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Ascertainment, prediction and implications of dementia diagnosis in a study of 'healthy' cognitive ageing: the Lothian Birth Cohort 1921

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For John,

And for Wilson & Barbara

Abstract

In the context of an ageing global population, dementia poses a significant public health challenge. While there is no cure, understanding the risks for dementia and how these may be minimised is key to reducing the impact of the disease. As life expectancy improves, increasing proportions of the population are expected to survive into advanced old age. As such, understanding the risks for dementia in the oldest-old and how these may differ from earlier old age is of increasing importance. The existing literature specific to the oldest-old is lower in volume and many of the findings are inconsistent.

The first two chapters provide a background to the thesis such that the reader may understand the context for the subsequent studies. The first of these chapters provides an overview of dementia, focussing on the impact of the disease and the requirement for further research. The concept of the oldest-old age group is described, along with a discussion regarding the complexities associated with studying those in advanced old age. The potential impact of diverse and complex health and disease profiles in this sector of the population are introduced. The thesis objectives are introduced within the text and summarised at the close of the chapter. The second chapter introduces the study cohort on which all of the studies included in the thesis are based – the Lothian Birth Cohort 1921 (LBC1921).

The present thesis had three primary objectives. The first was to determine incident cases of dementia in a study cohort of oldest-old participants: the LBC1921. Dementia cases in this cohort were ascertained using existing data primarily and the dementia ascertainment method was developed following a systematic review of such methodology within the literature. While no 'gold standard' method was found, the evidence on which the methodology for this thesis was developed is presented and

discussed. Using this method, 22.5% of the *n*=489 eligible participants were found to have developed dementia during the follow-up period. Comparing these results with 'expected' dementia rates in the cohort, the ascertainment method was determined to be relatively effective.

The second objective of this thesis was to investigate potential risk factors for dementia in oldest age, with a focus on those that would be considered modifiable. The first study of risk factors considered a range of potentially modifiable health and lifestyle factors including hypertension, diabetes, obesity, smoking, hypercholesterolaemia and physical activity. The most well documented genetic risk factor for Alzheimer's disease – *APOE* ε4 – was also included in the analyses. Contrary to other studies of dementia in the oldest-old, the presented study found that carrying at least one *APOE* ε4 allele continued to be a statistically significant risk factor for dementia in those aged over 79 years (OR: 2.23; 95% CI: 1.29, 3.86). A history of hypertension was shown to decrease the risk for incident dementia after age 79 years (OR: 0.47, 95% CI: 0.23, 0.98). This is a similar pattern to that described within the literature on the oldest-old but differs in direction from the association observed in earlier old age. The results also indicated an increased risk for dementia with greater lifetime leisure-based physical activity (OR: 1.17, 95% CI: 1.04, 1.32). This finding was again contradictory to the findings of studies of dementia in earlier old age. A history of statin-use was also observed to increase risk for dementia (OR: 3.39, 95% CI: 1.04, 11.02), while increased height reduced the risk for dementia (OR: 0.72, 95% CI: 0.55, 0.95). Overall, the findings suggested that the risk factor profile for dementia in the oldest-old, as observed in the LBC1921, differs from the risk factor profile in earlier old age. The second study of risk factors examined the association between physical fitness and dementia. The published study presented within the chapter considered three specific measures of fitness in oldest age: grip strength,

walking speed and lung function (FEV_1). These analyses did not demonstrate an association between any of the fitness measures at age 79 years and subsequent dementia; FEV_1 (HR per unit increase 1.30, $p = 0.37$), grip strength (HR 0.98, $p = 0.35$), walking speed (HR 0.99, $p = 0.90$). The findings were again different to those described in studies of younger participants and supported the possibility of a changed risk factor profile for dementia in oldest-age. The final study of risk factors considered whether DNA methylation-based measures of accelerated ageing may be associated with dementia risk. Such measures of accelerated ageing may be considered, in simplest terms, as whether someone's 'biological age' is more advanced than their chronological age. The results did not demonstrate any consistent association between recognised age acceleration measures and dementia.

The third objective of the thesis was to revisit previous studies of non-pathological cognitive ageing in the LBC1921 and determine whether previously unidentified cases of dementia had influenced the findings. The study looked at five previous studies, and four factors reported to be associated with poorer cognitive ageing: smoking, *APOE* ε4, reduced fitness and lower vitamin B12. After excluding those participants who had gone on to develop dementia, the analyses were repeated. The overall findings were unchanged from the original studies, with all four factors continuing to be associated with poorer cognitive ageing ($p<0.05$).

The final chapter of the thesis provides an overview and summary of the findings from the included studies. The general limitations, with regard to methodology and the study cohort, are outlined. The chapter closes with suggestions for further research.

Lay Summary

Dementia is, without question, a devastating disease. It has a profound effect on the individual, their family and friends, and society. It is a disease that is associated with ageing, and as the number of people surviving to old age increases across the world, the impact of the disease will be considerable. There is no cure currently available for dementia and the available treatments do not work for everyone. It is therefore vitally important to identify any factors that may increase or decrease one's risk of developing dementia. It is possible that the risk factors for dementia are different, depending on a person's age. Within the field of dementia research, there is less known about the very oldest in the population. The limited number of studies probably reflects the difficulties in recruitment and retention of study participants in this oldest age group. The study of the oldest-old age group is complex for additional reasons. Those in advanced old age are more likely to have accrued a number of health conditions or diseases. Similarly, the longer one lives, the greater the possibility of being exposed to external factors that might affect health and wellness. The result is that the health and disease profile of this sector of the population is complex and diverse. There is also the potential for significant overlap between features of health conditions and risk factors of interest, making the study of such risk factors in this age group more complicated. Given the improvements in health and social care, life expectancy is improved and as a result a larger proportion of the population is surviving to advanced old age. Understanding the risks for disease in this age-group has therefore grown in importance. The focus of this thesis was therefore to examine risk factors for developing dementia after age 79 years of age. All of the studies included in this thesis described the same group of people, a study group called the Lothian Birth Cohort 1921 (LBC1921). The participants were all born in 1921, live(d)

in the Lothian area of South-East Scotland and were enrolled in the study at age 79 years.

This thesis had three aims. The first was to identify those people within the study cohort who went on to develop dementia after enrolling in the study – incident cases of dementia. Existing studies were collected and reviewed in order to design a method for identifying dementia cases in the cohort. Using this method, it was discovered that 22.5% of those who were included in the study went on to develop dementia. A thorough examination of the findings suggested that the method was suitably effective, and the results could be used to investigate the risk factors for dementia in this cohort.

The second aim of the thesis was to investigate whether any risk factors for developing dementia after age 79 years could be identified; by comparing those who developed dementia with those who did not, several factors were investigated. The first study of risk factors demonstrated that a well-recognised genetic risk factor for dementia (*APOE* ε4) in earlier old age continued to be a risk factor for dementia in oldest age. The same study investigated several health and lifestyle factors that have been shown to be important risk factors for dementia in earlier old age and found that a history of high blood pressure and increased height both reduced one's risk for dementia after age 79 years, while increased levels of physical activity across adulthood and use of cholesterol-lowering drugs (statins) both increased risk for dementia. All of the findings from this study suggested that the risk factor profile for dementia in oldest-age differs from that in early old age. Some of the findings support the findings of other study groups, but others do not. These differences reinforce the importance of further study of dementia in this age group, so that a more conclusive picture can be drawn. The second study of risk factors examined physical fitness in more detail; whether physical fitness at age 79 years affects one's risk for developing

dementia. Fitness is an important target for intervention and as such it is of clear value to understand its role in dementia risk. The study considered three measures of fitness – grip strength, lung function and walking speed – but found that none were related to dementia risk. These findings would suggest that while physical activity promotion may improve other aspects of health, it would have little effect on dementia risk in this age-group. The third risk factor study considered epigenetic age acceleration. Epigenetic age may be thought of as a biological age – put simply, epigenetic age acceleration is a measure of whether one's body is ageing better or worse than one's actual age. This study investigated whether those who were ageing better (had a lower epigenetic age when compared with chronological age) were at a lower risk of developing dementia. Once again, the results suggested that there was no clear link between epigenetic measures of age acceleration and dementia.

The final aim of this thesis was to use the identified cases of dementia to re-examine the findings of previous studies of the Lothian Birth Cohort 1921. The cohort had originally been set up to investigate differences in 'normal' cognitive ageing – how different people's thinking and memory change with age, when there is no disease affecting the same (no dementia, for example). Several factors had been identified as risk factors for poorer normal cognitive ageing, but without knowing who went on to develop dementia it had not previously been possible to rule out that these findings were simply risk factors for dementia cases that had not yet been detected. The study looked at five previous studies, and four factors that were linked to less successful cognitive ageing: smoking, *APOE* ε4, reduced fitness and lower vitamin B12. When the studies were repeated – without those subjects who had gone on to develop dementia – the previous findings were unchanged. This showed that the original findings were likely to be correct and hadn't been affected by unidentified early cases of dementia.

Declaration

I declare that this thesis has been composed by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. I confirm that the work submitted is my own, except where publications or studies have included the contributions of additional authors. My contribution and those of the other authors to this work have been explicitly indicated below, and within the thesis.

The work presented in Chapter 3, Section 3.2 was previously published in *BMC Psychiatry* as "**Dementia ascertainment using existing data in UK longitudinal and cohort studies: a systematic review of methodology**" by RA Sibbett (student), TC Russ (supervisor), IJ Deary (supervisor) and JM Starr (supervisor). This study was conceived by RA Sibbett, IJ Deary and JM Starr. Author contributions (student's contributions in bold): devising the objectives of the review (**RAS**, IJD, JMS), writing search strategies (**RAS**, IJD, JMS), writing inclusion and exclusion criteria (**RAS**, TCR, IJD, JMS), developing the quality measure (**RAS**, TCR, JMS), performing the literature search (**RAS**), screening papers for eligibility and inclusion (**RAS**, TCR), led writing of the manuscript (**RAS**), manuscript revision (**RAS**, TCR, IJD, JMS). All authors read and approved the final manuscript.

The work presented in Chapter 4, Section 4.2 is an amended version of a study previously published in *BMC Psychiatry* as "**Risk factors for dementia in the ninth decade of life and beyond: a study of the Lothian birth cohort 1921**" by RA Sibbett (student), TC Russ (supervisor), IJ Deary (supervisor) and JM Starr (supervisor). This study was conceived by RA Sibbett, IJ Deary and JM Starr. Author contributions (student's contributions in bold): design of the study (**RAS**, IJD, JMS), data collection for dementia ascertainment (**RAS**, TCR), clinical assessment in NHS or research setting (TCR, JMS), dementia ascertainment consensus (**RAS**, TCR,

JMS), statistical analyses (**RAS**), interpretation of results (**RAS**), led writing of the manuscript (**RAS**), manuscript revision (**RAS**, TCR, IJD, JMS), obtained study funding (IJD, JMS). Author contributions to the amended version are unchanged. All authors read and approved the final manuscript.

The work presented in Chapter 5, Section 5.2 was previously published in *BMC Psychiatry* as "**Physical fitness and dementia risk in the very old: a study of the Lothian Birth Cohort 1921**" by RA Sibbett (student), TC Russ (supervisor), Mike Allerhand, IJ Deary (supervisor) and JM Starr (supervisor). This study was conceived by RA Sibbett, IJ Deary and JM Starr. Author contributions (student's contributions in bold): study design (**RAS**, MA, IJD, JMS), data collection for dementia ascertainment (**RAS**, TCR), clinical assessment in NHS or research setting (TCR, JMS), dementia ascertainment consensus (**RAS**, TCR, JMS), completed main statistical analyses (MA), contributed to statistical analyses (**RAS**), interpretation of results (**RAS**, MA, JMS), led writing of the manuscript (**RAS**), manuscript revision (**RAS**, TCR, IJD, JMS), obtained study funding (IJD, JMS). All authors read and approved the final manuscript.

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JMS), led writing of the manuscript (**RAS**), contributed to the writing of the statistical methods and results (**RAS**, DA), contributed to the writing of the DNA methylation calculation methods (**RAS**, RM), manuscript revision (**RAS**, RM, DA, IJD, JMS, TCR), obtained study funding (IJD, JMS). All authors read and approved the final manuscript (except JMS, who was deceased prior to before completion of the manuscript). [†*deceased December 2018*]

The work presented in Chapter 7, Section 7.2 was previously published in *Psychology and Ageing* as "**Does incipient dementia explain normal cognitive decline determinants? Lothian Birth Cohort 1921**" by RA Sibbett (student), TC Russ (supervisor), A Pattie, JM Starr (supervisor) and IJ Deary (supervisor). This study was conceived by RA Sibbett, IJ Deary and JM Starr. Author contributions (student's contributions in bold): study design (**RAS**, JMS, IJD), data collection for dementia ascertainment (**RAS**, TCR), clinical assessment in NHS or research setting (TCR, JMS), dementia ascertainment consensus (**RAS**, TCR, JMS), statistical analyses (**RAS**), interpretation of results (**RAS**), led writing of the manuscript (**RAS**), manuscript revision (**RAS**, TCR, IJD, JMS). All authors read and approved the final manuscript.

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1: Introduction: What is dementia?

1.1 Introduction to the chapter

The aim of this introductory chapter is to provide an overview of dementia such that the reader can understand the basis and context for the research questions posed in this thesis. The chapter therefore opens with a definition of dementia and an overview of the dementia statistics for the United Kingdom (UK). Whilst global dementia statistics are considered later in the chapter, it is important to outline the statistics for the country in which the examined study cohort is based. In doing so, the dementia statistics for the study cohort can be compared and contrasted with the population from which the participants are sampled, with any notable differences given appropriate consideration. By reflecting on such differences, one might make reasonable suggestions as to the relevance of the findings to the wider population. To provide a person-centred context to the introduction, the impact of dementia across the population hierarchy is explored – from the individual to society. Appreciating the impact of dementia is central to understanding why prevention, management and treatment are important, and necessary. If one considers the positive effect such strategies could have – on a personal and population level – one can acknowledge the requirement and justification for further research aimed at advancing knowledge and evidence in this field. The subsequent section of the introduction examines the scale of the challenge that addressing dementia poses across the world and explores the avenues by which the challenge may be approached. Included within this section is a general discussion regarding the role of ongoing dementia research. The current diagnostic methods for dementia are then outlined, along with a discussion regarding dementia within the spectrum of cognitive decline. This is an important consideration if one is to appreciate the potential

limitations of current dementia ascertainment methodology, including the possibility of misclassification. Not only is this relevant in dementia research, but also in the study of non-pathological cognitive ageing. Finally, the concept of the oldest-old age group is introduced and the complexities of studying this section of the population are discussed.

Across the chapter, the research questions considered in this thesis are introduced. Each of the final study questions aimed not only to provide research relevant to this thesis, but also to have value within the wider literature and the field of dementia research. The context of each study question within the literature will be considered within the individual study chapters. The chapter closes with a specific list of research objectives.

1.2 Dementia: an overview

1.2.1 Dementia: a definition and overview

The term dementia does not refer to a specific disease but is an umbrella term that describes a collection of symptoms, caused by a number of neurodegenerative and cerebrovascular conditions.(Alzheimer's Association Report, 2020) The most common of these conditions is Alzheimer's disease, which accounts for approximately 60-80% of dementia cases.(Alzheimer's Association Report, 2020) Other dementia subtypes include vascular dementia, dementia of mixed vascular and Alzheimer's aetiology, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease dementia and others. This thesis will consider all-cause dementia, i.e. it would not focus on any individual dementia subtype or aetiology. Dementia is characterised by a chronic or progressive cognitive decline that is of sufficient severity that activities of daily living are impaired. Whilst memory impairment is the most recognised cognitive deficit, other cognitive domains – such as attention, orientation, judgement, language,

abstract thinking and executive function – are often also affected. Depending on the type of dementia, changes in social behaviours may also be a prominent feature. Dementia is not limited to older persons, but the vast majority of cases arise in those aged over 65 years.

1.2.2 Incidence and prevalence of dementia in the UK

1.2.2.1 Overall incidence and prevalence

Based on evidence from a large UK study of dementia incidence – the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) II – it has been estimated that 209,600 people aged over 65 would be expected to develop dementia in the UK each year.(Matthews et al., 2016) This number is to equivalent one new case of dementia every 3 minutes in the UK alone.(Matthews et al., 2016)

An estimated 850,000 people were living with dementia in the UK in 2015, a number that equated to 1.3% of the total population, one in seventy-nine of the total population or one in fourteen of those aged over 65 years.(Prince et al., 2014) The percentage of the population living with dementia varies between different regions. In Scotland, the NHS Health Board with the highest proportion of the population living with dementia is NHS Western Isles (1.13 per 100 population), while in NHS Lothian – where our study cohort is based – rates are lower (0.75 per 100 population); dementia rates in NHS Lothian are close to those recorded for NHS Scotland as a whole (0.77 per 100 population).(Public Health Scotland, 2020) Prevalence rates are likely to correlate with the age profile of a region; those regions with the most older people would be expected to be those with the higher prevalence of dementia. Differences in dementia rates are likely to reflect not only the age distribution within a geographical area, but also the proportion of people with dementia that have a formal diagnosis within each area. Despite improvements, relatively high rates of undiagnosed

dementia persist across the UK; the dementia diagnosis rate for the Scotland for the has been reported to be 64-67%.(Scottish Government, 2013; Alzheimer's Research UK, 2018a). A number of factors may affect the diagnosis rate within a population; access to specialist services, public awareness, cultural beliefs, contact with health services, local interest of clinicians, and support or isolation in the community may all affect whether cognitive change is detected, reported and diagnosed.

1.2.2.2 Incidence and prevalence by age group and sex

The estimated prevalence of late-onset dementia, in the UK, increases for each five-year age group, from 60-64 years (0.9%) to 90-94 years (29.9%), and even further in those aged over 95 years (41.1%).(Prince et al., 2014) These estimates – produced for the Alzheimer's Society Dementia UK Update – are based on the outcome of an Expert Delphi Consensus, with access to the available literature.(Prince et al., 2014) The overall age-standardised prevalence determined by the consensus (7.1%) lay between those found by the MRC CFAS I study (7.5%) and the MRC CFAS II study (6.4%).(Prince et al., 2014) The pattern of exponentially increasing prevalence with increasing age observed within UK-based studies is consistent with that described in larger European and global studies.(Perera et al., 2018) In the UK, the estimated prevalence was higher for women than men for every age group over 75 years: 75-79 years, 6.6% for women, 5.3% for men; 80-84 years, 11.7% for women, 10.3% for men; 85-89 years, 20.2% for women, 15.1% for men; 90-94 years, 33% for women, 22.6% for men; 95+ years, 44.2% for women, 28.8% for men.(Prince et al., 2014) From age 60 to 74 years, the prevalence was similar for both sexes.(Prince et al., 2014) It is likely that the greater life expectancy in women translates to a higher prevalence of dementia in the oldest age groups.

Despite the increasing mortality associated with advancing age, MRC CFAS II has demonstrated that, in the UK, more than 40,000 incident cases arise annually in each age group over 80 years, reflecting the increasing incidence rates associated with increasing age.(Matthews et al., 2016) The same study reported higher incidence in women aged over 65 years, with approximately 135,000 cases occurring in the UK each year, compared with 74,000 cases per year in men aged over 65 years.(Matthews et al., 2016)

1.2.2.3 Trends in dementia incidence and prevalence in the UK

Evidence from population-based studies has suggested that both incidence and prevalence of dementia within the UK may be decreasing over time. On comparing the findings from the MRC CFAS I and the MRC CFAS II studies, a 20% drop in dementia incidence (95% CI: 0-40%) was observed in those aged over 65 years.(Matthews et al., 2016) In all but one age and sex group (women aged 80 to 84 years), the incidence rate was lower in the latter MRC CFAS II study.(Matthews et al., 2016) The overall reduction in incidence was however shown to be driven by a larger reduction in incidence in men, across all age groups.(Matthews et al., 2016) In 2020, the Alzheimer Cohorts Consortium produced a paper that reported that the incidence rate of dementia had declined by 13% (95% CI: 7-19%) per decade between 1988 and 2015.(Wolters et al., 2020) The analyses were based on the aggregated data from seven cohort studies based in Europe and the United States, including the MRC CFAS.(Wolters et al., 2020) A reduction in dementia prevalence was also observed between MRC CFAS I and MRC CFAS II (OR: 0.7, 95% CI: 0.6-0.9, p=0.003).(Matthews et al., 2013) Prevalence estimates for the UK based on MRC CFAS II suggested that the number of persons living with dementia was 24% less than that which would have been predicted based on MRC CFAS I estimates and

population ageing.(Matthews et al., 2013) The reduction in prevalence was driven by decreased rates in the non-care setting.(Matthews et al., 2013)

A number of suggestions have been made as to why dementia incidence and prevalence may be stabilising or reducing. Societal changes in early age such as improved nutrition, increased levels of education, and improved living conditions are likely to have improved physical and mental health in early and middle life.(Matthews et al., 2013; Wu et al., 2016) Such improvements may in turn have reduced dementia occurrence in later life.(Matthews et al., 2013; Wu et al., 2016) The improvements and changes in those mentioned societal factors were often dramatic in the early years of those studied in older age due to the impact of war, disease epidemic or famine.(Wu et al., 2016) Greater access to and availability of medical treatments across the life course for participants in the latter studies is also likely to have had an impact on reducing dementia prevalence.(Matthews et al., 2013; Wu et al., 2016) In particular, the prevention and treatment of vascular conditions has advanced considerably; as a recognised risk factor for dementia, the reduction in vascular disease may have had a role in reducing or stabilising dementia prevalence.(Matthews et al., 2013; Wu et al., 2016) As highlighted within the Lancet Commission Report 2020, we must consider the potential for this trend to reverse in the future as a result of increasing obesity, diabetes and physical inactivity within high-income countries.(Livingston et al., 2020)

1.2.2.4 Dementia and mortality

In England, since 2001, deaths from dementia have doubled in women, and increased by 60% in men.(Public Health England, 2017) In Scotland, since 2000, deaths from dementia or Alzheimer's disease have doubled for women, and almost tripled for men.(National Records of Scotland, 2017) In 2015, dementia and Alzheimer's disease

was the leading cause of death in women (accounting for 15.3% of deaths) and the second most common cause of death in men (accounting for 8.0% of deaths) in England.(Public Health England, 2017) In Scotland, deaths from dementia are now more frequently recorded than deaths from cerebrovascular disease.(National Records of Scotland, 2017) Whilst it is true that the number of deaths attributed to other conditions – such as heart disease or stroke – have reduced, deaths from dementia are known to have increased and these reductions cannot therefore explain why dementia has become a leading cause of death.(National Records of Scotland, 2017; Public Health England, 2017) The increase in deaths from dementia may be attributable to the ageing of the population, but it is likely that increased awareness of dementia and increased frequency of diagnosis have also played a role.(Public Health England, 2017)

1.3 What is the impact of dementia?

The impact of dementia is experienced not only by the individual, but also by carers, families, and the wider community. The effects can be physical, psychological, social and economic.

1.3.1 Impact on an individual

A diagnosis of dementia affects each individual differently. The effects depend on the impact that the symptoms have on the person and each individual's personality and situation prior to disease onset. In thinking about the impact on the individual, one might consider the potential for dementia to disrupt functionality in each area of a person's life including physical health, psychological health, employment, relationships, living situation, finances, leisure activities, independence and well-being.

A change in living situation may be necessary as a direct result of the symptoms of dementia. As a dementia syndrome increases in severity, a number of safety issues may arise meaning that it is no longer appropriate for a person to remain at home. Such issues may include wandering or becoming lost, leaving the house unlocked or the doors open, unreliable concordance with prescribed medication (including the possibility of accidental overdoses), or leaving on household items such as cookers, taps, microwaves or irons. There may also be concerns regarding a person with dementia's vulnerability due to their decision-making. Opening their home to strangers or agreeing to sign inappropriate contracts may be two such concerns. Some of these difficulties may be minimised using simple measures. Ovens can be disconnected to prevent unsupervised cooking, medications can be locked away and call screening systems can be used to prevent cold-calling. In the UK, a legal document termed 'Lasting Power of Attorney' (LPA) can be used to appoint another person or persons to make finance or welfare decisions on behalf of another.(Government of the United Kingdom) The nominated 'attorney' is typically a family member or close friend.(Government of the United Kingdom) The document would come into effect when the person was determined to lack capacity to make specific decisions.(Government of the United Kingdom) While the LPA and strategies described above are aimed at protecting the person and increasing the time that they are able to remain in the home, it is possible that this will be perceived as a loss of independence and could be emotionally detrimental. This is just one of a number of aspects of dementia that can affect a person's psychological and emotional wellbeing. Symptoms of depression are common in dementia and it can be difficult to diagnose a major depressive disorder given the overlap of symptoms. It is not only psychological health that can be impacted by a diagnosis of dementia; studies indicate that physical health is adversely affected by dementia. For example, a Danish study of survival after early-stage breast cancer patients demonstrated an increased

risk of death from breast cancer for those with a diagnosis of dementia.(Ewertz, Land, Dalton, Cronin-Fenton, & Jensen, 2018) An American study demonstrated that, when compared with controls, persons with Alzheimer disease had more co-morbid medical conditions, a higher burden of illness, greater costs of healthcare, greater use of hospital services and inpatient admissions.(Zhao, Kuo, Weir, Kramer, & Ash, 2008)

Receiving a diagnosis of dementia is likely to have significant implications regarding a person's ability to continue in employment. While employment is unlikely to be a concern for those in oldest-old age, this is likely to have an increased significance in early old age in the coming years. Increased retirement age and changes to pensions might be expected to lead to an increased number of people working beyond 65 years of age, resulting in more people developing dementia while still in employment.

1.3.2 Impact on friends and family

A sizeable proportion of the UK population – 24.6 million people or 38% of the total population – know a family member or close friend who is living with dementia.(Alzheimer's Research UK, 2018b) All of those with a connection to a person living with dementia will have a difference experience, but most will experience a change in the relationship as a result of the diagnosis. How profound such changes are is likely to be dependent on the closeness of the relationship, the severity of the impairment and related symptoms and the involvement that a person has in the day-to-day care and support of the person with dementia. The experience of caring for a person with dementia has been shown to differ considerably to caring for a person with another condition.(Ory, Hoffman, Yee, Tennstedt, & Schulz, 1999) Dementia caregivers spend a greater number of hours providing care and assist with a greater number of activities of daily living. Dementia caregivers also report comparatively more negative effects including greater caregiver stress, mental health and physical

health problems, and family conflict.(Ory et al., 1999) A study of carers of persons aged under 65 years with dementia showed that 59% of those in employment reduced their hours or left employment after the diagnosis.(Luscombe, Brodaty, & Freeth, 1998) With reducing income, it is not surprising that most participants of this study (89%) also reported financial difficulties after diagnosis.(Luscombe et al., 1998) Caregiver stress or strain is increased by the presence of certain behavioural and psychological symptoms of dementia. Symptoms such as wandering may require closer supervision while other symptoms, including disinhibition and aggression may be more difficult to manage – both physically and emotionally. Apathy, depression and anxiety are also likely to place emotional strain on the caregivers. Furthermore, one cannot underestimate the potential physical and psychological fatigue that may arise from the close monitoring that might be required to provide care and prevent harm or accident.

The strain on a caregiver and the emotional difficulties of watching a loved one in the final stages of dementia is illustrated by a US study that showed 72% of carers felt relief following the death of the patient, and over 90% believed that death would be a relief for the patient.(Schulz et al., 2003) In the same study, carer symptoms of depression were shown to decrease significantly within three months of the death.(Schulz et al., 2003) It is not only those with a carer's role who are affected by the diagnosis of dementia. Whilst the practical difficulties such as finances and employment may be less significant, emotional and psychological difficulties will remain. The person with dementia will usually have multiple roles within their social network, such as partner, parent, sibling, child, friend or colleague. The reciprocity in these relationships will likely decrease as the disease progresses and, as a result, each of these relationships will be changed.(Millenaar et al., 2016) While a friend might grieve the gradual loss of a friendship, a partner will find it increasingly difficult

to keep the person with dementia involved, becoming solely responsible for all major life decisions.(Millenaar et al., 2016) As the dementia process advances, changes in the reciprocity of a relationship can result in carers experiencing loneliness.

1.3.3 Impact on society

The financial impact of dementia on society is considerable, with a total cost in the UK of £26.3 billion, or an annual cost of £32,250 per person; £4.3 billion is spent on healthcare costs, while £10.3 billion is spent on social care costs.(Prince et al., 2014) Of the social care costs, £4.5 billion is publicly funded and £5.8 billion is privately funded.(Prince et al., 2014) Almost half of the total cost of dementia in the UK - £11.6 billion – is attributed to the cost of unpaid care. As the general population ages, there is likely to be increased pressure on hospitals, emergency departments and ambulance services. Those with dementia have been shown to utilise such services more frequently than those without dementia, after adjusting for comorbidities, resulting in even further strain on services.(Voss et al., 2017) Increased pressures on services such as housing – specialist care homes in particular, home support services, community healthcare services and day care services – would also be expected. Aside from the monetary implications, increasing the capacity of such services will also depend on the availability of adequately trained staff, hospital transport systems and the potential for increasing space within appropriate building structures.

1.3.4 Public perception

A research poll conducted by YouGov has revealed that more people are concerned about developing dementia than cancer.(YouGov UK, 2017) Dementia was the most feared condition with 38% naming it as their biggest fear. A second poll – carried out by Alzheimer's Research UK – reported that 42% of participants agreed that dementia

was the condition that they most feared getting in the future.(Stevens, 2018) The public concern regarding dementia is evidenced by the prominence of the condition within media. Striking headlines include “The dementia timebomb” (BBC: Science, 2014), “Study shows dementia is biggest killer in affluent areas” (BBC News: Wales, 2017) and “The nine lifestyle changes that could save you from dementia” (The Telegraph: Knapton, 2017). The use of emotive language, such as “save you”, “killer” or “timebomb”, reflects the way in which dementia is often perceived and discussed within society. The media also highlights the potential social problems facing those with dementia – such as vulnerability to crime (BBC News: Glasgow & West, 2018) and carer abuse (BBC News: Northampton, 2018). In opposition to the negative press regarding dementia are the reports describing the positivity and drive of researchers and society to make advances in the understanding and treatment of dementia and in the care of persons with dementia. It is likely, that by raising the profile of dementia through news stories, charitable fundraising, celebrity endorsement of campaigns and advertising, awareness of the condition will increase, leading to improved rates of presentation and diagnosis.

1.4 Addressing dementia

1.4.1 The scale of the challenge within the global population

As fertility declines and life expectancy increases, the global population is ageing. Global projections estimate that the number of people aged over 60 years will have increased from 13% of the population (962 million) in 2017 to 22% of the population (2.1 billion) in 2050.(United Nations, 2017) In 2017, Europe had the highest percentage of population aged over 60 years (25%), but the ‘squaring‘ of the population pyramid will continue over the coming decades and by 2050 all major areas of the world, save Africa, will have approximately one quarter or more of their

population aged over 60 years.(United Nations, 2017) In 2017, the number of persons aged over 80 years was 137 million and this number is projected to triple to 425 million by 2050.(United Nations, 2017)

As a disease closely associated with ageing, the number of dementia cases is also expected to increase. In 2015, 46.8 million people worldwide were estimated to be living with dementia, and the number rose to 50 million by 2018.(Patterson, 2018; Prince et al., 2015) This number is expected to reach an estimated 152 million by 2050.(Patterson, 2018) The number of people living with dementia is highest in Asia (22.9 million), followed by Europe (10.5 million), the Americas (9.4 million) and Africa (4 million).(Prince et al., 2015) This pattern is the same with regard to incidence.(Prince et al., 2015) There were estimated to be almost 10 million new cases globally in 2015, the equivalent of one new case every three seconds.(Prince et al., 2015) Projected estimates indicate that approximately one in three people (32%) born in 2015 will develop dementia in their lifetime.(Lewis, 2015) These estimations do not however take into consideration the potential for life expectancy to improve further in the future and do not include cases arising before sixty years of age; as such, these figures are likely to be an underestimation.(Lewis, 2015) Dementia is therefore one of the greatest public health challenges facing the ageing global population.

The monetary cost of providing care and support to those with dementia worldwide in 2015 was estimated to be US$818 billion, rising to US$1 trillion by 2018, and as dementia rates continue to increase, the worldwide costs are expected to reach $2 trillion by 2030.(Patterson, 2018; Prince et al., 2015) To provide a frame of reference for these values, the cost for global dementia care in 2015 was more than the market value of Apple and more than double the market value of Google in the same year.(Prince et al., 2015) If the cost of global dementia care in 2015 was a country, it

would have been the 18th largest in the world.(Prince et al., 2015) It is estimated that by 2050, 68% of persons with dementia will live in low or middle-income countries. With fewer resources to both provide and fund care in such countries, the impact of increasing dementia will only compound the burden of disease among people aged over 60 years in low- and middle-income countries, which is already greater than in high income countries.(Prince et al., 2015)

1.4.2 The importance of dementia research

Currently, dementia is not curable, and the treatments are not universally effective or universally tolerated.(Birks, 2006; Lanctôt et al., 2003; Tricco et al., 2018) Dementia research is therefore critical in order to develop strategies and treatments that will reduce the impact of this condition. Further dementia research may be considered in three broad categories: understanding dementia, developing treatments for dementia and, caring for those with dementia. Each area of dementia research is vitally important, and all are connected. Understanding dementia involves a vast number of scientific fields as the disease process is investigated across the system hierarchy. As examples, this includes investigating genetics, biomarkers, neuropathology, risk factors and environmental effects. The research included in this thesis would fall under the category of furthering the understanding of dementia. Further details regarding the specific areas of research for this thesis are outlined in the latter sections of this introduction.

The more that is understood about dementia – including aetiology, susceptibility, pathophysiology, and the relationship between pathology and symptomology – the more accurately and specifically studies can be directed in order to develop treatments or establish preventative measures. There is a worldwide push to move forward with drug development for dementia and the discovery of any disease-

modifying drug effective in the treatment of dementia would have an impact on the care of those with dementia, either by preventing the onset of new cases or by limiting the effect of the disease on those already diagnosed. Since 1998, only four drugs have been approved for the treatment of dementia, despite over 100 attempts being made to produce an effective drug.(Patterson, 2018) Furthermore, these drugs are symptomatic treatments as opposed to disease-modifying agents. Developing a new drug involves several stages of research, costing an estimated £1.15 billion and taking approximately 12.5 years.(Paul et al., 2010; The Association of the British Pharmaceutical Industry, 2018) Only 0.02% of researched new compounds will eventually receive licensing approval from a regulatory agency.(The Association of the British Pharmaceutical Industry, 2018) Despite the cost and difficulty in bringing an effective drug to market, the value and importance of drug discovery in dementia is reflected in the fact that the number of clinical trials in Alzheimer's disease has has increased in recent years.(Cummings, Lee, Ritter Sabbagh & Zhong, 2019) Other types of research are also of considerable importance in furthering knowledge and developing strategies for addressing dementia. For example, through research that evaluates care strategies for dementia, resources might be best utilised and the best possible experience for the person with dementia might be achieved.

The scale of the challenge posed by dementia is reflected in the launch of several large, collaborative research centres and by the amount of funding required to make such centres viable. One such centre is the UK Dementia Research Institute (UK DRI), set up using a £250 million investment from the Medical Research Council, Alzheimer's Society and Alzheimer's Research UK.(Hesse & Henstridge, 2018) The UK DRI aims to bring together expertise from various fields in order to advance the understanding of how dementia develops and progresses.(Hesse & Henstrideg, 2018) The primary objective of the institute is to discover novel means by which

dementia can be diagnosed, treated and prevented, and to bring these new strategies to the clinical domain more quickly.(Hesse & Henstridge, 2018) In 2014, the Medical Research Council also set up the £53 million Dementias Platform UK, a private-public partnership between universities and drug companies, with the primary aim of accelerating progress in dementia research.(Bauermeister et al., 2020) The importance of investing in dementia research has been acknowledged by the UK Government, with funding doubling between 2012 and 2015, to over £60million per year.(Department of Health, 2016) The importance of dementia research is also recognised by the wider community. In 2018, Join Dementia Research – a service that allows people to register their interest in taking part in dementia research – had 34,982 volunteers across the UK who had registered interest, and 9,637 volunteers who had been enrolled in studies through the service.(Join Dementia Research, 2018)

1.4.3 Dementia ascertainment

From this point on, the introduction focuses on topics that are more specifically relevant to this thesis. In doing so, the background and rationale for each of the thesis objectives are introduced.

Central to many dementia research studies is the identification of dementia cases. In this thesis, the ascertainment of dementia cases within a specific study cohort (the Lothian Birth Cohort 1921) would be a crucial first step. It would not only provide a measure of dementia incidence for the cohort but would also determine the dementia outcomes on which all of our subsequent studies were based. Dementia ascertainment in dementia research falls into two broad categories: 1. ascertainment for the purposes of selecting a cohort of persons with dementia, and 2. dementia ascertainment as an outcome measure of the study. Ascertainment methodologies vary depending on the specific requirements of the study. For example, clinical drug

trials will often require participants to meet detailed and specific eligibility criteria that are best established through clinical evaluation. Similarly, drug trials aimed at preventing the development, or progression of dementia are likely to require detailed clinical follow up in order to quantify the level of impairment and the potential benefit of the drug. While clinical assessment may be considered the gold-standard in dementia ascertainment, it is not without limitations. Multiple examiners may interpret signs or symptoms differently, resulting in differences in ascertainment.(Martin-Khan et al., 2012) Furthermore, different studies are likely to utilise different diagnostic criteria or have different requirements for eligibility, making comparisons between studies difficult. Clinical dementia ascertainment for each participant in a large study would involve considerable time and funding. This is of particular relevance in longitudinal studies, or studies across the life course where repeat assessments over long periods would be necessary. Studying subjects prior to dementia onset, through the life course, is essential for the thorough investigation of risk factors, causation and early detection. Prospective longitudinal studies using a clinical ascertainment procedure have the disadvantage that the results would only be available a considerable time after the commencement of the study.

One way to reduce the cost and time taken to achieve results is to use existing data. Accessing previously recorded data also limits the potential inaccuracies that would arise if information were collected using participant or carer recall and allows data to be collected for those participants who are lost to follow-up. The value of existing data is illustrated by the growing interest in the use of informatics in health research. As records become increasingly computer-based, accessing large volumes of linked data is ever more feasible. The Farr Institute of Health Informatics Research in the UK was established in 2013, with the purpose of enabling safe and secure access to health records in order to maximise the use of existing data and enable research on a

national scale.(Hemingway et al., 2020) The Farr institute made significant progress in beginning to grow the field of data science in health. The value of such an institute was demonstrated by the formation of the Health Data Research UK (HDRUK) institute, which became the successor to the Farr institute; the HDR UK was an expansion of the previous Farr institute, with additional research centres and longer-term funding.(Hemingway et al., 2020)

Existing data can take many forms, including both routinely collected data and data collected for the purposes of research. Research data, such as imaging results, may include information that can be used for a purpose other than that for which it was originally collected. Routinely collected data are not limited to those persons enrolled in a study and can therefore offer datasets on a large scale. Examples of such data include death certificates – completed for every deceased person in the UK, and discharge diagnoses for acute hospital admissions – completed following any discharge from an NHS hospital in the UK. Whilst health record data are often anonymised for the purposes of research, centres offering data linkage allow more than one record – such as General Practice records and hospital records – to be supplied for the same person, using an identifying key.

Existing data were key in performing dementia ascertainment for the study cohort included in this thesis. Having been recruited and enrolled in the study several years prior to the commencement of any dementia ascertainment procedure, prospective clinical assessment of each participant was not possible. However, both routinely collected data and research data were available for the purposes of ascertainment and subsequent analyses. The first crucial step in achieving the research aims addressed within this thesis was the development of a dementia ascertainment procedure for the cohort. In order to achieve the most effective possible procedure, the methodologies described within the literature were considered along with the data

sources available for use in this study. The first objective of this thesis was therefore the investigation and evaluation of dementia ascertainment procedures using existing data within the literature; the evidence gathered was then used to guide the development of an ascertainment procedure for use in the cohort discussed in this thesis. The second objective was to utilise this procedure to perform dementia ascertainment for the cohort.

1.4.4 How dementia might be addressed

When planning any research, it is important to consider the potential usefulness of the proposed study. Findings that could provide some insight into how dementia may be addressed might be considered to be most valuable. As such, the objectives within this thesis were chosen following careful consideration of their value in providing evidence that may be of use in reducing the impact of dementia.

When considering how to reduce the impact of dementia, it is necessary to outline the broad areas that must be addressed. Such areas include prevention, diagnosis, treatment, reducing the impact of existing disease, monitoring and reporting. Integral to developing preventative strategies is a comprehensive understanding of those factors that either increase or decrease the risk for dementia. For this reason, risk factors and protective factors associated with dementia are frequently investigated within the literature. While such studies have produced a significant body of evidence describing the risk factor profile for dementia in older persons, studies describing risk factors in the oldest-old are much fewer in number.(Sibbett, Russ, Deary, & Starr, 2017) It is important to understand whether risk factors for dementia are equally relevant across the life-course, such that preventative strategies can be implemented in order to achieve optimal effectiveness. The primary aim of this thesis was therefore to perform research studies that would provide further evidence to the literature, such

that we might further our understanding of dementia in the oldest-old. A more comprehensive overview of the concept of the 'oldest-old' age group is provided in section 1.5. The included studies focus on the investigation of risk factors for dementia in a specific cohort of participants aged over 79 years at baseline; the cohort is introduced in Chapter 2. Here, we outline the types of risk factor that are considered within this thesis, in order for that the reader may appreciate the rationale for our selections.

Risk factors and protective factors may be subdivided into those with a genetic basis, and those that might be considered to be environmental or lifestyle factors. Genetic factors are recognised to play an important role in dementia and a number of genetic factors have been proposed as being associated with risk for developing the condition. Genetic factors may be genetic variants or genetic mutations. Specific mutations in the amyloid precursor protein (*APP*), presenilin 1 and presenilin 2 genes result in a relatively rare autosomal dominant early onset dementia, termed familial Alzheimer's dementia. The more common late onset Alzheimer's dementia is not a genetic disease, but genetic factors have been shown to play a significant role. The most consistently reported genetic variant is Apolipoprotein E (*APOE*). The *APOE* ε4 allele has been shown to be associated with an increased risk for Alzheimer's disease, while the *APOE* ε2 allele is associated with a decreased risk. As a genetic risk factor, as opposed to a disease-causing mutation, the presence of an *APOE* ε4 allele does not reliably predict dementia and similarly, the absence of the allele does not eliminate the possibility of dementia. While *APOE* ε4 is widely accepted to be a risk factor for dementia in those aged over 65 years, its importance as a risk factor in those in very oldest-age has been challenged.(Corrada, Paganini-Hill, Berlau, & Kawas, 2013) The third objective of this thesis was to evaluate the role of *APOE* ε4 in the development

of dementia in our study cohort; thus adding to the evidence for this risk factor in oldest-age.

An environmental factor may be defined as an identifiable element in a subject's environment that influences the survival, function, regulation or growth of that subject; and in this instance, one that affects the likelihood of developing dementia. Factors can include:

- elements within the geographical environment – such as pollutants or occupational toxins,
- physical health factors – such as health diagnoses, medications, or physiological measures, and
- lifestyle measures – such as alcohol intake, smoking status, body mass index and participation in physical exercise.

Many such risk factors may be deemed modifiable and are therefore of considerable interest regarding the potential for risk reduction in dementia. A considerable number of studies have investigated potentially modifiable risk factors for dementia, but fewer studies have looked specifically at the oldest-old. Investigating potentially modifiable risk factors for dementia, and how these may differ in advanced old-age, is the primary focus of this thesis. The fourth objective of this thesis was to explore the associations between previously reported modifiable risk factors and dementia, in our study cohort of the oldest-old. The potentially modifiable risk factors for dementia selected for inclusion were based on current evidence within the literature, and this is discussed in the fourth chapter of the thesis.

Within those risk factors considered to be modifiable, some are more readily modifiable. For example, lifestyle factors such as fitness and body weight can be targeted with relatively simple measures. Furthermore, given the recognised

association between physical fitness and medical diagnoses such as hypertension and diabetes (Shook et al., 2012), targeting fitness could reduce any impact of such conditions on dementia rates. The fifth objective of this thesis was to explore in further detail, the association between specific fitness measures and the risk for incident dementia in oldest age.

While several risk factors have been proposed as having a role in dementia, there is no known single factor, or combination of factors that can accurately predict which persons in the population will go on to develop dementia. It is therefore likely that the aetiology of dementia involves a complex interaction between multiple factors, both genetic and environmental. Of particular research interest is the investigation of how environmental factors and genetic factors may be linked in dementia pathogenesis. Epigenetics is the study of changes in the phenotype that result from alterations in gene expression rather than alterations in the genetic code. Epigenetic modifications provide a means by which environmental factors can influence the development of dementia in persons who inherit the same genetic variants; as such, epigenetics may be thought of as a bridge between genetics and environment.(Foraker et al., 2015) One might therefore consider epigenetics to be the manner by which one could alter gene expression by making a change to one's environment – hence changing one's 'fixed' genetics to a potentially modifiable risk factor. The two most commonly studied epigenetic markers are DNA methylation and histone modification. DNA methylation results from the addition of a methyl group to the DNA molecule, often at a cytosine nucleotide that is adjacent to a guanine base (CpG dinucleotides). DNA methylation results in the activation, or more typically the repression of gene transcription.(Wen et al., 2016) Post-translational histone modifications can include the methylation and acetylation of lysine or arginine groups. The resulting changes in chromatin structure give rise to the observed alterations in gene expression.(Wen et al., 2016)

Previous studies have explored the potential for using measures of DNA methylation to predict age, and originally, the most consistently reported were those published by Hannum and Horvath in 2013.(Hannum et al., 2013; Horvath, 2013) The resulting estimates of age have been suggested to reflect one's biological age. Hannum described a method, based on a single cohort, by which age could be predicted based on measures of DNA methylation within whole blood; Horvath described a predictor of age based on measures of DNA methylation from several studies and multiple tissue types.(Hannum et al., 2013; Horvath, 2013; Marioni, Shah, McRae, Chen, et al., 2015) From these two 'epigenetic clock' measures, two measures of age acceleration have been described: extrinsic epigenetic age acceleration (EEAA) and intrinsic epigenetic age acceleration (IEAA).(Chen et al., 2016; Dugué et al., 2017) IEAA was based on Horvath's estimate of epigenetic age and estimates epigenetic ageing effects that are not influenced by differences in blood cell counts; EEAA was based on an epigenetic age calculated using the method described by Hannum and captured both intrinsic changes in methylation and extracellular blood cell composition changes.(Chen et al., 2016)

More recently, two novel DNA methylation-based measures of epigenetic age have been described: DNAm PhenoAge and DNAm GrimAge.(Levine et al., 2018; Lu et al., 2019) DNAm PhenoAge was developed by using "phenotypic age" as a reference, rather than chronological age, and was produced by regressing a phenotypic measure of mortality risk on CpGs.(Levine et al., 2018) DNAm GrimAge was developed by regressing time-to-death on DNA methylation-based biomarkers of mortality and morbidity (including several plasma proteins and smoking pack-years), producing a single composite biomarker of lifespan.(Lu et al., 2019) The observed discrepancies between chronological age and methylation-predicted age have been proposed as a potential explanation for the variability in risk for age-related diseases and

mortality.(Marioni, Shah, McRae, Chen, et al., 2015) Studies have provided evidence in support of this hypothesis: Marioni et al. concluded that measures of accelerated ageing, based on DNA methylation, can predict all-cause mortality after accounting for genetic, health and lifestyle factors (Marioni, Shah, McRae, Chen, et al., 2015), while Dugué et al. – using a pooled analysis of seven studies – demonstrated an association between DNA methylation-derived measures of accelerated ageing and increased cancer risk, after adjusting for relevant risk factors.(Dugué et al., 2017)

Given the importance of dementia as an age-related disease, the sixth objective of this thesis was to consider the association between DNA methylation–derived measures of accelerated aging and incident dementia, and determine whether this may be a valuable predictor of risk. If increased age acceleration was found to be associated with an increased risk for dementia, one might suggest that by discovering the underlying causes for age acceleration, risk for dementia could be reduced via targeted interventions.

1.4.5 Distinguishing dementia within the spectrum of cognitive decline

This topic is of particular relevance with regard to the study cohort on which all of the research included in this thesis is based. As a study cohort that was originally recruited to investigate non-pathological decline, dementia outcomes were not available until dementia ascertainment was completed for this thesis. As such, early studies were unable to exclude the possibility that preclinical or prodromal dementia was mistaken for ‘normal’ cognitive ageing and had influenced the findings.

Differentiating dementia from other types of cognitive decline is essential in dementia research to avoid erroneous conclusions. While this is a simple statement, the reality of achieving the same is more complex. Dementia exists within a spectrum of cognitive decline and differentiating dementia from other types of cognitive decline

can be difficult. This has implications for both dementia research and research into other types of age-related cognitive decline.

Current diagnostic techniques for dementia are based on the observation of clinical symptoms, which are typically compared with a set of well-recognised criteria. The most recognised of these criteria are those described in the Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (APA) and those described in the International Classification of Diseases (ICD), published by the World Health Organisation (WHO). These classification manuals have been revised several times since their inception, with the DSM and ICD now in their fifth and eleventh revisions, respectively. Each of these classification systems relies on a patient reaching a threshold, at which point a diagnosis of dementia can be made. This threshold typically corresponds to a decline in cognitive function with associated decline in functionality such that activities of daily living are impaired. In most cases – such as in the presence of Alzheimer's disease – the patient will not reach this threshold in a sudden or abrupt manner, but rather, cognitive function and general functionality will follow a more gradual downward trajectory. Prior to reaching the severity of the disease warranted for a clear diagnosis a degree of impairment is likely to be present. In this earlier phase, it is not always clear whether such a cognitive impairment will advance to the point where a diagnosis of dementia is made, or whether subtle cognitive changes will persist or even reverse.

Further to this, studies have indicated that the pathogenesis of Alzheimer's disease may begin long before any symptoms become clinically apparent. The concept of a 'preclinical' phase in dementia is described within the literature and is widely accepted.(Nitrini, 2010; Sperling et al., 2011) The term preclinical dementia describes the earliest period of the dementia process, where underlying pathological changes are present, but symptoms are either completely absent or are not of sufficient

severity ever to meet recognised criteria for mild cognitive impairment (MCI). In simple terms, cognitive function would be indistinguishable from normal variation or expected cognitive ageing. Studies have suggested that the period between the onset of pathological change and clinically identifiable symptoms could be as long as a decade, or even more.(Dubois et al., 2016; Sperling et al., 2011) While studies have shown early pathological changes in those who went on to develop dementia, as a result of death before dementia it is less clear whether these early changes will always lead to a clinical syndrome of dementia in the absence of death. Neuropathological studies have demonstrated dementia-type changes in the post-mortem brains of individuals who did not display clinically detectable cognitive impairment prior to death, but it is impossible to know whether these persons would have developed clinical dementia if they had lived longer.(Sperling et al., 2011) Another study has demonstrated that the proportion of study subjects without dementia with evidence of amyloid plaque build-up in the brain (one of the neuropathological changes associated with Alzheimer's disease) resembles the proportion diagnosed with dementia a decade later.(Sperling et al., 2011) One might hypothesize that such studies could be evidence for the preclinical phase of dementia. It is also possible, however, that these pathological changes are necessary, but not sufficient on their own to produce the clinical syndrome of dementia.(Sperling et al., 2011) Other factors – such as cognitive reserve or environmental exposures – may influence or reduce susceptibility or may alter the time taken for the emergence of clinical symptoms.(Sperling et al., 2011)

Disappointing results from clinical trials for dementia drugs may indicate that by the time the clinical symptoms are identifiable, the pathological process is too far advanced for therapeutic intervention.(Nitrini, 2010) The preclinical phase of the dementia process has been identified as a potentially crucial period for intervention

and is therefore of considerable interest to researchers.(Nitrini, 2010; Sperling et al., 2011) If a single marker were identified to have a firm connection with the development of clinical dementia, this would be a clear target for intervention, either directly or indirectly as an identifier for those persons who may benefit from other interventions. It would also be a valuable tool in selecting participants for studies of non-pathological cognitive ageing, limiting the potential influence of incipient dementia on findings.

While autopsy studies are informative with regard to early pathological changes in the brain tissue, in vivo markers of preclinical dementia would be required to identify susceptible patients clinically and target interventions. Identifying such a marker would have the additional advantage in research studies of being able to identify those persons who would have gone on to develop dementia when death occurs before criteria for a clinical diagnosis were met. Imaging techniques such as positron emission tomography (PET) and studies of cerebrospinal fluid (CSF) have shown promising results with regard to identifying in vivo markers for preclinical dementia.(Dubois et al., 2016; Mak et al., 2017; Sperling et al., 2011) A proposed hypothetical model suggests that early biomarkers are followed by biomarkers of neuronal damage, structural brain changes and finally, clinical symptoms.(Dubois et al., 2016) It has been suggested that the preclinical phase of dementia may be classified as different states; those who have a developing pathology but remain asymptomatic, and those who are asymptomatic but at risk of subsequent dementia.(Dubois et al., 2016) Similarly, biomarkers may be divided into those representing the presence of pathology at any point in the dementia process, and those that represent evidence of consequent damage.(Dubois et al., 2016) While the understanding of preclinical dementia has been much advanced in recent years, the challenge of identifying the most accurate and effective in vivo marker for dementia

pathology, and translating this into practice, remains.(Dubois et al., 2016; Mak et al., 2017)

Until there is a recognised and regularly utilised method, with proven reliability, by which study participants in the preclinical phase of dementia can be identified, it is likely that some such participants will be incorrectly included in studies of non-pathological cognitive ageing. Such inclusions may have an impact on findings. To determine the accuracy of reported results it is vital that the potential impact of preclinical dementia is evaluated retrospectively, using follow-up dementia data. A number of factors have been demonstrated to be associated with non-pathological cognitive aging for the study cohort considered in this thesis. The final component – and seventh objective – of this thesis was therefore be to re-examine these results in order to establish the potential impact of preclinical dementia on the findings. Details of those previous studies are discussed in Chapter 7.

1.5 The 'Oldest-Old'

1.5.1 Who are the oldest-old?

For many years, the 'older age' or 'elderly' population was widely referred to as a single homogenous group; those aged 65 years and above. This threshold for categorisation likely reflected typical retirement age, with post-retirement being considered to be older age.(Kydd, Fleming, Paoletti & Hvalic-Touzery, 2020) Within the literature, there has however been increasing interest in the group at the upper end of this age-bracket, often referred to as the 'oldest-old'. The definition of the oldest-old group varies within the literature, but is most often described as those aged over 80, 85 or 90 years of age.(Bullain & Corrada, 2013; Kydd et al, 2020; Tsoi et al., 2014) What constitutes oldest-old age is likely to have changed over time given the increase in the number of individuals surviving into these older age brackets. In the

research setting, past studies may have been limited to studying age groups with sufficient numbers of participants; as a result of improvements in life expectancy, oldest-old age thresholds may be higher in more recent studies. While the numerical threshold is debatable, the concept of there being an earlier old age and a later old age is generally accepted.

Age 80 years and above is frequently used within the literature to denote oldest-old age.(Erlangsen, Bille-Brahe & Jeune, 2003; Lucca et al., 2020; Mirkin & Weinberger, 2001) This perhaps reflects a theoretical halving of older age into 60-80 years and 80-100 years. While this might be an overly simplistic view – as ageing and age related decline is unlikely to be a linear process – there is no clear evidence for selecting a particular age 'cut-off'. Having been recruited to baseline testing at age 79 years, our study cohort closely resembled the 80+ age group and we therefore reflect other studies within the literature and use the term oldest-old within the thesis.

1.5.2 The complexity of the oldest-old age group

1.5.2.1 Complex variables

For many reasons, the study and care of those in this oldest population group can be complex.(Melzer et al., 2015; Studenski, 2008) Most persons reaching this age will have developed a number of health conditions, creating a complicated picture of health within an individual, and producing a diversity across the group.(Tsoi et al., 2014) Similarly, the longer one's life the more likely that they have been exposed to increasing numbers of external factors that may influence health and wellbeing, further complicating the 'health and disease profile' of this age group. While the range of health and lifestyle factors is likely to vary widely between individuals of this age, there may also be significant inter-person variation relating to a single variable. Taking diabetes as an example: the 'back-story' of a diagnosis of diabetes is likely to differ

significantly from one person to the next. Let us compare Person A, who developed type II diabetes at age 40, and maintained satisfactory control of blood sugar without the need for medication; Person B who developed type II diabetes at age 75 and had periods of poor control despite medication; and Person C who was diagnosed at age 50 and had significant complications relating to diabetes despite adequate blood sugar control. We can see that 'a history of diabetes' is not a straightforward binary variable, but one that may differ according to the clinical history. Most health variables of interest in risk factor studies are likely to be subject to similar complexities and with advancing age, such complexities might be expected to increase. In parallel with the increased likelihood of multiple chronic and acute illnesses, the likelihood of polypharmacy is also increased in oldest-old age.(Tsoi et al., 2014)

1.5.2.2 Additional complexities

The sample size in studies of the oldest-old are always going to be more limited than those in earlier old age as a result of recruitment challenges in oldest age.(Mody et al., 2008) Furthermore, studies are going to be subject to high rates of attrition due to illness and death.(Mody et al., 2008) Given the increased potential for hospital admission in this age-group, prospective follow up may also be affected by participant unavailability during planned testing dates. Participants may also change residence, or type of residence as a result of increasing support needs. This has the potential to interfere with studies depending on the study criteria and follow-up procedures. The relatively high proportions of sensory impairment and physical disability can be a barrier to inclusion in studies and can make the completion of certain components of assessment difficult or impossible. Such impairments can also 'cloud' or confuse the functional loss associated with a cognitive decline. Studies of oldest-old age participants must also consider the potential effects of easy fatiguability on data collection.(Mody et al., 2008) Lengthy testing procedures may result in poorer results

towards the end of the testing period as a result of fatigue. It is therefore important to add studies to the literature in order to build a larger volume of data relating to specific study questions, to allow for collation, comparison and potential meta-analyses.

1.5.2.3 Frailty in oldest-old age

Studies of the oldest-old may be further complicated by the varying degrees of frailty observed in this age group. Frailty may be defined as a decline in the reserve or resilience of body systems to withstand every-day stressors or acute stress and return to the pre-morbid condition; this may be simply considered as the reducing ability of the body to 'bounce-back' from an insult.(Kojima, Liljas & Iliffe, 2019; Xue, 2011) A widely accepted definition produced by the World Health Organisation (WHO) is as follows: "a clinically recognizable state in which the ability of older people to cope with everyday or acute stressors is compromised by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems".(World Health Organisation, 2017) Studies have considered a wide range of domains in the assessment of frailty, including both physical and psychological domains. One popular clinical definition of frailty is a phenotype model consisting of five physical items, produced by Fried et al.(Fried, et al., 2001) The five items include unintentional weight loss of ten pounds or more, slow walking speed, poor grip strength, self-reported exhaustion and low physical activity.(Fried, et al., 2001). It can therefore be seen that frailty would affect variables of interest in the study of dementia, including body mass index (as an assessment of obesity), grip strength and walking speed (as measures of fitness) and physical activity, complicating the investigation of the role of such risk factors in dementia.

In addition to the individual features of frailty having the potential to affect studies of risk factors for dementia in the oldest-old, overall frailty may have an impact on study

findings. Frailty has been shown to increase the risk for incident dementia.(Li et al., 2020) It is possible therefore that the decline in resilience puts one more at risk of dementia.(Li et al., 2020) One may also consider whether the association between frailty and dementia is explained by a shared or similar aetiological pathway.(Li et al., 2020) In support of this explanation, studies have shown that the rate of change in frailty and cognition are strongly correlated, with common neuropathological basis.(Buchman et al., 2014) Alternatively, one must consider whether reverse causation is giving rise to the observed relationship. Given that one might expect reduced activity and weight loss in dementia, such changes may occur as part of the prodromal phase of dementia, before dementia is diagnosed in a study.

Frailty is an important feature of health in oldest age, and is much more frequent in this age group than any other. Studies have demonstrated an exponential increase in the prevalence of frailty with increasing age, from approximately 6.5% in those aged 60-69, to 65% in those aged over 90 years.(Gale, Cooper & Sayer, 2015) As such, it is increasingly possible that features associated with frailty may dominate the clinical picture, complicating the appearance of the risk factor profile in the oldest-old. Frailty will therefore be considered in the later chapters, in the context of specific study results.

1.5.3 A potentially changing risk factor profile in oldest-old age

Perhaps unsurprisingly, given the various complexities of this age group, previous studies of risk factors for dementia in the oldest-old have not produced consistent or conclusive results. Studies of this age group have however produced results that suggest the risk factor profile for dementia in oldest-old age is changed from that in earlier old age. As noted in section 1.4.4, the importance of *APOE* ε4 has been questioned in oldest-old age.(Corrada et al., 2013) Hypertension – which is also a

recognised risk factor for dementia – has also been shown to decrease in potency with advancing age, with a possible reversing of the association in advanced old-age.(Corrada et al., 2017; Li et al., 2007) Another risk factor found to have a changed association in oldest-old age is hypercholesterolaemia. While hyperlipiaemia has been shown to be associated with increased risk in earlier old age, studies in the oldest-old have shown a lack of such an association, and possibly even a reduced risk for dementia.(Evans, Kawas, & Corrada, 2014; Piguet et al., 2003; Rastas et al., 2010)

It is not only health factors that have been suggested to differ in their association with dementia in oldest age; the associations between lifestyle factors and dementia in oldest-old age have have also been called into question. Participation in greater levels of vigorous exercise at approximately age 40, 70 and 90 years was not associated with incident dementia over 90 years.(Paganini-Hill, Kawas, & Corrada, 2016)

A potential change in the risk factor profile for dementia in oldest-old age is supported by evidence from other studies of health risks in oldest age. The recognised associations between traditional cardiovascular risk factors – including hypertension and hyperlipidaemia – and mortality have been shown to be absent, or even inverted in oldest-old age.(Vaes et al., 2017).

Studies have suggested that it is not only the risk factor profile that changes in dementia in the oldest-old. The neuropathological features of dementia observed in the post-mortem examination of oldest-old individuals have been shown to differ from what might be expected based on features observed in earlier old age.(Bullain & Corrada, 2013) Such differences can cause one to question whether the disease process for dementia in oldest-old age is different to that in earlier old age. Based on the current evidence, it is difficult to make a definitive statement in answer to this. What we do know, is that there are differences in how dementia may need to be

assessed based on differences in 'population norms' and non-dementia related functional impairment; we suspect that the risk factor profile might be changed; and that there is evidence that the neuropathology is changed.(Bullain & Corrada, 2013) The only way to make a more conclusive argument either way is to increase the volume of evidence within the literature.

The oldest-old age group is therefore an important area of research interest for multiple reasons including: the growing size of this group; the likely volume of studies required to produce adequately large volumes of data; and the complexity of the health and disease profile within the group. The studies contained within this thesis therefore aimed to add to the existing literature in this field.

1.6 Key epidemiological concepts in the thesis

Within this thesis a number of key epidemiological concepts are discussed; many of these are of particular relevance as a result of the characteristics and design of the study cohort, including their advanced age at recruitment. We introduce such concepts here and explore these further within the relevant chapters of the thesis.

