2)	125,815	15.1	(12.2,	18.4)	182,040	27.5	(21.8,	33.6)

Table 4-4: Prevalence of cognitive impairment stratified by 5 year age bands and sex based on CFAS II estimates applied to 2011 UK population estimates.

	CFAS II- 2011																			
	65 - 69				70 - 74				75 - 79				80 - 84				85 +			
	n	%	95% CI		n	%	95% CI		n	%	95% CI		n	%	95% CI		n	%	95% CI	
Men																				
NCI	186,367	12.7	(11.5,	14.0)	207,014	17.8	(16.5,	19.1)	208,824	23.1	(21.6,	24.6)	166,788	27.1	(25.2,	29.2)	126,460	28.0	(25.4,	30.7)
OCIND	793,195	54.2	(52.0,	56.5)	582,663	50.1	(48.3,	51.9)	388,720	43.0	(41.0,	44.8)	205,226	33.4	(31.2,	35.4)	102,873	22.8	(20.5,	25.0)
RMCI	375,223	25.6	(23.4,	27.7)	230,856	19.9	(18.3,	21.3)	129,001	14.3	(13.0,	15.4)	57,072	9.3	(8.2,	10.4)	23,948	5.3	(4.4,	6.2)
OCIND + FI	47,141	3.2	(2.6,	4.0)	56,173	4.8	(4.0,	5.7)	60,839	6.7	(5.8,	7.7)	52,091	8.5	(7.2,	9.90	42,349	9.4	(7.7,	11.5)
SCI	44,945	3.1	(2.4,	3.7)	52,335	4.5	(3.8,	5.3)	55,325	6.1	(5.2,	7.1)	46,371	7.5	(6.4,	8.8)	36,847	8.2	(6.7,	9.9)
Mild dementia	5,563	0.4	(0.2,	0.6)	10,583	0.9	(0.6,	1.3)	18,261	2.0	(1.5,	2.6)	24,969	4.1	(3.1,	5.1)	32,382	7.2	(5.5,	9.3)
Dementia	11,566	0.8	(0.5,	1.1)	23,493	2.0	(1.5,	2.6)	43,030	4.8	(3.9,	5.7)	62,484	10.2	(8.6,	11.7)	86,141	19.1	(16.0,	22.6)
Women																				
NCI	280,678	18.1	(16.4,	19.6)	311,740	24.0	(22.5,	25.5)	321,564	29.2	(27.8,	30.7)	280,529	31.8	(30.0,	33.6)	286,106	30.3	(27.8,	32.7)
OCIND	779,211	50.1	(48.0,	52.4)	572,260	44.0	(42.2,	45.8)	390,218	35.4	(33.9,	37.0)	225,077	25.5	(23.9,	27.1)	151,823	16.1	(14.5,	17.8)
RMCI	340,234	21.9	(20.0,	24.1)	209,300	16.1	(14.7,	17.5)	119,567	10.9	(9.8,	12.0)	57,748	6.5	(5.7,	7.4)	32,628	3.5	(2.9,	4.1)
OCIND + FI	52,404	3.4	(2.6,	4.1)	62,400	4.8	(4.0,	5.6)	68,985	6.3	(5.4,	7.1)	64,547	7.3	(6.3,	8.4)	70,631	7.5	(6.0,	8.9)
SCI	71,997	4.6	(3.8,	5.6)	83,980	6.5	(5.6,	7.3)	90,805	8.2	(7.3,	9.1)	83,002	9.4	(8.3,	10.6)	88,831	9.4	(8.0,	11.1)
Mild dementia	11,196	0.7	(0.5,	1.0)	21,320	1.6	(1.2,	2.1)	37,468	3.4	(2.8,	4.0)	55,894	6.3	(5.3,	7.3)	97,506	10.3	(8.4,	12.4)
Dementia	19,282	1.2	(0.9,	1.7)	39,000	3.0	(2.3,	3.9)	73,283	6.7	(5.6,	7.8)	116,203	13.2	(11.6,	14.9)	215,570	22.9	(19.9,	26.0)

4.3.3.1 NCI, OCIND, RMCI and OCIND with FI

In men there is a similar age trend in both 1991 and 2011 (tables 4.4 and 4.5), increasing steadily before levelling off and decreasing in the older age groups. In 1991 NCI increases slightly up to age seventy-five then decreases in the older age and in 2011 increases up until age seventy-nine before decreasing again. The trends look similar for women (tables 4.4 and 4.5), especially in the 2011 cohort, in 1991 however there is a lower prevalence of NCI. In both time points prevalence increases before stabilising at age 80.

Prevalence of OCIND decreases with age in men for both CFAS studies (tables 4.4 and 4.5), and overall is higher across the age groups for men in 2011 versus 1991. In women prevalence also decreases with age (tables 4.4 and 4.5), prevalence is closer between 1991 and 2011 than those seen in men. Prevalence of RMCI declines with age for men in 1991 and 2011 (tables 4.4 and 4.5), and male prevalence is lower in every age group in 2011 compared to 1991. Age trends in women are very similar to those of men, albeit with overall lower prevalence.

Age trends of OCIND with FI look slightly different between 1991 and 2011 (tables 4.4 and 4.5). In 1991 prevalence in men increases with age steadily until remaining stable after age 75. In 2011 however, there is a more linear increase with age in 1991 prevalence in women rises with age before stabilising before falling after age eighty-five. Comparatively, prevalence increases with age in each five year band in 2011, although from a lower base.

4.3.3.2 SCI, mild dementia, CFAS dementia

Age trends for SCI in men and women here are similar, there is an increase in prevalence with age in both 1991 and 2011. In 2011 prevalence for both sexes is lower in each age group, there is a slight difference in 1991, prevalence appears to stabilise after age 75 where it continues to increase for those aged 85+ in 2011 (tables 4.4 and 4.5). Overall prevalence is higher in women across all age groups in both CFAS studies. Mild dementia trends for age in men and women are like those seen in SCI. At both time points and in both sexes, prevalence increases with age and prevalence is lower in 2011 compared to 1991. Interestingly there is a larger drop in prevalence in male age groups between 1991 and 2011 compared to those seen in women (tables 4.4 and 4.5).

CFAS dementia prevalence has previously been published, for comparison, in this study prevalence trends with age for men and women are again similar to SCI and mild dementia, increasing with age for both men and women in both time points. Again, similarly to mild dementia although CFAS dementia decreases in all age groups between 1991 and 2011 the decrease is greater in men (tables 4.4 and 4.5).

4.3.4 Prevalence of MCI subtypes in Standardised United Kingdom Population

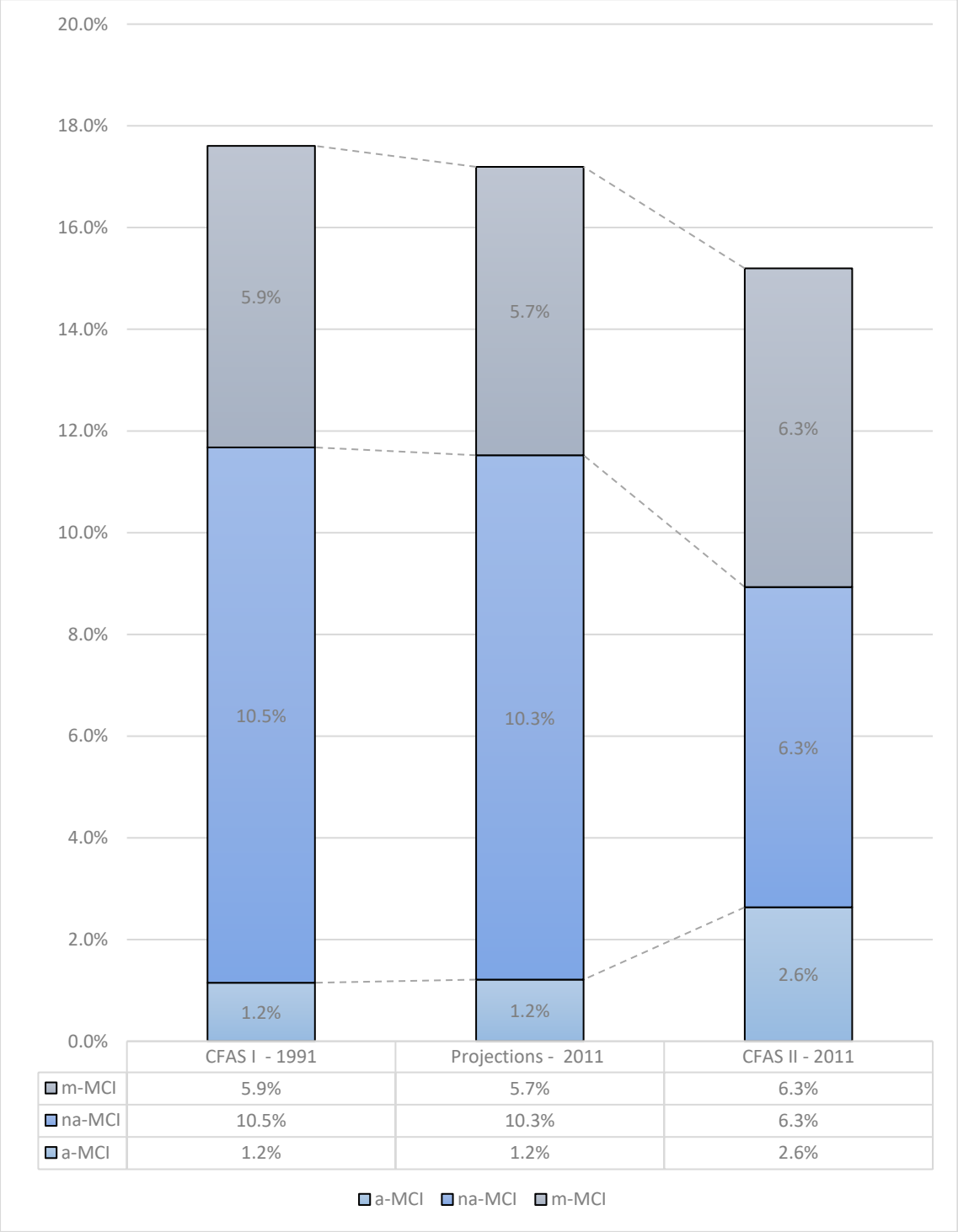
Cohort change in MCI was observed in some but not all definitions and subtypes of MCI in this study (Figure 4.3). As previously reported, of the two less restrictive MCI definitions without subtypes, RMCI was shown to remain stable between 1991 and 2011 (1,590,481, 17.6% 95% CI: 12.5, 22.9) versus (1,575,577, 15.2% 95% CI: 13.8, 16.6) while OCIND becomes more prevalent in 2011, from 3,331,809 to 4,191,265 cases (36.8%, 95% CI: 30.3, 43.6) versus (40.4%, 95% CI: 38.5, 42.3) (Table 4.6).

The disparity in time trends for these definitions is also reflected in MCI subtypes observed. The analysis found that prevalence related to each subtype shifted in different trajectories to each other (Figure 4.3). The most stable of the three subtypes was mMCI, while increasing proportionately, contrasting RMCI, remained relatively stable with 537,103 cases (5.9%, 95% CI: 3.12, 9.3) in 1991 versus 650,468 cases (6.3%, 95% CI: 5.4, 7.2). The only dramatic decrease in prevalence was seen in the naMCI subtype, which observed a drop in prevalence from 953,588 in 1991 (10.5%, 95% CI: 6.5, 15.1) to 653,576 in 2011 (6.3%, 95% CI: 5.4, 7.2). Interestingly the final result in prevalence of aMCI, contrasted the cohort change seen in naMCI, by prevalence more than doubling from 125,849 cases in 1991 (1.2%, 95% CI: 0.1, 3.1) to 273,468 cases in 2011 (2.6%, 95% CI: 2.0, 3.3), albeit from a low baseline figure.

Table 4-5: Cumulative Prevalence of aMCI, naMCI, mMCI, RMCI and OCIND in both 1991 and 2011, age based projections were estimated using 1991 observations applied to 2011 population figures. Estimates were established using multiple logistic regression modelling adjusted for age and sex with 95% confidence intervals established via bootstrapping with 1000 repetitions

		CFAS I - 1991					
CI Spectrum	Cases	Prevalence		95% CI			
aMCI	104,223	1.2%	(	0.14	,	2.9	)
naMCI	953,588	10.5%	(	6.48	,	15.1	)
mMCI	537,103	5.9%	(	3.15	,	9.3	)
		Age Based Projections for 2011					
aMCI	125,849	1.2%	(	0.1	,	3.1	)
naMCI	1,070,187	10.3%	(	6.3	,	14.9	)
m-MCI	588,662	5.7%	(	3.0	,	8.9	)
		CFAS II - 2011					
aMCI	273,468	2.6%	(	2.0	,	3.3	)
naMCI	653,576	6.3%	(	5.4	,	7.2	)
mMCI	650,468	6.3%	(	5.4	,	7.2	)

Figure 4-3: Cumulative Prevalence of aMCI, naMCI, and mMCI in both 1991 and 2011, age-based projections were estimated using 1991 observations applied to 2011 population figures. Estimates were established using multiple logistic regression modelling adjusted for age and sex with 95% confidence intervals established via bootstrapping with 1000 repetitions



4.3.5 MCI Subtype Prevalence by Age

Table 4.7 shows the prevalence of MCI subtypes (amnestic, non-amnestic and multiple) stratified by 5-year age bands based on estimates from CFAS I and CFAS II and standardized to UK 1991 population structure. This section will compare the prevalence trends with age for MCI subtypes.

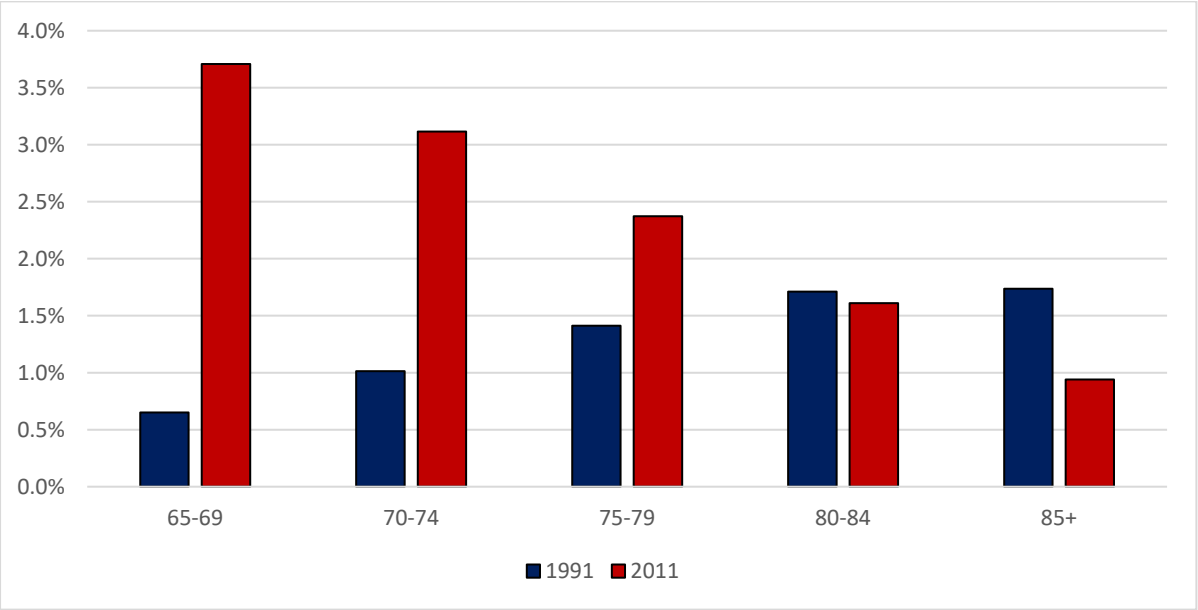
Table 4-6: Prevalence of aMCI, naMCI and mMCI in both 1991 and 2011 by age were estimated using 1991 observations applied to 2011 population figures.

	aMCI			naMCI			mMCI		
	cases	%	95 % CI	cases	%	95 % CI	cases	%	95 % CI
CFAS I - 1991									
65-69	18,170	0.7	(0.1, 2.10	368,002	13.2	(8.2, 18.6)	307,782	11.0	(6.3, 17.3)
70-74	23,108	1.0	(0.2, 2.3)	274,935	12.1	(7.9, 16.6)	144,700	6.3	(3.4, 9.3)
75-79	26,346	1.4	(0.2, 2.8)	184,593	9.9	(6.1, 14.2)	61,189	3.3	(1.4, 5.3)
80-84	21,436	1.7	(0.2, 3.9)	88,739	7.1	(3.9, 11.3)	18,507	1.5	(0.4, 2.9)
85+	15,164	1.7	(0.1, 5.8)	18,507	1.5	(0.4, 2.9)	4,925	0.6	(0.1, 1.4)
CFAS II - 2011									
65-69	111923	3.7	(2.9, 4.6)	243092	8.1	(6.8, 9.3)	374442	12.4	(10.8, 14.1)
70-74	76715	3.1	(2.5, 3.8)	180859	7.3	(6.4, 8.3)	171963	7.0	(6.0, 7.9)
75-79	47598	2.4	(1.9, 2.9)	122182	6.1	(5.3, 6.9)	71459	3.6	(2.9, 4.2)
80-84	24127	1.6	(1.2, 2.1)	67344	4.5	(3.8, 5.2)	24072	1.6	(1.2, 2.0)
85+	13104	0.9	(0.6, 1.3)	40098	2.9	(2.3, 3.5)	8532	0.6	(0.4, 0.9)

4.3.5.1 Amnestic Mild Cognitive Impairment (aMCI)

There is a clear change between 1991 and 2011 in the age trends in aMCI prevalence. In 1991 aMCI shows a linear increase as age increases, in contrast, 2011 prevalence estimates show that aMCI is highest in the youngest age groups and decreases as age increases. These trends result in the prevalence of aMCI being far higher in 2011 within the youngest population, however in the oldest population there is a lower prevalence of aMCI in 2011 (table 4.7 and figure 4.4).

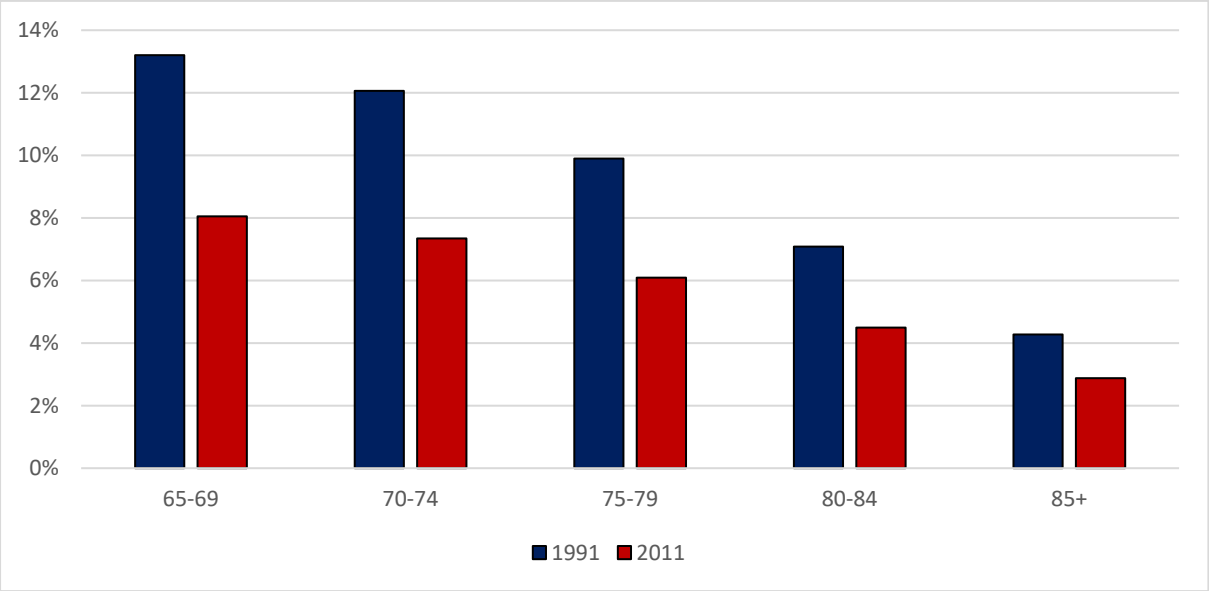
Figure 4-4: Prevalence of aMCI in both 1991 and 2011 by age were estimated using 1991 observations applied to 2011 population figures.



4.3.5.2 Non-Amnestic Mild Cognitive Impairment (naMCI)

Age trends in naMCI are more stable compared to the amnestic subtype, in both 1991 and 2011 prevalence decreases with age. Prevalence is lower in 2011 for every age group compared to 1991 (table 4.7 and figure 4.5).

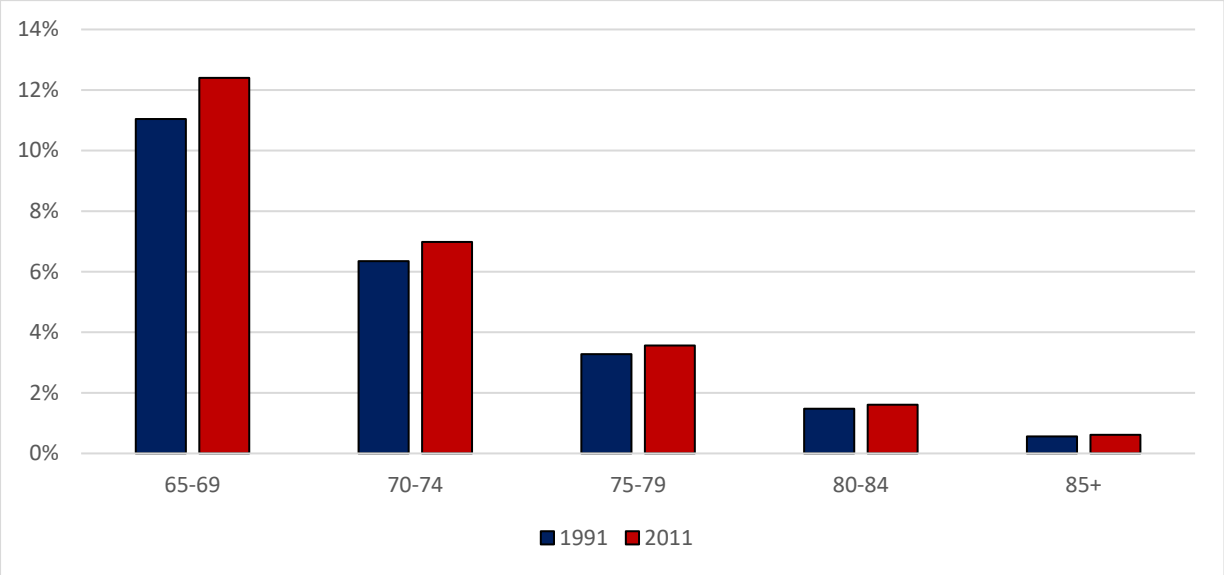
Figure 4-5: Prevalence of naMCI in both 1991 and 2011 by age were estimated using 1991 observations applied to 2011 population figures.



4.3.5.3 Multiple Mild Cognitive Impairment (mMCI)

Trends with age in mMCI appear similar to naMCI in that prevalence decreases with age at both time points, 1991 and 2011. They differ in that overall prevalence of mMCI is higher in 2011 compared to 1991 (table 4.7 and figure 4.6).

Figure 4-6: Prevalence of mMCI in both 1991 and 2011 by age were estimated using 1991 observations applied to 2011 population figures.



4.3.6 Prevalence of MCI subtype by age & sex

Tables 4.8 and 4.9 shows the cumulative prevalence of MCI subtypes (amnestic, non-amnestic and multiple) stratified by sex based on estimates from CFAS I and II and standardized to UK 1991 and 2011 population structure. This section will compare the prevalence trends with age for MCI subtypes

Table 4-7: Prevalence of aMCI, naMCI and mMCI in both 1991 and 2011 by age and sex were estimated using 1991 observations.

	CFAS I - 1991								
	aMCI			naMCI			mMCI		
	cases	%	95 % CI	cases	%	95 % CI	cases	%	95 % CI
Men									
65-69	9931	0.8	(0.0, 3.2)	186751	14.5	(9.5, 19.7)	152445	11.8	(6.6, 18.9)
70-74	12081	1.2	(0.1, 3.3)	132108	13.5	(8.9, 18.4)	67773	6.9	(4.1, 9.9)
75-79	12804	1.8	(0.3, 3.7)	82064	11.3	(6.8, 16.6)	26482	3.6	(1.8, 5.6)
80-84	9255	2.2	(0.3, 4.5)	34842	8.3	(4.4, 13.7)	7077	1.7	(0.6, 3.0)
85+	5047	2.4	(0.0, 5.5)	11133	5.3	(2.3, 9.9)	1421	0.7	(0.2, 1.4)
Women									
65-69	8239	0.6	(0.1, 1.1)	181251	12.1	(7.1, 17.8)	155337	10.4	(6.0, 15.9)
70-74	11027	0.9	(0.2, 1.5)	142827	11.0	(7.1, 15.2)	76927	5.9	(3.0, 8.8)
75-79	13542	1.2	(0.2, 2.2)	102529	9.0	(5.7, 12.7)	34707	3.1	(1.2, 5.1)
80-84	12181	1.5	(0.1, 3.6)	53897	6.5	(3.6, 10.0)	11430	1.4	(0.4, 2.8)
85+	10117	1.5	(0.1, 5.9)	26185	4.0	(1.9, 7.0)	3505	0.5	(0.1, 1.4)

Table 4-8: Prevalence of aMCI, naMCI and mMCI in both 1991 and 2011 by age and sex were estimated using 2011 observations.

	CFAS II - 2011								
	aMCI			naMCI			mMCI		
	cases	%	95 % CI	cases	%	95 % CI	cases	%	95 % CI
Men									
65-69	55632	3.8	(3.0, 4.7)	114338	7.8	(6.7, 8.9)	220186	15.0	(13.2, 17.0)
70-74	38495	3.3	(2.7, 4.0)	85829	7.4	(6.4, 8.3)	101763	8.8	(7.7, 9.8)
75-79	23685	2.6	(2.1, 3.2)	57494	6.4	(5.5, 7.2)	42036	4.7	(3.9, 5.3)
80-84	11501	1.9	(1.3, 2.4)	30258	4.9	(4.1, 5.7)	13653	2.2	(1.7, 2.7)
85+	5277	1.2	(0.8, 1.6)	15109	3.4	(2.7, 4.2)	4194	0.9	(0.7, 1.3)
Women									
65-69	56291	3.6	(2.8, 4.5)	128754	8.3	(7.0, 9.6)	154256	9.9	(8.5, 11.4)
70-74	38220	2.9	(2.4, 3.6)	95030	7.3	(6.5, 8.2)	70200	5.4	(4.6, 6.3)
75-79	23913	2.2	(1.7, 2.7)	64687	5.9	(5.1, 6.6)	29423	2.7	(2.1, 3.3)
80-84	12627	1.4	(1.1, 1.8)	37086	4.2	(3.6, 4.9)	10419	1.2	(0.9, 1.6)
85+	7827	0.8	(0.6, 1.1)	24990	2.7	(2.1, 3.3)	4338	0.5	(0.3, 0.7)

4.3.7 Chapter Summary

I. Prevalence of SCI, mild dementia and dementia have all decreased over the two decades.
II. OCIND, RMCI and OCIND with FI all remained stable.
III. There are differences between MCI subtypes, naMCI has decreased while mMCI remained stable and aMCI has increased between the two studies.
IV. Both OCIND and RMCI prevalence decreased with age while severe groups increased.
V. OCIND is by far the most prevalent cognitive state.

5 INCIDENCE OF MILD COGNITIVE IMPAIRMENT (MCI)

Chapter Overview

This chapter will discuss the two-year incidence and progression of MCI. It will show, using the CFAS II baseline and 2-year follow-up, how many people are developing MCI, while also investigating crucial transition pathways including: (1) the number of people who progress to more severe impairment and dementia from MCI; and, (2) those whose decline does not deteriorate or indeed improves.

I. The chapter is presented in two sections: The first section will look at the results of proportional transitions within the CFAS study, focusing only at the numbers of participants transitioning between groups and the proportion calculated using multiple imputation.
II. The second section will calculate the incidence rates for cognitive groups. These results are statistically modelled longitudinally using poison regression analysis.

5.1 Introduction

A key area of interest for researchers and clinicians is an extension to the work that has been done to identify the prevalence of MCI including investigation into the incidence of mild impairment (i.e. meaning the numbers of new cases of MCI over time) and knowledge of how many MCI cases go on to develop more severe cognitive impairment and dementia over a set period of time. Like the estimates of prevalence for MCI, the evidence surrounding the incidence rates are varied depending on the study, case definition for MCI and operationalisation of the diagnostic criteria. However, it has been reported that by pooling a number of MCI incidence estimates from large population-based studies the average incidence rate for MCI (expanded criteria) is approximately 47.9, ranging from 21.5 to 71.3, per 1000 person-years (Ward et al., 2012). Again, like prevalence, the incidence rate varies depending on the subtype or definition of MCI that has been operationalized, for example a-MCI showed a lower range of incidence rates (21.5 – 71.3 person-years) compared to expanded criteria (Ward et al., 2012). This variability impacts the ability of researchers to undertake cross-study comparisons and fully understand the social burden of the MCI syndrome. (Ward et al., 2012)

Literature surrounding the nature of how MCI progresses to more severe impairment is mixed. One study by Lopez et al. aimed to examine the incidence of MCI and patterns of progression from incident MCI to dementia in 285 cognitively normal subjects (mean age, 78.9 years) in the Cardiovascular Health Study–Cognition Study from 1998–1999 to 2010–2011. The study found that the age adjusted incidence of MCI was around 111.1 (95% CI: 88.1-143.0) per 1000-person years, representing around 70% of the study population with no cognitive impairment developing MCI. The study also investigated the numbers of people who got worse and those who improved or followed an `unstable path'. A total of 107 individuals progressed from MCI to dementia, representing around 53% of the study population. Additionally, the researchers measured the average time it took for MCI cases to convert to dementia which was 2.8 years ± 1.8 years (Lopez et al., 2012). The most complicated was assessing those who followed an `unstable path', and these represented around 20% of the population (40 cases). 19 cognitively normal cases (9.5%) converted to MCI and later returned to normal; 10 (5%) converted to MCI, to normal, and later back to MCI; 7 (3.5%) converted to MCI, to normal, to MCI, and later to dementia; and 4 (2%) converted to MCI, to normal, and later to dementia. There was an increased mortality rate among the cognitively normal group (110.10 per 1,000 person-years) compared to those with incident MCI who converted to dementia (41.32 per 1,000 person-years) (Lopez et al., 2012). There were a number of conclusions from the research; overall the study pointed out that there are competing elements of mortality and morbidity that influence the study of MCI incidence in the wider literature. With this in mind the study highlighted that the majority of people aged over the age of 80 years developed MCI over the time period of the study, additionally half of those individuals went on to develop dementia and symptoms of dementia took between 2 and 3 years to appear. Unsurprisingly the progression from normal to MCI or from normal to MCI to dementia is not always a linear pathway; subjects who developed MCI and later returned to normal can also subsequently progress to dementia (Lopez et al., 2012).

Trends in MCI incidence are complex to investigate, with studies showing contradictory findings. For example, Roberts et al. in 2012 looked at the incidence rates between subtypes, including amnestic and non-amnestic MCI. They also looked at sex differences in these incidence rates. From a population-based cohort

of 1,450 participants with no cognitive impairment at baseline, overall the 296 developed MCI over a 15-months follow-up period. Age and sex standardized incidence rates for MCI were found to be 63.6 per 1000 person-years, overall MCI incidence was found to be higher in men than in women (72.4 versus 57.3). The study also found that the incidence of amnestic MCI was higher than non-amnestic MCI (37.7 versus 14.7). Incidence rates were higher in men than women in the amnestic subtype (43.9 versus 33.3) as well as the non-amnestic subtype (20.0 versus 10.9). Education had an effect on the incidence of MCI; participants who had 12 or more years of education had higher rates than those who had been through higher education in both amnestic MCI (43.9 versus 32.5) and non-amnestic MCI (20.3 versus 10.2). (Roberts et al., 2012a)

Roberts et al. is one example where sex differences have been found in MCI incidence, however, in the wider literature the evidence is mixed at best. Along with Roberts a number of studies have produced figures showing incidence rates are higher in men like (38.7 Versus 22.8) (Bae et al., 2015) and (156.8 versus 70.3 per 1000 person-years) (Brodaty et al., 2013). However, there is just as much evidence that incidence rates are higher in women as shown by Larrieu et al. (11.6 versus 8.0) (Larrieu et al., 2002c)and Luck et al. (32.2 versus 17.4) (Luck et al., 2010b). Furthermore, there is equally opposing evidence that there is in fact no significant differences in incidence rates due to sex (Katz et al., 2012, Manly et al., 2008c, Ravaglia et al., 2008a). A recent study of MCI prevalence reviewed 25 studies including incidence rates for men and women for three MCI subtypes, here there was no significant sex differences for amnestic MCI (1.14, 95% CI: 0.76-1.71) 10 papers), non-amnestic MCI (1.15, 95% CI: 0.91-1.45) 6 papers) or all-type MCI (1.17, 95% CI 0.91-1.52) 9 papers). However, it is noted that although there were no significant differences the effect size across all IRR's suggest MCI incidence is slightly higher in men than it is in women (Au et al., 2017).

Several studies have investigated the pathways from MCI to severe impairment or dementia in different population setting. In 2001 a study by Unverzagt et al investigated MCI in a cohort of African American residents of Indianapolis. In addition to finding that the prevalence of cognitive impairment was 23.4%, they identified that 26% of those with MCI developed dementia over the 18-months follow-up period. The authors concluded there was evidence that cognitive impairment less

severe than dementia overall affected almost one in four community dwelling people aged over 65 years and was a major risk factor for the later development of dementia (Unverzagt et al., 2001a).

As the focus on MCI and early dementia detection has increased, there has been much focus on the role biomarkers play in the pathway from MCI to dementia. An example of this is in the biomarker C-PIB PET, an in vivo marker of brain amyloid load. A 2009 study by Okello et al investigated the role of C-PIB PET in patients with amnestic MCI, under the assumption that these patients were at an increased risk of developing Alzheimer's disease. The study found that 55% of patients with MCI had in fact showed an increased level of PIB retention at baseline and 82% developed Alzheimer's disease over three years (Okello et al., 2009b). There was only one case of a PIB negative patient progressing to Alzheimer's disease. Further analysis of the cohort showed that the higher the retention of PIB the faster patients developed Alzheimer's within one year (47%) ($p= 0.027$). The study is one of many that show the value of biomarkers like PIB, identifying that PIB positive (i.e. higher amyloid retention in the brain) MCI cases were significantly more likely to develop dementia (Okello et al., 2009b).

The assumption however that the inevitable pathway for MCI cases is to progress to severe cognitive impairment and dementia may be presumptive. Several studies have shown a contradicting outcome, with some cases of MCI reverting back to a state of `normal cognition' (Han et al., 2012). Trends were found by Ravaglia et al, in which 65% of baseline cases of MCI remained with MCI at 4 years follow up while 35% had reverted back to normal cognition (Ravaglia et al., 2008a). Further evidence from multi-ethnic cohorts have shown 47% of their MCI cases remain unchanged at 18-24 months follow up while 31% reverted back to normal cognition, though also highlighting that those with MCI were 2.8 times more likely to develop dementia than their non-MCI counterparts (Manly et al., 2008a).

Just as there are undoubtedly risk factors at play which impact the rate at which cases of MCI convert to dementia, there appear to be factors which can influence the reversion of MCI to normal cognition (Sanford, 2017). Cases where MCI is determined by a single cognitive domain appear to have higher reversion rates than those who have multiple impaired domains (Han et al., 2012, Manly et al., 2008a). A number of other factors have also been identified as increasing the rates of reverting

to normal cognition including: the presence of depression alongside MCI and the use of anticholinergic medications (Artero et al., 2008b), the absence of the apolipoprotein E4 allele (Roberts et al., 2014a), greater hippocampal volume on neuroimaging (Sachdev et al., 2013) and higher scores on cognitive testing (Roberts et al., 2014a).

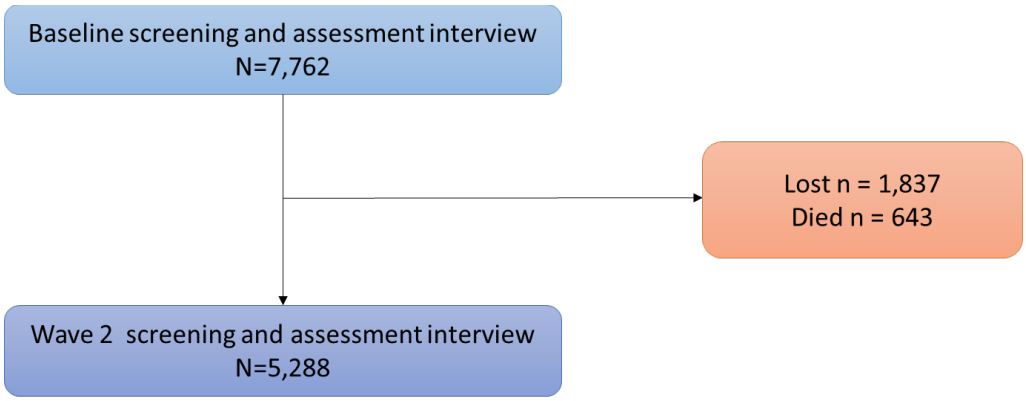
Therefore, in the first section of this chapter the aim is to use data from the CFAS II study to explore: The incidence of mild cognitive impairment captured in the definitions of OCIND and RMCI, as well as the incidence of severe cognitive impairment, mild dementia and DSM-III-R dementia captured in this chapter's dementia category. The second section of this chapter will go on to explore the incidence of dementia in those who were in the RMCI or OCIND groups at baseline, to estimate the rate at which mild cognitive impairment transitions to dementia.