Unmeasured confounding

The complex web of differing health conditions and lifestyle influences, the exact nature of which varies widely between persons, raises the possibility of unmeasured confounding in studies of the oldest-old; i.e. an extraneous variable has an effect on the independent and dependent variables being studied, resulting in an observation that does not reflect the actual association between the variables being studied.(Pourhoseingholi, Baghestani & Vahedi, 2012) Such unmeasured confounding has the potential to affect the results of studies of oldest-old age cohorts, including the LBC1921.

Collinearity

When examining the potential for confounding in a regression analysis, one must also consider the potential for collinearity between variables and the potential that collinearity is undermining the statistical significance of an independent variable. All of these issues make the design of studies and interpretation of results (both within a group and between groups) in the oldest-old more challenging; perhaps contributing to varying results between cohorts. A clearer picture of patterns of risk in the oldest-old will therefore require increased numbers of studies and detailed studies of any factor flagged as potentially important.

Reverse causation

With studies in oldest-old age, baseline measurements have the potential to be of increased proximity to the dementia outcome. While this may be limited by starting studies earlier in the life course and following participants to oldest-old age, this is not always feasible. Where it is not, the potential for reverse causation should be considered when examining observed associations. This would be important in our study given that most variables were measured at a baseline age of 79 years.

Competing risk

Death would also be a notable competing risk for dementia in our studies, given the potential for death to occur before dementia in a participant who would have gone on to develop dementia if they had not died. Further consideration will be given to the competing risk of death within relevant chapters of the thesis.

Association versus causation

When considering the veracity and direction of associations, one must also give thought to the nature of an observed relationship. In particular, whether we are observing causation or association. If the value of one variable provides information

about another, one can report the observation of an association but not causation. Before describing causation in any findings, it is useful to consider the guidelines described by Bradford Hill in his 1965 paper on association and causation.(Hill, 1965) He described nine viewpoints that one might consider; these include the strength, plausibility, consistency, biological gradient and temporality of an association.(Hill, 1965) In our study of dementia in oldest-old age, observations were unlikely to be described as causation; the complexities outlined previously increase the likelihood of there being other variables affecting the observed relationship that were not controlled for within the analyses. Furthermore, the inconsistencies in observations in studies of dementia in the oldest-old make identifying causation less likely.

Healthy survivor bias

Studies of oldest-old cohorts are also at risk of being affected by healthy survivor bias. Simply by being of oldest-old age means that those available to recruitment have survived several possible health or lifestyle factors that would be of interest in studies of risk factors. Studying only those who survive, and ignoring those who did not can lead to misleading conclusions. This potential for bias is revisited in the relevant chapters.

Selection bias

The study sample considered within the studies included in this thesis is potentially subject to selection bias as a direct result of recruitment procedures. While participants were not entirely self-selecting, they did need to agree to take part in testing. Certain characteristics – such as better physical and mental health, or an interest in the subject of cognitive ageing – may have introduced bias to the sample. Selection bias relating to sample recruitment is explored further in Chapter 2, where the cohort is introduced.

Missing data

Any data that might be considered to missing not at random has the potential to affect study findings. If one considers a variable measuring cognition, it could be postulated that those with poorer cognition would be less likely to complete the measure, thus leading to missing data for those with the poorest cognitive ability. The resulting dataset would therefore not be a true representation of the sample, and the results of analyses using these data might be misleading. Given the potential for cognitive and physical impairments in advanced old age, one must recognise the potential for such factors to affect the completeness of data and how the missing values might affect the analyses. The 'randomness' of missing data is discussed further in Chapter 2.

1.7 Core questions and statement of aims for thesis

This thesis will consider a single study cohort in addressing each of the described objectives. The second chapter will introduce and describe the study cohort from which the data for this thesis are derived – the Lothian Birth Cohort 1921. The subsequent chapters will address each of the research questions in turn, as outlined below.

Thesis objectives

Objective 1: Develop a method for ascertaining dementia using existing data. This would include an evaluation of the potential sources of data, based on evidence from the literature.

Objective 2: To use this method to perform dementia ascertainment in the study cohort (Lothian Birth Cohort 1921).

Objective 3: Explore the association between the *APOE* ε4 genotype and dementia in the oldest old.

Objective 4: Explore the association between potentially modifiable risk factors and dementia in the oldest old.

Objective 5: Explore the association between physical fitness in older age and dementia in oldest age.

Objective 6: Explore DNA methylation-based measures of accelerated ageing – as a proxy for accelerated biological aging – as a potential predictive factor for incident dementia in the cohort.

Objective 7: Examine the potential effect of preclinical, or prodromal, dementia on previous findings relating to risk factors for non-pathological cognitive ageing in the study cohort (Lothian Birth Cohort 1921).

2: An introduction to the study cohort: The Lothian Birth Cohort 1921

2.1 Introduction to the chapter

The data for this thesis were drawn from the Lothian Birth Cohort 1921 (LBC1921). This chapter provides a detailed description of the origins, recruitment and follow-up of the cohort. The LBC1921 was designed as a follow-up study of the Scottish Mental Surveys of 1932 (SMS1932). This survey had tested the general intelligence of almost all Scottish school pupils born in 1921. The Lothian Birth Cohort study aimed to exploit the rare opportunity that these childhood intelligence data provided for examining cognitive ageing from childhood to old age.

2.2 Background

The SMS1932 was designed and implemented by the Scottish Council for Research in Education.(Scottish Council for Research in Education, 1933) The primary objectives of the study were to investigate the rates of mental deficiency in Scotland and describe the distribution of intelligence throughout the community. Participants took part in the SMS1932 across all Scottish schools simultaneously, on June 1st, 1932, with only a very limited number being tested in the following days. A total of 87 498 pupils undertook the test: 43 288 girls and 44 201 boys. The intelligence test used in the survey was a version of the Moray House Test No.12 (MHT). The MHT was developed by Professor Godfrey Thompson, Bell Professor of Education at the University of Edinburgh (1925-1951). The MHT comprised 75 items (71 numbered questions), with a maximum score of 76 marks. It has been described as a test of verbal reasoning and included a number of different tasks including: following directions (14 items), same-opposites (11), word classification (10), analogies (8), practical items (6), reasoning (5), proverbs (4), spatial items (4), arithmetic (4), mixed sentences (3), cypher decoding (2), and other items (4).(Deary, Whalley, & Starr,

2009) In order to determine concurrent validity for the MHT, a sample of 1000 pupils – 500 girls and 500 boys – underwent individual testing.(Scottish Council for Research in Education, 1933) The test used was the Stanford revision of the Binet-Simon Test (standardised by Terman).(Deary et al., 2009; Terman, 1916) The test was modified for Scottish use by substituting American terminology for more familiar terms.(Scottish Council for Research in Education, 1933) Despite aiming for a representative sample, the 'Binet 1000' sample were determined to be of slightly higher intellectual ability when compared with the complete sample, particularly the boys.(Scottish Council for Research in Education, 1933) The concurrent validity of the MHT was however high – with a correlation between the MHT and Stanford-Binet Scale of 0.80 for boys and 0.76 for girls.(Deary et al., 2009) The idea for the Lothian Birth Cohort studies resulted from the discovery of ledgers containing the original results of the Scottish Mental Surveys.(Deary et al., 2009)

2.3 Recruitment and follow-up

From 1999, participants of the SMS1932 were identified, traced and recruited within the Lothian area of Scotland. Lothian is a region of South-East Scotland, in which the largest settlement is Edinburgh. Potential participants were identified by two means: through media advertisement or by the Community Health Index – area based lists of general practice registration. Five hundred and fifty participants attended baseline (wave 1) LBC1921 testing at approximately 79 years of age, almost seven decades after taking part in SMS1932. Surviving participants who continued to consent to inclusion in the LBC1921 study, attended up to four subsequent waves of follow-up testing, at roughly 83, 87, 90 and 92 years of age. The first aim of the LBC1921 study was to investigate molecular genetic influences of non-pathological cognitive ageing. Subsequent aims included the investigation of influences leading to variation in

lifetime cognitive ageing, studying the effects of single nucleotide polymorphisms and conducting a genome-wide association study.

Data on a wide range of variables were collected at each test wave, by questionnaire and in-person testing. Appropriately trained personnel completed the in-person testing at a suitable clinical research facility (Welcome Trust Research Facility, Western General Hospital, Edinburgh). Some of the same information was collected at multiple test waves whereas some information was collected at only a single wave of follow-up testing. In general, this reflected whether a variable was fixed (such as *APOE* ε4 carrier status), or liable to change (medical history, for example). Additional information variables were also introduced according to the developing research aims of the study. All collected data – original copies and computerised versions – were stored in accordance with study approvals. Specific details on how each data variable included in this thesis was collected or measured will be described within the relevant chapter.

2.4 Cohort demographics

All of the *N*=550 participants recruited to the LBC1921 were relatively healthy and living independently within the community. All participants were born in 1921. Females formed a slight majority within the cohort, numbering *n*=326 (57.5%) compared to *n*=234 (42.5%) males at enrolment. Participants had a mean age of 79.1 (SD: 0.6) years at baseline testing (in 1999), with a range of 77.7 years to 80.6 years. Overall, the cohort was cognitively normal at baseline, with a mean Mini-Mental State Examination score of 28.2 (range 18-30) for the *n*=548 participants with test scores available. A score of 23 or below is widely accepted to be suggestive of cognitive impairment and in the LBC1921, only *n*=9 participants scored less than 24 at recruitment. These participants were typically excluded from analyses to prevent the

possible inclusion of participants who were cognitively impaired at the outset of the study. Manual social classes were less well represented within the LBC1921: social class I, *n*=130 (23.6%); social class II, *n*=186 (33.8%); social class III, *n*=215 (39.1%); social class IV, *n*=11 (2%); social class V, *n*=6 (1.1%). Participants had spent a mean of 10.9 years (range 7 to 20.5 years) in formal, full-time education. We would note that in the 1930s – when the LBC1921 participants would have left school – the school leaving age in Scotland was 14. Age 11 IQ scores (derived from SMS1932 MHT test scores) and age 79 IQ scores were available for *n*=493 and *n*=540 participants, respectively. IQ scores were standardised, with a sample mean of 100 and standard deviation of 15, based on MHT scores corrected for age in days at testing. The standardised IQ scores at age 11 years ranged from 44.0 to 130.7, while the standardised IQ scores at age 79 years ranged from 35.6 to 123.9. As these scores were standardised on the sample, the low scores are relative to the sample, which had a higher mean cognitive score than the background population. To demonstrate how the cohort age 11 IQ scores compare with the general population more clearly, we can consider the raw MHT scores: 34.5 (SD: 15.5) was the mean score for Scotland, 37.3 (SD: 14.8) for those in Edinburgh schools, and 46.4 (SD: 12.1) for those recruited to LBC1921.(Deary, Gow, Pattie, & Starr, 2011; Starr, Pattie, Whalley, & Deary, 2008)

2.5 Attrition and missing data

Attrition – a loss of participants to follow-up – would be expected in any longitudinal study of older participants. The most obvious reason for attrition in this age-group would be death, but other factors – including poor physical health, poor mobility, cognitive decline, increased frailty, changes in living arrangements or support network – are also likely to feature. Although the baseline differences between returnees and non-returnees were relatively small, grip strength, lung function (FEV_1), MMSE and

age 79 IQ have all been shown to be poorer in those who did not return.(Deary, Gow, Pattie, & Starr, 2012) A history of cardiovascular disease was more common in those who did not return.(Deary et al., 2012) Participants may also opt out for less specific reasons, such as finding that attending for follow-up is tiring, no longer enjoyable or simply deciding that they would prefer to stop taking part. While the number of participants attending wave 1 (baseline) testing was *N*=550, the number attending was reduced at all subsequent waves: *n*=321 were assessed at wave 2 (mean age (SD) 83.4 (0.5) years), *n*=235 at wave 3 (mean age (SD) 86.6 (0.4) years), *n*=129 (plus 11 with dementia) at wave 4 (mean age (SD) 90.1 (0.1) years) and *n*=59 at wave 5 (mean age (SD) 92.1 (0.3) years.(Taylor, Pattie, & Deary, 2018)

Table 2.1 Number and age of participants at each LBC1921 test wave

	Test Wave				
	Wave 1	**Wave 2**	**Wave 3**	**Wave 4**	**Wave 5**
Age at testing (years (SD))	79.1 (0.6)	83.4 (0.5)	86.6 (0.4)	90.1 (0.1)	92.1 (0.3)
Number assessed	550	321	235	129 (+11 with dementia)	59

Given that one of the possible reasons for attrition may be cognitive decline or dementia, there is the potential for bias as those remaining in the study will have less cognitive impairment. For this reason, it is important to have methods of follow-up that do not require attendance, such as record linkage to death certificates and hospital records. Such sources will be discussed further in Chapter 3 where dementia ascertainment methods using existing data are explored. We would also note that any new diagnosis of dementia reported by a participant or carer resulted in a referral to

the Clinical Research Fellow (a registered medical doctor) for assessment in order to confirm the diagnosis and likely subtype classification for study purposes.

While the LBC1921 study aimed to collect the same set of data for each participant, some data were missing following each wave of testing. Data may have been missing for a number of possible reasons. As a result, the missing data probably included that which was missing completely at random, missing at random and not missing at random. Examples of how data might be missing completely at random are: a blood sample lost at a laboratory, or a questionnaire lost in the post. We would note that data missing completely at random are less likely in this cohort given the careful data collection and follow-up procedures. There is a possibility that some data were missing at random. Sex differences are often cited as potential reasons for data to be missing at random; men may be less likely to complete a depression assessment and women may be less likely to consent to weight measurement. In the LBC1921 these types of missing data are again likely to be few in number; research staff made a particular effort to encourage test completion in order to minimise this. Data missing not at random is unfortunately a possibility in the LBC1921. For example, individuals with cognitive decline may struggle to complete cognitive testing, leaving data incomplete. Similarly, participants with mobility issues might be unable to complete tests of walking speed, meaning these data were missing. While data collection staff aimed to minimise missing data, some missing data is unavoidable.

Data were more complete for some variables than for others. For example, of the total cohort (*N*=550) attending wave 1 testing, age 11 IQ scores were available for *n*=493 (89.6%), *APOE* ε4 status was available for *n*=543 (98.7%), sex was available for *n*=550 (100%), height was available for *n*=544 (98.9%), smoking status was available for *n*=549 (99.8%) and self-reported lifetime physical activity was available for *n*=367 (66.7%). Self-reported physical activity data were collected via a postal

questionnaire, completed sometime after attendance at wave 1 testing. The implication of these missing data would be that the number of participants included in an analysis would be limited to those with complete data for included variables.

2.6 Potential for bias in the cohort

Participants in observational studies chose whether to partake, and motivation must therefore be taken into account when considering the potential characteristics of a cohort. As described above, participants were recruited through advertising and through general practice lists. Individuals with an interest in cognitive ageing may have been more likely to consent to inclusion in the study, particularly in the case of those who responded to media advertisements. It is possible that increased interest was the result of personal or family experience with cognitive decline and as a result there is a potential for the recruited cohort to be at a greater risk for cognitive decline. By agreeing to participate in the study, participants were agreeing to take part in regular testing that involved time, and mental and physical effort. As such, participants were more likely to be fitter, with less health issues. Participants with an interest in research may also potentially be more educated or intelligent than the general population average. This would appear to be the case in LBC1921, where mean age 11 IQ was above the national and regional mean; there was also a slight restriction in the range of IQ scores. The main likely effect of this would be a slight lowering of the associations' effect sizes. A similar pattern is seen in the LBC1936.(Johnson, Corley, Starr & Deary, 2011) With these considerations in mind, we must recognise the potential for selection bias in our studies.

The missing data described above may also give rise to a selection bias. If data are not missing completely at random – for example when those with poorer physical health are less likely to be able to complete physical fitness tests – then the sample

with complete data (and therefore included in the analyses) will not represent the total population.

2.7 Study funding and ethical approvals

The Lothian Birth Cohort 1921 has been funded latterly by Age UK (the Disconnected Mind grant). Previous funding was provided by the UK Biotechnology and Biological Sciences Research Council (BBSRC) for wave 1 (15/SAG09977), a Royal Society-Wolfson Research Merit award to Professor Ian Deary for wave 2, the Chief Scientist Office (CSO) of the Scottish Government's Health Directorates for waves 3 (CZB/4/505) and 4 (ETM/55) and a questionnaire study between the first two waves (CZG/3/2/79), and the UK's Medical Research Council (MRC) Centenary Early Career Award to Dr Tom Booth for wave 5.(Taylor et al., 2018) Completed as part of this thesis, dementia ascertainment was funded by the Alzheimer Scotland Dementia Research Centre. Ethical approval for LBC1921 was provided by the Lothian Research Ethics Committee for test waves 1-3, and the Scotland A Research Ethics Committee for test waves 4 and 5. Participants attending from wave 4 provided informed, written consent for data linkage and access to health records.

2.8 Other studies describing dementia in the oldest-old

While studies investigating dementia in the oldest-old are less frequent within the literature, several cohort studies have been designed with this specific aim. *Table 2.2* outlines the basic parameters of studies that would be most relevant to this thesis.

Table 2.2 Existing studies of dementia in the oldest-old

Name of Study	Location of Study Participants	Age of Participants	Number of Participants
Study designed to investigate dementia in the oldest-old			
90+ Study	USA	90+ years	1600+
Leiden 85-Plus Study	Netherlands	85+ years	599
Vantaa 85+ Study	Finland	85+ years	601
WISE Study	USA	85+ years	1299
CAIDE85+ Study	Finland	85+ years	Estimated enrollment of 500
Monzino 80-plus Study	Italy	80+ years	2139
OCTO-Twin Study	Sweden	79+ years	702 (351 twin pairs)
Study not originally designed to investigate dementia in the oldest-old			
Eurodem Study	Combines data from studies in 10 European countries	85+ years	1623
Cache County Study	USA	85+ years	719
Kungsholmen Project	Sweden	90+ years	502
Canadian Study of Health and Aging	Canada	85+ years	1807

Initiated in 2003, The 90+ Study is based in the USA and reports to have over 1600 persons enrolled.(Gardner, Valcour, & Yaffe, 2013; UCI MIND) The initial participants recruited to the study were survivors of the earlier Leisure World Cohort Study (LWCS), which studied a retirement community in California.(Gardner et al., 2013) A 2017 study on hypertension and dementia in The 90+ Study cohort provided the following specifics regarding enrolled participants: of the 1554 participants who were enrolled by 17th July 2013, 891 were seen for in-person assessment at baseline; of those 891 participants, 601 were without dementia at baseline.(Corrada et al., 2017) Of the 663 participants not seen in-person at baseline, 45% were determined to have

dementia at baseline using other sources of information.(Corrada et al., 2017) The Leiden 85-Plus Study is a prospective population study based in Leiden, Netherlands and includes 599 participants.(Rostamian et al., 2017) The 705 inhabitants of Leiden who turned 85 years of age between the 1st of September 1997 and the 1st of September 1999 were eligible to participate; 85% of those eligible participated in the study.(Rostamian et al., 2017) Also a prospective population-based study, The Vantaa 85+ Study included 601 inhabitants of Vantaa, Finland who were aged 85 years or over on the 1st of April 1991.(Hall et al., 2019; Gardner et al., 2013 Clinical examination was completed for 553 participants (214 of whom had dementia at baseline), and neuropathological examination was performed on 304 participants.(Hall et al., 2019) The Monzino 80-plus Study included 2139 participants at baseline, of which 74% were female; participants were interviewed at home and resided in the Varese province of Italy.(Lucca et al., 2011) The OCTO-Twin Study (Origin of Variances in the Oldest-Old) was carried out between 1991 and 2002.(Karlsson et al., 2015; Maelstrom Research, 2020) Participants included 351 twin pairs, recruited from the Swedish population-based twin registry.(Karlsson et al., 2015; Maelstrom Research, 2020) Participants were followed up five times, at two-yearly intervals, with the aim of investigating aetiology of individual differences among twin-pairs age 80 and older, on a range of domains including health and functional capacity, cognitive functioning and psychological well-being.(Karlsson et al., 2015; Maelstrom Research, 2020) The Women Cognitive Impairment Study of Exceptional Aging (WISE) Study is an ancillary study to the Study of Osteoporotic Fractures, based in the USA.(Gardner et al., 2013; Yaffe et al., 2011) Of the 1338 participants who completed the cognitive test battery, 1299 were aged over 85 years.(Gardner et al., 2013; Yaffe et al., 2011) All five of these studies included a majority of female participants.(Corrada et al., 2017; Gardner et al., 2013) A relatively new study of the oldest-old, that is not yet complete, is the CAIDE85+ study.(NIH: U.S. National Library

of Medicine: ClinicalTrials.gov) The CAIDE85+ study is based in Eastern Finland and is the third follow up of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study, which began in 1998 with 2000 participants.(NIH: U.S. National Library of Medicine: ClinicalTrials.gov) These participants, in mid-life between 1972 and 1987, had previously taken part in the North Karelia, and FINMONICA survey studies.(NIH: U.S. National Library of Medicine: ClinicalTrials.gov) CAIDE85+ is due to start in May 2019 and complete in December 2020, with an estimated enrollment of 500 participants.(NIH: U.S. National Library of Medicine: ClinicalTrials.gov) Other studies – although not originally designed to investigate dementia in the oldest-old – have included older cohorts that have been used for this purpose.(Gardner et al., 2013) Such studies include the Eurodem study, the Cache County Study, the Kungsholmen Project and the Canadian Study of Health and Aging.(Gardner et al., 2013) The Eurodem study has investigated the prevalence, incidence and risk factors of dementia by combining data from dementia studies in ten European countries, (including the Leiden 85-Plus Study).(Gardner et al., 2013) In a study of dementia prevalence, the Eurodem Study included 1623 participants aged over 85 years, 73% of whom were female.(Gardner et al., 2013) The Cache County Study was established in 1995 with the aim of investigating risk factors for Alzheimer's and other dementias. Based in Utah, USA, approximately 14% (n=719) of the participants of the original study group were aged over 84 years at baseline.(Tschanz et al. 2005; Tschanz, Norton, Zandi & Lyketsos, 2014) The majority of those in this sub-group were again female (66%).(Gardner et al., 2013) The Kungsholmen Project is based in Stockholm, Sweden and has published study results based on a sub-set of participants (n=502) aged 90 years and over.(Gardner et al., 2013; von Strauss, Viitanen, De Ronchi, Winblad, & Fratiglioni, 1999; von Strauss, Fratiglioni, Viitanen, Forsell, & Winblad, 2000) In a study of dementia prevalence in the very old, The Canadian Study of Health and Aging included 1807 participants aged over 85 years,

of which 72% were female.(Ebly, Parhad, Hogan & Fung 1994; Gardner et al., 2013) All of the studies described have been located in Northern America or Europe, which may be expected given that areas with greater life expectancy would yield larger populations of persons in advanced old age. Studies such as the 90+ Study and WISE are predominantly made up of white subjects of high socioeconomic status. While the studies described above would provide valuable evidence describing dementia in the oldest-old, the limitation in study location and participant demographics would suggest that findings might not be applicable to the broader global population. As life expectancy improves in other countries and regions, studies of dementia in the oldest-old in these populations will be important in determining how applicable previous findings are from a global perspective. The LBC1921 demographics would be similar to those included in the previous studies of the oldest-old, with the cohort comprising mostly of white, European subjects of relatively high socioeconomic status and educational achievement. For this reason, results of previous studies would be comparable with results from study of the LBC1921 cohort, and vice versa. Furthermore, results from studies of the LBC1921 would add further detail to the existing evidence in that these studies could account for childhood intelligence.

As described within this chapter, the LBC1921 was not originally designed to investigate dementia. With a considerable proportion of the cohort deceased at the outset of the study period for this thesis, dementia outcomes were therefore determined using existing data as the primary data source. The next chapter explores such methodology within the literature, before discussing the procedure that was developed for dementia ascertainment in the LBC1921.

3: Dementia ascertainment using existing data

3.1 Introduction

Developing an effective dementia ascertainment procedure was a vitally important first step in addressing the objectives of this thesis. It was to be the basis on which all subsequent analyses were built. Further to this, the dementia outcomes determined in this body of work were to be incorporated into the LBC1921 dataset and be available to other researchers. Failure to produce a dementia ascertainment method of sufficient effectiveness and accuracy would limit the acceptance of any future findings based on dementia cases derived using this method.

Ideally, the ascertainment method would have replicated a recognised and consistently used method based on evidence of effectiveness. The optimal evidence base would have been a systematic review describing a 'best method' based on individual articles that had evaluated dementia ascertainment methodologies using existing data. At the commencement of this study, no such review was identified within the literature. Without a review of multiple articles, the next best option for determining a suitable methodology would have been the identification of any article describing the study and evaluation of dementia ascertainment methods using existing data. Again, a literature search revealed no such publication.

In the absence of such an evidence base, it was important to consider the methods for dementia ascertainment utilised by some of the large, well-recognised UK-based dementia studies. The Medical Research Council Cognitive Function and Ageing Studies (CFAS I and II) used evidence gathered from repeated screening and assessment interviews to determine a study diagnosis of dementia.(Matthews et al., 2013) For some analyses, these data were combined with death certificate data.(Brayne et al., 2006) Similarly, the Cambridge City over-75s Cohort (CC75C)

study determined consensus diagnoses using data from assessment interviews, informant information and death certificate data.(Brayne et al., 2009) The similarities between the methods of these studies is likely to be due to the fact that these cohorts were set-up in order to investigate dementia. They have therefore collected data in such a manner to optimise the accuracy of dementia ascertainment. As previously described, the LBC1921 study was not originally designed in order to investigate dementia and as such, the data collected were not optimised for this purpose. Having been commenced many years prior to the proposed ascertainment of dementia, prospectively determining cases was not possible, particularly given the large number of deaths that had already occurred in the cohort. Having determined that dementia cases would need to be ascertained using evidence from previously collected data, the next step was to identify any individual studies that had used such methods. From the previous literature searches it was apparent that no paper investigated this methodology as the main study topic; it was therefore necessary to identify articles describing this type of procedure within their reported methods. Given the number of dementia studies that could have potentially used existing data, either in full or in part, to ascertain dementia, a systematic approach was required in order to identify the maximum number of relevant articles. The decision was made to limit the investigation of methods to studies based within the UK only. Primarily, this was due to the wide variation in the type and availability of both healthcare and datasets across the world and because UK data sources would be directly relevant to this thesis. To guide the development of a dementia ascertainment method for LBC1921, it was necessary to examine the methods of any UK-based cohort or longitudinal study using existing data for dementia ascertainment. A systematic review was therefore designed and completed, with a view to describing the methods previously used, discussing the benefits or drawbacks of each, and finally, make recommendations for developing effective methods.

The success of the systematic review would hinge on the design of the literature search. The search strategy needed to include terms specific to the purpose of the review, including terms relevant to dementia, the UK and a longitudinal or cohort study type. Given that the review considered a methodology, rather than a study outcome, the search terms needed to be broad enough to prevent the unintentional exclusion of relevant articles. It was anticipated, therefore, that while the search was likely to return a large number of potentially relevant articles, a significant proportion would not be eligible for inclusion in the study. In order to design the most effective search strategy for identifying relevant articles the authors of the review used an iterative process to review and optimise the included terms, with the guidance from a librarian with expertise in literature search strategy.

The systematic review was designed and completed as described in the published systematic review in the subsequent section of this chapter. The completed systematic review was published in *BMC Psychiatry* with the aim that this would provide evidence for other researchers looking to design dementia ascertainment methods using existing data.

The full reference for the included paper is as follows:

Sibbett, RA., Russ, TC., Deary, IJ. and Starr, JM (2017). Dementia ascertainment using existing data in UK longitudinal and cohort studies: a systematic review of methodology. *BMC Psychiatry*, 17: 239. doi: https://doi.org/10.1186/s12888-017-1401-4

The author of this thesis is the first author of the published paper and made the following contributions to the manuscript: took part in devising the review objectives, writing the search strategy, writing the inclusion and exclusion criteria, developing and utilising the quality measure, performed the literature search, took part in screening

for inclusion and exclusion, led the writing of the manuscript and contributed to revisions of the same. The contributions of each additional author is detailed within the paper. The additional files for the published manuscript can be viewed within *Appendix 1* of this thesis, from page 231. The individual appendices can be viewed on the following pages:

The references for this paper are included within the published manuscript, in the referencing style of the journal. The references can be seen on pages 69-70 of the thesis.

3.2 Dementia ascertainment using existing data in UK longitudinal and cohort studies: a systematic review of methodology

(The published manuscript is included from the next page)

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RESEARCH ARTICLE Open Access

Dementia ascertainment using existing data in UK longitudinal and cohort studies: a systematic review of methodology

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Abstract

Background: Studies investigating the risk factors for or causation of dementia must consider subjects prior to disease onset. To overcome the limitations of prospective studies and self-reported recall of information, the use of existing data is key. This review provides a narrative account of dementia ascertainment methods using sources of existing data.

Methods: The literature search was performed using: MEDLINE, EMBASE, PsychInfo and Web of Science. Included articles reported a UK-based study of dementia in which cases were ascertained using existing data. Existing data included that which was routinely collected and that which was collected for previous research. After removing duplicates, abstracts were screened and the remaining articles were included for full-text review. A quality tool was used to evaluate the description of the ascertainment methodology.

Results: Of the 3545 abstracts screened, 360 articles were selected for full-text review. 47 articles were included for final consideration. Data sources for ascertainment included: death records, national datasets, research databases and hospital records among others. 36 articles used existing data alone for ascertainment, of which 27 used only a single data source. The most frequently used source was a research database. Quality scores ranged from 7/16 to 16/16. Quality scores were better for articles with dementia ascertainment as an outcome. Some papers performed validation studies of dementia ascertainment and most indicated that observed rates of dementia were lower than expected.

Conclusions: We identified a lack of consistency in dementia ascertainment methodology using existing data. With no data source identified as a "gold-standard", we suggest the use of multiple sources. Where possible, studies should access records with evidence to confirm the diagnosis. Studies should also calculate the dementia ascertainment rate for the population being studied to enable a comparison with an expected rate.

Keywords: Dementia, Research design and methodology

Background

As the global population ages and dementia rates increase, further research is required in order to reduce the impact on the individual and on society [1, 2] Key aspects of current dementia research include causation, risk factors, early detection, and prevention. In order to investigate such factors robustly – and avoid reverse causality – studies need to consider subjects prior to disease onset. Whether such studies concentrate on the entire life course or on a limited period prior to dementia onset, completing data collection prospectively can be time-consuming and costly. Recruiting those who already have a diagnosis in order to consider life-course risk and protective factors is limited by the potential inaccuracy or incompleteness of information recalled by participants and carers.

In order to overcome such limitations, the use of previously collected data is key. The value of existing data sets is demonstrated by the launch of The Farr Institute of Health Informatics Research in the UK, aimed at optimising the use of health records in research by facilitating the safe and secure use, and linkage of, electronic patient records, research data and routinely collected data [3].

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Using existing data in dementia research is not unusual. Death certificates are often utilised to complement clinical follow-up methods where study participants are lost to follow up [4, 5]. Although studies have used existing data for the purposes of dementia ascertainment, to our knowledge no review has been produced in order to collate and consider the various methods described. As a result, there is no clear guidance or standard to follow when designing a study using existing data for dementia ascertainment. The aim of this systematic review is therefore to provide a narrative account of the dementia ascertainment methods using existing data sources described in the literature, in order to provide evidence for potential approaches in future research. It should be noted that this review focuses on ascertainment from sources of existing data, rather than on the specific dementia criteria utilised by each study. This review is specifically aimed at providing a basis for dementia ascertainment methods for studies based in the UK, where there are highly developed systems allowing the capture of health outcomes from a variety of sources. This review will therefore not consider studies based out-with the UK, as datasets vary widely between countries and health systems. It is however likely that some of the data sources considered in this review will have an equivalent in other countries and so our conclusions will have relevance outside the UK.

Methods

The Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to guide the conduct and reporting of the present systematic review [6].

Selection criteria

The 'PICOS' approach (population, intervention, comparator, outcome, study design) was adopted in order to define the study question and build an appropriate search strategy. Given that this review would focus on methodology, the intervention and comparator were not applicable. The population (P) would be a UK-based cohort or population group, the outcome (O) would be the dementia ascertainment method and sources of existing data, and the study design (S) would be observational. This review aimed to guide future studies performing dementia ascertainment using existing data within the UK. This review will not consider populations out-with the UK as health data and systems vary from that which is available in the UK.

Data sources

Scholarly articles for inclusion in the review were identified through searching four separate electronic databases determined to be appropriate for dementia ascertainment methodology. The following databases were included: MEDLINE (from 1946), EMBASE (from 1980), PsychINFO (from 1987) and Web of Science (from 1900). The literature search took place on the 28th December 2015.

Search strategy

The study authors (who have expertise in dementia) developed the search strategy with input from a research librarian experienced in systematic review methodology. Each search included terms relating to: a) dementia; b) the UK; and c) longitudinal or cohort study type. The full electronic search strategy for MEDLINE is detailed in Additional file 1. No limitation parameters were used. The inclusion and exclusion criteria for this review aimed to strictly limit included papers to those using previously collected data for dementia ascertainment. Specifically, this required the exclusion of any paper where dementia status was used to select participants or where dementia was determined by prospective clinical review. The exclusion criteria needed to be extensive given the broad terms used for the initial literature search. Such broad search terms were required given that the area of interest was methodology, rather than the primary topic of a study.

The inclusion criteria for review articles were: a) Longitudinal or cohort studies applying retrospective dementia ascertainment methods; b) Dementia cases must be ascertained from a defined larger cohort/population; c) Ascertainment may be an outcome, or ascertainment may be performed in order to determine a cohort of participants with dementia; d) Dementia diagnoses were ascertained using existing data (in part or in full). Existing data included that which was collected routinely and that which was collected for previous research.

The exclusion criteria were: a) Study population based outside the United Kingdom; b) Articles published in non-English language; c) Participant self-referral/other referral to studies following advertising for persons with dementia; d) Participant/carer/health service response to census/survey; e) Participants included based on known neuropathological diagnosis of dementia; f) Direct referral of participants from NHS/voluntary services following advertising/request for referral of persons with dementia; g) Study participants recruited from hospital wards, outpatient clinics (or referrals to the same) or other services, unless documented that records/other existing data used to select cases; h) Study participants selected from an existing register of dementia cases, study/research centre, memory or old age psychiatry clinic patients, people prescribed cholinesterase inhibitors or dementia carers; i) Studies where dementia was not the primary condition or disease of interest, or at least of equal weight to another condition; j) Animal

models of dementia; k) Simulated cohorts; l) Ascertainment not for dementia diagnosis (i.e. cognitive decline 'suggestive of dementia', cognitive impairment); m) Systematic reviews (any systematic review on this specific topic would be included, but reviews producing summary data from several studies without any primary description of dementia case ascertainment would be excluded) /meta-analyses/case reports – i.e. any non-longitudinal or cohort study; n) Studies where dementia cases were ascertained entirely at baseline and/or prospectively in a clinical assessment setting; o) posters or abstracts; p) unclear description, additional duplicates or errors in citation.

Study selection

References were exported to and managed using the reference management software package Endnote X7.5. The results from each database search were compiled and any duplicates removed. Duplicates were identified and removed by the 'find duplicates' function within the Endnote software. Additional duplicates were then identified and removed manually. Records returned by the literature search were excluded sequentially. In an initial phase of screening, titles and abstracts were reviewed for eligibility by the first author, according to the inclusion and exclusion criteria. The threshold for inclusion at this phase was purposefully low, to prevent the exclusion of any relevant study. The full-texts of articles remaining following the initial screening were obtained and independently scrutinised by the first and second authors, according to the same inclusion and exclusion criteria. Any discrepancies between the final full-text lists for inclusion between the first and second authors were discussed and agreed upon at a meeting. It was planned that any disagreements persisting following the meeting would be discussed with a third author.

Where the list of eligible full-text articles included more than one article by the same study group or author(s), and described the same ascertainment methodology, we included only the article with the most comprehensive description of the methodology, and excluded all the others. This was done in order to prevent bias in our findings. We aimed to prevent double-counting of a single study which had given rise to multiple research outputs – where a single group or author had published multiple articles using the same methodology from a single project. Including all such articles would risk making it appear that a specific methodology or data source was used more frequently and more widely than in reality.

Data collection

The data extracted from the eligible full-text articles included: the author(s), the journal reference (including year of publication), the study topic or aim, whether dementia ascertainment was the outcome or where it was ascertained to form a cohort for further study, the source(s) of existing data for dementia ascertainment, the criteria for dementia ascertainment, and whether there was any validation procedure or comparison with expected dementia rates. Data were also extracted for the purpose of evaluating the quality of the methodology description, as detailed below.

Quality measure

A quality tool was developed by the authors in order to evaluate the description of dementia ascertainment methodology within each included article. The components of the quality measure were based on whether the paper contained sufficient information such that an incidence or prevalence rate could be calculated and the ascertainment rate could be compared with another population. The components of the quality measure considered the description of: a) the size of the baseline population; b) the age of the baseline population; c) the sex of the baseline population; d) the source of the baseline population; e) the ascertainment procedure and f) the date or time period studied. Each article was given a quality score, with a higher score indicating a higher-quality description of dementia ascertainment methodology. The maximum score was 16 and the full details of the quality tool are shown in Table 1.

Where more than one eligible article reported results based on the same study population and the same ascertainment method, the article with the highest score for the quality of description of dementia ascertainment methodology would be included and the others excluded from the final review. These exclusions would be important in order that studies or research groups with a high output of articles from the same study, using the same ascertainment methodology, did not bias the review findings. Specifically, we wanted to avoid certain methods appearing to be frequently used within the UK when the same study group was actually using them multiple times.

Results

Article selection

A total of 5031 citations were identified by the four separate database searches, including 2150 from MEDLINE, 1614 from EMBASE, 479 from PsychInfo and 788 from Web of Science. After collating the search results, 1486 duplicates were removed. The title and abstract for each of the remaining 3545 records was screened for suitability and it was determined that 360 full-text articles required full-text review. Of those selected for full-text review, it was agreed that 63 articles met the criteria for inclusion. A flow chart of study selection is shown in Fig. 1.

Table 1 Quality Tool

Quality tool components
1 Baseline population size A) Exact number (score = 3) B) Approximate number (score = 2) C) Other description of size (score = 1) D) Not specified (score = 0)
2 Baseline population age AI) Exact age range specified for total population (score = 4) AII) Broad age range specified for total population (score = 3) BI) Exact age range specified for analyses (score = 2) BII) Broad age range specified for analyses (score = 1) C) Not specified (score = 0)
3 Baseline population sex A) Specified (score = 1) B) Not specified (score = 0)
4 Baseline population A) Named with description (score = 2) B) Named only (score = 1) C) Not specified (score = 0)
5 Dementia ascertainment AI) Sources and specific criteria clearly described (score = 3) AII) Sources and specific criteria less clearly described (score = 2) B) Sources named but no specific criteria described (score = 1) C) Unclear/ not described (score = 0)
6 Dementia cases A) Number plus comparison to expected/ documented rate (*external UK comparison*) (score = 2) B) Number only (score = 1) C) Not specified (score = 0)
7 Time/ period/ date A) Specified B) Not specified/ unclear

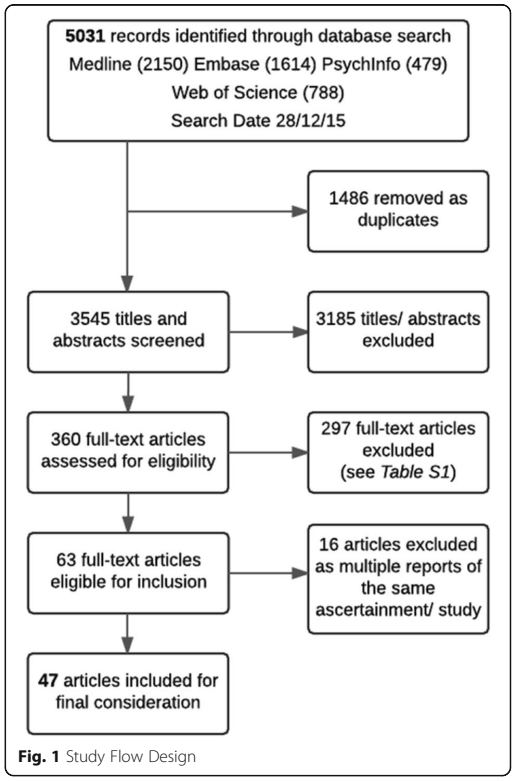

Fig. 1 Study Flow Design

The reasons for the exclusion of papers following full-text review differed between the first and second authors, largely since several papers could have been excluded for multiple reasons. Rather than excluding articles based on multiple exclusion criteria the authors made exclusions based on a primary exclusion criteria. Despite the differences, both authors excluded the same papers. The reasons for exclusion are therefore not detailed in Fig. 1, but presented in Additional file 2: Table S1. The most frequent reasons for the exclusion of full-text articles (combined total number excluded by both authors) were: cases ascertained entirely through baseline or prospective clinical assessment or new data only (n = 103), not a longitudinal or cohort study (n = 125) and participants recruited directly from hospitals, clinics or other service (n = 102). It would be expected that a large number of ineligible or irrelevant articles were returned by the literature search owing to the broad search parameters used in order to identify a methodology rather than a specific study topic. Many such articles also passed through the first phase of screening because the title and abstract did not contain sufficient detail regarding the study methodology in order for eligibility to be determined.

A number of the eligible articles reported results based on the same study population and the same ascertainment method was described multiple times. We identified nine groups of articles reporting the same methodology and n = 16 articles were excluded on this basis. Details of the excluded articles are shown alongside the articles chosen for inclusion in Additional file 3: Table S2.

Following this process, 47 papers remained for consideration in this review. An overview of the characteristics of the included studies can be seen in Table 2. The table includes: the topic of the article; whether dementia ascertainment was an outcome of the study or whether ascertainment was performed to build a cohort of subjects with dementia upon which further study was carried out; whether existing data was used in full or in part; the existing data sources utilised; the diagnostic criteria used; whether the article included a validation study of dementia ascertainment or a comparison between observed rates and expected rates; and the total score achieved when the quality tool was applied to each article. We determined that existing data was used in part when new data was used in any way to support

Table 2 Articles included in final review

Author	Study topic	Dementia outcome/ cohort[a]	Existing data use	Data sources	Dementia criteria	Validation/ comparison[b]	Quality score
Baker et al. [56]	Hip fracture risk and mortality in AD	Cohort	Full	THIN[e]	Diagnostic code for AD, OR Prescription for an AD defining drug.	No	9
Brayne et al. [31]	Dementia at death and prevention	Outcome	Part	Death certificates	ICD-10 codes for dementia.	Yes	15
Brayne et al. [30]	Neuropathological correlates of dementia	Outcome	Part	Death certificates	DSM-IV criteria using data from all sources including death certificates	Yes	15
Chen et al. [32]	Health care resource utilisation in AD	Cohort	Full	CPRD[f]	Diagnosis of AD.	No	8
Clarke et al. [4]	Dementia incidence	Outcome	Part	Death certificates, hospital case notes	'Diagnostic information' from both sources.	Yes	14
Cook et al. [37]	Incidence of stroke and seizure in AD	Cohort	Full	THIN[e]	Read codes for AD.	No	9
Crugel et al. [7]	Antipsychotic use in dementia	Cohort	Part	Electronic clinical records for trust (Rio)	Confirmed ICD-10 diagnosis of dementia.	No	7
Doll et al. [42]	Smoking and dementia	Outcome	Full	Death certificates	Dementia 'mentioned' on death certificate.	Yes	11
Dregan et al. [57]	Inflammation, related therapy and dementia	Outcome	Full	CPRD[f]	Diagnostic codes for dementia.	No	13
Goh et al. [13]	Angiotensin receptor blockers and dementia	Outcome	Full	CPRD[f]	Read codes for dementia.	No	14
Grant et al. [58]	Incontinence and dementia	Cohort	Full	THIN[e]	One or more codes dementia codes, OR Two or more prescriptions for drugs to treat dementia.	No	14
Guthrie et al. [16]	Psychotropic drug prescribing in dementia	Cohort	Full	SPICE-PC[h]	Read codes for dementia, OR Prescription of acetylcholinesterase inhibitor.	Yes	14
Heath et al. [9]	Vascular comorbidities in early onset dementia	Outcome	Full	General practice research dataset (unnamed)	Read codes for dementia, OR Prescription of acetylcholinesterase inhibitor.	Yes	16
Houttekier et al. [59]	Place of death in dementia	Both	Full	Death certificates	ICD-10 codes for dementia.	No	13
Imfeld et al. [11]	Epidemiology, comorbidities and medication in AD & VD	Outcome	Full	GPRD[g]	Stage I: read code for dementia, OR, prescription for acetylcholinesterase inhibitor. Stage II: algorithm for AD or VD (based on DSM-IV, NINCDS-ADRDA , NINDS-AIREN, NICE & SIGN).	Yes	9

Table 2 Articles included in final review *(Continued)*

Karlinsky et al. [60]	AD in twins	Outcome	Full	Hospital twin register, hospital case notes	Stage I: discharge diagnosis suggestive of dementia on register, Stage II: case note diagnosis of AD according to DSM-III-R criteria.	No	10
Keenan et al. [29]	Glaucoma and AD/ VD	Both	Full	Hospital Episode Statistics	ICD-10 diagnostic code for AD or VD.	No	15
Kehoe et al. [35]	Angiotensin targeting anti-hypertensives, mortality and hospitalisation in dementia	Cohort	Full	GPRD[g]	Read codes for dementia.	No	9
Lu et al. [61]	Gout and risk of AD	Outcome	Full	THIN[e]	Diagnostic codes for AD.	No	14
Martinez et al. [62]	Trends in antipsychotic drug use in dementia	Cohort	Full	CPRD[f]	Read codes for dementia.	No	9
McCarthy et al. [33]	Experience of dying with dementia	Both	Full	Death certificates	Dementia diagnosis coded.	No	8
McGonigal et al. [22]	Epidemiology of pre-senile AD	Outcome	Full	[d]ISD Scotland data for psychiatric hospitals, hospital records	Stage I: diagnostic codes for dementia in SMR, Stage II: NINCDS-ADRDA criteria and Hachinski score applied to records.	Yes	13
Morgan et al. [63]	Physical activity in midlife and dementia	Outcome	Part	Death certificates	Mention of dementia in either part one or part two of death certificate (used in conjunction with new data at consensus)	No	15
Newens et al. [26]	Ascertainment, incidence, prevalence & survival in pre-senile AD	Outcome	Part	Electronic hospital information systems ([c]HAA, MHE, Körner), neuroradiology records, case notes	Stage I: potential cases identified by ICD-9 codes from information systems, referrals for CT with dementing process, (*and contact with services*). Stage II: case notes for all examined for DSM-III-R criteria for dementia, then algorithm for pre-senile AD.	Yes	13
Palmer et al. [8]	Dementia and occupational exposure to solvents	Cohort	Full	CT records, hospital case notes	Exact criteria not specified.	No	7
Pendlebury et al. [5]	Risk of dementia after TIA and stroke	Outcome	Part	Clinical records (hospital & GP), death certificates	Recorded diagnosis of dementia in primary care record, DSM-IV criteria met after searching the primary care record or dementia listed on death certificate.	No	14
Perera et al. [34]	Response to acetylcholinesterase inhibition in dementia	Cohort	Full	Electronic medical records, hospital trust case register	Patients receiving Acetylcholinesterase Inhibitor.	No	8
Qizilbash et al. [14]	BMI and risk of dementia	Outcome	Full	CPRD[f], death certificates	Dementia term recorded in CPRD*, OR Dementia diagnosis on death certificate.	No	13
Rait et al. [17]	Survival in dementia	Both	Full	THIN[e]	Read codes for dementia.	Yes	10

Table 2 Articles included in final review *(Continued)*

Renvoize et al. [23]	Prevalence of young onset dementia	Outcome	Part	Local computerised information systems, medical and social care records	Stage I: discharge diagnosis of dementia in computer system, Stage II: "criteria for dementia" from notes (criteria not specified)	Yes	13
Reyniers et al. [18]	International variation in place of death in dementia	Cohort	Full	Death certificates	ICD-10 dementia diagnosis.	No	10
Russ et al. [10]	Geographical variation in dementia (Scottish sub-study only)	Outcome	Full	[d]ISD Scotland data, death certificates, records for a nursing home medical practice	ICD-9 & 10 codes for dementia from [d]SMR data and death certificates, and dementia status reported by a medical practice.	Yes	16
Ryan [27]	Hospital incidence rates in dementia	Outcome	Full	[d]ISD Scotland data.	ICD-8 & 9 codes for dementia.	Yes	14
Sampson et al. [24]	Differences in care for those with and without dementia	Cohort	Full	Medical notes	Formal diagnosis of dementia recorded.	No	13
Seshadri et al. [12]	Oestrogen replacement therapy and the risk of AD	Both	Full	GPRD*, GP records	Stage I: computer diagnosis of dementia, Stage II: records for each reviewed to confirm diagnosis based on NINCDS-ADRDA criteria.	Yes	14
Shah et al. [25]	Dementia and influenza vaccination uptake	Outcome	Full	THIN[e]	Read codes for dementia.	Yes	12
Sleeman et al. [19]	Place of death and dementia	Cohort	Full	Death certificates	ICD-10 codes for dementia.	No	8
Sorahan et al. [20]	AD, MND and PD in magnetic field exposure	Outcome	Full	Death records	ICD 9 & 10 codes for dementia.	No	12
Stephens et al. [28]	Prescribing of antipsychotics in dementia on the acute general hospital	Cohort	Full	Hospital Episode Statistics, linked to pharmacy records	ICD-10 code diagnosis of dementia.	No	9
Su et al. [64]	MMSE as a predictor of mortality	Cohort	Full	Hospital trust case register	ICD-10 codes for dementia.	No	14
De Vries et al. [65]	Dementia deaths in a hospice	Outcome	Full	Hospice case notes/ referrals	Formal diagnosis of dementia in the notes, other evidence in the notes (no exact criteria given).	Yes	12
Whalley et al. [66]	Effects of anticholinergic drugs on cognition	Outcome	Part	Clinical records, imaging results	Diagnoses based on ICD-10 criteria, using *all source* data.	No	15
Whalley et al. [67]	Childhood mental ability and dementia (Late onset sub-study only)	Outcome	Part	Psychiatric case register, hospital records	Stage I: diagnosis of dementia on register, Stage II: ICD-10 diagnosis of dementia in case notes.	No	14
White et al. [68]	Dementia, walking outdoors and getting lost	Outcome	Full	Missing persons reports	Presence of a key dementia term.	No	11
Wilcock et al. [69]	Educational intervention to improve the management of dementia	Outcome	Full	Electronic GP records	Search for dementia in records- exact criteria not specified.	No	10

Table 2 Articles included in final review *(Continued)*

Woodburn et al. [70]	Features of early onset dementia in Scotland	Cohort	Part	Psychiatric case register, neurology service records, case notes	Stage I: ICD-9 codes for dementia in register, Stage II: Feighner criteria for Organic Brain Syndrome applied to notes (criteria for neurology records not specified)	No	12
Wotton et al. [71]	Obesity and subsequent dementia	Outcome	Full	Hospital Episode Statistics linked with death records	ICD-9 & 10 codes for dementia.	No	14

[a]: Was dementia ascertainment performed as the study outcome, or was dementia ascertainment performed in order to form a dementia cohort for which another outcome was determined
[b]Did the paper perform a validation study for dementia ascertainment or compare incidence/ prevalence rate to expected rate
[c]*HAA*: Hospital Activity Analysis; MHE: Mental Health Enquiry system; Körner: Korner Episode Statstics (hospital information systems)
[d]*ISD* Scotland: Information Services Division Scotland (holds national datasets (SMR: Scottish Morbidity Records) of health outcomes/ diagnoses)
[e]*THIN*: The Health Improvement Network; [f]*CPRD*: Clinical Practice Research Datalink; [g]*GPRD*: General Practice Research Database; [h]*SPICE-PC*: Scottish Programme for Improving Clinical Effectiveness- Primary Care

ascertainment. New data included clinical assessment, informant interview and contact with services for information.

Sources of data

The sources of existing data described by the eligible articles were numerous and included general practice research databases (n = 16), case notes or records (n = 16), death certificates (n = 14), case registers (n = 5), national datasets (n = 6), electronic hospital information systems (n = 2), radiology records (n = 3), hospice records (n = 1), pharmacy records (n = 1) and missing person records (n = 1). Of the 47 included papers, 31 (66%) used only a single source of existing data for the purpose of ascertainment (Table 2). The highest number of different data sources used was three. The most commonly used data source in studies using a single data source was a research database, such as the General Practice Research Database (GPRD), the Clinical Practice Research Datalink (CPRD), The Health Improvement Network (THIN) or the Scottish Programme for Improving Clinical Effectiveness- Primary Care (SPICE-PC) (n = 14). The next-most used data source in articles using a single data source was death certificates (n = 9). When considering all included papers, the research database and case records or notes were equal as the most frequently used sources (n = 16), but in those papers using multiple sources only, case notes or records were the most frequently utilised source of existing data (n = 13). Figure 2 illustrates the source or sources of existing data used by each of the 47 articles.

Of the 36 papers using existing data only for the purpose of dementia ascertainment (i.e. no clinical component), 27 (75%) used only a single data source and the most frequently utilised data source was the research database (n = 14). Including the articles that only used existing data and used single or multiple sources, the research database remained the most frequently used (n = 16), but considering those using multiple sources separately, case notes were the most frequently used (n = 6).

The criteria utilised by the articles to determine a diagnosis of dementia from the data sources was varied. Most studies using death certificates for dementia ascertainment extracted a diagnosis based on the condition having been recorded on any part of the certificate. Others stated that dementia cases were recognised by specific ICD-10 codes listed on the certificate. Evidence from death certificates were also used in combination with evidence from other sources to determine cases. Case records were in many cases reported to be examined by a specialist medical doctor with training in dementia. Researchers often searched the case records for evidence to meet a specific diagnostic criteria, such as DSM-IV, ICD-10 or NINCDS-ADRDA criteria. In other cases, dementia diagnosis was taken as a formal diagnosis or mention of a diagnosis within in the notes. Researchers employed a number of different techniques when using databases to ascertain dementia diagnoses. These included searching the database for diagnostic codes, Read Codes derived from Quality and Outcomes Framework (QOF) codes, recorded diagnoses or prescriptions for dementia defining drugs. Some studies applied diagnostic criteria to evidence within the records. Other studies developed algorithms that combined a number of different criteria. Details of the criteria utilised by each study is shown in Table 2.

Quality measure

The quality measure was primarily a means of evaluating the description of the ascertainment methodology and the sources of data used. We identified significant discrepancies between the detail provided in the methodology of articles and the quality measure results give an indication of the completeness or lack of information provided by the authors. The quality measure is therefore closely related to our reporting of the sources used and how dementia was ascertained from each.

The breakdown of the quality measure results for each article are shown in Additional file 4: Table S3. When an article included sub-studies where dementia was included as an outcome in one study and for a dementia cohort study in another, the quality measure was performed on the outcome study due to the more specific detail included. Where only one sub-study met the inclusion criteria for this review, the results listed considered only the eligible sub-study. Overall, the quality scores ranged from 7/16 [7, 8] to 16/16 [9, 10] and the mean score achieved across all 47 papers was 12.0 (SD: 2.6). Quality scores were lower for studies using existing data alone for ascertainment (n = 36; mean = 11.5 (SD 2.6)), compared with studies using existing data in addition to other methodologies (n = 11; mean 13.4 (SD 2.3)) ($p < 0.05$). There was also a significant difference ($p < 0.001$) in quality scores between studies where dementia was either an outcome or both an outcome and the basis of forming a cohort (n = 31; mean = 13.0 (SD 2.1)), and studies where dementia ascertainment was performed to build a cohort (n = 16; mean = 10.2 (SD 2.6)).

The quality measure also included whether a validation study or comparison with expected dementia rate was performed. Given the importance of validating an ascertainment methodology in order to determine its effectiveness we have expanded on this further, as follows.

Studies reporting a validation procedure

Of the 47 papers included, relatively few performed a validation study for dementia cases or compared ascertainment

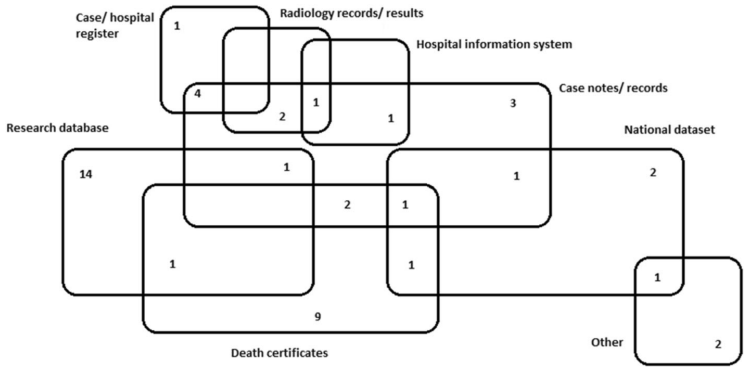

Fig. 2 Sources of Existing Data for all Included Articles

to previously documented rates. Imfeld et al. [11] completed a validation procedure for the algorithm used to identify cases within the General Practice Research Database (GPRD), and found up to 80% of Alzheimer's disease cases and up to 75% of vascular dementia cases were confirmed by GP questionnaire responses. Seshadri et al. [12] completed a validation of Alzheimer's disease cases identified using code algorithms for dementia or Alzheimer's disease within GPRD and confirmed only 48% cases as either possible or probable Alzheimer's disease according to NINCDS-ADRDA criteria. Authors did however report a much higher validation rate of 83% for those identified specifically as Alzheimer's disease cases within the GPRD, and for whom there was adequate data for validation [12]. Imfeld et al. [11] reported that the incidence rates of Alzheimer's disease found in their study, were three to six times lower than those found in previous European studies. Goh et al. [13] and Qizilbash et al. [14] did not perform any validation study, but referred to the above-mentioned work by Seshadri et al. [12, 15]. Using the Scottish Programme for Improving Clinical Effectiveness- Primary Care (SPICE-PC) database, Guthrie et al. [16] found that the prevalence of dementia was only about half of that found in epidemiological studies. Recording was found to be particularly poor in older age groups. Rait et al. [17] used The Health Improvement Network (THIN) database and on comparison with incidence rates demonstrated by the *EURODEM* study and Cognitive Function and Ageing Study (*CFAS)*, the incidence rates found by Rait et al. were shown to be significantly lower than would have been expected [17]. Heath et al. [9], who did not name the research database used, reported the prevalence in their population to be close to the middle of the range of previous estimates.

The under-reporting of dementia on death certificates was noted in articles in this review [10, 18–20]. Doll et al. [21] compared their findings to European statistics (EURODEM) and determined that they had only recorded 30% of dementia cases from death certificates. Russ et al. [10] found that compared to using multiple sources, death certification alone missed approximately 16–18% of dementia cases. The same study found that general practice records did not identify all cases identified by record linkage [10].

McGonigal et al. [22] tested the assumption that most patients with pre-senile Alzheimer's disease are known to psychiatric services. After consulting further data sources including death certificates, general hospital and neurology service records, and opinions within the medical community, the authors reported that approximately 97% of participants identified as having pre-senile dementia in their study were indeed cared for within psychiatric services [22]. Overall, McGonigal et al. [22] found that the annual incidence rates of pre-senile Alzheimer's disease, determined using hospital records, within their study population were comparable to annual incidence rates quoted by a national study using different ascertainment methods. It should be noted that some 11% of hospital records requested by McGonigal et al. [22] were either lost or contained insufficient data to apply the diagnostic criteria. If the proportion of probable dementia in missing records was the same as for the available records, 12% of cases would have been missed as a result [22]. Crugel et al. [7] did not perform any validation study but did note that it was known that the number of dementia cases identified using their electronic record system was lower than the number known to the hospital trust. Renvoize et al. [23], who used local computerised medical and social records for case identification, found a prevalence rate consistent with previous studies. Pendlebury et al. [5] state an awareness of

under-recording of dementia diagnoses in primary care records and Sampson et al. [24] report that dementia is under-diagnosed in the acute hospital setting. Shah et al. [25] also acknowledge the deficiencies in recognition and recording in primary care, and note that the prevalence found in their study is lower than what might be expected, based on epidemiological surveys. Newens et al. [26] used hospital information systems and clinical records to ascertain the incidence and prevalence of early onset dementia. The authors reported a similar prevalence rate to rates documented elsewhere.

Ryan [27] acknowledged potential diagnostic and clerical errors within the Scottish Morbidity Records (SMR) from Information Services Division (ISD) Scotland. A validity rate of 84% is quoted from a previous work by the same author [27]. Russ et al. [10] also note the likelihood that SMR datasets will miss some cases of dementia. Stephens et al. [28] highlight the possibility of under-recording in Hospital Episode Statistics (HES), particularly those with earlier or milder forms of dementia. Keenan et al. [29] question the reliability of dementia subtype diagnoses within HES. Those studies describing a validation study or making a comparison with expected rates are shown alongside their respective methodologies in Additional file 5: Table S4.

Brayne et al. [30], Brayne et al. [31] and Clarke et al. [4] made comparisons of prevalence with expected or previously documented rates. As these studies used existing data in part only, it is not possible to draw conclusions regarding the sources of existing data that were used based on these comparisons.

Discussion

Our systematic review identified 47 articles relevant for inclusion. 36 articles used existing data sources alone for dementia ascertainment, whilst 11 used existing data in conjunction with new data. The existing data sources utilised by the 47 articles included: research databases, death records, clinical notes, national datasets, hospital information systems, radiology records, missing person records, pharmacy records and hospice records. The most commonly used sources were research databases, clinical records and death records. The quality of the description of dementia ascertainment methodology varied widely, with scores from 7 to 16 out of a maximum score of 16. Most studies that completed a validation procedure for dementia ascertainment found that observed rates of dementia were lower than expected.

The initial literature search returned a substantial number of articles in comparison to the number that were included for final analysis. As this review considered a methodology rather than an outcome or specific dementia-related topic, it was necessary to write a broad and inclusive search strategy so as not to miss any relevant articles. As such, it was anticipated that a high proportion of articles would be excluded. The articles included in the final analysis covered a wide variety of specific study topics. The results of the quality measure varied widely, but those papers demonstrating the poorest scores for quality of description were, in nearly all cases, papers in which dementia ascertainment was performed in order to build a cohort for further study [7, 8, 19, 32–34]. This might be expected given that dementia ascertainment was not the focus of these studies and thus the descriptions of method concentrated on other aspects of the studies.

Our assessment of methodology is primarily a narrative account of the sources of existing data utilised in the included articles. The purpose of this review does not include repeating previous extensive literature that compares and comments on diagnostic criteria. The aim is to outline each source and provide some evidence regarding the usefulness or drawbacks of the source.

All of the research databases used by papers in this review rely on the collection of anonymised patient data contributed by participating general practices within the UK. Databases such as the Clinical Practice Research Database (CPRD) have been designed in order to facilitate data-linkage across services, including Hospital Episode Statistics [32]. General practice databases have been used widely in medical research and it has been reported that usage of the General Practice Research Database (GPRD) and Clinical Practice Research Database have resulted in over 800 and 1500 publications respectively [35, 36]. Each database collects data from several hundred general practices and provides records for millions of patients [13, 35, 37]. The volume of data available and the number of general practices involved in such databases indicate a clear benefit to the use of these resources. In order to determine the usefulness of general practice research databases, we must ascertain the validity of diagnostic coding for dementia within the databases. We might consider this in two ways: firstly, do diagnoses contained within the database correlate with information within the general practice records; and secondly, are dementia cases recorded within general practice records an accurate reflection of dementia rates within the population? Using GP questionnaires, Dunn et al. [38] completed a validation study of dementia cases and controls drawn from the GPRD and reported a confirmed diagnosis in 83% of recorded cases. This rate is similar to those reported for Alzheimer's disease by studies in this review: Imfeld et al. (80%) [11] and Seshadri et al. (83%) [12]. Seshadri et al. did, however, find a much lower validation rate when considering both dementia and Alzheimer's disease together (48%) [12]. Dunn et al. [38] did not consider dementia prevalence in the study population against previously reported national

statistics or alternative databases. In this review, Imfeld et al. [11], Guthrie et al. [16], and Rait et al. [17] all reported lower than expected ascertainment rates from the GPRD, SPICE-PC and THIN database respectively, when compared to previously documented incidence and prevalence. From the findings of the articles included in this review, we would suggest that dementia diagnoses within a general practice research database are not a completely accurate reflection of dementia cases known to the GP or within a population.

A distinct advantage of using death certificates for dementia ascertainment is their availability and the ease of data collection from this source. As dementia is not always the primary cause of death, the inclusion of the diagnosis on the death certificate relies on both the certifying doctor's familiarity with the patient's medical history and their opinion as to whether the diagnosis merits inclusion on the certificate. Despite the importance of dementia as a contributory factor or cause of death, rates of reporting on death certificates have historically been poor [39, 40]. A more recent Scottish study did however illustrate an improvement, with 71.5% of deceased patients from a group with known dementia having the diagnosis correctly recorded on their death certificate [41]. In this review, both Doll et al. [42] and Russ et al. [10] demonstrated such under-reporting. It is clear that, despite improvements in diagnosis and reporting, we cannot rely on death certificates to give a completely accurate reflection of dementia cases within a population and studies using this source alone are failing to achieve the best possible ascertainment rates.

The national datasets used by studies in this review include Scottish Morbidity Records (SMR) from the Information Service Division (ISD) of NHS National Services Scotland and Hospital Episode Statistics (HES). SMR are sets of permanently linked datasets, and specifically, SMR01 is a record of inpatient and day-case general hospital admissions, whilst SMR04 is a record of inpatient and day-case psychiatric admissions [43]. HES is a national dataset containing records of all admissions, outpatient appointments and A&E attendances at NHS hospitals in England [44]. In this review, Stephens et al. [28] and Keenan et al. [29] highlight the likelihood of under-recording or inaccuracies in the HES data, but a recent study found that when compared with dementia recording in CPRD and General Practitioner survey responses, HES was accurate in 85% of cases [45]. In order to make assurances regarding the quality of published statistics, ISD Scotland complete regular assessments of collected data. The report published in 2015 found an 89% accuracy for the main diagnosis and a 77.5% accuracy for dementia diagnoses in SMR01 [46]. In our review, Ryan [27] reports a validity rate of 84% based on a previous work. Out-with this review, Russ et al. [47] found that while SMR01 only recorded 53% of known cases of dementia, SMR04 recorded dementia 100% of the time in a cohort of people with known dementia. This would suggest that where a diagnosis of dementia has been made in a psychiatric unit, it is reliably reported within the national dataset SMR04. As most health assessment and treatment in the UK takes place within the National Health Service (NHS) it can be assumed that these datasets are representative of the whole population. They can also be used for large-scale studies. The main drawbacks of these datasets would be that any cases not seen in hospital services would be missed, they rely on cases having been diagnosed, the cases having been diagnosed correctly, and they rely on the diagnoses being recorded in the relevant record systems.

The findings of the study by McGonigal et al. [22] would suggest that psychiatric records and psychiatric case registers are valuable and accurate data sources for pre-senile dementia case ascertainment. It should however be noted that these are historical data, mostly over 30 years old, and admission policies for psychiatric hospitals in Scotland and the UK have changed over that period so this assumption may no longer be tenable. It is possible that a diagnosis, although recorded within clinical records, is simply incorrect. A 2012 Danish study highlighted this issue and in a study of 195 patients registered as having a diagnosis of early onset dementia, the authors found that the diagnosis was correct (according to DSM-IV or ICD-10 criteria) in just 58% of cases [48]. It would therefore seem reasonable to suggest that the most reliable diagnosis taken from written data sources will be where the evidence for diagnostic criteria is present as well as the diagnosis itself.

Studies aiming to evaluate the quality of source information might compare the data collected with information from a second source, for example paper medical records [49]. Concordance between two sources increases the likelihood of correctness, and completeness, but it should be recognised that no source can be assumed to be completely accurate – there is no true "gold-standard" [49]. A diagnosis present in more than one source may superficially appear to be reliable; however, we must consider the possibility that a diagnosis of dementia was initially entered into the notes in error and simply transcribed from one record to another. Between October 2014 and September 2015, the National Patient Safety Agency received almost 99,057 reports relating to failures in documentation from NHS organisations in England and Wales [50].

In using previously collected data for dementia case ascertainment, we are relying on diagnoses having been made and recorded. Using existing data is therefore most effective when diagnostic rates are high. Any population with a poor record for detecting dementia might yield

different study results, particularly if undiagnosed cases are associated with particular factors or variables. Regional variation in rates of diagnosis have been reported previously, suggesting that the use of existing data might be more reliable in some geographical areas [51, 52].

All of the sources described by studies included in this review have value, and all are likely to provide ascertainment data for a majority of cases within a population. It would be prudent, however, to be cautious in accepting any documented case as correct without evidence to substantiate the diagnosis. Similarly, if a single source is used, the possibility of missing cases should be considered. We must establish methods for minimising any error, but one should be realistic and accept that any dementia ascertainment method will be open to some error. The main drawback to using existing data of any kind is the potential for undiagnosed cases being missed. For this reason, the most accurate dementia ascertainment process is likely to include prospective follow-up with clinical assessment. Using such methods does however have its own limitations. Collecting prospective data in an ageing population is time-consuming and can lead to delays in the release of findings. This is particularly true if we are to consider influences across the life course or premorbid risk factors. Prospective studies are subject to attrition, due to death or other causes. Using clinical follow-up also restricts the size of a study cohort, with finite funding and resources available for each study. Also significant is the variability of clinical assessment methods across studies, making the comparison of study results less accurate. Within the UK there is an ongoing drive to improve rates of dementia diagnosis and, as such improvements are made, existing data will become increasingly accurate and their use for dementia ascertainment will become increasingly valuable in the study of dementia.

Considerations for future studies

The evidence for the accuracy of the sources discussed may not be comprehensive and conclusive, but we must attempt to make suggestions for a 'best possible' method when performing dementia ascertainment using existing data. In order to minimise any missed cases it would be sensible to collect data from multiple data sources. This might eliminate those cases that have simply failed to be recorded despite a diagnosis having been made. In accessing multiple sources, we may also be more confident that those without a recorded diagnosis are truly dementia free. The most useful method for determining whether any diagnoses are correct would be to consider evidence for a diagnosis within the existing data. Evidence consistent with diagnostic criteria for dementia may not only confirm recorded cases, but identify cases that have failed to be recorded.

When deciding which combination of sources to include in an ascertainment methodology it is useful to consider the advantages and disadvantages of each source, and which combination of sources are likely to yield the highest number of cases. Diagnoses derived from hospital records are of particular value given the high rates of hospital admission for persons with dementia. [53] At a given time-point, it has been estimated that 6% of inpatients in a general hospital have dementia, while 0.6% are aged over 65 and without dementia. [53] National datasets derived from hospital records (such as Hospital Episode Statistics) should contain the same diagnoses as the hospital records themselves. It is however possible that in some situations, such as when there is increased demand on a service, only the main diagnosis is coded. Although the list of diagnoses might be the same, the records could contain further detail to allow for confirmation of the diagnoses. In this sense they may be considered more accurate. The nature of datasets mean that a list of diagnoses, or list of participants with a particular diagnosis can however be made available for a much larger population and in a more time efficient manner. Both, therefore, have their advantages and disadvantages, but using both is unlikely to yield many additional cases. The choice of which to use of the two would depend on the requirements of the study. The similarities, advantages and disadvantages between GP records and GP research databases would be much the same as those described for hospital records. The benefit of GP records over hospital records are that they are more likely to contact records from external services such as social work and housing and contact is likely to be more frequent. These benefits might increase the chance of a diagnosis or symptoms having been recorded. Death certificates have the advantage of being readily available and they are particularly useful as follow-up for participants who do not provide consent for access to records or data linkage. For these reasons, death records would be a useful addition to any other source being used for ascertainment. The disadvantages are that they rely on the physician deeming the diagnosis significant enough to warrant inclusion on the death certificate and they are of no use in identifying dementia cases in the living. Death records and national datasets have the advantage of not being restricted to a specific locality or area, compared with electronic health records that might be held on a different system in each health board. The recording of dementia diagnoses within these sources depends on the proportion of dementia cases identified in the community- in the UK this has previously been shown to be less than 50%. [54].

All of the sources described are likely to identify dementia cases at the more severe end of the spectrum. Regardless of the source, the diagnosis of dementia is more likely to have been made if the condition is more severe and it is therefore more likely to have been recorded. In contrast, early cases are more likely to remain

undiagnosed and, as such, would not appear in any existing data. In the case of hospital or GP records or databases, the more severe the condition, the more likely they are to have had contact with a healthcare provider. Similarly, the higher the number of co-morbidities, the more likely they are to have contact with services. This regular contact with services for management of comorbidities may also mean that a diagnosis is more likely to have been made. The more severe the dementia, the more likely it is to be considered a significant factor in cause of death and it is therefore more likely to be recorded on a death certificate.

Clinical assessment is probably the best method for identifying early cases of dementia. There are however problems with non-random screening participation. [55] Early cases are more likely to be recorded in existing data if cases are being identified and diagnosed at an early stage within the community. Diagnoses are in turn more likely to be made if the physician is aware of the condition, appreciates the benefits of diagnosis and is confident in making a diagnosis, or referring for a specialist opinion. Investments in research and public health raise the awareness of dementia among physician, and the general population, meaning that patients are encouraged to present to services rather than accept that changes are merely a consequence of ageing.

Limitations of the review

Given the variability in the quality of the description of methodology for dementia ascertainment and, in particular, the number that did not provide sufficient information such that an incidence or prevalence rate for dementia could be derived, it was not possible to draw comparisons between the ascertainment rates for different methodologies. A future study considering dementia ascertainment methodologies, using existing data, in incidence and prevalence papers only, might provide the opportunity for direct comparison and an assessment of the effectiveness of different methodologies. It would also be worthwhile for such a study to include studies based out-with the UK. As our study did not, we may have missed ascertainment methodologies that could be replicated using UK sources of existing data. With the use of existing data in dementia studies continuing, it may be worthwhile to consider updating this review in due course. Given that, a single author performed phase one screening of titles and abstracts there is the potential for error. This is, however, unlikely given that the broad search strategy returned a large number of articles that were obviously not relevant to the review.

Conclusions

In conclusion, our review revealed a lack of consistency with regard to dementia ascertainment methodology using existing data in previous UK studies. Optimising ascertainment is of essential importance in order to increase statistical power, avoid selection bias and enable comparability between studies. We described the benefits of a number of sources of existing data including: death records, national datasets, research databases, and hospital records. Evidence suggested that although each was useful, none was completely accurate when used alone and we would therefore recommend that future studies use a combination of these data sources. Where possible, studies should access records with evidence to confirm, query, or refute the diagnosis. Studies should also calculate a dementia ascertainment rate for the study population to allow for comparison to an expected or previously documented rate. Not only would this help in judging the findings of an individual article, but it would also provide further evidence for guiding dementia ascertainment methodology using existing data.

Additional files

Additional file 1: MEDLINE search strategy. (DOCX 12 ksb)

Additional file 2: Table S1. Reasons for the exclusion of full-text Articles, by Author. (DOCX 13 kb)

Additional file 3: Table S2. Eligible articles excluded from final review. (DOCX 51 kb)

Additional file 4: Table S3. Quality measure result breakdown. (DOCX 114 kb)

Additional file 5: Table S4. Studies reporting a validation procedure. (DOCX 33 kb)

Abbreviations

AD: Alzheimer's disease; CC75C: Cambridge City over-75 s Cohort; CFAS: Medical Research Council Cognitive Function and Ageing Study; CPRD: Clinical Practice Research Database; DSM: Diagnostic and Statistical Manual of Mental Disorders; GPRD: General Practice Research Database; HAA: Hospital Activity Analysis; HES: Hospital Episode Statistics; ICD: International Classification of Diseases; ISD: Information Services Division; Körner: Körner Information System; MHE: Mental Health Enquiry; NHS: National Health Service; NICE: National Institute of Clinical Excellence; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; NLSAA: Nottingham Longitudinal Study of Activity and Ageing; SD: Standard deviation; SIGN: Scottish Intercollegiate Guidelines Network; SMR: Scottish Morbidity Records; SPICE-PC: Scottish Programme for Improving Clinical Effectiveness- Primary Care; THIN: The Health Improvement Network; UK: United Kingdom; VD: Vascular dementia

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Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Authors' contributions
RAS took part in devising the objectives of the review, writing the search strategies, writing the inclusion and exclusion criteria, developing the quality measure, performing the literature search and subsequent screening for eligibility and inclusion, performing quality assessment and writing of the manuscript. TCR took part in writing the inclusion and exclusion criteria, screening for eligibility and inclusion, advised on the development the quality measure, advised on the review methodology and contributed to revisions of the manuscript. IJD took part in devising the objectives of the review, advised on the writing of the search strategies, advised on the writing of the inclusion and exclusion criteria and contributed to revisions of the manuscript. JMS took part in devising the objectives of the review, advised on the writing of the search strategies, advised on the writing of the inclusion and exclusion criteria, advised on the development of the quality measure and contributed to revisions of the manuscript.

Ethics approval and consent to participate
No ethical approval required.

Consent for publication
Not applicable.

Competing interests
This review included previous works by some of the authors.

Publisher's Note

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3.3 Chapter discussion and conclusions

3.3.1 Further discussion on systematic review

Having completed an extensive review of the UK-based literature, it was clear that there was no previously described 'gold-standard' method for ascertaining dementia using existing data. Furthermore, there was considerable variability between studies in the range and number of data sources utilised for dementia ascertainment purposes. The information gathered would have been improved if a larger proportion of included articles had provided sufficient data for ascertainment rate calculation. One consideration for the future would be the usefulness of a study looking specifically at studies of incidence or prevalence using existing data, where study dementia ascertainment rates could be compared, thus providing further basis for the evaluation of optimal methods. While the review performed in this thesis was designed to specifically guide ascertainment methods in the UK, a future study like that described above, would benefit from the inclusion of studies based outside the UK. While data sources used outside the UK may not be directly applicable to UK-based study design, the types of datasets used may reflect types of data available in the UK. While the likely increased heterogeneity of context and healthcare systems resulting from such inclusions might be considered to have a negative impact on a review, the positive effect of a broader focus and the additional evidence gathered may outweigh this. There could be particular value in including European studies in a future review as these may be expected to share more similarities with UK studies and systems, as opposed to studies based in the United States of America for example. Given the number of studies that are carried out using centres across Europe, study design and completion in European countries may be expected to share similarities with UK studies; the observed methods may therefore be applicable

to the UK. Potentially relevant studies would include the European Prospective Investigation into Cancer and Nutrition (EPIC) - Murcia study, based in Spain; the study was originally designed to investigate potential associations between lifestyle and nutritional factors and cancer, but has been extended to investigate other outcomes, including dementia.(Andreu-Reinon et al., 2019) Dementia outcomes were determined using a two-step process: by linkage of the EPIC dataset with medical datasets, followed by the validation of potential cases through careful study of the medical records.(Andreu-Reinon et al., 2019) The relevance of such a study to our ascertainment method is clear considering this study also used a cohort originally set-up for other purposes and ascertained dementia using existing data. Such a study would add valuable evidence and information on the methods for determining incident dementia using existing data. Studies using existing data to support clinical ascertainment – such as the Rotterdam study, which has reported using medical records to support clinical assessment to determine cases of dementia – would also add valuable evidence that would be of relevance to the design of UK-based studies.(Ott et al., 1995)

Health service delivery, clinical guidelines and protocols in Europe may also share similarities with the UK. While no two countries will share the exact same model for delivering healthcare, the same can be said for the UK where the individual nations deliver healthcare slightly differently; the broad underlying principle of the national health service is however the same across the UK. The NHS provides healthcare for all citizens and is free at the point of service, funded by the government through tax payments. National health systems are described as following the Beveridge model, named for William Beveridge who designed the NHS in the UK, and such systems are employed in other countries within Europe including Portugal, Spain, Denmark and Italy.(Gobierno de Espana, 2019; Lameire, Joffe & Wiedemann, 1999; Wallace,

2013) Given the potential for similarities in healthcare delivery between such countries, dementia ascertainment procedures based on healthcare data from these countries may be applicable to studies in the UK. Future systematic reviews might therefore consider broadening the search strategy to include studies based in European countries.

In our study, we used search terms that related to dementia, longitudinal study type and the UK. While we used a multipurpose keyword search (searching all possible fields), there is a theoretical possibility that a study may not have included one or more of these terms in the included fields. While it is unlikely that the first two of these terms would not be included, there is a possibility that the UK, or some region thereof, was not included in one of the searched fields. If this were the case, then we would have accidentally omitted a study of interest. While this was a possibility, we would note that our search strategy identified all of the relevant studies that we were aware of and expected to find. Any future reviews of this kind might consider whether to omit these terms.

Without any statistical quantification regarding the relative effectiveness of differing ascertainment methods, it was difficult to produce a solid conclusion from the review and make a single recommendation for future studies. As detailed within the published paper, a quality tool was used to describe the amount of information on dementia ascertainment methodology contained within included papers. This was developed to provide an indication of whether studies contained sufficient detail to allow for an ascertainment rate to be calculated and compared to another population. It was based on the authors' opinion and did not replicate a previous tool from the literature. As such, it is accepted that this would have been approached differently by others and is open to criticism. If a future review were to concentrate on incidence or prevalence studies only, then it is likely that components of such a tool could be made more

specific. While the make-up and application of the tool can be questioned it is hoped that it satisfactorily provided the information that it was designed to do. It was included in order to give the reader an indication of the varying amounts of detail included in study methodologies and as evidence for why it was impossible to quantify results. Further to this, it was designed to highlight the importance of including such detail in future studies. Despite the limitations of the quality tool and being unable to produce a comparative quantification of the effectiveness of the studies, it was hoped, that gathering evidence from multiple previous studies into a single paper and discussing the potential advantages and disadvantages of the included data sources would prove to be a useful resource for other research teams.

3.3.2 Dementia ascertainment in the Lothian Birth Cohort 1921

It was determined that the most effective dementia ascertainment procedure for the LBC1921 study would be one that was developed based on the evidence gathered in the systematic review. In particular, the aim would be to maximise both sensitivity and specificity. Findings from the systematic review suggested that greater sensitivity would be obtained through the use of multiple data sources, with each data source ideally placed to 'fill the gaps' likely to be present in another. As the review highlights, specificity would be increased with the inclusion of a data source that would potentially provide details to support or refute a diagnosis. Based on the systematic review, three types of data source were identified as having benefits for inclusion in the LBC1921 dementia ascertainment procedure. First, a large dataset likely to include follow-up data for large proportion of participants. Second, a dataset that could provide additional details regarding signs, symptoms and diagnosis. Third, a dataset likely to be specifically rich in dementia data.

For the LBC1921 study, three primary data sources were therefore selected. Death certificates, as described within the review, are a widely-utilised and accepted source of dementia data. Given the number of participants known to be deceased at the outset of this study, death certificates would be a rich source of data. Publicly available, access would not be limited by consent procedures. This would be of particular relevance in the LBC1921, where consent to data linkage and access to medical records was not in place until the fourth wave of testing, by which time many of the participants had died. Death certificates would be valuable in providing data for those participants lost to follow-up by death, or for those lost to follow-up who then subsequently died. While death certificates have received criticism in the past regarding the reliability of dementia reporting, evidence gathered in the review indicated improvements in recent years. Since all deaths would have occurred after recruitment in 1999, it can be assumed that these improvements were applicable. It is not possible to exclude the possibility that dementia was erroneously omitted from a proportion of death certificates. It was hoped that utilising further sources would minimise this possibility. The second data source selected was local electronic hospital records (Trak system). These would be available for participants living in the Lothian area, who had provided consent to data linkage at the fourth wave of follow-up. Given the relatively late inclusion of this consent procedure in the LBC1921 study, the number of participants would be limited. In cases where there was access, electronic hospital records would provide a wealth of data including hospital correspondence, multi-disciplinary clinical notes, referrals from general practice, lists of coded diagnoses (ICD10), test results and imaging reports. This data source would be valuable not just in identifying cases, but also in providing evidence or detail to support or refute any dementia diagnoses. The final source of data would be psychiatric records. These would again be available for those participants who provided consent to data linkage. Psychiatric records would exist for those

participants who had been in contact with psychiatric services, meaning that these data would likely provide data on fewer participants than the previous data sources. Given, however, that dementia is frequently diagnosed and managed within psychiatric services, it was deemed to be of specific importance in the identification of cases. At the outset of this study, psychiatric records were held on a system separate to the general hospital records (PiMS system). At a first round of data collection for dementia ascertainment, a request was made to system management for a record of all diagnoses in this system for LBC1921 participants. Latterly, psychiatric records were incorporated into the general hospital system (Trak), meaning that in addition to lists of diagnostic codes, further details on diagnoses were available through psychiatric inpatient and outpatient letters.

While there was no possibility of performing prospective clinical assessment for all participants as part of the ascertainment procedure, additional information would be available for a small number who were seen for review in either the NHS or research setting. In the research setting, assessments were undertaken when memory impairment or decline was noted during the routine LBC1921 testing, or when a new diagnosis of dementia was self-reported. Participants seen by members of the research team within NHS clinics were asked for consent to share relevant information with the LBC1921 study.

Having determined the sources of data to be used in LBC1921, data was collected from each in repeated rounds of updated data collection, until a specific consensus date. The exact dates are provided within the study in section 4.2. Data included any evidence of dementia, cognitive impairment, or similar, along with any relevant additional information (for example, history of vascular disease or causes of death). The evidence collected for each participant was examined at a consensus meeting, which included the author of the thesis, a psychiatrist specialising in psychiatry of

older age and a medical geriatrician with substantial expertise in the field of dementia. Including more than one specialist with expertise in both the clinical diagnosis and study of dementia limited any bias that might result from individual difference in practice or interpretation of criteria. The consensus meeting took place within the NHS setting to allow for access to electronic hospital records for any (consented) participant where additional information was useful to make a consensus decision regarding dementia classification. The members of the consensus meeting discussed the strength of the evidence in each case and proposed an opinion as to the presence of dementia. Agreement was achieved for each case without the need for further discussion at a later date.

Cases were determined with differing degrees of certainty based on the volume and detail of the evidence for dementia gathered in each case. 'Probable' and 'possible' gradations had been used in previous dementia criteria and dementia studies to illustrate confidence in the diagnosis and these same terms were therefore employed to group cases by the strength of evidence for a dementia diagnosis.(Huang & Halliday, 2013; McKhann et al., 1984) The consensus team describe their rationale for each of the cases in a summary of criteria. The criteria describe the type of data collected from each data source. We provide an overview of the criteria, and the basis for each here, while a summarised version is provided in *Table 4.1*, in Section 4.2 (page 93). On a death certificate, dementia recording was fell into three categories. First, where there was no mention of dementia, second, where dementia was recorded as either a cause of death or contributing factor, and third, where cognitive impairment was recorded as a cause of death or contributing factor. Given that under-reporting of dementia is the most common criticism of death certificates for dementia ascertainment, it was assumed that where dementia was recorded, it was likely present. Any recording of dementia on a death certificate was therefore classified as

'probable' dementia. A record of cognitive impairment on a death certificate was classified as 'possible' dementia. The rationale was that for cognitive impairment to warrant inclusion on the death certificate – as a cause or contributor to death – it was likely to be of a significant severity, rather than a subtle change in cognition.

Similarly, cognitive impairment noted in hospital records was likely to represent a significant change in cognitive function and was classified as a 'possible' dementia case. This did not however include cases where cognitive impairment was noted to have resolved, been labelled as a delirium or if a potentially reversible cause of impairment was noted (a febrile illness for example). A diagnosis of 'probable' dementia was derived from one of three patterns of evidence within the hospital records; either recorded dementia with supporting diagnostic details, a recorded diagnosis of dementia without details, or no confirmed diagnosis, but sufficient data within records to meet ICD-10 diagnostic criteria. Where a possibility of dementia was raised within records, but there was insufficient evidence to confirm a diagnosis according to ICD-10 criteria, a case was classified as 'possible' dementia. A diagnosis of dementia confirmed on clinical review was termed as a 'probable' dementia case. It is important to note that all such diagnoses depended on the absence of evidence contradicting or opposing the presence of dementia. For example, where cognitive impairment was recorded in hospital records, but psychiatric correspondence detailed a likely diagnosis of mild cognitive impairment, the criteria determined that dementia was not present. While it was preferred that dementia cases were supported by details of diagnoses, the inability to access linked hospital records for every participant meant that this was not possible.

Given the paucity of articles exploring and quantifying the success of dementia ascertainment procedures in the systematic review, it was important that the outcomes of the method designed for use in the LBC1921 study be evaluated. It was

therefore planned that the results of the LBC1921 dementia ascertainment procedure would be compared with expected or predicted dementia rates for the cohort. This would not only allow LBC1921 researchers and readers of the study to gauge the reliability of the dementia outcome, but also provide evidence of the relative success or inadequacy of the method for those designing an ascertainment methodology. After dementia cases had been determined, the methodology would be further evaluated through the consideration of the usefulness of the included data sources. Specifically, the data sources providing evidence for each dementia case would be identified, such that the sources contributing most highly to the ascertainment procedure could be recognised. Similarly, any redundant data sources providing no unique data could be highlighted, with the suggestion that there is no need to include these in future ascertainment procedures. The results of these evaluations of effectiveness and usefulness are provided within the study included in the next chapter of the thesis.

4: Modifiable risk factors for dementia in the Lothian Birth Cohort 1921

4.1 Introduction

As highlighted in the main introduction, understanding the risk factors or protective factors for dementia is pivotal to the development of preventative strategies. Evidence-based medical, social and lifestyle strategies have been shown to reduce the impact of other significant health conditions, such as coronary heart disease, stroke and diabetes.(Law, Wald, & Rudnicka, 2003; World Health Organisation, 2010) The research behind such evidence has guided the development of risk assessment measures, monitoring techniques and risk reduction strategies.(Department of Health Physical Activity Health Improvement and Protection, 2011; National Institute for Health and Care Excellence, 2015, 2017) With increased understanding and evidence, a similar approach could potentially be designed for dementia syndromes, with strategies aimed at preventing or delaying the onset or progression of the disease.

Without a clear understanding of how, when or why the pathological processes for dementia begin, a life course approach to considering risk factors is particularly valuable. A life course approach would not only take into account those factors acting in later life, at a time close to dementia onset, but also mid-life factors – such as health conditions or fitness, and early-life factors – such as educational attainment.

Identifying potentially modifiable factors associated with dementia would be key to the design of preventative strategies. As such, a number of studies have attempted to identify any factor that could be targeted in order to decrease risk for dementia. Several factors have been further evaluated through the meta-analyses of results from multiple reports. Previous estimates suggest that up to fifty percent of Alzheimer disease cases occurring worldwide may be attributable to potentially modifiable risk

factors, thus, reinforcing the potential impact of risk reduction strategies.(Barnes & Yaffe, 2011) A recent report considered the impact of nine potentially modifiable risk factors for dementia – education, midlife hypertension, midlife obesity, midlife hearing loss, late life smoking, late life depression, late life physical activity, late life social isolation and late life diabetes.(Livingston et al., 2017) The findings suggested that 35% of dementia was attributable to these nine factors but the study authors acknowledge that this could be higher if other factors were included in the analyses.(Livingston et al., 2017) A second report used relative risks from existing meta-analyses to estimate the population-attributable risk of Alzheimer's disease for seven potentially modifiable risk factors – diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking and low educational attainment.(Norton, Matthews, Barnes, Yaffe, & Brayne, 2014) While the combined worldwide population-attributable risk for the seven factors was reported to be 49.4% (95% CI: 25.7-68.4), when the results were adjusted for associations between the risk factors the estimate reduced to 28.2% (95% CI: 14.2-41.5).(Norton et al., 2014) Therefore, after accounting for the non-independence between risk factors, it would appear that approximately thirty percent of cases of Alzheimer's disease worldwide may be attributable to potentially modifiable risk factors (as opposed the fifty percent of cases previously reported).(Norton et al., 2014)

A 2015 systematic review and Delphi consensus study collected and reviewed evidence from two-hundred and ninety-one epidemiological studies, with the purpose of evaluating the evidence for potentially modifiable risk factors for dementia.(Deckers et al., 2015) By considering the results of the systematic review alongside the results from the first round of the Delphi study, a panel of experts ranked the risk factors in order of importance with respect to primary prevention of dementia.(Deckers et al., 2015) The study highlighted depression, midlife hypertension, physical inactivity,

diabetes, midlife obesity, hyperlipidaemia and cigarette smoking as important factors associated with increased risk for dementia.(Deckers et al., 2015) A number of other factors including coronary heart disease, renal dysfunction, diet and cognitive activity were identified as requiring further study.(Deckers et al., 2015) The authors reported a considerable overlap between the factors identified in this study and those reported in previous reviews.(Deckers et al., 2015) As described within the next section of this chapter, this study forms the basis for our selection of risk factors to be considered in the first study of risk factors for dementia in the LBC1921.

We note that although several risk factors for dementia have been identified with some consistency within the literature, addressing such factors has been shown to be ineffective in prevention trials.(Andrieu, Coley, Lovestone, Aisen & Vellas, 2015) For example, while hypertension has been highlighted as a risk factor for dementia, in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG) study and the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) the reduction in risk for dementia associated with antihypertensive treatment did not reach statistical significance (hazard ratio [HR] 0·86, 95% CI 0·67 to 1·09, *p*=0·21 and relative risk reduction 12%, 95% CI 8% to 28%; *p*=0·2).(Andrieu et al., 2015) A 2016 paper by Moll van Charante et al. reported the results of a 6 year randomised control trial of a nurse-led multidomain intervention for cardiovascular risk factors - preDIVA. (Moll van Charante et al., 2016) Based in the Netherlands, the intervention consisted of 4-monthly nurse assessments where the following risks were assessed: smoking, blood pressure, diet, weight and physical activity; blood lipids and blood glucose were measured every 2 years.(Moll van Charante et al., 2016) Following assessment, tailored lifestyle advice was given according to cardiovascular risk management guidelines and drug treatment was prescribed where indicated.(Moll van Charante et

al., 2016) The intervention did not result in a reduction in all-cause dementia (hazard ratio [HR] 0·92, 95% CI 0·71 to 1·19; *p*=0·54).(Moll van Charante et al., 2016)

Dementia is a disease associated with ageing and dementia studies are therefore typically completed using older-age populations. Classically, studies of older age have included those aged over 65 years. Many of the articles included in previous reviews examined participants aged over 65 years.(Deckers et al., 2015) As a result of increasing longevity, the over-65 years age bracket is widening. Factors such as advancements in healthcare, changes in employment type and lifestyle habits have led to increased life expectancy in the UK. The Office of National Statistics (ONS) reported that in 1980 to 1982, five percent of males and fourteen percent of females could expect to live to at least ninety years of age.(Office for National Statistics, 2017) By 2014 to 2016, twenty-one percent of males and thirty-two percent of females could expect to reach at least ninety years.(Office for National Statistics, 2017) In 1987, the total number of persons aged over 90 years and living in the UK was 212,067; by 2017, this figure had risen to 579,776.(Office for National Statistics, 2018) As the number of persons surviving beyond ninety years increases, it is expected that the oldest-old will also represent an increasing proportion of those aged over 65 years.(Bullain et al., 2013)

With an increased proportion of the population surviving into oldest-age, it is necessary that studies consider whether risk factors for dementia are the same in early old age and more advanced old age. Understanding any differences in the risk factor profile for dementia with advancing age would allow for the appropriate targeting of preventative strategies and make the best use of available resources. The oldest-old has been varyingly defined as those aged over 80, 85 or 90 years of age.(U. Lucca et al., 2015) The fact that studies of this age group are less frequently documented within the literature may reflect the potential difficulties in recruiting and

retaining participants of advanced age. Co-morbid health conditions, physical frailty, cognitive decline, changes in living circumstances and mortality may all contribute to reduced recruitment and increased attrition. Despite such difficulties, studies including the 90+ Study, based in North America, and the Monzino 80-plus Study, based in Italy, have been designed to examine dementia in oldest-old populations.(Corrada, Sonnen, Kim, & Kawas, 2016; Ugo Lucca et al., 2015) Studies investigating dementia in the oldest old have proposed changes to the risk factor profile in oldest-age, when compared with earlier old-age.(Kawas, 2008)

As can be seen from our discussion thus far, there are already a number of studies that investigate risk factors for dementia in oldest-old age, and even more in earlier old age or older age in general. We therefore summarise our rationale for performing another study of risk factors in oldest-old age as follows:

1) Studies in this age-group are less numerous and a larger volume of data is required to make conclusions about the risk factor profile in oldest-old age;
2) As described in the introduction, the oldest-old age group is complex with regard to their health and disease profile – large numbers of studies are therefore likely to be required to decipher which risk factors are important;
3) Studies of the oldest-old typically have smaller sample sizes than earlier old age and a greater number of studies are therefore required in order to collect a volume of evidence equivalent to studies in earlier old age;
4) Trials designed to address risk factors identified in observational studies have been shown to be ineffective in reducing dementia risk, suggesting a complexity to these risk factors that is not yet understood and a requirement for further study to promote understanding.

We therefore suggest that further studies in this field and age-group are required. The subsequent section of the thesis therefore explores the risk factors for dementia in the LBC1921, an oldest age cohort. In doing so, the aim was to obtain further evidence that would either support or oppose the literature describing a changed risk factor profile for dementia in oldest age. The risk factors selected for consideration were drawn from the existing literature, as described within the study, and had a particular focus on those that could be described as potentially modifiable.

The study included in this chapter is an amended version of a peer-reviewed article, published during the course of this PhD.(Sibbett et al., 2017) In the original published version, a number of participants were included for whom it was later discovered that there were incomplete follow-up data. As soon as this was detected, the analyses were repeated, and the journal contacted and supplied with the new results. The amended version is included in place of the original to provide clarity between the correctly reported results and the further discussion within the thesis. The original published version however is supplied, along with the original supplementary materials, and the submitted corrigendum, as *Appendices 2i (page 258), 2ii (page 269) and 2iii* (page 276) respectively. The complete reference for the original publication is as follows:

Sibbett RA, Russ TC, Deary IJ, Starr JM: Risk factors for dementia in the ninth decade of life and beyond: a study of the Lothian birth cohort 1921. *BMC Psychiatry* 2017, 17(1):205.

The author of this thesis was the first author of the study and made the following contributions to the published work: assisted with study design, completed data collection for dementia diagnoses, completed the statistical analyses, interpreted the results, led the writing of the paper and contributed to revisions of the same. The

contributions made by the additional authors are detailed within the manuscript. The supplementary materials for the amended manuscript are provided in *Appendix 2iv*, from page 285. The individual appendices are provided on the following pages:

The references for this study are included within the main reference section for the thesis, from page 214.

4.2 Risk factors for dementia in the ninth decade of life and beyond: A study of the Lothian Birth Cohort 1921

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Abstract

Background: With increasing numbers of people surviving beyond eighty years, this section of the population demands attention to reduce the impact of dementia. In order to develop effective preventative strategies, it is essential to understand age-specific risk factor profiles for dementia: do risk factors for dementia in those in their sixties and seventies persist into oldest age? The aims of this study were to determine incident dementia and to investigate the risk profile for dementia from age 79 to 95 years in a well-characterised cohort.

Methods: Participants underwent intelligence testing at age 11 and were followed-up from at 79 years of age. Variables included: age, sex, age 11 IQ, *APOE* ε4, education, diabetes, hypertension, statin use, physical activity at leisure and in occupation, symptoms of depression, height, number of teeth, body mass index, blood pressure, cholesterol and HbA1c. Dementia cases were ascertained from death certificates, electronic patient records and clinical reviews. Logistic regression analysis determined the degree of risk for dementia associated with each variable. Analyses

were completed both with and without the physical activity variables due to the significant number of missing data for these variables.

Results: Of the eligible cohort, *n*=379 participants remained dementia-free and *n*=110 had developed probable dementia. When logistic regression analyses contained all variables, complete data was available for *n*=221 (*n*=48 with dementia). Results demonstrated that greater lifetime physical activity (OR: 1.17, 95% CI: 1.04, 1.32) and the use of statins (OR: 3.39, 95% CI: 1.04, 11.02) increased the risk for dementia. A reduction in risk for dementia was seen for hypertension (OR: 0.47, 95% CI: 0.23, 0.98). When physical activity variables were excluded, the number with complete data increased to *n*=355 (*n*=80 with dementia). Positive *APOE* ε4 carrier status was found to increase the risk for dementia (OR: 2.23; 95% CI: 1.29, 3.86), while increased height (OR: 0.72, 95% CI: 0.55, 0.95) was shown to be associated with a decreased risk.

Conclusions: Dementia incidence was consistent with expected rates. The risk profile for dementia in this cohort of participants aged 79-95 confirmed previous findings that risk factors differ for those over 79 years. Further evidence is recommended in order that the risk profile for this age group can be accurately determined.

Keywords: dementia, cohort, incidence, risk factor

4.2.1 Background

Without clear means of prevention or cure, dementia is recognised to be one of the greatest public health challenges facing the ageing global population. Dementia rates are known to increase exponentially with age, from 5.5 per 1000 person-years in those aged 70-74, to 30.5 per 1000 person-years in those aged 80-84.(Fratiglioni et al., 2000) With increasing numbers of people surviving into the ninth decade of life and beyond (Norton, Matthews, & Brayne, 2013), this section of the population demands attention in order to reduce the impact of dementia.(Knapp et al., 2007) Despite studies such as the 90+ Study (MiND) (North America) and the Monzino 80-plus Study (U. Lucca et al., 2015) (Italy) the oldest in the population remain less well represented in dementia research.

In order to develop effective preventative strategies for dementia and ensure that these are directed appropriately, it is essential to identify potentially modifiable risk factors and understand whether these persist into oldest age. Significant modifiable risk factors for dementia demonstrated by replication within the literature include: diabetes (Lu, Lin, & Kuo, 2009), hypertension (Rönnemaa, Zethelius, Lannfelt, & Kilander, 2011), hypercholesterolaemia (Anstey, Lipnicki, & Low, 2008), depression (Diniz, Butters, Albert, Dew, & Reynolds, 2013), smoking (Anstey, Sanden, Salim, & O'Kearney, 2007; Gelber et al., 2012), obesity (Gelber et al., 2012) and physical inactivity (Deckers et al., 2015; Gelber et al., 2012; Rovio et al., 2005). Previous studies have proposed that the risk factor profile for dementia changes with age, but the evidence is not conclusive.(Bullain et al., 2013; Kawas, 2008)

The present study draws on prospectively collected longitudinal data from the Lothian Birth Cohort 1921 (LBC1921). Participants were predominantly cognitively normal at baseline (aged 79 years) and underwent detailed follow-up from to age 95 years. As

a result, this study can add further evidence to the literature regarding risk factors for dementia in the oldest-old. Most participants in this cohort had also taken part in childhood intelligence testing at age 11 years. This is an unusual and valuable feature of the data for a study cohort of the oldest-old, given that lower childhood IQ has been shown to be a putative risk factor for dementia (McGurn, Deary, & Starr, 2008) and is associated with several modifiable risk factors.(Corley, Gow, Starr, & Deary, 2010; Corley, Gow, Starr, & Deary, 2012; Mõttus, Luciano, Starr, & Deary, 2013) Dementia ascertainment had not previously been performed in LBC1921 and, although a number of participants would have developed dementia during the study period, there had not been any clear means of identifying all such participants. Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was performed at each wave of follow-up and a small number were seen for clinical review following concerns raised regarding their cognitive function. Some participants self-reported a new diagnosis of dementia. This would have identified only a proportion of cases. There was no previous follow-up regarding dementia ascertainment for those who had died or left the study. Given the likelihood that participants with incident dementia were less likely to attend for follow-up, death records would be a valuable source of data for dementia ascertainment, particularly where a diagnosis of dementia failed to be recorded in the secondary care records.

The primary aims of this study were: i) to determine cases of incident dementia within the LBC1921 study cohort from age 79-95, and ii) to investigate whether recognised modifiable risk factors for dementia (diabetes, hypertension, hypercholesterolaemia, depression, smoking, physical inactivity, obesity) remained risk factors for dementia in the ninth decade and beyond. These modifiable risk factors were considered together with key non-modifiable factors including; age 11 IQ, *APOE* ε4 status, and measures associated with socio-economic status.

The present study primarily drew on existing data for dementia ascertainment. Given the variability in methodology for using routinely collected data in the literature, we aimed to quantify the effectiveness of our dementia ascertainment method as a secondary outcome.

4.2.2 Methods

4.2.2.1 Study population

The LBC1921 is described in detail elsewhere (Deary et al., 2011), and is outlined briefly here. Almost all Scottish school pupils born in 1921 had their general intelligence tested at age ~11 years as part of the Scottish Mental Survey 1932.(Scottish Council for Research in Education, 1933) Beginning in 1999, the LBC1921 was designed in order to follow up some of the same participants in later life with the primary aim of investigating non-pathological cognitive ageing.(Deary, Whiteman, Starr, Whalley, & Fox, 2004) The LBC1921 includes 550 participants recruited from the Lothian area of Scotland, as relatively healthy, community-dwelling volunteers, most of whom had taken part in intelligence testing in 1932. Lothian is an area in southeast Scotland in which the largest settlement is the city of Edinburgh. Participants underwent the first wave of testing at approximately 79 years of age. Those participants surviving and continuing to consent to inclusion in the study were re-tested at regular intervals, at mean ages of about 83, 87, 90 and 92 years of age. The data were collected by questionnaire and one-to-one testing and included measures of socio-demographic, psychological, cognitive, medical, physiological, and genetic factors. Those participants self-reporting a history of dementia or scoring less than 24 on the MMSE at baseline were excluded from our study (n=11), as were those who were missing baseline MMSE data (n=2). Deaths were ascertained prospectively, with records for participants supplied by the General Registrar's Office,

Scotland.(Starr & Deary, 2011) Ethical approval was provided by the Lothian Research Ethics Committee (test waves 1-3) and the Scotland A Research Ethics Committee (test waves 4-5). Participants attending from wave 4 provided written consent for data linkage and access to health records.

4.2.2.2 Dementia ascertainment

Surviving participants who continued to take part in the LBC1921 study were seen for routine follow-up as described previously. Follow-up for the purposes of detecting dementia diagnoses included the retrospective collection of evidence from the sources described below, from enrolment to age 95 years. Dementia cases were determined at a final consensus meeting on 15th December 2016. Death records for deceased participants were examined for evidence of cognitive impairment or dementia. Data from death records were collected from those available by 30th June 2016. For consenting participants, data were collected from medical and psychiatric electronic patient records for services in Lothian. Patients were located in the system using their Community Health Index (CHI) number, a unique number given to each patient within Scotland, recorded at every health service contact. Each hospital record accessed was read in full and examined for evidence of dementia or cognitive impairment since enrolment in the study. This included gathering both recorded confirmed diagnoses and evidence for diagnoses. Until 2014, general and psychiatric records were held on separate systems (Trak and PIMS respectively), but all records were subsequently incorporated into the Trak system. The final date for data collection from this source was 16th May 2016. For 26 participants, additional information was available as a result of clinical assessments undertaken by the authors (JMS or TCR) in the NHS or research setting. In the research setting, assessments were undertaken when impairment or decline was noted during the

routine LBC1921 testing, or when a new diagnosis of dementia was self-reported. Data from these sources were collected until the consensus date.

Each case with evidence of cognitive impairment or dementia was considered at a consensus meeting (RAS, TCR, JMS) which included both a geriatrician and a psychiatrist. The meeting agreed upon whether the evidence supported a diagnosis of dementia and determined the subtype of dementia. Depending on the strength of the evidence, the diagnosis and subtype were deemed either 'probable' or 'possible'. The criteria for probable and possible diagnoses utilised by the consensus are shown in *Table 4.1.* Any disagreement on diagnosis was resolved through discussion.

Table 4.1 Consensus criteria for dementia case ascertainment

CONSENSUS CRITERIA FOR DEMENTIA CASE ASCERTAINMENT	
PROBABLE DEMENTIA	**POSSIBLE DEMENTIA**
ANY of the following (without opposing evidence from same/ other source): -dementia diagnosis on death certificate (any part) -dementia diagnosed on clinical review (ICD-10/ DSM-IV) -dementia diagnosis in electronic general medical records (Trak) -dementia diagnosis in electronic psychiatric records (PIMS) -ICD-10 criteria for dementia diagnosis met by data within any existing records	*ANY of the following (without opposing evidence from same/ other source):* -recorded cognitive impairment on death certificate -cognitive impairment/ decline recorded in notes, but incomplete evidence to meet ICD-10 diagnostic criteria -possibility of dementia recorded in notes but no formal diagnosis/ incomplete evidence to meet ICD-10 diagnostic criteria

Dementia subtype diagnoses were made on a similar basis. Any dementia case with insufficient evidence to make a subtype diagnosis was classified as 'unknown' subtype. In order to minimise the risk of misclassification bias, probable dementia cases would be used as our primary outcome and possible cases would be excluded from the analyses. We would however repeat our analyses including possible dementia cases and include the results as supplementary information.

4.2.2.3 Variables

Modifiable risk factors assessed in the present study were identified by matching those consistently reported in the literature (diabetes, hypertension, depression, hypercholesterolaemia, smoking, obesity, and physical inactivity) (Deckers et al., 2015) with data collected at LBC1921 test waves. We also included the following variables: age, sex, *APOE* ε4 status, age 11 IQ, number of teeth (as a post-retirement measure of socio-economic status (Starr et al., 2008)), height, and years in full-time, formal education. The full list of included variables is detailed in *Appendix 2iv, Additional file 1: Table S4.1*.

Age at baseline was calculated according to the number of days between birth date and date attending wave 1 testing. The presence of at least one *APOE* ε4 allele was determined using genomic DNA isolated from venous blood.(Schiepers et al., 2011) Venous blood was also used to measure total serum cholesterol and HbA1c.(Deary et al., 2011) Any previous history of diabetes or hypertension, years in formal education, use of statins, and smoking status (previous, current or never) were self-reported by participants.(Schiepers et al., 2011) Body mass index (BMI) was calculated from height and weight, measured using a SECA stadiometer and digital SECA scales, respectively.(Starr et al., 2010) A trained research nurse measured sitting blood pressures (systolic and diastolic) using an Omron 705IT monitor.(Starr &

Deary, 2011) Remaining teeth were counted during the general physical assessment.(Starr et al., 2008) Symptoms of depression were evaluated using the self-reported Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) (HADS) at wave 1.(Gale et al., 2010) Only the scores for the depression sub-scale were considered. Physical activity was self-reported by participants as part of a retrospective questionnaire at wave 2 follow-up (~age 83).(Gow, Pattie, & Deary, 2017) Based on the methodology described by Hirvensalo and colleagues (Hirvensalo, Lampinen, & Rantanen, 1998), responses were scored on a six-item scale according to increasing levels of physical activity. Responses predominantly related to leisure-based activity: necessary movement, walking, walking/ outdoor exercises, exercising until sweating, exercising several times per week, keep fit/ heavy exercise. Participants indicated their perceived level of physical activity at three age ranges: 20-35, 40-55 and 60-75 years.(Gow et al., 2017) A lifetime score was calculated by the sum of the three scores. The physical effort required in a participant's previous occupation was assessed using a single item [Q21] from the Job Content Questionnaire (JCQ) by Karasek (Karasek et al., 1998) which was included, with permission, in the wave 2 questionnaire.

Age 11 IQ was derived from the results of the Moray House Test (MHT) no. 12, undertaken by participants in 1932.(Schiepers et al., 2011) Following correction for age at testing, the cohort MHT scores were converted to IQ scores, with a standardised sample mean score of 100 and SD of 15.(Schiepers et al., 2011) To demonstrate how the cohort IQ compares with the general population, we consider the raw MHT scores: 34.5 (SD: 15.5) was the mean score for Scotland, 37.3 (SD: 14.8) for those in Edinburgh schools, and 46.4 (SD: 12.1) for those recruited to LBC1921.(Starr et al., 2008)

4.2.2.4 Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics software version 21. The primary outcome of the study was the development of dementia. The analyses were completed for an outcome of probable dementia, with possible cases excluded. Univariate analysis was completed for each predictor variable, using either the Pearson chi-square or t-test. At this stage, a *p* value of <0.05 was used to demonstrate significant difference between those who developed dementia and those who did not. Binary logistic regression analysis was used to determine the risk for dementia associated with each predictor variable. For the purposes of logistic regression, the data for height and age 11 IQ were standardised so that a unit increase represented one standard deviation increase on the original scale. The following logistic regression models were completed using the 'backward conditional' function. The input for model 1 included all variables. The analyses for model 2 included all variables except lifetime physical activity and physical activity in occupation, which were excluded since data were missing for around one-third of eligible participants (33.4 to 39.3% missing, with zero to 14.1% missing for all other variables). The analyses for models 1 and 2 were repeated to include both probable and possible dementia in the outcome, and the results are made available in the supplementary information.

4.2.3 Results

4.2.3.1 Main findings

550 participants recruited to the LBC1921 attended the first wave of data collection. We excluded 9 participants with an MMSE score of less than 24 at baseline, 2 participants missing MMSE results at baseline, 2 participants who self-reported a diagnosis of dementia at baseline and 41 participants with no follow-up data available. The eligible cohort (*n*=496) included 285 (57.5%) females and 425 (85.7%) were

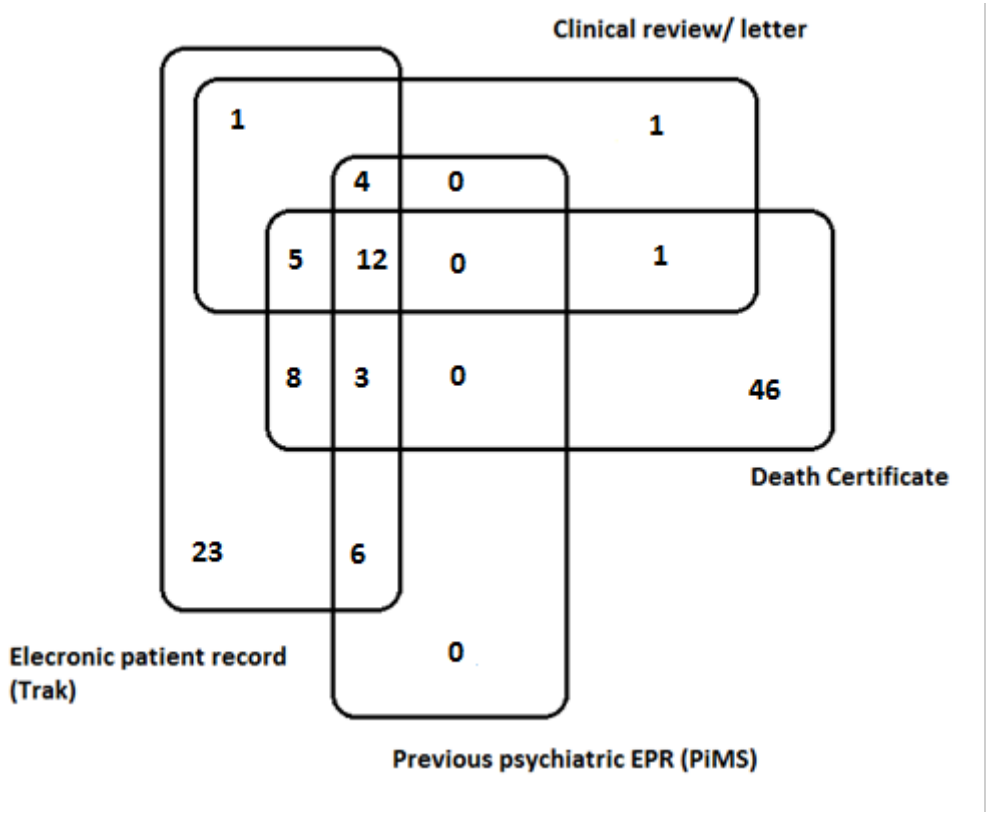
known to be deceased by the 30th of June 2016. The mean age in years at wave 1 was 79.1 years (SD: 0.6). *APOE* ε4 carrier status was available for 490 participants (98.8%), with 132 (26.6%) recorded as carriers. The mean (standardised) age 11 IQ score was 100.3 (SD: 14.9), calculated from the 447 scores available (90.1% of the eligible cohort). The mean MMSE score for the eligible cohort was 28.3 (SD: 1.5). Descriptive statistics for those eligible for inclusion, and those excluded are shown in *Table 4.2*.

Table 4.2 Descriptive statistics for those included & excluded from the study

	Eligible cohort participants (*n*=496)	**Participants excluded from study** (*n*=54)
Deceased		
Living	71 (14.3%)	42 (77.8%)
Deceased	425 (85.7%)	12 (22.2%)
Sex		
Male	211 (42.5%)	23 (42.6%)
Female	285 (57.5%)	31 (57.4%)
Age at wave 1		
Mean age in years	79.1 (SD: 0.6)	79.1 (SD: 0.5)
***APOE* ε4 carrier status**		
Carrier	132 (26.6%)	14 (25.9%)
Not carrier	358 (72.2%)	39 (72.2%)
Data missing	6 (1.2%)	1 (1.9%)
Age 11 IQ		
Data available	447 (90.1%)	46 (85.2%)
Data missing	49 (9.9%)	8 (14.8%)
Mean age 11 IQ	100.3 (SD: 14.9)	97.3 (SD: 16.2)
MMSE		
Data available	496 (100%)	52 (96.3%)
Data missing	-	2 (3.7%)
Mean MMSE	28.3 (SD: 1.5)	27.2 (SD: 2.8)

129 participants were found to have evidence of cognitive impairment or dementia in their records. A consensus diagnosis of probable dementia was agreed for 110 participants (38 probable Alzheimer disease, 25 probable vascular dementia, 9 probable mixed-type dementia, 1 probable progressive supra-nuclear palsy, 6 possible vascular dementia, 1 possible dementia in Parkinson's disease, and 30 of unknown subtype) and a diagnosis of possible dementia was determined for 7 participants (1 possible vascular dementia, 6 unknown subtype). The remaining 12 cases considered had either insufficient information for diagnosis or evidence contradictory to a diagnosis of dementia (for example, the evidence supports a diagnosis of delirium rather than dementia). *Figure 4.1* illustrates the number of probable cases ascertained by each data source, or combination of data sources. Almost two thirds of cases of probable dementia (63.6%) were determined based on a single source of information with the largest proportion of these single source diagnoses being based on death certificate data (*Figure 4.1*).

Figure 4.1 Number of probable dementia cases ascertained, by data source



All 7 cases of possible dementia were identified based on evidence from a single source (death certificate or electronic medical record). Of the 12 cases that did not meet the criteria for probable or possible dementia, 9 were determined based on a single data source, whilst the remaining 3 used two sources. The sources were as follows: 9 used evidence from the electronic medical records only, 1 used evidence from both the electronic medical records and the electronic psychiatric records and 2 used evidence from the electronic medical records and from clinical review.

Univariate analysis demonstrated significant differences between the group with probable dementia and the group without dementia for the following variables: positive *APOE* ε4 carrier status ($p<0.001$), lower BMI at age 79 ($p=0.027$), lifetime physical activity ($p=0.045$) and current smoking status at age 79 ($p=0.036$) (*Table 4.3*).

Table 4.3 Univariate analyses: comparisons between groups with and without probable dementia

Variable	No Dementia (*n*=379)	Probable Dementia (*n*=110)	Group Comparison p value (chi-square or t-test)
Age at wave 1 mean age in years (SD)	*n*=379 79.1 (0.6)	*n*=110 79.0 (0.6)	0.552
Sex % female	*n*=379 55.9	*n*=110 62.7	0.205
***APOE* ε4 carrier status**[a] % carrier *APOE* ε4	*n*=373 22.5	*n*=110 40.9	*<0.001*
Age 11 IQ (standardised) mean score (SD)	*n*=339 100.2 (14.5)	*n*=102 100.1 (16.1)	0.938
Teeth mean number of teeth (SD)	*n*=379 9.1 (9.3)	*n*=110 9.6 (8.9)	0.635
Height mean height in cm (SD)	*n*=378 163.6 (9.5)	*n*=107 162.1 (9.2)	0.140
Formal education mean number of years (SD)	*n*=378 10.9 (2.4)	*n*=109 11.0 (2.7)	0.736
History of diabetes % positive history	*n*=379 5.8	*n*=110 4.6	0.611
HbA1c mean HbA1c (SD)	*n*=329 5.7 (0.8)	*n*=98 5.7 (0.5)	0.771
History of hypertension % positive history	*n*=375 41.9	*n*=109 34.9	0.189
Systolic blood pressure mean BP in mmHg (SD)	*n*=377 168.6 (27.4)	*n*=109 166.0 (24.8)	0.374
Diastolic blood pressure mean BP in mmHg (SD)	*n*=377 83.0 (13.4)	*n*=109 81.8 (12.3)	0.401
Statin use % positive history	*n*=321 6.9	*n*=99 11.1	0.169
Total serum cholesterol mean (SD)	*n*=371 5.6 (1.1)	*n*=105 5.6 (1.1)	0.983
Depression (HADS) mean depression score (SD)	*n*=378 3.6 (2.3)	*n*=109 3.5 (2.4)	0.983
BMI -mean kg/m^2 (SD)	*n*=378 26.5 (4.2)	*n*=107 25.4 (4.0)	*0.027*

Smoking status % current smoker	*n*=379 8.7	*n*=109 2.8	*0.036*
Lifetime physical activity mean total lifetime score (SD)	*n*=251 8.7 (3.0)	*n*=74 9.5 (3.0)	*0.045*
Physical effort required in occupation mean score (SD)	*n*=229 2.1 (0.8)	*n*=69 2.3 (0.8)	0.070

Note. [a]one or more alleles. Italicized results demonstrate significance of $p<0.05$

Following the exclusion of possible cases of dementia (*n*=7), *n*=489 participants were included in the logistic regression analyses, of which *n*=110 had developed probable dementia. The results for these analyses are shown in *Table 4.4*. A history of hypertension was associated with a decreased risk for dementia in model 1 (OR: 0.47, 95% CI: 0.23, 0.98), while the same relationship approached significance in model 2. A higher lifetime leisure-based physical activity score (OR: 1.17, 95% CI: 1.04, 1.32) and use of statins (OR: 3.39, 95% CI: 1.04, 11.02) were both associated with an increased risk of dementia in model 1. The presence of an *APOE* ε4 allele increased the risk of dementia in the second model (OR: 2.23, 95% CI: 1.29, 3.86). Increased height was associated with a decrease in risk for incident dementia in model 2 (OR: 0.72, 95% CI: 0.55, 0.95). Although current smoking was included in both models, the relationship with dementia did not reach significance. Age did not demonstrate an effect in any model, as might be expected in this narrow-age cohort.

To investigate the relationship with physical activity further, analysis for a third model was completed in which three individual age groups scores (20-35, 40-55, 60-75 years) replaced the lifetime physical activity score. All other variables were also included. Increased physical activity at age 40-55 years was significantly associated with incident dementia (OR: 1.52, 95% CI: 1.12, 2.06). The results of this model are shown in *Appendix 2iv, Additional file 2, Table S4.2*.

Results for logistic regression analyses (models 1 and 2), repeated with possible cases included in the outcome, can be seen in *Appendix 2iv*, *Additional file 3, Table S4.3*.

Table 4.4 Logistic Regression Results

	Odds Ratios (95% CI) for Probable Dementia	
	Model 1 (*n*=221)	**Model 2 (*n*=355)**
***APOE* ε4**	-	2.23 (1.29,3.86)
Height (z score)	-	0.72 (0.55, 0.95)
Hypertension	0.47 (0.23,0.98)	0.63 (0.36,1.08)
Current smoking	0.14 (0.02, 1.17)	0.24 (0.05, 1.05)
Lifetime physical activity	1.17 (1.04,1.32)	-
Statin use	3.39 (1.04,11.02)	-
Years in education	0.86 (0.73, 1.01)	-

Note. The variables entered into the analyses for each model were as follows: Model 1- age, sex, *APOE* ε4 carrier status, age 11 IQ (z score), number of teeth, height (z score), years in education, history of diabetes, HbA1c, history of hypertension, systolic blood pressure, diastolic blood pressure, cholesterol, use of statins, HADS depression score, BMI, smoking status, physical activity in occupation, lifetime physical activity ('backward conditional' method); Model 2- as model 1, but physical activity in occupation and lifetime physical activity excluded ('backward conditional' method).

4.2.3.2 Validation study

In order to validate our case ascertainment method using existing data sources, we completed a validation study comparing diagnoses extracted from existing data with diagnoses made on clinical review. Clinical reviews were performed for 26 participants. Of the 24 who were diagnosed as having dementia on clinical review, 23 had a diagnosis of dementia in at least one source of existing data. This would suggest that we would miss 4% of cases using existing data alone. Two participants seen for clinical review were not diagnosed as having dementia, but both had a

diagnosis of dementia in the electronic medical records. This discrepancy might reflect the use of different diagnostic criteria, or the use of clinical judgement in clinical practice, particularly where evidence is ambiguous. Despite this discrepancy, our method would identify dementia in 88% of cases, with 4% being false negatives and 8% being false positives. Of the 17 cases identified as Alzheimer's disease (AD) on clinical review, 14 (82%) had AD listed as a diagnosis within at least one data source. Of the 14 cases, 5 (36%) also had a different subtype diagnosis recorded in existing data, 7 (50%) also had dementia of an unspecified subtype recorded, while 2 (14%) cases listed only AD. Of the 2 cases identified as vascular dementia on clinical assessment, 1 had vascular dementia listed as a diagnosis within the existing data. Of the 3 cases identified as mixed Alzheimer's and vascular dementia on clinical assessment 1 had a diagnosis of mixed dementia in the existing data. These findings demonstrate the usefulness of accessing records to find evidence that will support a subtype diagnosis based on recognised criteria. Our finding that overall dementia diagnoses were confirmed in 88% of cases is comparable, if not better than, validation procedures performed for other existing data sources or methodologies.

4.2.4 Discussion

This study found that 22.5% of eligible, initially cognitively normal participants from the LBC1921 developed dementia from age 79 to 95 years. At the time of this study, 420 of 489 eligible participants had died, including 89 who had died with dementia. A total of 21 participants with dementia were alive at age 95. Our analyses indicated that the presence of an *APOE* ε4 allele, greater lifetime leisure-based physical activity and statin-use increased the risk for dementia. A history of hypertension and increased height were found to reduce the risk for dementia.

The results of this study reinforce the importance of the *APOE* ε4 allele as a risk factor for the development of dementia.(Corrada, Paganini-Hill, Berlau, & Kawas, 2012; Keage et al., 2009) A number of studies have suggested a decline in the importance of *APOE* ε4 as a risk factor for dementia with advancing age.(Corrada et al., 2012; Juva et al., 2000) Somewhat to the contrary, our study has determined that *APOE* ε4 continues to be a risk factor for incident dementia from age 79 to 95.