5.2 Methods

5.2.1 CFAS II – Longitudinal sample

As previously detailed in the full methods chapter, CFAS II baseline consisted of a combined screen and assessment interview identical to that of the CFAS I interview. CFAS II baseline consisted of 7,762 individuals aged ≥ 65 years at recruitment in 2011. The sample was reassessed two years later in 2013. As shown in Figure 5.1 5,288 participants were re-seen at two-year follow-up, 1,837 did not respond at wave 2 and 643 had died.

Figure 5-1: CFAS II baseline and wave 2 study design including sample size at each wave and numbers of participants lost and died.



5.2.2 Outcome measures

For this longitudinal analysis four outcome were assessed including:

5.2.2.1 No cognitive impairment

This is identical to the NCI category implemented for the prevalence analysis (Chapter 4) and included those who scored above 24 on the MMSE examination or > 16th percentile cut-off score in any of the CAMCOG sub-domains including: language comprehension, language expression, remote memory, recent memory, learning memory, attention / calculation, praxis, abstract thinking, perception.

5.2.2.2 Other cognitive impairment no dementia (OCIND)

The definition for OCIND was broadened in the longitudinal analysis to include those with a MMSE ≥24. Participants have either a subjective memory complaint or a CAMCOG score ≤16th percentile in any domain with or without functional impairment.

5.2.2.3 Revised Mild Cognitive Impairment (RMCI)

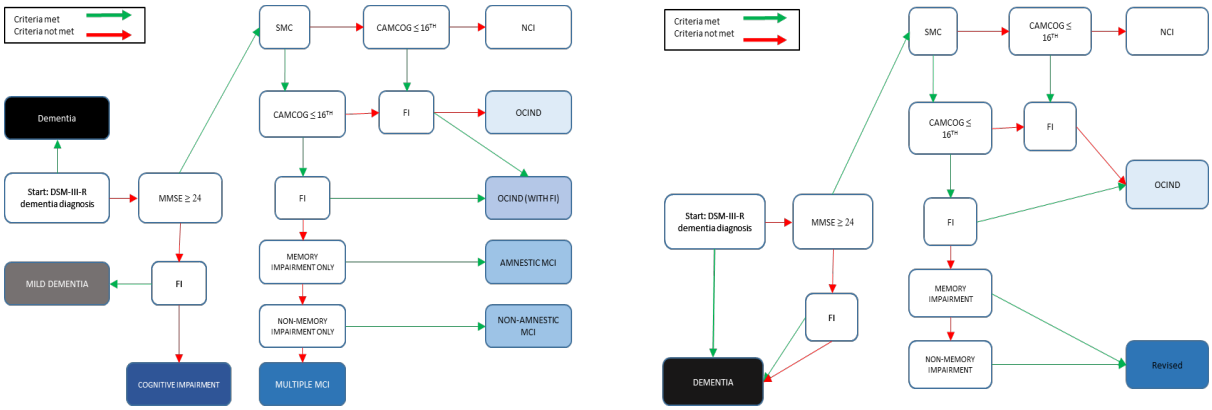
RMCI did not differ from the baseline definition. It includes those with a memory complaint, MMSE score ≥24, a CAMCOG score ≤16th percentile, without functional impairment. Amci, naMCI and mMCI, are all included in this definition, it therefore does not differentiate between memory or non-memory impairments.

5.2.2.4 Dementia

The dementia outcome is most significantly different in the longitudinal analysis compared to baseline. In the longitudinal analysis the severe cognitive impairment (SCI), mild dementia and dementia categories are combined into one variable. These means for the purposes of longitudinal analyses participants who showed an MMSE score of below 24 are categorised as dementia, regardless of functional impairment. This group also includes those who are captured by the CFAS algorithmic diagnosis of dementia based on DSM-III-R criteria.

Figure 5.2 shows the different cognitive categories used at baseline and the two-year follow-up waves.

Figure 5-2: Diagnostic flow chart showing the diagnosis of cognitive categories used in the baseline analysis of prevalence and the simplified longitudinal categories



5.2.3 Transition in cognitive groupings

Transitions were measured as the numbers of participants in each grouping that changed cognitive status from the baseline to wave 2, were lost at follow-up or died between baseline and wave 2. Proportions were calculated and back weighted for non-response using inverse probability weighting.

5.2.4 Calculating MCI incidence

5.2.4.1 Longitudinal analysis

In this part of the thesis, longitudinal rather than cross sectional modelling was implemented so using poisson regression was more appropriate. In calculating MCI incidence, a number of questions were asked:

I. What is the rate at which NCI cases at baseline develop MCI, OCIND or dementia at wave 2?

II. What is the rate at which MCI/ OCIND cases develop into dementia?

III. Are there differences in the Incidence rates of MCI to dementia, compared to the NCI and OCND groups?

5.2.4.2 Poisson regression modelling

Poisson regression fits models of the number of occurrences (counts) of an event (Sedgwick, 2014). The basic assumptions are as follows:

I. There is a quantity called the incidence rate that is the rate at which events occur. Examples are 5 per second, 20 per 1,000 person-years, 17 per square meter, and 38 per cubic centimetre.

II. The incidence rate can be multiplied by exposure to obtain the expected number of observed events. For example, a rate of 5 per second multiplied by 30 seconds means that 150 events are expected; a rate of 20 per 1,000 person-years multiplied by 2,000 person-years means that 40 events are expected; and so on.

III. Over very small exposures ε, the probability of finding more than one event is small compared with ε.

IV. No overlapping exposures are mutually independent.

Comparing rates is most easily done by calculating incidence-rate ratios (IRRs). IRR's were calculated to compare IR of outcomes for age, sex, geographical location and deprivation status (Sedgwick, 2014).

5.2.4.3 Incidence of MCI, OCIND and dementia

Population incidence was estimated by using baseline NCI as a reference for poisson regression adjusted for age and sex. Estimates from modelling were used to calculate incidence rates for each category as cases per 1000-person years.

5.2.4.4 Incidence of dementia

Dementia incidence was again measured using poisson regression modelling adjusted for age and sex. However, MCI and OCIND were both used as reference

categories in order to calculate the incidence rates for participants transitioning from MCI/OCIND at CFAS II baseline to CFAS II wave II.

5.2.5 Multiple Imputations

Between the CFAS II baseline and two years follow-up a number of participants were lost. Therefore, multiple imputation techniques for missing data were used to strengthen longitudinal analysis. Individuals who had died between baseline and follow up were dropped from the imputation model. This step was taken to ensure that dead participants were not imputed. Individuals were considered when calculating inverse probability weighting for non-response, which were applied to cross-sectional and longitudinal analyses.

Variables identified to have missing data were registered as imputed in Stata. This included the original variables used to construct the cognitive spectrum, including: ADL, CAMGOG, SMC, MMSE scores and dementia, education was also imputed (table 5.1 & 5.2). Twenty datasets in total were imputed using the multiple imputation chained equation (MICE) method. Components of the MCI criteria including global cognitive function (MMSE), memory and non-memory impairment (CAMCOG) were then passively imputed using data from imputed variables. Age and education specific cut-offs for CAMCOG scores were also modelled using the quantile regression techniques earlier described on the imputed data. Finally, the longitudinal outcomes were created passively using data from imputed variables

Table 5-1: Variables with missing data from CFAS II baseline, including the number of observations per imputed dataset (m) with numbers of complete, incomplete and imputed observations

	Observations per *m*			
CFAS II - Baseline Variables	Complete	Incomplete	Imputed	Total
Self-reported health	5235	53	53	5288
ADL	5224	64	64	5288
Remote memory	5205	83	83	5288
Recent memory	5239	49	49	5288
Language comprehension	5225	63	63	5288
Language expression	5203	85	85	5288
Recent memory	5211	77	77	5288
Learning memory	5261	27	27	5288
Attention / calculation	5186	102	102	5288
Praxis	5257	31	31	5288
Abstract thinking	5105	183	183	5288
Perception	5260	28	28	5288
Education	5227	61	61	5288
MMSE	5240	48	48	5288
Subjective memory complaint	5249	39	39	5288

Table 5-2: Variables with missing data from CFAS II wave 2, including the number of observations per imputed dataset (m) with numbers of complete, incomplete and imputed observations.

	Observations per *m*			
CFAS II - Wave 2 Variables	Complete	Incomplete	Imputed	Total
Orientation	5184	104	104	5288
Language comprehension	5142	146	146	5288
Language expression	5130	158	158	5288
Remote memory	5136	152	152	5288
Recent memory	5132	156	156	5288
Learning memory	5208	80	80	5288
Attention / calculation	5106	182	182	5288
Praxis	5208	80	80	5288
Abstract thinking	5043	245	245	5288
Perception	5209	79	79	5288
MMSE	5234	54	54	5288
Subjective memory complaint	4735	553	553	5288
Functional impairment	5138	150	150	5288
Dementia	5265	23	23	5288

5.3 RESULTS

5.4 PROPORTIONAL TRANSITION BETWEEN COGNITIVE STATES

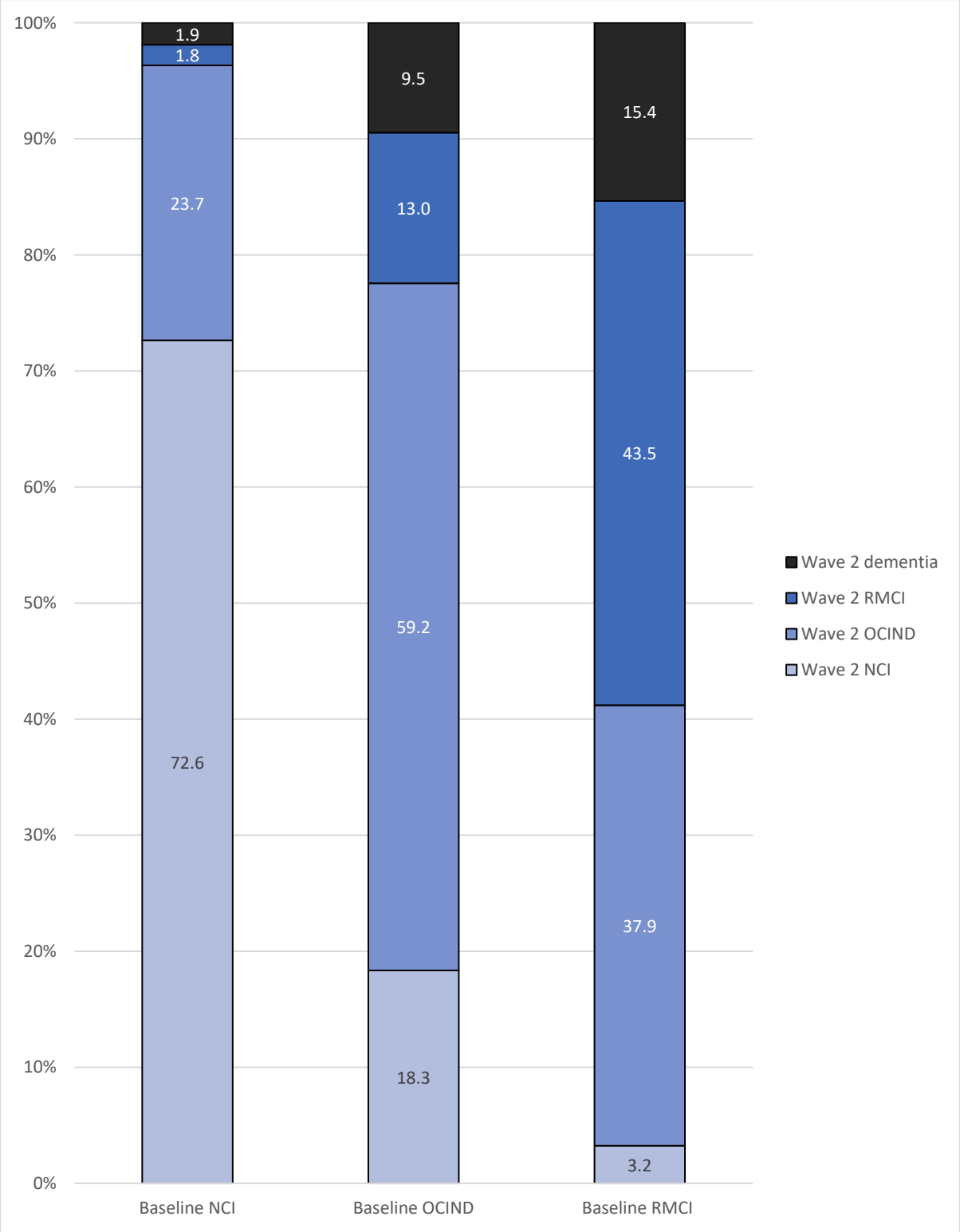
This initial results section will discuss the number of participants who begin in one cognitive category at baseline and transition into another, remain in the same category, are lost to follow-up or died at wave 2. Results are reported with raw data, proportions back weighted for non-response with 95% confidence intervals (table 5.3 & figure 5.3). Dementia was treated as an absorbing state.

Table 5-3: Observed number of participants at each cognitive group at baseline and observed transitions to groups at wave 2, including frequency of observations (n), proportion (%) and 95% Confidence intervals. proportions are calculated using multiple imputation.

Cognitive transition states									
Baseline	**n**	**proportion**	**95% CI**		**wave 2**	**n**	**proportion**	**95% CI**	
NCI	1235	22.4	21.2	23.5					
					NCI	830	72.6	(70.0,	75.2)
					OCIND	280	23.7	(21.2,	26.2)
					RMCI	21	1.8	(1.0,	2.5)
					dementia	22	1.9	(1.0,	2.8)
					Total	1153	100	.	.
OCIND	2461	45.6	44.3	47.0					
					NCI	399	18.3	(16.7,	19.9)
					OCIND	1408	59.2	(57.1,	61.3)
					RMCI	293	13.0	(11.6,	14.4)
					dementia	205	9.5	(8.2,	10.7)
					Total	2305	100	.	.
RMCI	1084	20.7	19.6	21.8					
					NCI	30	3.2	(2.1,	4.4)
					OCIND	475	37.9	(34.9,	41.0)
					RMCI	411	43.5	(40.4,	46.5)
					dementia	144	15.4	(13.1,	17.6)
					Total	1060	100	.	.

Key: NCI: No Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia. CI: Confidence Interval.

Figure 5-3: Cumulative proportion (%) of transition between baseline, NCI (No cognitive Impairment), OCIND (Other Cognitive Impairment No Dementia), RMCI (Revised Mild Cognitive Impairment) and dementia.



Key: NCI: No Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia, RMCI: Revised Mild Cognitive Impairment, CI: Confidence Interval.

5.4.1 Transition from No Cognitive Impairment (NCI)

At the baseline stage of CFAS II there were 1,235 (22%, 95% CI: 21.1, 23.5) participants who had no cognitive impairments. Of this group most participants did not develop any cognitive impairment with 830 (72.6%, 70.0, 75.2) still in the NCI category at wave 2. There were 280 (23.7%, 95% CI: 21.2, 26.2) participants who transitioned from the NCI to OCIND category, 21 (1.8%, 955 CI: 1.0, 2.5) who transitioned to RMCI and 22 (1.9%, 95% CI: 1.0, 2.8) who transitioned to the dementia category (Table 5.3). Eighty-two participants died between baseline and follow up and were therefore were excluded from the imputed analysis.

5.4.2 Transition from NCI by sex

Four hundred and forty-three (74.8%, 95% CI: 71.3, 78.3) women with NCI at baseline remained in the NCI category at wave 2 versus 387 (70.1%, 95% CI: 66.3, 74.0) men. A higher proportion of men transitioned into states with cognitive impairment than women, 146 (25.7%, 95% CI: 22.0, 29.4) men transitioned from NCI to OCIND versus 134 (22.0%, 95% CI: 18.6, 25.3) women. Eleven (2.1%, 95% CI: 0.8, 3.3) men transitioned from NCI to RMCI over 2 years versus 10 (1.5%, 95% CI: 0.6, 2.5) women, and 11 (2.1%, 95% CI: 0.7, 3.5) men transitioned to the dementia group versus 11 (1.7%, 95% CI: 0.6, 2.8) women (Tables 5.4 & 5.5).

5.4.3 Transition From Other Cognitive Impairment No Dementia (OCIND)

OCIND was the largest group at CFAS II baseline consisting of 2,461 (45.6%, 95% CI: 44.3, 47.0) participants. Of these most participants did not transition to a different group with 1,408 (59.2%, 95% CI: 57.1, 61.3) participants still in the OCIND category at wave 2. Three-hundred and ninety-nine (18.3%, 95% CI: 16.7, 19.9) who had OCIND at baseline no longer had any impairments at wave 2. 293 participants (13.0%, 95% CI: 11.6, 14.4) transitioned in the RMCI category and 205 (9.5%, 8.2, 10.7) transitioned to dementia (Table 5.3). One-hundred and fifty-six participants died between baselines and follow up and therefore were excluded from the imputed analysis.

5.4.4 Transition from OCIND by sex

Seven hundred and forty-one (59.4%, 95% CI: 56.6, 62.3) women who were in the OCIND category at baseline remained in OCIND at wave 2 versus 667 (59.0%, 955

CI: 55.9, 62.0) men. Proportion of those transitioning from OCIND to NCI were similar in men and women with 205 (18.2%, 95% CI: 16.0, 20.4) women transitioning to NCI versus 194 (18.5%, 95% CI: 16.1, 20.9) men. Transition from OCIND to RMCI was higher in men with 165 (14.9%, 95% CI: 12.7, 17.0) men transitioning versus 128 (11.3%, 95% CI: 9.5, 13.2) women. Transition to dementia was higher in women with 120 (11.0%, 95% CI: 9.1, 12.9) transitioning versus 85 (7.7%, 95% CI: 6.1, 9.3) men (Tables 5.4 & 5.5).

5.4.5 Transition from Revised Mild Cognitive Impairment (RMCI)

At CFAS II baseline there were a total of 1,084 (20.7%, 85% CI: 19.6, 21.8) participants in the RMCI category. There is a higher degree of transition between states from the RMCI group, with 475 (37.9%, 34.9, 41.0) transitioning to OCIND in wave 2; 411 (43.5%, 95% CI: 40.4, 46.5) participants remained stable in the RMCI group and 144 (15.4%, 95% CI: 13.1, 17.6) transitioned to dementia over the 2-years follow-up period (Table 5.3). Twenty-four participants died between baselines and follow up and were therefore excluded from the imputed analysis.

5.4.6 Transition from RMCI by sex

Of those who remained in the RMCI category from baseline to wave 2, a higher proportion of men remained stable with 220 (47.5%, 95% CI: 43.1, 52.0) versus 191 (39.9%, 95% CI: 35.7, 44.2) women, whereas transition to OCIND was higher in women with 256 (39.5%, 95% CI: 35.2, 43.8) transitioning versus 219 (36.2%, 95% CI: 31.9, 40.5) men. Finally transition to dementia was proportionally higher in women, with 83 (17.1%, 95% CI: 13.8, 20.5) women progressing to dementia from RMCI versus 61 (13.3%, 95% CI: 10.3, 16.3) men (Tables 5.4 & 5.5).

Table 5-4: Observed number of male participants at each cognitive group at baseline and observed transitions to groups at wave 2, including frequency of observations (n), proportion (%) and 95% Confidence intervals. proportions are calculated using multiple input.

Men - baseline	n	proportion	95% CI		wave 2	n	proportion	95% CI	
NCI	583	22.9	21.2	24.5					
					NCI	387	70.1	(66.3,	74.0)
					OCIND	146	25.7	(22.0,	29.4)
					RMCI	11	2.1	(0.8,	3.3)
					dementia	11	2.1	(0.7,	3.5)
					Total	555	100	.	.
OCIND	1,188	47.3	45.2	49.3					
					NCI	194	18.5	(16.1,	20.9)
					OCIND	667	59.0	(55.9,	62.0)
					RMCI	165	14.9	(12.7,	17.0)
					dementia	85	7.7	(6.1,	9.3)
					Total	1111	100	.	.
RMCI	523	21.3	19.7	23.0					
					NCI	15	3.0	(1.5,	4.5)
					OCIND	219	36.2	(31.9,	40.5)
					RMCI	220	47.5	(43.1,	52.0)
					dementia	61	13.3	(10.3,	16.3)
					Total	515	100	.	.

Key: NCI: No Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia. CI: Confidence Interval, RMCI: Revised Mild Cognitive Impairment.

Table 5-5: Observed number of female participants at each cognitive group at baseline and observed transitions to groups at wave 2, including frequency of observations (n), proportion (%) and 95% Confidence intervals. proportions are calculated using multiple imputation.

Women - baseline	n	proportion	95% CI		wave 2	n	proportion	95% CI	
NCI	652	22.0	20.4	23.5					
					NCI	443	74.8	(71.3,	78.3)
					OCIND	134	22.0	(18.6,	25.3)
					RMCI	10	1.5	(0.6,	2.5)
					dementia	11	1.7	(0.6,	2.8)
					Total	598	100	.	.
OCIND	1,273	44.3	42.4	46.2					
					NCI	205	18.2	(16.0,	20.4)
					OCIND	741	59.4	(56.6,	62.3)(
					RMCI	128	11.3	(9.5,	13.2)
					dementia	120	11.0	(9.1,	12.9)
					Total	1194	100	.	.
RMCI	561	20.1	18.6	21.7					
					NCI	15	3.5	(1.8,	5.1)
					OCIND	256	39.5	(35.2,	43.8)
					RMCI	191	39.9	(35.7,	44.2)
					dementia	83	17.1	(13.8,	20.5)
					Total	545	100	.	.

Key: NCI: No Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia. CI: Confidence Interval RMCI: Revised Mild Cognitive Impairment.

5.4.7 Transition to CFAS dementia (DSM-III-R)

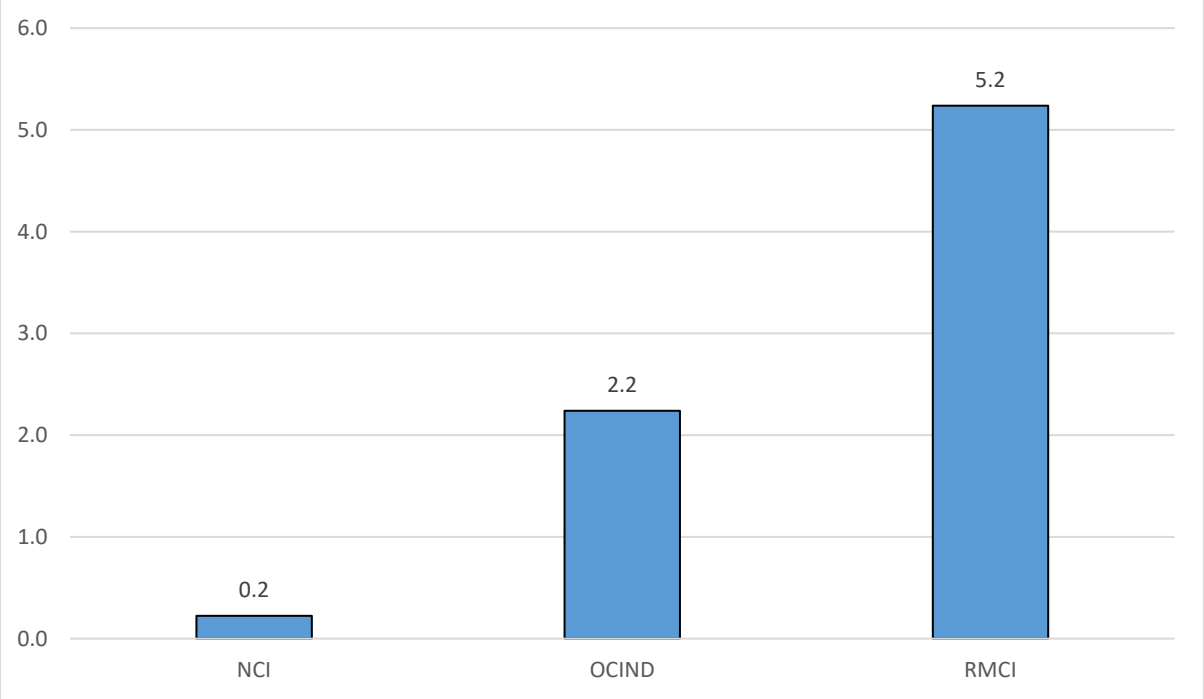
A total of 274 participants transitioned to CFAS dementia criteria specifically, algorithmically diagnosed via the DSM-III-R criteria. Five (0.2%, 95% CI: 0.0, 0.5) of these transitioned to CFAS dementia from the NCI group, 51 (2.2%, 95% CI: 1.6, 2.9) transitioned from the OCIND group and 51 (5.2%, 95% CI: 3.8, 6.6) transitioned to from the RMCI group. By far the most individuals to transition to the CFAS dementia category at wave 2 were from the dementia baseline category (167, 36.8%, 95% CI: 32.2, 41.4) (Table 5.6 & figure 5.4).

Table 5-6: Observed number of participants at each cognitive group at baseline transitioning to CFAS dementia (DSM-III-R) at wave 2, including frequency of observations (n), proportion (%) and 95% Confidence intervals. proportions are calculated using multiple imputation.

Baseline	n	proportion	95% CI	
NCI	5	0.2	(0.0,	0.5)
OCIND	51	2.2	(1.6,	2.9)
RMCI	51	5.2	(3.8,	6.6)

Key: NCI: No Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia, RMCI: Revised Mild Cognitive Impairment, CI: Confidence Interval.

Figure 5-4: Proportion (%) of participants at each cognitive group at baseline transitioning to CFAS dementia (DSM-III-R) at wave 2. Proportions are calculated using multiple imputation.



Key: NCI: No Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia, RMCI: Revised Mild Cognitive Impairment, CI: Confidence Interval.

5.4.7.1 CFAS dementia transition (sex differences)

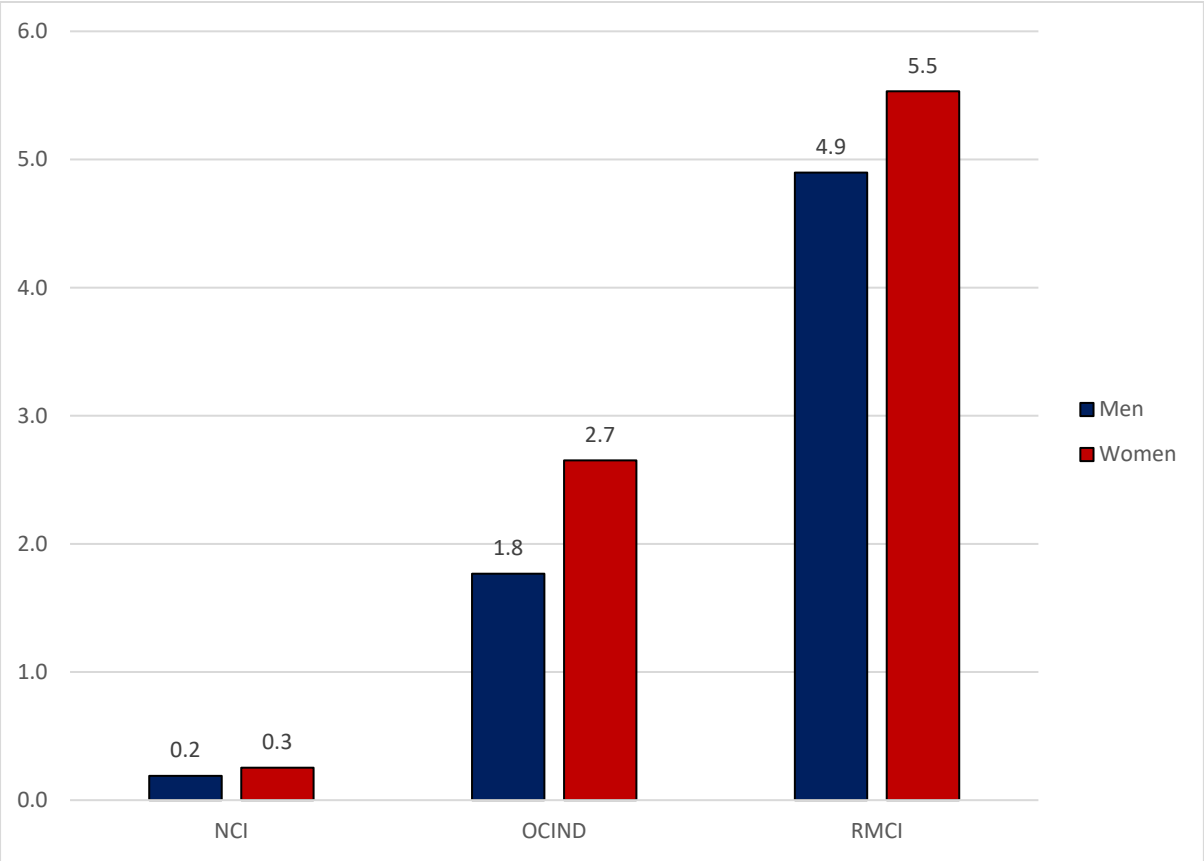
Transition from baseline cognitive impairment groups to CFAS dementia status was higher in women than men for all categories. Three (0.3%, 95% CI: 0.0, 0.7) NCI cases transitioned to CFAS dementia in women versus 2 (0.2%, 955 CI: 0.0, 0.6) in men; 30 (2.7%, 95% CI: 1.6, 3.7) cases of OCIND transitioned to CFAS dementia in women versus 21 (1.8%, 95% CI: 0.9, 2.6) in men. 27 (5.5%, 95% CI: 3.5, 7.6) women in the RMCI category at baseline developed CFAS dementia over the 2-years follow-up versus 24 (4.9%, 95% CI: 3.0, 6.8) men. Finally, 100 (35.8, 955 CI: 30.1, 41.5) women in the dementia category at baseline were in the CFAS dementia category at wave 2 versus 67 (38.7%, 95% CI: 31.2, 46.2) in men (table 5.7 & figure 5.5).

Table 5-7: Observed number of male and female participants at each cognitive group at baseline transitioning to CFAS dementia (DSM-III-R) at wave 2, including frequency of observations (n), proportion (%) and 95% Confidence intervals. proportions are calculated using multiple imputation

Baseline	n	proportion	95% CI	
Men				
NCI	2	0.2	(0.0,	0.6)
OCIND	21	1.8	(0.9,	2.6)
RMCI	24	4.9	(3.0,	6.8)
Women				
NCI	3	0.3	(0.0,	0.7)
OCIND	30	2.7	(1.6,	3.7)
RMCI	27	5.5	(3.5,	7.6)

Key: NCI: No Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia, RMCI: Revised Mild Cognitive Impairment, CI: Confidence Interval.

Figure 5-5: Proportion (%) of male and female participants at each cognitive group at baseline transitioning to CFAS dementia (DSM-III-R) at wave 2. proportions are calculated using multiple imputation



Key: NCI: No Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia, RMCI: Revised Mild Cognitive Impairment, CI: Confidence Interval

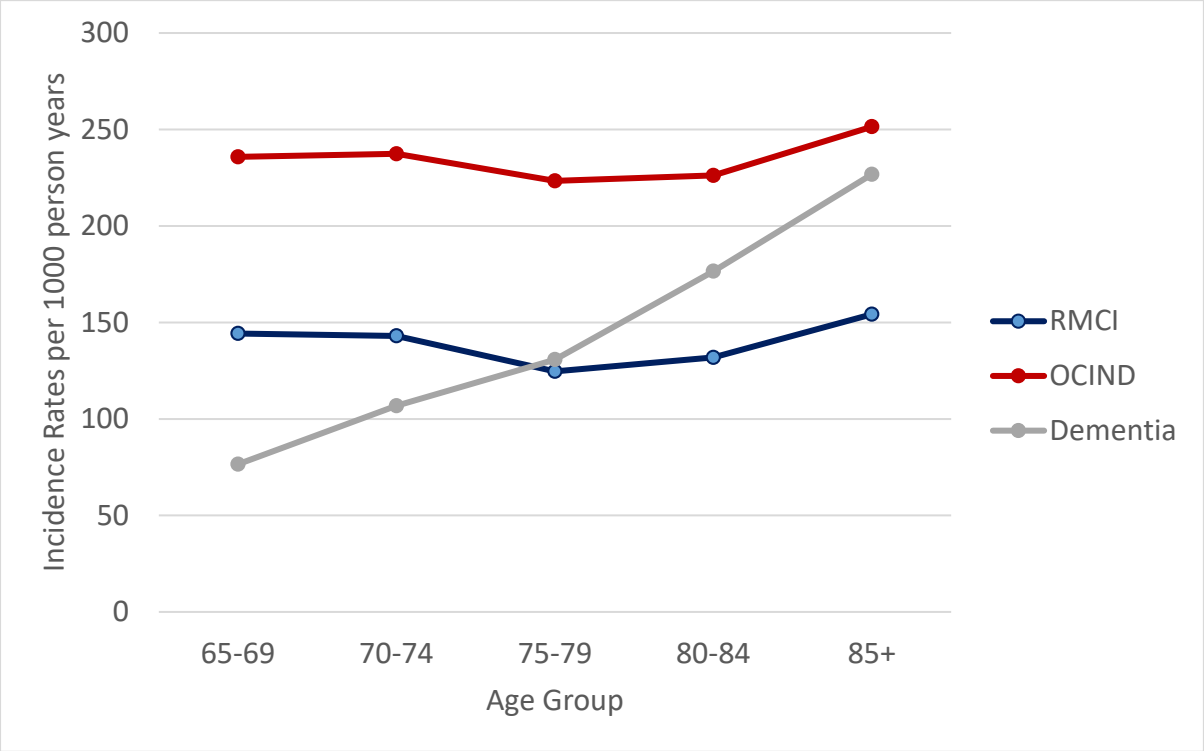
5.5 INCIDENCE OF MILD COGNITIVE IMPAIRMENT

In this second section of results, rather than observations and proportions of participants transitioning between states, statistical modelling is used to predict the numbers of incident cases of cognitive groupings using Poisson regression modelling and multiple imputation to impute missing data. Key results in this chapter include incidence rates (IR) of RMCI, OCIND and dementia, as well as the rate of incident dementia for those who have RMCI and OCIND at baseline.

5.5.1 Incidence rates of Revised MCI (RMCI), Other Cognitive Impairment no Dementia (OCIND) and Dementia

Figure 5.6 shows the IR and incidence risk ratios for individuals who have no cognitive impairment at baseline in CFAS II, who subsequently developed RMCI, OCIND or dementia in CFAS II wave 2. The analysis was performed to give an overall incidence rate for each grouping, age specific IR's, sex specific IR's, incidence by CFAS centre and by deprivation status.

Figure 5-6: Incidence rates (IR) for RMCI (Revised Mild Cognitive Impairment), OCIND (Other Cognitive Impairment) and dementia, results are stratified by 5-years age bands. Results are presented as new cases per 1000-person years. Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).



Key: NCI: No Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia, RMCI: Revised Mild Cognitive Impairment, CI: Confidence Interval

5.5.2 Incidence of Revised MCI (RMCI)

The overall IR of RMCI was 138.5 per 1000-person years (95% CI: 131.5, 145.5) (Table 5.8).

There was very little age trend for incident RMCI, remaining relatively stable across the age groups. Results show incidence falling slightly to its lowest at age group 75-79, interestingly incidence then begins to gradually increase and is highest in the 85+ age group. Incidence was higher in men compared to women. RMCI was highest in the Cambridge centre followed by Nottingham. The lowest incidence was in Newcastle. Results showed a trend with deprivation, RMCI incidence was highest in those who scored as most deprived. There was very little difference in the incidence of those moderately deprived compared to those least deprived. (Table 5.8).

Table 5-8: Incidence rates (IR) for RMCI (Revised Mild Cognitive Impairment) by age, sex, geographical location and deprivation (Townsend score). Results are presented as new cases per 1000-person years, effect sizes measured using Incidence Rate Ratio's (IRR). Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).