Our results also indicated that a history of hypertension by age 79 was associated with a reduction in risk for dementia. This result supports the findings of previous studies that have demonstrated that the association of hypertension with dementia changes towards later life.(Li et al., 2007) We might hypothesize that persons surviving and remaining dementia-free at the ninth decade of life, are no longer subject to any increased risk as a result of vascular factors such as hypertension. In simple terms, such risk factors have been used up and those with hypertension who were at the highest risk for dementia are more likely to have died from hypertension-related diseases prior to the onset of dementia. As a result, we might expect a paradoxical effect, much like that seen in this study. This hypothesis is supported by the direction of relationship for physical activity. Previous studies have hypothesized that a reduction in blood pressure is a consequence of the development of dementia and, although this mechanism is not fully understood, several processes have been proposed.(Iadecola et al., 2016; Li et al., 2007) Blood pressure may decline in early dementia due to the direct effect of neurodegeneration at the brainstem and hypothalamic nuclei – where arterial pressure is regulated – or it may be related to systemic changes such as weight loss, or any disease effecting the ability of the cardiovascular system to maintain perfusion pressures throughout the body.(Iadecola et al., 2016) Another possible explanation for the reduced risk is the potentially protective effect of antihypertensive agents, particularly as it is reported that

antihypertensive use in hypertension is higher in older age.(Forette et al., 2002; Johnson et al., 2012; NHS Digital, 2012; Scottish Government, 2013)

The findings relating to physical activity were more unexpected with higher levels of overall leisure activity throughout adulthood being linked with an increased risk of developing dementia. As a consequence of missing data, the findings relating to physical activity were obtained for a smaller sample size and we must therefore be cautious in drawing inferences from these findings, particularly as they contradict studies that have previously indicated a link between midlife inactivity and dementia.(Gelber et al., 2012; Rovio et al., 2005) The discrepancy between our findings and those of previous studies may be related to the method of data collection for these variables. Self-reporting physical activity levels throughout life at 79 years is likely to be subject to recall bias and variability between participants.

In this cohort, one standard deviation increase in height corresponded to 9.4cm which was associated with an approximately 28% reduction in odds of probable dementia (OR: 0.72, 95% CI: 0.55, 0.95). Our results are supported by the finding of a 2014 individual participant meta-analysis, that increasing height was related to a lower rates of death from dementia.(Russ, Kivimäki, Starr, Stamatakis, & Batty, 2014) As concluded by the authors, since height is regarded as a marker of factors in early life, it may be these that are related to risk of dementia.(Russ et al., 2014) Like *APOE* ε4, we have demonstrated that decreased height continues to be a significant risk factor for dementia in oldest age. By demonstrating that certain recognised dementia risk factors are unchanged in oldest age, we can be more confident in our findings that the risk associated with other factors is changed in oldest age.

The results also suggested an association between the use of statins and dementia, with statin-use increasing risk. This is contrary to the results of a Cochrane review of

two randomised control trials that found no evidence that statin-use was associated with dementia or cognitive decline.(McGuinness, Craig, Bullock, & Passmore, 2016) Similarly, a systematic review of the literature indicated that statin use in later life did not prevent cognitive decline or dementia in subsequent years.(Power, Weuve, Sharrett, Blacker, & Gottesman, 2015) Given these contradictions, we must consider whether this was a spurious finding, with the statin-use variable being subject to a confounding factor – such as indication – that was not included in our analyses.

Contrary to much of the existing literature, no other factor considered in this study was found to be associated with dementia. We should consider however, that the prevalence of some conditions, including diabetes and depression, in our cohort was low and as a result, we were unlikely to detect anything except large effects, higher than those estimated by meta-analyses.(Diniz et al., 2013; Lu et al., 2009) Power calculations determined that with binary logistic regression, setting alpha=0.05 and the group sizes fixed at *n*= 379 (participants without dementia) and *n*=110 (participants with dementia) with a base proportion of 5.8% (as for diabetes prevalence) in the n=379, a minimum prevalence of 15.2% would be required in the *n*=110 to detect a statistical difference with 80.0% power. Further investigation using case-control studies or much larger cohort studies are therefore required.

Moreover, given *n*=110 people with dementia, the number of participants with each subtype of dementia was too few for analysis by individual subtype: combining cases of different aetiology may have affected the analysis. As previously noted, some of the data collected relied on recollection by the participant and was therefore subject to potential variability in reporting. The associations between our variables may also have affected our analyses. We attempted to minimise this as far as possible, but such bias could not be eliminated without excluding important variables. By examining many different possible predictors for dementia, in more than one model, there is also

the potential for false positive findings. We limited the number of models in our analyses to two to reduce the chance of such false findings insofar as possible. A valuable strength of the study cohort is the presence of an intelligence test score from age 11.(Corley et al., 2012; Deary et al., 2011; McGurn et al., 2008) Each participant also underwent careful background assessment and thorough follow-up, providing a wealth of longitudinal data for the assessment of modifiable risk factors. The LBC1921 is a narrow-age cohort comprising ethnically, geographically and culturally homogenous participants, which means that we can rule out a number of potential confounding effects. Follow-up data were available for a satisfactory proportion of the original cohort to allow for analyses. The cohort demographics for those excluded from the analyses were similar to those included and it can therefore be assumed that the eligible cohort was a successful representation of the whole cohort. With a mean baseline MMSE of 28.1 (SD: 1.7) for those participants who subsequently developed dementia, we can be confident that we have identified truly incident, as opposed to prevalent, cases.

To assess the effectiveness of our dementia detection methodology, we sought to compare the incidence rate found against the rates determined by previous studies. Without knowing the age at diagnosis for a high proportion of dementia cases, the expected overall incidence over the study period had to be estimated (*see Appendix 2iv, Additional file 4*). Had all cases of dementia been ascertained, we would have expected approximately 148.7 cases (*see Appendix 2iv, Additional file 5, Table S4.4*). The 110 cases of dementia detected in this study therefore equates to 74.0% of the estimated number of cases arising over the same time period. This proportion is fairly consistent with a 2012 study of dementia diagnosis rates, which found that, within Lothian (the Health Board where the LBC1921 is resident), 68.3% of the expected cases of dementia had received a diagnosis.(Alzheimer's Society, 2012) We also

sought to establish whether cases identified as possible dementia would be confirmed with additional follow-up. Of the 7 possible dementia cases, 5 were deceased at the time of the consensus meeting and no further follow-up could be completed. Electronic hospital records for the 2 other cases were accessed on 10th January 2017 and both contained evidence from that confirmed a formal diagnosis of dementia. It should be noted that neither case was seen for clinical review by ourselves and we did not therefore influence the diagnosis having been made.

This study has demonstrated the benefits of using multiple data sources for ascertainment. Our study returned the greatest number of cases from death certificates, which identified 68.2% of all cases of probable dementia, and 84.3% of all deceased participants with probable dementia. This finding would be in line with a previous Scottish study that found 71.5% of patients who die with dementia have the diagnosis on their death certificate.(Russ, Batty, & Starr, 2012) Death certificates as a source of data benefit from their availability, but it is clear that the potential for missed cases remains. Many published UK studies utilising existing data for dementia ascertainment use only a single data source.(Doll, Peto, Boreham, & Sutherland, 2000; Imfeld, Bodmer, Schuerch, Jick, & Meier, 2013) As is the case with any dementia ascertainment procedure, the emphasis must be on achieving the most accurate representation of dementia incidence or prevalence within the population. Where possible, we would recommend that future studies consider inconsistencies between sources on a case-by-case basis. If there is reliable and consistent evidence in one source, the absence of a diagnosis in another source should not be assumed to equate to an absence of the disease. Where there is contradictory evidence, of similar weighting, from two or more sources, external evidence can be sought to clarify the diagnosis. This may take the form of a clinical review. Where no external evidence is available or possible, cases with contradictory evidence should be classified as

possible cases and excluded from the analyses due to the risk of misclassification. Using existing data offers savings in terms of researcher and participant time and the associated financial costs. This method also allows for large population studies, where clinical diagnostic work-up is not feasible due to scale.

4.2.5 Conclusions

In summary, the results of this study suggest that the presence of an *APOE* ε4 allele is a risk factor for incident dementia from age 79-95. A previous diagnosis of hypertension and increasing height were found to reduce the risk of incident dementia in the same age group. Statin-use was also found to increase risk for incident dementia after age 79 years. Increased leisure-based physical activity in adulthood was found to increase the risk for incident dementia but including this variable in the analyses reduced the study sample size and we must therefore be cautious in drawing inferences from this finding, particularly as it contradicts previous studies. Our findings would support the hypothesis that the risk profile for dementia alters with age, however, further evidence would be required before the risk profile for the ninth decade of life and beyond could be accurately described.

Abbreviations

APOE: Apolipoprotein E

BMI: Body Mass Index

CHI: Community Health Index

HADS: Hospital Anxiety and Depression Scale

LBC1921: Lothian Birth Cohort 1921

MHT: Moray House Test

MMSE: Mini-Mental State Examination

NHS: National Health Service

PIMS: Patient Information Management System

Trak: TrakCare

Declarations

Competing interests

The authors declare that they have no competing interests.

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Additional Information (as described in the text)

Additional file 1: Table S4.1. LBC1921 Data Variables for Inclusion in Analyses.

Additional file 2: Table S4.2. Logistic Regression Analysis with Physical Activity Age Groups.

Additional file 3: Table S4.3. Logistic Regression Analyses for Probable and Possible Dementia.

Additional file 4: Estimated Dementia Incidence.

Additional file 5: Table S4.4. Estimated Incidence of Dementia in LBC1921.

References: can be viewed in the main reference section of the thesis (from page 214)

4.3 Chapter summary and conclusions

Using the dementia ascertainment method developed in the previous chapter, we found that 22.5% of eligible participants of the Lothian Birth Cohort 1921 had developed dementia during the follow-up period. Assessments of validation for the methodology suggested that the ascertainment method was effective, and the results were therefore reliable enough to be used in the analyses of risk factors for dementia in the study cohort.

The analyses included in the study suggested a changed risk factor profile for dementia in oldest age when compared with that described within the literature for those in earlier old age. Specifically, our study found that a previous history of hypertension and increasing height reduced the risk for dementia in the cohort, while increased leisure-based physical activity in adulthood and the use of statins increased the risk for incident dementia. The presence of at least one *APOE* ε4 allele also increased the risk for dementia. None of the other factors considered in the study were found to be associated with an increase or decrease in risk for dementia. As noted in the study discussion, we have to contemplate whether a lack of power to detect an association contributed to some of the null findings. Other limitations of the study must also be taken into account when examining the findings. As described within the introductory chapters, the nature of the cohort and recruitment to the study may have affected our findings. Selection bias may have led to a reduced number of dementia cases when compared with national rates, as a result of increased intelligence and education within the cohort.

Considering health and lifestyle variables as individual risk factors may be misleading in this age-group given the likely levels of co-morbidity. Perhaps if one was able to produce a ‘health profile’ for each individual and compare these within the cohort, this

might be useful in the investigation of dementia risk in this age-group. In doing so, one would however have to address the potential oversimplification of variables within our study. We must think about whether the 'back story' to individual variables complicated our results. While we looked at health and lifestyle factors as simple binary variables (with a yes/ no response), in reality the background to a diagnosis is much more complex. Considering hypertension, there will be wide variability in age at diagnosis, treatment method, effectiveness of treatment. In oldest-old age this may be further complicated by additional considerations such as a purposeful under-treatment as a result of falls risk, or medication reduction due to the adverse effects of polypharmacy. While the majority of evidence from earlier in the life course suggests that increased blood pressure is associated with increased risks for cardiovascular disease, cognitive decline and mortality, the picture is less clear in the oldest-old.(Muller, Smulders, de Leeuw & Stehouwer, 2014) It has been suggested that increased blood pressure in those aged over 80 years may be a compensatory mechanism, by which organ perfusion is maintained and functional decline and morbidity are prevented. Muller, et al. 2014)

If we consider statin-use, this may be affected by age at starting, specific drug, dosage and compliance. In oldest-old age this may be further complicated by those who have had their statins discontinued, or if they were never started due to contraindications or side effects. Side effects such as memory impairment or confusion, increased risk of falls and weight loss have all been reported to be increased in those aged over 75 years. Statins can also interact with other medications and polypharmacy in the oldest-old age group might be expected given the levels of comorbidity in this section of the population. Statins may however be discontinued as medications are rationalised to prevent adverse outcomes relating directly to polypharmacy. The nature of and proportions of persons within the 'statin-user' group are therefore likely to be significantly different to those in earlier old age. Even those variables that may

initially appear to be simple, may be complicated in oldest-old age. While height is likely to be determined by genetic factors, absence of disease and childhood nutrition, height at age 79 years is potentially affected by changes in skeletal structure and general body composition. Osteoporosis, arthritis, kyphosis and decreased muscle mass can all reduce height and all are increasingly common with advancing age. Background factors are relevant in most health and lifestyle variables and we must consider whether this affected both our positive and null findings.

In our study, we note the likely collinearity between the height and BMI variables, given that the BMI calculation includes height; collinearity in a regression model reduces the ability of each variable to independently predict an outcome. We therefore suggest that future studies examine the collinearity between these variables and between other variables included in analyses.

We must also consider whether the changed direction of some associations from earlier old age are the result of reverse causation. As we note within the study discussion, it is possible that hypotension is caused by some dementia-related change within the brain, hence the association between absence of hypertension and dementia. Similarly, reduced physical activity in older age (and hence part of the lifetime assessment of physical activity) may be part of the prodromal phase of the dementia process. Other factors such as depression and weight loss have also been described as being part of the dementia prodrome, thus complicating the observed associations in oldest age.(Livingston et al., 2020) As a result of the advanced age at participant recruitment and the reported long duration of prodromal or preclinical dementia, the relative proximity of baseline testing and incident dementia potentially increases the possibility of detecting an association that is explained by reverse causation. While the data on LBC1921 participants were detailed, they were collected over a limited time period – from the age of 79 years. Aside from childhood IQ scores

and retrospective reports from participants, there were no data from across the life course. The suspected long duration of preclinical dementia and the previously reported effects of factors in midlife with regard to dementia risk reinforce the importance of collecting longitudinal data. The increasing availability of digital health records will make this a valuable resource for conducting longitudinal data analyses for the investigation of dementia in the oldest-old in future studies; electronic health data from across the life-course will enable the completion of larger studies, with better cost efficiency, incorporate data from different time points and thus allow for the analyses of data over time.(Zhao et al., 2019) To be utilised most effectively, so-called big data needs to be analysed and interpreted appropriately. Traditional statistical models may oversimplify the complex and non-linear interactions between variables, and as such, approaches that incorporate multiple risk factors and identify more subtle differences in relationships between variables and outcomes may be more effective at determining risk for dementia.(Obermeyer & Emanuel, 2016; Weng, Reps, Kai, Garibaldi & Qureshi, 2017) Newer statistical tools from the field of machine learning provide such an approach, addressing the limitations of standard models and exploiting the complex interactions between variables to improve accuracy in outcome prediction.(Obermeyer & Emanuel, 2016; Weng et al., 2017) Algorithms ae designed to learn rules from data; using patient-level observations at a starting point, the algorithm is able to search through a huge number of variables, combining them in a wide variety of non-linear and highly interactive ways, identifying the combinations that best predict the outcome.(Obermeyer & Emanuel, 2016) In doing so, machine learning is able to complete a vast number of analyses, using enormous volumes of data, the likes of which would have been impossible previously.(Obermeyer & Emanuel, 2016) Machine learning algorithms have been shown to improve the accuracy of cardiovascular risk prediction and it may follow therefore that such methods will improve the predictability of dementia outcomes.(Weng et al., 2017)

Machine learning algorithms may be of particular use in the study of dementia in the oldest-old given the potential complexities in the relationships between variables, as described within this thesis.

Based on several features of our findings and our cohort, such as the relatively low strength of association, the lack of plausibility for some variables and a lack of specificity (as described by Bradford Hill (1965)) and a the lack of consistency with other studies within the literature, we describe the observations as associations and do not make inferences with regard to causation.(Hill, 1965)

As detailed within the study, we recognise another potential inaccuracy of our findings relating to physical activity – the limitations in collecting retrospective historical physical activity data. Further to this, the relatively high levels of missing data for these variables made the accuracy of the results unclear.

Missing data may be particularly significant in studies of the oldest-old age group as physical and cognitive impairments limit the completion of specific assessments or testing.(Hardy, Allore, & Studenski, 2009) It may be expected that those demonstrating the greatest change in physical condition or cognition who are lost to follow-up, resulting in missing data and leading to inaccuracies in findings.(Sommerlad et al., 2020) In this study we chose to approach missing data using a complete case analysis methodology where only those cases with complete data were included in analyses; this method is used in other studies of risk factors for dementia within the literature.(Mukadam, Sommerlad, Huntley & Livingston, 2019) Alternative approaches to missing data, such as multiple imputation or maximum likelihood methods, are described within the literature, but none are without limitations.(Kang, 2013) We must however consider the possibility that by using an alternative approach to missing data, our findings may have been altered. A previous

study of variation in blood pressure and subsequent risk for dementia demonstrated that large variation in blood pressure over a period of years increased the risk for dementia; these findings were unchanged after imputing missing data using a multiple imputation method.(Ma et a., 2019) A second study exploring the potential association between participation in leisure-based physical activity and dementia found that using multiple imputation to account for missing data found results that were consistent with the primary analyses.(Sommerlad et al., 2020) While such findings might suggest that using an alternative approach in our study was less likely to result in significant differences in the findings, differences in the type and volume of missing data might give rise to differences in the effect that alternative approaches has on the findings of a study. If one chose to repeat a similar study to our own in the future, consideration should therefore be given to the use of an alternative approach, particularly where there are greater numbers of missing data.

With regard to the physical activity variable, we must also discuss the potential variability in the make-up of these scores. The lifetime activity score was the sum of the activity scores from three age periods; it follows that different participants could have a different pattern of activity across the lifetime, but arrive at the same total score. For example, one person may be very active in early age, fairly active in middle age and less active in older age, whereas another may be fairly active across the lifetime. It is possible that particular trends in activity are associated with differing levels of risk for dementia, and if this were the case then our analyses would not have identified this.

Given the close association between physical activity and physical fitness, we aimed to gather further evidence regarding this potential association by examining physical fitness at baseline and subsequent dementia. Details of this study are given in the Chapter 5.

5: Physical fitness in old age and subsequent dementia

5.1 Introduction

5.1.1 Physical activity and physical fitness

A number of different measures may be utilised in order to determine physical fitness. Such measures may include – among others – grip strength, walking velocity, gait assessment, lung function, exercise tolerance and timed sitting-to-standing. Levels of achievement on measures of physical fitness are likely to reflect participation in physical activity. In support of this hypothesis, previous evidence has demonstrated that physically active individuals aged over 65 years have greater cardio-respiratory fitness.(Department of Health Physical Activity Health Improvement and Protection, 2011) While activity and exercise may not be directly interchangeable when considering the findings of studies, there is likely to be a link between the two. A subject who partakes in regular activity is likely to perform better on tests of physical performance compared to a similar subject who does not. Where there is a physical, health or functional issue that may limit fitness, this is also likely to limit physical activity. One issue with examining the effect of physical activity across the life course – as noted in the previous chapter – is the potential for inaccuracy when asking participants to self-report exercise participation. How a participant will respond to questions regarding physical activity will depend on their perception of their physical activity; it will likely reflect how their exercise regimen compares to their peers or their own expectations. For example, a participant who walks for 30 minutes five days a week may consider this a low level of exercise if their peers take part in regular distance running, whilst a participant who follows the same walking regimen may consider their level of activity to be higher if their peers do not take part in any exercise. Similarly, if an individual was very active in early years, they may believe

that their activity level in older age is comparatively low, but an individual was relatively inactive in early life, may view the same level of activity in later life differently. It may be therefore that measures of physical fitness are a useful proxy for physical activity, and more accurate than self-reported physical activity.

5.1.2 Fitness as a modifiable risk factor in health

Physical activity and physical fitness are widely recognised to be important modifiable risk factors for multiple diseases. As such, increased physical activity is a key target for public health promotion.(Department of Health Physical Activity Health Improvement and Protection, 2011) The Department of Health for the UK describes a number of health benefits as a result of participation in regular physical activity. In adults, improved physical fitness through exercise has been proposed to reduce the risk for type II diabetes by up to 40%, cardiovascular disease by up to 35%, colon cancer by 30%, depression by up to 30%, hip fractures by up to 68% and breast cancer by 20%.(Department of Health Physical Activity Health Improvement and Protection, 2011) Reducing the prevalence of such conditions would reduce demand on health and social services, and the related costs. Based on five conditions linked to inactivity, the direct cost of physical inactivity for the NHS is approximated at £1.06 billion; this is however likely to be an underestimation given the positive impact of physical inactivity on a wide range of conditions.(Department of Health Physical Activity Health Improvement and Protection, 2011) Physical activity may also improve life expectancy and reduce overall mortality by up to 30%.(Department of Health Physical Activity Health Improvement and Protection, 2011) Physical inactivity is estimated to be responsible for one in six deaths in the UK (equal to the impact of smoking on UK mortality) and 6% of deaths globally (equal to the impact of elevated blood glucose on global mortality).(Department of Health Physical Activity Health Improvement and Protection, 2011)

Those health conditions described above are of particular relevance in older age. Individuals aged over 65 years are at greater risk of metabolic and cardiovascular disease, injury due to falls, malignancy, depression and cognitive deterioration.(Department of Health Physical Activity Health Improvement and Protection, 2011) Evidence from studies of adults and older adults has shown that partaking in either moderate or vigorous physical activity gives rise to similar health benefits in both adult age groups. The scientific evidence for adults aged over 65 years shows reductions in mortality, coronary heart disease, stroke, hypertension, type II diabetes, colon and breast cancer, for those who are more physically active or physically fit.(Department of Health Physical Activity Health Improvement and Protection, 2011; Farrell, Cortese, LaMonte, & Blair, 2007; Schmid et al., 2015; Sherrington et al., 2008; World Health Organization, 2010)

5.1.3 Fitness and cognitive impairment

A number of studies have also shown a relationship between lower physical fitness and poorer cognitive function in old age.(Auyeung et al., 2008; Deary, Whalley, Batty, & Starr, 2006; Rosano et al., 2005) A previous study of the Lothian Birth Cohort 1921 revealed similar findings: better overall physical fitness – as defined by a latent trait of grip strength, forced expiratory volume in one second (FEV_1) and six metre walking time – was associated with more successful cognitive ageing, contributing 3.3% additional variance to cognitive ability after adjusting for childhood cognitive ability.(Deary et al., 2006) Studies have also demonstrated an association between lower fitness levels and increased risk of dementia.(Kueper, Speechley, Lingum, & Montero-Odasso, 2017; Wang, Larson, Bowen, & van Belle, 2006) In the Adult Changes in Thought (ACT) Study, the age-specific incidence rate of dementia was 53.1 per 1000 person years for those who achieved poorer scores on a baseline test of physical function, while the age specific incidence rate for those who achieved

better scores was 17.4 per 1000 person years.(Wang et al., 2006) In this study, lower performance scores were shown to be associated with increased risk for dementia in both Alzheimer's disease and all-cause dementia.(Wang et al., 2006) While the results are not always consistent, studies have demonstrated associations with increased risk for dementia for a variety of fitness measures, including reduced global physical function, grip strength, balance and velocity of gait.(Kueper et al., 2017) While much of the evidence within the literature describes the association between fitness and dementia in earlier old age, some studies have considered this relationship in advanced old age. Notably, findings from the 90+ Study indicated an association between poorer physical performance and increased odds of dementia in the oldest-old.(Bullain, Corrada, Perry, & Kawas, 2016; Bullain et al., 2013) In these studies, strong associations with increased odds of dementia were seen for poorer performance in each of the following tasks: walking speed, repeated rising from a chair, grip strength and standing balance.(Bullain et al., 2016; Bullain et al., 2013)

These previous findings would indicate that physical fitness continues to be an important risk factor for dementia in oldest age. The aim of the subsequent study was to explore this association within the LBC1921, adding evidence to the literature on this less well-studied age group. Confirming the relationship between physical fitness and dementia in oldest-age – and how this may differ from other age groups – will be key to determining whether health strategies aimed at improving fitness and exercise participation has the additional benefit of reducing one's risk of developing dementia in oldest age.

The study included in this chapter was published in BMC Psychiatry and the complete reference is as follows:

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The author of this thesis was the first author and made the following contributions to the manuscript: assisted with study design, completed data collection for dementia ascertainment, took part in the dementia ascertainment consensus meeting, contributed to statistical analyses, led the writing of the manuscript and contributed to revisions of the same. We note that the Cox regression models and cumulative incidence graphs were completed by a contributing author – Mike Allerhand. The thesis author completed all other aspects of the statistical analyses. Supplementary materials for this publication are provided in *Appendix 3,* from page 292. The individual appendices are provided on the following pages:

The references for this paper are included within the published manuscript, in the referencing style of the journal. The references can be seen on pages 132-133 of the thesis.

5.2 Physical fitness and dementia risk in the very old: a study of the Lothian Birth Cohort 1921

(The published manuscript is included from the next page)

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Physical fitness and dementia risk in the very old: a study of the Lothian Birth Cohort 1921

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Abstract

Background: Previous studies have demonstrated that individual measures of fitness – such as reduced pulmonary function, slow walking speed and weak handgrip – are associated with an increased risk of dementia. Only a minority of participants included in these studies were aged over 80. The aim of this study was therefore to investigate the association between physical fitness and dementia in the oldest old.

Methods: Subjects ($n = 488$) were enrolled in the Lothian Birth Cohort 1921 and aged 79 at baseline. Dementia cases arising after enrolment were determined using data from death certificates, electronic patient records and clinical reviews. Fitness measures included grip strength, forced expiratory volume in 1 s (FEV_1) and walking speed over 6 m, measured at 79 years. Dementia risk associated with each fitness variable was initially determined by logistic regression analysis, followed by Cox regression analysis, where death was considered as a competing risk. *APOE* ε4 status, age, sex, height, childhood IQ, smoking, history of cardiovascular or cerebrovascular disease, hypertension and diabetes were included as additional variables. Cumulative incidence graphs were calculated using Aalen-Johansen Estimator.

Results: Although initial results indicated that greater FEV_1 was associated with an increased risk of dementia (OR (odds ratio per unit increase) 1.93, $p = 0.03$, $n = 416$), taking into account the competing risk of mortality, none of the fitness measures were found to be associated with dementia; FEV_1 (HR (hazard ratio per unit increase) 1.30, $p = 0.37$, $n = 416$), grip strength (HR 0.98, $p = 0.35$, $n = 416$), walking speed (HR 0.99, $p = 0.90$, $n = 416$). The presence of an *APOE* ε4 allele was however an important predictor for dementia (HR 2.85, $p < 0.001$, $n = 416$). Cumulative incidence graphs supported these findings, with an increased risk of dementia for *APOE* ε4 carriers compared with non-carriers. While increased FEV_1 was associated with reduced risk of death, there was no reduction in risk for dementia.

Conclusions: In contrast to previous studies, this study found that lower fitness beyond age 79 was not a risk factor for subsequent dementia. This finding is not explained by those with poorer physical fitness, who would have been more likely to develop dementia, having died before onset of dementia symptoms.

Keywords: Terms, Dementia, Cohort studies, Risk factors, Fitness

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Background

Overall physical fitness may be considered as the capacity of an individual's body to undertake varying degrees of physical activity. As such, physical fitness can reflect a person's ability to undertake the physical activities required to achieve day-to-day function. Overall physical fitness is comprised of a number of factors; the most important of which are probably muscular strength, muscular endurance, and cardiorespiratory or cardiovascular endurance. In the investigation of associations between fitness and disease, test measures should therefore reflect at least one of these components. Within the literature, tests of lung function, walking speed and grip strength are frequently used to measure physical fitness. Such measures reflect the components of physical fitness described above, with lung function tests providing a measure of cardiorespiratory function, grip strength providing a measure of muscular strength and walking speed providing a measure of both muscular endurance and cardiorespiratory endurance. A latent trait representing physical fitness can be extracted from these variables which is significantly associated with non-pathological cognitive change in this cohort of older adults at age ~ 80 years [1].

By examining the relationship between such physical fitness measures and disease, studies can determine whether fitness levels may be considered as a risk factor for disease. With widely recognised risk factors for dementia – such as age and *APOE* ε4 allele status – being fixed and unchangeable, identifying potentially modifiable risk factors would be of considerable value in contributing to the development of strategies aimed at reducing disease incidence. Such strategies are of particular importance in dementia, given the lack of cure or universally effective treatments. Several previous studies have therefore explored the potential association between physical fitness and dementia. Such studies have demonstrated that reduced pulmonary function [2–8], slow walking speed [9–13] and weak handgrip [9, 10, 14, 15] are associated with an increased risk of dementia. One might hypothesise that these findings reflect the importance of maintaining an optimal blood supply to the brain [16]. Specifically, if an individual has poor lung function, it is possible that blood oxygenation levels are below those required to maintain brain health. Furthermore, slow walking speed may be due to cardiovascular deficiencies and if the heart and circulatory system are struggling to meet the requirements of other areas of the body, it is possible that the brain is experiencing similar deficiencies. While none of these deficiencies may be dramatic enough to result in immediate clinical concern, it is possible that slight inadequacies that are present over a period of time could result in changes to brain structure or function. It is also possible that with increased fitness comes a reduction in other potential risk factors for dementia, such as hypertension, diabetes and increased body mass index [16]. The documented association between physical fitness and normal cognitive ageing [1], together with evidence that physical activity – which correlates with physical fitness – is a risk factor for dementia in generally younger populations [17], suggests that there is good a priori rationale to investigate whether such risk persists into the ninth decade and beyond.

Only a minority of participants included in the aforementioned studies were aged over 80 years. Those studies with an older mean participant age may involve participants from a wide age range (for example: mean age 80.3 years, age range 54–100 years) [14] and it is not therefore possible to draw any inferences regarding the relationship between fitness and dementia in oldest age given the potential influence of those younger participants included in the analyses. Based on current evidence, it remains unclear whether the patterns of association identified in early old age persist into oldest age. Within the literature, studies looking specifically at the oldest-old are typically fewer in number, likely as the result of difficulties in recruitment and retention of study participants, for reasons including co-morbidity and mortality. Understanding how the risk factor profile for dementia changes with age is vital in designing successful preventative strategies. In 2017, the number of persons aged 79 years or older in the UK was estimated to be 3,635,993; 5.5% of the total population [18]. As life expectancy increases and the global population ages, the number of persons reaching oldest-age are expected to grow, reinforcing the importance of understanding patterns of disease in this growing section of the population through further research.

This study considers the participants of the Lothian Birth Cohort 1921 (LBC1921), who were recruited at age 79 years and have undergone follow-up for dementia into their 90s. While a previous study of the LBC1921 had identified an association between superior physical fitness at age 79 years and improved cognitive aging [1], the effect of fitness at age 79 years on the development of dementia had not been investigated in this cohort. Measures of fitness collected at baseline (grip strength, time to walk 6 m and forced expiratory volume in 1 s (FEV_1)) reflected those commonly used within the literature and would therefore allow for comparisons with previous findings. As such, the study of physical fitness measures and dementia within this detailed, narrow-age cohort would be well-suited to add evidence, specific to the oldest-old, to the literature. Given the frequency of death within a cohort of advanced age we recognised the possibility that this may influence our findings. Such consideration was particularly important given that associations between reduced grip strength, reduced pulmonary function, reduced walking speed and increased

risk of death have been well documented [19, 20]. We therefore planned to consider death as a competing risk in our analyses.

The primary aim of this study was therefore to explore the association between three measures of physical fitness – grip strength, lung function and walking speed – and subsequent dementia in persons aged over 79 years.

Methods

Participants

Participants were members of the Lothian Birth Cohort 1921 (LBC1921), which is described more fully elsewhere [21]. Most had taken part in general intelligence testing at age 11, as part of the Scottish Mental Survey 1932 (SMS1932) [22]. Childhood cognitive test scores were available for 89.6% of those LBC1921 participants who attended baseline testing. Missing childhood cognitive data was likely to have resulted from school absence on the day of testing (due to sickness, for example), or be because the test results for some schools in Fife (a region neighbouring Lothian) were not found. From 1999, SMS1932 participants were traced and recruited for follow-up in later life, with the aim of investigating normal cognitive ageing [23]. Five-hundred and fifty participants, mostly from the Lothian area of Scotland, enrolled in the study and attended the first wave of testing. Participants were aged approximately 79 years at baseline. Surviving participants who continued to take part in the study were re-tested at four subsequent test waves; at ~ 83, 87, 90 and 92 years of age (approximately 3-yearly intervals). This interval was planned as the period over which the authors expected to be able to detect significant changes in some cognitive test scores, while balancing this against attrition. At each wave, data were collected by questionnaire and in-person testing. Participant deaths were ascertained prospectively, at regular intervals, with details supplied by the General Registrar's Office, Scotland. The Lothian Research Ethics Committee (test waves 1–3) and the Scotland A Research Ethics Committee (test waves 4–5) provided ethical approval for the study. From wave 4, attending participants provided consent for data linkage and access to health records.

Fitness variables

The three fitness measures included in this study were 6-m walk time, grip strength and forced expiratory volume in 1 s (FEV_1) [1]. Walking speed, grip strength and FEV_1 have all been shown to be valuable in evaluating physical and functional capacity [24–27]. Six-metre walk time was taken as the time in seconds for a participant to walk a measured length of 6 m, at a normal walking pace. Subjects were permitted to utilise any habitually used walking aid, while those who were unable to walk six metres would not participate in the test. A Jamar Hydraulic Hand Dynamometer was used to measure grip strength in kilograms, in the dominant hand; the best of three trials was recorded. FEV_1 was measured using a microspirometer, in units of litres per second; the best of three attempts was recorded. Taking three measurements is in line with guidance for clinical practice [28].

Additional variables

The analyses would also include variables deemed to be of potential importance with regard to their association with either physical fitness or dementia. In a previous study of the risk factors for dementia in LBC1921, positive *APOE* ε4 carrier status was found to increase risk, whereas a history of hypertension was found to reduce risk [29]. These variables were therefore included, along with the following important control variables: age, sex, height, age 11 IQ, smoking status, history of cardiovascular or cerebrovascular disease and history of diabetes. Age, sex and height are all key control variables given the direct impact on physical strength and fitness. Similarly, a history of cardiovascular or cerebrovascular disease and diabetes history were included given the potential association with physical fitness and dementia. When such conditions impact a person's ability to partake in exercise, fitness is likely to be adversely affected. The inclusion of age 11 IQ as a control variable is important given the known association with dementia [30] and other fitness-related factors [1, 31]. We also considered the potential impact of smoking status given the likely association with physical fitness, and lung function in particular. Whilst other factors were potentially associated with fitness, we could not include all possible risk factors, as this would have led to multiple hypotheses testing. We therefore adopted the hypothesis-driven approach described above, based on previous findings.

Data collection procedures

APOE ε4 status was determined using genomic DNA isolated from participants' venous blood. Any history of hypertension, diabetes, cerebrovascular or cardiovascular disease, smoking status (ex-, current-, or never-) and sex were self-reported by participants at the first wave of testing. A positive history of cerebrovascular or cardiovascular disease included those reporting previous stroke, transient ischaemic attack, myocardial infarction, angina, coronary artery bypass graft and angioplasty procedures and those who reported a positive history but did not specify the specific nature. A positive history of diabetes included those reporting any history of diabetes (any type or type unspecified). Age at baseline was taken from the number of days between date of birth and date of attendance at wave 1 testing. Age 11 IQ was calculated based on the results of the Moray House Test

(MHT) no.12, the general intelligence test taken by participants at age 11 as part of SMS1932 [21]. MHT scores were corrected for age at testing, then converted to IQ-type scores with a standardised mean score of 100 (SD 15). Height in centimetres was measured using a SECA stadiometer.

Dementia ascertainment

Follow-up for the purpose of dementia ascertainment has been described previously and involved the retrospective collection of evidence, from enrolment to age 95 years [29]. Data were collected from death certificates, electronic hospital records, and clinical reviews. Each death record available by 30th June 2016 was examined for evidence of dementia or cognitive impairment. Electronic hospital records and psychiatric records were accessed for participants who were willing and able to consent to data linkage. Any evidence for dementia or cognitive impairment since enrolment in the study – whether a confirmed diagnosis or evidence for a diagnosis – was recorded. Data were collected from electronic medical records to the 16th May 2016. Additional information was available for 26 participants who underwent clinical review by the authors (TCR, JMS), either in the NHS or research setting. Information from such reviews was collected up to 15th December 2016, when all of the evidence from each source was considered at a final dementia diagnosis consensus meeting (RAS, TCR, JMS). The evidence was examined against a previously described list of criteria for 'probable' or 'possible' dementia diagnosis [29]. Using these criteria, the meeting agreed upon the presence of a diagnosis and the subtype. Any disagreement was resolved through discussion.

Event variables

The events considered in these analyses would be dementia and death. Determination of these outcomes was as described above. Time to death was taken as the number of days between the date of attendance at wave 1 testing and date of death. For those who did not die, the censoring time was taken as the number of days between wave 1 testing and a date beyond that last date of data collection for any participant. Time to dementia was taken as the number of days between the date of attendance at wave 1 testing and the first date that a dementia diagnosis was noted in any of the available sources. If dementia was recorded on a death certificate only, and no duration was noted, the diagnosis was presumed to predate death by 6 months. If the duration was not given on the death certificate, but a diagnosis was recorded in another source, the earliest such date was used to determine the time to dementia. If sources had recorded cognitive decline, mild cognitive impairment and dementia, the date was taken as the earliest recording of a dementia diagnosis. If dementia was ascertained based on evidence within the records that did not include a formal diagnosis of dementia, the earliest mention of cognitive impairment was used to date dementia (as long as this did not specifically note the absence of a dementia syndrome). For those who did not develop dementia, the time to dementia variable was recorded as either the time to date of death or to a date beyond that last date of data collection for any surviving participant.

Participant exclusions

Any participant reporting a history of dementia or scoring 23 or less on the Folstein Mini Mental State Examination [32] (MMSE) at baseline was excluded from our analyses. Those without a valid MMSE score at baseline were also excluded, as were those without any follow-up data available. To minimise the potential for classification error, possible dementia cases were excluded from the analyses and probable dementia was used as the primary outcome in this study.

Statistical analysis

We first performed simple comparison analyses between the group who developed dementia and the group who did not, for each of the included variables. Univariate analyses were completed using either a Pearson chi-square (for categorical variables) or independent samples t-test (for continuous variables) (*IBM SPSS, Version 21).* A p value of < 0.05 was used to demonstrate a statistically significant difference. All subsequent steps in the analyses were completed using the *R* statistical software (version 3.3.3) [33].

The second stage of the analyses used binary logistic regression to examine the potential risks for dementia associated with the fitness measures. In a first model (logistic regression model 1) we included the fitness variables along with those factors known to be associated with dementia in our cohort and the other important control variables (FEV_1, grip strength, 6-m walk time, *APOE* ε4 carrier status, height, age, sex, history of hypertension, smoking status and age 11 IQ). The development of probable dementia was the outcome. In the second model (logistic regression model 2), the same variables were included, with the addition of a history of cardiovascular or cerebrovascular disease and a history of diabetes. A history of hypertension was considered separately to these other health variables as a statistically significant association with dementia had previously been observed within this cohort.

The main analyses used Cox regression models with death being included as a competing risk for dementia; in doing so, the influence of fitness on earlier death in the analysis of dementia development due to fitness was

considered. The models were completed using standard software for Cox regression with right-censored data and treating death as censored, (R package survival). The first and second Cox regression models (Cox regression models 1 and 2) included the same covariates as those described for logistic regression models 1 and 2. Both models fitted the data acceptably with concordance of 64%. Analysis of the scaled Schoenfeld residuals (R function cox.zph), showed all covariates complied with the proportional hazards assumption. As is recommended practice, we supported the results of Cox regression with graphs demonstrating cumulative incidence for each competing event; illustrating the time-varying risk of dementia, between covariate levels. The unbiased estimate of cumulative incidence was calculated using the Aalen-Johansen estimator [34], (R packages prodlim and mstate).

Results

Participant eligibility

A total of $N = 550$ participants recruited to LBC1921 attended baseline testing at age 79 years. We excluded the following participants from the analyses: participants with an MMSE score of less than 24 at baseline ($n = 9$), participants without a valid MMSE score at baseline ($n = 2$), participants reporting a history of dementia at baseline ($n = 2$), and participants with no follow-up data available for the purpose of dementia ascertainment ($n = 41$). One additional participant was excluded as the calculated time to dementia suggested that dementia predated attendance at wave 1 testing. From the remaining participants ($n = 495$), a consensus diagnosis of probable dementia was agreed for $n = 109$. Those participants with a possible diagnosis of dementia were excluded from the analyses ($n = 7$).

Participant demographics (Table 1)

The resulting eligible cohort ($n = 488$) included 280 females (57.4%) and 419 participants (85.9%) were known to be deceased [29]. This included 331 who died with no diagnosis of dementia. Descriptive statistics for those eligible for inclusion (both with and without dementia), and those excluded are shown in Table 1.

Event variables

The mean time to death for the $n = 419$ participants who were known to be deceased was 3144.5 days (SD: 1517.5). For those who survived, the time to death was taken as an arbitrary point beyond the last date of data collection for any participant; 6500 days. The mean time to dementia for the $n = 109$ who developed dementia was 3535.7 days (SD: 1283.3). A total of $n = 379$ participants remained dementia free; for these participants, time to dementia was taken either as the time to death for those who died ($n = 331$, mean = 2863.0 days, SD: 1469.4), or an arbitrary point beyond the last date of data collection for any participant ($n = 48$, 6500 days).

Dementia group comparison (Table 1)

Also included in Table 1 are the results of the group comparison analyses. Univariate analyses demonstrated little difference between those participants who developed dementia and those who did not. Only smoking status ($p < 0.001$) and *APOE* ε4 ($p < 0.001$) carrier status demonstrated statistically significant difference ($p < 0.05$).

Univariate analyses were also performed to compare those who died with those who survived. Lower FEV_1 and greater 6-m walk time were both associated with an increased risk of death ($p = 0.02$ and $p = 0.01$, respectively). The results for these univariate analyses are available in Additional file 1: Table S1.

Logistic regression results (Table 2)

The results of both logistic regression analyses demonstrated that *APOE* ε4 remains an important risk factor for dementia after age 79 years (logistic regression model 2: Odds Ratio (OR) 2.52 (95% confidence interval: 1.50, 4.22), $p < 0.001$). Both initial models also suggested that increased FEV_1 at age 79 increased the risk for subsequent dementia (logistic regression model 2: OR 1.93 (1.07, 3.57), $p = 0.03$). The only other variable that reached statistical significance was height, and only in the second model; increased height was shown to decrease risk for subsequent dementia (OR 0.95 (0.91, 1.00), $p = 0.04$).

Cox regression analyses (Table 2)

In both Cox regression models, *APOE* ε4 continued to be an important predictor for dementia (Cox model 2: Hazard Ratio (HR) 2.85 (95% confidence interval: 1.85, 4.41), $p < 0.001$). The results did however demonstrate that once death was considered within the analyses, the association between FEV_1 and dementia did not reach statistical significance in either model (Cox model 2: HR 1.30 (0.74, 2.30), $p = 0.37$). Neither grip strength (Cox model 2: HR 0.98 (0.94, 1.02), $p = 0.35$) nor walking speed (Cox model 2: HR 0.99 (0.87, 1.13), $p = 0.90$) was associated with dementia in either model. No other variable was demonstrated to be associated with dementia.

Cumulative incidence graphs

For the purposes of calculating cumulative incidence, FEV_1 results were divided into two groups, at a value of 1.8 l per second. This value was close to both the sample mean and median. The stacked cumulative incidence plot shown in Fig. 1 demonstrated that increased FEV_1 was associated with decreased risk of death but not dementia (Fig. 1). A second cumulative incidence plot

Table 1 Study Sample Demographics and Group Comparison

	Eligible Participants ($n = 488$)		Group Comparison p value (chi-square or t-test)	Excluded Participants ($n = 62$)
	Dementia ($n = 109$)	No Dementia ($n = 379$)		
Age	$n = 109$	$n = 379$		$n = 62$
-mean age in years (SD)	79.04 (0.55)	79.08 (0.59)	0.54	79.09 (0.53)
Sex	$n = 109$	$n = 379$		$n = 62$
-% female	62.4%	55.9%	0.23	58.1%
Living or deceased	$n = 109$	$n = 379$		$n = 62$
-% deceased	80.7%	83.3%	0.08	29.0%
MMSE score at baseline	$n = 109$	$n = 379$		$n = 60$
-mean score (SD)	28.10 (1.64)	28.33 (1.46)	0.16	27.27 (2.67)
Height	$n = 106$	$n = 378$		$n = 60$
-Mean height in cm (SD)	162.11 (9.21)	163.59 (9.45)	0.15	163.83 (8.53)
APOE ε4 carrier status	$n = 109$	$n = 373$		$n = 61$
-% carrier *APOE* ε4	41.3%	22.5%	*< 0.001*	27.4%
Age 11 IQ (standardised)	$n = 101$	$n = 339$		$n = 53$
-Mean score (SD)	100.19 (16.18)	100.22 (14.53)	0.98	98.21 (15.63)
FEV_1	$n = 106$	$n = 378$		$n = 60$
-mean rate in litres per second (SD)	1.95 (0.59)	1.84 (0.62)	0.12	2.03 (0.68)
Grip strength	$n = 106$	$n = 378$		$n = 60$
-mean strength in kilograms (SD)	25.89 (10.17)	26.46 (8.87)	0.57	28.18 (8.59)
6 m walk time	$n = 105$	$n = 377$		$n = 59$
-mean time in seconds (SD)	4.56 (1.53)	4.84 (2.11)	0.20	4.37 (1.29)
Smoking status	$n = 108$	$n = 379$		$n = 62$
-% ever smoker	42.6%	61.7%	*< 0.001*	50.0%
History of cardiovascular or cerebrovascular disease	$n = 104$	$n = 373$		$n = 58$
-% positive history	28.9%	28.2%	0.89	24.2%
History of hypertension	$n = 108$	$n = 375$		$n = 61$
-% positive history	35.2%	41.9%	0.21	41.0%
History of diabetes	$n = 109$	$n = 379$		$n = 62$
-% positive history	4.6%	5.8%	0.62	1.6%

Italicized results demonstrate significance of p<0.05

confirmed that the presence of an *APOE* ε4 allele was associated with an increased risk for dementia (Fig. 2).

Discussion

Contrary to the existing evidence within the literature [2–15], this study found that decreased fitness beyond age 79 was not a risk factor for subsequent dementia. More specifically, FEV_1, grip strength and walking speed at age 79 years were not found to be associated with dementia. Indeed, considering those who survive, greater FEV_1 is associated with an increased risk of dementia: that is, if you survive, having better respiratory function (a measure of fitness) when you are younger makes it more likely that you will develop dementia. Even when the effect of poor respiratory function on mortality risk is taken into account, being fitter as a younger adult does not confer any benefit with regards to dementia risk once you reach your ninth decade. This raises an important distinction because better physical fitness was associated with higher cognitive scores in oldest age, even after adjusting for childhood IQ, in this same cohort [1]. That is, having better physical fitness at age 79 was good for a person's cognitive ability but did not reduce the risk of developing dementia. As was observed in a previous study of the LBC1921, the presence of an *APOE* ε4 allele was however associated with an increased risk for dementia [29].

Table 2 Regression Results

	Odds/ Hazard Ratios (95% CI) for Probable Dementia			
	Logistic Regression Model 1	Cox Regression Model 1	Logistic Regression Model 2	Cox Regression Model 2
	Odds Ratios (95% CI)	Hazard Ratios (95% CI)	Odds Ratios (95% CI)	Hazard Ratios (95% CI)
	(*n* = 425)	(*n* = 425)	(*n* = 416)	(*n* = 416)
Sex (female)	0.77 (0.31, 1.85)	1.26 (0.56, 2.83)	0.86 (0.34, 2.11)	1.42 (0.63, 3.23)
Age (days)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Height (centimetres)	0.96 (0.92, 1.00)	0.97 (0.94, 1.01)	*0.95 (0.91, 1.00)*	0.97 (0.93, 1.01)
APOE ε4 carrier	*2.47 (1.49, 4.08)*	*2.72 (1.78, 4.14)*	*2.52 (1.50, 4.22)*	*2.85 (1.85, 4.41)*
Age 11 IQ	1.00 (0.98, 1.02)	0.99 (0.98, 1.01)	1.00 (0.98, 1.02)	1.00 (0.98, 1.01)
History of hypertension	0.64 (0.38, 1.05)	0.79 (0.51, 1.23)	0.64 (0.38, 1.06)	0.78 (0.50, 1.22)
Smoker (ever)	0.63 (0.38, 1.04)	0.92 (0.60, 1.40)	0.62 (0.37, 1.03)	0.94 (0.61, 1.45)
FEV_1 (l/s)	*2.05 (1.15, 3.75)*	1.43 (0.82, 2.48)	*1.93 (1.07, 3.57)*	1.30 (0.74, 2.30)
6 m walk time (s)	0.93 (0.79, 1.07)	0.99 (0.87, 1.13)	0.94 (0.79, 1.08)	0.99 (0.87, 1.13)
Grip strength (kg)	1.00 (0.96, 1.05)	0.98 (0.94, 1.02)	1.01 (0.96, 1.05)	0.98 (0.94, 1.02)
History of cardiovascular or cerebrovascular disease	–	–	1.08 (0.61, 1.86)	1.14 (0.72, 1.81)
History of diabetes	–	–	0.86 (0.19, 2.88)	1.39 (0.41, 4.66)

Logistic regression model 1 and Cox regression model 1: included FEV_1, grip strength, 6-m walk time, APOE ε4 carrier status, height, age, sex, history of hypertension, smoking status and age 11 IQ, with the development of probable dementia as the outcome. Logistic regression model 2 and Cox regression model 2: as logistic regression model 1 plus history of cardiovascular or cerebrovascular disease and history of diabetes. Results for Cox regressions show the hazard ratios and 95% confidence intervals. Statistically significant results are italicized

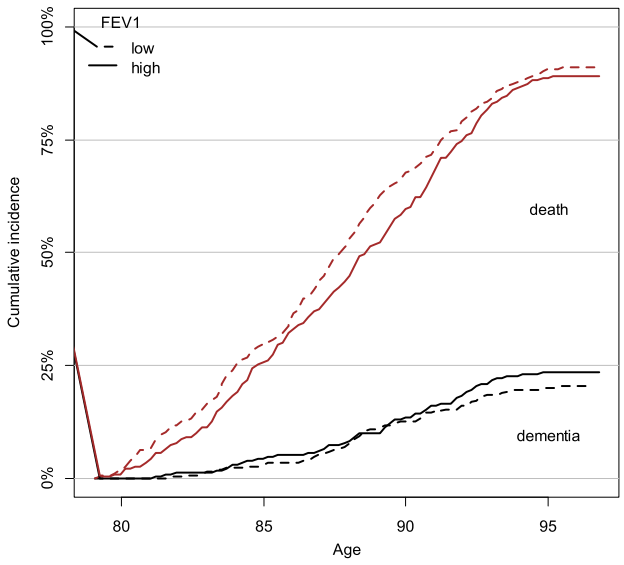

Fig. 1 Cumulative incidence of dementia and death (stacked) at 2 levels of FEV_1. Note. FEV_1 groups were split at 1.8 l per second

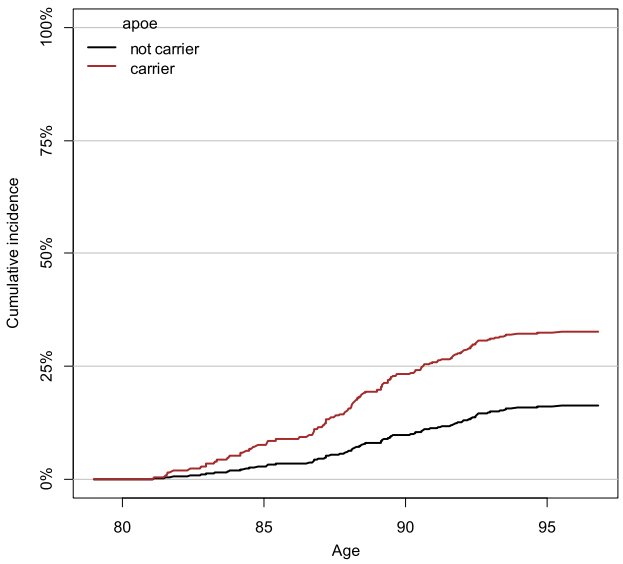

Fig. 2 Cumulative incidence of dementia for *APOE* ε4 carriers and non-carriers. Note. Predicted cumulative incidence of dementia (Aalen-Johansen estimator) for men aged 79 of average height, fitness (FEV, 6 m walking time, and grip strength), and age 11 IQ

Previous studies have repeatedly shown that poorer lung function, grip strength and walking speed are associated with increased risk for dementia [2–15]. The primary reason for this inconsistency may be that most previous studies have investigated the association in a younger population, or a population with a broader age range than the LBC1921 [2, 7]; the results of this study may differ simply because the results are specific to the oldest-old. We might also consider the impact of death on our finding. In our cohort, increased lung function at age 79 was associated with a reduce risk of death. We can therefore hypothesize that our null findings may be due to the fact that those with poorer fitness, who would have been more likely to develop dementia, would have died from another cause before developing dementia. Taking lung function as an example, in addition to death directly related to lung disease, death before dementia may occur because of diabetes, atherosclerosis or coronary heart disease, all of which are known to be associated with poorer lung function [5]. Given that our competing risks analyses accounts for this possibility, we would not expect to have found an increased risk of dementia for those with low FEV_1 if these people had survived.

In examining the potential influences on our findings it is worthwhile considering the fitness levels of the participants of the study, when compared with population norms. While predicted values for FEV_1 are less well established for those aged over 70 years, formulae published by the British Thoracic Society can be used to calculate the expected results for our study population [28]. Females included in our study achieved, an average, 94.5% of the predicted FEV_1 value, while males achieved 88.8% of the predicted value, based on mean age and height. Both of these were above the 80% cut-off used to demonstrate abnormality, and below the 100% threshold that would demonstrate better than expected lung function. The mean walking speed recorded for male and female study participants (137 cm per second and 118 cm per second, respectively) were similar to published normative values for persons aged in their 70s (133 cm per second and 127 cm per second for males and females respectively) [35]. Previously published expected median values for grip strength – measured using a Jamar Hydraulic Hand Dynamometer – also closely resemble those achieved in the present study [36]. For males, the expected median was 34.9 kg, and the achieved median and mean were 34 kg and 34.5 kg respectively. For females, the expected median was 20.9 kg, and the achieved median and mean were 20 kg and 20.3 kg respectively. One might expect the values for grip strength and walking speed to be slightly below expected levels because the reference values were for individuals aged 70–79 years and the participants of this study were at the uppermost limit of this age bracket. Based on these results one might assume that, with respect to grip strength, walking speed and FEV_1, this study cohort were not

of unusually high or low fitness and reflected a typical population of this age.

It is also possible that the lack of association observed in our results is the result of some type of resilience to disease. It is acknowledged within the literature that some individuals do not appear to be susceptible to the negative effects of certain lifestyle habits. For example, some heavy smokers do not develop lung disease [37]. Studies – including a large Medical Research Council funded study of UK Biobank data – have suggested that DNA variants may explain why some individuals can have relatively good lung health despite smoking [38, 39]. It is possible that there is a similar unidentified genetic resilience for dementia, such that those who are more susceptible to developing dementia because of certain risk factors will do so prior to oldest age, while those who are genetically resilient will continue to be resilient in oldest age, resulting in a lack of observed association.

The null findings of this study should not be overlooked as unimportant. If these associations are indeed only present in earlier old age, the fact that lung function, grip strength and walking speed were not significantly associated with dementia in our cohort, demonstrates an important difference between the risk profile for dementia in early old age and late old age.

Since the median age of dementia diagnosis in the UK, for example, is now over 80, if our findings are replicated, it means that for the majority of people who will develop dementia seeking to improve physical fitness is unlikely to have any effect on preventing the disease. Although our findings do not concur with previous reports, our findings are supported by other health-related analyses in this cohort that identified changes in the risk factor profile for dementia in advanced old age [29]. In the LBC1921, a history of hypertension was associated with a decreased risk of dementia, and increased physical activity in early adulthood was associated with an increased risk for dementia after age 79 years [29]. Whereas the relationship between physical activity and dementia was novel, other studies have described a change in the relationship between hypertension and dementia in the oldest old [40]. The results of the present study, together with these previous findings, would indicate that there is different risk profile for dementia in the oldest old, when compared with those in earlier old age.

Our findings therefore highlight two important differences. Firstly, it seems increasingly likely that the risk profile for dementia in oldest age differs from the risk profile in earlier old age. Secondly, that the risk profile for dementia in oldest age differs from the risk profile for less successful non-pathological cognitive ageing in the oldest old. Understanding the risk profiles for each of these separate processes and how they differ is important, as this knowledge will aid in the design and development of appropriate prevention and management strategies. Given that dementia is set to be one of the greatest public health challenges facing the ageing population, successful cost-effective prevention strategies are of vital importance.

Strengths and limitations

A significant strength of this study lies in the suitability of the cohort for these analyses. The minimal cultural, ethnic and geographical variability within the narrow-age cohort minimises confounding errors and means that the results are specific to the oldest old. We recognise, though, that this limits the generalisability of the results, and so additional studies are required in other groups. The availability of a childhood IQ score is a rare strength of the study, as is the detailed follow-up completed since enrolment in the study. The high mean baseline MMSE score (28.3, SD: 1.5) for those included in the analyses increases the likelihood that we identified incident cases of dementia, rather than prevalent cases. By including multiple measures of fitness it was possible to consider several components of fitness. Whilst this was a strength of our study, it could be argued that additional tests could have provided a more comprehensive assessment of fitness. We selected the additional variables for inclusion in the analyses based on the available evidence, but it is possible that there was some residual confounding due to a variable not considered in this study. It is not however possible to exclude all such possibilities without negatively affecting the analyses through multiple hypotheses testing. The dementia ascertainment method in this study has previously been shown to be effective and comparable with expected rates [29]. Having determined dementia cases retrospectively using existing data, it was not possible to accurately date the onset of dementia. For this reason, we cannot be entirely confident in the accuracy of the time to dementia variable. The method used to determine date of onset in this study, is however conservative and it is likely that dementia onset preceded our assigned date by some time. As such, the true competing risk of death is almost certainly less than we are adjusting for in the model. While we recognise this limitation of our study, it is not unique to our method; it is notoriously difficult to pinpoint the exact date of dementia onset, even in studies using prospective clinical follow-up. This is particularly true given that the most common form of dementia – Alzheimer's disease – has a gradual onset. A further limitation of our study is the possibility of missed cases. Our results could also have been affected by using an outcome of probable dementia of any subtype. The number of participants with each subtype of dementia was too few to perform individual analyses. It is also possible that the overall size of our study cohort had an impact on our findings, and that a larger sample size would have produced differing results.

Conclusions

The results of this study suggest that increased physical fitness at age 79 years does not reduce the risk for subsequent dementia. The early death of participants with poorer fitness, who would have been more at risk of dementia dying before developing dementia, might explain why the findings differ from studies of earlier old age.

Additional file

Additional file 1: Table S1. Group Comparison: Deceased and Living. (DOCX 14 kb)

Abbreviations

APOE ε4: Apolipoprotein E ε4; CHI: Community Health Index; CI: Confidence Interval; DNA: Deoxyribonucleic Acid; FEV_1: Forced Expiratory Volume in 1 s; IQ: Intelligence Quotient; LBC1921: Lothian Birth Cohort 1921; MHT: Moray House Test; MMSE: Mini Mental State Examination; NHS: National Health Service; OR: Odds Ratio; PIMS: Patient Information Management System; SD: Standard Deviation; SMS1932: Scottish Mental Survey 1932; Trak: TrakCare

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Availability of data and materials

The data analysed during this study are available on request from the Lothian Birth Cohort Study, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh. The data are not publically available due to them containing information that could compromise participant consent and confidentiality.

Authors' contributions

RAS, JMS, IJD and MA contributed to the design of the study. RAS completed data collection for dementia diagnoses, interpreted the results and led the writing of the paper. MA completed the statistical analyses. RAS contributed to the statistical analyses. JMS, TCR, MA and IJD contributed to the drafting and revision of the paper. RAS, JMS and TCR took part in the consensus meeting for dementia ascertainment. TCR assisted in the collection of data for dementia diagnoses. JMS and TCR performed clinical assessments in the NHS and research settings. IJD and JMS obtained funding for the study. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Lothian Research Ethics Committee (test waves 1–3) and the Scotland A Research Ethics Committee (test waves 4–5) provided ethical approval for the study. From wave 4, attending participants provided written consent for data linkage and access to health records.

Consent for publication

Not applicable.

Competing interests

Dr. Sibbett is funded by Alzheimer Scotland (2013- present; salary). Professor Deary and Professor Starr are supported by the Medical Research Council (salary component of the Centre for Cognitive Aging and Cognitive Epidemiology grant). Dr. Russ and Dr. Allerhand do not report any competing interest.

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5.3 Chapter summary and conclusions

The study described in Section 5.2 did not demonstrate any association between fitness at age 79 years and subsequent dementia. Contrary to previous findings, lower fitness – as described by grip strength, walking speed and lung function – did not result in an increased risk for dementia in this age-group. Once again, our findings provide further evidence for a changed risk factor profile for dementia in oldest-old age.

If our findings were repeated in other studies, it would demonstrate that the strategies or interventions aimed at reducing dementia risk should differ according to age. Understanding the role of physical exercise in dementia risk reduction in this age-group is important given that advancing age may give rise to an increasing number of barriers to participation in physical activity. As age advances it might be expected that co-morbid conditions which could affect exercise capability – such as increased general frailty and diseases affecting mobility or cardiorespiratory function – might be more common. If our findings are correct, one might suggest that the factors that constitute a 'healthy lifestyle' for dementia risk reduction are different in the oldest-old.

We do however have to consider the limitations of our study that might have resulted in the null finding; potential limitations such as the size of our study cohort and the uncertainty regarding the optimal fitness measures for consideration as discussed within the included paper. An important consideration in risk factor studies is the potential for observing a reverse association (or reverse causation), where the reported association actually arises as a result of features of the dementia prodrome.(Sommerlad et al., 2020) Physical inactivity is proposed to be part of the prodrome of dementia and as such, one might expect reduced levels of activity in the

years preceding diagnosis. This hypothesis is strengthened by the findings of a study by Sommerlad et al. (2020) who only found an association between reduced activity and increased risk for dementia where leisure activity was assessed at older ages, with less than ten years between activity assessment and dementia.(Sommerlad et al., 2020) As we note within our introduction to the chapter, physical activity and physical fitness are likely to be closely related and reduced physical fitness may therefore also be expected to be present in this prodromal phase. In support of this hypothesis, physical fitness has been shown to be lower in those with recently diagnosed mild cognitive impairment and dementia.(Hesseberg, Bergland, Rydwik & Brovold, 2016)

In this study, three measures of physical fitness were investigated. It is possible that if different measures, or further measures were examined, different results would have been observed. Regardless of which fitness measures were chosen, all are likely to be influenced by additional factors in oldest-old age. As discussed previously within the thesis, those in the oldest-old age group are likely to have a more complicated health and disease profile, and this will likely complicate the investigation of fitness in this age group. The prevalence of cardiovascular disease is known to increase with advancing age. The Scottish Health Survey 2019 reported that 44% of persons aged 75 years and over had at least one cardiovascular condition (excluding hypertension or diabetes), compared with 26% in those aged 65-74 years.(The Scottish Government, 2019) Rates were higher in males (The Scottish Government, 2019), and would be expected to be higher if hypertension was included in the prevalence statistics. Cardiovascular disease is likely to have an impact on the overall health status of an individual, but may also have a direct impact on most individual measures of fitness. In our study, grip strength and walking speed are most likely to be negatively impacted by cardiovascular illness. Appreciating how these conditions

affect fitness is not as simple as grouping participants by the presence or absence of a condition; each condition is likely to affect an individual differently, and thus affect fitness differently. The impact of disease on fitness will also be influenced by premorbid fitness and an individual's resilience or reserve. As discussed within the main introduction to the thesis, resilience or reserve is central to the concept of frailty. Frailty may be determined using different methods; the most common methods are i) a frailty index based on a measure of accumulated deficits, or ii) a clinical assessment criteria based on a proposed clinical phenotype of frailty.(Rockwood, Andrew & Mitnitski, 2007) The phenotype criteria include measures such as unintentional weight loss, low physical activity, slowness of gait, exhaustion and weakness.(Fried, 2001) The crossover between this frailty measure and our assessment of fitness is clear; two of our measures of fitness – grip strength and walking speed – are two of the five recognised phenotypic criteria for frailty. A frailty index, such as that developed for use in the Canadian Study of Health and Aging, is constructed using a large number of variables – many of which might also be viewed as measures of physical fitness.(Rockwood et al, 2005) Like the phenotype criteria, many variables have direct overlap with, or have influence on, the fitness assessment measures used in our study.(Rockwood et al., 2005) Examples would include – poor muscle tone in limbs, bradykinesia, impaired mobility, musculoskeletal problems, lung problems and respiratory problems.(Rockwood et al., 2005) It is clear that there is a complex relationship between fitness and frailty, and given the frequency of frailty in old age, this will affect the study of, and interpretation of results from, studies of physical fitness and dementia in the oldest-old age group.