	RMCI Wave II					
Baseline	IR	95% CI		IRR	95% CI	
Overall	138.5	(131.5,	145.5)			
Age Group						
65-69	144.3	(131.6,	157.0)	1.0	.	.
70-74	143.1	(129.4,	156.7)	1.0	(0.9,	1.1)
75-79	124.7	(110.4,	138.9)	0.9	(0.7,	1.0)
80-84	131.9	(113.3,	150.4)	0.9	(0.8,	1.1)
85+	154.2	(127.2,	181.3)	1.1	(0.9,	1.3)
Sex						
Male	148.1	(138.2,	157.9)	1.0	.	.
Female	129.6	(119.8,	139.4)	0.9	(0.8,	1.0)
Centre						
Cambridge	166.2	(151.8,	180.6)	1.0	.	.
Newcastle	122.0	(110.3,	133.8)	0.7	(0.6,	0.8)
Nottingham	134.8	(123.2,	146.5)	0.8	(0.7,	0.9)
Deprivation						
Least	127.0	(116.0,	137.9)	1.0	.	.
Moderate	127.6	(116.0,	139.2)	1.0	(0.9,	1.1)
Most	162.4	(147.6,	177.1)	1.3	(1.1,	1.5)

Key: Revised Mild Cognitive Impairment, CI: Confidence Interval, IR: Incidence Rate, IRR: Incidence Rate Ratio.

5.5.3 Age and sex specific RMCI incidence

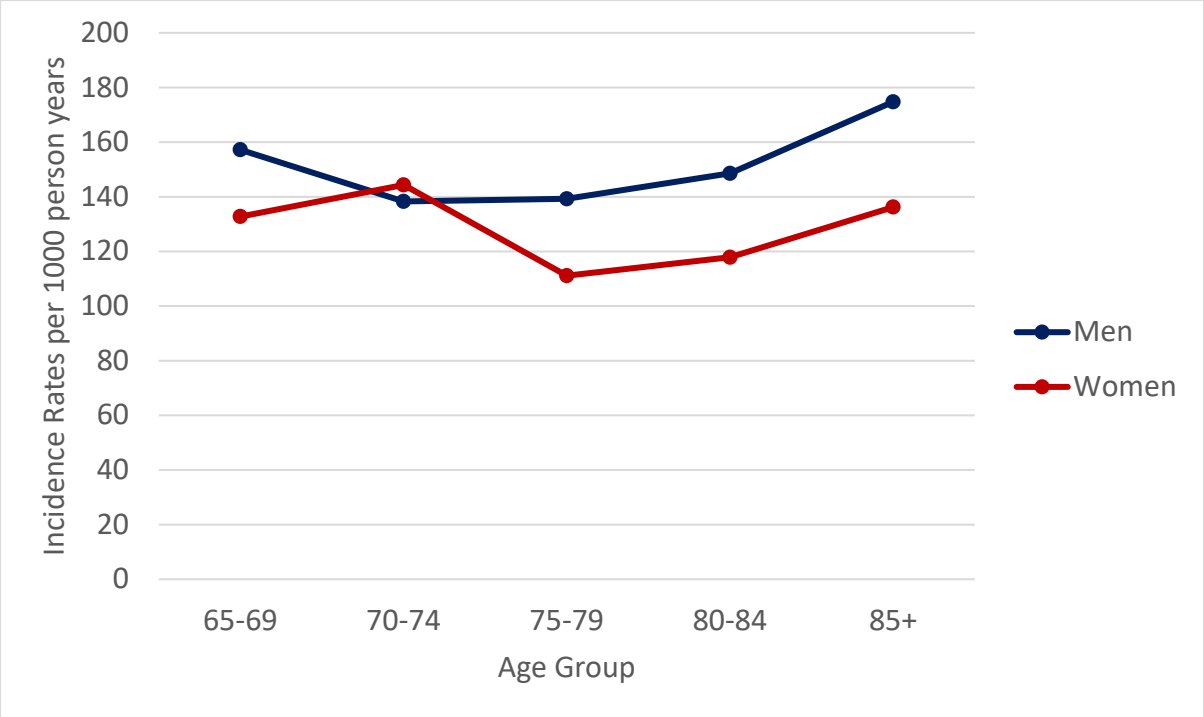
There were significant associations between age and RMCI incidence in men such that incidence increased with age (Table 5.9 & Figure 5.7). Trends in women were similar to those observed in men although incidence was lower across most age categories, except the 70-74 group where incidence was higher in women (Table 5.9 & Figure 5.7).

Table 5-9: Incidence rates (IR) for RMCI (Revised Mild Cognitive Impairment) by age & sex. Results are presented as new cases per 1000-person years, effect sizes measured using Incidence Rate Ratio's (IRR). Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).

	RMCI Wave II					
Baseline	IR	95% CI		IRR	95% CI	
Men						
65-69	157.2	(140.2,	174.2)	1.0	.	.
70-74	138.3	(118.4,	158.2)	0.9	(0.7,	1.1)
75-79	139.2	(118.8,	159.7)	0.9	(0.7,	1.1)
80-84	148.6	(120.4,	176.7)	0.9	(0.8,	1.2)
85+	174.8	(137.1,	212.5)	1.1	(0.9,	1.4)
Women						
65-69	132.8	(113.9,	151.7)	1.0	.	.
70-74	144.4	(126.0,	162.7)	1.1	(0.9,	1.3)
75-79	111.1	(91.3,	130.9)	0.8	(0.7,	1.1)
80-84	117.9	(92.8,	143.0)	0.9	(0.7,	1.1)
85+	136.2	(98.9,	173.6)	1.0	(0.8,	1.4)

Key: RMCI: Revised Mild Cognitive Impairment, IR: Incidence Rate, IRR: Incidence Rate Ratio.

Figure 5-7 Incidence rates (IR) for RMCI (Revised Mild Cognitive Impairment) by age & sex. Results are presented as new cases per 1000-person years. Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).



Key: RMCI: Revised Mild Cognitive Impairment.

5.5.4 Incidence of Other Cognitive Impairment No Dementia (OCIND)

The overall incidence rate of OCIND was higher than that of RMCI 233.5 per 1000-person years (95% CI: 228.4, 238.6) (table 5.10). The analysis also showed that OCIND incidence followed the same trend with age as RMCI, described above. OCIND incidence appears too decreased to its lowest point at the 75-79 age group before gradually increasing to its highest point in the 85+ age group (table 5.10 and figure 5.6). There was a higher incidence rate for OCIND in men than women, although there was also no evidence of any significant sex difference (IRR: 1.0, 95% CI: 0.9, 1.0) (table 5.10). Like the results of RMCI, incidence of OCIND was also highest in Cambridge and almost identical in Newcastle and Nottingham. There was no evidence geography having a significant effect on OCIND incidence between Cambridge, Newcastle (IRR: 0.9, 95% CI: 0.9, 1.0) or Nottingham (IRR: 0.9, 95% CI: 0.9, 1.0) (table 10). Trends in OCIND incidence and deprivation were not found in

the analysis. Similar to the trend with age, incidence rates decrease from the least deprived to moderate deprivation group, before rising in the most deprived group where incidence is highest. The results no deprivation effect for those in the moderate (IRR: 1.0, 95% CI: 0.9, 1.0) or most deprived group (IRR: 1.1, 95% CI: 1.0, 1.1) (table 5.10).

Table 5-10: Incidence rates (IR) for OCIND (Other Cognitive Impairment no Dementia) by age, sex, geographical location and deprivation (Townsend score). Results are presented as new cases per 1000-person years, effect sizes measured using Incidence Rate Ratio's (IRR). Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).

	OCIND Wave II				
Baseline	IR	95% CI		IRR	95% CI
Overall	233.5	(228.4,	238.6)		
Age Group					
65-69	235.8	(226.8,	244.8)	1.0	. .
70-74	237.4	(228.0,	246.8)	1.0	(1.0, 1.1)
75-79	223.4	(211.8,	235.0)	0.9	(0.9, 1.0)
80-84	226.2	(212.2,	240.2)	1.0	(0.9, 1.0)
85+	251.4	(233.6,	269.3)	1.1	(1.0, 1.2)
Sex					
Male	236.9	(229.7,	244.1)	1.0	. .
Female	230.6	(223.4,	237.8)	1.0	(0.9, 1.0)
Centre					
Cambridge	250.1	(241.0,	259.2)	1.0	. .
Newcastle	225.0	(216.0,	233.9)	0.9	(0.9, 1.0)
Nottingham	228.4	(219.6,	237.3)	0.9	(0.9, 1.0)
Deprivation					
Least	230.6	(222.4,	238.7)	1.0	. .
Moderate	225.3	(216.4,	234.2)	1.0	(0.9, 1.0)
Most	244.8	(234.8,	254.8)	1.1	(1.0, 1.1)

Key: OCIND: Other Cognitive Impairment No Dementia, IR: Incidence Rate, Incidence Rate Ratio, and CI: Confidence Interval.

5.5.5 Age and sex specific OCIND incidence

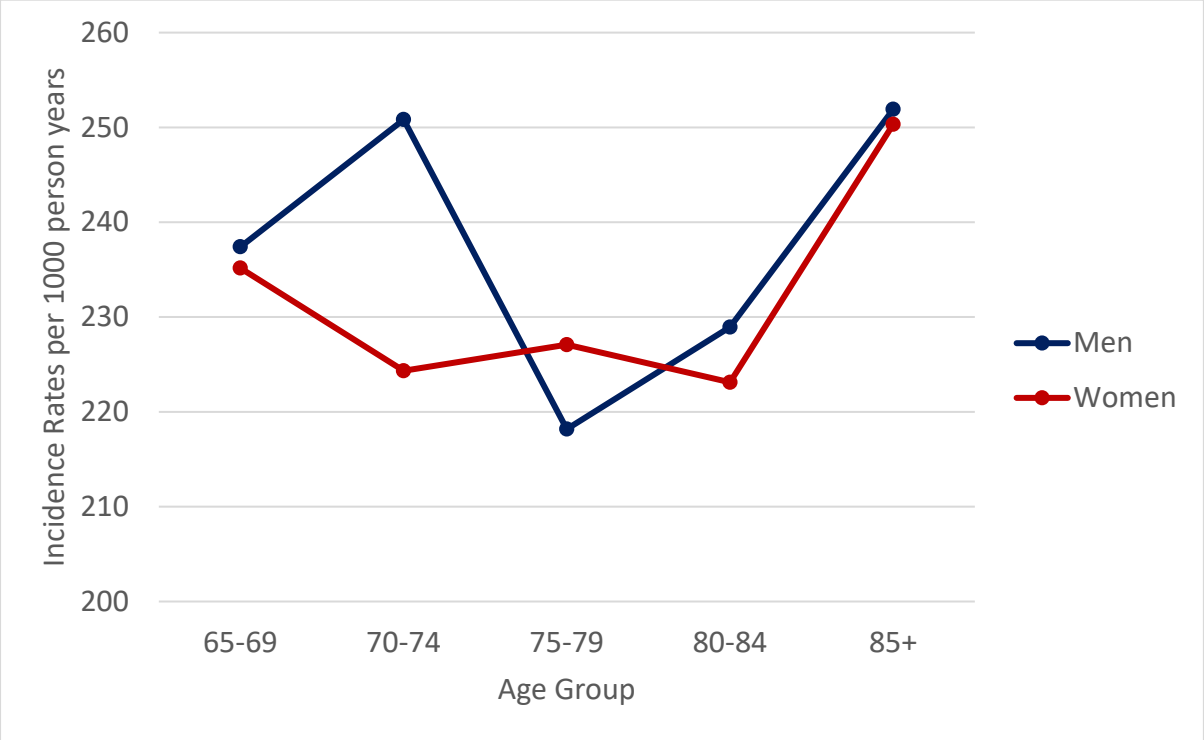
Age specific incidence of OCIND in both men and women show there is no association with increasing age. In both men and women incidence with age is a relatively unstable relationship. In men incidence increased between age groups 65-69 and 70-74, incidence then decreases rapidly to its lowest point at age group 75-79, it then increases again to being highest in the 85+ age group (table 5.11 and figure 5.8). Incidence in women is just as unstable, decreasing at first before rising higher at age group 75-79. Unlike in men, incidence then decreases again, and is at its lowest point at ages 80-84; similarly, to men incidence then increases to its highest point in the 85+ group (table 5.11 and figure 5.8)

Table 5-11 Incidence rates (IR) for OCIND (other cognitive impairment no dementia) by age & sex. Results are presented as new cases per 1000-person years, effect sizes measured using Incidence Rate Ratio's (IRR). Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).

	OCIND Wave II					
Baseline	IR	95% CI		IRR	95% CI	
Men						
65-69	237.4	(224.7,	250.1)	1.0	.	.
70-74	250.8	(238.5,	263.2)	1.1	(1.0,	1.1)
75-79	218.2	(201.0,	235.4)	0.9	(0.8,	1.0)
80-84	228.9	(208.5,	249.4)	1.0	(0.9,	1.1)
85+	251.9	(224.9,	278.9)	1.1	(0.9,	1.2)
Women						
65-69	235.2	(222.7,	247.7)	1.0	.	.
70-74	224.3	(210.2,	238.5)	1.0	(0.9,	1.0)
75-79	227.1	(211.6,	242.6)	1.0	(0.9,	1.1)
80-84	223.1	(204.2,	242.1)	0.9	(0.9,	1.0)
85+	250.3	(226.7,	274.0)	1.1	(1.0,	1.2)

Key: OCIND: Other Cognitive Impairment No Dementia, IR: Incidence Rate, Incidence Rate Ratio, and CI: Confidence Interval.

Figure 5-8: Incidence rates (IR) for OCIND (other cognitive impairment no dementia)) by age & sex. Results are presented as new cases per 1000-person years. Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).



5.5.6 Incidence of Dementia

Overall incidence of dementia in CFAS II was IR: 140.6 per 1000-person years (95% CI: 133.8, 147.4) (table 5.12). Incidence of dementia increased exponentially with each increasing age group (table 5.12 and figure 5.6). In this analysis incidence rates were higher in women, although there was no significant association between sex and dementia incidence (IRR: 1.1, 95% CI: 1.0, 1.2) (table 5.12). As with the analysis of RMCI and OCIND incidence of dementia is highest in Cambridge there is evidence of a geographical location effect, with lower incidence in both Newcastle (IRR: 0.7, 95% CI: 0.6, 0.8) and Nottingham (IRR: 0.7, 95% CI: 0.6, 0.8) (table 5.12). There is a clear deprivation trend in on incident dementia. Incidence increased with increasing deprivation scores, for those in the moderately deprived group (IRR: 1.2, 95% CI: 1.0, 1.3) and in the most deprived IR: 186.2 per 1000-person years (IRR: 1.8, 95% CI: 1.5, 2.0) (table 5.12).

Table 5-12 Incidence rates (IR) for dementia by age, sex, geographical location and deprivation (Townsend score). Results are presented as new cases per 1000-person years, effect sizes measured using Incidence Rate Ratio's (IRR). Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).

	Dementia Wave II					
Baseline	IR	95% CI		IRR	95% CI	
Overall	140.6	(133.8,	147.4)			
Age Group						
65-69	76.5	(62.5,	90.6)	1.0	.	.
70-74	106.8	(92.3,	121.3)	1.4	(1.1,	1.8)
75-79	130.8	(116.2,	145.3)	1.7	(1.4,	2.1)
80-84	176.6	(160.0,	193.1)	2.3	(1.9,	2.80
85+	226.8	(208.9,	244.7)	3.0	(2.4,	3.6)
Sex						
Male	131.2	(119.8,	142.5)	1.0	.	.
Female	146.4	(137.7,	155.2)	1.1	(1.0,	1.2)
Centre						
Cambridge	186.1	(170.6,	201.5)	1.0	.	.
Newcastle	124.7	(114.1,	135.3)	0.7	(0.6,	0.8)
Nottingham	125.4	(113.2,	137.6)	0.7	(0.6,	0.8)
Deprivation						
Least	104.9	(93.8,	116.0)	1.0	.	.
Moderate	123.2	(112.3,	134.0)	1.2	(1.0,	1.3)
Most	186.2	(171.6,	200.8)	1.8	(1.5,	2.0)

Key: IR: Incidence Rate, Incidence Rate Ratio, CI: Confidence Interval.

5.5.7 Age and sex specific dementia incidence

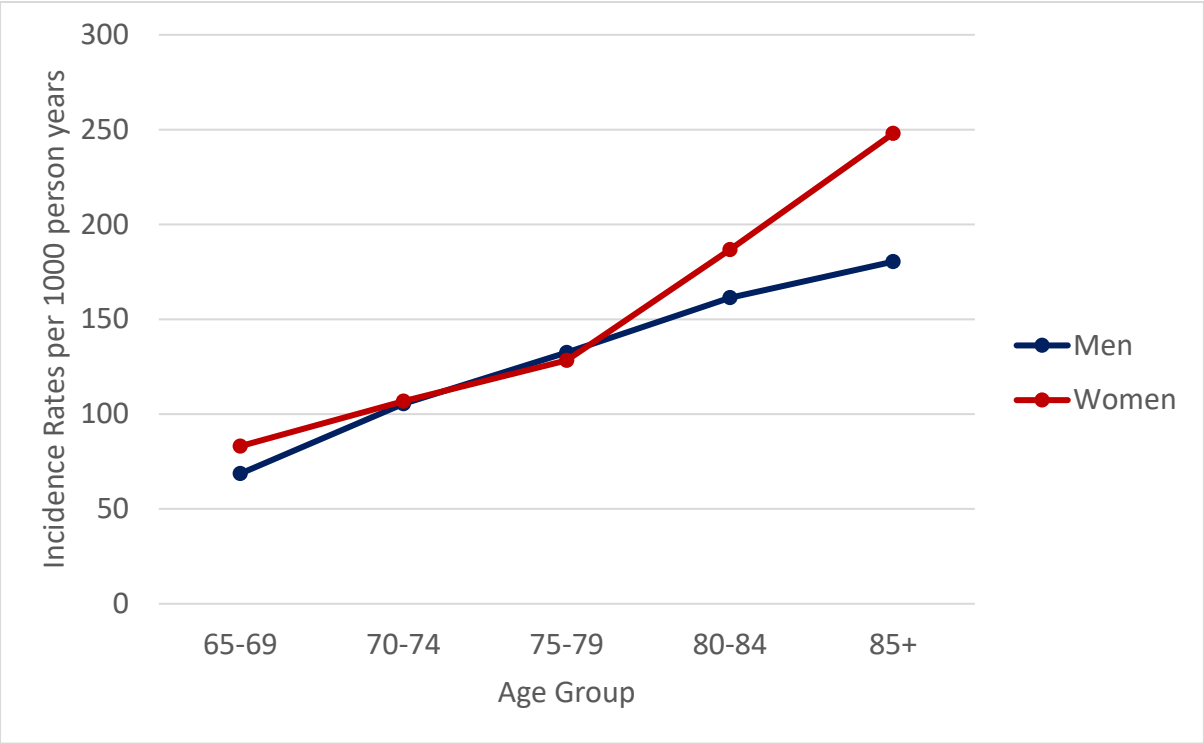
Age specific incidence rates also increase with age when analysed for only men, however the trend is slightly different. In men age increases steadily and begins to plateau towards the oldest age groups. In women, however, the increase is gradual up until age group 75-79 before increasing more rapidly toward the oldest-old (table 5.13 & figure 5.9).

Table 5-13: Incidence rates (IR) for dementia by age & sex. Results are presented as new cases per 1000-person years, effect sizes measured using Incidence Rate Ratio's (IRR). Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).

	Dementia Wave II				
Baseline	IR	95% CI	IRR	95% CI	
Men					
65-69	68.7	(49.0, 88.3)	1.0	.	.
70-74	105.5	(84.3, 126.6)	1.5	(1.1,	2.2)
75-79	132.5	(111.1, 153.9)	1.9	(1.4,	2.7)
80-84	161.4	(133.0, 189.8)	2.4	(1.7,	3.3)
85+	180.4	(146.6, 214.2)	2.6	(1.9,	3.7)
Women					
65-69	83.1	(63.3, 102.9)	1.0	.	.
70-74	106.8	(87.2, 126.5)	1.3	(1.0,	1.7)
75-79	128.3	(108.7, 148.0)	1.5	(1.2,	2.0)
80-84	186.8	(166.4, 207.1)	2.2	(1.7,	2.9)
85+	248.0	(227.4, 268.6)	3.0	(2.3,	3.8)

Key: IR: Incidence Rate, Incidence Rate Ratio, CI: Confidence Interval.

Figure 5-9 Incidence rates (IR) for dementia by age & sex. Results are presented as new cases per 1000-person years. Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).



5.5.8 Rates of incident dementia from mild cognitive impairment baseline

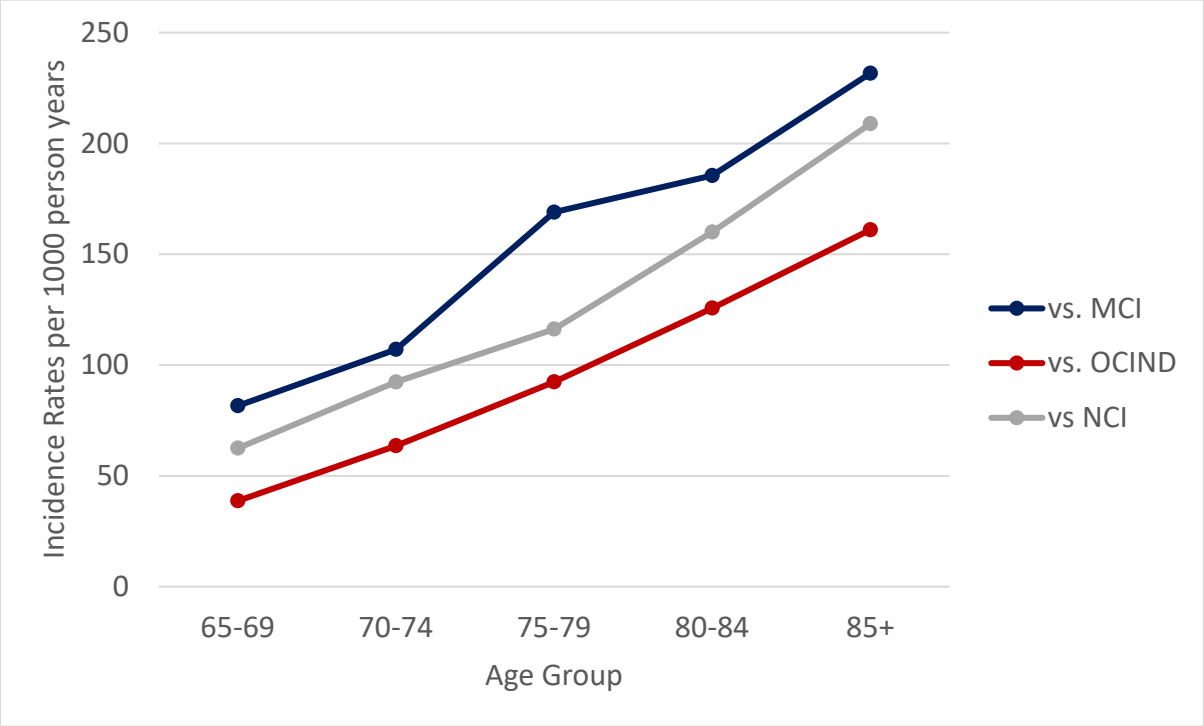
The next phase of the analysis will focus on those cases with cognitive impairment at baseline, categorised as RMCI or OCIND. This was measured by estimating incidence rates of dementia over the 2-years CFAS II follow-up using only RMCI or OCIND populations at baseline (Table 5.14 & Figure 5.10).

Table 5-14: Incidence rates (IR) for incident dementia from baseline RMCI (revised mild cognitive impairment) and OCIND (other cognitive impairment no dementia) by age, sex, geographical location and deprivation (Townsend score). Results are presented as new cases per 1000-person years, effect sizes measured using Incidence Rate Ratio's (IRR). Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).

	vs. MCI						vs. OCIND					
Dementia incidence	IR	95% CI		IRR	95% CI		IR	95% CI		IRR	95% CI	
Overall	152.6	(145.4,	159.8)	1.0	.	.	89.5	(84.3,	94.6)	1.0	.	.
Age Group												
65-69	81.6	(66.6,	96.7)	1.0	.	.	38.7	(30.8,	46.6)			
70-74	107.1	(92.1,	122.0)	1.3	(1.0	1.7	63.6	(53.7,	73.4)	1.6	(1.3,	2.1)
75-79	169.0	(152.0,	186.0)	2.1	(1.7	2.6	92.4	(80.6,	104.1)	2.4	(1.9,	3.0)
80-84	185.5	(168.6,	202.4)	2.3	(1.8	2.8	125.7	(111.8,	139.6)	3.2	(2.6,	4.1)
85+	231.7	(214.8,	248.5)	2.8	(2.3	3.5	161.1	(144.7,	177.4)	4.2	(3.3,	5.2)
Sex												
Male	137.7	(126.0,	149.4)	1.0	.	.	76.4	(68.6,	84.1)	1.0	.	.
Female	162.3	(153.0,	171.6)	1.2	(1.1	1.3	98.9	(91.9,	105.8)	1.3	(1.1,	1.5)
Centre												
Cambridge	175.3	(160.8,	189.7)	1.0	.	.	111.6	(100.5,	122.7)	1.0	.	.
Newcastle	153.6	(141.6,	165.7)	0.9	(0.8	1.0	87.4	(79.0,	95.9)	0.8	(0.7,	0.9)
Nottingham	131.3	(118.5,	144.2)	0.7	(0.7	0.9	74.3	(65.6,	82.9)	0.7	(0.6,	0.8)
Deprivation												
Least	120.6	(108.2,	132.9)	1.0	.	.	64.9	(57.0,	72.8)	1.0	.	.
Moderate	146.2	(134.1,	158.3)	1.2	(1.1	1.4	83.1	(74.7,	91.6)	1.3	(1.1,	1.5)
Most	178.7	(164.9,	192.5)	1.5	(1.3	1.7	114.3	(103.6,	124.9)	1.8	(1.5,	2.1)

Key: RMCI: Revised Mild Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia, IR: Incidence Rate, Incidence Rate Ratio, and CI: Confidence Interval

Figure 5-10 Incidence rates (IR) for incident dementia from baseline MCI (revised mild cognitive impairment) and OCIND (other cognitive impairment no dementia) Results are presented as new cases per 1000-person years Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).



Key: NCI: No Cognitive Impairment, MCI: Revised Mild Cognitive Impairment, OCIND: Other Cognitive Impairment No Dementia, IR: Incidence Rate, Incidence Rate Ratio, and CI: Confidence Interval.

5.5.9 Transition rates from RMCI to dementia

The overall rate of participants transitioning from RMCI to dementia over the 2-years follow up was 152.6 per 1000-person years (95% CI: 145.4, 159.8) (table 5.14 & figure 5.10). Transition to dementia from RMCI showed a linear trend increase with age. (Table 14 & figure 10). Dementia incidence from baseline RMCI cases was found to be higher in women compared to men, however there was only weak evidence for sex differences (IRR: 1.2, 95% CI: 1.1, 1.3) (table 5.14 & figure 5.10). Incidence of dementia is highest in cases of RMCI who were based in Cambridgeshire, incidence was lower in Newcastle and lower again in Nottingham. Results showed evidence for a location effect for Nottingham compared to Cambridge (IRR: 0.7, 95% CI: 0.7, 0.9) but not for Newcastle (table 5.14 & figure 5.10). The analysis showed a deprivation trend in the transition from RMCI to dementia. Rates were higher in both the moderate and most deprived groups, with analysis showing increasing evidence for a deprivation effect on incident dementia from RMCI (IRR: 1.2, 95% CI: 1.1, 1.4; IRR: 1.5, 95% CI:1.3, 1.7) (table 5.14 & figure 5.10).

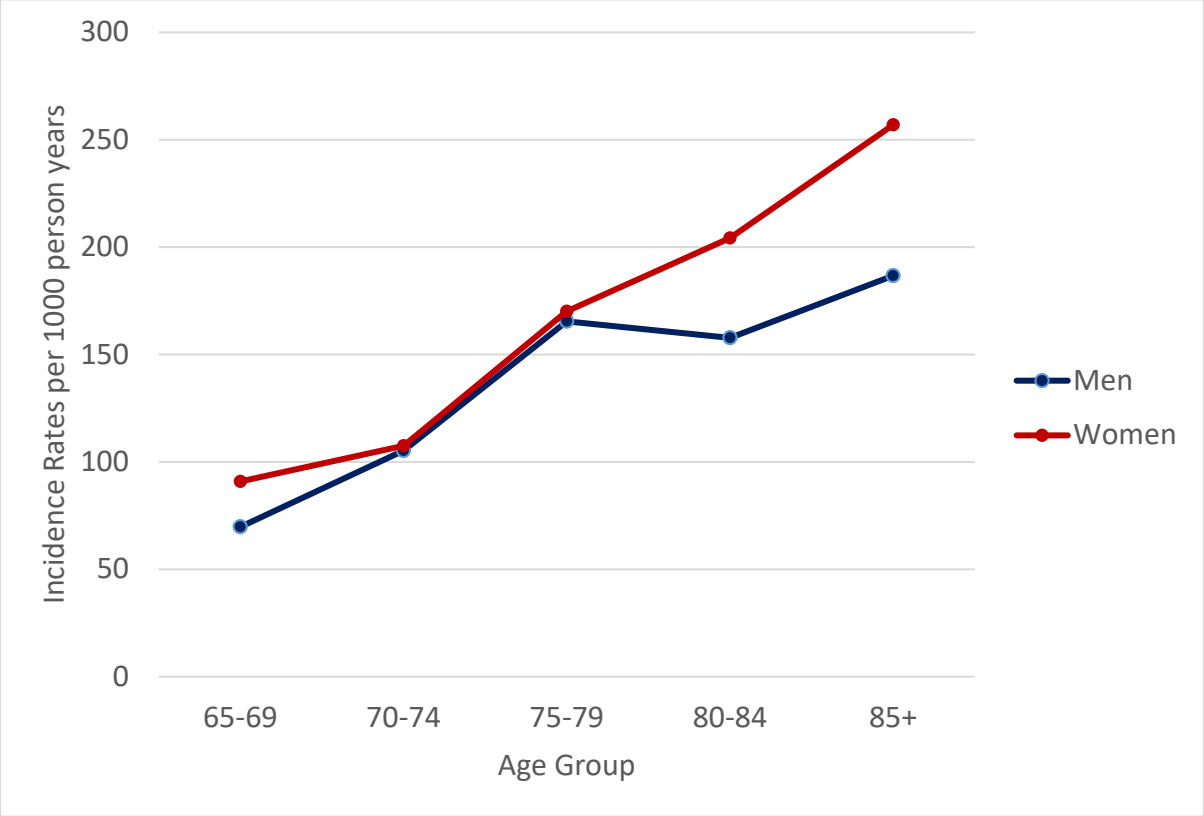
5.5.10 Age and sex specific transition rates from RMCI to dementia

Transition rates to incident dementia from RMCI show a clear trend increasing with age, in both men and women rates are lowest in the youngest age group, although lower in men at this age overall. Rates increase for both sexes and are almost identical at age groups 70-74 and 75-79. The two sexes differ in the oldest age groups, with rates in women increasing more rapidly, while incidence in men decreases initially before increasing to the highest rate in the 85+ group (table 5.15 & figure 5.11).

Table 5-15: Age and sex specific Incidence rates (IR) for incident dementia from baseline RMCI (revised mild cognitive impairment) and OCIND (other cognitive impairment no dementia) by age, sex, geographical location and deprivation (Townsend score). Results are presented as new cases per 1000-person years, effect sizes measured using Incidence Rate Ratio's (IRR). Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).

	vs. RMCI					vs. OCIND				
Dementia Incidence	IR	95% CI		IRR	95% CI	IR	95% CI		IRR	95% CI
Men										
65-69	69.8	(49.9,	89.7)	1.0	. .	33.6	(23.0,	44.3)	1.0	. .
70-74	105.3	(83.6,	127.0)	1.5	(1.1, 2.1)	56.7	(43.5,	69.9)	1.7	(1.1, 2.5)
75-79	165.5	(141.1,	189.8)	2.4	(1.7, 3.3)	90.4	(73.5,	107.3)	2.7	(1.9, 3.9)
80-84	157.8	(130.9,	184.7)	2.3	(1.6, 3.2)	101.4	(80.5,	122.3)	3.0	(2.1, 4.4)
85+	186.7	(153.8,	219.6)	2.7	(1.9, 3.7)	118.3	(91.4,	145.3)	3.5	(2.4, 5.2)
Women										
65-69	90.9	(69.4,	112.5)	1.0	. .	42.9	(31.5,	54.3)	1.0	. .
70-74	107.5	(87.1,	128.0)	1.2	(0.9, 1.6)	68.4	(54.1,	82.7)	1.6	(1.1, 2.2)
75-79	170.1	(147.0,	193.3)	1.9	(1.4, 2.5)	93.3	(77.2,	109.4)	2.2	(1.6, 3.0)
80-84	204.3	(182.8,	225.8)	2.2	(1.7, 2.9)	144.5	(125.7,	163.2)	3.4	(2.5, 4.5)
85+	256.9	(237.8,	276.1)	2.8	(2.2, 3.6)	188.4	(167.5,	209.2)	4.4	(3.3, 5.9)

Figure 5-11: Age and sex specific Incidence rates (IR) for incident dementia from baseline RMCI (revised mild cognitive impairment) and OCIND (other cognitive impairment no dementia) Results are presented as new cases per 1000 person years Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).



5.5.11 Transition rates from OCIND to dementia

The overall rate of participants transitioning from RMCI to dementia over the 2-year CFAS II follow up was IR: 89.5 per 1000-person years (95% CI: 84.3, 94.6) (table 5.14 & figure 5.10).

5.5.12 Transition rates from OCIND to dementia by age

There is a clear exponential trend for transition rates from baseline OCIND to incident dementia as age increases. Transition rates from OCIND were found to be higher in women than in men with evidence of a sex difference (IRR: 1.3 95% CI: 1.1, 1.5) (table 5.14 & figure 5.11).

Similarly, to the analysis of RMCI, transition from OCIND to dementia was highest in Cambridgeshire. Participants who were based in Newcastle (IRR: 0.8, 95% CI: 0.7, 0.9) and Nottingham (IRR: 0.7, 95% CI: 0.6, 0.8) had lower rates of transition,

showing both locations having an effect compared to Cambridge (table 5.14 & figure 5.10).

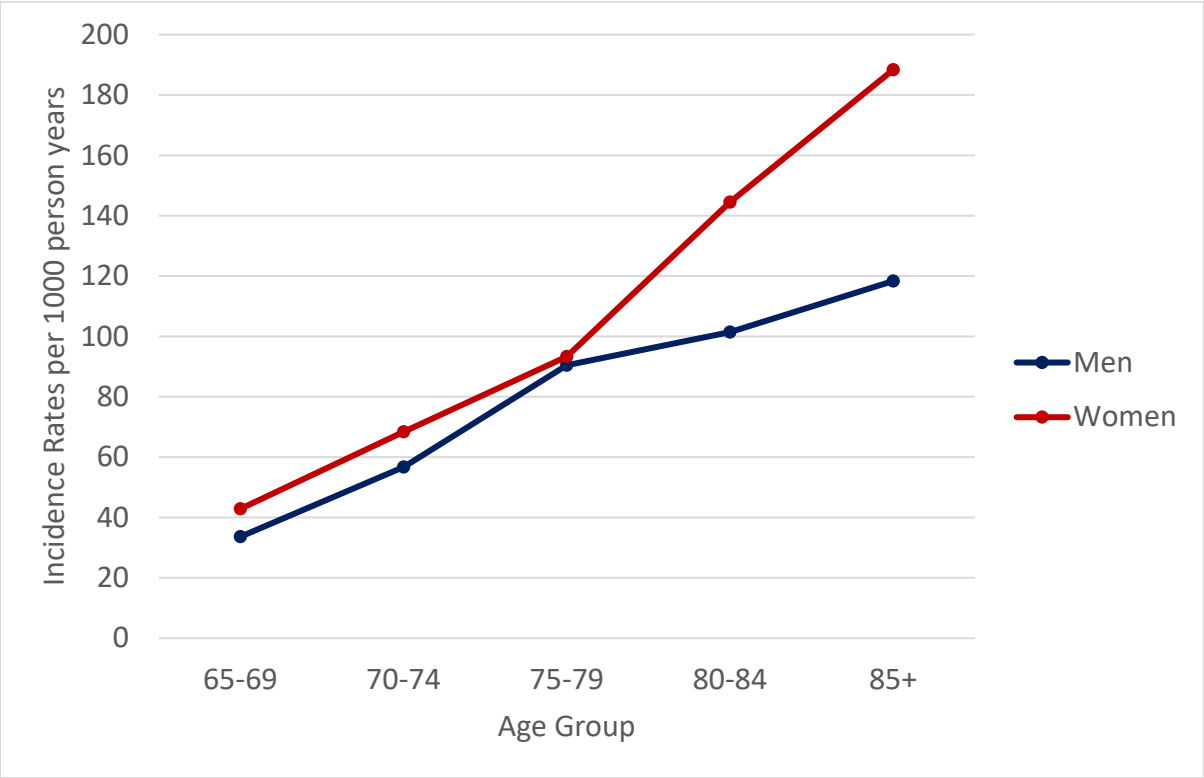
5.5.13 Transition rates from OCIND to dementia by deprivation

There was a deprivation trend associated with higher transition from OCIND. Transition was lowest in the least deprived group and increased in the moderate deprivation group (IRR: 1.3, 95% CI: 1.1, 1.5) and highest in those in the most deprived group (IRR: 1.8, 95% CI: 1.5, 2.1) with increasing evidence of a deprivation effect (table 5.14 & figure 5.11).