In our study, we also note the potential for a healthy survivor bias to affect the findings. By studying those who reached age 79 years and remained relatively healthy, we might be obscuring an association by excluding participants who had died or were too

unwell to enrol. If we look at smoking and lung function in particular, smoking related lung disease may have restricted an individual's ability to enrol, and likewise it may have caused death prior to age 79. By selecting healthy survivors at age 79 for our study, we may inadvertently be introducing a selection bias to the study sample when investigating the association between lung function and dementia.

When reviewing the study findings, one must give consideration as to whether there was sufficient statistical power to detect an association, or whether insufficient power may have contributed to the failure to reject the null hypotheses.(Hoenig & Heisey, 2001) It is important to recognise that a study with a small sample size may not be able to detect an important difference, resulting in a Type 2 error. It would be useful to be able to show whether truthful conclusions could be based on the non-significant results observed in this study. Power calculations are generally recommended to take place prior to data collection, to determine the minimum size of a study sample required to detect an association. In our case, recruitment and data collection had already taken place, resulting in a fixed sample size. Expert opinion within the literature states that retrospective power analyses are not reliable or meaningful, and are not therefore reported to be good practice.(Gilbert & Prion, 2016; Goodman & Berlin, 1994; Hoenig & Heisey, 2001) Retrospective or observed power is calculated using the collected data and as such, the power analysis assumes that the observed effects are true – which may not be the case.(Hoenig & Heisey, 2001) For example, if a non-significant test result is used to calculate power, one would expect a low power, leading to the potentially false assumption that the original analyses lacked sufficient power to detect a positive association.(Hoenig & Heisey, 2001) Even if calculations of observed power were not subject to such limitations, the specific modelling methods used in this study complicate the calculation of statistical power,

and make it less likely that we could produce a realistic or meaningful value for statistical power.

While these issues mean that we do not report a specific value for statistical power, we can make general comments about the potential impact of statistical power in our study. In general, it can be assumed that the larger the sample, the greater the power. Given the relatively small size of our study sample, the possibility of there being inadequate power to detect associations in this study is recognised. Obviously, larger sample sizes are required to have sufficient power to detect smaller effects. For example, Cohen (1992) offers guidance for Pearson's (product-moment) correlation coefficient *r*.(Cohen, 1992) With alpha fixed at 0.05 and power at 0.80, with an effect size (*r*) of 0.1, the necessary sample size is at least 783.(Cohen, 1992) When *r* is medium (0.3) or large (0.5), the necessary sample size is smaller, at 85 and 28, respectively.(Cohen, 1992) If the alpha is .01, which might be adopted to avoid a greater Type 1 error rate, the respective numbers are 1163, 125, and 41.(Cohen, 1992) Broadly speaking, then, in the area of cognitive ageing, where associations tend to be small, the typical necessary numbers are in the several to high hundreds. Most analyses in cognitive ageing will be more complex than just a correlation, of course and, therefore, the minimum Ns needed will also depend on other factors, such as how many and which covariates are in the model, and what strategy for correction for multiple testing is implemented.

We can therefore state that, based on our non-significant findings, we failed to reject the null hypotheses, but not that we accept the null hypothesis to be true. The limitations in statistical power of our study reinforce the importance of larger studies to further investigate our finding that increased physical fitness at age 79 years does not reduce the risk for subsequent dementia.

The past two chapters have considered individual potentially modifiable risk factors for dementia. It has however been suggested that the aetiology of dementia may be a complex interaction between genetic and environmental or lifestyle factors. The study of epigenetic modifications explores how changes in the environment can give rise to changes in how DNA is expressed. Epigenetic modifications may therefore be key to understanding interactions between genetics and environment. The subsequent chapter will therefore explore how one type of genetic modification might be used to predict risk for dementia.

6: DNA methylation-based measures of accelerated ageing and dementia in the Lothian Birth Cohort 1921

6.1 Introduction

The study of epigenetics considers the effect produced by interactions between genetics and external factors. The prefix ‘epi-‘ is of Greek origin and translates to mean upon, on, above or in addition to. One may therefore consider a simplified representation of the concept of epigenetics as follows: additional external information is layered on top of the genetic code and changes the expression of this underlying code. In essence, the addition of this external information alters how the same DNA sequence is ‘read’ and expressed within the individual: a change in phenotype without a change in genotype. Such modifications have been shown to be transmitted to daughter cells in a non-genetic heritable pattern.(Weinhold, 2006)

Epigenetics is not a new term, nor is it a novel field of research. Since the term first appeared in print, researchers have endeavoured to uncover evidence that gene function could be altered by more than just changes in gene sequence.(Weinhold, 2006) The history of the field of epigenetics predates the creation of such terminology and it could be argued that the possibility of such a phenomenon began with the evolutionary theories of Charles Darwin.(Shields, 2019) In 1956, Conrad Waddington – often referred to as the father of epigenetics – published a paper in which he successfully demonstrated an inherited characteristic that was acquired in response to an environmental stimulus.(Noble, 2015; Waddington, 1956) Coining the term ‘epigenetic landscape’, Waddington showed that by changing the chemical composition or temperature of the environment, embryo fruit flies could be persuaded to show different thorax and wing structures; the adult could display a different phenotype from the same genotype.(Noble, 2015) Modern day epigenetic research

has been much advanced by the progression in technology and experimental procedure. Multiple types of epigenetic modifications have been identified and described thus far. The most commonly studied epigenetic markers involve modifications of DNA (methylation) or histone proteins (methylation, phosphorylation, acetylation, ubiquitylation and sumolyation).(Ptashne, 2007) Histone modification influences gene expression via two mechanisms: by changing chromatin structure or by regulating the binding of effector molecules.(Bannister & Kouzarides, 2011; Wen et al., 2016) The majority of studies of histone modification focus on their role in the regulation of transcription, but histone modifications can also affect the regulation of other DNA processes, such as repair, replication and recombination.(Bannister & Kouzarides, 2011; Wen et al., 2016) DNA methylation also affects gene transcription, through activation or more typically repression. This chapter will not focus on histone modification but will explore how measures of DNA methylation may be used in the assessment of risk for dementia.

As discussed within the previous chapters of this thesis, the risk factor profile and aetiology of dementia is not completely understood. While several individual genetic and environmental factors have been identified to play a role in the development of dementia, it is thought that interactions between the two may be of key importance. Such interactions may offer some explanation as to the variation in penetrance of genes associated with dementia. For these reasons, the study of epigenetics is therefore of considerable interest in dementia research.

Within the main introduction to the thesis, we described how measures of DNA methylation have been used to estimate an individual's age: DNAm age. More specifically, DNAm age is described as an estimate of one's biological age. As a result, DNAm age has been suggested to be a better measure of risk regarding mortality and age-related disease than chronological age. Differences between

DNAm age and chronological age have been used to give a measure of accelerated ageing, with accelerated biological ageing being provided as a potential explanation as to why some individuals age more successfully than others. This may be the avoidance of age-related conditions or the persistence of features of less advanced age.

Given that age is the most important risk factor for dementia, measures of biological age are of clear interest in understanding dementia risk. If accelerated biological ageing were associated with dementia risk, any factors identified to affect biological ageing would be clear targets for intervention. The study in Section 6.2 therefore aimed to examine the association between well-recognised DNA methylation-based measures of accelerated ageing and incident dementia within the LBC1921.

The study included in Section 6.2 entitled “DNA methylation-based measures of accelerated biological ageing and the risk of dementia in the oldest-old: A study of the Lothian Birth Cohort 1921” by RA Sibbett et al. was published in *BMC Psychiatry* in February 2020. The complete reference is as follows:

Sibbett, RA., Altschul, DM., Marioni, RE., Deary, IJ., Starr, JM., Russ, TC. DNA methylation-based measures of accelerated biological ageing and the risk of dementia in the oldest-old: a study of the Lothian Birth Cohort 1921. BMC Psychiatry 2020, 20: 91.

The author of this thesis was the first author and made the following contributions to the manuscript: contributed to study design, performed data collection for dementia ascertainment, took part in the dementia ascertainment consensus, contributed to statistical analyses and the interpretation of results, led writing of the manuscript and contributed to revisions of the manuscript.

We would note that Drew Altschul contributed to the writing of the statistical methods and results and Riccardo Marioni contributed to the writing of the DNA methylation calculation methods. The competing risk regression models and cumulative incidence graph were completed by the second author – Drew Altschul – with the thesis author completing all other aspects of the statistical analyses. The supplementary materials for this manuscript can be viewed in *Appendix 4,* from page 294. The individual appendices are provided on the following pages:

The references for this paper are included within the published manuscript, in the referencing style of the journal. The references can be seen on page 158 of the thesis.

6.2 DNA methylation-based measures of accelerated biological ageing and the risk of dementia in the oldest-old: A study of the Lothian Birth Cohort 1921

(The published manuscript is included from the next page)

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DNA methylation-based measures of accelerated biological ageing and the risk of dementia in the oldest-old: a study of the Lothian Birth Cohort 1921

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Abstract

Background: Previous studies have demonstrated an association between DNA methylation-based measures of accelerated ageing and age-related health outcomes and mortality. As a disease closely associated with advancing age, we hypothesized that DNA methylation-based measures of accelerated ageing might be associated with risk for dementia. This study therefore aimed to examine the association between four recognised measures of age acceleration and subsequent dementia.

Methods: Study subjects ($n = 488$) were members of the Lothian Birth Cohort 1921. Dementia case ascertainment used data from death certificates, electronic hospital records, and clinical reviews. Venous blood samples were taken at baseline, at age 79 years. DNA methylation and measures of epigenetic age were calculated in accordance with Horvath's epigenetic clock tutorial, using the online calculator (https://dnamage.genetics.ucla.edu/). From these values, four measures of accelerated ageing were calculated: extrinsic epigenetic age acceleration (EEAA), intrinsic epigenetic age acceleration (IEAA), AgeAccelPheno and AgeAccelGrim. Competing risk regression models – with death as a competing risk – were performed to examine the association between each measure of accelerated ageing and incident dementia. *APOE* ε4 status, sex, age, smoking status, history of cardiovascular disease, cerebrovascular disease, hypertension, and diabetes were included as covariates.

Results: None of the multivariate models revealed a positive association between increased epigenetic age acceleration and dementia risk. Across all included models, never-smoking increased risk for dementia (HR 1.69 [1.06, 2.71], $p = 0.03$), and having no *APOE* ε4 alleles reduced risk for dementia (HR 0.44 [0.29, 0.67], $p < 0.001$).

Conclusions: The present study did not demonstrate any consistent association between DNA methylation-based measures of accelerated ageing and dementia in subjects aged over 79 years. Further, larger studies – including separate analyses of dementia subtypes – are required to further investigate the potential association between DNA methylation-based measures of accelerated ageing and dementia.

Keywords: Dementia, DNA methylation, Accelerated ageing, Epigenetic age

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Background

As the global population ages, diseases closely associated with advancing age are projected to increase in number as a result. Dementia is one such disease, the most common cause for which is Alzheimer's disease (AD). As the number of dementia cases increases, so will the economic and social care requirements [1]. Managing the impact of dementia will therefore pose a significant public health challenge. Gaining a comprehensive understanding of the risk factors for dementia is a vital step in addressing this challenge.

It is recognised that both genetic and environmental factors contribute to the development of dementia. There is, however, considerable variability in the risk that one will develop the disease. It is thought therefore, that the aetiology is likely to be a complex interaction between genetic and environmental factors. Epigenetics could be considered to be a bridge between genes and the environment, with exposure to environmental factors giving rise to alterations in gene expression, via epigenetic mechanisms [2]. Unsurprisingly, the study of epigenetics is an area of considerable research interest and it may prove to be important in understanding dementia risk.

Older age is widely recognised to be the most significant risk factor for dementia. However, it is clear that some individuals age more successfully than others, in that, for some, advancing age has less effect on physical robustness, health (and disease) status and cognitive function [3, 4]. The explanation for individual differences in the effect of ageing is also likely to be multifactorial, with genetic, lifestyle and health factors all playing a role [3]. It has been suggested that each individual has a biological or physiological age that may differ from chronological age and is the result of such factors. Furthermore, studies have shown that each individual may have a series of biological ages, depending on the biomarker used to estimate age, suggesting that the biological ageing process may not just vary between individuals, but also within each individual [5].

Patterns of a specific epigenetic modification within the DNA sequence – DNA methylation – have been used in previous studies to calculate estimates of biological age. DNA methylation is one of the most frequently-studied epigenetic marks and occurs with the addition of a methyl group to the DNA molecule, typically at a cytosine nucleotide that precedes a guanine nucleotide – CpG sites [2]. Such estimates of age are typically referred to as the 'epigenetic age' or 'DNAm (DNA methylation) age' and are suggested to reflect both an individual's biological age and their susceptibility to age-related health outcomes [6]. DNA methylation-based estimates of age have been shown to be consistent across biological sample types, including blood and various tissues [6]. Whereas epigenetic age has been shown to correlate highly with chronological age, significant discrepancies between the two are noted at the individual level [6]. Studies comparing chronological age with epigenetic age found that there was an increased risk of all-cause mortality for those exhibiting accelerated ageing – i.e. those who had higher epigenetic age than chronological age – after adjusting for related genetic, health and lifestyle factors [6, 7]. Furthermore, the offspring of persons surviving to 105–109 years of age have been shown to have a lower epigenetic age than age-matched controls [8]. A number of suggested risk factors for dementia have also been shown to be associated with greater age acceleration; poorer physical fitness, lower cognitive ability, lower socioeconomic status, greater body mass index, higher total cholesterol to high-density lipoprotein cholesterol ratios, hypertension and smoking (greater pack-years) have all been shown to be associated with greater age acceleration (calculated using DNA methylation-based measures) [9, 10]. Based on these previous findings, we hypothesized that measures of accelerated biological ageing based on DNA methylation would be a valuable predictor of dementia risk.

This study would consider four recognised DNA methylation-based measures of accelerated ageing: the two first-generation measures of age acceleration – intrinsic epigenetic age acceleration (IEAA) and extrinsic epigenetic age acceleration (EEAA) – and the two novel estimates of age acceleration – AgeAccelPheno (based on PhenoAge) and AgeAccelGrim (based on GrimAge). The rationale for including the older measures was that these have been the most consistently reported in the literature and there is therefore more evidentiary basis that these measures were valid and appropriate for inclusion in our study. The novel measures were included on the basis that these have been shown to be more accurate predictors of mortality, time-to-death and other morbidities than the earlier measures [11, 12].

The earlier measures – IEAA and EEAA – were based on methods for estimating epigenetic age described by Horvath [13] and Hannum et al. [14], respectively, in 2013 [6]. Horvath's epigenetic age estimate is based on DNA methylation at 353 CpGs, while Hannum's epigenetic age estimate is based on DNA methylation at 71 CpGs. Both age acceleration measures compare epigenetic age estimates with chronological age in order to define age acceleration. The age acceleration measures also differ however, in that IEAA is independent of changes in blood cell composition, whereas EEAA incorporates age-related changes in blood cell composition [6]. Whereas the epigenetic age estimates produced using these measures have demonstrated statistically significant associations with age-related conditions, the effect sizes seen have been relatively small [11].

Levine et al. proposed that a new, more successful DNA methylation-based measure of epigenetic age may be developed by using "phenotypic age" as a reference,

rather than chronological age [11]. So-called "phenotypic aging measures" are based on clinical biomarkers (albumin, creatinine, serum glucose, C-reactive protein, lymphocyte percent, mean cell volume, red cell distribution width, alkaline phosphatase, white blood cell count) and age, and had previously been shown to be associated with differences in risk for mortality, physical and cognitive function, facial ageing and life expectancy [11]. In 2018, Levine et al. published the novel measure for epigenetic age, produced by regressing a phenotypic measure of mortality risk on CpGs: DNAm PhenoAge [11].

More recently, Lu et al. published another novel measure of epigenetic age, termed DNAm GrimAge [12]. In a two-step process, the authors began by identifying DNA methylation-based biomarkers of mortality and morbidity including several plasma proteins and smoking pack-years; time-to death was then regressed onto these biomarkers, producing a single composite biomarker of lifespan: DNAm GrimAge [12]. By adjusting the measure for chronological age, the authors produced a measure of age acceleration: AgeAccelGrim [12]. Each of the four measures are in units of year.

Given the differences in how each measure arrives at a calculation of epigenetic age acceleration, and the differences between measures in the accuracy of prediction for other outcomes shown in previous studies, one would not necessarily expect our results to be consistent between age acceleration measures. Because the novel methods have been shown to be more accurate predictors of morbidity and mortality in previous studies, we might expect that these measures would be more accurate in predicting incident dementia.

In summary, we explore the associations between four DNA methylation-based measures of accelerated ageing and $n = 109$ cases of incident dementia from a cohort of $n = 488$ individuals, who were healthy when recruited at age 79 years, and followed-up for approximately 16 years. Given the known association between accelerated ageing and mortality, we recognised the potential for death to affect our findings. Death is therefore considered as a competing risk in our analyses.

Methods

Participants

Participants were members of the Lothian Birth Cohort 1921 (LBC1921), recruited from 1999, with baseline testing at mean age 79 years. The cohort has been described in detail within the literature and an overview will be provided here [15, 16]. All participants were born in 1921, and most had taken part in a general intelligence test at age 11 years – the Scottish Mental Survey 1932 (SMS1932) [17, 18]. The survey was completed within Scottish schools and used a validated test of intelligence. SMS1932 participants were recruited for follow-up in later life, with the aim of investigating the possible determinants of non-pathological cognitive ageing [19]. Five-hundred and fifty relatively healthy and independently living participants, residing mostly in and around the Lothian area of Scotland, enrolled in the study and attended baseline testing. Surviving participants who remained in the study were re-tested at four subsequent test waves; at approximately 83, 87, 90 and 92 years of age [16]. Test waves used questionnaires and in-person testing and collected medical, physiological, genetic, cognitive, psychological and socio-demographic data. Information regarding participants who had died was provided at regular intervals by the General Registrar's Office, Scotland.

Only those participants scoring 24 or higher on the Folstein Mini Mental State Examination (MMSE) [20] at baseline ($n = 539$) were included in the present study. Similarly, those reporting a history of dementia at baseline ($n = 2$) were not included. These exclusions were made in order to minimise the possibility that we were including prevalent cases of dementia in our analyses. Without such exclusions there is the possibility that we could falsely identify an association between epigenetic age acceleration and risk for incident dementia – when we were in fact identifying an association between epigenetic age acceleration and existing dementia. Ethical approval for the study was provided by the Lothian Research Ethics Committee (test waves 1–3) and the Scotland A Research Ethics Committee (test waves 4–5). From wave 4 onwards, participants were asked to provide consent for data linkage and access to health records.

Measures of DNA methylation

Blood samples extracted at wave 1 (mean age 79) were used in the present study. DNA was extracted from whole blood samples at MRC Technology, Western General Hospital, Edinburgh, UK. Methylation typing was performed at the Welcome Trust Clinical Research Facility, Western General Hospital, Edinburgh. DNA samples were bisulphite converted and hybridised to the 12 sample Illumina HumanMethylation450BeadChips using the Infinium Methylation protocol and Tecan robotics.

Extensive quality control was conducted, as reported in Zhang et al., [21] to leave a dataset consisting 470,278 CpG sites from 436 LBC1921 participant observations. Briefly, one sample from each duplicate pair (same sample from the same wave) was removed, along with one sample from each replicate pair (same sample, different analysis set). Samples and CpG sites with low call rates (95% of CpGs and samples with $P < 0.01$) were excluded, as were XY probes.

Following this initial screening process, the raw IDAT files for these 436 individuals underwent a separate

quality control analysis. This was conducted in accordance with the recommended analysis procedure in Hovarth's epigenetic clock tutorial (https://dnamage.genetics.ucla.edu/), to help reduce missing CpG values. Raw DNAm IDAT files were read into R, using minfi, and were normalised using the noob (normal-exponential convolution using out-of-band probes) method, implemented by the preprocessNoob() function. This method estimates background noise from out-of-band probes and removes it for each individual sample; and performs dye-bias normalisation whereby a subset of control probes estimate the dye bias. The getBeta() function of minfi was used to obtain noob-normalised methylation beta values.

Measures of epigenetic age

The online calculator developed by Hovarth (https://dnamage.genetics.ucla.edu/) was used to determine measures of epigenetic age (Intrinsic Epigenetic Age, Extrinsic Epigenetic Age, DNAm GrimAge, and DNAm PhenoAge) from the beta values described above. The age calculator performed a further normalisation process on the LBC1921 methylation data entered into the algorithm. Age acceleration measures were obtained for PhenoAge and GrimAge by extracting residuals from the model of epigenetic age on chronological age.

Intrinsic epigenetic accelerated aging (IEAA), and extrinsic epigenetic accelerated ageing (EEAA) have been described in detail within the literature by Chen et al. [6] IEAA is defined as the residual that resulted from a multivariate regression of epigenetic age – calculated using the Hovarth epigenetic age measure – on chronological age and measures of blood cell counts [6]. EEAA was based on the epigenetic age calculated using the measure described by Hannum et al., with a weighted average of Hannum's age estimate being produced in order to increase the contribution of certain blood cell types (known to change with age) on the age estimation [6]. The resulting age estimate was regressed on chronological age in a univariate model, with EEAA representing the resulting residual variation [6].

Additional variables

Covariates included in the main statistical models were as follows: age, sex, *APOE* ε4 carrier status, ever-smoking status, history of hypertension, history of diabetes and history of either cardiovascular or cerebrovascular disease. Genomic DNA was isolated from participants' venous blood in order to determine *APOE* ε4 status. Participants were classified as carriers if they possessed one or more *APOE* ε4 alleles. Date of birth, sex, smoking history and history of hypertension, diabetes, cerebrovascular, and cardiovascular disease were self-reported by participants at the first wave of testing. Age was calculated as the number of days between date of birth and date of attendance at wave 1 testing. Additional analyses were performed to further investigate the component parts of AgeAccelGrim; additional covariates therefore included the DNAm-based surrogates for seven proteins and smoking pack years (beta-2 microglobulin (DNAm B2M), cystatin-C (DNAm Cystatin C), growth differentiation factor 15 (DNAm GDF-15), plasma activator-inhibitor 1 (DNAm PAI-1), Leptin (DNAm Leptin), adrenomedullin (DNAm ADM), and tissue inhibitor metalloproteinase 1 (DNAm TIMP-1) and DNAm PACKYRS.

It was important to determine the association between chronological age and dementia, before exploring whether DNA methylation-based measures of accelerated aging could be of greater predictive value in assessing dementia risk, hence the inclusion of chronological age in the analyses. Given the narrow-age nature of our cohort, there is little variance in age and we would not expect to observe a statistically significant association between age and dementia; the chronological age variable would not therefore be included in subsequent statistical models if this assumption was confirmed. *APOE* ε4 carrier status was included because of the known association with dementia, particularly as this association had been replicated in earlier studies of this cohort [22]. Smoking status was introduced given the recognised effect that smoking has on DNA methylation [23], and the potential for this to affect the findings. Furthermore, whereas smoking had not been found to be associated with dementia in previous studies of this cohort, it has been reported to be an important risk factor within the literature. A history of hypertension, diabetes and cardiovascular or cerebrovascular disease were included given the potential association with earlier death and dementia. Furthermore, such health outcomes increase with advancing age and so greater epigenetic age could be associated with susceptibility to these conditions [24, 25]. An interaction term for sex and measure of accelerated ageing was included as sex is strongly linked to both AgeAccelPheno and AgeAccelGrim. Whereas other factors – such as age 11 IQ – could be proposed to be associated with dementia [26], such variables have not been shown to be important with regard to dementia risk in this cohort and were not therefore included [22, 27]. Our hypothesis-driven approach, based on previous findings aimed to minimise the inclusion of variables that would not be relevant in this sample, and reduce the possibility of multiple hypotheses testing.

Dementia ascertainment

Dementia case ascertainment in LBC1921 has been described previously in detail [22]. Briefly, cases were ascertained retrospectively, up to age 95 years, based on evidence collected from death certificates, medical records, and a small number of clinical assessments [22]. Death certificates available by the end of June 2016 were

examined for any recording of either dementia or cognitive decline, in any position. For each participant who consented to data linkage and access to records, local electronic hospital records were reviewed and any evidence for dementia or cognitive decline was collected. Prior to 2014, psychiatric records were held on a separate electronic system and diagnoses were supplied to the study in the form of ICD-9 and ICD-10 codes for those who had been in contact with psychiatric services. ICD-9 and 10 codes that were relevant to the dementia ascertainment process are shown in Additional file 1: Figure S1. Latterly, psychiatric records were merged with the general hospital system and accessed as previously described. Data for each consenting participants were accessed using their Community Health Index (CHI) number, a unique identifier specific to each NHS patient in Scotland and recorded at each contact. The last date for data collection from medical records was the 16th of May 2016. Additional evidence was available for a small proportion of participants (n = 26) who underwent clinical review by one of the authors (TCR, JMS), either in the NHS or research setting. Any participant who reported a new diagnosis of dementia at routine LBC1921 follow-up, or any participant for whom a concern was raised regarding cognitive decline, was referred for such clinical assessment. Data from such reviews were collected up to 15th December 2016, when all of the evidence gathered was reviewed and discussed at a final dementia diagnosis consensus meeting (RAS, TCR, JMS). The meeting agreed upon the presence of a diagnosis and the subtype, using a previously described list of criteria for 'probable' or 'possible' dementia diagnosis [22]. Any disagreement was resolved through discussion. To minimise the potential for introducing classification error to the results, possible dementia cases were excluded from the analyses.

Time-to-event variables

The events included in this study are dementia and death, determined as described above. The number of days between the date of attendance at wave 1 testing and date of death gave the 'time to death'. For those who did not die, the censoring time was taken as the number of days between wave 1 testing and a date beyond that last date of data collection for any participant (6500 days after baseline testing). The number of days between the date of attendance at wave 1 testing and the first date that a dementia diagnosis was noted in any of the available sources gave the 'time to dementia'. Where dementia was recorded on a death certificate and no duration was given, and dementia was not recorded in another source, the diagnosis was presumed to predate death by six months. Where the duration was not given, but a diagnosis was recorded in another source, the earliest such date was used to determine the date of onset. If sources recorded both cognitive impairment and dementia, the date of dementia onset was taken as the earliest recording of a dementia diagnosis. If dementia diagnosis was determined based on evidence that did not include a formal diagnosis of dementia, the earliest mention of cognitive impairment was used to date onset (as long as the same record did not specifically note the absence of a dementia syndrome). For participants who remained dementia-free, the 'time to dementia' variable was taken as either the time to date of death or to a date beyond that last date of data collection for any surviving participant (6500 days after baseline testing).

Statistical analysis

The first step in analysing the data was to demonstrate any statistically significant differences ($p < 0.05$) between the group who developed dementia and the group who did not. Univariate analysis – using either the Pearson chi-square or t-test (*IBM SPSS, Version 21*) – was completed for each variable that would be included in the main analyses. The same software was used to calculate the level of correlation between the measures of epigenetic age acceleration. *R* statistical software, (package 'cmprsk' in *R version 3.5.1*) was used to perform all subsequent steps in the analyses.

The main analyses were completed using competing risk regression (CRR) models, in which death was considered a competing risk for dementia. Having been considered in a number of previous studies, the association between age acceleration measures and death would not be a primary focus of this study; incident dementia after age 79 years was the primary outcome to be reported. Death and dementia compete for risk in that they non-independently occur. This changes the risk function that a given variable may have with an outcome. For example, older individuals are likely to both die and get dementia. Two individuals might both die at the same time, before being diagnosed with dementia. One of these individuals would have developed dementia in a few months had they lived, the other would not have developed dementia for several years. In a more standard logistic or Cox model predicting only dementia diagnosis, both individuals would be censored out of the analysis at the time of death, and the information on the competing risk of death is ignored. Competing risk regression models take into account the information from a competing risk and reweights the primary outcome risk in light of competing outcomes. The first CRR regression model (CRR 1) explored the association between age and dementia, with chronological age (at baseline testing) being the only variable included. Chronological age was excluded from subsequent models as it did not prove to be statistically significant in this first model. The second model (CRR 2) examined measures of accelerated aging as a marker of biological ageing; the covariates included in

the model were the given DNA methylation measure of accelerated ageing, sex, *APOE* ε4 carrier status, and a DNA methylation age acceleration and sex interaction term. The interaction term was to be excluded from subsequent models if it did not reach statistical significance. The third model (CRR 3) included these same variables, with the addition of ever-smoking status. The final model (CRR 4) included three additional health outcome variables – history of hypertension, history of diabetes, and history of cardiovascular or cerebrovascular disease. Accelerated ageing, sex and *APOE* ε4 are also included in this model. Smoking status is included if it was statistically significant in model 3.

The main findings of the CRR analyses were supported with cumulative incidence plots for each competing event (dementia and death); these illustrate the time-varying risk of dementia, between covariate levels. The Aalen-Johansen estimator was used to calculate the unbiased estimate of cumulative incidence. In addition to the CRR models, logistic regression models would be completed to establish the associations between variables and dementia, when death outcomes are not considered. The results would be made available within the supplementary materials.

Results

Cohort demographics

The complete LBC1921 cohort included $N = 550$ participants who were recruited and attended baseline testing at age 79 years. The participants eligible for these analyses did not include those who had an MMSE score of less than 24 at baseline ($n = 9$), those without a valid MMSE score at baseline ($n = 2$), those who reported a history of dementia at baseline ($n = 2$), and those with no follow-up data available for the purpose of dementia ascertainment ($n = 41$). For one participant, the calculated time to dementia suggested that dementia predated attendance at wave 1 testing and they were also excluded from the study sample. Of those who were eligible for inclusion in this study ($n = 495$), a consensus diagnosis of probable dementia was agreed for $n = 109$ and a consensus diagnosis of possible dementia was agreed for $n = 7$. Those with possible dementia were excluded from the analyses, resulting in a final study sample of $n = 488$ participants. Exclusions were made on a step-wise basis as shown in Fig. 1, with a total of $n = 62$ participants excluded from these analyses. Over half of the included participants were female (57.4%, $n = 280$) and over three-quarters were known to be deceased by the 30th of June 2016 (85.9%, $n = 419$). Of those who were deceased, 79.0% ($n = 331$) had died without a diagnosis of dementia. Descriptive statistics for those included and excluded are shown in Table 1, alongside group comparison statistics for those with and without dementia.

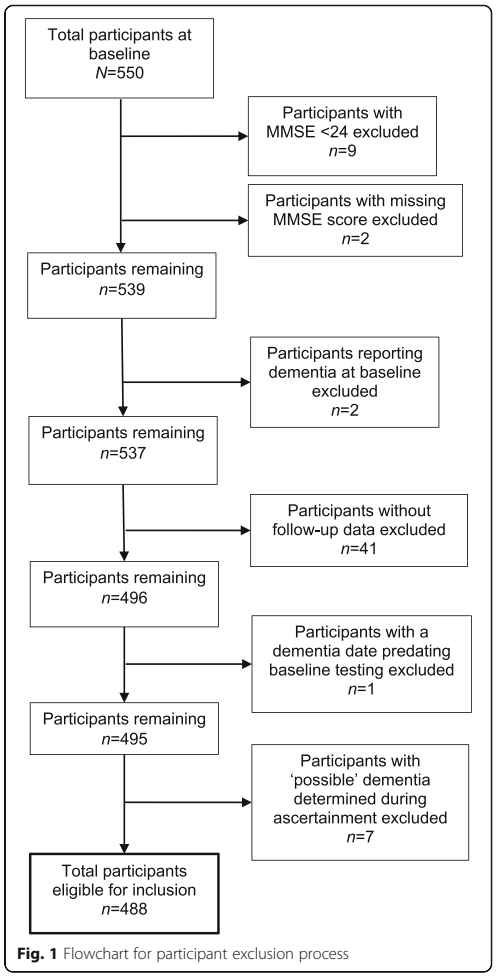

Fig. 1 Flowchart for participant exclusion process

Dementia group comparison

Univariate analyses demonstrated little difference between those eligible participants who developed dementia and those who did not. Positive ever-smoking status ($p < 0.001$), greater smoking pack years ($p = 0.016$), increased DNAm GrimAge age acceleration (AgeAccelGrim) ($p < 0.001$) and increased extrinsic epigenetic accelerated ageing (EEAA) ($p = 0.047$) reduced the risk for dementia, while positive *APOE* ε4 ($p < 0.001$) carrier status increased the risk for dementia.

Time-to-event variables

The mean time to dementia and the mean time to death for the eligible study sample were 3371.0 (SD: 1724.7)

Table 1 Study sample demographics and univariate analyses

	Eligible Participants ($n = 488$)		Group Comparison p value (chi-square or t-test)	Excluded Participants ($n = 62$)
	Dementia ($n = 109$)	No Dementia ($n = 379$)		
Age	$n = 109$	$n = 379$		$n = 62$
-mean age in years (SD)	79.04 (0.55)	79.08 (0.59)	0.540	79.09 (0.53)
Sex	$n = 109$	$n = 379$		$n = 62$
% female	62.4%	55.9%	0.230	58.1%
Living or deceased	$n = 109$	$n = 379$		$n = 62$
% deceased	80.7%	87.3%	0.081	29.0%
MMSE score at baseline	$n = 109$	$n = 379$		$n = 60$
mean score (SD)	28.10 (1.64)	28.33 (1.46)	0.156	27.27 (2.67)
APOE ε4 carrier status	$n = 109$	$n = 373$		$n = 61$
% carrier *APOE* ε4	41.3%	22.5%	< 0.001	27.9%
Age 11 IQ (standardised)	$n = 101$	$n = 339$		$n = 53$
mean score (SD)	100.19 (16.18)	100.22 (14.53)	0.982	98.21 (15.63)
Smoking status	$n = 108$	$n = 379$		$n = 62$
% ever smoker	42.6%	61.7%	< 0.001	50.0%
Lifetime smoking packs*	$n = 108$	$n = 376$		*n = 58*
mean total packs (SD)	4359.83 (8016.04)	6616.27 (8740.85)	0.016	*3880.78 (6609.45)*
History of hypertension	$n = 108$	$n = 375$		$n = 61$
% positive history	35.2%	41.9%	0.212	41.0%
History of diabetes	$n = 109$	$n = 379$		$n = 62$
% positive history	4.6%	5.8%	0.624	1.6%
History of cardiovascular or cerebrovascular disease	$n = 104$	$n = 373$		$n = 59$
% positive history	28.9%	28.2%	0.889	22%
EEAA	$n = 88$	$n = 295$		$n = 53$
mean (SD)	0.37 (7.27)	2.35 (8.41)	0.047	−0.27 (6.68)
IEAA	$n = 88$	$n = 295$		$n = 53$
mean (SD)	−0.64 (5.60)	0.80 (6.84)	0.074	0.59 (5.13)
AgeAccelGrim	$n = 88$	$n = 295$		$n = 53$
mean (SD)	−1.30 (4.14)	0.66 (4.64)	< 0.001	−0.39 (4.91)
AgeAccelPheno	$n = 88$	$n = 295$		$n = 53$
mean (SD)	0.21 (6.56)	1.75 (7.63)	0.087	0.53 (6.55)

Note. *Lifetime smoking packs calculated by number of packs (20 cigarettes) smoked per year multiplied by the number of years smoking

days and 3618.9 (SD: 1829.3) days, respectively. The mean time to death for deceased participants ($n = 419$) was 3144.5 days (SD: 1517.5). For the participants who survived, the 'time to death' variable value was taken as the number of days between baseline testing and a date beyond the last date of data collection for any participant; 6500 days. The mean time to dementia for those who developed dementia ($n = 109$) was 3535.7 days (SD: 1283.3). For the participants who remained free of dementia ($n = 379$), 'time to dementia' variable value was taken either as the time to death for those who died ($n = 331$, mean = 2863.0 days, SD: 1469.4), or time to a date beyond the last date of data collection for any participant for those who survived ($n = 48$; 6500 days).

Main analyses

The first competing risk model (CRR 1), included a single variable – chronological age (at baseline). In our study cohort ($n = 488$), chronological age at baseline did not demonstrate a statistically significant association with incident dementia (HR 1.00 [95% CI 1.00, 1.00], $p = 0.61$). Chronological age was not, therefore, included in subsequent competing risks models. The variables included in each model are shown in Fig. 2.

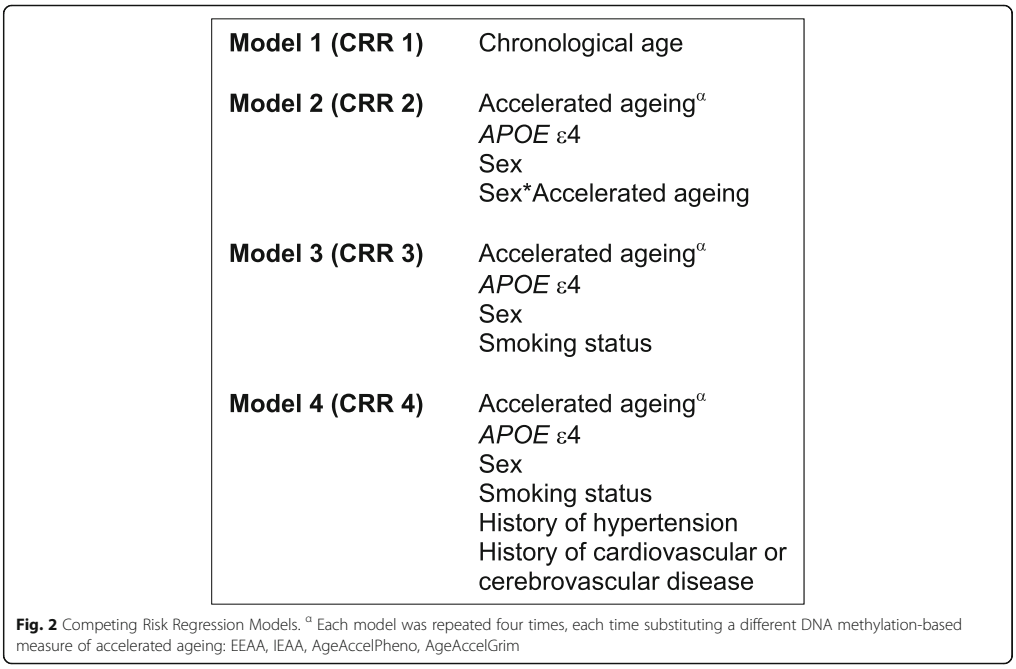

Fig. 2 Competing Risk Regression Models. [a] Each model was repeated four times, each time substituting a different DNA methylation-based measure of accelerated ageing: EEAA, IEAA, AgeAccelPheno, AgeAccelGrim

All subsequent models included a measure of accelerated ageing and each was completed four times – using EEAA, IEAA, AgeAccelPheno and AgeAccelGrim, in turn, as the measure of accelerated ageing (CRR models X_{EEAA}, X_{IEAA}, $X_{AgeAccelPheno}$ and $X_{AgeAccelGrim}$ respectively). The results for models 2–4 (for each age acceleration measure) are shown in Table 2. CRR 2 included four covariates: measure of accelerated ageing, sex, *APOE* ε4 carrier status and a sex by measure of accelerated ageing interaction term. In CRR $2_{AgeAccelGrim}$, where AgeAccelGrim was used as the measure of accelerated ageing, greater accelerated ageing was associated with lower risk of incident dementia (HR 0.89 (0.81, 0.97), $p = 0.009$). In the same model, carrying no *APOE* ε4 alleles was associated with a lower risk for incident dementia (HR 0.45 (0.30, 0.69), $p < 0.001$). A relationship between sex and incident dementia was not demonstrated (HR 0.84 (0.53, 1.34), $p = 0.46$). Similarly, the association between the sex by AgeAccelGrim interaction term and dementia did not reach statistical significance (HR 1.05 (0.94, 1.18), $p = 0.38$). When model 2 was repeated, using IEAA, EEAA and AgeAccelPheno (CRR 2_{IEAA}, 2_{EEAA} and $2_{AgeAccelPheno}$ respectively), the association between accelerated ageing and dementia did not reach statistical significance. *APOE* ε4 negative carrier status associated with a lower risk for incident dementia in each of the three models. CRR 3 included the same covariates as model 2, with the addition of smoking status (ever smoker versus never smoker). Given its lack of statistical significance, the sex by age acceleration interaction term was dropped from subsequent models. In CRR $3_{AgeAccelGrim}$, the association between accelerated ageing (AgeAccelGrim) and dementia no longer reached statistical significance (HR 0.95 (0.89, 1.01), $p = 0.09$). Lifelong non-smoking (never smoking status) was associated with a higher risk of incident dementia (HR 1.69 (1.06, 2.71), $p = 0.03$). Negative *APOE* ε4 status continued to be associated with a lower risk of dementia (HR 0.44 (0.29, 0.67), $p < 0.001$). In CRR 3_{IEAA}, 3_{EEAA} and $3_{AgeAccelPheno}$ there was no statistically significant relationship between accelerated ageing and dementia. Lifelong non-smoking status was associated with a higher risk of incident dementia in all three models; negative *APOE* ε4 carrier status was again associated with a lower risk of incident dementia in the three models. In CRR $4_{AgeAccelGrim}$ – which included history of hypertension, diabetes, cardiovascular or cerebrovascular disease as covariates – only *APOE* ε4 carrier status (HR 0.41 (0.27, 0.64), $p < 0.001$) and smoking status (HR 1.69 (1.05, 2.73), $p = 0.03$) reached statistical significance, with negative *APOE* ε4 carrier status reducing risk for incident dementia and never-smoking status increasing the risk for incident dementia. The same two variables reached statistical significance for the models including EEAA, IEAA and AgeAccelPheno as measures of accelerated ageing.

Table 2 Competing risk regression analyses results for EEAA, IEAA, AgeAccelPheno and AgeAccelGrim

	Hazard Ratios (95% Confidence Interval) for Probable Dementia											
	Results for EEAA			Results for IEAA			Results for AgeAccelPheno			Results for AgeAccelGrim		
	Model 2 (n = 383)	Model 3 (n = 382)	Model 4 (n = 371)	Model 2 (n = 383)	Model 3 (n = 382)	Model 4 (n = 371)	Model 2 (n = 383)	Model 3 (n = 382)	Model 4 (n = 371)	Model 2 (n = 383)	Model 3 (n = 382)	Model 4 (n = 371)
Measure of age acceleration	0.96 (0.92, 1.00)	0.98 (0.95, 1.01)	0.98 (0.95, 1.01)	0.97 (0.92, 1.02)	0.98 (0.95, 1.01)	0.98 (0.95, 1.01)	0.96 (0.93, 1.00)	0.99 (0.96, 1.02)	0.99 (0.96, 1.03)	0.89 (0.81, 0.97)	0.95 (0.89, 1.01)	0.95 (0.89, 1.01)
Sex (female)	0.92 (0.58, 1.44)	0.87 (0.55, 1.40)	0.87 (0.53, 1.41)	1.02 (0.66, 1.59)	0.93 (0.60, 1.44)	0.94 (0.56, 1.47)	1.06 (0.68, 1.63)	0.97 (0.63, 1.49)	0.97 (0.62, 1.52)	0.84 (0.53, 1.34)	0.83 (0.51, 1.36)	0.84 (0.51, 1.38)
APOE ε4 (non-carrier)	0.43 (0.28, 0.65)	0.42 (0.28, 0.64)	0.40 (0.26, 0.60)	0.43 (0.28, 0.67)	0.43 (0.28, 0.65)	0.40 (0.26, 0.61)	0.43 (0.28, 0.67)	0.43 (0.28, 0.65)	0.40 (0.26, 0.61)	0.45 (0.30, 0.69)	0.44 (0.29, 0.67)	0.41 (0.27, 0.64)
Age acceleration by Sex interaction term	1.03 (0.97, 1.09)	–	–	1.01 (0.95, 1.08)	–	–	1.04 (0.98, 1.10)	–	–	1.05 (0.94, 1.18)	–	–
Smoker (never)	–	2.00 (1.30, 3.07)	1.97 (1.27, 3.06)	–	2.01 (1.31, 3.09)	1.98 (1.28, 3.07)	–	2.02 (1.30, 3.14)	2.00 (1.27, 3.17)	–	1.69 (1.06, 2.71)	1.69 (1.05, 2.73)
History of hypertension	–	–	0.73 (0.47, 1.15)	–	–	0.75 (0.48, 1.17)	–	–	0.74 (0.47, 1.16)	–	–	0.71 (0.45, 1.12)
History of diabetes	–	–	1.24 (0.44, 3.44)	–	–	1.23 (0.45, 3.40)	–	–	1.22 (0.44, 3.42)	–	–	1.20 (0.44, 3.30)
History of cardiovascular or cerebrovascular disease	–	–	0.75 (0.44, 1.28)	–	–	0.74 (0.44, 1.27)	–	–	0.74 (0.44, 1.27)	–	–	0.75 (0.44, 1.27)

Each model was repeated as a logistic regression model, with probable dementia as the outcome. In these analyses – where death was not considered – the association between AgeAccelGrim and dementia reached statistical significance in models 2 and 3 ($p < 0.05$) and approached significance in model 4 ($p = 0.06$). In each case, greater age acceleration reduced the risk for subsequent dementia. The association between AgeAccelPheno, EEAA, IEAA and dementia was not statistically significant in any model. Being a non-carrier for the *APOE* ε4 allele was associated with a reduced risk for dementia in every model ($p < 0.001$). Being a never-smoker increased the risk for dementia in every model where it was included ($p < 0.05$). The complete results for the logistic regression are available in Additional file 2: Table S1.

Components of AgeAccelGrim

Given that the association observed between AgeAccelGrim and dementia was the only significant finding regarding the age acceleration measures when examined using competing risk regression analyses (CRR $2_{\text{AgeAccelGrim}}$), and that the direction of association was opposite to what we might have expected, we wished to investigate it further. Based on the change in statistical significance observed following the introduction of a smoking variable, we hypothesized that the association seen had been related to the smoking component of the age acceleration measure. By separating out the individual components of AgeAccelGrim, we were able to look at the association between the DNA methylation-based surrogate biomarker for smoking pack years and dementia on its own to see if any association we were seeing for the measure overall was mirrored in what was observed for this component. The components on which the AgeAccelGrim measure was based were therefore considered in turn. Model 2 was repeated eight times, each time substituting a component of the measure for AgeAccelGrim. The components included DNA methylation-based surrogate markers for smoking pack years (DNAm PACKYRS) and seven plasma proteins – beta-2 microglobulin (DNAm B2M), cystatin-C (DNAm Cystatin C), growth differentiation factor 15 (DNAm GDF-15), plasma activator-inhibitor 1 (DNAm PAI-1), Leptin (DNAm Leptin), adrenomedullin (DNAm ADM), and tissue inhibitor metalloproteinase 1 (DNAm TIMP-1). Each was entered into a competing risk regression model along with *APOE* ε4 carrier status and sex. An interaction term was not included given that it was not previously found to be statistically significant. Only the association between the DNAm PACKYRS component and dementia reached statistical significance (HR: 0.97 [0.95, 0.99], $p = 0.007$). The complete results for these component analyses are provided in Additional file 3: Table S2.

These analyses were again repeated as logistic regression analyses. The association between DNAm PACKYRS and dementia once again reached statistical significance ($p < 0.05$). The complete results for these analyses are provided in Additional file 4: Table S3.

Cumulative incidence graphs

Figure 3 shows cumulative incidence plots for the two competing events: dementia and death. The general direction of the cumulative incidence plot does seem to support the direction of the association observed between AgeAccelGrim and dementia in CRR $1_{\text{AgeAccelGrim}}$, with increased risk for dementia for those with lower levels of age acceleration. Based on the figure, it would appear that the reversal and divergence of the association between age acceleration and dementia begins 10 years after baseline, when subjects are aged approximately 89 years. In contrast with the unclear pattern demonstrated for dementia, the cumulative incidence plot indicated a greater risk for death for those with highest levels of accelerated ageing (calculated using AgeAccelGrim in our study) compared with those with lowest levels of age acceleration. This result reinforced the patterns of association shown in previous studies, where higher age acceleration was associated with a greater risk of mortality [7].

Correlation between measures of age acceleration

In this study cohort, positive correlations were shown between each of the four measures of epigenetic age acceleration ($0.259 \leq r \leq 0.439$) (Additional file 5: Table S4). The strongest correlation was seen between EEAA and AgeAccelGrim ($r = 0.439$), but this was only marginally greater than the correlations observed between EEAA and AgeAccelPheno ($r = 0.424$), AgeAccelPheno and AgeAccelGrim ($r = 0.416$) and AgeAccelPheno and IEAA ($r = 0.403$). The weakest correlation was seen between IEAA and AgeAccelGrim ($r = 0.259$); this may reflect the fact that IEAA is based on Horvath's original measure which was developed using multiple tissue types, while AgeAccelGrim was developed using blood methylation data alone [12].

Discussion

This study aimed to determine whether DNA methylation-based measures of accelerated ageing were associated with risk for dementia in the oldest-old. The results did not demonstrate any consistent relationship between DNA-based measures of accelerated ageing and incident dementia. The initial findings suggested that increased AgeAccelGrim may be associated with decreased risk for incident dementia in those aged over 79 years. However, on subsequent testing the results indicated that smoking might explain this association, and more specifically, that it was likely to be the collinear relationship between GrimAge and smoking that had given rise to this finding.

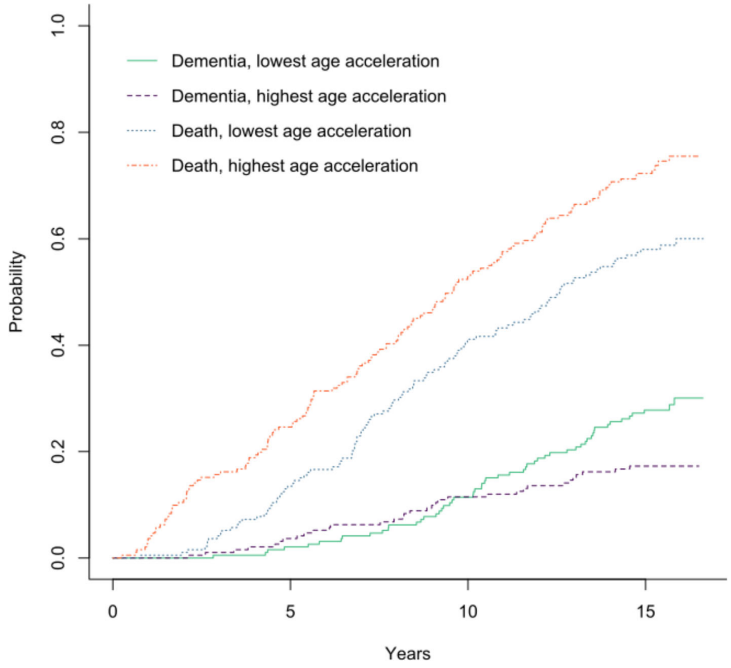

Fig. 3 Cumulative incidence plots for AgeAccelGrim: death and dementia. *Note.* The two groups for each event (death and dementia) were formed from the half of participants with higher age acceleration levels who experienced that event and the half with lower age acceleration levels that experienced that same event. A steeper rising line indicates that individuals in this group were at greatest risk for the event, e.g., in general, individuals were more at risk for death than dementia

Comparison with previous findings

Whereas a number of studies have suggested an increased risk for dementia associated with DNA methylation patterns at specific loci or with increased DNA methylation age, we are not aware of any studies that specifically examined the relationship between methylation-based measures of accelerated ageing and dementia [28–31]. For this reason, it is not possible for us to directly compare our findings. We can however consider previous notable findings relating DNA methylation and dementia.

Investigating how a change in the expression of DNA alters the risk of developing the dementia is of clear value in both furthering our understanding of the pathogenesis of the disease and in guiding the development of effective treatments. To this end, several studies have considered how specific changes in DNA methylation affect one's risk of developing dementia, with notable epigenetic changes being observed between subjects with dementia and controls [30]. Recent studies have indicated that DNA methylation may indeed contribute to the pathogenesis of dementia. For example, the *APOE* gene (variants of which are recognised to be important in dementia risk) has been shown to be differently methylated in Alzheimer's disease (AD) [32]. Specifically, reduced methylation levels at a well-defined CpG island within the fourth exon of the *APOE* gene in brain tissue were observed in AD subjects when compared with controls; these differences in methylation levels were observed in both the hippocampus and frontal lobe regions of the brain, where AD pathophysiological changes were abundant [32]. Furthermore, DNA methylation levels were increased in the presence of an *APOE* ε4 allele in controls, but not in AD subjects [32]. Studies have also reported changes in DNA methylation, in relation to AD, at several other genes [30]. In 2014, De Jager et al. and Lunnon et al. published the results of two large-scale epigenome-wide association studies (EWAS) in Alzheimer's disease [33–35]. Differences in methylation were reported at a number of loci, including four that were independently identified in both studies: *ANK1, RPL13, C10orf54-CDH23* and *RHBDF2* [33–35]. A 2016 systematic review by Wen et al. described studies reporting higher methylation levels of several genes (observed in peripheral blood cells or brain tissue of AD patients)

including *OPRK1*, *BDNF*, *UQCRC1*, *HTERT*, *TREM2*, *TBX2AR*, *SORBS3*, *SPTBN4*, and *CREB* promotors and the synaptophysin gene [30]. Lower levels of methylation of a number of other genes were reported in the blood or brain tissues of AD subjects, including *PIN1*, *FAAH*, *ALOX5*, *DR4*, *TNFA*, *COX-2*, *NF-kβ*, *CRTC1* and *S100A2* [30]. Other studies have also suggested differences in global DNA methylation – i.e. the overall level of methylcytosine within the genome – between AD subjects and controls [30]. While the results described are not consistent across all studies, the evidence would seem to support the hypothesis that DNA methylation plays an important role in dementia.

Findings relating to DNAm age and dementia are of particular relevance here given the direct relationship between DNA methylation-based age and measures of accelerated ageing. Levine at al. (2018) tested for an association between pathologically determined AD and DNAm PhenoAge in the dorsolateral prefrontal cortex [11]. They found that when comparing same-age individuals, the dorsolateral prefrontal cortex appeared more than one year older in those with AD [11]. Furthermore, DNAm PhenoAge was associated with typical neuropathological signs of AD including neurofibrillary tangles, amyloid load and neuritic plaques [11]. A previous Swedish longitudinal study examined the association between DNAm age (calculated using Hovarth's epigenetic clock) and dementia and the authors reported that increased DNAm age was a statistically significant predictor for dementia ($\beta = 0.16$, $p = 0.019$) [28]. This was however a small study, with $n = 11$ dementia cases, and the logistic regression analyses were adjusted for gender only [28]. DNAm age was calculated at a time when $n = 6$ of these cases were already diagnosed, and $n = 5$ were diagnosed in the following four years [28]. We must therefore consider whether this study describes an association between advanced DNAm age in existing dementia, as opposed to increased DNAm age predicting dementia.

Based on these previous findings, one might have expected that the present study would have identified a similar association between accelerated ageing and dementia. There may be a number of reasons why this was not the case, and these are discussed within the context of the mechanisms and limitations of the study below.

Mechanisms

Whereas chronological age is widely recognised to be associated with dementia, this was not the case in our study cohort. It is probable that the absence of such an association in this study can be attributed to the use of a narrow-age cohort. In studies of methylation age and dementia using participants of a wider age-range, chronological age would likely be an important covariate for inclusion. As has been shown previously in this study cohort [22, 27], the presence of at least one *APOE* ε4 allele was related to an increased risk of incident dementia. As such, it remains an important covariate for inclusion in studies of dementia in those aged over 80 years.

The results of the analyses included in this study did not find any consistent relationship between DNA-based measures of accelerated ageing and incident dementia. Only one model yielded a result for accelerated ageing that reached statistical significance at conventional levels. Indeed, this result contradicted the hypothesised results, with increased accelerated ageing (AgeAccelGrim) being associated with a reduced risk for incident dementia. This finding would contradict those previous studies that have shown an association between increased methylation age and greater risk for developing age-related health outcomes [6, 7]. Given the unexpected direction of this association, one must consider the robustness of this finding. Given that the magnitude of the association was relatively small and was not observed in any subsequent model it may be that this was a chance finding that does not demonstrate a true association. In this study, the introduction of a smoking variable meant that the association between AgeAccelGrim and dementia no longer reached statistical significance. Such a finding might be expected given that GrimAge is built, in part, on smoking related data and the two are extremely collinear, correlating at approximately 0.9. We note that the direction of association between smoking and dementia in this study is the same as that for AgeAccelGrim and dementia. We therefore suggest that an association between smoking and dementia seems to explain the observed relationship between AgeAccelGrim and dementia. Our finding that the DNA methylation-based marker for smoking pack years was the only component of AgeAccelGrim associated with dementia in this cohort provided further evidence for this explanation.

In these analyses, a lifelong history of non-smoking was associated with an increased risk for dementia. While the direction of this association may defy the expected and contradict previous studies, it is in line with a general pattern observed in this cohort of individuals aged over 79 years [22]. A previous study of the LBC1921 has also demonstrated an increased risk for dementia after age 79 years with greater lifetime physical activity, and a decreased risk for dementia for those with a history of hypertension at age 79 years [22]. Similarly, other factors that have previously been shown to increase risk for dementia in studies of earlier old age have been found to have no effect on risk in this cohort of participants aged over 79 years [22, 27]. In a previous study of physical fitness and dementia in the LBC1921, a positive history of ever-smoking was observed to decrease risk for dementia, but in that study the association did not reach statistical significance [27]. It would therefore appear that the statistical significance of the

association between ever-smoking and dementia within our cohort is dependent on the covariates included in the analyses. It is possible that the direction of the association between age acceleration and dementia observed in these analyses simply reflects of the direction of the association between smoking and dementia in this this cohort, but we acknowledge that the inconsistency in statistical significance means that we must treat the association observed in this study with caution. We must also consider whether survival to age 79 years or recruitment at age 79 years have influenced our smoking-related findings. It is possible that those individuals who were most likely to have experienced greater risk for dementia as a result of previous or current smoking had died earlier to age 79 years, leaving only those who would remain unaffected or in some way 'resistant' to the negative effects of smoking. Similarly, we must consider the possibility that those who would have been more likely to develop dementia a result of their smoking history had done so prior to recruitment age and would not therefore have been eligible to enrol in the LBC1921 study. Given that susceptibility for lung disease is variable between persons [36], one might suggest that there is a similar variability in susceptibility for dementia and those who remained dementia free at age 79 would be those with a reduced susceptibility, giving rise to an apparent reduction in risk for smokers.

Implications

Without any consistent results it is difficult to draw any comparisons between the age acceleration measures considered in this study, and how useful each might be in establishing risk for incident dementia. Furthermore, the lack of positive findings regarding dementia in the present study limits the clinical implications specific to dementia. There is a clear requirement for further study in this field; a full appreciation of the role of DNA methylation and DNA methylation-based measures of accelerated ageing in dementia could be of considerable value in furthering our understanding of the risks for dementia and identifying potential targets for risk reduction. Our null finding might initially suggest that future similar studies were not required. Given some of the limitations of our study cohort however, we cannot assume that our study answers this research question conclusively, particularly given that this has not been investigated previously within the literature. Our suggestion for larger studies would be to overcome the potential limitations of our study that may have given rise to the null finding. A stand-alone study can rarely be taken as conclusive evidence and additional studies would therefore either add strength to, or refute, our null finding.

Strengths and limitations

The study cohort used in these analyses has a number of strengths. The LBC1921 is a narrow-age cohort of persons aged 79 years of age at baseline; this means that the study does not suffer from the major confounding effect of chronological age. As such, the cohort is suited to the study of dementia in the oldest-old. Given the homogeneous nature of the cohort participants, confounding errors resulting from age, ethnic, cultural and geographical variability would be unlikely. Participants have taken part in a detailed longitudinal follow-up procedure, and death ascertainment for the cohort is complete. Previously published assessments of validation have shown the dementia ascertainment methods used in this study to be effective and incidence rates to be comparable with expected rates for the cohort [22]. We cannot however exclude the possibility of missed or misclassified cases of dementia in our cohort. In particular, a limitation of our study is the potential that we missed cases of preclinical or prodromal dementia in participants who died prior to developing clinical dementia. In addition to this, it is possible that cases of preclinical or prodromal dementia present at the time we concluded our ascertainment would have gone on to develop dementia after that date.

The indication of a possible reverse association (to that which was expected) for AgeAccelGrim, combined with the surprising association with never smoking (in addition to those unusual associations observed in previous manuscripts), could suggest a cohort effect; it is possible that something specific about this study sample – such as a survivor bias, or something else about the nature of recruitment – may have influenced the results.

A p value of 0.05 was used to determine significance for all models. We did not therefore specifically compensate for potential erroneous inferences arising from multiple testing.

Whereas the LBC1921 is a detailed cohort, it is however limited in size. Studies of DNA methylation-based measures of accelerated ageing and dementia within larger cohorts are required to provide further evidence in this field. As noted above, there were insufficient numbers of eligible study subjects to further investigate whether DNA methylation age mediates the risk of smoking. This study cohort did not have a sufficient number of confirmed cases of dementia of the Alzheimer's type to allow for a specific analysis of this outcome. Again, larger studies with subjects who had confirmed dementia aetiology would allow for such analyses.

Another strength of this study was the inclusion of death as a competing risk. We hypothesised that death could affect the results, given the recognised association between age acceleration and mortality. When we repeat model $2_{\mathrm{AgeAccelGrim}}$ as a simple Cox regression analysis (without death as a competing risk), the effect size for AgeAccelGrim was reduced and did not reach statistical significance (HR 0.99 (0.93, 1.06)).

In order to complete our study using a competing risks type analyses, it was necessary to have 'time to event' variables, including a 'time to dementia' for those who developed the condition during the follow-up period. We have described within the methods the manner by which such estimates were determined for these analyses. We must however recognise the uncertainty that exists regarding the accuracy of this estimate. The nature of dementia and the often gradual onset mean that it is difficult to pin-point an exact date of onset. Furthermore, the variability in how each individual perceives their own symptoms and the differing stages at which one may present for cognitive assessment mean that when diagnoses are ascertained from records, time of onset may be even harder to determine. Depending on the source of data available for dementia ascertainment, the date of diagnosis was not always listed, making it even more difficult to calculate a time to dementia estimate. In this study, the methods for calculating the time to dementia aimed to provide the most accurate estimate that was possible using the available information, but the potential for inaccurate estimates to have affected the results is acknowledged.

Finally, while we must consider the potential for inaccuracy in self-reported smoking data. This is however less relevant in this study given the accuracy of the DNA methylation based marker for smoking.

Conclusion

In conclusion, the present study did not demonstrate any consistent association between DNA methylation-based measures of accelerated ageing and dementia in subjects aged over 79 years. Further, larger studies – including analyses of separate dementia subtypes – are required to further investigate the potential association between DNA methylation-based measures of accelerated ageing and dementia.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12888-020-2469-9.

Additional file 1: Figure S1. ICD-9 and ICD-10 codes relevant to dementia ascertainment.

Additional file 2: Table S1. Logistic Regression Analyses Results for EEAA, IEAA, AgeAccelPheno and AgeAccelGrim.

Additional file 3: Table S2. Competing risk regression models for components of AgeAccelGrim.

Additional file 4: Table S3. Logistic regression models for components of AgeAccelGrim.

Additional file 5: Table S4. Pearson correlations for epigenetic age acceleration measures in LBC1921.

Abbreviations

AgeAccelGrim: Age acceleration calculated from GrimAge; AgeAccelPheno: Age acceleration calculated from PhenoAge; *APOE* ε4: Apolipoprotein E ε4; CHI: Community Health Index; CI: Confidence Interval; CRR: Competing risk regression model; DNA: Deoxyribonucleic Acid; DNAm: DNA methylation; EEAA: Extrinsic Epigenetic Age Acceleration; GrimAge: DNA methylation age, calculated using the GrimAge procedure; HR: Hazard Ratio; IEAA: Intrinsic Epigenetic Age Acceleration; LBC1921: Lothian Birth Cohort 1921; MHT: Moray House Test; MMSE: Mini Mental State Examination; PhenoAge: DNA methylation age, calculated using the PhenoAge procedure; SD: Standard Deviation; SMS1932: Scottish Mental Survey 1932

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Authors' contributions

Authors made the following contributions: study design (RAS, RM, IJD, TCR, JMS), data collection for dementia ascertainment (RAS, TCR), clinical assessment in NHS or research setting (TCR, JMS), dementia ascertainment consensus (RAS, TCR, JMS), completed statistical analyses (DMA), contributed to statistical analyses (RAS), interpreted results (RAS, DMA, JMS), led writing of the manuscript (RAS), contributed to the writing of the statistical methods and results (RAS, DMA), contributed to the writing of the DNA methylation calculation methods (RAS, RM), manuscript revision (RAS, RM, DMA, IJD, JMS, TCR), obtained study funding (IJD, JMS). All authors read and approved the final manuscript.

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The funding body did not contribute to the design of the study or the collection, analysis, or interpretation of data, or in writing the manuscript.

Availability of data and materials

The data utilised and described within this study are available on request from the Lothian Birth Cohort Study, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh. The data are not publically available due to them containing information that might compromise participant confidentiality and consent.

Ethics approval and consent to participate

The Lothian Research Ethics Committee provided ethical approval for LBC1921 test waves 1–3 (LREC/1998/4/183, LREC/2003/7/23, 1702/98/4/183) and the Scotland A Research Ethics Committee provided ethical approval for the LBC1921 test waves 4 and 5 (10/MRE00/87, 10/MRE00/87). From wave 4, attending participants provided written consent for data linkage and access to health records.

Consent for publication

Not applicable.

Competing interests

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Publisher's Note

6.3 Chapter summary and conclusions

Our study did not find any consistent association between DNA methylation-based measures of accelerated ageing and dementia in those aged over 79 years. Increased age acceleration (AgeAccelGrim) – based on the GrimAge estimate of epigenetic age – was observed to be associated with a reduced risk for dementia in a single model but following further examination we concluded that this result was likely to be explained by an association between smoking and dementia. In this study, a history of never-smoking was found to be associated with an increased risk for dementia. Once again, this is a change from the pattern of risk for smoking that is described in younger cohorts. It is however, in line with other risk factors for dementia in LBC1921 that have shown a reversal in the direction of association, from those described in early old age.

As outlined within the study discussion, our study was subject to a number of limitations, such as our having inadequate numbers of dementia cases of specific aetiologies in order to do separate analyses for each. We also note that in our analyses investigating AgeAccelGrim, we included a smoking variable. Within the study, we report the high levels of correlation between the two and by including both in the model we therefore introduce collinearity. This is perhaps unsurprising given that smoking related data is one component of GrimAge. As noted in previous chapters, by including collinear variables in a regression model, the statistical significance of those colinear variables is undermined and one cannot trust the observed *p* values for each. With this in mind, we might question whether the introduction of a smoking variable allows us to make inferences regarding the nature of the association as we do within the paper. While this particular analysis may have this limitation, we follow it up with analyses examining the components of AgeAccelGrim (without an additional smoking variable), and this confirms our

suspicion that the association between AgeAccelGrim and dementia is explained by smoking status.

Our study considered measures of age acceleration at a single time point – at age 79. As such, we consider the DNA methylation-based measures of biological age acceleration as a static entity, whereas in reality it is subject to change with time and age.(Bjornsson et al., 2008; Wang et al., 2018) Studies of monozygotic twins have demonstrated the increasing divergence in methylation patterns with advancing age.(Fraga et al., 2005) Observed long-term differences in epigenetic modifications are suggested to be explained by internal and external factors such as smoking, diet and physical activity.(Fraga et al., 2005) It follows that as one ages, the more time there is for an individual to be influenced by factors affecting the epigenome. While one might consider epigenetic modifications in advanced age to be an accumulation of influences and events from across the life course, one must also consider the possibility for acute changes to result in short-term changes in DNA methylation. For example, one previous study has indicated that alcohol intoxication can give rise to short-term changes in DNA methylation.(Koller et al., 2019) Another study demonstrated an increase in DNA methylation ten minutes after a social stress test, followed by a decrease in methylation ninety minutes later.(Unternaehrer et al., 2012) Such findings might therefore suggest that it is possible for short-term changes close to baseline testing to have affected DNA methylation-based measurements in LBC1921. While most studies of DNA methylation-based epigenetic clocks have examined epigenetic age using cross-sectional data, a 2019 meta-analysis of longitudinal cohort data investigated how the difference between chronological age and epigenetic age changes over time, between childhood and old age.(Marioni et al., 2019) This study used data from five separate cohorts (including LBC1921 and LBC1936) and showed that epigenetic age increases more slowly than chronological

age, particularly in the oldest population.(Marioni et al., 2019) With all of these findings in mind, one might consider whether repeating DNA methylation-based measures of accelerated biological ageing at more than one time point might lead to a clearer appreciation of an individual's biological ageing. Future studies might wish to consider monitoring DNA methylation-based measures of accelerated ageing over several time points in order to establish a pattern or trend over time and determine whether this is a more accurate predictor of dementia risk in the oldest-old.

There is a clear requirement for further studies to clarify the presence or absence of any association between DNA methylation-based measures of accelerated ageing and dementia, particularly given the current lack of any similar studies within the literature.

Considering the potential limitations of any study is an essential step in interpreting the results and appreciating the validity of the conclusions. The LBC1921 was originally designed to investigate non-pathological cognitive ageing, with a number of factors being identified as having an association with poorer cognitive ageing outcomes. As dementia ascertainment had not been confirmed at the time of these studies, it had not been possible to exclude the possibility that the results had been affected by the inclusion of people with preclinical or prodromal dementia. In the subsequent chapter of the thesis we therefore revisit a number of these previous studies in order to examine the potential impact of preclinical/ prodromal dementia on the findings.

7: The impact of preclinical dementia in Lothian Birth Cohort 1921 studies of non-pathological cognitive ageing

7.1 Introduction: Previous findings of the LBC1921

As outlined in the second chapter of this thesis, the LBC1921 study was originally designed to investigate differences in the non-pathological cognitive ageing process. Changes in cognition – even in the absence of dementia – have been shown to be associated with a decline in independence, health, quality of life, decision-making and well-being.(Corley, Cox, & Deary, 2017) The impact of such declines would be experienced not only by the individual, but also by society. The resulting increase in demand on social care and health care – and the associated costs – would be particularly challenging to address in the context of an ageing population. Understanding the determinants of improved cognitive ageing is therefore of key importance to both individuals and society. Studies identifying factors that predispose individuals to an accelerated rate of non-pathological decline may guide strategies and interventions aimed at maintaining cognitive health, much like the studies that led to the widely recognised strategies aimed at improving cardiovascular health. Since the start of the LBC1921 study in 1999, researchers have explored a number of potential determinants of cognitive ageing including genetic factors, social factors, lifestyle factors, health diagnoses and physiological measures. While the LBC studies (LBC1921 and the younger LBC1936 cohort) have indicated that the primary determinant for cognitive ability in older age is cognitive ability in childhood, differences in childhood cognitive ability have not been shown to influence the rate of change in cognitive ability between childhood and older age.(Corley et al., 2017) Several other factors have however been implicated in influencing non-pathological age-related cognitive change in LBC1921. For example, the presence of an *APOE* ε4

allele, lower physical fitness, smoking, the use of neuro-active medications, polypharmacy, lower serum vitamin B-12 have all previously been shown to be associated with less successful cognitive ageing in the LBC1921.(Deary et al., 2003; Deary et al., 2006; Deary et al., 2002; Deary, Whiteman, Pattie, et al., 2004; Starr et al., 2004; Starr, Pattie, Whiteman, Deary, & Whalley, 2005) The availability of childhood intelligence data for participants in the Lothian Birth Cohorts has been shown to be particularly valuable in the study of cognitive ageing. Factors that were initially found to be associated with poorer cognitive function in older age were not associated after controlling for age 11 IQ.

Prior to the dementia ascertainment described in the earlier chapters of this thesis, it was not possible for analyses of LBC1921 data to account for incipient dementia. As highlighted within previous LBC1921 articles, a potential limitation of these studies was the possible impact of unrecognised dementia cases on the findings.(Deary et al., 2002) While such an effect was reduced as far as feasible – by excluding those with a low Mini Mental State Examination (MMSE) score and those self-reporting dementia, it was not possible to guarantee that the findings were not erroneously representing associations with dementia. This limitation was shared with other published studies of normal age-related cognitive changes.

The design of the LBC1921 study means that this limitation was of particular relevance in early studies of the LBC1921. With details of childhood cognitive ability being available at the commencement of the study, cognitive change could be calculated following a single round of testing at baseline (at age 79 years). While this was clearly advantageous in producing results quickly, it meant that analyses could be performed early in the study and without results from further follow-up, and importantly, before future diagnoses of dementia could be determined. For this reason, it was important to revisit early-published results demonstrating significant

associations between different factors and cognitive ageing, using those ascertained cases of dementia to explore the potential impact of preclinical dementia on the original findings. Reviewing any article describing a variable that has a documented association with dementia would be crucial given the particular risk that these analyses erroneously identified a relationship with incipient dementia, and not non-pathological cognitive ageing. With this in mind, we looked back at the LBC1921 research studies published since the establishment of the study cohort in 1999; in total, five previous articles were selected for review. The four variables identified as having an association with cognitive ageing in these articles were *APOE* ε4 genotype, physical fitness, serum vitamin B-12 and smoking status. The findings from these original reports, the methods by which each was re-examined, and the results of these new analyses are described in the subsequent section of this chapter.

The following study was published by *Psychology and Aging* in 2018. The complete reference is as follows:

Sibbett, R. A., Russ, T. C., Pattie, A., Starr, J. M., & Deary, I. J. (2018). Does incipient dementia explain normal cognitive decline determinants? Lothian birth cohort 1921. *Psychology and Aging, 33*(4), 674-684.

The author of this thesis was the first author of the published paper and made the following contributions: contributed to study design, completed data collection for dementia ascertainment, took part in the dementia ascertainment consensus meeting, completed statistical analyses, interpreted the results of the analyses, led the writing of the manuscript and contributed to revisions of the same. The supplementary materials for this manuscript can be viewed in *Appendix 5,* from page 301. The individual appendices are provided on the following pages:

The references for this paper are included within the published manuscript, in the referencing style of the journal. The references can be seen on pages 174-176 of the thesis.

7.2 Does incipient dementia explain normal cognitive decline determinants? Lothian birth cohort 1921.

(The published manuscript is included from the next page)

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Does Incipient Dementia Explain Normal Cognitive Decline Determinants? Lothian Birth Cohort 1921

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The presence of an apolipoprotein E (*APOE*) ε4 allele, lower physical fitness, smoking, and lower serum vitamin B-12 have been reported as contributing to poorer cognitive function in LBC1921 at age 79, after adjusting for childhood intelligence. Because incident dementia was not previously ascertained within LBC1921, it is possible that preclinical or unrecognized cases at age 79 influenced findings. Dementia cases arising over approximately 16 years of follow-up were determined by a consensus using evidence from electronic medical records, death certificates, and clinical reviews. The analyses from the original reports were repeated after the exclusion of those who had developed dementia. In a subsequent set of analyses, the authors considered the potential impact of terminal decline, excluding those participants who died within 4 years of baseline testing. Positive *APOE* ε4 status was found to be associated with poorer Logical Memory (Wechsler, 1987) at age 79 ($F(1, 355) = 8.16$, $p = .005$, $\eta_p^2 = 0.022$; $n = 359$) and lower Moray House Test (Scottish Council for Research in Education, 1933) score at age 79 ($F(1, 357) = 4.27$, $p = .04$, $\eta_p^2 = 0.012$; $n = 363$). Lower age 79 IQ was associated with smoking ($F(2, 360) = 3.67$, $p = .026$, $\eta_p^2 = 0.020$; $n = 367$), lower vitamin B-12 ($S\beta = 0.11$, $p = .014$; $n = 367$), and poorer physical fitness ($S\beta = 0.21$, $p < .001$; $n = 359$). Only the relationship with physical fitness remained significant after excluding those who died within 4 years of baseline ($S\beta = 0.203$, $p < .001$; $n = 310$). Unrecognized dementia had little or no effect on determinants of lifetime cognitive ageing in LBC1921. Terminal decline may have accounted for the associations with age 11 to age 79 cognitive change.

Keywords: dementia, cognitive ageing, cognitive ability, risk factors, cognitive decline

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Cognitive function in older age is a critical factor in maintaining independence and well-being (Fillit et al., 2002). Some aspects of cognitive ability are known to decline with advancing age, even in the absence of dementia (Robert S. Wilson et al., 2002). As the global population ages, it is therefore increasingly important to understand the determinants of differences in normal cognitive ageing. Furthermore, with an improved understanding of normal cognitive ageing it might be possible to distinguish it more clearly from pathological ageing. This will become increasingly important as the diagnosis of neurodegenerative conditions shifts earlier and earlier to prodromal and preclinical states. Evidence for the association between many different factors and nonpathological cognitive ageing are documented within the literature. A 2010 systematic review highlighted smoking and the apolipoprotein E (*APOE*) ε4 genotype as risk factors for greater cognitive decline, whereas better physical health was identified as a protective factor (Plassman, Williams, Burke, Holsinger, & Benjamin, 2010).

The interpretation of findings relating to normal cognitive ageing is, however, often limited by the difficulty in distinguishing whether observed associations might be explained by the presence

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This study re-examines the findings of five previous reports of the Lothian Birth Cohort, 1921. We thank the participants of the LBC1921; all authors on the original articles; and those Lothian Birth Cohort team members who participated in data collection for LBC1921. The Alzheimer Scotland Dementia Research Centre is funded by Alzheimer Scotland and the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology is part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1; Biotechnology and Biological Sciences Research Council and Medical Research Council). IJD and JMS are supported by Dementia Platform United Kingdom (Medical Research Council).

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of the early stages of neurodegeneration (preclinical or prodromal Alzheimer's disease, for instance) in some participants. This is particularly important when investigating factors such as depression and impaired physical fitness that might themselves be early symptoms of neurodegenerative disease (Plassman et al., 2010). Articles describing normal cognitive ageing typically exclude participants with known or suspected dementia at baseline or at the time of analysis. In most cases, studies perform dementia ascertainment in parallel with monitoring cognitive change, either using a planned dementia assessment protocol or recording the diagnosis as an incidental finding (Packard et al., 2007). A lag period between collecting the cognitive function results and determining dementia status is, however, necessary to reduce the number of incipient cases missed. Studies that retrospectively exclude participants who went on to develop dementia during an extended period of follow-up are rarer (Bretsky, Guralnik, Launer, Albert, & Seeman, 2003; Feng et al., 2012; Fillenbaum et al., 2001; Fitzpatrick et al., 2007; Praetorius, Thorvaldsson, Hassing, & Johansson, 2013; Small, Dixon, McArdle, & Grimm, 2012; Yaffe et al., 1999). Previous prospective studies have confirmed a subtle cognitive decline in nondemented participants of older-age, who went on to develop dementia (Bäckman, Jones, Berger, Laukka, & Small, 2005; Lange et al., 2002). A meta-analysis of previous studies has shown that *APOE* ε4 is significantly associated with adverse effects on a number of domains of cognitive function in nondemented older-adults (Wisdom, Callahan, & Hawkins, 2011). *APOE* ε4 carriers performed significantly poorer on tests of episodic memory ($d = -0.14$ (-0.21, -0.07), $p < .01$), global cognitive ability ($d = -0.05$ (-0.10, -004), $p < .05$), executive functioning ($d = -0.06$ (-0.12, -0.004), $p < .05$), and perceptual speed ($d = -0.07$ (-0.13, -0.01), $p < .05$; Wisdom et al., 2011). One of the studies included in the meta-analysis did, however, indicate that the association between *APOE* ε4 and cognitive function did not remain when those with preclinical dementia were excluded from the sample (Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Lange et al., 2002). Such studies highlight the importance of evaluating the impact of preclinical dementia when investigating the determinants of nonpathological cognitive ageing. Like most studies of their kind, early studies of possible determinants of normal cognitive ageing between age 11 and age 79 in the Lothian Birth Cohort, 1921 (LBC1921) did not have a follow-up period in which to determine incident dementia. We address and correct this limitation in the present report, providing further evidence regarding the potential effect of preclinical dementia on studies of nonpathological cognitive ageing.

LBC1921 is a narrow-age cohort ($N = 550$), mostly recruited from the City of Edinburgh and its surrounding area. Most participants had taken part in a Scottish national intelligence test aged 11 years (Deary, Gow, Pattie, & Starr, 2012). Participants were recruited at a mean age of 79 years and have been followed-up into their 90s. Studies of this cohort have reported four factors associated with almost-lifetime cognitive ageing, from age 11 to age 79 years (i.e., factors associated with cognitive function at age 79 years after adjusting for childhood IQ): smoking, lower physical fitness, *APOE* ε4 status, and vitamin B-12 levels. Smoking was associated with greater relative cognitive decline from age 11 to age 79 within the LBC1921 (Deary et al., 2003). A lower level of overall physical fitness at 79 years was associated with less successful cognitive ageing (Deary, Whalley, Batty, & Starr, 2006). Specifically, a higher mental test score at age 79, after adjustment for intelligence at age 11, was correlated with increased FEV_1 (forced expiratory volume in 1 second; a measure of lung function), decreased 6-metre walk time, and increased grip strength after adjusting for intelligence at age 11 (Deary et al., 2006). Possessing an *APOE* ε4 allele was associated with both poorer Logical Memory Test scores at age 79, and cognitive decline from age 11 to age 79 in this cohort (Deary, Whiteman, Pattie, & Starr, 2004; Deary et al., 2002). Lower serum vitamin B-12 levels at age 79 was associated with greater relative cognitive decline from age 11 to age 79 (Starr, Pattie, Whiteman, Deary, & Whalley, 2005).

In these previous studies, LBC1921 was treated as a homogeneous group with regard to cognitive ageing, but the cohort might have contained at least two separate groups: that is, one group with "normal" or nonpathological cognitive ageing, and another group who are subject to accelerated cognitive change because of a pathological process, most likely dementia. This is of particular importance given the recognized associations between *APOE* ε4, smoking, physical fitness, and dementia, in addition to the associations with cognitive ageing mentioned above. A systematic review and Delphi consensus study published in 2014 concluded that both smoking and physical inactivity were important modifiable risk factors for dementia (Deckers et al., 2015). The review included a meta-analysis of eight studies that found that current smoking was associated with a 59% increase in risk for Alzheimer's disease (Deckers et al., 2015; Peters et al., 2008). Further to the evidence linking physical inactivity and dementia, there is evidence within the literature specifically linking poorer grip strength, lung function, and walking speed with dementia (Camargo et al., 2016; Yoon et al., 2015). The oldest in the population are less well represented in dementia research and as such, the majority of the evidence for smoking and physical inactivity as risk factors for dementia is taken from studies involving participants in either earlier old age or from a wide age range. Some studies have refuted the importance of these risk factors with advancing age (Piguet et al., 2003; Verghese et al., 2003; Wang, Fratiglioni, Frisoni, Viitanen, & Winblad, 1999), but the paucity of studies investigating such factors in the oldest-old mean that it is not possible to conclusively rule out the possibility that these risk factors had an effect on the findings of the original articles considered in this study. Possession of an *APOE* ε4 allele has been shown to increase the risk of dementia, and Alzheimer's dementia in particular (Corder et al., 1993). While the potency of *APOE* ε4 as a risk factor has been shown to reduce in oldest-age, the same meta-analysis confirms that it continues to increase the risk for dementia in oldest-age cohorts (Farrer et al., 1997). The presence of at least one *APOE* ε4 allele has also been shown to increase the risk for dementia after age 79 in LBC1921 (Sibbett, Russ, Deary, & Starr, 2017b). Therefore, it remains an important consideration in this study. The relationship between vitamin B-12 and dementia is less clear, with studies demonstrating inconsistent findings (Agnew-Blais et al., 2015). A 2012 systematic review found no association between serum vitamin B-12 levels and risk of dementia, but did demonstrate an association between poor vitamin B-12 status and increased risk of dementia in studies using alternative biomarkers of vitamin B-12 status (holotranscobalamin and methylmalonic acid; O'Leary, Allman-Farinelli, & Samman, 2012). Low levels of serum B-12 and elevated total homocysteine—that may be caused by vitamin B-12 deficiency—have been linked with increased risk of dementia in the oldest-old (Kivipelto et al.,

2009; Wang et al., 2001). Notwithstanding the inconsistencies between studies, and in particular between studies of early old age and the oldest-old, it is important to test whether the apparent associations of vitamin B-12, physical fitness, smoking, and *APOE* ε4 genotype with nonpathological cognitive ageing in LBC1921 were driven by a subgroup who subsequently developed dementia.

The LBC1921 findings listed above were based on analyses conducted soon after the sample was recruited aged around 79 years. At that time, people with possible dementia were excluded if they scored <24 on the MMSE or reported a dementia diagnosis at baseline. After the participants had been followed up for approximately 16 more years, it was possible to ascertain incident dementia cases and to repeat the previous analyses excluding people who subsequently developed dementia to isolate any group with true "normal" cognitive ageing.

In addition to performing these sensitivity analyses, we also planned to use the available follow-up data to investigate the possible impact of so-called "terminal decline" on the original findings. Cognitive decline has been found to accelerate in the years before death, with one particular study demonstrating accelerated cognitive decline 43 months from death (R. S. Wilson, Beckett, Bienias, Evans, & Bennett, 2003). The original LBC1921 findings that are reconsidered in this article were produced shortly after recruitment, and any effect of terminal decline was not, therefore, examined. To investigate the possible role of terminal decline we, therefore, repeat the previously reported analyses after excluding those eligible participants who died within 4 years of baseline testing at 79 years.

Method

Participants

Participants were members of the LBC1921. Most had taken part in the Scottish Mental Survey of 1932 (SMS1932), completing a validated test of general intelligence, the Moray House Test No. 12, at age 11 years. The LBC1921 is described in detail elsewhere, and, at recruitment, comprised 550 community-dwelling, generally healthy older people, mostly from the Lothian area of Scotland, who were recruited to follow-up at mean age 79.1 years (*SD*: 0.6; Wave 1; Deary et al., 2012). Surviving participants underwent four subsequent waves of follow up at mean ages of 83, 87, 90, and 92 years (Waves 2 to 5). Study data included measures of sociodemographic, psychological, cognitive, medical, physiological, and genetic factors, collected by questionnaire and clinical testing. Dates and causes of death were supplied prospectively by the National Records of Scotland (previously General Registrar's Office, Scotland). The Lothian Research Ethics Committee (test Waves 1–3) and the Scotland A Research Ethics Committee (test Waves 4–5) provided ethical approval for the studies. From Wave 4, participants provided written consent for data linkage and access to health records. In line with the previous cognitive ageing articles, only participants with an age-79 Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) score of 24 or higher and no self-reported history of dementia at Wave 1 were included in these sensitivity analyses (Deary et al., 2003, 2004, 2006; Starr et al., 2005). We considered repeating our analyses using a stricter MMSE cut-off to identify those who might subsequently develop dementia, but a receiver operator characteristic (ROC) curve determined that the discriminating power of the MMSE was insufficient to determine future dementia outcomes (area under curve = 0.54) in this cohort, and it was in fact little better than random allocation. It is possible that the variation in cognitive reserve between individuals limits the use of the MMSE as a predictive tool.

Dementia Ascertainment

Dementia ascertainment methodology for this cohort has been described previously (Sibbett et al., 2017b), and will be outlined briefly here. Evidence for subsequent dementia or cognitive impairment after recruitment was collected from death records, and medical and psychiatric electronic records. For a small number of participants, additional information was available as a result of clinical assessments, performed in the research or NHS setting by the authors (JMS and TCR). Data were collected up to June 2016, when participants were aged approximately 95 years. Each case with any evidence suggestive of dementia or cognitive decline was considered at a consensus meeting that included both a geriatrician and a psychiatrist. The meeting agreed whether the evidence supported a diagnosis of dementia. Dementia cases were determined to be possible or probable cases according to a standard set of criteria (see Table 1). For the purposes of these sensitivity analyses, both probable and possible cases were considered dementia cases and, therefore, excluded from the main analyses.

Cognitive Testing

Participants took a validated test of general mental ability (the *Moray House Test (MHT) No. 12*) at age 11 and age 79 (Scottish Council for Research in Education, 1933). The test consisted of 75 items, completed over 45 min and the maximum achievable score was 76. The MHT scores were corrected for age (in days) and converted to IQ-type scores (*Mean* = 100, *SD* = 15). At age 79, an additional battery of cognitive tests was administered to assess some major domains of cognitive function. Verbal declarative

Table 1
Consensus Criteria for Dementia Case Ascertainment (Adapted From Sibbett et al., 2017b)

ANY of the following (without opposing evidence from same/other source)
Probable dementia
Dementia diagnosis on death certificate (any part)
Dementia diagnosed on clinical review (ICD-10/*DSM-IV*)
Dementia diagnosis in electronic general medical records (Trak)
Dementia diagnosis in electronic psychiatric records (PIMS)
ICD-10 criteria for dementia diagnosis met by data within any existing records
Possible dementia
Recorded cognitive impairment on death certificate
Cognitive impairment/decline recorded in notes, but incomplete evidence to meet ICD-10 diagnostic criteria
Possibility of dementia recorded in notes but no formal diagnosis/ incomplete evidence to meet ICD-10 diagnostic criteria

Note. ICD-10 = International Statistical Classification of Diseases and Related Health Problems-Tenth Revision; *DSM-IV* = *Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition*; Trak = TrakCare; PIMS = Patient Information Management System.

memory was assessed using the Logical Memory subtest from the Wechsler Memory Scale-Revised (Wechsler, 1987). Participants were read a short story (story A) containing 25 memory items and immediately after this they were asked to recall as much as possible. This was repeated for a second story (story B). After a delay of approximately 30 min, participants were asked to recall as much detail as possible from both stories. Immediate and delayed test scores were summed to form a single score ranging from 0 to 100. The phonemic Verbal Fluency test (Lezak, 1995) was used as a measure of one facet of executive function. Participants were required to name as many words as possible beginning with the letter C in 1 min. This process was repeated for the letters F and L and the total number of correct words given is the overall test score. Raven's Standard Progressive Matrices (Raven & Court Jr, 1977) was used as a measure of nonverbal or abstract reasoning. The test comprised 60 items, with each item representing a pattern that required completion. The score was given by the number of items completed correctly within the 20-minute time limit.

Exposures Associated With Cognitive Decline in Previous Studies

LBC1921 participants provided samples of venous blood at baseline, aged 79. Venous blood was used for DNA extraction. *APOE* ε4 status was determined by polymerase chain reaction (PCR) amplification of a 227 base pair fragment of the *APOE* gene containing two polymorphic sites that account for three alleles: ε2, ε3, and ε4 (Wenham, Price, & Blundell, 1991). These alleles were distinguished by restriction digest with the enzyme *Cfo1*, followed by electrophoresis in 4% NuSieve gel. Venous blood samples collected at a clinical research facility were used to measure serum vitamin B-12.

Grip strength in the dominant hand was measured using a Jamar Hydraulic Hand Dynamometer, and the best of three trials was used. Lung function was recorded as forced expiratory volume in 1 s (FEV_1), measured using a microspirometer; the best of three attempts was recorded. The time taken to walk 6 m at a normal pace was recorded. Grip strength, FEV_1, and 6-m walk-time were correlated and were combined using principal component analysis to obtain a summary fitness trait (we use the term trait, though strictly speaking this is a score from a first unrotated component). Smoking status was reported by participants, and coded as never-, ex-, or current-smoker. Time from enrolment to death was calculated by subtracting the age in days at baseline testing from the age in days at death.

Statistical Analyses

For each of the original cognitive ageing reports (Deary et al., 2002, 2003, 2004, 2006; Starr et al., 2005), the most significant findings were selected to be investigated in these sensitivity analyses. We included two articles that investigated the effect of *APOE* ε4 on cognitive ageing (Deary et al., 2002, 2004). The first (named Article 1 hereafter) demonstrated that possessing an *APOE* ε4 allele was significantly associated with greater cognitive decline from age 11 to age 79 using the same test of mental ability at both ages (Deary et al., 2002). In the second *APOE* ε4 article (named Article 2 hereafter), the main finding was that the presence of at least one *APOE* ε4 allele contributed significantly to lower Logical Memory test scores at age 79 (Deary et al., 2004). It was important to consider both articles given the relevance of memory decline in dementia and general cognitive decline.

Current smoking was significantly associated with a lower score on age 79 IQ (age-adjusted MHT scores at age 79, though it was stated in the report as age 80) compared with ex-smokers and never-smokers (Deary et al., 2003). Lower serum vitamin B-12 at age 79 was associated with greater relative cognitive decline between age 11 and 79 (Starr et al., 2005). The main finding from the physical fitness article was that lower general physical fitness component—derived from principal component analysis of three individual measures—was significantly associated with greater relative cognitive decline from age 11 to age 79 (Deary et al., 2006).

Each exposure (*APOE* ε4 status, smoking, vitamin B-12, and general physical fitness) was considered separately in the first instance; in each case, the analytical approach used repeated that of the previous reports. We then conducted analyses that included all four of these exposure variables simultaneously. The method and model for each analysis was as follows. *APOE* ε4 (Article 1): General linear modeling, with MHT score at age 79 (standardized as an IQ-type score) as the outcome or dependent variable, MHT score at age 11 (standardized as an IQ-type score) as covariate and sex and *APOE* ε4 carrier status as fixed factors; *APOE* ε4 (Article 2): General linear modeling, with Raven's Standard Progressive Matrices, Logical Memory subtest, and Verbal Fluency test scores as dependent variables, sex and *APOE* ε4 status as fixed factors, and age 11 IQ as covariate; Smoking: General linear modeling, with age 79 IQ as the dependent variable, sex and smoking as fixed factors, and age 11 IQ as covariate; Vitamin B-12: Linear regression, with age 79 IQ as the dependent variable and vitamin B-12, age 11 IQ, sex, *APOE* ε4 status, smoking status, use of statins and number of prescribed drugs as independent variables; Physical fitness: Linear regression, with age 79 IQ as the dependent variable and sex, age 11 IQ, fitness trait, smoking status, *APOE* ε4 status and social class as independent variables; Combined analyses: (a) Linear regression including the four main variables simultaneously (*APOE* ε4 status, smoking status, vitamin B-12, and fitness trait), plus age 11 IQ and sex, with IQ at age 79 as the outcome variable; (b) Multivariate general linear modeling, with Raven's Matrices, Verbal fluency and Logical Memory as dependent variables, *APOE* ε4 status, sex, and smoking status as fixed factors and fitness, vitamin B-12 and age 11 IQ as covariates. To improve the clarity of the effect size, we also present estimated marginal means (95% confidence interval [CI]) with related effect size (Cohen's *d*) for categorical risk factors. For comparison, this is given alongside the same statistics for the study cohort when dementia cases were included. After each of the individual analyses, we completed a subsequent analysis in which participants with probable dementia, or no dementia were included. Forming a between-groups variable, we included an interaction term with the risk factor to determine whether it varied as a function of the inclusion group. Finally, we repeated the each of the main individual analyses after the exclusion of those participants who had died within 4 years of baseline testing. The methods and models were as shown above. Statistical analyses used IBM SPSS, Version 21.

Results

There were 550 participants attended the baseline wave of data collection at age 79 years. For each analysis, we excluded 130

participants: 2 participants had reported a diagnosis of dementia at Wave 1; 9 participants scored less than 24 on the MMSE at Wave 1; 2 participants were missing MMSE scores at baseline; and there were 117 participants for whom we had ascertained a diagnosis of dementia in about 16 years of follow up, to age 95 years. Each analysis then repeated the other exclusion criteria and requirements as recorded in the original reports and, as a result, the number of participants with complete data for each analysis varied slightly between the separate outcomes. The numbers providing full data for each analysis were as follows: *APOE* ε4, (Article 1) $n = 363$ (Article 2) $n = 359$; smoking, $n = 367$; vitamin B-12, $n = 367$; and physical fitness, $n = 359$.

APOE ε4

***APOE* ε4 Article 1: MHT score as outcome (Deary et al., 2002).** Of 363 participants with complete data, 210 (57.9%) were female and 79 (21.8%) possessed at least one *APOE* ε4 allele. On general linear modeling, a lower MHT score at age 11 years was associated with a lower MHT score at age 79 ($F(1, 357) = 239.4$, $p < .001$, $\eta_p^2 = 0.401$). Sex was also associated with MHT score at age 79 ($F(1, 357) = 4.76$, $p = .03$, $\eta_p^2 = 0.013$) as was the presence of an *APOE* ε4 allele ($F(1, 357) = 4.27$, $p = .04$, $\eta_p^2 = 0.012$; see Table 2). These results were consistent with those of the original study, which found a similar effect size for each of the three variables (see Table 1). The exclusion of dementia cases had very little impact on the effect size ($d = -0.23$ (-0.44, -0.03); $d = -0.26$ (-0.51, -0.01) and estimated marginal means (see Table 3). The complete results for each of the main sensitivity analyses and those for the combined analyses are shown in supplementary material File A, Tables S1–S7.

***APOE* ε4 Article 2: Logical Memory, Raven's Matrices, and verbal fluency as outcomes (Deary et al., 2004).** Of the 359 participants with full data for these analyses, 208 were female (57.9%) and 78 were carriers of at least one *APOE* ε4 allele (21.7%). On univariate analyses (*t* test) there was no significant difference between those with and without an *APOE* ε4 allele in age 11 IQ, $p = .50$, or age 79 MMSE, $p = .48$. On general linear modeling, positive *APOE* ε4 status was found to contribute to a lower Logical Memory test score at age 79 years ($F(1, 355) = 8.16$, $p = .005$, $\eta_p^2 = 0.022$), but not to Raven's Matrices ($F(1, 355) = 3.56$, $p = .06$, $\eta_p^2 = 0.010$), or to Verbal Fluency ($F(1, 355) = 26.52$, $p = .664$, $\eta_p^2 = 0.001$) tests' scores. The findings from this analysis replicate those found in the original article (see Table 2). In both the original and new analyses, age 11 IQ contributed significantly to all three measures whereas sex contributed to Raven's Matrices only. The effect size (Cohen's *d*) relating to Logical Memory test score remained relatively stable after the exclusion of those participants who went on to develop dementia ($d = -0.35$ (-0.56, -0.14); $d = -0.36$ (-0.61, -0.11); see Table 3).

Smoking

Of the 367 participants with data available for these analyses, 211 were female (57.5%). There were 189 participants were ex-smokers (51.5%), 30 were current smokers (8.2%), and 148 were never smokers (40.3%). The mean age at starting smoking was 18.4 years (*SD*: 5.5) years (range of 7–60 years), and only four ever-smokers started before the age of 11. On general linear

Table 2
Main Findings From the Sensitivity Analyses and Terminal Decline Analyses, Compared With Findings From the Original Articles

Exposure	Outcome	Main sensitivity analyses results			Original report results[a–e]			Terminal decline analyses results[g]		
		Test statistic	Significance	Effect size (η_p^2)	Test statistic	Significance	Effect size (η_p^2)	Test statistic	Significance	Effect size (η_p^2)
APOE ε4 + (Article 1)	Age 79 MHT[f] score	$F(1, 357) = 4.27$	.04	.012	$F(1, 461) = 5.2$[a]	.02[a]	.011[a]	$F(1, 306) = 1.30$	.255	.004
APOE ε4 + (Article 2)	Logical Memory Test Score- age 79	$F(1, 355) = 8.16$	.005	.022	$F(1, 457) = 7.84$[b]	.005[b]	.017[b]	$F(1, 304) = 2.95$	.087	.010
Smoking	Age 79 IQ	$F(2, 360) = 3.67$	.026	.020	$F(2, 463) = 3.3$[c]	.039[c]	.014[c]	$F(2, 308) = 1.97$	.141	.013
Vitamin B-12	Age 79 IQ	$S\beta = .11$	.014	—	$S\beta = .095$[d]	.011[d]	—	$S\beta = .087$	.075	—
Fitness[h]	Age 79 IQ	$S\beta = .21$	<.001	—	$S\beta = .170$[e]	<.001[e]	—	$S\beta = .203$	<.001	—

[a] Deary et al. (2002). [b] Deary et al. (2004). [c] Deary et al. (2003). [d] Starr, Pattie, Whiteman, Deary, and Whalley (2005). [e] Deary, Whalley, Batty, and Starr (2006). [f] Moray House Test. [g] Main analyses excluding participants who died within 4 years of baseline testing. [h] Fitness general component formed using principal component analysis of sex- and height- adjusted 6-metre walk time, grip strength, and FEV_1.

Table 3
Estimated Marginal Means and Effect Sizes for Categorical Risk Factors

Exposure	Outcome test	Grouping	Dementia included		Dementia excluded		Dementia and death within 4 years excluded	
			Estimated marginal mean (95% CI)	Effect size Cohen's *d* (95% CI)	Estimated marginal mean (95% CI)	Effect size Cohen's *d* (95% CI)	Estimated marginal mean (95% CI)	Effect size Cohen's *d* (95% CI)
APOE ε4 (Article 1)	Age 79 MHT Score	*APOE* ε4 carrier	98.28 [96.24, 100.33]		98.86 [96.38, 101.34]		100.53 [97.95, 103.12]	
		APOE ε4 noncarrier	100.93 [99.74, 102.11]	−.23 [−.44, −.03]	101.82 [100.50, 103.14]	−.26 [−.51, −.01]	102.23 [100.87, 103.58]	−.16 [−.43, .12]
APOE ε4 (Article 2)	Verbal Fluency	*APOE* ε4 carrier	39.95 [37.86, 42.04]		40.68 [38.04, 43.32]		41.45 [38.56, 44.33]	
		APOE ε4 noncarrier	39.98 [38.73, 41.22]	.00 [−.21, .20]	40.02 [38.61, 41.43]	.06 [−.20, .31]	40.18 [38.67, 41.69]	.11 [−.17, .38]
	Raven's Matrices	*APOE* ε4 carrier	30.73 [29.37, 32.09]		30.86 [29.22, 35.51]		31.52 [29.73, 33.32]	
		APOE ε4 noncarrier	31.77 [30.96, 32.58]	−.14 [−.34, .07]	32.65 [31.77, 33.53]	−.24 [−.49, .01]	32.80 [31.86, 33.74]	−.17 [−.45, .10]
	Logical Memory	*APOE* ε4 carrier	28.67 [26.49, 30.84]		29.38 [26.67, 32.08]		30.93 [27.96, 33.90]	
		APOE ε4 noncarrier	32.93 [31.64, 34.23]	−.35 [−.56, −.14]	33.82 [32.37, 35.26]	−.36 [−.61, −.11]	34.02 [32.47, 35.58]	−.25 [−.52, .02]
Smoking	Age 79 IQ	Current Smoker	95.80 [92.00, 99.59]		96.28 [92.25, 100.32]		98.15 [94.06, 102.24]	
		Ex-smoker	100.73 [99.31, 102.16]	−.44 [−.8, −.08]	101.27 [99.69, 102.84]	−.45 [−.84, −.06]	101.96 [100.28, 103.64]	−.36 [−.78, .06]
		Never-smoker[a]	100.92 [99.28, 102.56]	−.43 [−.79, −.06]	102.43 [100.53, 104.32]	−.53 [−.92, −.13]	102.68 [100.82, 104.54]	−.41 [−.83, .01]

Note. CI = confidence interval.
[a] Never smoking compared with current smoking.

modeling, smoking was found to be associated with a lower IQ at age 79 years ($F(2, 360) = 3.67$, $p = .026$, $\eta_p^2 = 0.020$; see Table 2). Age 11 IQ was also found to be significant, whereas sex was not. As shown in Table 2, the original article also found a significant association between smoking and age 79 IQ. The effect size (Cohen's *d*) was relatively unaffected by the exclusion of dementia cases when current smoking was compared with ex-smoking ($d = -0.44$ (-0.8, -0.08); $d = -0.45$ (-0.84, -0.06)) and similarly, when current smoking was compared with never smoking ($d = -0.43$ (-0.79, -0.06); $d = -0.53$ (-0.92, -0.13); see Table 3). IQ at age 79 was significantly lower for current smokers, compared with both ex-smokers ($p = .024$, *mean difference* = −5.0, 95% CI [−9.3 to −0.7]) and never-smokers ($p = .007$, *mean difference* = −6.2, 95% CI [−10.6 to −1.7]), and again, this replicated findings from the original article.

Vitamin B-12

Of the 367 participants eligible for inclusion in these analyses, 211 were female (57.5%) and 326 had serum vitamin B-12 levels available (88.8%). The mean vitamin B-12 level was 388 (*SD* 162) ng/L. To prevent bias from participants with very high serum levels that were the result of treatment for vitamin B-12 deficiency, those with a serum level more than 3 *SD*s higher than the mean were excluded ($n = 8$). The resulting mean level for included cases was 374.0 (*SD* 134.5) ng/L. Serum vitamin B-12 levels were standardized and stored as *z* scores for the purposes of analyses. As in the original article, the linear regression results demonstrated a significant association between lower vitamin B-12 and lower age 79 IQ ($S\beta = 0.124$, $p = .006$, R^2 change = 0.015). After adjusting for sex, *APOE* ε4 status, smoking status, use of statins, and number of prescribed drugs, vitamin B-12 continued to be associated significantly with age 79 IQ ($S\beta = 0.110$, $p = .014$, R^2 change = 0.012; see Table 2). This was again the same outcome of the analysis in the original article ($S\beta = 0.095$, $p = .011$). We replicate the association between vitamin B-12 and age 79 IQ by repeating our analysis without excluding dementia cases ($S\beta = 0.087$, $p = .022$, $R^2 = 0.007$).

Physical Fitness

A total of 359 participants met the inclusion criteria for these analyses, of which 208 were female (57.9%). The sex and height adjusted fitness measures—grip strength, 6-m walk time, and FEV_1— were all significantly correlated ($p \leq .01$). Principal component analysis identified a single component that accounted for 48% of the total variance. The loadings on this first unrotated component—termed "fitness"—were as follows: grip strength = 0.75; 6-m walk time = −0.65; $FEV_1 = 0.68$. In the present analyses, age 11 IQ was not significantly associated with FEV_1 (0.097, $p = .067$) as it was in the original report ($p = .03$; Deary et al., 2006). IQ at age 79 correlated significantly with all three individual fitness measures (grip strength = 0.154, $p = .003$; 6-m walk time = −0.193, $p < .001$; $FEV_1 = 0.174$, $p = .001$) and with the combined fitness trait (0.231, $p < .001$). Linear regression analyses showed that the variables contributing significantly ($p \leq .05$) to variance in IQ scores at age 79 were: age 11 IQ (38.3% of variance); fitness (4.7%), sex (0.8%), and social class (1.8%). Fitness accounted for a higher percentage of variance in this analysis when compared with the original analysis (3.3%; see Table 2). When dementia cases were included, the follow-

ing variables were found to contribute to age 79 IQ: age 11 IQ (42.4% of variance); fitness (3.1%), social class (1.2%), sex (0.7%), and *APOE* ε4 (0.6%). Smoking status did not demonstrate a significant contribution to variance in either analysis ($p > .05$).

We repeated each of the main analyses with the study sample comprising of participants with probable dementia, or no dementia. Dementia status was included as a between-groups variable and we included an interaction term with the risk factor to determine whether the effect varied as a function of the dementia group. The interactions between dementia and *APOE* ε4 status, dementia and smoking status, dementia and vitamin B-12 level, and dementia and fitness were not significantly associated with standardized MHT test score or IQ at age 79. The *APOE* ε4 carrier status by dementia status interaction was associated with Raven's Matrices test score at age 79 ($p = .006$), but not Logical Memory or Verbal Fluency test scores. Further details of these results can be seen in supplementary material File B.

Combined Analyses

Linear regression including the four main exposure variables (*APOE* ε4 status, smoking status, vitamin B-12, and fitness trait) showed that age 11 IQ (34.2%), fitness (5.6%), vitamin B-12 (2.1%), and sex (1.7%) contributed significantly (all $p < .01$) to variance in age 79 IQ. When dementia cases ($n = 103$) were included in the analysis, age 11 IQ (39.9%), fitness (3.4%), vitamin B-12 (1.1%), and sex (1.1%) continued to contribute significantly to variance ($p < .01$). *APOE* ε4 status and smoking did not enter into the models.

Multivariate general linear modeling showed positive *APOE* ε4 status to be associated with lower Logical Memory test scores at age 79 years ($F(1, 301) = 5.5$, $p = .02$, $\eta_p^2 = 0.018$). Lower levels of general physical fitness at age 79 years was associated with both lower Verbal Fluency ($F(1, 301) = 12.3$, $p = .001$, $\eta_p^2 = 0.039$) and lower Raven's Matrices ($F(1, 301) = 18.0$, $p < .001$, $\eta_p^2 = 0.056$) test scores. When dementia cases ($n = 103$) were included in the same analysis, the same associations were found: *APOE* ε4 and Logical Memory ($F(1, 392) = 5.5$, $p = .02$, $\eta_p^2 = 0.014$); fitness and Verbal Fluency ($F(1, 392) = 12.8$, $p < .001$, $\eta_p^2 = 0.032$); fitness and Raven's Matrices ($F(1, 392) = 13.6$, $p < .001$, $\eta_p^2 = 0.034$). In addition, lower vitamin B-12 was associated with lower Raven's Matrices test scores ($F(1, 392) = 5.6$, $p = .02$, $\eta_p^2 = 0.014$). Smoking did not contribute significantly to any of the three outcomes.

Terminal Decline

The number of participants who died within 4 years of baseline testing and were, therefore, excluded from the "terminal decline" analyses were as follows: *APOE* (Article 1), $n = 52$; *APOE* (Article 2), $n = 50$; smoking, $n = 52$; vitamin B-12, $n = 52$; fitness, $n = 49$. After the exclusion of these participants—and those who had developed dementia—the resulting cohort size for reanalyses ranged from $n = 309–315$. The main individual analyses were repeated and the association between fitness and age 79 IQ remained significant ($S\beta = 0.203$, $p < .001$). The results for *APOE* ε4 (Article 1: $F(1, 306) = 1.30$, $p < .255$, $\eta_p^2 = 0.004$; Article 2: $F(1, 304) = 2.95$, $p = .087$, $\eta_p^2 = 0.010$), smoking ($F(2, 308) = 1.97$, $p = .141$, $\eta_p^2 = 0.013$) and vitamin B-12 ($S\beta = 0.087$, $p = .075$) did not reach significance (see Table 2). The estimated marginal means and effect sizes (Cohen's *d*) for the categorical variables are shown in Table 3. The complete results for the terminal decline analyses are shown in supplementary material File A, Tables S1–S5.

Power Calculations

We completed post hoc power calculations to describe the statistical power of the new analyses, relative to the original analyses. The statistical power to detect an effect of the same magnitude at $p < .05$, as was observed for the complete study sample, was reduced after the exclusion of dementia cases in each analyses. The reduction in power ranged from 3% (from 0.99 to 0.96 for the physical fitness analysis) to 18% (0.60 to 0.49 for the smoking analysis). The statistical power was reduced further after the additional exclusion of those participants who died within 4 years of baseline testing; with reductions in power ranging between 6% (from 0.96 to 0.93 for physical fitness) and 28% (from 0.58 to 0.42 for *APOE* ε4 Article 1 and from 0.60 to 0.43 for the smoking analysis).

Discussion

These sensitivity analyses, completed by repeating analyses conducted in five of our team's previous reports after excluding participants who subsequently developed dementia, verified previous findings of LBC1921 studies. The presence of an *APOE* ε4 allele, smoking, lower physical fitness, and lower vitamin B-12 were all associated with greater relative cognitive decline between age 11 and 79 years even after excluding those who had developed dementia in the next 16 years. The effect sizes were similar in magnitude to the previous findings and, therefore, we can be more confident that prodromal or undiagnosed dementia had little influence on the original findings. However, our analyses did suggest that terminal decline could have influenced the results, with only physical fitness remaining significant after the exclusion of those who died within 4 years of baseline testing. With a smaller sample size, we had less power for these analyses and, therefore, we are cautious when considering the results.

Comparison With Previous Literature

Like the original articles that investigated the relationship between *APOE* ε4 and cognitive ageing, we found that the presence an *APOE* ε4 allele contributed to poorer performance on a Logical Memory test at age 79 years, and contributed to general cognitive decline from age 11 to age 79. Using a robust method to exclude dementia cases we have minimized the possibility that dementia had caused some of the effect seen previously. Our findings agree with a previous meta-analysis, which found that *APOE* ε4 carriers performed poorer on tests of episodic memory, global cognitive ability, executive function and perceptual speed (Wisdom et al., 2011). The effect sizes for episodic memory and global cognitive ability were noted to increase with advancing age (Wisdom et al., 2011). Our results did not remain significant after accounting for possible terminal decline. Several studies have considered the effect of *APOE* ε4 on mortality and although a relationship is described, it is typically explained by the presence of dementia. If we accept our results as correct, despite the reduced sample size, it is possible that the participants who demonstrated a link between *APOE* ε4 and cognitive decline in our main analyses would in fact have gone on to develop dementia had they survived.

The findings for smoking and cognitive decline from the present analyses were consistent with the original article (Deary et al., 2003).

Our findings also agree with the conclusions of other previous studies identifying smoking as a risk factor for cognitive decline (Yaffe et al., 2009), and recording an increased risk of decline in current smokers when compared with never-smokers and ex-smokers (Sabia et al., 2012). The potential for underestimating the effect of smoking on cognition as a result of higher rates of death and dropout among smokers is noted from the results of a previous study (Sabia et al., 2012). If risk of death is increased among smokers, this may explain why the relationship between smoking and cognition becomes nonsignificant after the exclusion of participants who die within 4 years of baseline testing—if a terminal decline in cognitive ability means that you are more likely to be closer to death, then perhaps you are simply also more likely to be closer to death if you are a smoker. In addition to failing to reach significance, the effect size for the relationship is reduced. Our final set of analyses included all of the main variables considered in this article, and smoking status did not reach significance in either. This is probably because of the inclusion of the fitness variable and the likely link between smoking and fitness.

We found that a 134.8 ng/L (1 *SD*) decrease in serum vitamin B-12 level at age 79 was associated with lower IQ scores at the same age. This relationship is in line with that found in the original article. Our results provide weight to the evidence for this relationship that exists within the literature, which is of particular importance given the conflicting evidence for this association (O'Leary et al., 2012). Although the effect size is relatively unchanged after the exclusion of those participants dying within 4 years of enrolment, the association between vitamin B-12 and cognition is no longer significant. Reduced dietary intake or reduced absorption can contribute to lower levels of serum vitamin B-12 and those who are unwell are therefore at an increased risk. It may be therefore, that cognitive function and vitamin B-12 both decline toward death and are not truly associated.

We must consider whether the consistency between the results when dementia cases were included and when cases were excluded is related to the possibility that the factors examined in this article are no longer associated with an increased risk for dementia after age 79. There is evidence to support this within the literature, with studies reporting no association between risk factors (vitamin-B-12, smoking, physical fitness) and dementia (Crystal et al., 1994; Piguet et al., 2003; Verghese et al., 2003; Wang et al., 1999), or at least a declining strength of association (*APOE* ε4; Corrada, Paganini-Hill, Berlau, & Kawas, 2013; Farrer et al., 1997). These findings have not, however, been comprehensively reinforced, and as a result, there is no widely accepted risk factor profile for dementia in the oldest-old. This likely relates to the difficulties in recruiting healthy persons in oldest age, and the potential for high rates of attrition because of morbidity and mortality in such cohorts (Sumic, Michael, Carlson, Howieson, & Kaye, 2007). Until there is a sufficient body of evidence disputing any risk factor for dementia in the oldest-old that is an accepted risk factor for dementia in earlier old-age, studies must continue to evaluate the effect of preclinical dementia in studies of nonpathological cognitive ageing.

We acknowledge the possibility that terminal decline has influenced our findings for vitamin B-12, smoking and *APOE* ε4, but we consider these results with caution given the reduced sample sizes (n = 309–315) for each of these analyses. The statistical power was reduced after these exclusions, relative to the original analyses, meaning that we were less likely to detect any association. We note that for physical fitness—the only finding that remained significant in these analyses—the reduction in power (relative to the complete sample) was only 6%, compared with a reduction in power of between 18 and 28% for the other analyses—none of which demonstrated a significant association. Furthermore, excluding a group likely to be experiencing cognitive decline reduces the amount of decline in remaining participants. If there is less variability in cognitive decline among those who remain in the sample, the likelihood of identifying factors associated with cognitive decline is diminished. Larger studies are required to reduce the impact of such an effect. A potentially effective way of reducing this effect when selecting dementia cases would be to identify probable cases of incipient dementia using ante-mortem neuroimaging data or postmortem neuropathological data. This could, however, lead to the potential misclassification of some participants, because pathological features of Alzheimer's disease have been found in persons who died without cognitive impairment (Savva et al., 2009). Given the possible impact of terminal decline, we would suggest that studies investigating risk factors for cognitive decline in older age account for death occurring after 4 years or less within their analyses.

Fitness was found to be significantly associated with age 79 IQ in this article and the original article (Deary et al., 2006). After the exclusion of those participants who died within 4 years of testing, this was the only relationship that remained significant ($p < .001$). These results are in line with previous studies that have identified a relationship between increased fitness or exercise and decreased cognitive decline (Fitzpatrick et al., 2007; Taniguchi, Yoshida, Fujiwara, Motohashi, & Shinkai, 2012; Wendell et al., 2014). The results of our four main analyses go further than simply reinforcing previous findings—they add some validation to those studies without dementia follow-up (Bretsky et al., 2003; Fillenbaum et al., 2001; Sabia et al., 2012; Taniguchi et al., 2012). Given that the lack of follow-up for dementia ascertainment is so often a major criticism of studies investigating normal cognitive ageing, our findings are valuable in demonstrating the minimal impact of incident dementia in these follow-up analyses.

Strengths and Limitations

The accuracy of the findings is limited by the possibility that participants who might otherwise have developed dementia could have died from other causes before the onset of dementia. By definition—as a result of excluding those who later developed dementia—fewer participants were included in each analysis than in previous studies. With the exception of not having knowledge of incipient dementia, the limitations present in the original studies persist. For example, we might expect the smokers in our cohort to be biased to being particularly fit, given that by age 80 they were relatively unaffected by serious smoking-related illness or death. We did not have sufficiently frequent cognitive assessments to investigate terminal decline fully and we, therefore, simply omitted those participants who died within 4 years of cognitive assessment at age 79 years. We cannot be confident in our findings relating to the effect of terminal decline because of reduced sample size, but given the possibility of an effect, we recommend that future studies account for death in their analyses. Our dementia ascertainment procedure did not include neuropathological examination after death. Whereas we could not exclude the presence of

pathological findings typically associated with dementia syndromes, current evidence has shown that such findings are frequently observed within the brain tissues of older persons who died without cognitive impairment (Savva et al., 2009). Such findings demonstrate that, whereas pathological findings can confirm the etiology of dementia, their presence alone does not necessarily equate to the presence of a clinical dementia syndrome. This study aimed to determine the presence of the clinical syndrome of dementia; we would not, therefore, have expected this limitation to affect our results. As described in an earlier study (Sibbett et al., 2017b), our robust dementia ascertainment procedure included evidence gathered from multiple sources of data—including clinical assessment—and, as such, we were able to limit the number of potential missed cases. There will, however, always be limitations in the accuracy of such a methodology (Sibbett, Russ, Deary, & Starr, 2017a), primarily because the quality and quantity of available data will vary between participants. As such, we cannot entirely exclude the possibility that using a procedure with optimized sensitivity to identify cases may have found further cases and had an effect on the findings. A significant strength of our study is that we were able to include age 11 IQ in all analyses—both original and new—and so protect from the possibility of reverse causation by the influence of childhood IQ; in effect, we were able to have near-lifetime cognitive change as the outcome variable in these analyses. Using the LBC1921 as our study population also has a number of other benefits. Possible confounding effects are limited because of their ethnically, culturally, and geographically homogeneous nature, general good health, and narrow-age of the cohort. We recognize, though, that this also limits generalizability.

Conclusions

These sensitivity analyses verify previous findings and demonstrate that preclinical or prodromal dementia had little influence on five LBC1921 studies that examined influences on nonpathological cognitive ageing. The presence of an *APOE* ε4 allele, smoking, lower physical fitness and lower vitamin B-12 were all associated with greater relative nonpathological lifetime cognitive decline. These findings allow us to suggest that the impact of incipient dementia would be minimal in studies with a similar methodology of excluding from analyses participants who self-report a diagnosis of dementia and/or score below an appropriate cut-off on a brief cognitive screening test.

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7.3 Chapter summary and conclusions

The described study revisited and repeated the primary analyses of five individual previous studies and included an analysis combining all of the studied factors together. In addition to these repeated analyses, our study included a further repeat of each of the five analyses, in which the potential impact of terminal decline was examined. As such, the described study was an extensive and thorough re-evaluation of the previous findings, in the context of dementia and death outcomes occurring since the completion of these early studies.

In repeating the primary analyses of the previous studies, we found that our analyses verified the findings of the original reports, suggesting that incipient dementia had minimal influence on the conclusions of the original papers. Not only did the patterns of association remain the same, but the magnitude of the effect sizes were much unchanged from the original results. These findings were important, not only in reinforcing the veracity of these findings, but they also suggest that incipient dementia is unlikely to have influenced findings from other LBC1921 studies. Beyond this, the findings offer some level of validation to findings from other study groups without adequate follow-up for dementia ascertainment. We must however recognise the possibility that we did not identify every case of dementia and that unrecognised cases continued to influence the findings. It is also possible that some other cause for cognitive decline was influencing those associations seen in the original and repeat analyses. Previous studies have demonstrated an acceleration in non-pathological cognitive decline in the years preceding death – so-called terminal decline.(Karr, Graham, Hofer, & Muniz-Terrera, 2018) While the exact onset of this decline in relation to time of death has been reported with some variability, the rate of decline has been shown to increase markedly in the 3 to 4 years before death.(Wilson, Beck, Bienias, & Bennett, 2007) Given the high numbers of deaths in our cohort, it was

important to consider if such decline had influenced the original findings. Our additional analyses found that the original findings for smoking, *APOE* ε4, vitamin B-12 may indeed have been influenced by such terminal decline. When we excluded those participants who died within 4 years of baseline testing and repeated the analyses, only the association between physical fitness and cognitive decline reached statistical significance. While it was possible that a reduction in sample size had an impact on our findings, the results suggest that future studies of cognitive decline in advanced old age should – where possible – account for possible terminal decline in their analyses, given the elevated risk of imminent death that is associated with advancing old age.

8: Discussion

8.1 General findings

This presented thesis had three primary aims. The first of these was to determine dementia incidence within the study cohort – the Lothian Birth Cohort 1921. With dementia cases identified, the next aim was to investigate potential risk factors associated with dementia in this cohort of the oldest-old, with a particular focus on potentially modifiable risk factors. The final aim was to re-examine previous findings of the Lothian Birth Cohort 1921 study. Previously published studies had identified factors associated with non-pathological cognitive ageing, and by excluding the people who had gone on to develop dementia (and who presumably had preclinical/ prodromal dementia when tested) the aim was to reduce the possibility that the original studies had erroneously identified an association with preclinical dementia. This final chapter provides an overview and discussion of the findings within this thesis, and how these relate to both the existing literature and the original objectives. The potential strengths or limitations of the work resulting from methodology or sample selection will be considered alongside recommendations for future research.

8.1.1 Dementia ascertainment methodology

The first objective of this thesis was to ascertain dementia cases and therefore determine dementia incidence for the Lothian Birth Cohort 1921. In order to identify dementia cases within the study cohort, it was necessary to either identify a previously described effective ascertainment methodology, or to develop one for this purpose. No such ‘gold-standard’ methodology had been previously published within the literature and it was therefore necessary to gather evidence to guide the development of an ascertainment method for the Lothian Birth Cohort 1921. The evidence gathered

and subsequent development of ascertainment methodology are described in full within Chapter 3.

Based on the findings of the study described in Section 4.2, the dementia ascertainment method designed for the LBC1921 cohort was found to be relatively effective. As such, one can be confident in using the identified cases for further study, both within this thesis and in LBC1921 studies completed by other researchers. Furthermore, the methods described may be considered by others who are designing their own dementia ascertainment methodologies. Having previously investigated the ascertainment methodologies utilised in other studies and found a lack of detail in many published papers, it was important that this study described the ascertainment method clearly. By providing details of the methodology, together with a description of the assessments used to determine validity, the relative effectiveness of the methods used may be easily compared with the results of future ascertainment studies. While the likelihood of there being missed cases is recognised, this would be anticipated with any study using existing data as the primary source for dementia ascertainment, and it can be said that these were minimised as far as possible in this cohort.

8.1.2 Dementia incidence in the Lothian Birth Cohort 1921

Our study found that 22.5% of eligible participants developed dementia during the follow-up period (approximately sixteen years). As shown within the study included in Section 4.2, the number identified equated to approximately 74% of cases that would have been predicted for a cohort of this size and age; predictions were based on the findings of a large study that pooled data on dementia incidence from eight population-based studies in seven European countries.(Fratiglioni et al., 2000) The discrepancy between expected cases and identified cases was likely to be

multifactorial. It is widely recognised that a number of persons with dementia are not diagnosed; in the Lothian region of Scotland dementia diagnosis rates have been previously reported as 68.3%.(Alzheimer's Society, 2012) Our ascertainment procedure would have been less likely to identify undiagnosed cases given the relative paucity of detailed clinical data that was the result of the number of participants who were unable to provide consent to access medical records. This would be particularly true for those participants who were lost to routine follow-up, as changes in cognition may have been identified during repeated cognitive test batteries. We would however have identified those persons with dementia, but without a diagnosis, who continued to attend study waves for follow-up as a decline in cognitive ability would have resulted in a referral for clinical assessment as described previously. Another potential explanation for dementia rates to be lower than expected in this cohort is the relatively high levels of education and socioeconomic class.