5.5.14 Age and sex specific transition rates from OCIND to dementia

Rates of transition show a clear trend increasing with age. Similar to transition from RMCI, rates are lower in men overall, in both sexes rates are lowest in the youngest age groups and like RMCI they converge at age group 75-79. Also like the trend with RMCI, the trends differ in the older groups, with rates in women increasing more rapidly with age in women compared to men (table 5.14 and figure 5.12).

Figure 5-12: Age and sex specific Incidence rates (IR) for incident dementia from baseline OCIND (other cognitive impairment no dementia) Results are presented as new cases per 1000-person years Rates were adjusted for non-response and missing data using inverse probability weighting and multiple imputation (m=20).



5.6 CHAPTER SUMMARY

5.6.1 Incidence Trends

I. In the UK the overall incidence rate for RMCI, is 138.5 per 1000-person years (95% CI: 131.5, 145.5). The incidence rate for OCIND was 233.5 per 1000-person years (95% CI: 228.4, 238.6) and the incidence rate for dementia was 140.6 per 1000-person years (95% CI: 133.8, 147.4).

II. Dementia shows a clear increasing trend with age. This was not observed in the incidence rates for RMCI and OCIND.

III. RMCI and OCIND incidence rates did not differ significantly by gender.

IV. There was a significant geographical difference in incidence rates of dementia and RMCI, with rates being significantly higher in Cambridgeshire than both Newcastle and Nottingham.

V. Incidence of dementia and RMCI was found to be significantly higher in participants with higher levels of deprivation.

5.6.2 Transition rates to dementia

I. Overall the rates of those transitioning to dementia was higher in participants in the RMCI compared to the OCIND group.
II. Risk of transition to dementia from RMCI and OCIND was seen to increase with age
III. Dementia incidence from RMCI and OCIND was significantly higher in women compared to men.
IV. Transition rates were lower in Newcastle and Nottingham compared to Cambridgeshire.
V. Higher levels of deprivation were also found to be a significant factor in increasing the rate of transition from both RMCI and OCIND to dementia.

6 IDENTIFYING RISK FACTORS FOR MILD COGNITIVE IMPAIRMENT (MCI) AND DEMENTIA IN THE POPULATION

Chapter overview

The layout of this chapter closely resembles that of the previous chapter on MCI incidence. Previous chapters have so far discussed the prevalence of cognitive impairment and used cross sectional analysis to highlight the number of cases of cognitive impairment and the proportion of the older aged population these cases make up. Chapter 5 discussed incident cognitive impairment, cases where older people with no cognitive impairment developed impairments over the 2-year follow up, as well as new cases of dementia from those who had MCI at baseline.

This chapter will build on these results exploring both cross sectional and longitudinal analyses and is displayed in three parts.

I. The first part of this chapter will use cross sectional analyses to investigate lifestyle and medical co-morbidities for increased risk of baseline cognitive impairment.
II. The second shall use the wave 2 follow up of CFAS II to investigate these same factors to investigate whether they are associated with increased risk of incident cognitive impairment.
III. Finally, longitudinal analysis will investigate the effect of potential risk factors on the transition from cases of MCI to dementia over the 2 year follow up.

6.1 Introduction

There is abundant evidence from various studies that numerous biological, social and environmental factors are associated with cognitive decline. Many factors such as age, education, poor health, vascular risk factors (VRF) and PD have been strongly associated with dementia (Chen et al., 2009, Vadikolias et al., 2012) (19, 20). A better understanding of these risk factors could allow clinicians to identify those individuals who have been diagnosed with MCI who are more likely to develop dementia (Prince et al., 2016). It is important to highlight that the diagnosis of MCI commonly excludes a large proportion of individuals with comorbid medical and psychiatric health conditions (Collie and Maruff, 2002, Stephan et al., 2011).

There is a growing amount of evidence that VRF such as angina, diabetes, and hypertension are associated with impairments in the early stages of cognitive decline (Stephan et al., 2009). Recently, findings have shown that Type 2 diabetes is

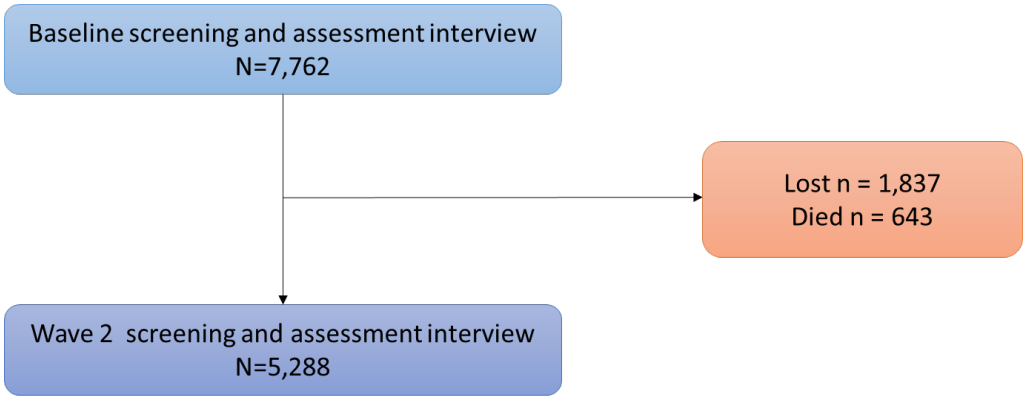
associated with an increased risk of MCI (Ciudin et al., 2017, Luchsinger et al., 2007, Luchsinger et al., 2009, Li et al., 2016). One study however, found no association with MCI but demonstrated that diabetes significantly accelerated the progression of MCI to dementia (Xu et al., 2010a). Cardiovascular disease in particular has consistently been associated with cognitive impairment and dementia (28-30) (Breteler et al., 1994, DeCarli, 2003, Roberts et al., 2010, Roberts et al., 2013). Multiple studies have shown that naMCI occurred more frequently in individuals with cardiovascular disease, particularly in women (Roberts et al., 2013). This finding reinforces the theory that naMCI is more likely to have a vascular aetiology (Luchsinger et al., 2009). Therefore, considering that vascular disease may be a modifiable risk factor, the prevention of vascular disease through life-style interventions and medication may reduce the likelihood of developing naMCI and delay the progression to dementia. Furthermore, findings have shown that individuals with Parkinson's disease (PD) are more susceptible to develop MCI (Roberts et al., 2010). It has also been proposed that individuals with PD who have MCI are more likely to progress to dementia than those with PD who have normal cognition (Roberts et al., 2010, Roberts et al., 2013).

6.2 Methods

6.2.1 CFAS II – Longitudinal sample

As previously detailed in the full methods chapter, CFAS II baseline consisted of a combined screen and assessment interview that was an augmented version on the CFAS I interview. CFAS II baseline consisted of 7,762 individuals over the age of 65 recruited in 2011/2012, subsequently 5,288 of the original sample were followed up 2 years later in 2013/2014. 1837 of the baseline sample did not take part at wave 2 with 643 died between baseline and follow-up (Figure 6.1).

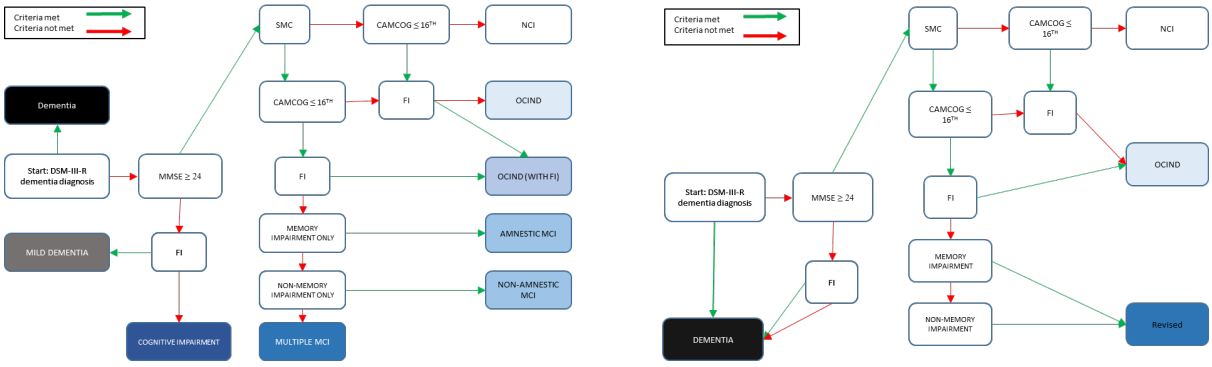
Figure 6-1 CFAS II baseline and wave 2 study design including sample size at each wave and numbers of participants lost and died.



6.2.2 Outcome description

Full details of the cognitive outcomes are described in chapter 4 and chapter 5. Briefly we sought to classify the entire cognitive spectrum of the older population from normal cognition, through mild cognitive impairment to dementia. Those without study diagnosis of dementia were classified: normal cognitive impairment (NCI), RMCI, other cognitive impairment not dementia (OCIND - with and without functional impairment) and dementia group including severe cognitive impairment with and without functional impairment and those with CFAS dementia diagnosis (figure 6.2).

Figure 6-2 diagnostic flow chart showing the diagnosis of cognitive categories used in the baseline analysis of prevalence and the simplified longitudinal categories.



6.2.3 Risk factors

A full description of risk factors investigated is included in chapter 3. In brief, risk factors included socio-demographic factors such as age, sex, deprivation, smoking status, marital status, education and loneliness. Health factors and medical comorbidities were also investigated such as self-reported health, Parkinson's disease, stroke, heart attack, angina, peripheral vascular disease, and diabetes mellitus.

6.2.4 Cross sectional & longitudinal modelling

Modelling for cross sectional risk factors was carried out using binary logistic regression analysis, results presented as odds ratios (OR) with 95% confidence intervals (95% CI). Longitudinal modelling was carried out using Poisson regression modelling using outcome specific person years as the exposure, results are presented as incidence rate ratios (IRR) with 95% CI's. All analysis was inverse probability weighted for non-response and longitudinal attrition. Missing data was also addressed using multiple imputation techniques, for missing data within risk factors and cognitive groups.

6.2.5 Multiple imputation of missing risk factor data

Multiple imputation was again used in response to issues of missing data, risk factor variables in particular had missing data at CFAS II baseline. Multiple imputation models have been previous described in detail in both chapters 3 and 5, briefly however, risk factors were imputed using the same MICE model used for variables in the modelling of incidence. Table 6.1 shows the risk factor variable with imputed data, including loneliness, self-reported health, smoking status, peripheral vascular disease, stroke, Parkinson's disease, Angina, heart attack and diabetes mellitus. Over all 20 data sets were imputed (m=20) for both the cross sectional and longitudinal risk factor analysis.

Table 6-1 Variables with missing data from CFAS II baseline, including the number of observations per imputed dataset (m) with numbers of complete, incomplete and imputed observations.

	Observations per *m*			
CFAS II - Baseline Variables	Complete	Incomplete	Imputed	Total
Loneliness	5228	60	60	5288
Self-reported health	5235	53	53	5288
Smoking status	5217	71	71	5288
Marital status	5276	12	12	5288
Peripheral vascular disease	5221	67	67	5288
Stroke	5220	68	68	5288
Parkinson's disease	5221	67	67	5288
Angina	5221	67	67	5288
Heart Attack	5221	67	67	5288
Diabetes Mellitus	5221	67	67	5288

6.3 Results

6.3.1 Cross sectional risk factors for RMCI, OCIND and dementia

Cross sectional analysis was conducted using binary logistic regression for each outcome of RMCI, OCIND and dementia, where the cognitive impairment was coded to = 1 and no cognitive impairment (NCI) was the referent category coded to = 0. Impairment groups were modelled by age, sex, education, deprivation, smoking status, marital status, loneliness, self-reported health and medical co-morbidities shown in table 6.2. Analysis was undertaken using multiple imputation for missing data and inverse probability weighted for non-response. Cross sectional risk is presented as odds ratios (OR) with accuracy of estimate presented as 95% Confidence Intervals.

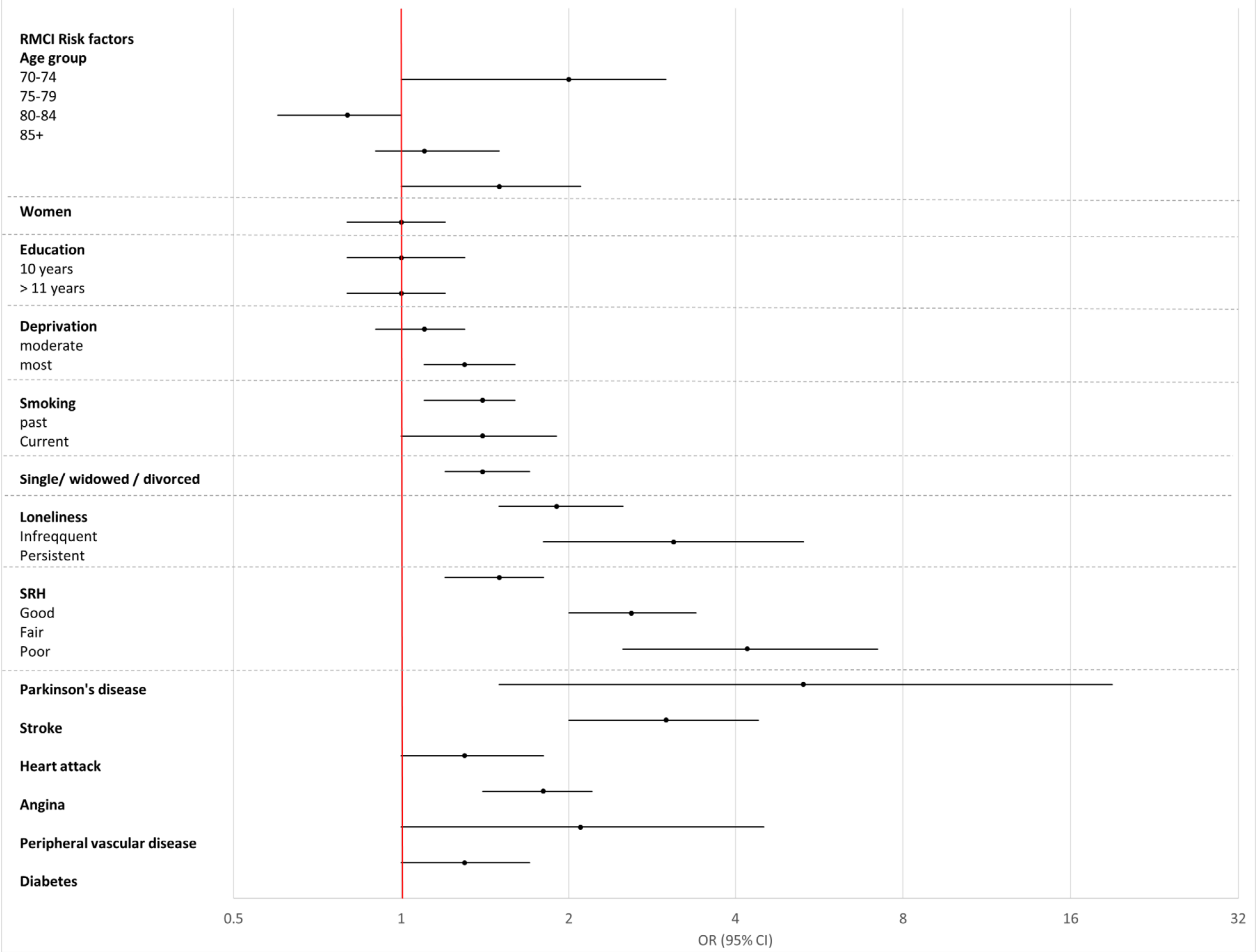
Table 6-2: Results from the cross-sectional analyses of risk factors for revised mild cognitive impairment (RMCI), other cognitive impairment no dementia (OCIND), and dementia. Baseline risk was modelled using logistic regression analysis, results presented as odds ratios (OR) with 95% Confidence intervals (95% CI), adjusted for age and sex. Multiple imputation (m=20) was used to impute missing data and analysis was inverse probability weighted for non-response.

	RMCI			OCIND			Dementia		
Risk factors	OR	95% CI		OR	95% CI		OR	95% CI	
Age Group									
65-69	1.0	.	.	1.0	.	.	1.0	.	.
70-74	1.0	(0.8,	1.3)	0.9	(0.7,	1.0)	1.8	(1.2,	2.6)
75-79	0.8	(0.6,	1.0)	0.8	(0.7,	1.0)	2.8	(1.9,	4.1)
80-84	1.1	(0.9,	1.5	1.0	(0.8,	1.2)	4.6	(3.1,	6.8)
85+	1.5	(1.0,	2.1)	1.5	(1.1,	2.0)	11.1	(7.2,	17.1)
Sex									
Women	1.0	(0.8,	1.2)	1.0	(0.8,	1.1)	1.4	(1.1,	1.7)
Education (years)									
≤ 9	1.0	.	.	1.0	.	.	1.0	.	.
10	1.0	(0.8,	1.3)	1.0	(0.8,	1.2)	0.7	(0.5,	1.0)
≥ 11	1.0	(0.8,	1.2)	1.0	(0.8,	1.3)	0.4	(0.3,	0.5)
Deprivation									
Least	1.0	.	.	1.0	.	.	1.0	.	.
Moderate	1.1	(0.9,	1.3)	1.0	(0.9,	1.2)	1.5	(1.1,	2.0)
Most	1.3	(1.1,	1.6)	1.2	(1.0,	1.5)	2.4	(1.8,	3.1)
Smoking status									
Never smoked	1.0	.	.	1.0	.	.	1.0	.	.
Past smoker	1.4	(1.1,	1.6)	1.2	(1.0,	1.4)	1.5	(1.2,	1.9)
Current smoker	1.4	(1.0,	1.9)	1.4	(1.1,	1.8)	3.4	(2.4,	4.8)
Marital Status									
Married / cohabiting	1.0	.	.	1.0	.	.	1.0	.	.
Single/widowed/ divorced	1.4	(1.2,	1.7)	1.1	(0.9,	1.2)	1.6	(1.2,	2.1)
Loneliness									
Not at all	1.0	.	.	1.0	.	.	1.0	.	.
Infrequent	1.9	(1.5,	2.5)	1.3	(1.0,	1.6)	2.4	(1.7,	3.2)
Frequent/ persistently	3.1	(1.8,	5.3)	1.9	(1.2,	3.2)	4.0	(2.1,	7.6)
Self-reported health									
Excellent	1.0	.	.	1.0	.	.	1.0	.	.
Good	1.5	(1.2,	1.8)	1.3	(1.1,	1.5)	1.4	(1.0,	2.0)
Fair	2.6	(2.0,	3.4)	1.9	(1.6,	2.4)	3.6	(2.5,	5.2)
Poor	4.2	(2.5,	7.2)	3.6	(2.2,	5.8)	13.4	(7.2,	25.0)
Co-morbidities									
Parkinson's	5.3	(1.5,	19.0)	2.1	(0.6,	7.8)	6.6	(1.5,	28.9)
Stroke	3.0	(2.0,	4.4)	2.2	(1.5,	3.2)	6.5	(4.1,	10.4)
Heart attack	1.3	(1.0,	1.8)	1.1	(0.9,	1.4)	1.3	(0.9,	1.9)
Angina	1.8	(1.4,	2.2)	1.4	(1.2,	1.8)	1.2	(0.8,	1.7)
Peripheral vascular disease	2.1	(1.0,	4.5)	1.6	(0.8,	3.3)	2.1	(0.7,	5.8)
Diabetes	1.3	(1.0,	1.7)	1.2	(1.0,	1.5)	1.4	(1.0,	2.0)

6.3.2 Cross-sectional risk factors for RMCI

The following section describes the results of cross-sectional analysis for risk factors for RMCI.

Figure 6-3: Results of cross-sectional logistic regression analysis of risk factors for revised mild cognitive impairment (RMCI) including age, sex, education, deprivation smoking status, marital status, self-reported health (SRH), Parkinson's disease, stroke, heart attack, angina, peripheral vascular disease and diabetes. Results presented as odds ratios (OR) with 95% confidence intervals (95% CI) and adjusted for age and sex. Missing data was accounted for via multiple imputation (m=20) and inverse probability weighted for non-response and longitudinal attrition.



6.3.2.1 Age, sex and education

There was no association between age and baseline RMCI in the first 4 age groups including those aged 70-74 (OR: 1.0, 95% CI: 0.8, 1.3), 75-79 (OR: 0.8, 95% CI: 0.6, 1.0) and aged 80-84 (OR: 1.1, 95% CI: 0.9, 1.5). Participants who were aged over 85 were at increased risk of baseline RMCI (OR: 1.5, 95% CI: 1.0, 2.1) (table 2 and figure 3). Although OR's and 95% CI's show weak associations with age, overall

there is an interesting trend with risk appearing to decrease from a high point in the youngest group before falling rapidly and gradually increasing again (figure 6.3).

There was no significant association between sex and increased risk of baseline RMCI (OR: 1.0, 95% CI: 0.8, 1.2) (table 6.2 & figure 6.3). Education was measured in three groups, there were no associations found between education and risk of baseline RMCI for those with 10 years (OR: 1.0, 95% CI: 0.8, 1.3) or ≥ 11 years full time education (1.0, 95% CI: 0.8, 1.2) (table 6.2 and figure 6.3).

6.3.2.2 Deprivation, smoking, marital status and loneliness

There appears to be trend for increasing risk for RMCI as deprivation increases, there is a relatively weak association attributed to moderate deprivation levels (OR: 1.1, 95% CI: 0.9, 1.3) (table 2 and figure 3), there is more evidence for those who were in the most deprived group (OR: 1.3, 95% CI: 1.1, 1.6) (table 6.2 & figure 6.3). CFAS II participants who are either past or current smokers both showed an increased risk of baseline RMCI, although both categories showed similar odds, 95% CI's showed stronger evidence of increased risk in past smokers (OR: 1.4, 95% CI: 1.1, 1.6; versus OR: 1.4, 9%% CI: 1.0, 1.9) (table 6.2 and figure 6.3). Marital status was shown to be a significant risk factor for baseline RMCI, individuals who are single, widowed or divorced were at higher risk compared to those who are either married or cohabiting (OR: 1.4, 95% CI: 1.2, 1.7) (table 6.2 and figure 6.3). A clear trend can be seen as feelings of loneliness increase risk of RMCI at baseline increases (figure 6.3), participants who responded to feeling infrequent loneliness risk was increased by a factor of OR: 1.9 (95% CI: 1.5, 2.5) compared to those who responded by not feeling lonely at all. Feelings of frequent or persistent loneliness showed an even higher increase in risk (OR: 3.1, 95% CI: 1.8, 5.3) (table 6.2).

6.3.2.3 Self-reported health (SRH) & medical co-morbidities

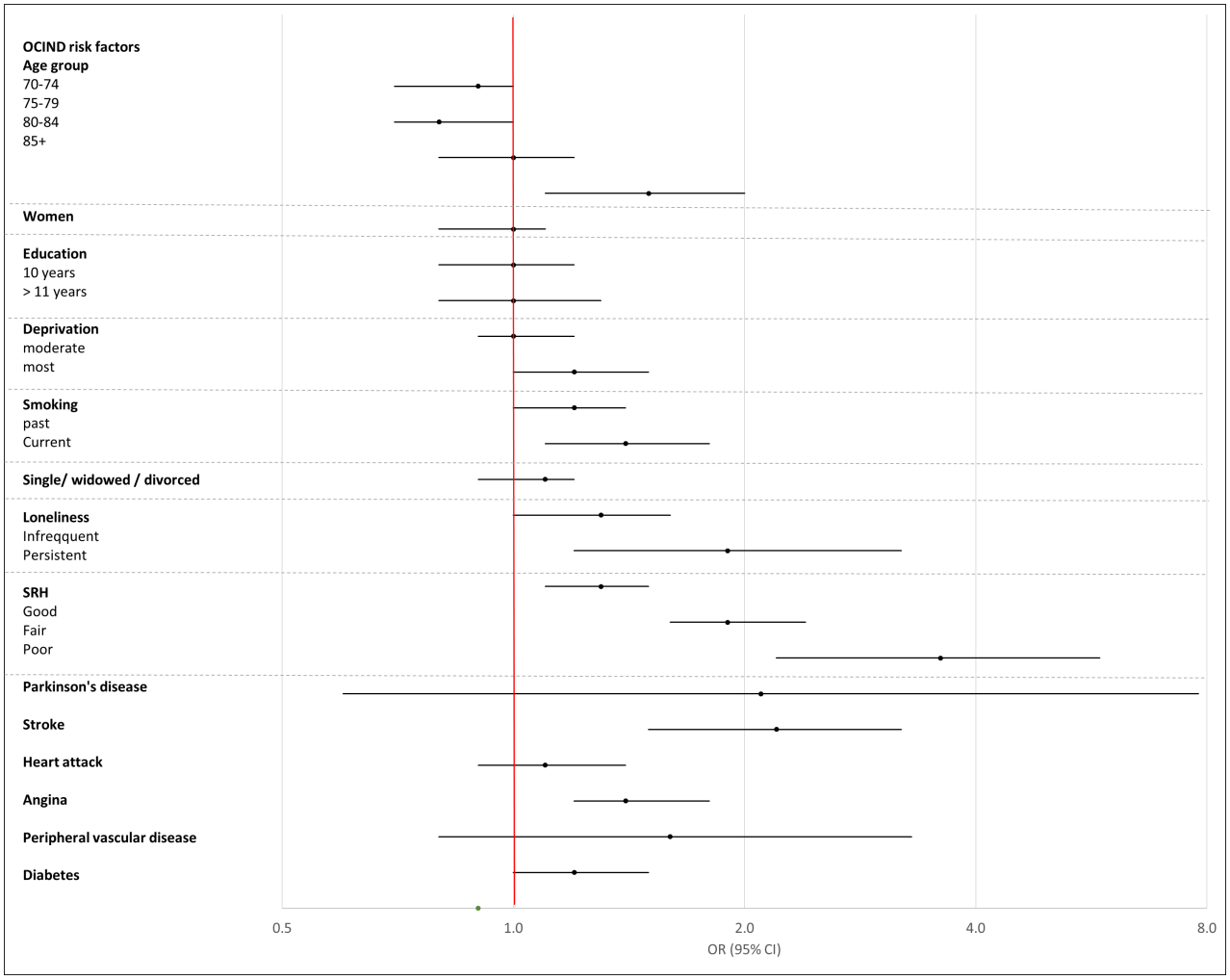
SRH was strongly associated with increased risk of baseline RMCI. Figure 6.3 shows a strong trend, good SRH showed higher risk than those who reported excellent SRH (OR: 1.5, 95% CI: 1.2, 1.8), risk increased again for those who reported fair (OR: 2.6, 95% CI: 2.0, 3.4) and poor SRH showed a very association with RMCI (OR: 4.2, 95% CI: 2.5, 7.2) (table 6.2 and figure 6.3).

All the medical co-morbidities measured showed an increased risk of RMCI with differing amounts of evidence (figure 6.3). Parkinson's disease showed the biggest effect size for increased risk of RMCI at baseline, wide 95% CI's should be considered (OR: 5.3, 95% CI: 1.5, 19.0), stroke (OR: 3.0, 95% CI: 2.0, 4.4) and peripheral vascular disease (OR: 2.1, 95% CI: 1.0, 4.5) was strongly associated with baseline RMCI. Heart attack (OR: 1.3, 95% CI: 1.0, 1.8) and diabetes (OR: 1.3, 95% CI: 1.0, 1.7) showed increased risk to a smaller degree (table 6.2 & figure 6.3).

6.3.3 Cross sectional risk factors for OCIND

The following section describes the results of cross-sectional analysis for risk factors for OCIND.

Figure 6-4: Results of cross-sectional logistic regression analysis of risk factors for other cognitive impairment no dementia (OCIND) including age, sex, education, deprivation smoking status, marital status, self-reported health (SRH), Parkinson's disease, stroke, heart attack, angina, peripheral vascular disease and diabetes. Results presented as odds ratios (OR) with 95% confidence intervals (95% CI) and adjusted for age and sex. Missing data was accounted for via multiple imputation (m=20) and inverse probability weighted for non-response and longitudinal attrition.



6.3.3.1 Age, sex and education

The effect of age on risk of OCIND (figure 6.4) was similar to that seen in RMCI, again risk decreases with age initially, falling to its lowest in the 75-79 age group, before gradually increasing again as age increases with those in the 85+ age group being most at risk overall (OR: 1.5, 95% CI: 1.1, 2.0) (table 2). The risk of OCIND was similar for both men and women in CFAS II (OR: 1.0, 95% CI: 0.8, 1.1) (table 6.2 & figure 6.4). Trends with education again appear to be similar to those seen with baseline RMCI, there was no change in risk for those with 10 years (OR: 1.0, 95%

CI: 0.8, 1.2) or ≥ 11 years of education (OR: 1.0, 95% CI: 0.8, 1.3) (table 6.2 and figure 6.4).

6.3.3.2 Deprivation, smoking, marital status and loneliness

A trend in increasing risk of OCIND and deprivation is not as clear as previously seen in RMCI. There was no association found between being in the moderately deprived group (OR: 1.0 , 95% CI: 0.9, 1.2), but there was a weak association between being in the most deprived group and baseline OCIND (OR: 1.2, 95% CI: 1.0, 1.5) (table 6.2 and figure 6.4). When compared to participants who had never smoked, there was a small increased risk in past smokers (OR: 1.2, 95% CI: 1.0, 1.4), current smokers there was a stronger effect on risk of baseline OCIND (OR: 1.4, 95% CI: 1.1, 1.8). (Table 6.2 and figure 6.4). There was no cross-sectional relationship between marital status and risk of OCIND. Single, widowed or divorced participants showed a very weak effect and little evidence for a marital status effect on OCIND risk (OR: 1.1, 95% CI: 0.9, 1.2) (table 6.2 and figure 6.4).

The results of the analysis of loneliness are again similar in OCIND compared to RMCI, there is a clear association between risk of OCIND and loneliness. Results show a gradual increase in risk for both infrequent feelings of loneliness (OR: 1.3, 95% CI: 1.0, 1.6) as well as strong evidence of increased risk for those who reported frequent / persistent feelings of loneliness (OR: 1.9, 95% CI: 1.2, 3.2) (table 6.2 and figure 6.4).

6.3.3.3 Self-Reported Health (SRH) & medical co-morbidities

Worsening self-reported health was associated with increased risk of baseline OCIND. There was some evidence of an increased risk for those who reported good self-perceived health (compared with excellent) (OR: 1.3, 95% CI: 1.1, 1.5) participants who reported fair self-perceived health (OR: 1.9, 95% CI: 1.6, 2.4) and poor self-perceived health was strongly associated with baseline OCIND (OR: 3.6, 95% CI: 2.2, 5.8) (table 6.2 and figure 6.4) with a clear increasing trend across categories.

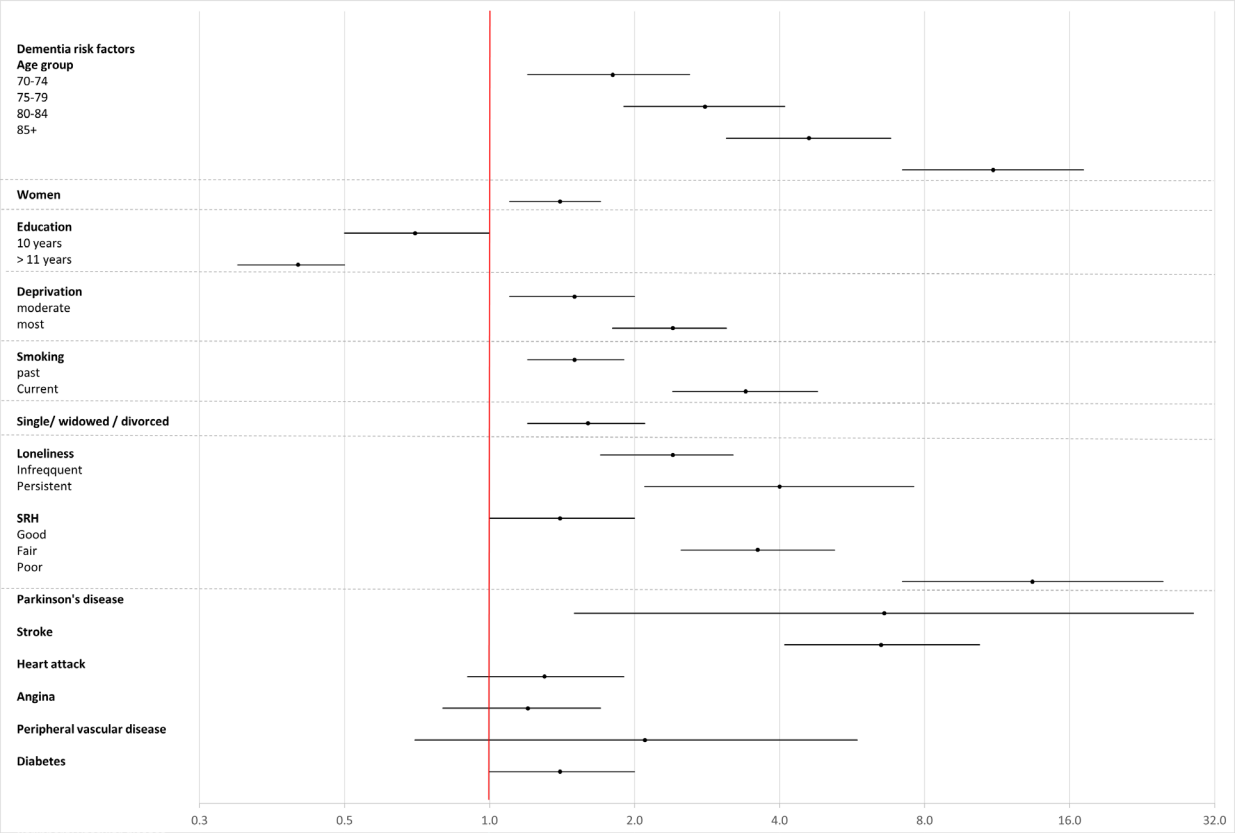
Two of the medical co-morbidities were found to be significantly associated with a higher risk baseline OCIND were strokes (OR: 2.2, 95% CI: 1.5, 3.2) and angina (OR: 1.4, 95% CI: 1.2, 1.8). All other conditions also showed an increased odds of

baseline OCIND, however 95% CI were often wide, Parkinson's disease (OR: 2.1, 95% CI: 0.6, 7.8), peripheral vascular disease (OR: 1.6, 95% CI: 0.8, 3.3), or the effect was a fairly small heart attack (OR: 1.1, 95% CI: 0.9, 1.4), and diabetes mellitus (OR: 1.2, 95% CI: 1.0, 1.5) (table 6.2 and figure 6.4).

6.3.4 Cross sectional risk factors for dementia

The following section describes the results of cross-sectional analysis for risk factors for dementia.

Figure 6-5: Results of cross-sectional logistic regression analysis of risk factors for dementia including age, sex, education, deprivation smoking status, marital status, and self-reported health (SRH), Parkinson's disease, stroke, heart attack, angina, peripheral vascular disease and diabetes. Results presented as odds ratios (OR) with 95% confidence intervals (95% CI) and adjusted for age and sex. Missing data was accounted for via multiple imputation (m=20) and inverse probability weighted for non-response and longitudinal attrition.



6.3.4.1 Age, sex and education

Increased age was associated with an increased risk of dementia, showing and exponential trend across all five age bands, risk of baseline dementia was lowest compared to the youngest group in those aged 70-74 (OR: 1.8, 95% CI: 1.2, 2.6), increasing in the 75-79 group (OR: 2.8, 95% CI: 1.9, 4.1), in the 80-84 group (OR:

4.6, 95% CI: 3.1, 6.8) and highest in the 85+ group (OR: 11.1, 95% CI: 7.2, 17.1) (table 6.2 and figure 6.5). There were significant sex differences seen in the cross-sectional analysis of dementia with women found to be at a slightly increased risk of baseline dementia (OR: 1.4, 95% CI: 1.1, 1.7) (table 2 and figure 5).

Overall there is a strong trend for more years of full-time education and reduced dementia risk, odds were reduced in those with 10 years of education (OR: 0.7, 95% CI: 0.5, 1.0). There was a strongly reduced risk of baseline dementia in those who have 11 or more years of education (OR: 0.4, 95% CI: 0.3, 0.5). (Table 2 and figure 5).

6.3.4.2 Deprivation, smoking, marital status and loneliness

Deprivation was significantly associated with increased risk of baseline dementia. Figure 6.5 shows a clear trend for increasing dementia risk in both the moderate deprivation (OR: 1.5, 95% CI: 1.1, 2.0) and most deprivation groups (OR: 2.4, 95% CI: 1.8, 3.1) (table 6.2). Smoking is strongly associated with baseline dementia risk. Although current smokers were found to be the most at-risk group (OR: 3.4, 95% CI: 2.4, 4.8), past smokers were also at a higher risk then those who are in the never smoked category (OR: 1.5, 95% CI: 1.2, 1.9) (table 6.2 and figure 6.5).

Marital status was significantly associated with dementia, those who are single, widowed or divorced were at a significantly higher risk of baseline dementia than those married or cohabiting (OR: 1.6, 95% CI: 1.2, 2.1) (table 2 and figure 5). CFAS II participants who reported feelings of infrequent loneliness (OR: 2.4, 95% CI: 1.7, 3.2) and frequent / persistent loneliness (OR: 4.0, 95% CI: 2.1, 7.6) were strongly associated with increased risk of baseline dementia (table 6.2 and figure 6.5).

6.3.4.3 Self-reported health (SRH) & medical co-morbidities

Participants who reported having good self-perceived health resulted in increased odds of baseline dementia (OR: 1.4, 95% CI: 1.0, 2.0), those who reported fair self-perceived health (OR: 3.6, 955% CI: 2.5, 5.2) and poor self-perceived health (OR: 13.4, 95% CI: 7.2, 25.0) showed a strong significant association with increased risk of baseline dementia. These results show a clear trend for increased risk of dementia and more frequent feelings of loneliness (table 6.2 and figure 6.5).

In the analysis of medical comorbidity risk factors for baseline dementia only two were found to have a strong effect to increase risk including Parkinson's disease (OR: 6.6, 95% CI: 1.5, 28.9) and stroke (OR: 6.5, 4.1, 10.4) (table 6.2 and figure 6.5). Further conditions showed evidence of a strong effect size such as peripheral vascular disease (OR: 2.1, 95% CI: 0.7, 5.8) and diabetes mellitus (OR: 1.4, 95% CI: 1.0, 2.0) (table 6.2 and figure 6.5) which also reported wide confidence intervals or they reported relatively weak effects like heart attack (OR: 1.3, 95% CI: 0.9, 1.9) and angina (OR: 1.2, 95% CI: 0.8, 1.7) (table 6.2 and figure 6.5).

6.3.5 Longitudinal risk factors for RMCI, OCIND and dementia

Longitudinal analysis was conducted using Poisson regression for each outcome of RMCI, OCIND and dementia where the cognitive impairment was coded to = 1 and no cognitive impairment (NCI) was the referent category coded to = 0. Impairment groups were modelled by age, sex, education, deprivation, smoking status, marital status, loneliness, self-reported health and medical co-morbidities shown in table 3. Analysis was undertaken using multiple imputation for missing data and inverse probability weighted for non-response, longitudinal attrition and death. Longitudinal risk is presented as incidence rate ratios (IRR) with accuracy of estimate presented as 95% Confidence Intervals.

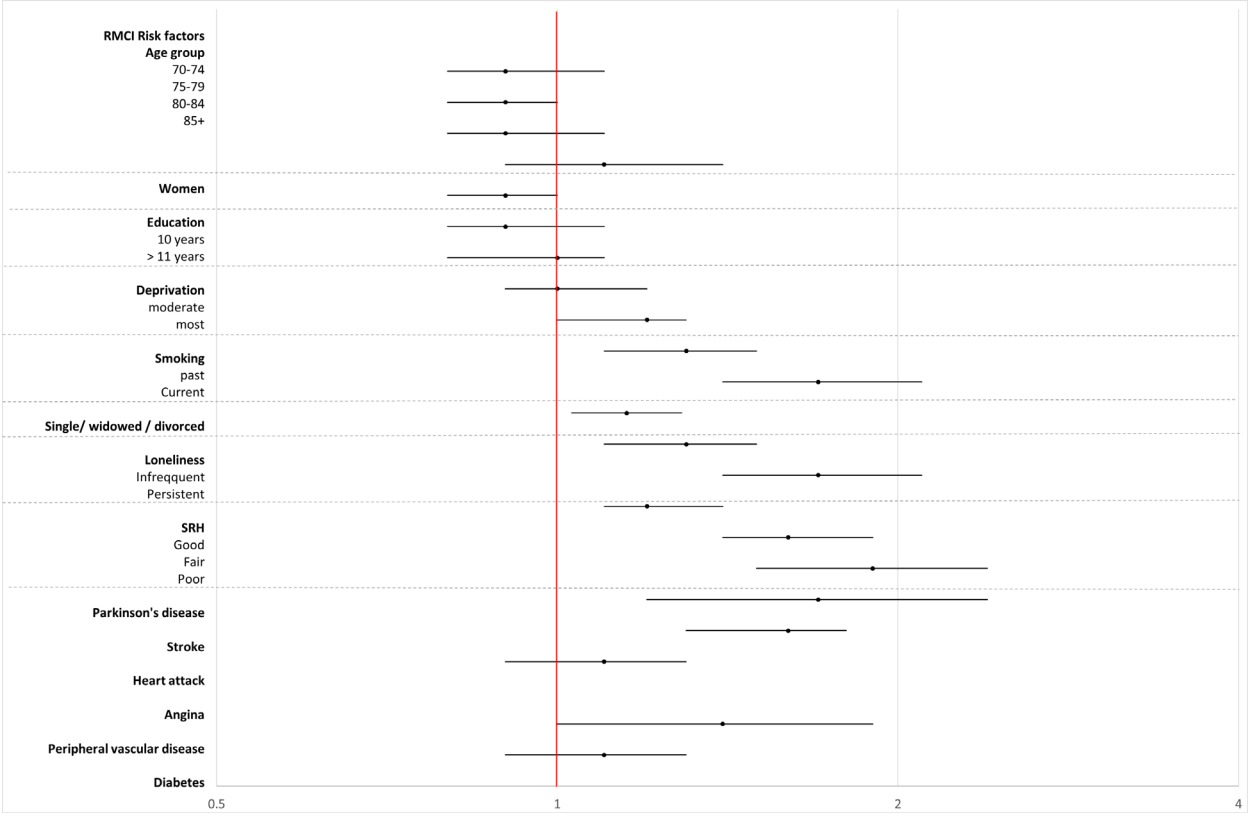
Table 6-3 Results from the longitudinal analyses of risk factors for revised mild cognitive impairment (RMCI), other cognitive impairment no dementia (OCIND), and dementia. Risk was modelled using Poisson regression analysis, results presented as incidence rate ratios (IRR) with 95% Confidence intervals (95% CI), adjusted for age and sex. Multiple imputation (m=20) was used to impute missing data and analysis was inverse probability weighted for non-response.

	RMCI			OCIND			Severe CI / dementia		
Risk factors	IRR	95% CI		IRR	95% CI		IRR	95% CI	
Age Group									
65-69	1.0	.	.	1.0	.	.	1.0	.	.
70-74	0.9	(0.8,	1.1)	1.0	(0.9,	1.0)	1.4	(1.1,	1.7)
75-79	0.9	(0.8,	1.0)	1.0	(0.9,	1.0)	1.8	(1.4,	2.3)
80-84	0.9	(0.8,	1.1)	1.0	(0.9,	1.0)	2.5	(2.0,	3.0)
85+	1.1	(0.9,	1.4)	1.1	(1.0,	1.2)	3.2	(2.6,	4.0)
Sex									
Women	0.9	(0.8,	1.0)	1.0	(0.9,	1.0)	1.1	(1.0,	1.3)
Education (years)									
≤ 9	1.0	.	.	1.0	.	.	1.0	.	.
10	0.9	(0.8,	1.1)	1.0	(0.9,	1.1)	0.9	(0.8,	1.0)
≥ 11	1.0	(0.8,	1.1)	1.0	(1.0,	1.1)	0.7	(0.6,	0.8)
Deprivation									
Least	1.0	.	.	1.0	.	.	1.0	.	.
Moderate	1.0	(0.9,	1.2)	1.0	(0.9,	1.1)	1.2	(1.1,	1.4)
Most	1.2	(1.0,	1.3)	1.0	(1.0,	1.1)	1.6	(1.4,	1.8)
Loneliness					,				
Not at all	1.0	.	.	1.0	.	.	1.0	.	.
Infrequent	1.3	(1.1,	1.5)	1.0	(1.0,	1.1)	1.4	(1.2,	1.5)
Frequent/ persistently	1.7	(1.4,	2.1)	1.2	(1.1,	1.3)	1.6	(1.4,	1.9)
Self-reported health									
Excellent	1.0	.	.	1.0	.	.	1.0	.	.
Good	1.2	(1.1,	1.4)	1.1	(1.0,	1.1)	1.3	(1.1,	1.6)
Fair	1.6	(1.4,	1.9)	1.2	(1.2,	1.3)	2.0	(1.6,	2.3)
Poor	1.9	(1.5,	2.4)	1.4	(1.3,	1.5)	2.7	(2.2,	3.3)
Co-morbidities									
Parkinson's	1.7	(1.2,	2.4)	1.2	(1.0,	1.5)	1.8	(1.4,	2.3)
Stroke	1.6	(1.3,	1.8)	1.2	(1.1,	1.3)	1.8	(1.6,	2.0)
Heart attack	1.1	(0.9,	1.3)	1.1	(1.0,	1.1)	1.2	(1.0,	1.3)
Angina	1.3	(1.2,	1.5)	1.1	(1.0,	1.2)	1.2	(1.0,	1.3)
Peripheral vascular disease	1.4	(1.0,	1.9)	1.0	(0.9,	1.3)	1.3	(0.9,	2.0)
Diabetes	1.1	(0.9,	1.3)	1.1	(1.0,	1.2)	1.3	(1.1,	1.4)

6.3.6 Longitudinal risk factors for incident RMCI

The following section describes the results of longitudinal analysis for risk factors for RMCI.

Figure 6-6: Results of longitudinal Poisson regression analysis of risk factors for revised mild cognitive impairment (RMCI) including age, sex, education, deprivation smoking status, marital status, self-reported health (SRH), Parkinson's disease, stroke, heart attack, angina, peripheral vascular disease and diabetes. Results presented as odds ratios (OR) with 95% confidence intervals (95% CI) and adjusted for age and sex. Missing data was accounted for via multiple imputation (m=20) and inverse probability weighted for non-response and longitudinal attrition.



6.3.6.1 Age, sex and education

Compared to cross-sectional results, longitudinally there was no increased risk of RMCI with age at each age group including, 65-69 (IRR: 0.9, 95% CI: 0.8, 1.1), 70-74 (IRR: 0.9, 95% CI: 0.8, 1.0), 75-79 (IRR: 0.9, 95% CI: 0.8, 1.1) and those aged over 85 years (IRR: 1.1, 95% CI: 0.9, 1.4) (table 6.3 and figure 6.6).

Risk for RMCI was similar for both men and women (IRR: 0.9, 95% CI: 0.8, 1.0) (table 6.3 and figure 6.6). There were also no longitudinal associations found

between risk of incident RMCI and years of full-time education, in participants with 10 years (IRR: 0.9, 95% CI: 0.8, 1.1) and 11 or more years of education (IRR: 1.0, 95% CI: 0.8, 1.1) (table 6.3 and figure 6.6).

6.3.6.2 Deprivation, smoking, marital status and loneliness

Compared to cross-sectional analysis there is less evidence of deprivation trend for risk of longitudinal RMCI. There was no association for those in the moderate deprivation group (IRR: 1.0, 95% CI: 0.9, 1.2), but there was slightly increased risk in the most deprivation group (IRR: 1.2, 95% CI: 1.0, 1.3) (table 6.3 and figure 6.6). Longitudinally smoking was found to be associated with risk for RMCI risk, current smokers were found to be significantly more at risk of developing RMCI over 2 years, past smokers also showed a higher but with a slightly reduced effect size (IRR: 1.3, 95% CI: 1.1, 1.5 & IRR: 1.2, 95% CI: 1.0, 1.30 (table 6.3 and figure 6.6).

Participants at baseline who were single, widowed or divorced showed a weak association with increased risk of RMCI compared to those who were married or cohabiting (IRR: 1.2, 95% CI: 1.0, 1.3) (table 6.3 and figure 6.6). Similarly, to trends seen at baseline, there is a longitudinal trend for increased risk of incident RMCI found in participants who reported infrequent feelings of loneliness (IRR: 1.3, 95% CI: 1.1, 1.5) and those who reported frequent/ persistent feelings of loneliness (IRR: 1.7, 95% CI: 1.4, 2.1) (table 6.3 and figure 6.6).

6.3.6.3 Self-reported health (SRH) and medical co-morbidity

Self-reported health was found to be significantly associated with an increased risk of incident RMCI. Risk of incident RMCI was higher in those who reported good self-perceived health (IRR: 1.2, 95% CI: 1.1, 1.4), fair self-perceived health (IRR: 1.6, 95% CI: 1.4, 1.9) and poor self-perceived health (IRR: 1.9, 95% CI: 1.5, 2.4) (table 6.3 and figure 6.6). Again, with a strong trend.

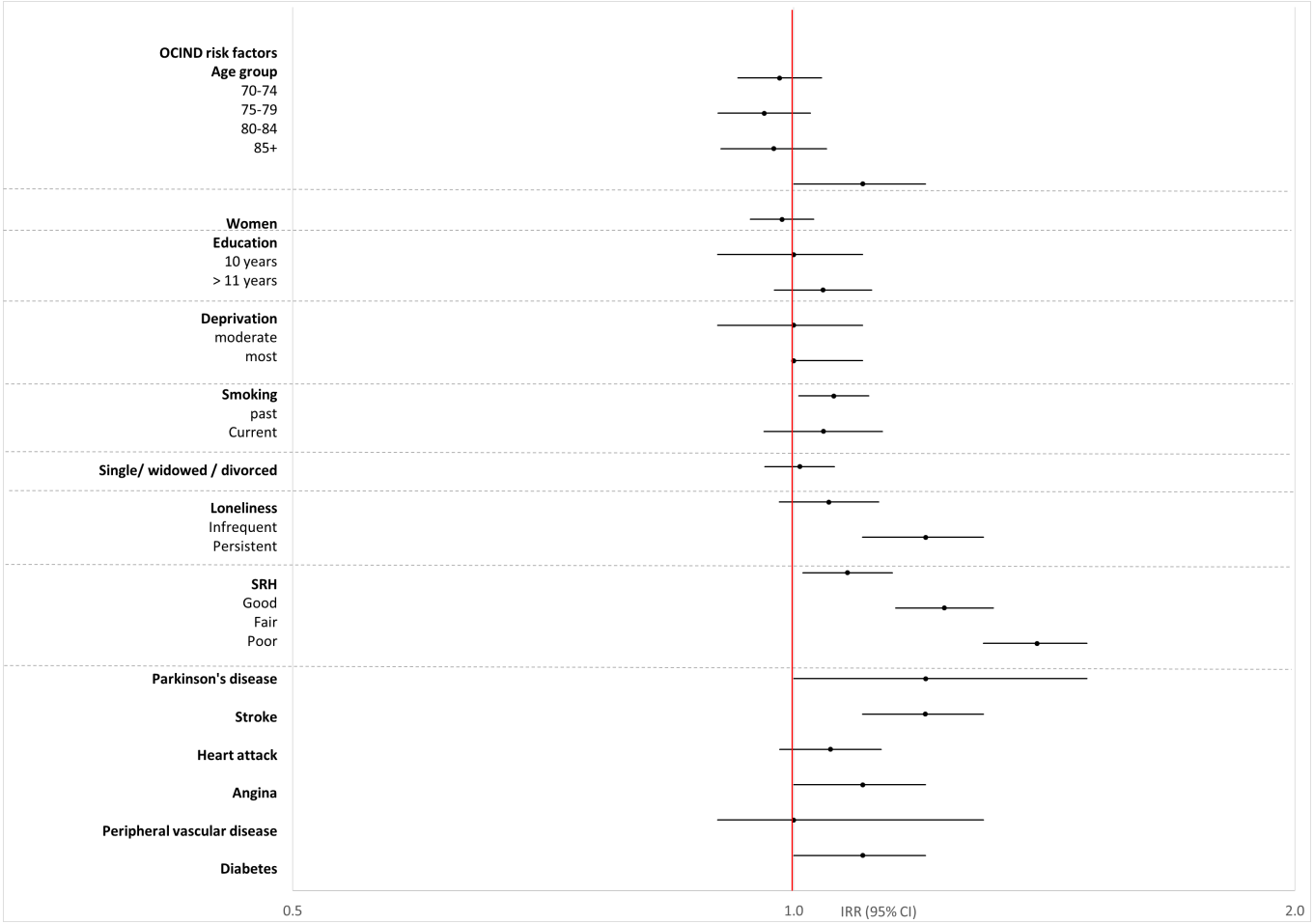
There is strong evidence for several co-morbidities being associated with increased incidence of RMCI such as Parkinson's disease (IRR: 1.7, 95% CI: 1.2, 2.4), stroke (IRR: 1.6, 95% CI: 1.3, 1.8), peripheral vascular disease (IRR: 1.4, 95% CI: 1.0, 1.9) and angina (IRR: 1.3, 95% CI: 1.2, 1.5) (table 6.3 and figure 6.6). A number of other conditions showed increased odds ratios, with much weaker effect sizes, including

heart attack (IRR: 1.1, 95% CI: 0.9, 1.3) and diabetes mellitus (IRR: 1.1, 95% CI: 0.9, 1.3) (table 6.3 and figure 6.6).

6.3.7 Longitudinal risk factors for incident OCIND

The following section describes the results of longitudinal analysis for risk factors for OCIND.

Figure 6-7: Results of longitudinal poisson regression analysis of risk factors for other cognitive impairment no dementia (OCIND) including age, sex, education, deprivation smoking status, marital status, self-reported health (SRH), Parkinson's disease, stroke, heart attack, angina, peripheral vascular disease and diabetes. Results presented as odds ratios (OR) with 95% confidence intervals (95% CI) and adjusted for age and sex. Missing data was accounted for via multiple imputation (m=20) and inverse probability weighted for non-response and longitudinal attrition.



6.3.7.1 Age, sex and education

There were no significant associations between incident OCIND and increasing age groups compared to the youngest including, those aged 70-74 (IRR: 1.0, 95% CI: 0.9, 1.0), 75-79 (IRR: 1.0, 95% CI: 0.9, 1.0), 80-84 (IRR: 1.0, 95% CI: 0.9, 1.0).

Those who were in the over 85 age group showed a relatively higher risk for incident OCIND, although the effect size is very small (IRR: 1.1, 95% CI: 1.0, 1.2) (table 6.3 and figure 6.7). There was no significant difference found between men and women for increased risk of incident OCIND (IRR: 1.0, 95% CI: 0.9, 1.0) (table 6.3 and figure 6.7). There was no trend found between education and risk of incident OCIND, for either participants with 10 years of full-time education (IRR: 1.0, 95% CI: 0.9, 1.1) or with 11 or more years in full time education (IRR: 1.0, 95% CI: 1.0, 1.1) (table 6.3 and figure 6.7).

6.3.7.2 Deprivation, smoking, marital status and loneliness

Neither moderate (IRR: 1.0, 95% CI: 0.9, 1.1) or the most deprived (IRR: 1.0, 95% CI: 1.0, 1.1) were found to be significantly associated with increased risk of incident OCIND (table 6.3 and figure 6.7). There were no longitudinal associations found between smoking status and incident OCIND risk, neither for those who are past smokers (IRRR: 1.1, 95% CI: 1.0, 1.1) or current smokers (IRR: 1.0, 95% CI: 1.0, 1.1) (table 6.3 and figure 6.7). Participants at baseline who are single, widowed or divorced were not found to be at any increased risk of incident OCIND than those who are married or cohabiting (IRR: 1.0, 95% CI: 1.0, 1.1) (table 6.3 and figure 6.7).

The analysis of loneliness showed a trend with more frequent feelings of loneliness, albeit a weak one. Infrequent feelings of loneliness were not found to be associated with increased risk of incident OCIND (IRR: 1.0, 95% CI: 1.0, 1.1) while those who reported feelings of frequent/ persistent loneliness were associated with increased risk (IRR: 1.2, 95% CI: 1.1, 1.3) (table 6.3 and figure 6.7).

6.3.7.3 Self-reported health (SRH) and medical co-morbidities

There was a trend for worsening self-perceived health and risk for incident OCIND, as with the cross-sectional analysis there is a gradually increasing effect size. Reporting good self-perceived health did not show a significant association (IRR: 1.1, 95% CI: 1.0, 1.1), whereas fair self-perceived health was a significant result (IRR: 1.2, 9%% CI: 1.2, 1.3), as was poor self-perceived health (IRR: 1.4, 95% CI: 1.3, 1.5) (table 6.3 and figure 6.7).

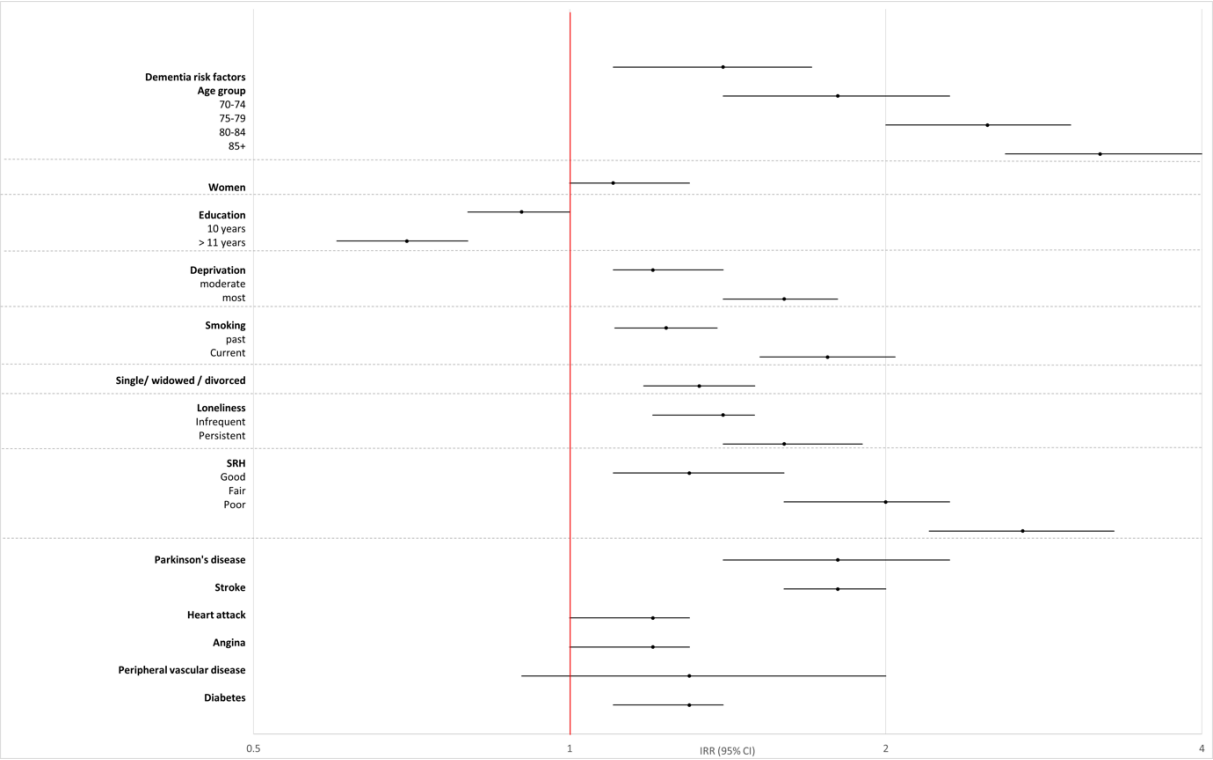
6.3.7.4 Medical co-morbidities

There is much less evidence for increased risk of OCIND and medical comorbidities. There were only two conditioned which showed an increased risk including stroke (IRR: 1.2, 95% CI: 1.1, 1.3) and Parkinson's disease (IRR: 1.2, 95% CI: 1.0, 1.5). All of the remaining conditions showed no effect on longitudinal OCIND risk including heart attack (IRR: 1.1, 95% CI: 1.0, 1.1), angina (IRR: 1.1, 95% CI: 1.0, 1.2), angina (IRR: 1.0, 95% CI: 0.9, 1.3) and diabetes mellitus (IRR: 1.1, 95% CI: 1.0, 1.2) (table 6.3 and figure 6.7).

6.3.8 Longitudinal risk factors for incident dementia

The following section describes the results of longitudinal analysis for risk factors for OCIND.

Figure 6-8: Results of longitudinal poisson regression analysis of risk factors for dementia including age, sex, education, deprivation smoking status, marital status, and self-reported health (SRH), Parkinson's disease, stroke, heart attack, angina, peripheral vascular disease and diabetes. Results presented as odds ratios (OR) with 95% confidence intervals (95% CI) and adjusted for age and sex. Missing data was accounted for via multiple imputation (m=20) and inverse probability weighted for non-response and longitudinal attrition.



6.3.8.1 Age, sex and education

As with the cross-sectional analysis, there is again an exponential increase in longitudinal dementia risk as age increases (figure 6.8). Risk for dementia increases in every age group from 70-74 (IRR: 1.4, 95% CI: 1.1, 1.7), 75-79 years (IRR: 1.8, 95% CI: 1.4, 2.3), 80-84 years (IRR: 2.5, 95% CI: 2.0, 3.0) and those aged over 85 years (IRR: 3.2, 95% CI: 2.6, 4.0) (table 3 and figure 8). Unlike at baseline there was no sex difference found in the risk of incident dementia (IRR: 1.1, 95% CI: 1.0, 1.3) (table 6.3 and figure 6.8). Longitudinally there remained a clear trend for dementia risk and education. Participants with 10 years of full-time education showed a slightly reduced risk of incident dementia (IRR: 0.9, 95% CI: 0.8, 1.0) and those with 11 years or more in full time education had stronger effect in reducing risk of incident dementia (IRR: 0.7, 95% CI: 0.6, 0.8) (table 6.3 and figure 6.8).

6.3.8.2 Deprivation, smoking, marital status and loneliness

There was a clear trend for higher levels of deprivation being associated with incidence of dementia. Those in the moderate deprivation group showed a small effect size (IRR: 1.2, 95% CI: 1.1, 1.4) whereas those in the most deprived group were more strongly associated with incident dementia (IRR: 1.6, 95% CI: 1.4, 1.8) (table 3 and figure 8). As with the cross-sectional analysis there is a clear association with smoking and incident dementia, both past smokers (IRR: 1.2, 95% CI: 1.1, 1.4) and current smokers (IRR: 1.8, 95% CI: 1.5, 2.0) were found to be at increased risk of developing incident dementia at wave 2 compared to those who had never smoked (table 6.3 and figure 6.8).

Marital status was found to increase risk for incident dementia, participants who at baseline were single, widowed or divorced were at an increased risk of developing incident dementia at wave 2 (IRR: 1.3, 95% CI: 1.2, 1.5) compared to those who were married or cohabiting (table 6.3 and figure 6.8). Again, there is a clear trend for frequent feelings of loneliness being associated with incident dementia for both groups who report infrequent loneliness (IRR: 1.4, 95% CI: 1.2, 1.5) and who report frequent/ persistent feelings of loneliness (IRR: 1.6, 95% CI: 1.4, 1.9) (table 6.3 and figure 6.8).

6.3.8.3 Self-reported health (SRH) and medical co-morbidities

Worsening self-reported health was significantly associated with incident dementia, for all groups including who report good self-perceived health (IRR: 1.3, 95% CI: 1.1, 1.6), those who report fair self-perceived health (IRR: 2.0, 95% CI: 1.6, 2.3) and poor self-perceived health (IRR: 2.7, 95% CI: 2.2, 3.3) (table 6.3 and figure 6.8).

Half of the medical conditions analysed were found to be strongly associated with increased risk of incident dementia including, Parkinson's disease (IRR: 1.8, 95% CI: 1.4, 2.3), stroke (IRR: 1.8, 95% CI: 1.6, 2.0) and diabetes mellitus to a lesser degree (IRR: 1.3, 95% CI: 1.1, 1.4). Several other conditions showed increased risk, with a reduced effect size including, heart attack (IRR: 1.2, 95% CI: 1.0, 1.3), angina (IRR: 1.2, 95% CI: 1.0, 1.3) and peripheral vascular disease (IRR: 1.3, 95% CI: 0.9, 2.0) with wide confidence intervals (table 6.3 and figure 6.8).

6.3.9 Risk factors for transition to dementia from RMCI and OCIND.

Longitudinal analysis was conducted using Poisson regression for dementia coded to = 1 and RMCI or OCIND was the referent category coded to = 0. Impairment groups were modelled by age, sex, education, deprivation, smoking status, marital status, loneliness, self-reported health and medical co-morbidities shown in table 4. Analysis was undertaken using multiple imputation for missing data and inverse probability weighted for non-response. Longitudinal risk is presented as incidence rate ratios (IRR) with accuracy of estimate presented as 95% Confidence Intervals.

Table 6-4: Results from the longitudinal analyses of risk factors for transition to dementia from revised mild cognitive impairment (RMCI), other cognitive impairment no dementia (OCIND). Risk was modelled using Poisson regression analysis, results presented as incidence rate ratios (IRR) with 95% Confidence intervals (95% CI), adjusted for age and sex. Multiple imputation (m=20) was used to impute missing data and analysis was inverse probability weighted for non-response.

	vs. RMCI			vs. OCIND		
Risk factors	IRR	95% CI		IRR	95% CI	
Age Group						
65-69	1.0	.	.	1.0	.	.
70-74	1.4	(1.1,	1.7)	1.7	(1.3,	2.1)
75-79	2.1	(1.7,	2.6)	2.4	(1.9,	3.1)
80-84	2.3	(1.9,	2.9)	3.3	(2.6,	4.2)
85+	2.9	(2.4,	3.5)	4.2	(3.4,	5.3)
Sex						
Women	1.2	(1.1,	1.3)	1.3	(1.1,	1.5)
Education (years)						
≤ 9	1.0	.	.	1.0	.	.
10	0.9	(0.8,	1.0)	0.8	(0.7,	1.0)
≥ 11	0.7	(0.6,	0.8)	0.5	(0.5,	0.6)
Deprivation						
Least	1.0	.	.	1.0	.	.
Moderate	1.2	(1.1,	1.4)	1.3	(1.1,	1.6)
Most	1.4	(1.2,	1.6)	1.6	(1.4,	1.9)
Loneliness						
Not at all	1.0	.	.	1.0	.	.
Infrequent	1.1	(1.0,	1.2)	1.4	(1.2,	1.6)
Frequent/ persistently	1.2	(1.0,	1.4)	1.4	(1.1,	1.8)
Self-reported health						
Excellent	1.0	.	.	1.0	.	.
Good	1.0	(0.9,	1.2)	1.2	(1.0,	1.4)
Fair	1.2	(1.0,	1.4)	1.6	(1.3,	1.9)
Poor	1.6	(1.3,	1.9)	2.1	(1.7,	2.7)
Co-morbidities					,	
Parkinson's	1.2	(0.9,	1.7)	2.0	(1.4,	2.9)
Stroke	1.2	(1.1,	1.4)	1.6	(1.3,	1.8)
Heart attack	1.0	(0.9,	1.2)	1.1	(0.9,	1.4)
Angina	0.9	(0.8,	1.1)	1.0	(0.9,	1.2)
Peripheral vascular disease	0.9	(0.6,	1.4)	1.1	(0.7,	1.7)
Diabetes	1.1	(1.0,	1.3)	1.2	(1.0,	1.4)

Figure 6-9: Results of longitudinal poisson regression analysis of risk factors for transitioning from baseline revised mild cognitive impairment (RMCI) to dementia at wave 2 including age, sex, education, deprivation smoking status, marital status, self-reported health (SRH), Parkinson's disease, stroke, heart attack, angina, peripheral vascular disease and diabetes. Results presented as odds ratios (OR) with 95% confidence intervals (95% CI) and adjusted for age and sex. Missing data was accounted for via multiple imputation (m=20) and inverse probability weighted for non-response and longitudinal attrition.

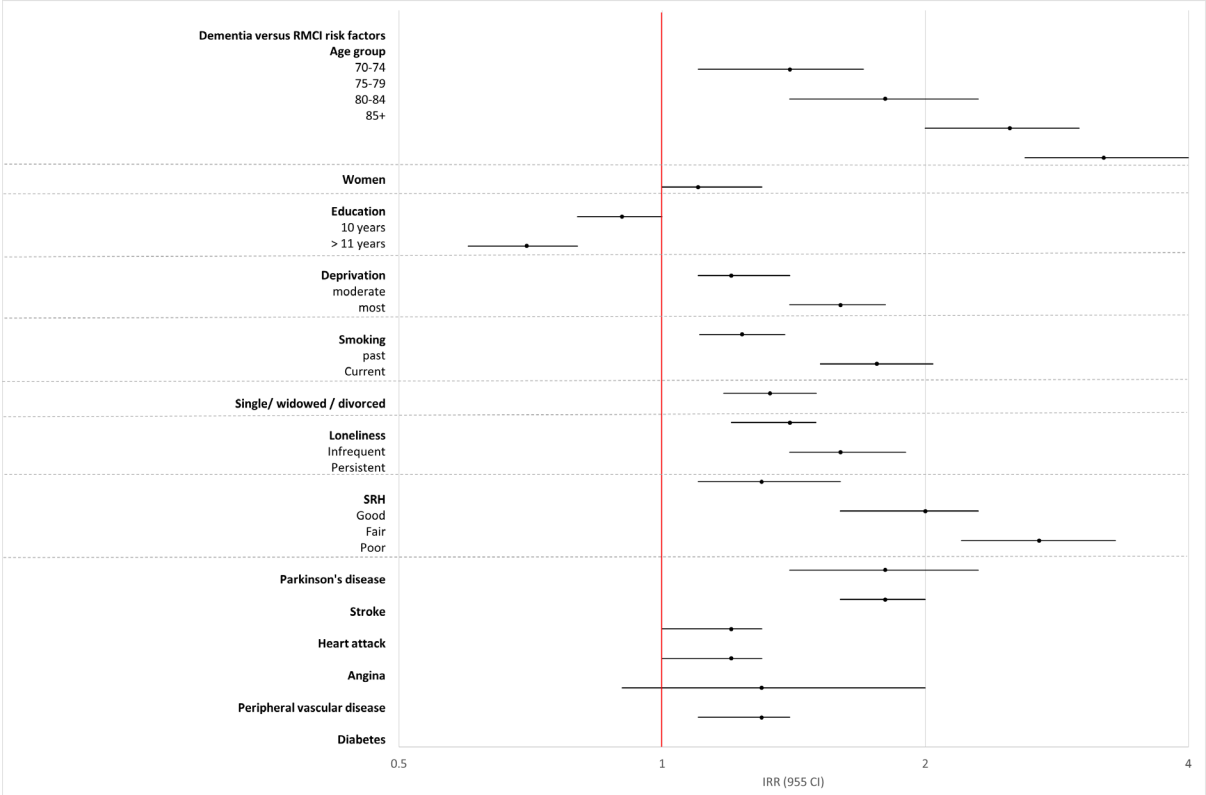
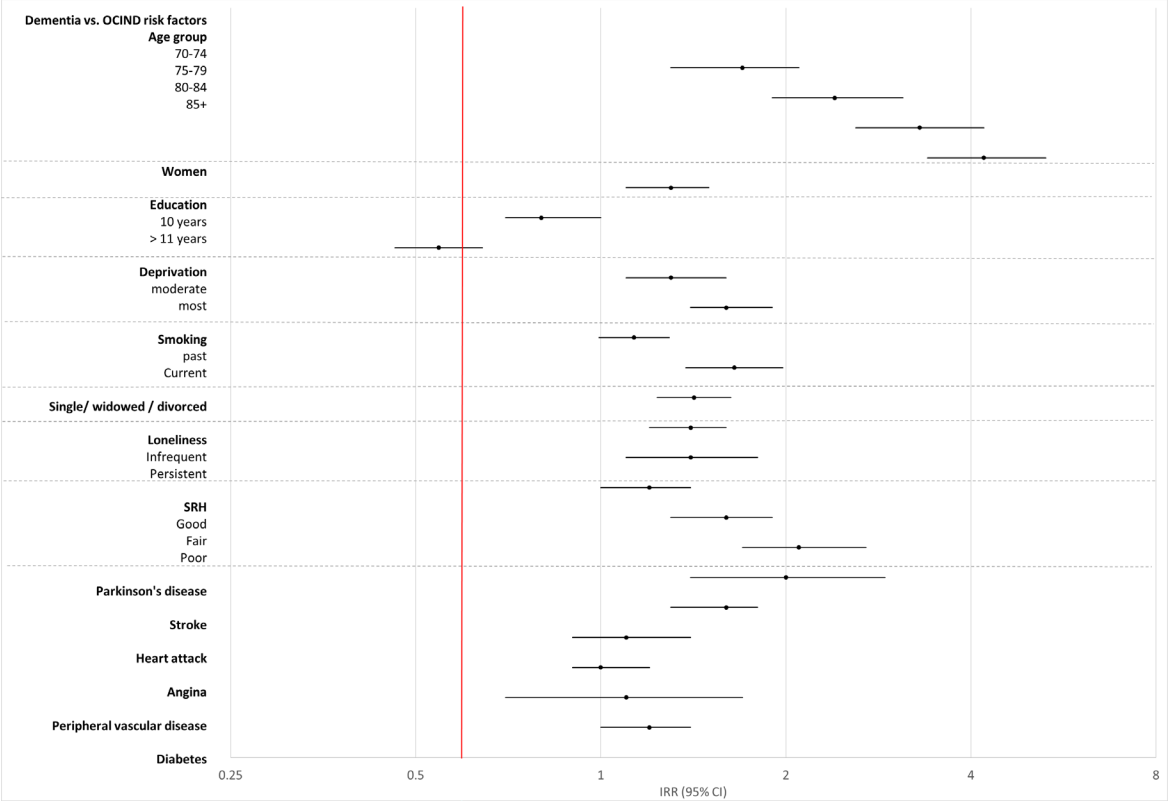


Figure 6-10: Results of longitudinal poisson regression analysis of risk factors for transitioning from baseline other cognitive impairment no dementia (OCIND) to dementia at wave 2 including age, sex, education, deprivation smoking status, marital status, self-reported health (SRH), Parkinson's disease, stroke, heart attack, angina, peripheral vascular disease and diabetes. Results presented as odds ratios (OR) with 95% confidence intervals (95% CI) and adjusted for age and sex. Missing data was accounted for via multiple imputation (m=20) and inverse probability weighted for non-response and longitudinal attrition.