8.1.3 Risk factors for dementia

8.1.3.1 Comparisons with previous studies of the oldest-old

As noted within the main introduction and in each relevant Chapter of this thesis, existing studies of risk factors for dementia in oldest-age have produced inconsistent findings. While the studies based on the LBC1921 described in Chapters 4 to 6 are unlikely to provide any definitive clarity, it is hoped that the results will add to the volume of research on this topic and will aid in producing a more conclusive risk factor profile in the future. Here, we provide an overview of our findings and how these compare to the existing literature from studies of the oldest-old cohorts.

APOE ε4 genotype

Based on a large volume of previous research, the *APOE* ε4 genotype is recognised to be an important risk factor for dementia, and Alzheimer's disease in particular.(Corrada, et al., 2013) All of our risk factor studies found that the presence of at least one *APOE ε*4 allele continues to be an important risk factor for dementia over age 79 years. The study detailed in Chapter 4 looked specifically at *APOE* ε4 as a risk factor for dementia in the LBC1921 and found that the presence of at least one *APOE* ε4 allele more than doubled the risk for incident dementia (OR: 2.23 ; 95% CI: 1.29, 3.86). This pattern of risk was also shown in the studies of other risk factors included in Chapters 5 and 6. Other studies specific to the oldest-old have however questioned the importance of *APOE* ε4 in the oldest-old. Results from the 90+ Study suggested that the association between *APOE* ε4 and dementia was age dependent, and that *APOE* ε4 is no longer a risk factor for dementia in oldest-age.(Corrada et al., 2013) Findings from other studies have supported this conclusion.(Juva et al., 2000) Our results would therefore seem to disagree with much of the existing literature on dementia in the oldest-old. While it is not possible to modify one's risk with regard to *APOE* ε4 status, it is important to understand its role in dementia risk in oldest age.

Hypertension

Contrary to the observed association between midlife hypertension and dementia in studies of younger subjects, several studies have shown that hypertension in later life is not a risk factor for dementia in oldest-age. The 90+ Study showed that onset of hypertension after age 80 years reduced the risk of subsequent dementia.(Corrada et al., 2017) Risk was reduced further with hypertension onset after 90 years of age.(Corrada et al., 2017) The results of the study also suggested a trend for decreasing risk with increasing severity of hypertension.(Corrada et al., 2017) Other

studies have also reported a reduced risk for dementia with increased systolic blood pressure in those aged over 85 years.(Li et al., 2007; Ruitenberg et al., 2001) In the Adult Changes in Thought (ACT) Study, a systolic blood pressure over 160 mmHg was associated with a non-significant reduction in dementia risk (HR: 0.64, 95% CI: 0.32, 1.30).(Li et al., 2007) A pooled analysis of the Rotterdam and Gothenburg H-70 Studies demonstrated a reduced risk for dementia with increasing systolic blood pressure (HR: 0.89, 95% CI: 0.82, 0.97 per 10 mmHg) in those aged over 85.(Ruitenberg et al., 2001) While the significance of these relationships varied, the pattern demonstrated was consistent. Our finding that a history of hypertension reduces risk for dementia (OR: 0.47, 95% CI: 0.23, 0.98 (Chapter 4)) would be in line with this pattern of evidence.

Smoking

Ever-smoking

The study included in Section 6.2 found an association between never smoking and an increased risk for subsequent dementia (HR 1.69, 95% CI: 1.06, 2.71, p=0.03). While the direction of this relationship may seem unusual and disagree with the results of other studies of dementia, it is in line with the patterns seen in this cohort for other health and lifestyle factors such as physical activity and hypertension; it may be that this finding therefore represents part of the changed risk factor profile in oldest-age. We would however be cautious in accepting this finding without further evidence as the same pattern of association did not reach statistical significance in the study detailed in Section 5.2, where the association between ever-smoking and dementia did not reach statistical significance (HR: 0.94, 95% CI: 0.61, 1.45). Furthermore, we must consider whether selection bias or survival bias has influenced this finding. The 90+ Study found no association between a history of ever-smoking at enrolment and

incident dementia (HR: 0.95, 95% CI: 0.74, 1.21).(Paganini-Hill et al., 2016) The discrepancy between the findings of the 90+ Study and previously reported findings in earlier old age may reflect a change in the risk associated with advancing age, but it may also be related to the 90+ Study having very few participants who were current smokers at recruitment.(Paganini-Hill et al., 2016)

Current smoking

The study detailed in Section 4.2 found that in the LBC1921, the association between current smoking and dementia did not reach statistical significance (OR: 0.14, 95% CI: 0.02, 1.17). A previous systematic review and meta-analysis that included studies of participants aged 65 years and over demonstrated an increased risk for Alzheimer's disease for current smokers compared with never or non-smokers (summary ratio 1.59, 95% CI: 1.15, 2.20), but not for ex-smokers compared with never smokers (summary ratio 0.99, 95% CI: 0.81, 1.23).(Peters et al., 2008) It is possible that our results differed from those of the meta-analysis due to a change in the risk factor profile with advancing age. We would however note that the meta-analyses considered Alzheimer's disease rather than all-cause dementia and this may also have altered the findings.

Overall, our findings add evidence to the literature suggesting that current smoking or ever-smoking do not increase the risk for dementia in this age-group. Further investigation of the role of smoking (ever and current) is required to better understand the role of this risk factor in dementia in oldest-age.

Hypercholesterolaemia

A Finnish study of the oldest-old – the Vantaa 85+ Study – found no statistically significant difference between the baseline blood lipid (HDL cholesterol, LDL

cholesterol and triglyceride) levels of those who went on to develop dementia during follow-up, and those who did not.(Rastas et al., 2010) A study of the 90+ Study participants also found no association between blood cholesterol and dementia in the oldest-old.(Evans et al., 2014) Similarly, our study from Section 4.2 did not find any association between blood cholesterol levels at age 79 years and subsequent dementia. The Sydney Older Persons Study however – a study of participants aged over 75 years – concluded that hypercholesterolaemia reduced the risk for cognitive decline and dementia ($p<0.05$).(Piguet et al., 2003) While this finding differs from that of the Vantaa 85+ Study, the 90+ Study and the LBC1921 study, all add evidence for the changing role of cholesterol in dementia risk with advancing age.

Previous studies in earlier old age have however noted that raised cholesterol at specific periods in the life course might be more significant with regard to dementia risk in later life.(Alonso et al., 2009; Anstey et al., 2008) One meta-analysis concluded that raised cholesterol in midlife was associated with increased risk for dementia but raised cholesterol in later life was not.(Anstey et al., 2008) In the LBC1921, statin-use was observed to increase risk for dementia (OR: 3.39, 95% CI: 1.04, 11.02) (Section 4.2). This is contrary to a paper reporting that within the 90+ Study, a history of statin-use decreased the risk for dementia (HR: 0.58, 95% CI: 0.39-0.85, p=0.005).(Evans et al., 2014)

Physical activity and physical fitness

The 90+ Study also explored the potential associations between different exercise types – active exercise, less-active exercise and vigorous exercise – and incident dementia.(Paganini-Hill et al., 2016) Participation in active or other exercise at recruitment to the 90+ Study was not associated with incident dementia.(Paganini-Hill et al., 2016) Furthermore, active or other exercise 20 years prior to the 90+ Study (1980s) was not associated with incident dementia.(Paganini-Hill et al., 2016) The

90+ Study was a follow-up from the Leisure World Cohort Study, which had collected data on vigorous exercise participation at age 40 years, then in 1983 and 1998.(Paganini-Hill et al., 2016) Vigorous activity in midlife (age 40) was not associated with dementia in oldest-age (HR: 1.12, 95% CI: 0.84, 1.50); neither was greater participation in vigorous activity in older age (1983 HR: 0.81, 95% CI: 0.58, 1.12; 1998 HR: 1.22, 95% CI: 0.83, 1.78).(Paganini-Hill et al., 2016) The absence of a relationship between midlife physical activity and dementia contradicts previous findings for those in earlier old age – including a meta-analysis that found physical inactivity increased the risk of dementia by 39% - once again suggesting a changing risk factor profile with advancing age.(Deckers et al., 2015) The findings of the 90+ Study also contradicts the findings of the Oregon Brain Ageing Study which found an association between increased exercise and decreased risk of cognitive decline (defined by MMSE < 24 or CDR ≥ 0.5 on two consecutive assessments) in healthy women aged over 85 years.(Sumic, Michael, Carlson, Howieson, & Kaye, 2007) The study included in Section 4.2 suggested that increased physical activity across adulthood increased the risk for dementia after age 79 years (OR: 1.17, 95% CI: 1.04, 1.32). While we might question how robust our findings are with regard to physical activity – as a result of reduced participant numbers for these analyses – it is possible that we are observing a change in the risk associated with previous physical activity, much like that which was observed in the 90+ Study. Unlike the 90+ Study that had detailed assessments of participation in physical activity from different points in the life course, our study relied on retrospective reporting of the same by study subjects. It was therefore necessary to use a more 'concrete' variable to examine the potential relationship between physical activity and dementia, hence the study included in Section 5.2 that examined measurable fitness levels at age 79 years. While we did not observe any association between measures of physical fitness at age 79 years and subsequent dementia (FEV_1 (HR: 1.30, p=0.37); grip strength (HR: 0.98, p=0.35);

walking speed (HR: 0.99, *p*=0.90)), other studies have demonstrated findings that are more in line with those seen in earlier old age. As noted in the introduction to Chapter 5, the 90+ Study has demonstrated an association between poorer performance on fitness tasks (walking speed, chair stands, grip strength and standing balance) and increased risk for dementia in those aged over 90 years.(Bullain et al., 2016; Bullain et al., 2013) Our lack of any observed association in the LBC1921 would therefore contradict both the findings of studies in earlier old age and of other studies in oldest age.

Cardiovascular and cerebrovascular disease

The study in Section 4.2 did not demonstrate any elevated or decreased risk for dementia with a history of cardiovascular or cerebrovascular disease, but we must consider whether this was because we included a history of a number of conditions together. The prevalence of individual conditions within LBC1921 would not have been sufficient to allow us to investigate these factors individually. Identifying the role of vascular factors in dementia risk in the oldest-old is of considerable importance and value given the overlap with preventative strategies for cardiovascular and cerebrovascular disease and the potential for risk modification. The 90+ Study examined a number of vascular diseases and their association with all-cause dementia. The authors of the study found an increased risk of dementia was associated with a history of congestive heart failure, stroke and heart valve.(Corrada, Mozaffar, et al., 2016) Again, hypertension was shown to decrease risk.(Corrada, Mozaffar, et al., 2016) Previous myocardial infarction, transient ischaemic attack, arrhythmia, coronary artery disease, hypercholesterolaemia and diabetes were not found to be associated with either an increased or decreased risk for dementia.(Corrada, Mozaffar, et al., 2016) The study draws an important distinction between hypertension and other vascular risk factors. In finding that the direction of

the association differs between hypertension and other vascular factors, it suggests that survival bias is less likely to explain the pattern observed for hypertension and dementia.(Corrada, Mozaffar, et al., 2016) The fact that the 90+ Study found different levels of association with dementia for different vascular conditions might explain why when considered together, as they were in our study, the association failed to reach significance and why our results differed from those previous findings.

Diabetes

The Vantaa 85+ Study explored the association between diabetes and dementia in the oldest-old and found that the incidence of dementia was twice as high in those with diabetes, when compared to those without (HR: 2.09, 95% CI: 1.34, 3.25).(Ahtiluoto et al., 2010) The same study found that dementia incidence was doubled for those with diabetes compared to those without for both Alzheimer's disease (HR: 2.45, 95% CI: 1.33, 4.53) and vascular dementia (HR: 2.15, 95% CI: 1.06, 4.36).(Ahtiluoto et al., 2010) The WISE study did not however find diabetes to be a risk factor for dementia. The study included in Chapter 4 of this thesis considered diabetes as a possible risk factor, but like the WISE study, we found no statistically significant association between history of diabetes and subsequent dementia.

Education and childhood intelligence

While the 90+ Study and WISE both found that lower levels of education were associated with an increased risk for dementia in oldest age, the same was not found for the LBC1921 (OR: 0.86, 95% CI: 0.73, 1.01).(Corrada, Brookmeyer, Berlau, Paganini-Hill, & Kawas, 2008; Yaffe et al., 2011) We would however note that the 90+ Study found that this was true for women, but not men and WISE only includes female participants.(Corrada et al., 2008) Furthermore, the study in Section 4.2 of this thesis found no association between childhood IQ and dementia in oldest age. The LBC1921

cohort is fairly unique in that it has childhood cognitive data available for most participants. Given how unusual this is, it is not possible to consider our results in the context of other such studies of oldest age. The childhood intelligence scores gathered by the SMS1932 have however been used previously to investigate the link with future dementia. The childhood intelligence scores used in the LBC1921 were also derived from those gathered in the SMS1932. A large follow-up study of 16,097 girls and 16,370 boys found that those in the lowest intelligence group had a greater risk of dementia (from age 65 to 92 years) when compared with those in the highest intelligence group.(Russ et al., 2017) As with the findings for education, this association was stronger in women (HR: 1.51, 95% CI: 1.29, 1.76) than men (HR: 1.19, 95% CI: 0.98, 1.44).(Russ et al., 2017)

8.1.3.2 A changing risk factor profile for dementia in oldest-age

As described within the conclusions of the papers included in Sections 4.2, 5.2 and 6.2, the results of these studies suggest that the dementia risk factor profile specific to the oldest-old differs from that described within the literature for early old age, or across old age. While we found that the presence of an *APOE* ε4 allele (OR: 2.23, 95% CI: 1.29, 3.86) and reduced height (0.72, 95% CI: 0.55, 0.95) continued to be associated with an increased risk for dementia in oldest age, a number of other risk factors were no longer important with regard to dementia risk; in some cases, the direction of association was actually shown to reverse from that described in earlier old age. Unlike the findings of previous studies and meta analyses, our studies did not find a statistically significant association between measures of physical fitness, symptoms of depression, body mass index, hypercholesterolaemia, a history of diabetes, cardiovascular disease or cerebrovascular disease (at age 79 years) and dementia. While the findings for smoking were somewhat inconsistent, we demonstrated a possible reversal in the direction of association between ever-

smoking and dementia, with a history of never-smoking being associated with an increased risk for dementia (HR 1.69, 95% CI: 1.06, 2.71, *p*=0.03) (Section 6.2). Similarly, our results suggested that higher levels of leisure-based physical activity across the lifetime was associated with a greater risk for dementia (OR: 1.17, 95% CI: 1.04, 1.32), thus demonstrating another reversal from the pattern of risk described in earlier old age. Finally, we found that a history of hypertension reduced the risk for dementia (OR: 0.47, 95% CI: 0.23, 0.98). This reversal from earlier old age is supported by other studies in oldest age, as detailed in the previous discussion section.

The evidence within the literature and from our studies is however inconsistent regarding the risk factor profile in oldest-age, and the mechanisms by which the effects of certain factors are altered are also unclear. One suggested mechanism by which factors known to increase risk for dementia in early old age may not appear to be risk factors in oldest-old is a survival effect; those who survive and remain dementia-free despite the effect of the risk factors may be in some way resilient to them.(Gardner et al., 2013) Or in simple terms, those who were at increased risk of dementia or death may have already died or developed dementia at an age earlier than that being studied.

While other potential mechanisms have been proposed for the differences observed, none have been accepted conclusively. For example: the effect of anti-hypertensives has been suggested as a possible explanation for the reversal of the association with hypertension in oldest age, but the 90+ Study did not find any such association, and results demonstrating an association between hypertension and reduced dementia risk were much unchanged after controlling for antihypertensive use.(Corrada et al., 2017) It has been suggested that hypertension is associated with reduced risk for dementia as higher blood pressure in oldest-age may compensate for age-related

vascular change and result in the maintenance of adequate cerebral perfusion; cognitive decline and dementia have been shown to be more frequent in individuals with low cerebral perfusion.(Corrada et al., 2017) Alternatively however, it is also possible that low blood pressure is a consequence of incipient or preclinical dementia, resulting from pathological changes in areas of the brain involved in blood pressure regulation.(Ruitenberg et al., 2001) This hypothesis is supported by studies that have demonstrated declining blood pressure in the years prior to, and the years following dementia diagnosis.(Ruitenberg et al., 2001) Other types of selection bias have also been proposed as an explanation for the findings. It is possible that those participants with hypertension who would develop dementia, would either have done so prior to age 80 years, or would have died from another hypertension-related condition prior to developing dementia. The result would be the underestimated incidence in those surviving with hypertension.(Corrada et al., 2017) One can therefore see that while the reversal of risk relating to hypertension and dementia is supported by a number of studies, the mechanisms by which this change comes about are unclear.

8.1.3.3 DNA methylation-based measures of accelerated ageing

Given the reported association between DNA methylation-based measures of accelerated ageing and age-related health outcomes and mortality, we hypothesised that the same measures may also be associated with an increased risk for dementia (as another age-related health outcome). The study detailed in Section 6.2 did not however find any consistent association between DNA methylation-based measures of accelerated ageing and dementia. Without any previous studies – either in earlier old age or in oldest age – it is not possible to make comparisons with the previous literature or with any changes in the impact of this factor with advancing age. Further research is needed to examine this potential risk factor, establish whether it may be

a useful indicator of risk and if so – which factors or mechanisms give rise to this elevated risk.

8.1.4 Impact of preclinical dementia on previous findings

With evidence showing that the preclinical phase of dementia may be more than a decade long and with no recognised manner by which such participants should be identified and excluded from studies, a short duration of follow-up for dementia ascertainment may not be sufficient to accurately identify those who were in this early phase of dementia at recruitment or testing. With approximately sixteen years of follow-up the LBC1921 study was suited to performing such analyses. While the LBC1921 study may have longer follow-up for dementia ascertainment than some other studies, follow-up in this age group is limited by death. At present, there is no manner by which those participants with preclinical dementia at recruitment, but died before developing clinical symptoms, can be identified. It is therefore impossible to exclude the possible impact of incipient dementia, only limit this as far as is feasible with the available resources. While some studies use post-mortem neuropathological signs to determine the presence of dementia, evidence within the literature is unable to confirm that such changes will always lead to clinical dementia. If such methods were used to identify preclinical dementia – for the purposes of exclusion – studies risk excluding normal variants from their analyses, resulting in another potential bias. Our study in Chapter 7 used follow-up data in order to assess the potential impact of preclinical dementia on early studies of non-pathological cognitive decline in the LBC1921. The results suggested that preclinical dementia had little or no effect on the original findings. The long duration of follow-up of the LBC1921 cohort also allowed us to investigate the potential impact of imminent death on the original findings. The results of these additional analyses did suggest that death within 4 years influenced the results. When those participants who died within 4 years were excluded

from the repeat analyses, most associations no longer reached statistical significance. Our results highlight the importance of using follow-up data in order to establish the potential impact of both subsequent dementia and imminent death.

8.2 Implications

One might consider the implications of this thesis in two broad categories – implications for epidemiology and implications for clinical practice. More specific descriptions of the potential implications are discussed below.

8.2.1 Ascertainment and dementia incidence

As discussed previously, we determined that our ascertainment methodology was relatively effective in identifying incident cases of dementia within the cohort. We therefore suggest that this method is also suitable for use in other studies. By including sufficient detail on how our ascertainment was carried out, and subsequently comparing our findings with expected rates, our ascertainment studies are a useful addition to the literature in that they may help guide ascertainment methods in future studies. Our robust analysis of dementia ascertainment in LBC1921 has led to a similar dementia ascertainment approach being adopted in the larger LBC1936 study. The incidence study detailed in Chapter 4 adds further evidence to the literature regarding dementia incidence in this age group. Given the difficulties associated with recruiting and retaining study participants of this age, each addition to the literature is valuable. While ours is not a large study of incidence, the data could be used in combination with that from other studies to complete a larger study of incidence. When the younger Lothian Birth Cohort 1936 has completed dementia ascertainment it may be useful to combine these results with our own to produce a single larger set of study data.

The main implications and uses of the ascertainment and incidence section of the thesis would therefore be:

1) To guide future ascertainment methods using existing data (particularly in LBC1936),
2) To add to the evidence regarding dementia incidence in the oldest-old, and
3) To provide details of dementia cases in LBC1921 to be used in other studies of the LBC1921

8.2.2 Risk factors

The studies within this thesis supplement the growing awareness that dementia is a life-course condition which develops over many decades. Thus, when in the life course particular factors are harmful is crucial to guiding the health and lifestyle advice given to those within different age groups; for example, you might not give the same advice to a fifty year-old and an eighty year-old.

The clinical and public health implications of our risk factor studies are however less straightforward than we might have expected. Studies of earlier old age have produced evidence for a range of modifiable risk factors that may be addressed in order to prevent dementia. As detailed within the Lancet Commission report 2020, as many as 40% of dementia cases may be preventable if 12 factors – including hypertension, smoking, low education, low physical activity and head injury – are addressed.(Livingston et al., 2020) It would have been relatively straightforward if our studies had produced similar findings as those in earlier old age, thus enabling us to propose modifications that might prevent dementia in this age group.

The majority of variables considered in this thesis produced null findings. Such variables included those that were previously identified as being important in early old age (diabetes, obesity, education, depression, physical fitness), and others that to our

knowledge had not yet been investigated (DNA methylation-based measures of accelerated biological ageing). While the null findings mean that it is not possible for us to state that addressing these factors would any potential positive effect on dementia, we do not dismiss them as unimportant findings. Positive and negative findings regarding risk for dementia are both key in developing risk profiles for dementia. Risk profiling on an individual level is key to developing personalised medicine whereby clinicians can provide someone with specific advice about their own risk profile and how they might address individual factors in order to reduce risk. The importance and potential impact of such an approach is highlighted by Brain Health Scotland, an initiative that focuses on improving brain health on a national level.(Alzheimer Scotland & Scottish Government, 2020) The primary objective of Brain Health Scotland is to reduce dementia incidence over the next decade, by increasing public awareness of the principles for maintaining brain health, and by providing access to the necessary interventions for dementia prevention.(Alzheimer Scotland & Scottish Government, 2020)

We do however note that there are limitations to our studies that might have affected our null findings. Similar limitations mean that we must be cautious in reporting the clinical implications of our positive findings. It is possible that some of these limitations have given rise to erroneous results. If we consider the positive association between never smoking and increased risk for dementia observed in Chapter 6, we must be mindful that the same pattern was not seen in our other studies of the same cohort. This might lead us to suspect the veracity of this association. If this finding were to be replicated in other studies in this age group, the possibility of a healthy survivor bias would remain. As we note within Chapter 4, we are also cautious in accepting the finding that increased physical activity across the lifetime increases the risk for dementia. Regardless of how robust the evidence for these two associations, it is

unlikely that it would result in any change to public health advice given the elevated risks for morbidity and mortality associated with smoking and physical inactivity.

Our study in Chapter 4 found that a history of hypertension is associated with a reduction in risk for dementia. We are not confident in proposing the clinical implications of this finding, as a result of the limitations described elsewhere in the thesis. Given that this finding is supported by some other reports within the literature, we might cautiously suggest that the patterns observed between hypertension and dementia add evidence for the potential protective effect of hypertension in oldest-old. It is however unlikely that the protective effect outweighs the risks associated with hypertension in all persons simply because they are over a certain age. For this reason, it is unlikely that there would be standardised guidance for the under-treatment of hypertension; it does however support the suggestion that there should not be a standardised approach to treat all hypertension to the same degree in this oldest-old age group. It is more likely that treatment will continue be determined on an individual basis, primarily based on the presence of frailty or the adverse effects of antihypertensive treatment.

The *APOE* ε4 allele was identified as being associated with an increased risk for dementia throughout our risk factor studies. It is not a modifiable factor, but we would suggest that it is included in studies of dementia in the oldest-old age group.

While is clear that the clinical and public health implications of our risk factor studies are lacking, we propose that our studies add to the body of literature regarding dementia in the oldest-old and as such, may prove to be useful in the future.

8.2.3 Studies of cognitive ageing in LBC1921

The implications of the study detailed in Chapter 7 would primarily relate to other studies of cognitive ageing. Firstly, studies of cognitive ageing already completed in LBC1921, but without knowledge of dementia outcomes, can show that dementia outcomes did not affect these early studies, and are therefore more unlikely to have affected other studies. Similarly, studies of cognitive ageing in other study cohorts, also without dementia follow-up, can be more confident in their findings given our results. Future studies of LBC1921 can now incorporate our dementia outcomes into their studies to minimise the potential effect of preclinical or prodromal dementia on their findings.

Our study did however demonstrate that terminal decline might have influenced the findings. We would therefore suggest that this is an important consideration in similar studies. It is difficult however to exclude terminal decline from studies in the oldest-old age group. The more advanced the age of a cohort, the more likely they are closer to death and as such, excluding those who died within a certain number of years further limits the size of what is unlikely to be a large sample.

8.3 Limitations

The potential limitations of each study are described within the relevant chapters. In this section, there will be a broad overview of limitations arising from the study design or the cohort itself.

8.3.1 Methodology

With dementia being the outcome of interest throughout this thesis, it is important to acknowledge any limitations related to how cases were identified. Incorrectly classifying individuals as having developed dementia, or vice versa, could have

implications for all analyses. Most likely, such errors would dilute any association. The potential limitations of our ascertainment methodology are detailed within Chapter 4. We highlight the potential for missed cases and in particular, any potential deficiencies in the availability of follow-up information that might have led to the same. Our methods aimed to reduce this possibility as far as possible, but we recognise this possibility remains as a result of our methodology. Further to the possibility of missing diagnosed or diagnosable cases of dementia, we must also consider the possibility that unrecognised cases of preclinical dementia affected our findings, and in particular the study described in Chapter 7. With no means by which to identify preclinical dementia, any subject with preclinical dementia who died prior to developing the full clinical syndrome required for diagnosis would not be identified. This limitation is not however unique to this study or methodology. Until there is clear evidence for a recognised biomarker for the preclinical stage of dementia participants who are in the very early stages of the condition would not be identified by clinical assessment or by recordings in existing data.

While every effort was made to include appropriate covariates in each study design, it could be suggested that additional variables should have been included in each of the included studies. The potential for having missed a necessary variable and the effect this could have had on the findings is acknowledged. It is however not possible to include every potential variable without affecting the analyses and the inclusions were therefore based on the available evidence, with reasoning described within each individual study.

8.3.2 The Lothian Birth Cohort 1921

The first limitation to consider is the size of the study sample. With *N*=550 participants enrolled at baseline, the cohort size is clearly not of the magnitude of some large

population studies. The study sample sizes for analyses described within this thesis are often further reduced as a result of missing data. As such, the power to detect small effects is limited. While the cohort size may be considered to be relatively small, it is a very detailed cohort with a considerable volume and variety of data available for participants. The availability of childhood intelligence data is particularly unusual for an older-age study group.

In a study cohort of this size, the number of dementia cases identified would also be limited. The number of cases of different subtypes of dementia were expected to be too few to allow for analyses specific to each subtype of dementia. This was compounded by the fact that a large proportion of cases lacked sufficient detail or evidence to be classified by subtype. It is possible that any lack of findings in our studies may be attributable to our having a single outcome of all-cause dementia. It is noted that many of the previous findings relating DNA methylation to dementia have been specific to Alzheimer's disease, and it is possible that by including cases of other aetiology has influenced the results. In LBC1921 the prevalence of some conditions – such as specific types of vascular disease – was not sufficient to allow for individual analyses.

We might also consider the potential limitations of the data collection methods used in the LBC1921. While many variables were prospectively collected in a detailed and thorough manner, the fact that participants were not recruited until age 79 years meant that information pre-dating recruitment relied on participant recall. Some of those variables included in this thesis – such as reporting of lifetime physical activity or details of smoking pack-use or cessation – would be subject the typical inaccuracies related to the retrospective recollection of information. Inaccuracies may arise for a number of reasons, including simple errors in recall or by minimising potentially harmful behaviours or maximising good behaviours. Self-report of

behaviours such as smoking have been shown to vary in their accuracy.(Andersen, Philibert, Gibbons, Simons, & Long, 2017) Another limitation of recruiting at an advanced age is the potential for a healthy survivor bias; where only those surviving certain risks, diseases or conditions are recruited. The surviving sample might demonstrate changed or unexpected associations, through the unintentional exclusion of those who were unable to be recruited due to the adverse effects of the same conditions survived by participants. As participants volunteered or consented to participate, there may also be an element of self-selecting bias. Those with a family history or particular concern regarding cognitive decline may have been more inclined to take part in the study. A selection bias may also occur as those who volunteer to participate are typically those who are generally physically and mentally healthier, more well educated and those with fewer social concerns. With baseline testing at age 79 years, some of the dementia outcomes might be expected to occur following a fairly short window of time. While cases of dementia at baseline were excluded, preclinical or prodromal cases of dementia might have remained. For this reason, we note the possibility of observing associations that are the result of reverse causation.

While our dementia ascertainment method was shown to be suitably effective, further detail would likely have been available if more participants had survived to wave 4 of testing and had consented to access to records and to data linkage. The younger LBC1936 cohort provided this consent from baseline and will therefore likely have a richer source of data from which dementia cases can be identified and confirmed.

Finally, we must reflect on the potential limitations in generalisability of any findings based on data from the Lothian Birth Cohort 1921. By design, the cohort includes participants of a single birth-year and all resided within a small geographical area.

8.3.3 Complexities of the Oldest-Old Age Group

Several characteristics of the oldest-old age group might have led to limitations in our studies. As noted throughout the thesis, the increased likelihood of complex health and lifestyle profiles in this age group may have affected our findings.

Within the studies of risk factors, we included many variables that we treated in a somewhat simplified fashion; this is particularly true in section 4.2 where we considered a larger number of factors in one set of analyses. While we looked at factors such as smoking and hypertension as simple yes/no binary type variables, in reality, these variables are much more complex and require further thought. It could be suggested that such variables increase in complexity with advancing age given the increased likelihood of comorbidity and the divergent effects of various life influences.

If one considers hypertension, there are a number of factors that one might need to consider; is it treated with antihypertensives, how long was it present before it was treated, what was the age of onset, is it ongoing? The 'the back story' of hypertension might be expected to be even more complicated in oldest-age given the increased likelihood of co-morbidity and the increased time for exposure to external influences. As an example, one individual may have developed hypertension at age 40 years and had this treated with antihypertensive medication until age 80 when these were discontinued due to a risk of falls, with a degree of hypertension left purposefully untreated. If we compare this with another individual who developed hypertension at age 75 years and continues on antihypertensive treatment we can see that a response of 'yes' for previous hypertension can mean very different things. Using the same 'yes/no' hypertension variable to assess hypertension as a risk factor therefore has clear limitations in this age-group. In Chapter 4 we also note the potential beneficial effect of raised blood pressure in advanced old age; it may serve to maintain organ perfusion and therefore limit decline in the function of the organ system. It is

possible that such limitations have affected our findings and it reinforces the need to investigate these observed risk factor associations in more detail in future studies.

A number of other factors considered in our studies are subject to similar complexities. Any of our health variables – including diabetes, cardiovascular disease, cerebrovascular disease – are likely to represent a diverse range of back-stories to their diagnosis. Variability in age at onset, duration, treatments, effectiveness of treatment, treatment compliance, disease complications and severity would be expected for all such factors. Different combinations of comorbidities between participants may also complicate the investigation of individual health variables in this age group, potentially making it more difficult to identify an association. Medication use – such as statins, which were observed to be associated with increased risk for dementia in Chapter 4 – will also have variability between persons. Age at commencement, severity of underlying disease, compliance and the exact type of drug used. Side effects of statins – such as confusion, weight loss and falls – are noted to be increased in oldest-old age; as a result, many of those who would have been prescribed this medication in earlier old age, will not be in advanced old age. This may give rise to differences in observed associations between statins and dementia in early old age and later old age.

Lifestyle factors are also likely to have a wide range of different histories. If we consider ex-smoking then we can see why this might mean something very different for different individuals. One participant may have commenced smoking at age 15, and stopped at age 25; another may have started at age 20 and stopped the day before recruitment to LBC1921; and a third may have started at age 17, stopped at age 35, restarted at age 50 and stopped at age 70. One can see the potential in variability in age at smoking and duration of smoking, and this does not even take into account further potential variability including the number of cigarettes used, whether

cigarettes were hand rolled, and whether filters were used. The simplified categorisation of smoking used in our studies will therefore be subject to similar limitations as those noted for hypertension.

By looking at variables in this simplified, binary way, there is a potential for missing an association, or revealing one that is not as simple as it first appears to be. If we chose to include additional variables that would describe many of these background features, we would introduce the possibility of a Type 1 error, through multiple hypothesis testing. We might therefore consider our analyses – with a simplified handling of variables – to be a basis for identifying 'potential' risk factors of interest in the cohort which should then be investigated in more detailed individual analyses.

As discussed elsewhere in the thesis, other features of oldest-old age may complicate the study of this age group and thus give rise to limitations. In section 5.3 we note the overlap between features of declining fitness and features of frailty. Decreased walking speed and grip strength are both commonly reported features of frailty and investigating the association between such factors and dementia will therefore be complicated by the presence of frailty. Changes in cognition or memory can also form part of the frailty assessment and as such, frailty may also overlap with dementia, further complicating the assessment of associations between variables and cognitive outcomes.(Rockwood et al., 2005) Given the increased frequency of frailty with advancing age, frailty must be given due consideration as a potential limiting factor in studies of the oldest-old.

Overall, it is clear that there are a number of factors that make the investigation of risk factors for dementia in the oldest-old more complicated. For this reason, further studies are required to complete a clearer picture of dementia risk factors in the oldest-old age group.

8.4 Recommendations for future research

Dementia ascertainment

It is anticipated that the details and results of the dementia ascertainment in LBC1921 will be of particular use to the researchers completing the planned dementia ascertainment in the LBC1936 – the larger (*N*=1091), younger, 'sister' cohort to LBC1921. It would be suggested that the LBC1936 dementia ascertainment method utilises those sources that proved valuable in this study, while exploring any additional data sources that may further reduce missed cases or add further evidence to support identified cases. In this study, both death records and hospital records were shown to yield useful information, and in particular, each identified cases that would have been missed by the other. The psychiatric records on the other hand, did not identify any cases that were not identified by other means. This is most likely the result of the migration of psychiatric records onto the general hospital system during the period of data collection. As such, it demonstrates that for any future dementia ascertainment procedures in this region (including the LBC1936), psychiatric records need not be consulted as they would provide little, if any, additional information.

Three additional data sources that could be considered for future studies include national datasets, general practice records and prescribing data. The Scottish Morbidity Records from the Information Services Division of NHS Scotland provide lists of diagnostic codes following contacts with NHS services. While most dementia cases would likely overlap with those identified from hospital records, it is possible that any person with dementia whose treatment was provided outwith the study locality, and therefore not included on the regional computerised records, would be identified. This would be of particular use where participants were based over a larger

geographical area, or where movement out of the region was regular. In the LBC1936 study, some SMR data are available and consideration should be given to expanding these to include more recent data. In older age, it is not uncommon for a change in residence to take place, whether it be to a residence with additional support, care or to simply downsize. When such moves take place, they may be out of the Lothian region, perhaps to be closer to family living elsewhere. SMR data might therefore provide data to assist in dementia ascertainment for these persons, for whom death certificates might be the only data source available.

Given that dementia-specific drugs, such as Donepezil, are generally first prescribed by a specialist, prescribing data would also likely have significant overlap with the data gathered from hospital records. It is however possible that prescribing data would again identify a participant with dementia who was initially treated outwith the region covered by local hospital records. Accessing such records will therefore have similar benefits to the SMR data.

While general practice records could also provide evidence for those who previously lived outwith the region, the records would also likely be rich with evidence that could support or oppose diagnoses listed in other sources. These data would therefore increase the possibility of both identifying dementia and dementia subtype classification. While we discuss these potential data sources with reference to the LBC1936 in particular, the rationale would be the same for other similar cohort studies in Scotland, or the United Kingdom. Rather than simply including all of these data sources in a dementia ascertainment methodology, it would be useful to perform an additional review or study to guide the inclusion and exclusion of such sources of data. While the systematic review detailed in Chapter 3 was valuable in designing the ascertainment method for LBC1921, there is the potential for gaining further information through an additional review. By focusing on studies of dementia incidence and/ or prevalence, the relative successes of different methodologies could

be more easily compared and contrasted as studies of this type would include specific numerical data on dementia ascertainment rates within populations or study cohorts. In order to gain the maximum benefit from such a review, studies completed both within and outwith the UK should be included. As noted within Chapter 3, European studies may be particularly informative. An additional option for obtaining further evidence for sources might be a study looking specifically at the concurrence of diagnoses within various data sources. For example, by using a cohort where dementia cases had been prospectively identified using accepted clinical assessment methods, one could obtain various types of records/ data sources and investigate whether dementia diagnoses were recorded and recorded accurately in each. The results of such a study might provide evidence of the most useful sources of existing data, and where overlap occurs between sources. Gathering a robust body of evidence on which dementia ascertainment methods using existing data could be built will be of particular value given the increasing use of existing electronic linked data. Both the review and study described above would be valuable to the LBC1936 and the wider field of dementia research.

Once a method for dementia ascertainment in LBC1936 has been developed and completed, it would be recommended that researchers perform similar validation studies to those described within Chapter 4 to allow for reasoned judgements on the effectiveness of any additional evidence and the overall ascertainment findings.

In addition to the possibility of adding new sources of evidence to the ascertainment methodology, there are features of the LBC1936 that might suggest that one would expect improved ascertainment rates from LBC1921, using the same methodology as described in Chapter 4. As LBC1936 is a younger cohort, there is more potential for performing clinical reviews where there is any suggestion of cognitive impairment on routine follow-up testing. This may lead to more cases being identified than would

have self-presented to health services for assessment, increasing diagnosis rates for the cohort. Unlike the LBC1921 participants, LBC1936 participants were consented for access to medical records and data linkage from recruitment and as such, there is the potential for more cases to be identified. Furthermore, such records are likely to reveal further detail on dementia diagnoses and this, together with the fact that the overall cohort is larger, may be sufficient to allow for analyses that consider the effects of different dementia subtypes.

Risk factors

The results obtained from the studies described in this thesis support the theory of a changed risk factor profile for dementia in the oldest old. While risk factors for dementia in earlier old age are not completely understood, there is a much larger body of evidence on which to draw conclusions. The same is required to allow the risk factor profile in the oldest-old to be better understood. Historically, recruitment and retention of participants of this age has been difficult, but improvements in life expectancy are likely to go some way to reduce this barrier to research. There is a particular requirement for further studies of potentially modifiable risk factors for dementia in the oldest-old. By demonstrating relationships that conflicted with previous findings, we reinforce the need for further study in this age-group in order to determine whether the findings were particular to this cohort or whether they might be observed in other study groups.

The complexities of this population age group are described throughout the thesis. Such complexities will require the gathering of detailed background data for study participants, such that these complexities might be considered and addressed in the study of risk factors for dementia in oldest-old age. If we consider the ‘background’ to certain variables we can see that considerable detail is required for a single variable

of interest to reduce the possibility of confounding. The association between dementia and the use of a specific medication for example could be affected by a number of other variables, such as indication, duration of use, age at prescription and adherence to recommended regime. While our studies looked at potential risk factors as relatively 'simplified' variables, further studies examining each variable in more detail may provide valuable additional information. Detailed data collection and considered design of analyses is therefore required to minimise such effects.(Power et al., 2015) In order to gather such detailed data, the size of studies may well continue to be limited in size. By completing further studies in smaller sized cohorts (like LBC1921 and LBC1936), larger volumes of data for this age group can be produced. With larger volumes of evidence that is specific to this age-group, systematic reviews and meta-analyses can be performed in order to evaluate the consistency in findings and report with increasing confidence the relevance and impact of such factors. While our studies are relatively small and may not be considered to be particularly impactful on their own, we hope that our data may be used in future meta-analyses in order to produce larger data sets with more conclusive findings. Given the similarities between the cohort demographics of LBC1921 and LBC1936, combining these data sets for future studies may be of particular value. Combining the data sets will result in a larger sample size, and include data from an earlier age as a result of the earlier-age recruitment of LBC1936.

As noted previously, the size of our study cohort may have resulted in particular limitations which affected our findings. In particular, where we did not have sufficient numbers of cases for individual analyses – important associations could have been missed. Studies that are large enough to allow for the individual analyses of individual vascular factors for example, will be valuable in order to challenge or reinforce the findings of the 90+ Study. Similarly, we were limited by the number of dementia cases

and we were unable to classify each as having a probable aetiology. Larger studies that examine risk factors for specific dementia subtypes will be an extremely valuable addition to the literature. Given the results of previous studies relating DNA methylation to Alzheimer's disease, it would be of particular value to repeat the study of DNA methylation-based measures of accelerated ageing and dementia in larger cohorts where the analyses could be repeated for individual subtypes of dementia.

We note that there may be a valuable opportunity to examine risk factors for dementia in the LBC1936, addressing the limitations described above. In particular, a further study of potentially modifiable risk factors may be more informative given the larger size of the cohort, and the possibility of there being sufficient statistical power to investigate variables of interest. For example, where we did not have sufficient power to detect an association between diabetes and dementia, there may be a sufficient number of cases of diabetes in LBC1936 to provide adequate statistical power. We suggest that studies of the LBC1936 might consider performing analyses with 'simplified' factors, before moving on to detailed investigation of individual factors. The larger cohort size and the availability of detailed clinical records for most participants may also mean that the LBC1936 is able to identify sufficient numbers of participants with specific types of dementia to allow for individual analyses. We would therefore suggest that a further study of DNA methylation-based measures of accelerated biological ageing be performed, using Alzheimer's type dementia as a primary outcome, if there were a sufficient number of cases to allow for analyses. Given that the association between DNA methylation-based measures of accelerated ageing and dementia has not been described within the literature, except within LBC1921, we would suggest that this be investigated further in other study cohorts.

Most existing studies of the oldest-old have been completed in Europe or Northern America and include predominantly Caucasian participants of relatively high socio-

economic background and education. Historically, it was populations in these geographical areas that had the greatest life expectancy, and studies of this age group were therefore most relevant in these regions. As life expectancy improves out-with these geographical areas, studies should also include populations residing in these areas. Future studies should therefore consider providing evidence that would be applicable to those from different populations.

Preclinical dementia

As we have done in our study of LBC1921 cognitive ageing studies (Chapter 7), we recommend that when dementia ascertainment is complete for LBC1936 that these cases are utilised in studies of cognitive ageing in this cohort to reduce the potential impact of preclinical or prodromal dementia on the findings. For existing studies, this could be done retrospectively as it was for LBC1921, while the data could also be used in future studies.

Given the potential effect of preclinical dementia within the study cohort, it would be beneficial for future studies to be able to exclude any participant with a biomarker for preclinical dementia at baseline, thus limiting the potential for reverse causality. Similarly, such a marker could be used to identify any participant who had developed preclinical dementia during the study period, enabling accurate classification of disease development. As research studies improve the understanding of this early stage in the disease, identifying a marker that reliably identifies those persons who will develop the clinical dementia syndrome becomes increasingly possible. Dementia studies would undoubtedly benefit from the availability of such a marker.

8.5 Summary of findings

This thesis had three primary aims: 1) to ascertain dementia cases in the Lothian Birth Cohort 1921 using existing data, 2) to investigate possible risk factors for dementia in his oldest-old cohort and whether these differ to the risk factors described in earlier old age, and 3) to examine whether preclinical dementia had affected previous findings for risk factors in non-pathological cognitive ageing. A dementia ascertainment method was developed using evidence gathered from a systematic review of similar methods. In an eligible cohort of *n*=489 participants, we identified that *n*=110 had developed probable dementia during the follow-up period, equating to approximately 22.5% of the cohort. Validation studies demonstrated that the methods were suitably effective.

Three separate studies of potential risk factors for dementia were completed and the overall picture was of a changed risk factor profile for dementia in the oldest-old. In our first study of potentially modifiable risk factors, we found that a history of hypertension at age 79 years was associated with a decreased risk for dementia, while increased physical activity in adulthood was associated with an increased risk for dementia. Both results represented a change in direction of the associations reported in earlier old age. The results also suggested that a history of statin-use increased the risk for dementia. Previous studies in earlier old-age did not demonstrate any significant association between statins and dementia. We did however find that the presence of at least one *APOE* ε4 allele continued to be associated with an increased risk for dementia after age 79 years, while increased height reduced the risk for dementia. Our second study indicated that physical fitness – as measured by lung function, grip strength and walking speed – was not a risk factor for dementia after age 79 years. In our third study we did not find any consistent association between DNA methylation-based measures of accelerated ageing and

dementia, but the results did suggest that a history of never smoking may increase the risk for dementia. Despite many having been shown to be important in earlier old age, none of the other risk factors that we investigated were found to be associated with dementia after age 79 years. We do however recognise that some of the limitations of our study sample may have reduced our ability to detect all associations. Given the ongoing inconsistencies in the findings of studies investigating dementia in the oldest-old, the relatively small volume of literature describing the same, and the limitations of our studies, there is a clear requirement for further research in this area.

The final study included in the thesis looked again at five previous studies of the LBC1921, aiming to determine the effect, if any, of preclinical or prodromal dementia on the original findings. The focus of these previous studies was to investigate four potential determinants of non-pathological ('normal) cognitive ageing; within these previous studies, smoking, *APOE* ε4, reduced fitness and lower vitamin B12 had all been shown to be associated with poorer cognitive ageing. After excluding those participants who had gone on to develop dementia, the analyses were repeated in the same manner that they were originally conducted. The overall findings were unchanged from the original studies, with all four factors continuing to be associated with poorer cognitive ageing ($p<0.05$). These findings suggested that, in LBC1921, preclinical dementia did not impact the observed associations. The potential for some cases of dementia to remain unrecognised is acknowledged, but this was minimised as far as possible in this cohort. While excluding participants who went on to develop dementia did not affect the overall findings, the exclusion of those who died within the first 4 years after baseline testing did. Following these exclusions, only the association between physical fitness and cognitive ageing remained statistically significant. These findings suggested that so-called 'terminal decline' in the years preceding death might have influenced the original findings. We would note that the reduction in sample size

for these analyses reduced the statistical power to detect an association, but we would suggest that terminal decline is an important consideration in future studies of oldest-old age participants.

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10. Appendices

Appendix 1. Supplementary material to Section 3.2

Supplementary Materials for:

Sibbett, RA et al. Dementia ascertainment using existing data in UK longitudinal and cohort studies: a systematic review of methodology. *BMC Psychiatry* 2017

Contents

Additional File 1: Medline Search Strategy

Medline Search Strategy

1. dementia/ or alzheimer disease/ or aphasia, primary progressive/ or primary progressive nonfluent aphasia/ or dementia, vascular/ or cadasil/ or dementia, multi-infarct/ or diffuse neurofibrillary tangles with calcification/ or frontotemporal lobar degeneration/ or frontotemporal dementia/ or lewy body disease/ or "pick disease of the brain"/

2. dementia*.mp.

3. alzheimer*.mp.

4. "primary progressive aphasia*".mp.

5. "primary progressive non?fluent aphasia*".mp.

6. (vascular adj2 dementia*).mp.

7. cadasil.mp.

8. "multi?infarct dementia".mp.

9. "diffuse neurofibrillary tangles with calcification".mp.

10. "fronto?temporal lobar degeneration".mp.

11. (fronto?temporal adj2 dementia*).mp.

12. ("lewy bod*" adj2 (dementia* or disease*)).mp.

13. (pick* adj2 (dementia* or disease*)).mp.

14. (presenile adj2 dementia*).mp.

15. (senile adj2 dementia*).mp.

16. (semantic adj2 dementia*).mp.

17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18. great britain/ or england/ or northern ireland/ or scotland/ or wales/

19. england.mp.

20. english.mp.

21. scotland.mp.

22. scottish.mp.

23. wales.mp.

24. welsh.mp.

25. "northern ireland".mp.

26. "n ireland".mp.

27. ni.mp.

28. "northern irish".mp.

29. "n irish".mp.

30. gb.mp.

31. gbr.mp.

32. "great britain".mp.

33. britain.mp.

34. british.mp.

35. uk.mp.

36. "united kingdom".mp.

37. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. population surveillance/ or public health surveillance/ or sentinel surveillance/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/

39. cohort*.mp.

40. longitudinal.mp.

41. surveillance.mp.

42. follow?up.mp.

43. prospective.mp.

44. retrospective.mp.

45. 38 or 39 or 40 or 41 or 42 or 43 or 44

46. 17 and 37 and 45

Additional File 2 Table S1: Reasons for the Exclusion of Full-Text Articles, by Author

Reasons for the Exclusion of Full-Text Articles	
First Author (n=297)	**Second Author (n=297)**
a) Not UK (n=28) b) Non-English language (n=1) c) Self-referral/ other referral to studies (n=5) d) Response to census/ survey (n=0) e) Known neuropathological diagnosis (n=6) f) Direct referral (n=7) g) Recruited from hospital, clinics, referrals, other services (n=69) h) Existing register of cases, study, memory clinic patients, anticholinesterase users or carers (n=23) i) Dementia not the primary condition of interest (n=7) j) Animal models of dementia (n=0) k) Simulated cohorts (n=2) l) Ascertainment not for dementia (n=1) m) Not longitudinal or cohort study (n=42) n) Cases ascertained entirely through baseline and/ or prospective clinical assessment/ new data only (n=61) o) posters or abstracts (n=21) p) unclear/ errata/ additional duplicates (n=24)	a) Not UK (n=5) b) Non-English language (n=1) c) Self-referral/ other referral to studies (n=0) d) Response to census/ survey (n=0) e) Known neuropathological diagnosis (n=0) f) Direct referral (n=13) g) Recruited from hospital, clinics, referrals, other services (n=33) h) Existing register of cases, study, memory clinic patients, anticholinesterase users or carers (n=41) i) Dementia not the primary condition of interest (n=9) j) Animal models of dementia (n=0) k) Simulated cohorts (n=0) l) Ascertainment not for dementia (n=3) m) Not longitudinal or cohort study (n=83) n) Cases ascertained entirely through baseline and/ or prospective clinical assessment/ new data only (n=42) o) posters or abstracts (n=44) p) unclear/ errata/ additional duplicates (n=23)

Additional File 3 Table S2: Eligible Articles Excluded from Final Review

GROUP	INCLUDED/ EXCLUDED	AUTHOR	STUDY TOPIC	DEMENTIA OUTCOME OR COHORT†	EXISTING DATA USE	DATA SOURCES	QUALITY SCORE
1	Included	Brayne et al. (C. Brayne et al., 2006)	Dementia at death and prevention	Outcome	Part	Death certificates	15
1	Excluded	Nicoll et al. (Nicoll et al., 2011)	Association between APOE, neuropathology and dementia	Outcome	Part	Death certificates	11
1	Excluded	Valenzuela et al. (Valenzuela et al., 2012)	Cognitive lifestyle and protection from dementia	Outcome	Part	Death certificates	13
1	Excluded	Wharton et al. (Wharton et al., 2011)	Epidemiological neuropathology	Outcome	Part	Death certificates	7
2	Included	Brayne et al. (Carol Brayne, Kathryn Richardson, Fiona E. Matthews, et al., 2009)	Neuropathological correlates of dementia	Outcome	Part	Death certificates	15
2	Excluded	Perales et al. (Perales et al., 2014)	Health related quality of life	Cohort	Part	Death certificates	13
3	Included	Clarke et al. (Clarke et al., 1996a)	Dementia incidence	Outcome	Part	Death certificates, hospital case notes	14
3	Excluded	Morgan et al. (K. Morgan et al., 1992)	Incidence of dementia	Outcome	Part	Death certificates, hospital case notes	13

3	Excluded	Morgan et al. (K. Morgan et al., 1993)	Incidence of dementia	Outcome	Part	Death certificates, hospital case notes	13
3	Excluded	Morgan et al. (K. Morgan & Lilley, 1994)	Risk factors for incident dementia	Outcome	Part	Death certificates, hospital case notes	12
4	Included	Imfeld et al. (Imfeld, Pernus, Jick, & Meier, 2013)	Epidemiology, comorbidities and medication in AD & VD	Outcome	Full	GPRD*	9
4	Excluded	Imfeld et al. (Imfeld, Bodmer, Schuerch, Jick, & Meier, 2013a)	Risk of stroke in AD or VD	Cohort	Full	GPRD*	8
4	Excluded	Imfeld et al. (Imfeld, Bodmer, Schuerch, Jick, & Meier, 2013b)	Seizures in AD or VD	Cohort	Full	GPRD*	8
5	Included	Newens et al. (Newens, Forster, Kay, et al., 1993)	Ascertainment, incidence, prevalence & survival in pre-senile AD	Outcome	Part	Electronic hospital information systems (ᵀHAA, MHE, Körner), neuroradiology records, hospital case notes	13
5	Excluded	Kay et al. (Kay, Forster, & Newens, 2000)	Survival, place of death and death certification in pre-senile dementia	Outcome	Part	Electronic hospital information systems (ᵀHAA, MHE, Körner),	12

						neuroradiology records, hospital case notes	
5	Excluded	Newens et al. (Newens, Forster, & Kay, 1993)	Death certification after a diagnosis of pre-senile dementia	Cohort	Part	Electronic hospital information systems (THAA, MHE, Körner), neuroradiology records, case notes	8
6	Included	Keenan et al. (Keenan, Goldacre, & Goldacre, 2015)	Glaucoma and AD/ VD	Both	Full	Hospital Episode Statistics	15
6	Excluded	Keenan et al. (Keenan, Goldacre, & Goldacre, 2014)	Macular degeneration, AD and dementia	Both	Full	Hospital Episode Statistics	14
7	Included	Wotton et al. (Wotton & Goldacre, 2014)	Obesity and subsequent dementia	Outcome	Full	Hospital Episode Statistics linked with death records	14
7	Excluded	Goldacre et al. (Goldacre, Yeates, Goldacre, & Keenan, 2015)	Cataract surgery and dementia	Cohort	Full	Hospital Episodes Statistics linked with mortality records	8
7	Excluded	Smolina et al. (Smolina, Wotton, & Goldacre, 2015)	Risk of dementia in diabetes	Outcome	Full	Hospital Episode Statistics, linked to death records	13

8	Included	Sorahan et al. (Sorahan & Kheifets, 2007b)	AD, MND and PD in magnetic field exposure	Outcome	Full	Death records	12
8	Excluded	Sorahan et al. (Sorahan & Mohammed, 2014)	Neurodegenerative disease and magnetic field exposure	Outcome	Full	Death records	10
9	Included						
9	Excluded	Staff et al. (Staff et al., 2010)	Brain volume and survival	Outcome	Part	Case notes, imaging results	15

[†]: Was dementia ascertainment performed as the study outcome, or was dementia ascertainment performed in order to form a dementia cohort for which another outcome was determined.
[†]HAA: Hospital Activity Analysis; MHE: Mental Health Enquiry system; Körner: Korner Episode Statstics (hospital information systems).
**GPRD: General Practice Research Database*

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Additional File 4 Table S3: Quality Measure Result Breakdown

	1	2	3	4	5	6	7	Total Score
Baker et al. (Baker, Cook, Arrighi, & Bullock, 2011)	C	BII	B	A	AI	B	A	9
Brayne et al. (C. Brayne et al., 2006)	A	AII	A	A	AI	A	A	15
Brayne et al. (C. Brayne et al., 2009)	A	AII	A	A	AI	A	A	15
Chen et al. (L. Chen, Reed, Happich, Nyhuis, & Lenox-Smith, 2014)	C	BII	B	A	AII	B	A	8
Clarke et al. (Clarke et al., 1996b)	A	AII	A	A	AII	A	A	14
Cook et al. (Cook et al., 2015)	C	BII	B	A	AI	B	A	9
Crugel et al. (Crugel, Paton, Singh, Jeboda, & Treloar, 2012)	D	C	B	B	AI	A	A	7
Doll et al. (Doll, Peto, Boreham, & Sutherland, 2000a)	A	C	A	A	AII	A	A	11
Dregan et al. (Dregan, Chowienczyk, & Gulliford, 2015)	A	AII	A	A	AII	B	A	13
Goh et al. (Goh et al., 2015)	A	AII	A	A	AI	B	A	14
Goldacre et al. (Goldacre et al., 2015)	D	BII	B	B	AI	A	A	8
Grant et al. (Grant, Drennan, Rait, Petersen, & Iliffe, 2013)	A	AI	B	A	AI	B	A	14
Guthrie et al. (Guthrie, Clark, & McCowan, 2010)	A	AII	B	A	AI	A	A	14
Heath et al. (Heath, Mercer, & Guthrie, 2015)	A	AI	A	A	AI	A	A	16
Houttekier et al. (Houttekier et al., 2010)	A	AII	B	A	AI	B	A	13
Imfeld et al. (Imfeld, Bodmer, et al., 2013a)	C	BII	B	A	AI	B	A	8
Imfeld et al. (Imfeld, Bodmer, Schuerch, Jick, & Meier, 2013c)	C	BII	B	A	AI	B	A	8
Imfeld et al. (Imfeld, Pernus, et al., 2013)	C	BII	B	A	AI	A	A	9
Karlinsky et al. (Karlinsky, Macdonald, & Berg, 1992)	B	AII	B	A	AII	B	B	10
Kay et al. (Kay et al., 2000)	B	AI	B	B	AII	A	A	12
Keenan et al. (Keenan et al., 2014)	A	AII	A	A	AII	A	A	14
Keenan et al. (Keenan et al., 2015)	A	AII	A	A	AI	A	A	15

Kehoe et al. (Kehoe, Davies, Martin, & Ben-Shlomo, 2013)	C	BII	B	A	AI	B	A	9
Lu et al. (N. Lu et al., 2014)	A	AII	A	A	AI	B	A	14
Martinez et al. (Martinez, Jones, & Rietbrock, 2013)	C	BII	B	A	AI	B	A	9
McCarthy et al. (McCarthy, AddingtonHall, & Altmann, 1997)	C	BII	B	A	AII	B	A	8
McGonigal et al. (McGonigal et al., 1993)	B	AI	B	B	AI	A	A	13
Morgan et al. (G. S. Morgan et al., 2012)	A	AI	A	A	AI	B	A	15
Morgan et al. (K. Morgan et al., 1992)	A	AII	A	A	AII	B	A	13
Morgan et al. (K. Morgan et al., 1993)	A	AII	A	A	AII	B	A	13
Morgan et al. (K. Morgan & Lilley, 1994)	A	AII	B	A	AII	B	A	12
Newens et al. (Newens, Forster, Kay, et al., 1993)	B	AI	B	B	AI	A	A	13
Newens et al. (Newens, Forster, & Kay, 1993)	D	BII	B	B	AI	A	A	8
Nicoll et al. (Nicoll et al., 2011)	A	AII	A	A	B	B	B	11
Palmer et al. (Palmer, Inskip, Martyn, & Coggon, 1998)	C	BI	B	B	B	B	A	7
Pendlebury et al. (Pendlebury et al., 2015)	A	AII	A	A	AI	B	A	14
Perales et al. (Perales et al., 2014)	A	AII	B	A	AI	B	A	13
Perera et al. (G. Perera, Khondoker, Broadbent, Breen, & Stewart, 2014)	C	C	B	A	AI	B	A	8
Qizilbash et al. (Qizilbash et al., 2015)	A	AII	A	A	AII	B	A	13
Rait et al. (Rait et al., 2010)	C	BII	B	A	AI	A	A	10
Renvoize et al. (Renvoize, Hanson, & Dale, 2011)	B	AI	A	B	AII	A	A	13
Reyniers et al. (Reyniers et al., 2015)	A	BII	B	B	AI	B	A	10
Russ et al. (Russ et al., 2015)	A	AI	A	A	AI	A	A	16
Ryan (D. H. Ryan, 1994)	A	AII	B	A	AI	A	A	14
Sampson et al. (Sampson, Gould, Lee, & Blanchard, 2006)	A	AII	A	B	AI	B	A	13
Seshadri et al. (Seshadri et al., 2001)	A	AII	A	A	AI	B	A	14

Shah et al. (Shah, Carey, Harris, DeWilde, & Cook, 2012)	A	AI	B	A	AII	B	A	12
Sleeman et al. (Sleeman et al., 2014)	C	BII	B	B	AI	B	A	8
Smolina et al. (Smolina et al., 2015)	A	AII	B	A	AI	B	A	13
Sorahan et al. (Sorahan & Kheifets, 2007a)	A	C	A	A	AI	A	A	12
Sorahan et al. (Sorahan & Mohammed, 2014)	A	C	A	B	AI	B	A	10
Staff et al. (Staff et al., 2010)	A	AI	A	A	AI	B	A	15
Stephens et al. (Stephens, Chikh, & Leufkens, 2014)	B	BII	B	B	AI	B	A	9
Su et al. (Su et al., 2014)	A	AII	A	A	AI	B	A	14
Valenzuela et al. (Valenzuela et al., 2012)	A	AII	A	A	AII	B	A	13
De Vries et al. (Vries & Nowell, 2011)	A	AII	B	A	AII	B	A	12
Whalley et al. (Whalley et al., 2012)	A	AI	A	A	AI	B	A	15
Whalley et al. (Whalley et al., 2000)	A	AI	B	A	AI	B	A	14
Wharton et al. (Wharton et al., 2011)	A	C	B	A	B	C	A	7
White et al. (White & Montgomery, 2015)	A	BII	B	A	AII	A	A	11
Wilcock et al. (Wilcock et al., 2013)	A	BII	B	A	AII	B	A	10
Woodburn et al. (Woodburn & Johnstone, 1999)	B	AI	B	B	AI	B	A	12
Wotton et al. (Wotton & Goldacre, 2014)	A	AII	A	A	AI	B	A	14

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Additional file 5: Table S4. Studies reporting a validation procedure.