6.3.9.1 Age, sex and education

There was a clear age trend for increasing risk of transitioning to dementia from both OCIND and RMCI (figures 6.9 and 6.10). Increasing age was associated with transition to dementia for all ages including 70-74 (RMCI, IRR: 1.4, 95% CI: 1.1, 1.7; versus OCIND: IRR: 1.7, 95% CI: 1.3, 2.1), 75-79 (RMCI: IRR: 2.1, 95% CI: 1.7, 2.6; versus OCIND 2.4, 95% CI: 1.9, 3.1), 80-84 (RMCI: IRR: 2.3, 95% CI: 1.9, 2.9; versus OCIND: IRR: 3.3, 95% CI: 2.6, 4.2), and for those over the age of 85 (RMCI: IRR: 2.9, 95% CI: 2.4, 3.5; versus OCIND: IRR: 4.2, 95% CI: 3.4, 5.3) (table 6.4, figures 6.9 and 6.10). Sex differences were also found for increased risk of transition from both RMCI and OCIND with women being at higher risk (RMCI: IRR: 1.2, 95% CI: 1.1, 1.3; versus OCIND: 1.3, 95% CI: 1.1, 1.5) (table 6.4, figures 6.9 and 6.10).

There is a trend showing more years of full-time education was associated with decreased risk of transitioning from both RMCI and OCIND, there was a small effect size for those with 10 years (RMCI: IRR: 0.9, 95% CI: 0.8, 1.0; versus OCIND: IRR: 0.8, 95% CI: 0.7, 1.0). Participants with 11 or more years of education however showed a much stronger effect (RMCI: IRR: 0.7, 95% CI: 0.6, 0.8; versus OCIND: IRR: 0.5, 95% CI: 0.5, 0.6) (table 6.4, figures 6.9 and 6.10).

6.3.9.2 Deprivation, smoking, marital status and loneliness

As with dementia incidence there is a deprivation trend for increased risk of transitioning to dementia for RMCI and OCIND. A small effect was seen in moderate deprivation category (RMCI: IRR: 1.2, 95% CI: 1.1, 1.4; versus OCIND: IRR: 1.3, 95% CI: 1.1, 1.6), with the effect size growing stronger again for those in the most deprived group (RMCI: IRR: 1.4, 9%% CI: 1.2, 1.6; versus OCIND: 1.6, 95% CI: 1.4, 1.9) (table 6.4, figures 6.9 and 6.10). Similar results were found for risk of incident dementia from smoking in both the baseline RMCI and OCIND groups. There were no significant associations with past smoking for either RMCI or OCIND (RMCI IRR: 1.0, 95% CI: 0.9, 1.2; versus OCIND IRR: 1.1, 95% CI: 1.0, 1.3). There was however a significantly increased risk in current smokers in both baseline conditions compared to those who had never smoked (RMCI IRR: 1.5, 95% CI: 1.3, 1.7; OCIND IRR: 1.6, 95% CI: 1.4, 2.0) (table 6.4, figures 6.9 and 6.10).

The association between marital status and risk of incident dementia differed between those in the RMCI and OCIND groups at baseline. Being single, widowed or divorced was shown to increase risk of developing incident dementia in those who were in the OCIND category at baseline (IRR: 1.4, 95% CI: 1.2, 2.0) but not those in the RMCI category (IRR: 1.1, 95% CI: 1.0, 1.2) (table 4, figures 9 and 10). There is a clear trend showing loneliness increases risk for transition to dementia from baseline OCIND and to a lesser degree RMCI, including those reporting infrequent loneliness (RMCI: IRR: 1.1, 95% CI: 1.0, 1.2; versus OCIND: IRR: 1.4, 95% CI: 1.2, 1.6) and frequent' persistent loneliness (RMCI: IRR: 1.2, 95% CI: 1.0, 1.4; versus OCIND: IRR: 1.4, 95% CI: 1.1, 1.8) (table 6.4, figures 6.9 and 6.10). Although the effect size was stronger for those in the baseline OCIND group, there is still evidence of trend in RMCI.

6.3.9.3 Self-reported health (SRH) and medical co-morbidities

There is a clear trend showing worsening SRH being associated with increased risk of transition from both baseline RMCI and OCIND, with risk increasing gradually in every category. Good self-perceived health showed a weak association with transition to incident dementia in OCIND but not RMCI (RMCI: IRR: 1.0, 95% CI: 0.9, 1.2; versus OCIND: IRR: 1.2, 95% CI: 1.0, 1.4), fair self-perceived health was associated with increased risk from OCIND and RMCI (RMC: IRR: 1.2, 95% CI: 1.0, 1.4; versus OCIND: IRR: 1.6, 95% CI: 1.3, 1.9) with the effect growing stronger for those reporting poor self-perceived health at baseline (RMCI: IRR: 1.6, 95% CI: 1.3, 1.9; versus OCIND: IRR: 2.1, 9%% CI: 1.7, 2.7) (table 6.4, figures 6.9 and 6.10).

Parkinson's disease was associated with increased risk of transition to dementia in OCIND and RMCI, with the strongest effect seen for RMCI (RMCI: IRR: 1.2, 95% CI: 0.9, 1.7; versus OCIND: IRR: 2.0, 95% CI: 1.4, 2.9), a similar association was found for stroke (RMCI: IRR: 1.2, 95% CI: 1.1, 1.4; versus OCIND: IRR: 1.6, 95% CI: 1.3, 1.8). Diabetes was one condition where there was an effect seen for those with OCIND but not RMCI (RMCI: IRR: 1.1, 95% CI: 1.0, 1.3; versus OCIND: IRR: 1.2, 95% CI: 1.0, 1.4). There were no associations found for risk of dementia and the remaining co-morbidities including heart attack (RMCI: IRR: 1.0, 95% CI: 0.9, 1.2; versus OCIND: 1.1, 95% CI: 0.9, 1.4), angina (RMCI: IRR: 0.9, 95% CI: 0.8, 1.1; versus OCIND: IRR: 1.0, 95% CI: 0.9, 1.2) or peripheral vascular disease (table 6.4, figures 6.9 and 6.10)

6.4 Multivariable Risk Factor Analysis

This sections shows the results of the risk factor modelling via multivariable regression analysis to take into account possible confounding by all covariates.

6.4.1 Multivariable cross sectional risk factors

In many cases the results from the multivariable model are similar to those adjusted for only age and sex. However a few changes are seen including a reduced effect of age, deprivation smoking, marital status, self-reported health and among medical comorbidities. Loneliness however appeared to have a stronger effect. (Table 6.5)

6.4.2 1.1.1 Multivariable Longitudinal risk factors

Overall results were similar in the multivariable model, although slightly reduced effect sizes can be seen across the covariates. This was seen in both analyses for risk of incident cases and risk of transition to dementia. (Tables 6.6 and 6.7)

Table 6-5 : Results from the cross-sectional analyses of risk factors for revised mild cognitive impairment (RMCI), other cognitive impairment no dementia (OCIND), and dementia. Baseline risk was modelled using logistic regression analysis, results presented as odds ratios (OR) with 95% Confidence intervals (95% CI), adjusted for all covariates. Multiple imputation (m=20) was used to impute missing data and analysis was inverse probability weighted for non-response.

	RMCI			OCIND			Dementia		
Risk factors	**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**	
Age group									
70-74	1.0	(0.8,	1.2)	0.8	(0.7,	1.0)	1.5	(1.0,	2.3)
75-79	0.7	(0.6,	0.9)	0.8	(0.6,	1.0)	2.3	(1.5,	3.6)
80-84	1.0	(0.7,	1.3)	0.9	(0.7,	1.1)	3.2	(2.0,	5.1)
85+	1.2	(0.8,	1.8)	1.4	(1.0,	1.9)	7.2	(4.2,	12.1)
Women	0.9	(0.8,	1.1)	1.0	(0.8,	1.1)	1.5	(1.1,	2.0)
Education									
10 years	1.0	(0.8,	1.3)	1.0	(0.8,	1.2)	0.8	(0.5,	1.1)
> 11 years	1.1	(0.9,	1.5)	1.1	(0.9,	1.4)	0.4	(0.3,	0.6)
Deprivation									
moderate	1.1	(0.9,	1.3)	1.0	(0.9,	1.2)	1.4	(1.0,	1.9)
most	1.1	(0.9,	1.4)	1.1	(1.0,	1.4)	1.4	(1.0,	2.0)
Smoking									
past	1.3	(1.1,	1.5)	1.1	(1.0,	1.3)	1.1	(0.9,	1.5)
current	1.1	(0.8,	1.5)	1.2	(0.9,	1.6)	2.0	(1.2,	3.1)
Single/widowed/divorced	1.1	(0.9,	1.4)	0.9	(0.8,	1.1)	1.0	(0.8,	1.4)
Loneliness									
infrequent	1.8	(1.3,	2.3)	1.2	(0.9,	1.5)	2.1	(1.4,	2.9)
persistent	2.6	(1.5,	4.5)	1.6	(1.0,	2.7)	2.7	(1.4,	5.4)
SRH		,							
Good	1.4	(1.1,	1.7)	1.2	(1.0,	1.5)	1.3	(0.9,	1.9)
Fair	2.1	(1.6,	2.8)	1.7	(1.4,	2.2)	2.5	(1.7,	3.8)
Poor	3.2	(1.8,	5.7)	2.9	(1.7,	4.8)	9.4	(4.8,	18.3)
Parkinson's disease	5.2	(1.4,	18.9)	1.7	(0.5,	6.2)	4.5	(1.1,	18.2)
Stroke	2.6	(1.7,	3.9)	1.9	(1.3,	2.7)	5.1	(3.0,	8.5)
Heart Attack	0.9	(0.7,	1.3)	0.8	(0.6,	1.1)	1.0	(0.6,	1.7)
Angina	1.4	(1.0,	1.8)	1.3	(1.0,	1.6)	0.7	(0.5,	1.1)
Peripheral Vascular disease	1.4	(0.6,	3.4)	1.2	(0.6,	2.5)	1.5	(0.5,	5.1)
Diabetes	1.0	(0.8,	1.4)	1.0	(0.8,	1.3)	1.1	(0.7,	1.6)

Table 6-6 Results from the longitudinal analyses of risk factors for revised mild cognitive impairment (RMCI), other cognitive impairment no dementia (OCIND), and dementia. Risk was modelled using Poisson regression analysis, results presented as incidence rate ratios (IRR) with 95% Confidence intervals (95% CI), adjusted for all covariates. Multiple imputation (m=20) was used to impute missing data and analysis was inverse probability weighted for non-response.

	RMCI			OCIND			Dementia		
Risk factors	IRR	**95% CI**		IRR	**95% CI**		IRR	**95% CI**	
Age group									
70-74	0.9	(0.8,	1.1)	1.0	(0.9,	1.0)	1.2	(1.0,	1.5)
75-79	0.9	(0.7,	1.0)	0.9	(0.9,	1.0)	1.6	(1.3,	1.9)
80-84	0.9	(0.8,	1.1)	1.0	(0.9,	1.0)	1.9	(1.6,	2.4)
85+	1.0	(0.8,	1.3)	1.1	(1.0,	1.2)	2.4	(2.0,	3.0)
Women	0.9	(0.8,	1.0)	1.0	(0.9,	1.0)	1.1	(1.0,	1.3)
Education									
10 years	0.9	(0.8,	1.1)	1.0	(0.9,	1.1)	0.9	(0.8,	1.0)
> 11 years	1.1	(0.9,	1.2)	1.1	(1.0,	1.1)	0.8	(0.7,	0.9)
Deprivation									
moderate	1.0	(0.9,	1.2)	1.0	(0.9,	1.1)	1.2	(1.0,	1.4)
most	1.1	(1.0,	1.2)	1.0	(0.9,	1.1)	1.3	(1.1,	1.5)
Smoking									
past	1.1	(1.0,	1.3)	1.0	(1.0,	1.1)	1.1	(1.0,	1.3)
current	1.1	(0.9,	1.3)	1.0	(0.9,	1.1)	1.4	(1.2,	1.6)
Single/widowed/divorced	1.0	(0.9,	1.2)	1.0	(0.9,	1.0)	1.1	(1.0,	1.3)
Loneliness									
infrequent	1.2	(1.0,	1.4)	1.0	(1.0,	1.1)	1.2	(1.1,	1.4)
persistent	1.5	(1.2,	1.8)	1.1	(1.0,	1.2)	1.3	(1.1,	1.6)
SRH									
Good	1.2	(1.0,	1.4)	1.1	(1.0,	1.1)	1.3	(1.1,	1.5)
Fair	1.5	(1.3,	1.8)	1.2	(1.1,	1.3)	1.6	(1.3,	1.9)
Poor	1.7	(1.3,	2.1)	1.3	(1.2,	1.4)	2.1	(1.7,	2.6)
Parkinson's disease	1.5	(1.0,	2.2)	1.2	(1.0,	1.5)	1.5	(1.1,	2.1)
Stroke	1.4	(1.2,	1.7)	1.1	(1.1,	1.2)	1.4	(1.3,	1.6)
Heart Attack	0.9	(0.7,	1.1)	1.0	(0.9,	1.1)	1.0	(0.9,	1.2)
Angina	1.2	(1.0,	1.4)	1.0	(1.0,	1.1)	1.0	(0.9,	1.1)
Peripheral Vascular disease	1.1	(0.8,	1.6)	1.0	(0.8,	1.2)	0.9	(0.6,	1.4)
Diabetes	0.9	(0.8,	1.1)	1.0	(1.0,	1.1)	1.1	(1.0,	1.3)

Table 6-7 Results from the longitudinal analyses of risk factors for transition to dementia from revised mild cognitive impairment (RMCI), other cognitive impairment no dementia (OCIND). Risk was modelled using Poisson regression analysis, results presented as incidence rate ratios (IRR) with 95% Confidence intervals (95% CI), adjusted for all covariates. Multiple imputation (m=20) was used to impute missing data and analysis was inverse probability weighted for non-response.

	vs. RMC			vs. OCIND		
Risk factors	**IRR**	**95% CI**		**IRR**	**95% CI**	
Age group						
70-74	1.3	(1.0,	1.6)	1.5	(1.1,	1.9)
75-79	2.0	(1.6,	2.4)	2.0	(1.6,	2.6)
80-84	2.1	(1.7,	2.6)	2.5	(1.9,,	3.2)
85+	2.7	(2.2,	3.3)	3.2	(2.5,	4.1)
Women	1.2	(1.1,	1.3)	1.2	(1.1,	1.4)
Education						
10 years	0.9	(0.8,	1.0)	0.9	(0.7,	1.0)
> 11 years	0.7	(0.6,	0.8)	0.6	(0.5,	0.7)
Deprivation		,				
moderate	1.2	(1.1,	1.4)	1.3	(1.1,	1.5)
most	1.3	(1.1,	1.4)	1.3	(1.1,	1.5)
Smoking						
past	1.0	(0.9,	1.1)	1.1	(0.9,	1.2)
current	1.3	(1.2,	1.5)	1.3	(1.1,	1.6)
Single/widowed/divorced	1.0	(0.9,	1.2)	1.2	(1.0,	1.4)
Loneliness						
infrequent	1.0	(0.9,	1.1)	1.2	(1.1,	1.4)
persistent	1.1	(0.9,	1.3)	1.2	(0.9,	1.5)
SRH						
Good	1.0	(0.8,	1.1)	1.2	(1.0,	1.4)
Fair	1.1	(0.9,	1.3)	1.3	(1.1,	1.7)
Poor	1.5	(1.2,	1.8)	1.8	(1.4,	2.3)
Parkinson's disease	1.2	(0.9,	1.6)	1.9	(1.3,	2.8)
Stroke	1.1	(1.0,	1.3)	1.3	(1.1,	1.6)
Heart Attack	1.1	(0.9,	1.3)	1.1	(0.9,	1.3)
Angina	0.8	(0.7,	0.9)	0.8	(0.7,	1.0)
Peripheral vascular disease	0.9	(0.6,	1.3)	1.0	(0.6,	1.5)
Diabetes	1.1	(1.0,	1.2)	1.1	(0.9,	1.3)

6.5 Chapter summary

6.5.1 Age, sex and education

I. For both RMCI and OCIND risk appears higher for the youngest ages before dropping rapidly and gradually increasing again.
II. Longitudinally, in RMCI and OCIND risk is relatively flat with age and only increasing in the over 85 group. The same trend is seen for risk of transitioning from RMCI and OCIND to dementia.
III. Cross-sectional analysis showed there is a clear trend showing more years spent in education reduces risk of dementia, however there was no such trend for RMCI or OCIND.
IV. There were education trends found in transition from both RMCI and OCIND to dementia.

6.5.2 Deprivation, smoking, marital status and loneliness

I. Similar deprivation trends were seen across all cross-sectional analysis with greater deprivation being associated with increased risk of cognitive impairment. Longitudinal results mostly showed the same trend
II. The analysis of smoking status yielded identical results to that of deprivation, with smoking being associated with an increased risk in every case except for incident OCIND.
III. Loneliness was one factor that had an effect in every analysis both cross-sectionally and longitudinally.

6.5.3 Self-reported health (SRH) and medical co-morbidities

I. All analysis found trends of worsening SRH being associated with increased risk of RMCI, OCIND and dementia at baseline and longitudinally.

6.5.4 Medical co-morbidities

I. The most consistent of the risk factors measured were Parkinson's disease and stroke increasing risk in dementia, RMCI and OCIND.
II. There was less evidence that peripheral vascular disease and diabetes as significant risk factors. Overall co-morbidities tended to have stronger effects on RMCI and dementia compared to OCIND.

7 DISCUSSION

Overview

The aim of this final chapter is to reflect on the findings of the thesis. The chapter will discuss the analyses presented and the results in the context of the wider literature, as well as give an overview of the impact the work has on public health and clinical practise. Strengths and limitations will also be discussed. Finally the chapter will conclude on how the work presented here can be taken forward.

7.1 Prevalence of Mild Cognitive Impairment (MCI)

The work presented in this thesis has shown new insights into the prevalence of MCI and dementia. The definition of MCI was carefully crafted using evidence from the literature. As shown in chapter 2, there has been a clear narrowing of the preferred definition of MCI in population-based studies, therefore Petersen's revised MCI criteria formed the basis of how MCI was operationalized in this project. However, the aim was not just to look at this diagnosis, it was to update the definition to measure a number of nuanced stages of cognitive decline. This has given an insight into the prevalence of those with no cognitive impairment to revised MCI while also how prevalent other cognitive impairment which is not dementia, in other words, mild cognitive impairment which does not meet RMCI criteria, including those with functional impairments. It was also able to capture previously missed individuals from the more severe end of the spectrum. In addition to those meeting DSM-III-R dementia criteria as previous CFAS studies have shown, the criteria implemented here included those who had severe cognitive impairment without dementia and those who had mild dementia defined as those with severe cognitive impairment who also had functional impairment.

There is debate in the literature surrounding how MCI should be defined and implemented in population-based samples. A number of studies suggest that Petersen's definition is too restrictive and therefore misses out many people who would otherwise be defined as MCI; an example of this could be individuals who are cognitively impaired on neuropsychological testing but do not present a subjective complaint, or they are impaired in physical functioning. On the other hand, there are others that argue that using a broader definition such as OCIND captures too many older people who are not at risk of further decline. By mapping several of these definitions including RMCI and OCIND with and without functional impairment, the

prevalence of both states can be measured and compared. This project has shown that by far the largest group in the older age population is those who fall into the OCIND category. The main finding from these analyses have shown that over the two decades that were compared the trends between MCI and dementia and its mildest forms are very different. In the analysis of dementia, mild dementia and severe cognitive impairment there were clear cohort effects showing prevalence decreasing over twenty years. In contrast, RMCI and OCIND had remained relatively stable in the face of dementia and its mildest forms decreasing in prevalence.

The results in this analysis also highlighted new trends in the prevalence of domain specific MCI subtypes. The results are broadly in line with the findings of the wider literature surrounding MCI subtypes; prevalence is higher in naMCI and mMCI, while lower in the more restrictive aMCI group. New insights from this have been able to show changing prevalence over time, which showed that while naMCI and mMCI have reduced in prevalence aMCI is the only MCI subtype that increased. This indicated that certain risk factor reduction could be at play in the pathology of non-memory domains whereas memory impairment most related to Alzheimer's disease is the least affected by risk factor reduction.

Overall the results of the prevalence study are in line with previous findings. Generally in the literature prevalence has been reported to range between 12% and 18%, with prevalence reported here of 15% in 2011 fitting comfortably in that range. However, there are disagreements with previous literature reporting age trends in the prevalence of MCI. In this analysis almost all results showed prevalence of MCI decreasing with age, there was only one case where it did not and that was aMCI prevalence in 1991, however 2011 prevalence trends showed that aMCI like the other definitions decreased with age. Therefore, the results from this prevalence study contradict other works which imply a degenerative aetiology to MCI. The results here suggest that transition is common not to severe impairment but within milder states and is often absorbed by the OCIND definition. Previous studies have suggested there is evidence although weak of higher prevalence in men, the results also suggest this with prevalence estimates of MCI being higher in men although with only weak effects.

It can be difficult to interpret prevalence of MCI in the context of previously published research as the prevalence of MCI has been found to vary widely between studies.

Although in similar populations the average prevalence is found to range from 12% to 18%, prevalence has been found to vary from as low as 0.6% (95% CI: 0.3, 0.9) in a population of Chinese elderly aged 65 years and older (n=2,014; aMCI Petersen criteria) to 63.3% in non-demented Philippine elderly aged 65 years and older (n=120; MCI based on MMSE neuropsychological assessment tool) (ref). Much of this variability is undoubtedly due to the lack of standardized operationalization of MCI in different populations as shown in the example above (aMCI versus MMSE cut off). Indeed an ongoing review of MCI prevalence has so far found numerous criteria are used to diagnose MCI including:

Eight that used criteria for aMCI (aMCI) (Das et al., 2007a, Sosa et al., 2012, Juarez-Cedillo et al., 2012, Li et al., 2013, Jia et al., 2014, Ding et al., 2015, Ogunniyi et al., 2016, Rao et al., 2018), three that used criteria for naMCI (Lee et al., 2012, Li et al., 2013, Rao et al., 2018) and five that used criteria for mMCI (Juarez-Cedillo et al., 2012, Li et al., 2013, Xu et al., 2014, Ogunniyi et al., 2016, Rao et al., 2018). In the later studies, four further divided MCI to include whether cognitive impairment was presented as single domain aMCI, single domain aMCI or multi domain aMCI (Juarez-Cedillo et al., 2012, Li et al., 2013, Xu et al., 2014, Ogunniyi et al., 2016, Das et al., 2007a, Ding et al., 2015). Six studies used the definition of CIND (Mejia-Arango and Gutierrez, 2011, Shi et al., 2013, Brucki, 2013, Guimarães et al., 2014, Zhang et al., 2014, Cesar et al., 2016). Two studies defined cognitive impairment using cognitive test scores only (Montaño et al., 2013, Li et al., 2018), two studies) used MCI criteria similar to MCI and CIND without directly referencing a particular criteria (Huang et al., 2005, Baiyewu et al., 2002) and one study used criteria for the definition of questionable dementia (Jia et al., 2014). The remaining studies defined MCI using the International Working Group on MCI definition (Paddick et al., 2015) or the NIA-AA definition (Vancampfort et al., 2017). Only one study, included subtypes categorized by cause, namely: prodromal Alzheimer's disease, cerebrovascular disease, vascular risk factors and other diseases (Jia et al., 2014).

There is additional evidence that there is also a wide range in prevalence rates between studies using the same criteria, and as well between studies reporting the MCI prevalence rate for the same country. On the other hand, studies reporting MCI prevalence rates for multiple countries (Sosa et al., 2012, Pilleron et al., 2015), using

the same research methods, find more comparable MCI prevalence estimates between countries.

7.2 Incidence of Mild Cognitive Impairment (MCI)

In the UK the overall incidence rate for RMCI, is 138.5 per 1000-person years (95% CI: 131.5, 145.5). The incidence rate for OCIND was 233.5 per 1000-person years (95% CI: 228.4, 238.6) and the incidence rate for dementia was 140.6 per 1000-person years (95% CI: 133.8, 147.4). With regard to age, as expected, dementia shows a clear increasing trend with age. This was not observed in the incidence rates for RMCI and OCIND. Indeed, in both these groups incidence rates were found to be higher in the younger age groups before falling as age increases and then increasing again for those aged over 85. This contradicts previous findings where incidence of cognitive impairment generally increases with age (refs). Rather, the findings suggest that transition between cognitive states is very flexible, although many older people develop MCI, it is a state that can quickly be transitioned out of.

Incidence trends by sex also differed in OCIND, RMCI and dementia groups. Similar to previous studies dementia incidence was significantly higher in women than in men. In contrast, RMCI and OCIND incidence rates did not differ significantly by gender. There was a significant geographical difference in incidence rates of dementia and RMCI, with rates being significantly higher in Cambridgeshire than Newcastle and Nottingham. The trend was not reflected in the incidence of OCIND, where there were significant differences in rate across location. Incidence of dementia and RMCI was found to be significantly higher in participants with higher levels of deprivation, again although overall incidence rates of OCIND were higher in those more deprived the associations were not found to be significant.

As with MCI prevalence it can be difficult to evaluate evidence as incidence rates can vary from study to study. There is evidence that the proportional progression rate from normal cognition to MCI is around 6% per year in a study of Americans over 70 years of age (Roberts et al., 2012b). In comparison this study showed a lower progression rate of only 1.8% (95% CI: 1.0, 2.5) over two years follow up. Rates in the American study were reported to be lower in younger age groups, and it is therefore possible that as CFAS includes individuals from age sixty-five this has an effect on the progression rate. Several studies have produced incidence rates for

MCI, typically found to be around 47.9 (range 21.5-71.3) per 1000 person years for revised Petersen criteria (Ravaglia et al., 2008a, Manly et al., 2008d, Solfrizzi et al., 2004a). The results from this thesis predict much higher incidence rates of 138.5 (95% CI: 131.5, 145.5) per 1000 person years. In this thesis I was not able to investigate the incidence rates of MCI subtypes. In previous literature subtype prevalence, specifically for aMCI has been much lower than the expanded MCI criteria. Studies have shown aMCI to be around three times lower than RMCI 15.2 (range 8.5-25.9) per 1000 person years (Tervo et al., 2004, Caracciolo et al., 2008, Verghese et al., 2006, Busse et al., 2003, Larrieu et al., 2002a). Although incidence of aMCI was not estimated in this study, prevalence estimates are consistent showing a much lower prevalence of aMCI compared to RMCI, it could be hypothesised that the incidence of aMCI would also be lower than that seen in RMCI, although full investigation would be needed to support this with evidence. There is also mixed evidence in the literature for age trends in MCI incidence. Results from this thesis suggest incidence dips before rising again in older age groups, there appears to a trend although the evidence for the effect of age was weak. In a review of MCI incidence rates of five studies reported no significant increases due to age (Busse et al., 2003, Ravaglia et al., 2008a, Larrieu et al., 2002a), two on the other hand did report age as a significant factor for higher incidence (Solfrizzi et al., 2004a, Caracciolo et al., 2008).

The rate of those transitioning to dementia in the UK from RMCI was 152.6 per 1000-person years (95% CI: 145.4, 159.8), and for OCIND was 89.5 per 1000-person years (95% CI: 84.3, 94.6). Overall the rate of those transitioning to dementia was higher in participants in the RMCI group compared to the OCIND group. Risk of transition to dementia from RMCI was seen to increase with age, with the exception of men aged 80-84 years. This trend was also found in the OCIND group, with statistically significant higher rates in each increasing age group. Dementia incidence from RMCI and OCIND was significantly higher in women compared to men. Dementia transition rates from RMCI and OCIND were found to be significantly associated with geographical location, with lower rates in Newcastle and Nottingham compared to Cambridgeshire. Higher levels of deprivation were also found to be a significant factor in increasing the rate of transition from both RMCI and OCIND to dementia.

Measuring the transition to dementia from MCI has similar challenges to those mentioned above, with varying rates derived from heterogeneous diagnostic criteria. Progression rates found in this study were comparatively high for RMCI, results were similar to those found in the Aging Demographics and Memory Study (117 per 1000 person years; United States) (Plassman et al., 2008); Conselice Study of Brain Ageing (140 per 1000 person years; Italy)(Ravaglia et al., 2008b); Kungsholmen Project (approximately 100 per 1000 person years; Sweden)(Palmer et al., 2008) and the Cache County Study of Memory and Aging (120 per 1000 person years; United States) which used a definition for cognitive impairment no dementia (CIND)(Peters et al., 2013). Several other studies measured incidence of dementia from MCI cases which were comparatively lower then RMCI findings in this study but were similar to those seen in transition from OCIND including results from the Italian Longitudinal Study of Aging (38 per 1000 person years; Italy) (Solfrizzi et al., 2004b) ; North Manhattan Study (74 (aMCI) and 41 (naMCI) per 1000 person years with progression to AD; United States) (Manly et al., 2008b) ; Korean Longitudinal Study on Health and Aging (86 per 1000 person years; Korea) (Han et al., 2012) and, Personnes Agées QUID (83 (aMCI) and 71 (OCIND) per 1000 person years; France) (Larrieu et al., 2002b). Similar trends in transition have been seen in other studies, including transition increasing with age, higher transition in older women compared to older men and higher incidence of dementia from MCI compared to those with no cognitive impairment (Roberts et al., 2014b). As with prevalence incidence and conversion rates vary widely between studies, this is a weakness of MCI research in general, and it is through multiple factors are at play including differences in study design, criteria for MCI diagnosis, and frequency of evaluation and assessment of dementia (Roberts et al., 2014b).

7.3 Identifying Risk Factors for Mild Cognitive Impairment (MCI)

In cross-sectional analyses there were interesting trends found between RMCI and OCIND and increasing age, which differed from the exponential increase in risk for dementia with increasing age. For both RMCI and OCIND risk appears higher for the youngest ages before dropping rapidly and gradually increasing again. One theory for this is that mild cognitive impairment does not degenerate as dementia does, indeed although people can have high risk of MCI, it is a condition that can be

transitioned out of easily. The effect of age is different longitudinally, in RMCI and OCIND risk is relatively flat with age and only increasing in the over eighty-five year's age group. Risk of dementia increases exponentially with age both in cross-sectional and longitudinal analysis. The same trend is seen for risk of transitioning from RMCI and OCIND to dementia. The only sex differences that were seen was in risk for dementia and transition to dementia, there were no sex differences seen at baseline or longitudinally for RMCI and OCIND. The findings shown here appear to be contradictory to previous literature around the association between MCI and age. Although the evidence has been mixed, a number of studies have suggested that MCI is degenerative in nature, due to possible AD pathology, and therefore risk increases with age similarly to that seen in dementia, the results here do not corroborate this (Okello et al., 2009a). Several studies have found incident MCI to be associated with increasing age (Solfrizzi et al., 2004b, Tervo et al., 2004, Caracciolo et al., 2008, Manly et al., 2008d). There is disagreement in the literature to the extent of age effects for MCI, like the results of this study effects found tend to be small (Petersen et al., 2014a). Although, the results of this study appear to be unique in showing incidence decreasing with age at first before increasing in older age groups. Reviews have suggested that MCI is a transient state by nature, the results here support and suggest that participants are likely to transition out of MCI and OCIND in younger age groups (Petersen et al., 2014a). Similarly sex differences in the literature are rare, with most showing very small if any significant sex differences (Solfrizzi et al., 2004b, Tervo et al., 2004).

There was a marked difference between dementia and mild impairment for trends with education. In cross-sectional analyses there was a clear trend showing more years spent in education reduces risk of dementia, however there was no such trend for RMCI or OCIND. This was the case again in longitudinal analysis, there were education trends found in transition from both RMCI and OCIND to dementia. Lower levels of education is thought to increase risk of MCI, as seen in dementia. Findings from studies have been inconsistent when investigating education effects, there is supporting evidence for the findings of this study showing no education effect for MCI (Manly et al., 2008d), although other have found significant education effects (Solfrizzi et al., 2004b, Tervo et al., 2004).

Quite similar deprivation trends were seen across all cross-sectional analysis with greater deprivation being associated with increased risk of cognitive impairment. The strongest trend was seen for baseline dementia, followed by RMCI and smaller in OCIND. Longitudinal results mostly showed the same trend, with greater deprivation associated with higher risk of incident RMCI, OCIND, dementia and dementia transition from RMCI and OCIND, there was no deprivation trend found for incident OCIND. The analysis of smoking status yielded identical results to that of deprivation, with smoking being associated with an increased risk for all cognitive states except for incident OCIND. Loneliness was one factor that had an effect in every analysis, strongly increasing risk of RMCI, OCIND and dementia both in cross-sectional and longitudinal analyses, as well as increasing risk of transitioning from RMCI and OCIND to dementia. Deprivation and loneliness have been shown to be a risk factor for cognitive impairment in many previous studies and the results from this analysis are consistent with those findings. Smoking has been associated with cognitive decline and dementia, again the results from this thesis are consistent with those findings. Deprivation is a factor that so far is not well researched in the existing literature, there is evidence from papers investigating the effects of cognitive reserve which show an education effect, often used as a proxy measure for deprivation, on cognitive impairment (Meng and D'Arcy, 2012b). On the other hand there is conflicting evidence from studies of socio-economic status and occupation, which as proxies for deprivation show inconsistent trends with cognitive decline (Harrison et al., 2015).

SRH was like loneliness one of the most consistent risk factor analysed. All analysis found trends of worsening SRH being associated with increased risk of RMCI, OCIND and dementia at baseline and longitudinally, and it also increased the risk of transitioning from RMCI and OCIND to dementia. SRH has not been as well studied as other risk factors however evidence has been shown that SRH can predict survival in older people with mild to moderate cognitive impairment (Walker et al., 2004). There is more evidence to support loneliness and factors associated to it such as less physical, social or cognitive activities being associated with increased risk of MCI (Miller et al., 2012, Marioni et al., 2012a).

All of the comorbidities measured increased risk of dementia and mild impairment to varying degrees. The most consistent of the risk factors measured were Parkinson’s

disease and stroke increasing risk in dementia, RMCI and OCIND. Angina and heart attack were also found to increase risk across the groups, however often having smaller effect sizes and wider confidence intervals. There was less evidence that peripheral vascular disease and diabetes were significant risk factors. Overall co-morbidities tended to have stronger effects on RMCI and dementia compared to OCIND. In terms of cardio-metabolic risk factors, the results from these analyses are consistent with much of the literature. Vascular risk factors have been extensively investigated and similar to this study show mixed results. In cross sectional studies risk factors such as stroke, Parkinson's and heart disease are associated with an increasing risk of MCI (Di Carlo et al., 2000, Frisoni et al., 2000, Artero et al., 2008a, Atti et al., 2010). Longitudinally however the evidence is much weaker (Solfrizzi et al., 2004b, Monastero et al., 2007, Luck et al., 2010a). These trends from vascular factors are mirrored in the evidence for diabetes, showing diabetes having a strong effect on baseline MCI (Artero et al., 2008a, Atti et al., 2010, Roberts et al., 2008) but not incidence (Solfrizzi et al., 2004b, Luck et al., 2010a, Xu et al., 2010b). A suggested explanation for this is that there is competing risk among individuals with these conditions, as they are at increased risk of dementia or death, MCI may not be detected in the follow up (Petersen et al., 2014a).

Residual or unmeasured confounding must also be taken into account in the interpretation of the regression analyses for progression to dementia. There were a number of covariates not included in this analysis that have been highlighted in the literature as being possible factors in the transition from MCI to dementia. Reviews of the literature have pointed to lifestyle and medical comorbidities such as Anxiety, Apathy, Traumatic Brain Injury, Alcohol use being possible risk factors for transition. There is also a body of evidence that from studies of biomarker status which were not possible to replicate in this analysis, including medial temporal lobe atrophy on MRI, hypo metabolic pattern consistent with AD on FDG-PET, positive amyloid PET scan. It is possible therefore the results may have been different if these had been included as possible confounders (Petersen, 2016a, Petersen et al., 2014a).

7.4 Implications for Public Health and Clinical Practise

Determining how best to identify individuals with MCI and the prevalence of the condition will have important implications for planning intervention trials (e.g. clinical

trial recruitment protocols), treatment (where available e.g. personalised medicine), public health surveillance (e.g. monitoring and assessment of potential disease burden), budgeting and education (e.g. prevention programmes).

While cohort effects of prevalence were observed there were differences. Cognitive impairment and mild dementia do not share the same level of decrease as has been previously observed in dementia with both groups seeing a far greater reduction. When we combine the estimates of dementia, mild dementia and cognitive impairment in the older population together it corresponds to over one million people in 2018 with many likely to have very similar care needs to those with a diagnosis of dementia. In contrast, the proportion of cases with NCI and OCIND (without FI) increased. A possible explanation for this is that the trends in population ageing along with improvements in education, health care and reduction of cardiovascular risk factors associated with cognitive impairment have led to a greater proportion of older people with no impairment. Further, where cognition has declined it remains mild rather than declining to the point of impairment. Interestingly the prevalence of MCI has remained stable since 1991. The estimated prevalence is consistent with other large cohort studies internationally, with the average prevalence of MCI from consensus criteria around 12% and 18%. 24-28

There is much debate in the literature about the variance in MCI prevalence estimates from epidemiological studies (Petersen, 2016a). Evidence suggests that the inconsistency is largely due to a lack of standardised diagnostic criteria and homogenous study designs, methodology and populations (Winblad et al., 2004). For decades, the main area of disagreement has been around how to define mild impairment by neuropsychological testing; for example, tighter definitions such as scoring 1.5 standard deviations from normal on memory domain tests show much lower prevalence's compared to the DSM-V criteria of between 1-2 standard deviations on non-specified domain testing (Sachdev et al., 2015). Recently the criteria for MCI has narrowed with the introduction of consensus criteria (Winblad et al., 2004) and different subtypes (amnestic MCI, non-amnestic MCI and multiple MCI) with the aim to help improve diagnostic accuracy (Petersen, 2016a). Consensus criteria were selected for this study, for reasons stated earlier, and different changes over time may be obtained if a different definition were used. But this is beyond the scope of the current investigation.

The results show that since 1991 there has been a shift in the cognitive burden within the older population; although the prevalence of dementia and its mild dementia forms may be declining, OCIND is increasing and MCI is stable. These results have a number of implications for strategic planning for cognitive impairment and dementia. First, they provide further evidence alongside studies (Hall et al., 2009, Langa et al., 2017, Rocca et al., 2011b) 29-31 that have found a decline in risk of cognitive impairment (measured using CIND) in older aged populations; extending the findings for the first time by showing that although severe cognitive impairment and the mildest forms of dementia have decreased, mild impairment in the form of OCIND has increased and MCI has remained stable. Strategic planning for the numbers of people with dementia will have to be adjusted to budget correctly as the prevalence of the disease declines, however, this analysis shows that despite these trends, there is still a significant number of people with cognitive impairment and mild dementia who may indeed be missed from formal dementia diagnosis but who have similar care needs. Planning for increasing numbers of people with OCIND and MCI is more complex, evidence suggests patients diagnosed with MCI prefer to undergo testing to predict dementia risk in the future; due to ever changing technologies, guidelines for diagnosis and management for MCI means testing is likely to be uncertain (Wikler et al., 2013).. Diagnostic testing for MCI can incur heavy financial costs, and so far, interventions to prevent or delay progression to dementia have limited efficacy (Le Couteur et al., 2013, Brayne and Davis, 2012). Planning for the future must involve policy makers and clinicians discussing the balance of risks and benefits of interventions, also involving patient's views on interventions in later life.

Results from longitudinal analysis have shown interesting trends with age and MCI, in both cases incidence was high in the younger old, rapidly decreases before gradually increasing again. This taken in combination with the results that prevalence is highest in the younger old, is evidence of the fluidity of the MCI diagnoses, implying that older people can transition to MCI at an early stage However, they can just as easily transition out of the MCI State. Again, raising questions around the validity of screening for MCI.

Trends with deprivation raises the questions around health inequalities in the UK, adding to the evidence that those most at risk in the population are in the areas with most deprivation. Results suggest that changes seen in the population that have

prevented dementia, haves also impacted on severe cognitive impairment. However, what is not clear is whether lifestyle factors such as education and improved cardiovascular and metabolic health are having the same reductive effect on MCI (Langa and Levine, 2014, Geda et al., 2010). Indeed, the findings suggest that the increase in OCIND and stability of MCI could reflect “normal cognitive ageing” among a population which is substantially older. As well as the financial burden, a diagnosis of MCI can lead to emotional distress and social stigma; cognitive decline is a subject of fear among older people and patients may thus prefer foregoing the diagnosis all together (Langa and Levine, 2014, Small et al., 2008, Geda et al., 2010, Le Couteur et al., 2013, Brayne and Davis, 2012). In light of this care must be taken not to wrongly identify people with MCI as a clinical condition, which may be “normal cognitive ageing”. Clinical decision making in regarding MCI will likely change in light of an effective disease modifying agent for pre-dementia being identified. In the meantime, evidence suggests it is through healthy lifestyle behaviours, better educational attainment, minimizing risks from polypharmacy and comorbidities in the wider population which should be further encouraged to reduce risk of severe cognitive impairment (Langa and Levine, 2014).

7.5 Strengths and Weaknesses

Cognitive Function and Ageing Studies (CFAS)

Work in this thesis was carried out using CFAS, which are longitudinal cohorts by design. Longitudinal studies are designed to allow continuous or repeated measures, following participants for a period of time, which in many cases can be years or decades. In general, longitudinal studies are observational, that is they do not apply any influence on the participants within the study, data can be collected on a wide range of exposures and outcomes, in quantitative or qualitative in nature. Longitudinal studies can offer great insights into the study of specific risk factors and how they influence the development of disease, or indeed how treatment can effect disease outcomes over varying lengths of time. Cohorts are designed with pre-determined populations in mind, the older aged population in CFAS for example, which means appropriate statistical analyses can be performed to investigate changes over time for either the group as a whole, or specific groups within the population (Caruana et al., 2015).

CFAS is a multicentre population-based study of the older population in England. Participants were derived from an extensive range of sociodemographic backgrounds and geographical centres. The population-based design reduces the possibility that selection bias will negatively affect the results. The study also involves a cross-sectional and longitudinal analysis and was focused on examining risk factors for MCI, and MCI progression to dementia which is not often examined in the literature.

Like all research studies CFAS has disadvantages that are common to population cohort design studies. Incomplete or interrupted follow-up of individuals is often cited as a disadvantage to the study design. Indeed CFAS I and II lost participants due to attrition for several reasons, such as participants had moved away from the area, did not wish to take part in the follow-up wave, were too ill or had died. Loss to follow-up can affect how representative the sample is to the population as a whole. This can be a particular disadvantage for those who may have died due to age related disease such as dementia, of which the purpose of the study is to investigate. It can sometimes be difficult when evaluating evidence from longitudinal cohorts to separate the reciprocal impact of certain exposures and outcomes, as often one can potentiate the other. This can be more of an issue when the induction period between exposure and occurrence is prolonged. Care must be taken also to employ statistical techniques that account for intra-individual correlation of measures. (Caruana et al., 2015).

Although there are areas of longitudinal study design that can be disadvantageous, and indeed no study is without weakness, a number of steps were taken throughout this work to strengthen the analyses. From the outset inverse probability weighting was applied to the study design, this meant that analyses add extra weight to participants whose demographics were less likely to be recruited into the study at baseline or be lost due to longitudinal attrition, this reduces bias introduced into the study via non-response. In a number of variables of interest there was missing data, meaning if this went unaddressed the results could be biased as those with missing data would be excluded. Due to this multiple imputation by chained equation was implemented to impute any missing data and reduce bias in the analyses (Caruana et al., 2015).

A limitation of using CFAS I data is the large role weighting plays in the analysis, as only a 20% sample of the full population went on to undergo a thorough cognitive assessment. Previous CFAS studies have shown sensitivity analysis suggesting the results of this method to be robust, and the studies have gone on to publish numerous high profile results using this method. It must however be noted that no amount of sensitivity analysis can fully corrected for having a larger sample, therefore it must be taken into account that a degree of bias could be introduced into the results because of this design (Matthews et al., 2013a).

Although the key methodologies of CFAS I and II are identical, CFAS I comprised a two-stage design with the complete cognitive assessment on a subsample, though the analysis does take this fully into account. CFAS II was designed to avoid this complexity while retaining the ability to compare results across the two studies. Dementia was diagnosed algorithmically using the AGECAT validated with DSM-III-R. With the introduction of new DSM-V criteria, it is unknown whether prevalence of dementia or MCI may have differed had these criteria been applied. Understanding population change in MCI has been complicated by the lack of standardised cut-off scores, age norms, changing criteria including DSM-V creating an unstable environment. The advantage of using population-based data is that it was collected without applying criteria and can be used to operationalise criteria that were not developed at the time of the study. Here we used consensus criteria for MCI which has been shown when compared with the recent DSM-V criteria of mild neurocognitive disorder having 98.6% diagnostic overlap (Winblad et al., 2004, American Psychiatric Association, 2013).

Using the methodology of self-report, there is potential that response bias may affect the prevalence of medical conditions present among the different cognitive groups. However, many studies have consistently demonstrated that using the patient self-report is a reliable methodology to collect data on patient co-morbidity (Corser et al., 2008). One of the main limitations of this study is that this analysis was only focused on incident MCI of all types, due to small numbers of incident cases. Further studies may be able to identify risks within the different subtypes of MCI, however even with large population-based studies these conditions are rare. This is important considering that aMCI and naMCI embody different aetiologies (Michaud et al., 2017), therefore different risk factors may underlie different pathological

mechanisms. Furthermore, the findings of this study were largely based on a Caucasian sample and may not be representative of other ethnic groups. It is possible that there may be different risk factors in different groups. This has been indicated in several studies (Luchsinger et al., 2007, Li et al., 2012).

This analysis was focused on identifying potential risk factors that influence transition in two periods that are clinically important: (i) transition from normal cognition to MCI (ii) transition from MCI to dementia. The current study provided evidence that several health conditions increased the risk for MCI. Certain health conditions identified e.g. diabetes, stroke, heart attack represent modifiable risk factors that could be possible targets for prevention and treatment of MCI and progression to dementia. Reducing the risk of common health conditions is likely to be a crucial strategy in the future to combat cognitive decline (Norton et al., 2014).

One technique with potential to strengthen the analysis was that of multi state modelling. This technique is especially useful when investigating the likelihood of transitioning between different health states, in effect would have given stronger evidence of probabilities of transitioning from NCI to MCI, NCI to OCIND, back transitions from MCI or OCIND to NCI, transitions between MCI and OCIND and transition to dementia (Terrera et al., 2018). Although multi state modelling would have strengthened the analysis, it is a complex procedure, especially under conditions with smaller number of transitions. Unfortunately, the time required to learn the techniques and implement them properly were not possible in the timeframe of the project.

An area that this study was not able to investigate was the more recent developments in the introduction of biomarkers into the MCI definition. It is now well accepted that the pathology of dementia begins many years before becoming symptomatic. It follows therefore that developing methods of detecting those at high risk of developing dementia or with mild cognitive impairment using a combination of sensitive neuropsychological testing and identification of potential biomarkers in a younger population is increasingly becoming the focus of neurodegenerative disease research (Saunders et al., 2018). The CFAS studies unfortunately did not collect biological data, therefore making it impossible to analyse the effect of biomarkers for amyloid-B, neurofibrillary tangles or markers for inflammation or cerebrovascular disease (Saunders et al., 2018).

A number of limitations to this study stems from the study design and data available to accurately define the concept of MCI. CFAS relies heavily on tests such as the CAMCOG and MMSE to establish cognitive impairment, both of which must accept a margin of error for detection of impairment. They are even less sensitive to the earliest cognitive changes in MCI where there are currently no established cut points. In more recent studies brain imaging and biomarker data are being used to increase sensitivity of detecting cognitive impairment, however the unique ability of CFAS is to compare two identical studies over time, in order to compare these studies like for like the trade-off is that more modern techniques could not be compared. Therefore, in studies using tests which are more optimised for detecting early cognitive changes may be more reliable in estimating ‘caseness’.

A further example of this limitation is in the ability to use the CFAS data to establish functional impairment. Again, due to the initial study design of CFAS I was established over 20 years ago the data available is not optimised to detect functional impairment with high levels pf specificity. The CFAS data available was limited by being overly reliant on physical impairments. More recent measures such as the Amsterdam ADL neuropsychological measures are more specialised reflect cognitive functioning (Sikkes et al., 2013). Arguably this is not just a limitation of the CFAS data, but also the definition of MCI itself as there is no definitive definition or standardised

Measurement. It must be acknowledged that in this particular analysis it is possible that limited measures of functional impairment could have impacted the cases of MCI and dementia.

CFAS was designed initially to estimate the prevalence and incidence of cognitive impairment and dementia and detect changes of such over time; the design of the study makes it unique in its ability to do this. Compared to other more general studies of ageing and health there is fewer rich data surrounding physical ill health measures. Although this does not have a direct bearing on the analysis of MCI, it is a limitation of the studies ability to take into account some relevant physical comorbidities that could be important confounders in analyses, which should be taken into account when interpreting the results from the study.

7.6 Future Research Directions

The previous sections highlight the importance of uniform methods for identification of MCI cases. In addition, new criteria should especially focus on the operationalisation of MCI criteria, and on: (1) which cognitive domains should be tested; (2) which reference group (e.g. same age or healthy younger participants) should be used to define cut-off scores for neuropsychological assessment tests; (3) which subgroups need specific cut-off scores for neuropsychological assessment tests (e.g. for each education level / cultural background); (4) include or exclude people with other mental disorders; and, (5) how should decline in cognition be assessed (by asking participant, or informant, or should cognitive performance be tested over time). Next, another important factor influencing MCI prevalence rates is how dementia is diagnosed as this has direct influence on the number of MCI cases. An example is the 10/66 study showing a relatively low MCI prevalence rate for eight LMICs (Sosa et al., 2012). Dementia in this study diagnosed with the 10/66 study algorithm which seem to include milder dementia cases than if dementia is diagnosed with the DSM criteria, and therefore probably lead to a lower number of MCI cases (Prince et al., 2008, Paddick et al., 2013).

The work presented in this thesis adds new ideas around the direction of studying MCI. The use of a more comprehensive spectrum of cognitive decline is becoming more popular as a way of understanding cognition and impairment. In the future it would be possible to include more neurodegenerative disease within a spectrum such as presented in this study. Research is shifting to the idea of redefining diseases into a spectrum of neurodegeneration encompassing Parkinson's disease, Alzheimer's disease and Lewy body disease etc.

There is a great deal of research specifically in the progression of aMCI to Alzheimer's disease, understandably as this is the most prevalent form of dementia. There is much more scope for investigating the trajectories of non-memory related cognitive impairment. As shown in this analysis the vast majority of MCI prevalence consists of non-memory impairment or both memory and non-memory impairment, this group is even bigger when taking into consideration the proportion of the older population who fall into the OCIND category. There is interesting research to be

done on how non-memory domain impairment transitions or progresses to not only dementia but to other neurodegenerative diseases such as Parkinson's disease.

Focus on understanding risk factors for neurodegenerative disease is also becoming increasingly important for the future. There are interesting areas of research focusing on cognitive reserve and cognitive lifestyles which consider the risks established in this study such as deprivation, education and loneliness. Other theory's such as indexes of frailty which similarly to the comorbidities investigated in this study are assessing the effects of accumulated health deficits. Building on this work is the assessment of the moderating effect of accumulated risk factors on the presentation and progression of neurodegenerative disease.

In the clinical setting there is an emerging reliance on biomarkers for the identification of early signs of dementia. However, the utility of these biomarkers is repeatedly brought into question. It is therefore of increasing importance to further understanding the role biomarkers play in cognitive decline. There is also increasing interest into how biological ageing is measured. Understanding components and models of biological ageing are interesting avenues into the early detection of dementia and mild cognitive impairment and newer cohorts such as the UK biobank are making this research possible.

One of the key insights from this work is the detection of large proportions of older people who have to varying degrees cognitive impairment and functional impairment who do not fall under the diagnosis of dementia. Until there is effective pharmacological intervention for cognitive decline, it is imperative that there is understanding of the proper care needs of this group of the older population, whose needs are likely to be complex. The focus of research so far, has been into the identification of pharmacological treatment, and while this is important for the future, there is an immediate need for understanding how to better care and support people living with cognitive impairment and dementia. There is an increasing body of evidence that this thesis builds on that points to large proportions of dementia and cognitive impairment being preventable due to lifestyle and risk factor modification. Therefore the continuing development of large longitudinal cohorts of ageing are necessary to take this research forward, ideally including neuropsychological data as well as measures of biological risk factors.

MCI is a key research area aimed at identifying individuals at high risk of future dementia which is a major concern for Low- and Middle-Income Countries (LMIC), where the majority of the burden of these diseases exists. Yet, there is very little research into brain health in LMICs and most don't have policies in place to deal with the social and economic burdens of dementia, nor are they undertaking risk reduction to lessen future numbers. Whether MCI is a useful concept in LMIC settings will have important implications for informing strategies for identifying individuals who would benefit from intervention to reduce their dementia risk.

One of the main findings from this work has been to show how much early cognitive decline is not captured by the MCI criteria. A large proportion of the population have been identified with early cognitive changes with and without functional impairments. Therefore one of the roles of this piece of work must be to ask challenging questions of the concept of MCI itself. This work has added to the evidence base that suggests MCI is a concept that has proven to be extremely difficult to define in terms of population research and clinical practise. One thing that is clear after decades of research into MCI the aetiological underpinnings of the diagnosis remain unclear, as indeed is the prognostic value of the definition. One must be open to the viewpoint that if after all this time we remain unclear what is causing MCI and indeed whether diagnosing MCI has any real value, the option of abandoning the concept all together should remain an option.

APPENDIX A – CONFERENCE ATTENDANCE & TEACHING

Conference attendance

I. CFAS Annual Scientific Meeting: London, 2015 – 2018 – Oral presentation

II. Alzheimer's Society Annual Research Conference: London, 2015 – 2018 – Oral and poster presentations

III. International Association of gerontology and geriatrics: San Francisco, US, 2017 – Poster Presentation

IV. Alzheimer's Association International Conference: London, UK, 2017 – Symposium presentation

Teaching

I. Planned, wrote and delivered a number of undergraduate and postgraduate seminars including: MPharm, Introduction to Statistics for Pharmacists; MBBS, Health Economics; MBBS, Living with Long Term Conditions.

II. Written and delivered lectures including: 2017: BSc Biomedical Sciences, Population Ageing & Public Health; MSc Public Health and Health Service Research, Introduction to Quantitative Research Methods: Causation

III. Demonstrated for practical teaching sessions: Psychology BSc, Research Methods and Skills

IV. Supervision of student BSc & MSc dissertation research projects.

V. Marked student coursework and essays.

APPENDIX B – PAPERS AND ABSTRACTS

I. Richardson, C. Stephan, B.C.M. Robinson, L. Brayne, C. Matthews, F 'Secular Trends in the Prevalence of Mild Cognitive Impairment (MCI)', European Journal of Epidemiology. (Under Review)

II. Richardson, C., Matthews, F., Robinson, L. and Stephan, B.C.M. 'THE CHANGING FACE OF MILD COGNITIVE IMPAIRMENT (MCI) AND MILD DEMENTIA', Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 13(7), pp. P544-P545.

Work outside of this PhD

III. Matthews, F. & Richardson, C.: NIH Collaboration Report: Relationships between Education, Deprivation and Incident Dementia: 2018

IV. Joint 1st Author: Lavrencic, L.M., Richardson, C., Harrison, S.L., Muniz-Terrera, G., Keage, H.A.D., Brittain, K., Kirkwood, T.B.L., Jagger, C., Robinson, L. and Stephan, B.C.M. (2017) 'Is There a Link Between Cognitive Reserve and Cognitive Function in the Oldest-Old?', The Journals of Gerontology: Series A, pp. glx140-glx140.

V. Wang, X.-N., McGovern, N., Gunawan, M., Richardson, C., Windebank, M., Siah, T.-W., Lim, H.-Y., Fink, K., Li, J.L.Y., Ng, L.G., Ginhoux, F., Angeli, V., Collin, M. and Haniffa, M. (2014) 'A Three-Dimensional Atlas of Human Dermal Leukocytes, Lymphatics, and Blood Vessels', J Invest Dermatol, 134(4), pp. 965-974.

APPENDIX C - CFAS II ADDITIONAL DATA INFORMATION

The following document details some key information regarding the CFAS II datasets and measurements.

CFAS II variables in need of explanation

The following contains information on some of the key variables used across the CFAS II datasets:

CENTRE	11 = Cambridgeshire 12 = Newcastle 13 = Nottingham
IDENT	Participant project number (unique within centre)
WAVE	Wave of the interview (items stamped with xx_w1 reflect wave 1; xx_w2 reflect wave 2)
SEX	1 = male; 2 = female
DOB	Date of birth listed is the format of day/month/year (dd/mm/yyyy)
DATE	Date of interview in the format of day/month/year (dd/mm/yyyy)
BREAK	Details the last question number which an answer was given for (i.e. on which question did the interview terminate)
PRIORITY	Indicates whether the interview entered priority mode (shortened version of the interview consisting of the cognitive section so that an MMSE score can be obtained along with medication questions and observer ratings)
QUITQ	Indicates at which question the priority mode was initiated
HAS_ELIG	Indicates if the interview required a HAS interview (informant)
EHAS_ELIG	Indicates if the interview required a EHAS interview (informant)
SEVENS	Total score on serial seven question (Q325 at w1; Q308 at w2). This total score is a component for generating the MMSE score
MMSE	MMSE score (please note this would have been re-calculated after all data cleaning had been performed to incorporate interviewer coding errors to MMSE scored items)
MMSE_GP	MMSE group – 1 = MMSE 1-17; 2 = MMSE 18-21; 3 = MMSE 22-25; 4 = MMSE 26-30
AGECAT	AGECAT score. If one or more agecat questions are missing then AGECAT = 0. This variable is the laptop definition of AGECAT. The laptop AGECAT has been used for sampling.
DX	Full agecat algorithm (0 = normal; 1 = demented; 2 = depression; 3 = anxiety)

ORG Indicates organicity level within dx

DEP Indicates depression level within dx

ANX Indicates anxiety level within dx

ALGORITHM_DX Dx score as calculated from running the AGECAT algorithm. Please note dx should be used over the algorithm_dx as the dx score reflects any additional information such as vignette notes which were used when the algorithm could not be run or did not appear to give a representative score.

PROXY The main dataset will contain all the participant ID numbers included in that wave of interviewing. If only informant interviews were conducted then certain questions could be mapped across into the main dataset as well as leaving the full informant interview data in its entirety in the separate HAS and EHAS datasets.

The proxy variable indicates in the main dataset whether the information recorded there comes from a participant interview (proxy = 0); whether questions in that dataset have been mapped from an EHAS interview with an informant (proxy = 1); or if the data has been mapped from a HAS interview with an informant (proxy = 2)

N85 Indicates if the data was mapped from a Newcastle 85+ study participant (N85 = 1)

XX_EDITED Variables appearing in the dataset with '_edited' reflect where changes were made to the data post-interview during data cleaning. For example such checking included where the status of accommodation did not match up with status of living in an institution (both coded by interviewer at time of interview). Necessary paperwork was checked and changes applied to the data - accommodation variable changes are listed in (v6_edited in w1; v7_edited in w2) and changes in whether the participant was living in an institution are listed in (v9_edited in w1; v10_edited in w2). These edited accommodation and institution variables should replace the answers recorded by the interviewer if an edited answer is present.

AUDIT Variable reflecting participation status at each wave with the following labels: 1 = interview done; 2 = dead; 3 = dead at present wave but also had refused present wave; 4 = refused; 5 = moved; 6 = HAS needed but not obtained; 7 = interview done but data corrupted; 8 = lost before present wave; 9 = not applicable

AUDIT_HAS Reflects HAS interview status: 1 = eligible for HAS and completed; 3 = eligible for HAS but not completed and no reason recorded why; 4 = eligible for HAS but refused (refusal could be by participant or informant); 5 = HAS only interview completed; 6 = not eligible for HAS but HAS completed; 9 = not applicable

CFAS II measurements

Mini Mental State Examination (MMSE) (Folstein, 1975)

The table below details the questions in both the wave 1 and wave 2 interviews which are involved in calculating the MMSE score **(mmse_w1 / mmse_w2)**. The component questions have been re-coded and can be found in the main datasets **(mmse01 - mmse26)**. All are worth one point with the exception of **mmse16** (serial seven's score) which is worth a maximum of five points.

VARIABLE	QUESTION	WAVE 1	WAVE 2
mmse01	Name of city/town/village	Q17	Q21
mmse02	Day of week today?	Q22	Q26
mmse03	Date today – day	Q23	Q27
mmse04	Date today – month	Q24	Q28
mmse05	Date today – year	Q25	Q29
mmse06	Season	Q266	Q249
mmse07	County	Q267	Q250
mmse08	Name two main streets nearby	Q268	Q251
mmse09	On what floor of building?	Q269	Q252
mmse10*	What is this called? (pencil)	Q277	Q260
mmse11*	What is this called? (wristwatch)	Q278	Q261
mmse12*	Repeat: 'No ifs, ands or buts'	Q292	Q275
mmse13-15	Repeat 3 words: apple table penny	Q320-Q322	Q303-Q305
mmse16	Sevens	Q325	Q308
mmse17-19	Recall 3 words: apple table penny	Q326-Q328	Q309-Q311
mmse20*	Read and do: Close your eyes	Q329	Q312
mmse21*	Copy this diagram (pentagon)	Q331	Q314
mmse22*	Write a sentence	Q337	Q320
mmse23*	Paper – take in right hand	Q339	Q322
mmse24*	Paper – fold in half	Q340	Q323
mmse25*	Paper – place on lap	Q341	Q324
mmse26	Address of this place?	Q16/Q18	Q20/Q22

Key: * Physical items

mmse_gp

The MMSE scores have been grouped into the following 4 category group:

mmse	mmse_gp
26 – 30	4
22 – 25	3

18 – 21	2
0 – 17	1
Missing / uncertain of which above group the individual falls within	.

The Cambridge Cognitive Examination (CAMCOG) and subscales (Roth, 1988)

CAMCOG and its subscales has been coded up

Cognitive function	Subscale	Variable	Description	Wave 1	Wave 2	Points	Total
Orientation		scgor	Day*	Q22	Q26	1	10
			Date*	Q23	Q27	1	
			Month*	Q24	Q28	1	
			Year*	Q25	Q29	1	
			Season*	Q266	Q249	1	
			County*	Q267	Q250	1	
			Town	Q17	Q21	1	
			Streets*	Q268	Q251	1	
			Floor*	Q269	Q252	1	
			Place*	Q16/Q18	Q20/Q22	1	
Language	Comprehension	scglc	.Nod	Q273	Q256	1	9
			.Touch	Q272	Q255	1	
			.Ceiling	Q270	Q253	1	
			.Tap	Q271	Q254	1	
			Hotel	Q276	Q259	1	
			Village	Q274	Q257	1	
			Radio	Q275	Q258	1	
			.Read1	Q329	Q312	1	
			.Read2	Q330	Q313	1	
Language	Expression	scgle	Hammer	Q291	Q274	1	21
			Chemist	Q290	Q273	1	
			Bridge	Q288	Q271	2	
			Opinion	Q289	Q272	2	
			.Name obj.	Q280-Q285	Q263-Q268	6	
			Fluency	Q287	Q270	6	
			.Ifs*	Q292	Q275	1	
			.Address	Q343	Q326	2	
Memory	Remote	scgmm	WW1	Q311	Q294	1	6

			WW2	Q312	Q295	1	
			German	Q313	Q296	1	
			Russian	Q314	Q297	1	
			Mae	Q315	Q298	1	
			Kidnap	Q316	Q299	1	
Memory	Recent	scgcm	Queen	Q317	Q300	1	4
			Heir	Q318	Q301	1	
			PM	Q147	Q130	1	
			News	Q319	Q302	1	
Memory	Learning	scglm	.Recall pics	Q293-Q298	Q276-Q281	6	17
			.Recog. pics	Q299-Q304	Q282-Q287	6	
			.Recall addr.	Q352-Q356	Q335-Q339	5	
Attention/ Calculation		scgac	Count	Q324	Q307	2	8
			Sevens*	Q325	Q308	5	
			Calculation	Q351	Q334	1	
Praxis		scgpr	.Pentagon*	Q331	Q314	1	12
			.Spiral	Q332	Q315	1	
			.Cube	Q333	Q316	1	
			.Clock	Q334-Q336	Q317-Q319	3	
			.Envelope	Q342	Q325	1	
			.Wave	Q347	Q330	1	
			.Cut	Q345	Q328	2	
			.Teeth	Q346	Q329	2	
Abstract thinking		scgat	Similarities	Q357-Q360	Q340-Q343	8	8
Perception		scgpc	.Faces	Q361-Q362	Q344-Q345	2	8
			.Views	Q363-Q368	Q346-Q351	6	
TOTAL		ccog					103

Key: * Items in MMSE also / . physical items

As in CFAS I, CAMCOG was scored with a maximum of 103 points with three items of the standard CAMCOG interview (Roth, 1988) not included in the calculation. The omitted items were the tactile recognition of coins (which is omitted in the revised CAMCOG-R (Roth, 1998)); calculating their sum, and recognition of two people in the room. These items counted for 4 points and hence the

maximum score that could be achieved was 103 rather than 107. The subscales are defined as in CAMCOG-R (Roth, 1998) except the attention/calculation and the perception subscales which are worth one point less due to an item missing.

Questions that may have been missed due to sensory or motor impairment (the 'physical items' identified above by a dot before the description) were recoded to 0 (i.e. treated as not able to answer the questions).

When just one item was missing, 0 was imputed so that the whole scale would not be missing. The various subscales were calculated before this final stage.

Number of people with complete CAMCOG score by interview:

	Wave 1	**Wave 2**
Number interviewed	7,762	5,288
CAMCOG score obtained	7,085 (91%)	5,109 (97%)
Missing CAMCOG score	677 (9%)	179 (3%)

References:

Williams, J. G., Huppert, F. A., Matthews, F. E., & Nickson, J. (2003). Performance and normative values of a concise neuropsychological test (CAMCOG) in an elderly population sample. *International journal of geriatric psychiatry*, *18*(7), 631-644.

Roth, M., Huppert, F. A., Tym, E., & Mountjoy, C. Q. (1988). The Cambridge examination for mental disorders of the elderly (CAMDEX). *The Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)*.

Roth, M., Huppert, F. A., Mountjoy, C. Q., & Tym, E. (1998). The Cambridge examination for mental disorders of the elderly– revised. *The Cambridge Examination for Mental Disorder of the Elderly-revised*.

ADL-IADL disability / IADL disability / No ADL or IADL disability

Our classification splits people into one of four groups. The first is those who have ADL-IADL disability and is based on activities of daily living (ADL) and instrumental activities of daily living (IADL). This group require help at least several times per week. The second is those who have IADL disability and are not in the first group, and this is based on two IADLs. This group require help regularly. The third group is those that have no ADL or IADL disability, and the fourth group is those who were unclassifiable due to their pattern of missing data.

ADL-IADL disability requiring help at least several times per week (disab = 2)

Questions which determine ADL-IADL disability in screen/combined screen and assessment interviews are:

Q533 Are you able to wash all over or bath?
Q539 Are you able to prepare and cook a hot meal? [This is an IADL]
Q542 Are you able to put on your shoes and socks or stockings?

Possible answers to questions above:

0 = (No), needs help

1 = (Yes), some difficulty *(Use of special aids: Code 1)* 2 = (Yes), no difficulty

Q559 Mobility of subject *(possible answers:)*

1 = Usually ambulant non-housebound
2 = Usually ambulant housebound
3 = Chairfast permanently
4 = Bedfast permanently

A person has ADL-IADL disability if they need help with washing or hot meals or shoes and socks (any of the first three questions answered 0) or if they cannot get around outside (last question answered as 2, 3 or 4).

It is inferred that if a person answered the first few questions showing they were unfocussed in time, they have ADL-IADL disability. These people were asked a select subset of questions (i.e. went into priority mode) which did not include the above questions.

If a person did not need help with washing or hot meals or shoes and socks (i.e. all of first three questions answered 1 or 2) and they could get around outside (i.e. last question rated 1) then they were divided into IADL disability or no ADL or IADL disability.

<u>IADL disability (disab = 1)</u>

A person has IADL disability if they need help with heavy housework or shopping and carrying heavy bags.

Q537 Are you able to do the heavy housework?
Q538 Are you able to shop and carry heavy bags?

<u>No ADL or IADL disability (disab = 0)</u>

A person has no ADL or IADL disability if they do not need help with washing, hot meals, shoes and socks, heavy housework or shopping and carrying heavy bags, and they can get around outside. If a person did not need help with the two IADLS* and had some missing data on the ADLs then they were coded as having no ADL or IADL disability (by the hierarchical nature of ADL and IADL). Also a person could be recoded to no ADL or IADL disability if they had one IADL missing and ADL disability had been ruled out.
These ways of dealing with missing data affected a very small number of people
* *For this paragraph, preparing a hot meal is treated as an ADL*

<u>Unclassifiable (disab = -1)</u>

This only affects people who did not answer all of the questions above. This includes a lot of cognitively frail people who went into priority mode but not immediately after the first few questions.

disab	**Wave 1**

0 (No ADL or IADL impairment)	4,975
1 (IADL impairment)	1,495
2 (ADL impairment)	981
Missing	311
Total	7,762

Modified Townsend Disability Scale

This scale consists of 9 activities: cutting own toenails, washing all over or bath, getting on a bus (replaced running to catch a bus in Townsend (1979)), going up and down stairs, heavy housework, shopping and carrying heavy bags, preparing and cooking a hot meal, reaching an overhead shelf and tying a good know in string (Bond, 1982).

For each activity, a person was assigned a score of 2 if they needed help; 1 if they had some difficulty or used aids in order to complete the activity; and 0 if they had no difficulty and did not need any use of aids.

The scores (**town**) from these activities are added up to form a score from 0 – 18 where 0 is no functional incapacity and 18 is very severe functional incapacity.

The relevant questions are as follows listed in the format wave 1 / wave 2:

Q532 / Q505 Able to cut own toenails
Q533 / Q506 Able to wash all over
Q534 / Q507 Able to get on a bus
Q535 / Q508 Able to go up and down stairs
Q537 / Q510 Able to do heavy housework
Q538 / Q511 Able to shop and carry heavy bags
Q539 / Q512 Able to prepare and cook a hot meal
Q540 / Q513 Able to reach an overhead shelf
Q541 / Q514 Able to tie a good knot in a piece of string
Q559 / Q532 Degree of mobility of subject

Getting on a bus, and to a lesser extent, going up and down stairs were quite often missing, and so a score of 2 was imputed if a person's mobility as assessed by interviewer (Q559/Q532) was poor. If these activities were still missing then if not asked, a score of 2 was given, and if no answer or the interviewee didn't know, a score of 1 was given.
A person had an unclassifiable score (town= -1) if they were missing an answer to any questions other than getting on a bus and going up and down stairs. This mostly happened to people who went into priority mode due to being disorientated in time and space.

This scale of functional incapacity has also been dichotomized (**towng**) where a score of 1 is given if the scale was 11-18, and 0 if the scale was 0-10. If someone did not have a modified Townsend Disability score, but they were likely (or certainly) going to fall one side of 10/11, they were coded.

References:

Bond, J., & Carstairs, V. D. (1982). *Services for the elderly*. Edinburgh: Scottish Home and Health Department.

Townsend, P. (1979). Poverty in the United Kingdom. Harmondsworth, UK; Pelican

Dementia Scale of Blessed (1968)

As has been done by other researchers (e.g. Roth, 1998), the section on personality, interests and drive has been discarded and a score from 0-17 has been produced. The score has been composed for individuals where an informant was interviewed (**bless_w1, bless_w2**).

The items of the scale, their corresponding questions, ways of dealing with missingness and maximum points are outline below. The comment 'go to other interviews' means go to the same question(s) on earlier or later informant interviews. Earlier interviews are used if they were unable to perform the task. Later interviews are used if they were able to perform the task.

1) Inability to perform household tasks (max score = 1)
Q51 Does s/he have difficulty performing common household tasks, for example, can s/he make a cup of tea? (Recode 9 ('due to disability') to 0 ('no difficulty')) *If missing:*
Q50 Is s/he less able to take care of her/himself without
help? *If still missing:* go to other interviews.

2) Inability to cope with small sums of money (max score = 1)
Q52 Does s/he have difficulty managing small amounts of money?
If missing: go to other interviews. *If still missing:* assume can't use money if Q52 not asked, recode to 0.

3) Inability to remember short lists of items, e.g. in shopping (max score = 1)
Q19 Can s/he remember short lists of items when shopping? (For example if s/he went to buy 3 things
would s/he remember them or be able to tell someone else what s/he
needs?) *If missing:* go to other interviews.
If still missing: Q18 Has s/he had any difficulty with her/his memory? (If yes: Have you noticed any change over the last year or two?)

4) Inability to find way about indoors (max score = 1)
Q30 Does s/he have difficulty finding the way around the home (or ward), or finding the toilet?
If missing: go to other interviews.
If still missing: and few or no problems with Q31 (see below), assume fine on this question.

5) Inability to find way about familiar streets (max score = 1)
Q31 Has s/he had difficulty finding the way around the neighbourhood, for example, to the shops or post office near home? (If yes, Has there been any change in the last year or two?)
If missing: Q22 Has s/he had difficulty finding her/his direction or has lost the way when you have been out together or s/he has been out alone? Have you noticed any change over the last year or two?
If still missing: and few or many problems with Q30 (see above), assume difficulty with this question. *If still missing:* go to other interviews.

6) Inability to interpret surroundings (max score = 1)
Q28 Does s/he have difficulty in telling the difference between people such as visitors, relatives and doctors?
If missing: Q29 Does s/he ever mistake you (or (other) family members or friends) for someone else? *If still missing:* go to other interviews.

7) Inability to recall recent events (max score = 1)
Q21 Is there difficulty remembering what happened yesterday? *If missing:* go to other interviews.
If still missing: Q27 Does s/he have difficulty remembering when s/he last saw you?

8) Tendency to dwell in the past (max score = 1)
Q25 Does s/he tend to talk about what happened long ago rather than in the present? *If missing:* go to other interviews.

9) Eating (max score = 3)
Q56 Does s/he have difficulty feeding her/himself?
If missing: go to other interviews.

10) Dressing (max score = 3)
Q53 Does s/he have difficulty dressing? In what way? (Is help needed?) (Recode 9 ('due to disability') to 0
('no difficulty'))
If missing: go to other interviews.

11) Complete sphincter control (max score = 3)
Q57 Does s/he ever wet or soil her/himself by mistake? (How often?) *If missing:* go to other interviews.

Questions from items 4, 5, 9 and 11 featured in skip sections and hence persons not entering the skip section have no difficulties.

Many people did not have an answer to item 5 (inability to find way about familiar streets). It was fairly common for people to have up to 2 answers missing for the first 8 items (often items 4 and 5). As none of these questions dominate the scale, 0 was imputed for up to 2 of these questions, and a score given.

There is a bias in that cognitively frail people were more likely to have HAS interviews than cognitively intact people.

References:

Blessed, G. T. B. E., Tomlinson, B. E., & Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *The British Journal of Psychiatry*.

Roth, M., Huppert, F. A., Mountjoy, C. Q., & Tym, E. (1998). The Cambridge examination for mental disorders of the elderly– revised. *The Cambridge Examination for Mental Disorder of the Elderly-revised*.

Hachinski Ischaemic Score (HIS)

The HIS (Hachinski et al. 1975) has been coded up on all those who we classified as demented and for whom we had informant interviews. The notes of Wade et al. 1987 were particularly helpful.

The questions and points for each component are given below which add up to a maximum of 18 points. A score greater than 7 points suggests vascular impairment. All questions are from informant (HAS) interviews unless stated otherwise. Answers to questions are given in brackets like this (first answer that would score positively / second answer that would score positively … : first answer that would score negatively / second answer that would score negatively).

With the exception of components D (Nocturnal confusion) and E (Relative preservation of personality), just one piece of evidence was enough to get the whole component positively scored. For D, both questions had to be answered 'Yes'. For E, one piece of evidence in favour of a change in personality was enough to score it negatively. Components were missing if there was no evidence in favour or against the component. When appropriate, answers from backup questions were used to reduce the number of missing components and missing HIS scores. With the exception of component A (abrupt onset), this affected very few individuals and so these questions are not mentioned.

A) Abrupt onset (max score = 2)
Q107 Did (the problems/symptoms/illness) happen suddenly, in a matter of hours or over days, or did it happen slowly over weeks or months? (>=0.5 months: <0.5 months)

Backup questions - any evidence from:
Q34 Did these problems with memory begin rapidly or gradually? (Rapid onset 1-3 days probable/certain
/Rapid onset 4-21 days probable/certain: Gradual onset probable/certain)
Q41 Have these difficulties with thinking and making decisions developed in a gradual manner or have they come on suddenly? (Sudden : Gradual)
Q59 Have these (aphasia/apraxia) difficulties developed gradually or did they come on suddenly? (Sudden : Gradual)

B) Stepwise deterioration (max score = 1)
Q42 Have these difficulties (with thinking and making decisions) developed in steps and stages? (Yes : No)

C) Fluctuating course (max score = 2)
Q81 Are there periods lasting days or weeks when his/her thinking seems quite clear and then muddled?
(Yes : No)
Q110 Has the (present illness) tended to vary a lot, day to day, week to week, becoming worse and then perhaps improving for a while - up and down? (If yes, how much did it vary? How long did these periods last?)
(Mild/Moderate or marked fluctuation : No fluctuations)

D) Nocturnal confusion (max score = 1)
Q83 Are there long periods during the day when s/he is lucid and not confused (that is, knows where s/he is and knows what s/he is doing and saying)? (Yes : No) AND
Q84 Does s/he get confused at night, wander about or talk nonsense? (Yes : No)

E) Relative preservation of personality (max score = 1) - includes preservation of insight

Q60 Have you noticed any changes in his/her personality such as the way s/he behaves socially (with other people)? (No : Yes)
Q72 How does s/he treat you (his/her relatives, friends) now. Is there a tendency to show a lack of interest, concern or affection? (No : Mild/Severe)
Q640 (subject interview) Observer rating: Lack of insight into present disability (No : Yes)

F) Depression (max score = 1)

dep - calculated from the AGECAT algorithm in the subject interview dataset
(dp3/dp4/dp5/dn3/dn4/dn5 : d0/d1/d2)
Q87 Has there been any indication that s/he may be depressed, for example, is there a loss of interest or enjoyment in things in general? (Yes : No) Q92 Do you think s/he is depressed? (Yes : No)

G) Somatic complaints (max score = 1)

Q613 (Subject interview) Observer rating: Gait normal, just unsteady (Mild/Severe : Absent)
Q442 (Subject interview) Do you suffer from regular headaches? (Yes, non-specific : No/Yes, migraine)
Q181 (Subject interview) Do you often feel dizzy? (More than once per week : No or rarely)
Q278 Does s/he have a tendency to fall? (Yes : No)

H) Emotional incontinence (max score = 1)

Q269 If something happens to make subject laugh or feel sad or cry, is it sometimes difficult to control? (Fairly certain/Unsure but probably : No)

I) History of hypertension (max score = 1)

Q261 & Q262 Has s/he ever had high blood pressure? How was it treated? (Hypertension probable/Certain and Medication Probable/Certain: No/ Yes but not treated)

J) History of strokes (max score = 2)

Q268 Has there ever been a stroke or a time when part of the body became paralysed? (If YES when was that? Did it happen suddenly? (Probably/Certainly after age 40 : No history of stroke or sudden paralysis)

K) Evidence of associated atherosclerosis (max score = 1)

Q259 Has a heart attack ever been diagnosed by a doctor when several weeks rest was advised? (Probable/Certain : No)
Q256 Has there ever been pain or discomfort in the legs on walking that goes away with rest? (Intermittent Claudication Probable/Certain : No)
Q260 Has there ever been pain or discomfort in the chest that goes away with rest? (Angina pectoris Probable/Certain : No)

L) Focal neurological symptoms (max score = 2)

Q264 Has s/he ever had sudden blindness in one eye? (Probable/Certain : No)
Q265 Has s/he ever had weakness or difficulty with speech, memory or vision which got better after a day? (Yes : No)
Q266 Has there been a weakness in one arm or one leg, or an arm and a leg on the same side of the body? (Probably lasted <24hrs/Certainly lasted <24 hrs/ probably lasted 24+hrs/Certainly lasted 24+hrs :
No)
Q625 (Subject interview) Observer rating: Dysarthria due to brain damage (Yes: No)

M) Focal neurological signs (max score = 2)

Q611 (Subject interview) Observer rating: Obvious evidence of paralysis or stroke (mild/severe : no)
Q189 (Subject interview) Observer rating: One or more limbs appear to be wholly or partially paralysed, or one side of the face (yes left sided/yes right sided/other : no)

There are fewer missing here because often the scores of people, who had just a few missing components, would fall into one group irrespective of the missing values had they been observed.

References:

Hachinski, V. C., Iliff, L. D., Zilhka, E., Du Boulay, G. H., McAllister, V. L., Marshall, J., ... & Symon, L. (1975). Cerebral blood flow in dementia. *Archives of neurology*, *32*(9), 632-637.

Wade, J. P. H., & Hachinski, V. C. (1987). Multi-infarct dementia. *Dementia*, London: Churchill Livingstone, 209-28.

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Social class and Social economic group

During the wave 1 interview, participants are asked to give details of their main occupation and where applicable give these details for their partner also. The occupation questions in the wave 1 interview fall within the section of Q45-Q57.

A program called CASCOT (http://www2.warwick.ac.uk/fac/soc/ier/software/cascot/), developed by Warwick University was used to convert the occupation details given at interview into the Standard Occupational Classification (SOC) developed by the UK Office for National Statistics. The resulting data is the social class (**SC**) and social economic group (**SEG**) for participants in cases where codings could be completed.

Townsend Deprivation Index

The Townsend deprivation score is a measure of area-based socio-economic status. It does not include a component that overlaps with the individual indicators of socio-economic status. It is a composite measure that takes into account the proportion of unemployed, yet economically active, individuals aged 16-59/64, the proportion of households who do not possess a car, the proportion of households with more than one person per room, and the proportion of households that are not owner-occupied. The higher the score, the more deprived the area.

References:

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APPENDIX D – CFAS QUESTIONNAIRE

Q4 Are you Married, Single, Widowed or divorced? (If NO are you separated or cohabiting) 1. Married 2. Cohabiting 3. Single 4. Widowed 5. Divorced/separated 7. No answer 6. Not asked. If Q4 = 4 or 5 ask Q5	

Q40 How many years did you spend in full time education Answer in years ___ Don't know 77	Q40 Include all years in any education.

This next section of questions is about your memory. *Q136 Have you ever had any difficulty with your memory? 0. No 1. Yes	

8. No answer 9. Not asked	
IF YES ASK Q137 OTHERWISE SKIP TO Q138	
*Q137 Was/is that a problem for you? 0. No 1. Yes, moderate 2. Yes, severe 8. No answer 9. Not asked	Q137 Rate as a problem if the respondent says that it is a problem

Q212 Do you feel lonely? 0. No 1. Infrequently 2. Frequently/Persistently 8. No answer 9. Not asked	Q212 Here R simply admits to feeling lonely. The reasons for feeling lonely are not explored and the feeling itself is simply rated. It should fulfil the criteria of being unpleasant and not under voluntary control, but it is not necessarily out of proportion to the circumstances as these in any case would be difficult to judge.

The next part of the interview is concerned with memory and concentration and you might need your reading glasses for some of the questions. **Some of the questions I am going to ask will seem rather easy. Having said that, no-one is expected to be able to manage them all, so please don't worry if feel you have made a mistake.**	This section forms part of the cognitive examination. Some of the items (those marked with a star) are part of the Mini Mental State Examination. If you seem to be losing the subject's co-operation ask these items as a priority. It is important that you speak slowly and clearly. If the subject appears not to have heard or understood, repeat the question (unless the item specifically prohibits repetition). Any

	item that is not attempted or refused mark as incorrect. DO NOT CORRECT IF A WRONG ANSWER IS GIVEN.
* Q266 What is the season? 0. Incorrect 1. Correct 9. Not asked.	Allow flexibility when seasons change March= winter/spring June= spring/summer September= summer/autumn Late Nov/Dec = autumn/winter
Can you tell me where we are now? For instance *Q267 What county are we in? 0. No 1. Yes 9. Not asked	
*Q268 Name two main streets nearby (or near to your home) 0. Incorrect 1. Correct 9. Not asked	Not including R's own street.
*Q269 What floor of this building are we on? 0. Incorrect	

1. Correct 9. Not asked	
LANGUAGE **Now I'm going to ask you to do some things so please listen carefully.** DO NOT PROMPT. REPEAT THE ENTIRE INSTRUCTION IF NECESSARY Q270 Before looking at the ceiling please look at the floor. 0. Incorrect 1. Correct 9. Not asked	Should the respondent not complete the full sequence then the whole instruction may be repeated, without change in tone or tempo, to ensure that it has been heard and understood. Prompting and coaching stage by stage are not allowed. If respondent is physically incapable code 9 and note why in the vignette.
Q271 Tap each shoulder twice with two fingers keeping your eyes shut. 0. Incorrect 1. Correct 9. Not asked	
Q272 Touch your right ear with your left hand. 0. Incorrect 1. Correct 9. Not asked IF Q270, Q271 AND Q272 CORRECT SKIP TO Q274 OTHERWISE ASK Q273	
Q273 Please nod your head.	

0. Incorrect 1. Correct 9. Not asked	
I am going to ask you some questions and would like you to answer yes or no.	
Q274 Are villages larger than towns? 0. Incorrect 1. Correct 9. Not asked	
Q275 Was there wireless/radio in this country before television was invented? 0. Incorrect 1. Correct 9. Not asked	
IF BOTH Q274 AND Q275 CORRECT SKIP TO Q277, OTHERWISE ASK Q276	
Q276 Is this place a hotel? 0. Incorrect 1. Correct 9. Not asked	
SHOW PENCIL *Q277 What is this called?	Q277-Q285 For these questions accurate naming is required. Descriptions of function or approximate answers are not acceptable. For example: used to tell the time, for wristwatch, would be incorrect.

0. Incorrect 1. Correct 9. Not asked	Present the objects to the subject and allow them to be held. Put the objects out of sight before proceeding. In the case of approximate answers, you should say 'Can you think of another word for it?'
SHOW WRISTWATCH *Q278 What is this called? 0. Incorrect 1. Correct 9. Not asked	
SHOW ENVELOPE Q279 What is this called? 0. Incorrect 1. Correct 9. Not asked	
Later on I'm going to give you a name and address to write on this envelope. When you have finished doing that I'd like you to do the following: turn it over, seal it, and write your initials on the back. Could you remember to do that then, without me reminding you?	Illustrate the actions whilst giving the instructions.
I am going to show you some pictures of objects. Please tell me the name of each one.	
Q280 SHOW PICTURE OF SHOE 0. Incorrect 1. Shoe, sandal 9. Not asked	

Q281 SHOW PICTURE OF TYPEWRITER 0. Incorrect 1. Typewriter 9. Not asked	
Q282 SHOW PICTURE OF SCALES 0. Incorrect 1. Scales 9. Not asked	
Q283 SHOW PICTURE OF SUITCASE 0. Incorrect 1. Suitcase, portmanteau, case 9. Not asked	
Q284 SHOW PICTURE OF BAROMETER 0. Incorrect 1. Barometer 9. Not asked	
Q285 SHOW PICTURE OF TABLE LAMP 0. Incorrect 1. Table lamp, lamp 9. Not asked	
Q286 Now I'd like you to tell me as many different words beginning with the letter S as you can think of in one minute	Q286 Record words on a separate sheet. Do not count repetitions and do not allow proper nouns. If respondent

Nn Number recorded 99 Not asked	get stuck, encourage him/her with 'Can you think of any more?
Q287 Name as many different animals as you can think of. You will have one minute to do this. Nn Number recorded 99 Not asked	Q287 Record names of animals on a separate sheet. Only if respondent asks for clarification, explain that animals include birds, insects, humans etc. If respondent gets stuck, encourage him/her with 'Can you think of any more?'
Q288 What is a bridge? 0. Incorrect 1. Cross the bridge 2. Goes across a river etc 9. Not asked	
Q289 What is an opinion? 0. Incorrect 1. A good opinion of someone 2. A person's idea about something 9. Not asked.	
IF BOTH Q288 AND Q289 SCORE 2 SKIP TO Q292	
Q290 Where do people usually go to buy medicine?	Correct answer: chemist, pharmacy

0. Incorrect 1. Chemist, pharmacy, surgery, supermarket 9. Not asked	(accept locally appropriate answer)
Q291 What do you do with a hammer? 0. Incorrect 1. Any correct use 9. Not asked	Q291 The answer does not have to be specific. If you can't code the answer seek clarification; say 'Can you tell me more about that?'
*Q292 **I am now going to say something and I would like you to repeat it after me.** No Ifs, ands or buts' 0. Incorrect 1. Correct (exact phrase only) 9. Not asked	Q292 Only one presentation is allowed so it is essential that you read the phrase clearly and slowly, enunciating all the S's
MEMORY	
Q293 Can you tell me what were the object in the coloured pictures I showed you a little while ago? A. Shoe, sandal 0. Incorrect	Q293 This is a test of memory so either a description or accurate names are acceptable. If the respondent incorrectly named an object in the earlier questions (Q199-

1. Correct 9. Not asked	Q204) and uses the same name again, count as correct.
Q294 Typewriter 0. Incorrect 1. Correct 9. Not asked	
Q295 Scales 0. Incorrect 1. Correct 9. Not asked	
Q296 Suitcase, portmanteau, case 0. Incorrect 1. Correct 9. Not asked	
Q297 Barometer 0. Incorrect 1. Correct 9. Not asked	
Q298 Table lamp, lamp 0. Incorrect 1. Correct 9. Not asked	
Q299 SHOW PICTURES FOR RECOGNITION IN HANDBOOK. Which of these did I show you before? A. Shoe, sandal	

0. Incorrect 1. Correct 9. Not asked	
Q300 Typewriter 0. Incorrect 1. Correct 9. Not asked	
Q301 Scales 0. Incorrect 1. Correct 9. Not asked	
Q302 Suitcase, portmanteau, case 0. Incorrect 1. Correct 9. Not asked	
Q303 Barometer 0. Incorrect 1. Correct 9. Not asked	
Q304 Table lamp, lamp 0. Incorrect 1. Correct 9. Not asked	
Now I'm going to ask you some questions about the past.	

Q305 Who was the US president who was shot in Texas? 0. Incorrect 1. John F Kennedy 9. Not asked	
Q306 What is Yoko Ono famous for? 0. Incorrect 1. Wife of Beatle John Lennon 9. Not asked	
Q307 Who was the first man to set foot on the moon? 0. Incorrect 1. Neil Armstrong 9. Not asked	
Q308 What was Edmund Hilary famous for? 0. Incorrect 1. First to reach summit of Mount Everest. 9. Not asked	
Q309 Who was the first woman Prime Minister of India? 0. Incorrect 1. Indira Ghandi 9. Not asked	

Q310 Who was the famous cinema actress who married Prince Ranier of Monaco? 0. Incorrect 1. Grace Kelly 9. Not asked	
Q311 Can you tell me when the first world war began? 0. Incorrect 1. 1914 within 1 year 9. Not asked	
Q312 Can you tell me when the second world war began? 0. Incorrect 1. 1939 within 1 year 9. Not asked	
Q313 Who was the leader of the Germans in the Second World War? 0. Incorrect 1. Hitler 9. Not asked	
Q314 Who was the leader of the Russians in the Second World War? 0. Incorrect 1. Stalin 9. Not asked	
Q315 What was Mae West famous for?	

0. Incorrect 1. Entertainer, film star 9. Not asked	
Q316 Who was the famous flyer whose son was kidnapped? 0. Incorrect 1. Lindbergh 9. Not asked	
Q317 What is the name of the present King or Queen? 0. Incorrect 1. Correct 9. Not asked	
Q318 Who will follow her (him) 0. Incorrect 1. Correct 9. Not asked	If respondents jump to William ask who constitutionally will follow her
Q319 What has been in the news in the past week or two? 0. Incorrect 1. Correct 9. Not asked	If a general answer is given, e.g. 'War' ask for details.

I am going to say three words. After I have finished saying all three, I want you to repeat them. Remember what they are because I am going to ask you to say them again in a few minutes. **NAME THE FOLLOWING 3 WORDS TAKING 1 SECOND TO SAY EACH:** Apple, Table, Penny. *Q320 Apple 0. Not named on first try 1. Names on first try	If any errors or omissions are made on the first attempt, repeat all the names until the respondent learns all three (maximum of five repeats). Record number of repeats (record 0 if all correct on first attempt)
*Q321 Table 0. Not named on first try 1. Names on first try	
*Q322 Penny 0. Not named on first try 1. Names on first try	
* Q323 RATE NUMBER OF REPEATS REQUIRED TO GET ALL THREE CORRECT (MAXIMUM OF 5) 0. All correct first try 1. 1 Repeat 2. 2 Repeats 3. 3 Repeats 4. 4 Repeats 5. 5 Repeats 7. Did not get all 3 correct	

ATTENTION/ CONCENTRATION	
Q324 Now I would like you to count backwards from 20 0. Two or more errors 1. One error 2. Correct 9. Not asked	Q324 If respondent makes a mistake and spontaneously corrects it, count as correct.
*Q325 Now I would like you to take 7 away from 100. Now take 7 away from the number you got. Now keep subtracting 7 until I tell you to stop. Record answers given in the following format. Nn, nn, nn, nn, nn, 888 No answer 999 Not asked	If the participant needs prompting, it is important not to repeat the answer given by him/her. If the participant asks if the answer is correct, respond with *you're doing fine* do not say yes or no. If R comes to a halt in the series and gives no answer then code 888 followed by 999
MEMORY RECALL What were the three words I asked you to repeat a little while ago? *Q326 Apple 0. Not recalled 1. Recalled 9. Not asked *Q327 Table 0. Not recalled 1. Recalled	This is a memory item. If an incorrect word was consistently repeated, e.g. stable instead of table, and is recalled here, count as correct.

9. Not asked *Q328 Penny 0. Not recalled 1. Recalled 9. Not asked	
LANGUAGE: READING COMPREHENSION *Q329 Read this page and then do as it says. SHOW READING COMPREHENSION ON CARD – CLOSE YOUR EYES. 0. Incorrect 1. Correct 9. Not asked	It is not necessary for the respondent to read aloud. If respondent reads instruction but fails to carry out action, say 'Now do what it says'. Rate 1 only if action is carried out correctly.
Q330 Now this page. SHOW READING COMPREHENSION – IF YOU ARE OLDER THAN 50 PUT YOUR HANDS BEHIND YOUR HEAD 0. Incorrect 1. Correct 9. Not asked	
PRAXIS	
*Q331 Please would you copy this design?	Each pentagon should have 5 clear sides and 5 clear corners and overlap should form a diamond.

OFFER DRAWING SHEET PENTAGON 0. Incorrect 1. Correct 9. Not asked	
Q332 And now this design – SPIRAL 0. Incorrect 1. Correct 9. Not asked	Q332 Three connected loops are required in the correct orientation.
Q333 And now this – 3D HOUSE 0. Incorrect 1. Correct 9. Not asked	Q333 Requires windows, door, and chimney in correct position and in 3D representation with all angles. Smoke may be omitted.
Q334 Draw a large clock face and put all the numbers in. A. Clock Face 0. Incorrect 1. Correct (circle or square) 9. Not asked	Q334 'Large' is important; to enable all the numbers to fit in. Square or round is acceptable. If the only numbers marked are for each quarter of an hour, prompt for all numbers.
Q335 All numbers 0. Incorrect 1. Correct 9. Not asked	Numbers may be in Roman (I,II,III…) or Arabic (1,2,3…) style

Q336 Now set the hands to ten past eleven. 0. Incorrect 1. Correct 9. Not asked	
*Q337 Write a complete sentence on this sheet of paper. 0. Incorrect 1. Correct 9. Not asked	Q337 Indicate the bottom of the drawing sheet. Ask the respondent what s/he has written and transcribe it underneath if it is illegible. Spelling and grammar are not important. The sentence must have a subject (real or implied) and a verb. 'Help' or 'Go away' are acceptable. Do not take dictation.
*Q338 RATE; IS THE SUBJECT RIGHT OR LEFT-HANDED? 1. Right-handed 2. Left-handed 7. Unable to judge	
READ THE FULL STATEMENT, STRESSING THE WORDS IN CAPITALS AND THEN HAND OVER THE PIECE OF PAPER. I am going to give you a piece of paper. When I do, take the paper in your **RIGHT** hand. Fold the paper in half with **BOTH** hands, and put the paper down on your **LAP**. *Q339 Right hand 0. Incorrect 1. Correct 9. Not asked	Read the statement and then hand to the respondent a sheet of paper. Make a point of handing to the respondent's midline. Do not repeat instructions or coach. Score a move as correct only if it takes place in the correct sequence. Stress the words in emboldened type.

*Q340 Folds 0. Incorrect 1. Correct 9. Not asked	
*Q341 Lap 0. Incorrect 1. Correct 9. Not asked	
DON'T TAKE THE PAPER BACK. HAND AN ENVELOPE TO THE RESPONDENT.	
Q342 Now put the paper in the envelope. 0. Incorrect 1. Correct 9. Not asked	
Q343 Write this name and address on the envelope: George Smith, 38 Mill Road, Blackpool SAY Please try to remember this name and address as I shall be asking you about them later on. RATE Legible address 0. Incorrect 1. Poor but acceptable	This question concerns writing to dictation and not memory so you can present the name and address word by word if necessary. Spelling and neatness are not important. Criterion is whether letter is likely to reach exact destination: e.g. Gorg Smth is acceptable, 83 is incorrect. If respondent is unable to write or visually impaired say the address slowly, twice, and ask him/her to remember it.

2. Correct 9. Not asked	
Q344 HERE THE SUBJECT SHOULD REMEMBER YOUR EARLIER REQUEST TO SEAL THE ENVELOPE AND WRITE THEIR INITIALS ON THE BACK. WAIT A FEW SECONDS TO ALLOW THEM TO REMEMBER 0. No correct action 1. One action with prompt 2. Both actions with prompt 3. One action without prompt, one with 4. Seals and writes own name without prompt 5. One action without prompt only TAKE ENVELOPE BACK	
Now I would like you to carry out a simple action	
Q345 Show me how you would cut with scissors. 0. Incorrect 1. Response is concrete 2. Correct mime 9. Not asked	Q345-Q346 Here a correct mime is needed. If the respondent uses fingers to represent scissors or brush, say 'Pretend you are holding scissors (or Brush)' Rate for best effort.

IF SCORES 2 SKIP TO Q348	
Q346 Show me how you would brush your teeth with a toothbrush. 0. Incorrect 1. Response is concrete 2. Correct mime 9. Not asked	Q346 Rate for best effort Score 1 if respondent makes a brushing movement but not as though holding a toothbrush.
IF SCORES 2 SKIP TO Q348	
Q347 Can you show me how you would wave goodbye? 0 Incorrect 1. Correct 9. Not asked	
CALCULATION I am now going to place a coin into your hand and I want you to tell me what it is without looking at it. PALM DOWN; PLACE IN RESPONDENT'S HAND, ONE AT A TIME. Q348 1p 0. Incorrect 1. Correct 9. Not asked	

Q349 10p 0. Incorrect. 1. Correct 9. Not asked TAKE THE COINS BACK	
Q350 HAND TWO COINS AS IF THEY ARE DIFFERENT ONES How much money does this make? 0. Incorrect 1. Correct (11p) 9. Not asked	Respondent may look at coins to see if s/he was correct. Mental calculation is rated here - no pen & paper
Q351 If someone gave you this amount (11p) as change from £1, how much did you spend? 0. Incorrect 1. Correct (89p) 9. Not asked	Q351 Mental calculation is required. Paper and pencil are not allowed.
Q352 What was the name and address you wrote on the envelope a short time ago? Recalls: George 0. Not recalled 1. Recalled 9. Not asked	

Q353 Recalls: Smith 0. Not recalled 1. Recalled 9. Not asked	
Q354 Recalls: 38 0. Not recalled 1. Recalled 9. Not asked	
Q355 Recalls: Mill Road 0. Not recalled 1. Recalled 9. Not asked	
Q356 Recalls: Blackpool 0. Not recalled 1. Recalled 9. Not asked	
ABSTRACT THINKING **I am going to name two things and I'd like you to tell me in what way they are alike. For example, a dog and a**	

monkey are alike because they are both animals. Q357 In what way are an apple and a banana alike? 0. Round, have calories 1. Food, grow, have peel 2. Fruit 9. Not asked	
IF SCORE IS LESS THAN 2 SAY They are also alike because they are both fruit.	
Q358 In what way are a shirt and a dress alike? 0. Have buttons 1. To wear, made of cloth, keep you warm 2. Clothing, garments 9. Not asked	
Q359 In what way are a table and a chair alike? 0. Wooden, have 4 legs 1. Household objects, used for meals 2. Furniture	

9. Not asked	
Q360 In what way are a plant and an animal alike? 0. Useful to man, carry germs 1. Grow, need food, natural 2. Living things 9. Not asked	
PERCEPTION VISUAL SHOW RECOGNITION OF FAMOUS PEOPLE IN BOOKLET Who is this? Q361 A. Queen 0. Incorrect 1. Correct 9. Not asked Q362 B. Pope 0. Incorrect 1. Pope, Archbishop, Bishop 9. Not asked	Q360 Score as correct if picture is recognised. Correct name is not required.
SHOW RECOGNITION OF OBJECTS IN BOOKLET These are pictures of objects taken from unusual angles. Can you tell me what they are?	Q360-Q368 Criterion is whether the object is recognised, not that it is named correctly, and therefore descriptions of function are acceptable.

Q363	A. Spectacles 0. Incorrect 1. Correct 9. Not asked	
Q364	B. Shoe 0. Incorrect 1. Correct 9. Not asked	
Q365	C. Purse, suitcase, briefcase 0. Incorrect 1. Correct 9. Not asked	
Q366	D. Cup and saucer 0. Incorrect 1. Correct 9. Not asked	
Q367	E. Telephone 0. Incorrect 1. Correct 9. Not asked	
Q368	F. Pipe 0. Incorrect 1. Correct 9. Not asked	

In this part of the interview, I would like you to do some activities which resemble the kinds of memory and concentration tasks which people do in their everyday lives.	
Q369 First I am going to read you a short news story of just a few lines. Please listen carefully and try to remember it just the way I say it, as close to the same words as you can. When I have finished I would like you to tell me everything you can remember even if you are not sure. Are you ready?	**Selection criteria applies.**
READ FROM THE SCREEN AVOIDING EYE CONTACT IN A CLEAR MATTER OF FACT WAY AT A MEDIUM PACE.	
Anna Thompson of South London, employed as a cook in a school canteen, reported at the Police Station that she had been held up on the High Street the night before, and robbed of twenty-six pounds. She had four small children, the rent was due and they had not eaten for two days. The officers, touched by the woman's story, took up a collection for her. PAUSE FOR A FEW SECONDS Now tell me as much about the story as you can remember. 0. Nothing recalled 1. Something recalled	

2. No attempt made 9. Not asked	
Q370 The next task is a measure of how rapidly you can do something. I want to see how quickly you can work through this list crossing out all the Ps and Ws. Start at the top left hand corner where the arrow is and work along the line. Then go to the beginning of the next line and work across the line again as if you were reading a page. Carry on this way crossing out all the Ps and Ws with one mark of the pencil like this. Please work as quickly and as accurately as you can. I will tell you when to stop. HAND RESPONDENT A PENCIL AND SAY You may begin now. WHEN 1 MINUTE HAS ELAPSED MARK THE PAGE WHERE THE RESPONDENT FINISHED	Demonstrate by pointing whilst giving instructions. Demonstrate by making a mark in the blank section at the top of the page
Q370 0. Task completed 1. Task not completed (specify) 2. Not attempted 9. Not asked	
Q371 Task not completed (please specify)	

Text……..	
Q372 Do you remember the short news story I read to you a few minutes ago? Now I would like you to tell me the story again. Tell me everything you can remember even if you are not sure. IF NOTHING REMEMBERED PROMPT WITH: The story was about a woman who was robbed. 0. Nothing recalled 1. Something recalled 2. Not attempted 9. Not asked	**Ask only If appropriate** Q372 Do not give any further help after the first prompt other than general encouragement.
Q373 As I explained earlier we would be most grateful if you would provide us with a saliva sample which will be retained for research into ageing. Are you happy to provide a saliva sample? 0. No 1. Yes If YES: Check that the consent form signed and collect the specimen.	Make sure they have not been drinking, smoking or chewing gum for 30 minutes prior to collection of sample. Hand over the sample pot and ask them to spit into it until it reaches the level shown at figure 2 in the instruction leaflet enclosed with sample. Put lid on and screw the cap on securely, Mix gently for at least 10 seconds. Put the participant's bar code securely onto the base of the sample pot and put into a sealed bag. To make more saliva, ask them to close their mouth and wiggle their tongue or rub their cheeks.

HEALTH/RISK FACTORS **This last part of the interview is about your health and your day to day activities.** Q374 Would you say that for someone of your age, your own health in general is: 0. Excellent 1. Good 2. Fair 3. Poor 7. Don't know 9. Not asked	
Q396 Angina 0. No 1. Yes	
Q397 Intermittent Claudication 0. No 1. Yes IF RATED NO CONTINUE OTHERWISE SKIP TO Q399	
Q409 Sugar Diabetes 0. No 1. Yes	

Q412 Parkinson's Disease 0. No 1. Yes IF RATED YES SKIP TO Q418	
Q418 Stroke 0. No 1. Yes	Record only episodes that lasted for 24 hours or longer with partial paralysis in left or right arm and/or leg, blindness in eye/s, or speech disturbance. Ensure that respondent doesn't mean a heart attack.
Q423 Heart Attack? 0. No 1. Yes	
Q396 Angina 0. No 1. Yes	
Q397 Intermittent Claudication 0. No 1. Yes IF RATED NO CONTINUE OTHERWISE SKIP TO Q399	
SMOKING	
Q500 Do you smoke?	

0. No 1. Yes 8. No answer 9. Not asked	
IF NO SKIP TO Q502	
Q501 How many cigarettes do you smoke in a day? 0. Cigars/pipe only 1. Only smoke occasionally 2. 1 – 3 3. 4 – 9 4. 10 – 19 5. 20 – 29 6. 30+ 8. No answer 9. Not asked	Q501 Record amount currently smoked.
Q502 Have you ever smoked? 0. No 1. Yes 8. No answer 9. Not asked	
	The following questions (Q532-Q550) take the same form and these notes should be applied consistently throughout. It will be necessary to

I would now like to ask you some questions about day to day activities, which some people find difficult. I would like to know if you are able, or if you have any difficulty with the following activities. Q532 Are you able to cut your own toenails? (IF YES: Do you have difficulty cutting your own toenails? 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	probe in order to confirm the use of aids in carrying out activities of daily living. Using scissors as an aid to cut toenails does not count, as we would all normally use these. However, specially adapted furniture or the use of adapted cooking utensils would count as special aids. Probing will also be necessary to establish whether the subject would be able to undertake the activity in the absence of another person. This particularly applies to men when asking about household activities as they may never undertake such activities but it could equally apply to women where someone else is available.
Q533 Are you able to wash all over or bathe? (IF YES: Do you have difficulty washing all over or bathing?) 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	People with mental frailties who cannot undertake activities because of their mental frailty should be coded as needing help. Rate 0 - Needs help if the subject requires assistance from another person to undertake the activity. Do not use this code if they could undertake the activity for themselves but someone usually does it for them. Rate 1 - Some difficulty if the subject reports difficulty undertaking activity or if they report no difficulty but use an aid.

	Rate 2 - No difficulty if the subject is able to undertake this activity by themselves without difficulty and without the use of aids or help from others.
Q534 Are you able to get on a bus? (IF YES: Do you have difficulty?) 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
Q535 Are you able to go up and down stairs? (IF YES: Do you have difficulty?) 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
Q536 Are you able to do the light housework? (IF YES: Do you have difficulty?)	Light housework – (e.g. vacuuming, mopping floors, ironing, making beds.

0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
Q537 Are you able to do the heavy housework? (IF YES: Do you have difficulty?) 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	Q537 Heavy housework – (e.g. cleaning windows, scrubbing floors).
Q538 Are you able to shop and carry heavy bags? (IF YES: Do you have difficulty?) 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
Q539 Are you able to prepare and cook a hot meal? (IF YES: Do you have difficulty?)	Q539 If the subject claims they never have to cook a hot meal because this is always done for them, ask them to make the

0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	judgement as to whether they could if they had to.
Q540 Are you able to reach an overhead shelf? (IF YES: Do you have difficulty?) 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
Q541 Are you able to tie a good knot in a piece of string? (IF YES: Do you have difficulty?) 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	

Q542 Are you able to put on your shoes and socks or stockings? (IF YES: Do you have difficulty?) 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
Q543 Do you have any difficulty using a telephone i.e. looking up numbers, dialing etc? 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
Q544 Do you have any difficulty taking medicine (preparing and taking correct dose)? 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	

Q545 Do you have any difficulty managing money (paying bills/writing cheques or using an ATM to remove or deposit money)? 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
Q546 Do you have any difficulty following TV programmes or movies and remembering details of the stories? 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
Q547 Do you have difficulty with household tasks such as making yourself a cup of tea? 0. No 1. Yes 2. Impossible 8. No answer 9. Not asked	
Q548 Have you needed any help recently to check your change after spending small amounts of money? 0. No	

1. Yes 8. No answer 9. Not asked IF EITHER Q547 OR Q548 RATED 1 RATE 549, OTHERWISE SKIP TO Q550.	
Q559 Establish degree of mobility of subject. 1. Usually ambulant non house bound 2. Usually ambulant house bound 3. Chairfast permanently 4. Bedfast permanently 7. Unable to establish mobility	Q559 Where subject's degree of mobility is obvious you may code from observation or from information already obtained. However check that the observed state is permanent and not temporary i.e. the subject is not expected to improve markedly in the short term. If in doubt overestimate degree of disability and notify. • Rate 1 for people who are usually able to get out without assistance. • Rate 2 for people who can get about on the level inside but who never go out of the house or garden without assistance. • Rate 3 for people who spend all their time confined to a chair or who need help to transfer from the chair to the toilet or bed. Use this rating for a wheelchair user even if they can get out of the house. • Rate 4 for people who spend all their time confined to bed

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