Article	**Source/ Methodology**	**Validation/ Comparison Result**
Doll et al.(Doll et al., 2000a)	Death Certificates: Dementia 'mentioned' on death certificate.	-30% of dementia cases recorded on death certificates when compared to EURODEM statistics
Guthrie et al.(Guthrie et al., 2010)	*SPICE-PC: Read codes for dementia, OR Prescription of acetylcholinesterase inhibitor.	-prevalence approximately half of expected
Heath et al.(Heath et al., 2015)	Unnamed general practice research database: Read codes for dementia, OR Prescription of acetylcholinesterase inhibitor.	-prevalence was close to middle of expected range
Imfeld et al.(Imfeld, Pernus, et al., 2013)	*GPRD: Stage I- read code for dementia, OR, prescription for acetylcholinesterase inhibitor. Stage II- algorithm for AD or VD (based on DSM-IV, NINCDS-ADRDA, NINDS-AIREN, NICE & SIGN).	-80% AD cases and 75% VD cases confirmed by GP questionnaire -incidence rates of AD 3-6 times lower than previous studies
McGonigal et al.(McGonigal et al., 1993)	‡ISD Scotland Data for psychiatric hospitals & hospital records: Stage I: diagnostic codes for dementia in SMR, Stage II: NINCDS-ADRDA criteria and Hachinski score applied to records.	-97% of participants with pre-senile dementia were cared for within psychiatric services -annual incidence of presenile dementia determined using hospital records comparable to annual incidence rates quoted by a national study.
Newens et al.(Newens, Forster, Kay, et al., 1993)	Electronic hospital information systems: Stage I: potential cases identified by ICD-9 codes from information systems, referrals for CT with dementing process, (*and contact with services*).	-prevalence rate similar to rates documented elsewhere

	Stage II: case notes for all examined for DSM-III-R criteria for dementia, then algorithm for pre-senile AD	
Rait et al.(Rait et al., 2010)	*THIN: Read codes for dementia.	-incidence rates significantly lower than expected when compared with EURODEM and CFAS studies
Renvoize et al.(Renvoize et al., 2011)	Computerised medical and social records: Stage I: discharge diagnosis of dementia in computer system, Stage II: “criteria for dementia” from notes (criteria not specified)	-prevalence rate found to be consistent with previous studies
Russ et al.(Russ et al., 2015)	ISD Scotland data, death certificates, records for a nursing home medical practice: ICD-9 & 10 codes for dementia from SMR data and death certificates, and dementia status reported by a medical practice.	-when compared to multiple sources, death certificates missed 16-18% of cases -general practice records did not identify all cases identified by record linkage
Ryan et al.(D. H. Ryan, 1994)	‡ISD Scotland data: ICD-8 & 9 codes for dementia.	-validity rate of 84% quoted from a previous work by the same author
Seshadri et al.(Seshadri et al., 2001)	*GPRD, GP records: Stage I: computer diagnosis of dementia, Stage II: records for each reviewed to confirm diagnosis based on NINCDS-ADRDA criteria	-confirmed 48% of probable or possible AD cases according to NINCDS-ADRDA -confirmed 83% of AD cases where there was adequate data for validation
Shah et al.(Shah et al., 2012)	*THIN: Read codes for dementia	-prevalence noted to be lower than expected, based on epidemiological surveys

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Appendix 2. Supplementary material to Section 4.2

Appendix 2i

(*The published manuscript is included from the next page*)

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RESEARCH ARTICLE Open Access

Risk factors for dementia in the ninth decade of life and beyond: a study of the Lothian birth cohort 1921

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Abstract

Background: With increasing numbers of people surviving beyond eighty years, this section of the population demands attention to reduce the impact of dementia. In order to develop effective preventative strategies, it is essential to understand age-specific risk factor profiles for dementia: do risk factors for dementia in those in their sixties and seventies persist into oldest age? The aims of this study were to determine incident dementia and to investigate the risk profile for dementia from age 79 to 95 years in a well-characterised cohort.

Methods: Participants underwent intelligence testing at age 11 and were followed-up from at 79 years of age. Variables included: age, sex, age 11 IQ, *APOE* ε4, education, diabetes, hypertension, statin use, physical activity at leisure and in occupation, symptoms of depression, height, number of teeth, body mass index, blood pressure, cholesterol and HbA1c. Dementia cases were ascertained from death certificates, electronic patient records and clinical reviews. Logistic regression analysis determined the degree of risk for dementia associated with each variable. Analyses were completed both with and without the physical activity variables due to the significant number of missing data for these variables.

Results: Of the eligible cohort, $n = 410$ participants remained dementia-free and $n = 110$ had developed probable dementia. When logistic regression analyses contained all variables, complete data was available for $n = 234$ ($n = 48$ with dementia). Results demonstrated that positive *APOE* ε4 carrier status (OR: 2.15, 95% CI: 1.04, 4.42) and greater lifetime physical activity (OR: 1.14, 95% CI: 1.02, 1.28) increased the risk for dementia. A reduction in risk for dementia was seen for hypertension (OR: 0.47, 95% CI: 0.23, 0.98). When physical activity variables were excluded, the number with complete data increased to $n = 377$ ($n = 80$ with dementia). *APOE* ε4 remained significant (OR: 2.37; 95% CI: 1.37, 4.07), as did hypertension (OR: 0.55; 95% CI: 0.32, 0.93).

Conclusions: Dementia incidence was consistent with expected rates. The risk profile for dementia in this cohort of participants aged 79–95 confirmed previous findings that risk factors differ for those over 79 years. Further evidence is recommended in order that the risk profile for this age group can be accurately determined.

Keywords: Dementia, Cohort, Incidence, Risk factor

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Background

Without clear means of prevention or cure, dementia is recognised to be one of the greatest public health challenges facing the ageing global population. Dementia rates are known to increase exponentially with age, from 5.5 per 1000 person-years in those aged 70–74, to 30.5 per 1000 person-years in those aged 80–84 [1]. With increasing numbers of people surviving into the ninth decade of life and beyond [2], this section of the population demands attention in order to reduce the impact of dementia [3]. Despite studies such as the 90+ Study [4]. (North America) and the Monzino 80-plus Study [5]. (Italy) the oldest in the population remain less well represented in dementia research.

In order to develop effective preventative strategies for dementia and ensure that these are directed appropriately, it is essential to identify potentially modifiable risk factors and understand whether these persist into oldest age. Significant modifiable risk factors for dementia demonstrated by replication within the literature include: diabetes [6], hypertension [7], hypercholesterolaemia [8], depression [9], smoking [10, 11], obesity [11]. and physical inactivity [11–13]. Previous studies have proposed that the risk factor profile for dementia changes with age, but the evidence is not conclusive [14, 15].

The present study draws on prospectively collected longitudinal data from the Lothian Birth Cohort 1921 (LBC1921). Participants were predominantly cognitively normal at baseline (aged 79 years) and underwent detailed follow-up to age 95 years. As a result, this study can add further evidence to the literature regarding risk factors for dementia in the oldest-old. Most participants in this cohort had also taken part in childhood intelligence testing at age 11 years. This is an unusual and valuable feature of the data for a study cohort of the oldest-old, given that lower childhood IQ has been shown to be a putative risk factor for dementia [16]. and is associated with several modifiable risk factors [17–19]. Dementia ascertainment had not previously been performed in LBC1921 and, although a number of participants would have developed dementia during the study period, there had not been any clear means of identifying all such participants. Mini-Mental State Examination (MMSE) [20]. was performed at each wave of follow-up and a small number were seen for clinical review following concerns raised regarding their cognitive function. Some participants self-reported a new diagnosis of dementia. This would have identified only a proportion of cases. There was no previous follow-up regarding dementia ascertainment for those who had died or left the study. Given the likelihood that participants with incident dementia were less likely to attend for follow-up, death records would be a valuable source data for dementia ascertainment, particularly where a diagnosis of dementia failed to be recorded in the secondary care records.

The primary aims of this study were: i) to determine cases of incident dementia within the LBC1921 study cohort from age 79–95, and ii) to investigate whether recognised modifiable risk factors for dementia (diabetes, hypertension, hypercholesterolaemia, depression, smoking, physical inactivity, obesity) remained risk factors for dementia in the ninth decade and beyond. These modifiable risk factors were considered together with key non-modifiable factors including; age 11 IQ, *APOE* ε4 status, and measures associated with socio-economic status.

The present study primarily drew on existing data for dementia ascertainment. Given the variability in methodology for using routinely collected data in the literature, we aimed to quantify the effectiveness of our dementia ascertainment method as a secondary outcome.

Methods

Study population

The LBC1921 is described in detail elsewhere [21], and is outlined briefly here. Almost all Scottish school pupils born in 1921 had their general intelligence tested at age ~ 11 years as part of the Scottish Mental Survey 1932 [22]. Beginning in 1999, the LBC1921 was designed in order to follow up some of the same participants in later life with the primary aim of investigating non-pathological cognitive ageing [23]. The LBC1921 includes 550 participants recruited from the Lothian area of Scotland, as relatively healthy, community-dwelling volunteers, most of whom had taken part in intelligence testing in 1932. Lothian is an area in southeast Scotland in which the largest settlement is the city of Edinburgh. Participants underwent the first wave of testing at approximately 79 years of age. Those participants surviving and continuing to consent to inclusion in the study were re-tested at regular intervals, at mean ages of about 83, 87, 90 and 92 years of age. The data were collected by questionnaire and one-to-one testing and included measures of socio-demographic, psychological, cognitive, medical, physiological, and genetic factors. Those participants self-reporting a history of dementia or scoring less than 24 on the MMSE at baseline were excluded from our study (n = 11), as were those who were missing baseline MMSE data (n = 2). Deaths were ascertained prospectively, with records for participants supplied by the General Registrar's Office, Scotland [24]. Ethical approval was provided by the Lothian Research Ethics Committee (test waves 1–3) and the Scotland A Research Ethics Committee (test waves 4–5). Participants attending from wave 4 provided written consent for data linkage and access to health records.

Dementia ascertainment

Surviving participants who continued to take part in the LBC1921 study were seen for routine follow-up as described previously. Follow-up for the purposes of detecting dementia diagnoses included the retrospective collection of evidence from the sources described below, from enrolment to age 95 years. Dementia cases were determined at a final consensus meeting on 15th December 2016. Death records for deceased participants were examined for evidence of cognitive impairment or dementia. Data from death records were collected from those available by 30th June 2016. For consenting participants, data were collected from medical and psychiatric electronic patient records for services in Lothian. Patients were located in the system using their Community Health Index (CHI) number, a unique number given to each patient within Scotland, recorded at every health service contact. Each hospital record accessed was read in full and examined for evidence of dementia or cognitive impairment since enrolment in the study. This included gathering both recorded confirmed diagnoses and evidence for diagnoses. Until 2014, general and psychiatric records were held on separate systems (Trak and PIMS respectively), but all records were subsequently incorporated into the Trak system. The final date for data collection from this source was 16th May 2016. For 26 participants, additional information was available as a result of clinical assessments undertaken by the authors (JMS or TCR) in the NHS or research setting. In the research setting, assessments were undertaken when impairment or decline was noted during the routine LBC1921 testing, or when a new diagnosis of dementia was self-reported. Data from these sources were collected until the consensus date.

Each case with evidence of cognitive impairment or dementia was considered at a consensus meeting (RAS, TCR, JMS) which included both a geriatrician and a psychiatrist. The meeting agreed upon whether the evidence supported a diagnosis of dementia and determined the subtype of dementia. Depending on the strength of the evidence, the diagnosis and subtype were deemed either 'probable' or 'possible'. The criteria for probable and possible diagnoses utilised by the consensus are shown in Table 1. Any disagreement on diagnosis was resolved through discussion.

Dementia subtype diagnoses were made on a similar basis. Any dementia case with insufficient evidence to make a subtype diagnosis was classified as 'unknown' subtype. In order to minimise the risk of misclassification bias, probable dementia cases would be used as our primary outcome and possible cases would be excluded from the analyses. We would however repeat our analyses including possible dementia cases and include the results as supplementary information.

Table 1 Consensus criteria for dementia case ascertainment

CONSENSUS CRITERIA FOR DEMENTIA CASE ASCERTAINMENT	
PROBABLE DEMENTIA	POSSIBLE DEMENTIA
ANY of the following (without opposing evidence from same/other source):	ANY of the following (without opposing evidence from same/other source):
- dementia diagnosis on death certificate (any part) - dementia diagnosed on clinical review (ICD-10/DSM-IV) - dementia diagnosis in electronic general medical records (Trak) - dementia diagnosis in electronic psychiatric records (PIMS) - ICD-10 criteria for dementia diagnosis met by data within any existing records	- recorded cognitive impairment on death certificate - cognitive impairment/decline recorded in notes, but incomplete evidence to meet ICD-10 diagnostic criteria - possibility of dementia recorded in notes but no formal diagnosis/incomplete evidence to meet ICD-10 diagnostic criteria

Variables

Modifiable risk factors assessed in the present study were identified by matching those consistently reported in the literature (diabetes, hypertension, depression, hypercholesterolaemia, smoking, obesity, and physical inactivity) [12]. with data collected at LBC1921 test waves. We also included the following variables: age, sex, *APOE* ε4 status, age 11 IQ, number of teeth (as a post-retirement measure of socio-economic status [25]), height, and years in full-time, formal education. The full list of included variables is detailed in Additional file 1: Table S1.

Age at baseline was calculated according to the number of days between birth date and date attending wave 1 testing. The presence of at least one *APOE* ε4 allele was determined using genomic DNA isolated from venous blood [26]. Venous blood was also used to measure total serum cholesterol and HbA1c [21]. Any previous history of diabetes or hypertension, years in formal education, use of statins, and smoking status (previous, current or never) were self-reported by participants [26]. Body mass index (BMI) was calculated from height and weight, measured using a SECA stadiometer and digital SECA scales, respectively [27]. A trained research nurse measured sitting blood pressures (systolic and diastolic) using an Omron 705IT monitor [24]. Remaining teeth were counted during the general physical assessment [25]. Symptoms of depression were evaluated using the self-reported Hospital Anxiety and Depression Scale [28]. (HADS) at wave 1 [29]. Only the scores for the depression sub-scale were considered. Physical activity was self-reported by participants as part of a retrospective questionnaire at wave 2 follow-up (~age 83) [30]. Based on the methodology described by Hirvensalo and colleagues [31], responses were scored on a six-item scale according to increasing levels of physical activity.

Responses predominantly related to leisure based activity: necessary movement, walking, walking/outdoor exercises, exercising until sweating, exercising several times per week, keep fit/heavy exercise. Participants indicated their perceived level of physical activity at three age ranges: 20–35, 40–55 and 60–75 years [30]. A lifetime score was calculated by the sum of the three scores. The physical effort required in a participant's previous occupation was assessed using a single item [Q21] from the Job Content Questionnaire (JCQ) by Karasek [32, 33]. which was included, with permission, in the wave 2 questionnaire.

Age 11 IQ was derived from the results of the Moray House Test (MHT) no. 12, undertaken by participants in 1932 [26]. Following correction for age at testing, the cohort MHT scores were converted to IQ scores, with a standardised sample mean score of 100 and SD of 15 [26]. To demonstrate how the cohort IQ compares with the general population, we consider the raw MHT scores: 34.5 (SD: 15.5) was the mean score for Scotland, 37.3 (SD: 14.8) for those in Edinburgh schools, and 46.4 (SD: 12.1) for those recruited to LBC1921 [25].

Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics software version 21. The primary outcome of the study was the development of dementia. The analyses were completed for an outcome of probable dementia, with possible cases excluded. Univariate analysis was completed for each predictor variable, using either the Pearson chi-square or t-test. At this stage, a p value of <0.05 was used to demonstrate significant difference between those who developed dementia and those who did not. Binary logistic regression analysis was used to determine the risk for dementia associated with each predictor variable. For the purposes of logistic regression, the data for height and age 11 IQ were standardised so that a unit increase represented one standard deviation increase on the original scale. The following logistic regression models were completed using the 'backward conditional' function. The input for model 1 included all variables. The analyses for model 2 included all variables except lifetime physical activity and physical activity in occupation, which were excluded since data were missing for around one-third of participants (33.3 to 39.0% missing, with zero to 14.2% missing for all other variables). The analyses for models 1 and 2 were repeated to include both probable and possible dementia in the outcome, and the results are made available in the supplementary information.

Results

Five hundred fifty participants recruited to the LBC1921 attended the first wave of data collection. We excluded 9 participants with an MMSE score of less than 24 at baseline, 2 participants missing MMSE results at baseline, 2 participants who self-reported a diagnosis of dementia at baseline and 10 participants with no follow-up data available. The eligible cohort (n = 527) included 305 (57.9%) females and 425 (80.6%) were known to be deceased by the 30th of June 2016. The mean age in years at wave 1 was 79.1 years (SD: 0.6). *APOE* ε4 carrier status was available for 521 participants (98.9%), with 139 (26.4%) recorded as carriers. The mean (standardised) age 11 IQ score was 100.1 (SD: 14.8), calculated from the 473 scores available (89.8% of the eligible cohort). The mean MMSE score for the eligible cohort was 28.3 (SD: 1.5). Descriptive statistics for those eligible for inclusion, and those excluded are shown in Table 2.

One hundred twenty nine participants were found to have evidence of cognitive impairment or dementia in their records. A consensus diagnosis of probable dementia was agreed for 110 participants (38 probable Alzheimer disease, 25 probable vascular dementia, 9 probable mixed-type dementia, 1 probable progressive supra-nuclear palsy, 6 possible vascular dementia, 1 possible dementia in Parkinson's disease, and 30 of unknown subtype) and a diagnosis of possible dementia was determined for 7 participants (1 possible vascular dementia, 6 unknown subtype). The remaining 12 cases

Table 2 Descriptive statistics for those included & excluded from the study

	Eligible cohort participants (n = 527)	Participants excluded from study (n = 23)
Deceased		
Living	102 (19.4%)	11 (47.8%)
Deceased	425 (80.6%)	12 (52.2%)
Sex		
Male	222 (42.1%)	12 (52.2%)
Female	305 (57.9%)	11 (47.8%)
Age at wave 1		
Mean age in years	79.1 (SD: 0.6)	79.2 (SD: 0.5)
APOE ε4 carrier status		
Carrier	139 (26.4%)	7 (30.4%)
Not carrier	382 (72.5%)	15 (65.2%)
Data missing	6 (1.1%)	1 (4.3%)
Age 11 IQ		
Data available	473 (89.8%)	20 (87.0%)
Data missing	54 (10.2%)	3 (14.3%)
Mean age 11 IQ	100.1 (SD: 14.8)	97.8 (SD: 19.6)
MMSE		
Data available	527 (100%)	21 (91.3%)
Data missing	-	2 (8.7%)
Mean MMSE	28.3 (SD: 1.5)	25.2 (SD: 3.3)

considered had either insufficient information for diagnosis or evidence contradictory to a diagnosis of dementia (for example, the evidence supports a diagnosis of delirium rather than dementia). Figure 1 illustrates the number of probable cases ascertained by each data source, or combination of data sources. Almost two thirds of cases of probable dementia (63.6%) were determined based on a single source of information with the largest proportion of these single source diagnoses being based on death certificate data (Fig. 1).

All 7 cases of possible dementia were identified based on evidence from a single source (death certificate or electronic medical record). Of the 12 cases that did not meet the criteria for probable or possible dementia, 9 were determined based on a single data source, whilst the remaining 3 used two sources. The sources were as follows: 9 used evidence from the electronic medical records only, 1 used evidence from both the electronic medical records and the electronic psychiatric records and 2 used evidence from the electronic medical records and from clinical review.

Univariate analysis demonstrated significant differences between the group with probable dementia and the group without dementia for the following variables: positive *APOE* ε4 carrier status ($p < 0.001$), lower BMI at age 79 ($p = 0.026$) and current smoking status at age 79 ($p = 0.039$) (Table 3).

Following the exclusion of possible cases of dementia ($n = 7$), $n = 520$ participants were included in the logistic regression analyses, of which $n = 110$ had developed probable dementia. The results for these analyses are shown in Table 4. In both models the presence of an *APOE* ε4 allele increased the risk of dementia (model 2 OR: 2.37, 95% CI: 1.37, 4.07). A history of hypertension was associated with a decreased risk for dementia in both models (model 2 OR: 0.55, 95% CI: 0.32, 0.93). Increased height was associated with a decrease in risk for incident dementia in model 2 (model 2 OR: 0.73, 95% CI: 0.56, 0.96) and the same relationship approached significance in model 1 (model 1 OR: 0.71, 95% CI: 0.49, 1.01). A higher lifetime leisure-based physical activity score was associated with an increased risk of dementia in model 1 (OR: 1.14, 95% CI: 1.02, 1.28). Although current smoking was included in both models, the relationship with dementia did not reach significance. Age did not demonstrate an effect in any model, as might be expected in this narrow-age cohort.

To investigate the relationship with physical activity further, analysis for a third model was completed in which three individual age groups scores (20–35, 40–55, 60–75 years) replaced the lifetime physical activity score. All other variables were also included. Increased physical activity at age 20–35 years was significantly associated with incident dementia (OR: 1.35, 95% CI: 1.06, 1.73). The results of this model are shown in Additional file 2: Table S2.

Results for logistic regression analyses (models 1 and 2), repeated with possible cases included in the outcome, can be seen in Additional file 3: Table S3.

Validation study

In order to validate our case ascertainment method using existing data sources, we completed a validation

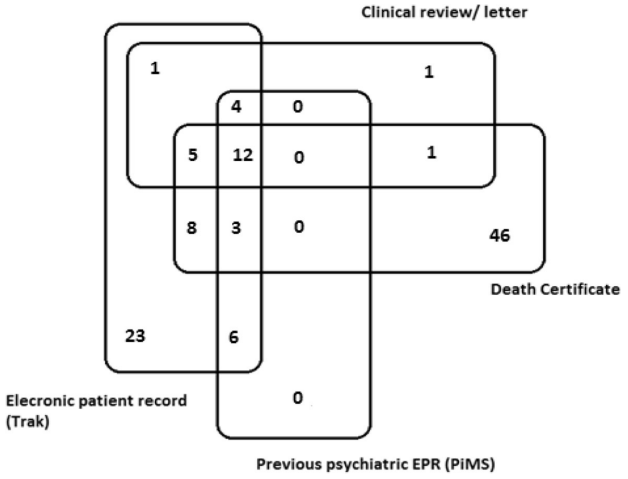

Fig. 1 Number of probable dementia cases ascertained, by data source

Table 3 Univariate analyses: comparisons between groups with and without probable dementia

Variable	No dementia (*n* = 410)	Probable dementia (*n* = 110)	Group comparison *p* value (chi-square or t-test)
Age at wave 1	*n = 410*	*n* = 110	
-mean age in years (SD)	79.1 (0.6)	79.0 (0.6)	0.610
Sex	*n = 410*	*n* = 110	
-% female	56.6	62.7	0.247
APOE ε4 carrier status[a]	*n = 404*	*n* = 110	
-% carrier *APOE* ε4	22.5	40.9	*<0.001*
Age 11 IQ (standardised)	*n = 365*	*n* = 102	
-mean score (SD)	100.0 (14.5)	100.1 (16.1)	0.948
Teeth	*n = 410*	*n* = 110	
-mean number of teeth (SD)	9.2 (9.4)	9.6 (8.9)	0.706
Height	*n = 409*	*n* = 107	
-mean height in cm (SD)	163.6 (9.4)	162.1 (9.2)	0.144
Formal education	*n = 409*	*n* = 109	
-mean number of years (SD)	10.9 (2.4)	11.0 (2.7)	0.732
History of diabetes	*n = 410*	*n* = 110	
-% positive history	5.4	4.5	0.731
HbA1c	*n = 356*	*n* = 98	
-mean HbA1c (SD)	5.7 (0.8)	5.7 (0.5)	0.703
History of hypertension	*n = 406*	*n* = 109	
-% positive history	42.1	34.9	0.171
Systolic blood pressure	*n = 408*	*n* = 109	
-mean BP in mmHg (SD)	168.9 (27.3)	166.0 (24.8)	0.315
Diastolic blood pressure	*n = 408*	*n* = 109	
-mean BP in mmHg (SD)	83.1 (13.2)	81.8 (12.3)	0.352
Statin use	*n = 347*	*n* = 99	
-% positive history	7.5	11.1	0.250
Total serum cholesterol	*n = 401*	*n* = 105	
-mean (SD)	5.7 (1.1)	5.6 (1.1)	0.891
Depression (HADS)	*n = 409*	*n* = 109	
-mean depression score (SD)	3.5 (2.3)	3.5 (2.4)	0.966
BMI	*n = 409*	*n* = 107	
-mean kg/m^2 (SD)	26.4 (4.2)	25.4 (4.0)	*0.026*
Smoking status	*n = 410*	*n* = 109	
-% current smoker	8.5	2.8	*0.039*
Lifetime physical activity	*n* = 273	*n* = 74	
-mean total lifetime score (SD)	8.7 (3.1)	9.5 (3.0)	0.058
Physical effort required in occupation	*n = 248*	*n* = 69	
-mean score (SD)	2.1 (0.8)	2.3 (0.8)	0.065

[a]One or more alleles
Italicized results demonstrate significance of $p<0.05$

study comparing diagnoses extracted from existing data with diagnoses made on clinical review. Clinical reviews were performed for 26 participants. Of the 24 who were diagnosed as having dementia on clinical review, 23 had a diagnosis of dementia in at least one source of existing data. This would suggest that we would miss 4% of cases using existing data alone. Two participants seen for clinical review were not diagnosed as having dementia,

Table 4 Logistic regression results

	Odds ratios (95% CI) for probable dementia	
	Model 1 (n = 234)	Model 2 (n = 377)
APOE ε4	2.15 (1.04,4.42)	2.37 (1.37,4.07)
Height (z score)	0.71 (0.49, 1.01)	0.73 (0.56, 0.96)
Hypertension	0.47 (0.23,0.98)	0.55 (0.32,0.93)
Current smoking	0.18 (0.02, 1.41)	0.25 (0.06, 1.09)
Lifetime physical activity	1.14 (1.02,1.28)	-

The variables entered into the analyses for each model were as follows:
Model 1- age, sex, *APOE* ε4 carrier status, age 11 IQ (z score), number of teeth, height (z score), years in education, history of diabetes, HbA1c, history of hypertension, systolic blood pressure, diastolic blood pressure, cholesterol, use of statins, HADS depression score, BMI, smoking status, physical activity in occupation, lifetime physical activity ('backward conditional' method);
Model 2- as model 1, but physical activity in occupation and lifetime physical activity excluded ('backward conditional' method)

but both had a diagnosis of dementia in the electronic medical records. This discrepancy might reflect the use of different diagnostic criteria, or the use of clinical judgement in clinical practice, particularly where evidence is ambiguous. Despite this discrepancy, our method would identify dementia in 88% of cases, with 4% being false negatives and 8% being false positives. Of the 17 cases identified as Alzheimer's disease (AD) on clinical review, 14 (82%) had AD listed as a diagnosis within at least one data source. Of the 14 cases, 5 (36%) also had a different subtype diagnosis recorded in existing data, 7 (50%) also had dementia of an unspecified subtype recorded, while 2 (14%) cases listed only AD. Of the 2 cases identified as vascular dementia on clinical assessment, 1 had vascular dementia listed as a diagnosis within the existing data. Of the 3 cases identified as mixed Alzheimer's and vascular dementia on clinical assessment 1 had a diagnosis of mixed dementia in the existing data. These findings demonstrate the usefulness of accessing records to find evidence that will support a subtype diagnosis based on recognised criteria. Our finding that overall dementia diagnoses were confirmed in 88% of cases is comparable, if not better than, validation procedures performed for other existing data sources or methodologies.

Discussion

This study found that 21.2% of eligible, initially cognitively normal participants from the LBC1921 developed dementia from age 79 to 95 years. At the time of this study, 420 of 520 eligible participants had died, including 89 who had died with dementia. A total of 21 participants with dementia were alive at age 95. Our analyses indicated that the presence of an *APOE* ε4 allele and greater lifetime leisure-based physical activity increased the risk for dementia. A history of hypertension and increased height were found to reduce the risk for dementia.

The results of this study reinforce the importance of the *APOE* ε4 allele as a risk factor for the development of dementia [34, 35]. A number of studies have suggested a decline in the importance of *APOE* ε4 as a risk factor for dementia with advancing age [34, 36]. Somewhat to the contrary, our study has determined that *APOE* ε4 continues to be a significant risk factor for incident dementia from age 79 to 95.

Our results also indicated that a history of hypertension by age 79 was associated with a reduction in risk for dementia. This result supports the findings of previous studies that have demonstrated that the association of hypertension with dementia changes towards later life [37]. We might hypothesize that persons surviving and remaining dementia-free at the ninth decade of life, are no longer subject to any increased risk as a result of vascular factors such as hypertension. In simple terms, such risk factors have been used up and those with hypertension who were at the highest risk for dementia are more likely to have died from hypertension-related diseases prior to the onset of dementia. As a result, we might expect a paradoxical effect, much like that seen in this study. This hypothesis is supported by the direction of relationship for physical activity. Previous studies have hypothesized that a reduction in blood pressure is a consequence of the development of dementia and, although this mechanism is not fully understood, several processes have been proposed [37, 38]. Blood pressure may decline in early dementia due to the direct effect of neurodegeneration at the brainstem and hypothalamic nuclei- where arterial pressure is regulated- or it may be related to systemic changes such as weight loss, or any disease effecting the ability of the cardiovascular system to maintain perfusion pressures throughout the body [38]. Another possible explanation for the reduced risk is the potentially protective effect of antihypertensive agents, particularly as it is reported that antihypertensive use in hypertension is higher in older age [39–42].

The findings relating to physical activity were more unexpected with higher levels of overall leisure activity throughout adulthood being linked with an increased risk of developing dementia. As a consequence of missing data, the findings relating to physical activity were obtained for a smaller sample size and we must therefore be cautious in drawing inferences from these findings, particularly as they contradict studies that have previously indicated a link between midlife inactivity and dementia [11, 13]. The discrepancy between our findings and those of previous studies may be related to the method of data collection for these variables. Self-reporting physical activity levels throughout life at 79 years is likely to be subject to recall bias and variability between participants.

In this cohort, one standard deviation increase in height corresponded to 9.3 cm which was associated with an approximately 27% reduction in odds of possible

or probable dementia (OR: 0.73, 95% CI: 0.56, 0.96). Our results are supported by the finding of a 2014 individual participant meta-analysis, that increasing height was related to a lower rates of death from dementia [43]. As concluded by the authors, since height is regarded as a marker of factors in early life, it may be these that are related to risk of dementia [43]. Like *APOE* ε4, we have demonstrated that decreased height continues to be a significant risk factor for dementia in oldest age. By demonstrating that certain recognised dementia risk factors are unchanged in oldest age, we can be more confident in our findings that the risk associated with other factors is changed in oldest age.

Contrary to much of the existing literature, no other factor considered in this study was found to be associated with dementia. We should consider however, that the prevalence of some conditions, including diabetes and depression, in our cohort was low and as a result, we were unlikely to detect anything except large effects, higher than those estimated by meta-analyses. [6, 9]. Power calculations determined that with binary logistic regression, setting alpha = 0.05 and the group sizes fixed at n = 410 (participants without dementia) and n = 110 (participants with dementia) with a base proportion of 5.4% (as for diabetes prevalence) in the n = 410, a minimum prevalence of 14.1% would be required in the n = 110 to detect a statistical difference with 80.0% power. Further investigation using case-control studies or much larger cohort studies are therefore required.

Moreover, given n = 110 people with dementia, the number of participants with each subtype of dementia was too few for analysis by individual subtype: combining cases of different aetiology may have affected the analysis. As previously noted, some of the data collected relied on recollection by the participant and was therefore subject to potential variability in reporting. The associations between our variables may also have affected our analyses. We attempted to minimise this as far as possible, but such bias could not be eliminated without excluding important variables. By examining many different possible predictors for dementia, in more than one model, there is also the potential for false positive findings. We limited the number of models in our analyses to two to reduce the chance of such false findings insofar as possible. A valuable strength of the study cohort is the presence of an intelligence test score from age 11 [16, 18, 21]. Each participant also underwent careful background assessment and thorough follow-up, providing a wealth of longitudinal data for the assessment of modifiable risk factors. The LBC1921 is a narrow-age cohort comprising ethnically, geographically and culturally homogenous participants, which means that we can rule out a number of potential confounding effects. Follow-up data were available for a satisfactory proportion of the original cohort to allow for analyses. The cohort demographics for those excluded from the analyses were similar to those included and it can therefore be assumed that the eligible cohort was a successful representation of the whole cohort. With a mean baseline MMSE of 28.1 (SD: 1.7) for those participants who subsequently developed dementia, we can be confident that we have identified truly incident, as opposed to prevalent, cases.

To assess the effectiveness of our dementia detection methodology, we sought to compare the incidence rate found against the rates determined by previous studies. Without knowing the age at diagnosis for a high proportion of dementia cases, the expected overall incidence over the study period had to be estimated (see Additional file 4). Had all cases of dementia been ascertained, we would have expected approximately 166 cases (see Additional file 5: Table S4). The 110 cases of dementia detected in this study therefore equates to 66.2% of the estimated number of cases arising over the same time period. This proportion is fairly consistent with a 2012 study of dementia diagnosis rates, which found that, within Lothian (the Health Board where the LBC1921 is resident), 68.3% of the expected cases of dementia had received a diagnosis [44]. We also sought to establish whether cases identified as possible dementia would be confirmed with additional follow-up. Of the 7 possible dementia cases, 5 were deceased at the time of the consensus meeting and no further follow-up could be completed. Electronic hospital records for the 2 other cases were accessed on 10th January 2017 and both contained evidence from that confirmed a formal diagnosis of dementia. It should be noted that neither case was seen for clinical review by ourselves and we did not therefore influence the diagnosis having been made.

This study has demonstrated the benefits of using multiple data sources for ascertainment. Our study returned the greatest number of cases from death certificates, which identified 68.2% of all cases of probable dementia, and 84.3% of all deceased participants with probable dementia. This finding would be in line with a previous Scottish study that found 71.5% of patients who die with dementia have the diagnosis on their death certificate [45]. Death certificates as a source of data benefit from their availability, but it is clear that the potential for missed cases remains. Many published UK studies utilising existing data for dementia ascertainment use only a single data source [46, 47]. As is the case with any dementia ascertainment procedure, the emphasis must be on achieving the most accurate representation of dementia incidence or prevalence within the population. Where possible, we would recommend that future studies consider inconsistencies between sources on a case-by-case basis. If there is reliable and consistent evidence in one source, the absence of a diagnosis in another source

should not be assumed to equate to an absence of the disease. Where there is contradictory evidence, of similar weighting, from two or more sources, external evidence can be sought to clarify the diagnosis. This may take the form of a clinical review. Where no external evidence is available or possible, cases with contradictory evidence should be classified as possible cases and excluded from the analyses due to the risk of misclassification. Using existing data offers savings in terms of researcher and participant time and the associated financial costs. This method also allows for large population studies, where clinical diagnostic work-up is not feasible due to scale.

Conclusions

In summary, the results of this study suggest that the presence of an *APOE* ε4 allele is a risk factor for incident dementia from age 79–95. A previous diagnosis of hypertension and increasing height were found to reduce the risk of incident dementia in the same age group. Increased leisure-based physical activity in adulthood was found to increase the risk for incident dementia, but including this variable in the analyses reduced the study sample size and we must therefore be cautious in drawing inferences from this finding, particularly as it contradicts previous studies. Our findings would support the hypothesis that the risk profile for dementia alters with age, however, further evidence would be required before the risk profile for the ninth decade of life and beyond could be accurately described.

Additional files

Additional file 1: Table S1. LBC1921 Data Variables for Inclusion in Analyses. (DOCX 11 kb)

Additional file 2: Table S2. Logistic Regression Analysis with Physical Activity Age Groups. (DOCX 13 kb)

Additional file 3: Table S3. Logistic Regression Analyses for Probable and Possible Dementia. (DOCX 14 kb)

Additional file 4: Estimated Dementia Incidence. (DOCX 15 kb)

Additional file 5 Table S4. Estimated Incidence of Dementia in LBC1921. (DOCX 15 kb)

Abbreviations

APOE: Apolipoprotein E; BMI: Body mass index; CHI: Community health index; HADS: Hospital anxiety and depression scale; LBC1921: Lothian Birth Cohort 1921; MHT: Moray house test; MMSE: Mini-mental state examination; NHS: National health service; PIMS: Patient information management system; Trak: TrakCare

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Availability of data and materials

The data analysed during this study are available on request from the Lothian Birth Cohort Study, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh. The data are not publically available due to them containing information that could compromise participant consent and confidentiality.

Authors' contributions

RAS, JMS and IJD contributed to the design of the study. RAS completed data collection for dementia diagnoses, statistical analyses, interpreted the results and led the writing of the paper. JMS, IJD and TCR contributed to the drafting and revision of the paper. RAS, JMS and TCR took part in the consensus meetings for dementia ascertainment. TCR assisted in the collection of data for dementia diagnoses. JMS and TCR performed clinical assessments in the NHS and research setting. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Ethical approval was provided by the Lothian Research Ethics Committee (test waves 1–3) and the Scotland A Research Ethics Committee (test waves 4–5). Participants attending from wave 4 provided written consent for data linkage and access to health records.

Publisher's Note

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Appendix 2ii

Additional file 1: Table S1. LBC1921 data variables for inclusion in analyses

LBC 1921 Data Elements Selected for Inclusion
Age- *from birth to wave 1 testing*
Sex
Age 11 IQ score (standardised)
Interview/ questionnaire measures:
Years in full-time, formal education- *self reported at wave 1*
Self-reported history of diabetes- *at wave 1*
Self-reported history of hypertension- *at wave 1*
Statin use- *at wave 1*
Self-reported smoking status- *at wave 1*
Physical activity at age 20-35, 40-55 and 60-75- *self-reported at wave 2*
Physical effort required in occupation- *self-reported at wave 2*
Symptoms of depression (HADS depression score)- *at wave 1*
Physical measures:
Number of teeth remaining- *at wave 1*
Height- *at wave 1*
Body mass index (BMI)- *at wave 1*
Sitting systolic & diastolic blood pressure- *at wave 1*
Blood measures:
Total serum cholesterol- *at wave 1*
HbA1c- *at wave 1*
APOE e4 carrier status

Additional file 2: Table S2. Logistic Regression Analysis with Physical Activity Age Groups

	Odds Ratios (95% CI) for Probable Dementia
	Model 3 (n=234)
***APOE* ε4**	2.20 (1.07. 4.53)
Height (z score)	0.69 (0.48, 1.00)
Hypertension	0.46 (0.22, 0.96)
Current smoking	0.16 (0.02, 1.29)
Physical activity, age 20-35 years	1.35 (1.06, 1.73)

Note. The variables entered into the analyses were as follows: age, sex, *APOE* ε4 carrier status, age 11 IQ (z score), number of teeth, height (z score), years in education, history of diabetes, HbA1c, history of hypertension, systolic blood pressure, diastolic blood pressure, cholesterol, use of statins, HADS depression score, BMI, smoking status, physical activity in occupation, physical activity at age 20-35, physical activity at age 40-55, physical activity at age 60-75 ('backward conditional' method).

Additional file 3: Table S3. Logistic Regression Analyses for Probable and Possible Dementia

	Odds Ratios (95% CI) for Probable and Possible Dementia	
	Model 1 (n=237)	**Model 2 (n=382)**
***APOE* ε4**		**2.24 (1.32,3.78)**
Height*		**0.74 (0.57,0.96)**
Education	**0.86 (0.74,1.00)**	
Hypertension	0.57 (0.29,1.12)	
BMI		0.95 (0.89,1.01)
Current smoker	0.31 (0.07,1.43)	0.37 (0.11,1.26)
Lifetime physical activity	**1.13 (1.01,1.25)**	-

Note. The variables entered into the analyses for each model were as follows: *Model 1*- age, sex, *APOE* ε4 carrier status, age 11 IQ (z score), number of teeth, height (z score), years in education, history of diabetes, HbA1c, history of hypertension, systolic blood pressure, diastolic blood pressure, cholesterol, use of statins, HADS depression score, BMI, smoking status, physical activity in occupation, lifetime physical activity ('backward conditional' method); *Model* 2- as model 1, but physical activity in occupation and lifetime physical activity excluded ('backward conditional' method).

Additional file 4

Estimated dementia incidence

A European meta-analysis described annual incidence rates of dementia of 1.6% in those aged 75-79 years, 3.1% in those aged 80-84 years, 4.9% in those aged 85-89 and 7% in those aged 90 and over.[1] In order to formulate the estimate, our calculations needed to take into consideration the number of participants who died in the preceding year, and the cohort size adjusted accordingly. Participants with a diagnosis of dementia at death were not counted as 'deaths' as expected cases had already been excluded from calculations for the following year as a result of a positive diagnosis. Taking the above values as the expected annual incidence rates, we would expect that of our eligible cohort of 520 participants (excluding those identified as possible dementia), 169 participants would have developed dementia by the conclusion of our study (*additional table 3*).

The 110 cases of dementia ascertained in this study therefore equates to 66.2% of the estimated number of cases arising over the same time period. Given that our ascertainment method primarily relied on diagnosed cases of dementia, it is useful to consider the proportion detected in the context of diagnostic rates for the region. A 2012 study of dementia prevalence and diagnosis rates found that within Lothian 68.3% of the expected cases of dementia had received a diagnosis.[2] We can be confident in our assumption that not all cases of dementia are diagnosed in the community, as in our cohort, cases of previously undiagnosed dementia were identified on clinical review, following concerns raised at routine follow-up. Overall, it can be seen that the number of cases of dementia ascertained in this study corresponded fairly closely to the predicted number of diagnosed cases for the same cohort. With the number of cases detected falling below the total estimate of 166.1, it is unlikely that our ascertainment method has falsely identified any

participants without dementia, as having dementia. We expected incidence to be lower in our cohort, than the rates described for the general population, as a result of higher IQ and generally good health at baseline. Conversely, these participants are motivated to take part in research and therefore may be more likely to be motivated to access health services. Further to this, undergoing regular cognitive testing may have highlighted any issues with memory that might not have been otherwise noted.

References

1. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF. **Incidence of dementia and major subtypes in Europe: A collaborative study of population based cohorts.** Neurologic Diseases in the Elderly Research Group. *Neurology* 2000; **54** (11 Suppl. 5): S10-S15.
2. Alzheimer's Society. **Mapping the Dementia Gap 2012: Progress on improving diagnosis of dementia 2011-2012.** http://www.healthcare-today.co.uk/doclibrary/documents/pdf/826_Mapping_the_dementia_gap.pdf. Accessed 9 August 2016.

Additional file 5: Table S4. Estimated incidence of dementia for LBC 1921

Age (years)	**Number disease free after previous year**	**Number deceased in the previous year**	**Sample size at age** (living, dementia-free)	**Expected annual incidence** (EURODEM)	**Estimated number of cases expected**
79	520	1	519	1.6%	8.3
80	510.7	4	506.7	3.1%	15.7
81	491	20	471	3.1%	14.6
82	456.4	22	434.4	3.1%	13.5
83	420.9	17	403.9	3.1%	12.5
84	391.4	26	365.4	3.1%	11.3
85	354.1	28	326.1	4.9%	16.0
86	310.1	24	286.1	4.9%	14.0
87	272.1	28	244.1	4.9%	12.0
88	232.1	22	210.1	4.9%	10.3
89	199.8	33	166.8	4.9%	8.2
90	158.6	20	138.6	7%	9.7
91	128.9	25	103.9	7%	7.3
92	96.6	20	76.6	7%	5.4
93	71.2	17	54.2	7%	3.8
94	50.4	15	35.4	7%	2.5
95	32.9	4	28.9	7%	2 (*deduct 1)
					Total= 166.1

*(*Less than half of the year studied, therefore 1 expected case from 2 was deducted from total)*

Appendix 2iii

Corrigendum

We contributed a paper on potential risk factors for dementia in the ninth decade of life and beyond.(Sibbett et al., 2017) Here we report some changes to the results owing to our having discovered that we did not have complete follow-up data for 31 participants who were included in our original analyses (5.9% of our previously described eligible cohort). In view of this, we cannot be completely certain that these participants had not developed dementia and we have therefore repeated our analyses following the exclusion of these participants. The changes observed in the main findings are relatively minor. Dementia incidence in the cohort was only very slightly increased from that quoted in the original paper (22.5%). The proportion of expected cases identified was greater (73%). The main logistic analyses in the original analyses (models 1 and 2) demonstrated significant relationships with dementia for four variables: *APOE* ε4, height, history of hypertension and lifetime physical activity. In the updated main analyses, significant associations with dementia were observed for the same four variables with minimal changes in odds ratios. We also found an additional significant association between use of statin medication and increased risk for dementia, which we consider should be treated with caution given that it emerges with a minor decrease in the analytic sample. For clarity we detail the resulting changes in our main findings in updates of Tables 2-4.

Tables:

Table 2 (updated): Descriptive statistics for those included & excluded from the study

	Eligible cohort participants (*n*=496)	**Participants excluded from study** (*n*=54)
Deceased		
Living	71 (14.3%)	36 (75.0%)
Deceased	425 (85.7%)	12 (25.0%)
Sex		
Male	211 (42.5%)	23 (42.6%)
Female	285 (57.5%)	31 (57.4%)
Age at wave 1		
Mean age in years	79.1 (SD: 0.6)	79.1 (SD: 0.5)
***APOE* ε4 carrier status**		
Carrier	132 (26.6%)	14 (25.9%)
Not carrier	358 (72.2%)	39 (72.2%)
Data missing	6 (1.2%)	1 (1.9%)
Age 11 IQ		
Data available	447 (90.1%)	46 (85.2%)
Data missing	49 (9.9%)	8 (14.8%)
Mean age 11 IQ	100.3 (SD: 14.9)	97.3 (SD: 16.2)
MMSE		
Data available	496 (100%)	52 (96.3%)
Data missing	-	2 (3.7%)
Mean MMSE	28.3 (SD: 1.5)	27.2 (SD: 2.8)

Table 3 (updated): Univariate analyses: comparisons between groups with and without probable dementia

Variable	**No Dementia** (n=379)	**Probable Dementia** (n=110)	**Group Comparison p value** (chi-square or t-test)
Age at wave 1 -mean age in years (SD)	n=379 79.1 (0.6)	n=110 79.0 (0.6)	0.552
Sex -% female	n=379 55.9	n=110 62.7	0.205
APOE ε4 carrier status[a] -% carrier APOE ε4	n=373 22.5	n=110 40.9	*<0.001*
Age 11 IQ (standardised) -mean score (SD)	n=339 100.2 (14.5)	n=102 100.1 (16.1)	0.938
Teeth -mean number of teeth (SD)	n=379 9.1 (9.3)	n=110 9.6 (8.9)	0.635
Height -mean height in cm (SD)	n=378 163.6 (9.5)	n=107 162.1 (9.2)	0.140
Formal education -mean number of years (SD)	n=378 10.9 (2.4)	n=109 11.0 (2.7)	0.736
History of diabetes -% positive history	n=379 5.8	n=110 4.6	0.611
HbA1c -mean HbA1c (SD)	n=329 5.7 (0.8)	n=98 5.7 (0.5)	0.771
History of hypertension -% positive history	n=375 41.9	n=109 34.9	0.189
Systolic blood pressure -mean BP in mmHg (SD)	n=377 168.6 (27.4)	n=109 166.0 (24.8)	0.374
Diastolic blood pressure -mean BP in mmHg (SD)	n=377 83.0 (13.4)	n=109 81.8 (12.3)	0.401
Statin use -% positive history	n=321 6.9	n=99 11.1	0.169
Total serum cholesterol -mean (SD)	n=371 5.6 (1.1)	n=105 5.6 (1.1)	0.983
Depression (HADS)	n=378	n=109	

-mean depression score (SD)	3.6 (2.3)	3.5 (2.4)	0.983
BMI -mean kg/m^2 (SD)	n=378 26.5 (4.2)	n=107 25.4 (4.0)	*0.027*
Smoking status -% current smoker	n=379 8.7	n=109 2.8	*0.036*
Lifetime physical activity -mean total lifetime score (SD)	n=251 8.7 (3.0)	n=74 9.5 (3.0)	*0.045*
Physical effort required in occupation -mean score (SD)	n=229 2.1 (0.8)	n=69 2.3 (0.8)	0.070

[a]One or more alleles

Italicized results demonstrate significance of $p<0.05$

Table 4 (updated): Logistic Regression Results

	Odds Ratios (95% CI) for Probable Dementia	
	Model 1 (n=221)	**Model 2 (n=355)**
***APOE* ε4**	-	2.23 (1.29,3.86)
Height (z score)	-	0.72 (0.55, 0.95)
Hypertension	0.47 (0.23,0.98)	0.63 (0.36,1.08)
Current smoking	0.14 (0.02, 1.17)	0.24 (0.05, 1.05)
Lifetime physical activity	1.17 (1.04,1.32)	-
Statin use	3.39 (1.04,11.02)	-
Years in education	0.86 (0.73, 1.01)	-

The variables entered into the analyses for each model were as follows: Model 1- age, sex, APOE ε4 carrier status, age 11 IQ (z score), number of teeth, height (z score), years in education, history of diabetes, HbA1c, history of hypertension, systolic blood pressure, diastolic blood pressure, cholesterol, use of statins, HADS depression score, BMI, smoking status, physical activity in occupation, lifetime physical activity ('backward conditional' method); Model 2- as model 1, but physical activity in occupation and lifetime physical activity excluded ('backward conditional' method)

Additional Table S2 (updated): Logistic Regression Analysis with Physical Activity Age Groups

	Odds Ratios (95% CI) for Probable Dementia
	Model 3 (n=221)
Years in education	0.86 (0.73, 1.01)
Statin use	3.16 (0.98, 10.16)
Hypertension	0.46 (0.22, 0.96)
Current smoking	0.13 (0.02, 1.08)
Physical activity, age 40-55 years	1.52 (1.12, 2.06)

Note. The variables entered into the analyses were as follows: age, sex, *APOE* ε4 carrier status, age 11 IQ (z score), number of teeth, height (z score), years in education, history of diabetes, HbA1c, history of hypertension, systolic blood pressure, diastolic blood pressure, cholesterol, use of statins, HADS depression score, BMI, smoking status, physical activity in occupation, physical activity at age 20-35, physical activity at age 40-55, physical activity at age 60-75 ('backward conditional' method).

Additional Table S3 (updated): Logistic Regression Analyses for Probable and Possible Dementia

	Odds Ratios (95% CI) for Probable and Possible Dementia	
	Model 1 (n=227)	**Model 2 (n=366)**
***APOE* ε4**	-	2.18 (1.28, 3.70)
Height (z score)	-	0.73 (0.56, 0.96)
Statin use	3.09 (0.97, 9.92)	-
Years in education	0.86 (0.74, 1.01)	-
Hypertension	0.54 (0.27,1.09)	-
BMI	-	0.94 (0.89, 1.01)
Current smoking	0.29 (0.06, 1.39)	0.36 (0.10, 1.26)
Lifetime physical activity	1.16 (1.03, 1.30)	-

Note. The variables entered into the analyses for each model were as follows: Model 1- age, sex, *APOE* ε4 carrier status, age 11 IQ (z score), number of teeth, height (z score), years in education, history of diabetes, HbA1c, history of hypertension, systolic blood pressure, diastolic blood pressure, cholesterol, use of statins, HADS depression score, BMI, smoking status, physical activity in occupation, lifetime physical activity ('backward conditional' method); Model 2- as model 1, but physical activity in occupation and lifetime physical activity excluded ('backward conditional' method).

Additional file 5: Table S4. Estimated incidence of dementia for LBC 1921

Age (years)	**Number disease free after previous year**	**Number deceased in the previous year**	**Sample size at age** (living, dementia-free)	**Expected annual incidence** (EURODEM)	**Estimated number of cases expected**
79	489	1	488	1.6%	7.8
80	480.2	4	476.2	3.1%	14.8
81	461.4	20	441.4	3.1%	13.7
82	427.7	22	405.7	3.1%	12.6
83	393.1	17	376.1	3.1%	11.7
84	364.4	26	338.4	3.1%	10.5
85	327.9	28	299.9	4.9%	14.7
86	285.2	24	261.2	4.9%	12.8
87	248.4	28	220.4	4.9%	10.8
88	209.6	22	187.6	4.9%	9.2
89	178.4	33	145.4	4.9%	7.1
90	138.3	20	118.3	7%	8.3
91	110	25	85	7%	6
92	79	20	59	7%	4.1
93	54.9	17	37.9	7%	2.7
94	35.2	15	20.2	7%	1.4
95	18.8	4	14.8	7%	1 (*deduct 0.5)
					Total= 148.7

*(*Less than half of the year studied, therefore 0.5 expected cases from 1 was deducted from total)*

References:

1.Sibbett RA, Russ TC, Deary IJ, Starr JM: **Risk factors for dementia in the ninth decade of life and beyond: a study of the Lothian birth cohort 1921**. *BMC Psychiatry* 2017, **17**(1):205.

Appendix 2iv

Additional file 1: Table S4.1. LBC1921 data variables for inclusion in analyses

LBC 1921 Data Elements Selected for Inclusion
Age- *from birth to wave 1 testing*
Sex
Age 11 IQ score (standardised)
Interview/ questionnaire measures:
Years in full-time, formal education- *self reported at wave 1*
Self-reported history of diabetes- *at wave 1*
Self-reported history of hypertension- *at wave 1*
Statin use- *at wave 1*
Self-reported smoking status- *at wave 1*
Physical activity at age 20-35, 40-55 and 60-75- *self-reported at wave 2*
Physical effort required in occupation- *self-reported at wave 2*
Symptoms of depression (HADS depression score)- *at wave 1*
Physical measures:
Number of teeth remaining- *at wave 1*
Height- *at wave 1*
Body mass index (BMI)- *at wave 1*
Sitting systolic & diastolic blood pressure- *at wave 1*
Blood measures:
Total serum cholesterol- *at wave 1*
HbA1c- *at wave 1*
APOE e4 carrier status

Additional file 2: Table S4.2 (updated): Logistic Regression Analysis with Physical Activity Age Groups

	Odds Ratios (95% CI) for Probable Dementia
	Model 3 (n=221)
Years in education	0.86 (0.73, 1.01)
Statin use	3.16 (0.98, 10.16)
Hypertension	0.46 (0.22, 0.96)
Current smoking	0.13 (0.02, 1.08)
Physical activity, age 40-55 years	1.52 (1.12, 2.06)

Note. The variables entered into the analyses were as follows: age, sex, *APOE* ε4 carrier status, age 11 IQ (z score), number of teeth, height (z score), years in education, history of diabetes, HbA1c, history of hypertension, systolic blood pressure, diastolic blood pressure, cholesterol, use of statins, HADS depression score, BMI, smoking status, physical activity in occupation, physical activity at age 20-35, physical activity at age 40-55, physical activity at age 60-75 ('backward conditional' method).

Additional file 3: Table S4.3 (updated): Logistic Regression Analyses for Probable and Possible Dementia

	Odds Ratios (95% CI) for Probable and Possible Dementia	
	Model 1 (n=227)	**Model 2 (n=366)**
***APOE* ε4**	-	2.18 (1.28, 3.70)
Height (z score)	-	0.73 (0.56, 0.96)
Statin use	3.09 (0.97, 9.92)	-
Years in education	0.86 (0.74, 1.01)	-
Hypertension	0.54 (0.27,1.09)	-
BMI	-	0.94 (0.89, 1.01)
Current smoking	0.29 (0.06, 1.39)	0.36 (0.10, 1.26)
Lifetime physical activity	1.16 (1.03, 1.30)	-

Note. The variables entered into the analyses for each model were as follows: Model 1- age, sex, *APOE* ε4 carrier status, age 11 IQ (z score), number of teeth, height (z score), years in education, history of diabetes, HbA1c, history of hypertension, systolic blood pressure, diastolic blood pressure, cholesterol, use of statins, HADS depression score, BMI, smoking status, physical activity in occupation, lifetime physical activity ('backward conditional' method); Model 2- as model 1, but physical activity in occupation and lifetime physical activity excluded ('backward conditional' method).

Additional file 4

Estimated dementia incidence

A European meta-analysis described annual incidence rates of dementia of 1.6% in those aged 75-79 years, 3.1% in those aged 80-84 years, 4.9% in those aged 85-89 and 7% in those aged 90 and over.[1] In order to formulate the estimate, our calculations needed to take into consideration the number of participants who died in the preceding year, and the cohort size adjusted accordingly. Participants with a diagnosis of dementia at death were not counted as 'deaths' as expected cases had already been excluded from calculations for the following year as a result of a positive diagnosis. Taking the above values as the expected annual incidence rates, we would expect that of our eligible cohort of 489 participants (excluding those identified as possible dementia), 148.7 participants would have developed dementia by the conclusion of our study (*additional table S4.4)*.

The 110 cases of dementia ascertained in this study therefore equates to 74% of the estimated number of cases arising over the same time period. Given that our ascertainment method primarily relied on diagnosed cases of dementia, it is useful to consider the proportion detected in the context of diagnostic rates for the region. A 2012 study of dementia prevalence and diagnosis rates found that within Lothian 68.3% of the expected cases of dementia had received a diagnosis.[2] We can be confident in our assumption that not all cases of dementia are diagnosed in the community, as in our cohort, cases of previously undiagnosed dementia were identified on clinical review, following concerns raised at routine follow-up. Overall, it can be seen that the number of cases of dementia ascertained in this study corresponded fairly closely to the predicted number of diagnosed cases for the same cohort. With the number of cases detected falling below the total estimate of 148.7, it is unlikely that our ascertainment method has falsely identified any

participants without dementia, as having dementia. We expected incidence to be lower in our cohort, than the rates described for the general population, as a result of higher IQ and generally good health at baseline. Conversely, these participants are motivated to take part in research and therefore may be more likely to be motivated to access health services. Further to this, undergoing regular cognitive testing may have highlighted any issues with memory that might not have been otherwise noted.

References

1. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF. **Incidence of dementia and major subtypes in Europe: A collaborative study of population based cohorts.** Neurologic Diseases in the Elderly Research Group. *Neurology* 2000; **54** (11 Suppl. 5): S10-S15.
2. Alzheimer's Society. **Mapping the Dementia Gap 2012: Progress on improving diagnosis of dementia 2011-2012.** http://www.healthcare-today.co.uk/doclibrary/documents/pdf/826_Mapping_the_dementia_gap.pdf. Accessed 9 August 2016.

Additional file 5: Table S4.4. Estimated incidence of dementia for LBC 1921

Age (years)	**Number disease free after previous year**	**Number deceased in the previous year**	**Sample size at age** (living, dementia-free)	**Expected annual incidence** (EURODEM)	**Estimated number of cases expected**
79	489	1	488	1.6%	7.8
80	480.2	4	476.2	3.1%	14.8
81	461.4	20	441.4	3.1%	13.7
82	427.7	22	405.7	3.1%	12.6
83	393.1	17	376.1	3.1%	11.7
84	364.4	26	338.4	3.1%	10.5
85	327.9	28	299.9	4.9%	14.7
86	285.2	24	261.2	4.9%	12.8
87	248.4	28	220.4	4.9%	10.8
88	209.6	22	187.6	4.9%	9.2
89	178.4	33	145.4	4.9%	7.1
90	138.3	20	118.3	7%	8.3
91	110	25	85	7%	6
92	79	20	59	7%	4.1
93	54.9	17	37.9	7%	2.7
94	35.2	15	20.2	7%	1.4
95	18.8	4	14.8	7%	1 (*deduct 0.5)
					Total= 148.7

*(*Less than half of the year studied, therefore 0.5 expected cases from 1 was deducted from total)*

Appendix 3. Supplementary material to Section 5.2

Supplementary material for:

Sibbett, RA et al. Physical fitness and dementia risk in the very old: a study of the Lothian Birth Cohort 1921. *BMC Psychiatry* 2017.

Contents

Additional file 1: Table S1. Group Comparison: Deceased and Living

	Eligible Participants (n=488)		**Group Comparison p value (chi-square or t-test)**
	Deceased (n=419)	**Not Deceased** (n=69)	
Age -mean age in years (SD)	n=419 79.07 (0.59)	n=379 79.12 (0.58)	0.51
Dementia or no dementia -% deceased	n=419 21.0%	n=69 30.4%	0.08
Height -Mean height in cm (SD)	n=415 163.29 (9.30)	n=69 163.13 (10.08)	0.90
APOE ε4 carrier status -% carrier APOE ε4	n=413 28.3%	n=69 17.4%	0.06
Age 11 IQ (standardised) -Mean score (SD)	n=381 99.77 (15.18)	n=59 103.12 (12.74)	0.11
FEV_1 -mean rate in litres per second (SD)	n=415 1.84 (0.62)	n=69 2.03 (0.59)	**0.02**
Grip strength -mean strength in kilograms (SD)	n=415 26.26 (9.10)	n=69 26.75 (9.59)	0.68
6 metre walk time -mean time in seconds (SD)	n=413 4.88 (2.10)	n=69 4.21 (1.10)	**0.01**
Smoking status -% ever smoker	n=418 58.9%	n=69 49.3%	0.14
History of cardiovascular or cerebrovascular disease -% positive history	n=411 28.7%	n=66 25.8%	0.62
History of hypertension -% positive history	n=415 41.5%	n=68 33.8%	0.24
History of diabetes -% positive history	n=419 6.0%	n=69 2.9%	0.30

Note: For results highlighted in bold, p<0.05

Appendix 4. Supplementary material to Section 6.2

Supplementary material for:

Sibbett, RA et al. DNA methylation-based measures of accelerated biological ageing and the risk of dementia in the oldest-old: A study of the Lothian Birth Cohort 1921. *BMC Psychiatry* 2020.

Contents

Additional file 1: Figure S1. ICD-9 and ICD-10 codes relevant to dementia ascertainment

ICD-9 Codes	ICD-10 Codes
046.1 Creutzfeldt-Jakob disease	**F00** Dementia in Alzheimer's disease
290.0 Senile dementia, simple type	**F01** Vascular dementia
290.1 Presenile dementia	**F01.1** Multi-infarct dementia
290.2 Senile dementia, depressed or paranoid type	**F02** Dementia in diseases classified elsewhere
290.3 Senile dementia with acute confusional state	**F02.0** Dementia in Pick's disease
290.4 Arteriosclerotic dementia	**F02.1** Dementia in Creutzfeldt-Jakob disease
290.8 Other senile and presenile organic psychotic conditions	**F02.2** Dementia in Huntington's disease
290.9 Unspecified senile and presenile organic psychotic conditions	**F02.3** Dementia in Parkinson's disease
291.2 Other alcoholic dementia	**F02.4** Dementia in HIV
292.82 Drug induced persisting dementia	**F03** Unspecified dementia
294.0 Korsakov's psychosis, alcoholic	**F05.1** Delirium superimposed on dementia
294.1 Dementia in conditions classified elsewhere	**F06.7** Mild cognitive disorder
294.8 Other organic psychotic conditions: Other	**G30** Alzheimer disease
294.9 Other organic psychotic conditions: Unspecified	**G30.0** Alzheimer disease with early onset
331.0 Alzheimer's disease	**G30.1** Alzheimer disease with late onset
331.1 Pick's disease	**G30.8** Other Alzheimer disease
331.2 Senile degeneration of the brain	**G30.9** Alzheimer disease, unspecified
331.82 Dementia: Lewy body	**G31.0** Circumscribed brain atrophy: Frontotemporal dementia, Pick disease, progressive isolated aphasia
333.4 Huntington's chorea	**G31.1** Senile degeneration of the brain not classified elsewhere
797 Senility without mention of psychosis	**G31.8** Other specified degenerative diseases of nervous system: Grey-matter degeneration, Lewy body(dies)(dementia)(disease), subacute necrotising encephalopathy

(ICD9Data.com; World Health Organisation, 2016)

Additional file 2: Table S1: Logistic Regression Analyses Results for EEAA, IEAA, AgeAccelPheno and AgeAccelGrim

	Odds Ratios (95% Confidence Interval) for Probable Dementia											
	Results for EEAA			Results for IEAA			Results for AgeAccelPheno			Results for AgeAccelGrim		
	Model 2 (*n*=383)	Model 3 (*n*=382)	Model 4 (*n*=371)	Model 2 (*n*=383)	Model 3 (*n*=382)	Model 4 (*n*=371)	Model 2 (*n*=383)	Model 3 (*n*=382)	Model 4 (*n*=371)	Model 2 (*n*=383)	Model 3 (*n*=382)	Model 4 (*n*=371)
Measure of age acceleration	-0.05 (-0.11, 0.00)	-0.03 (-0.07, 0.00)	-0.03 (-0.07, 0.01)	-0.04 (-0.11, 0.03)	-0.03 (-0.07, 0.01)	-0.02 (-0.07, 0.02)	-0.05 (-0.10, 0.00)	-0.02 (-0.06, 0.02)	-0.02 (-0.05, 0.02)	-0.14 (-0.27, -0.03)	-0.08 (-0.15, -0.01)	-0.07 (-0.14, 0.00)
Sex (female)	-0.16 (-0.70, 0.40)	-0.21 (-0.76, 0.34)	-0.20 (-0.78, 0.37)	-0.03 (-0.54, 0.50)	-0.14 (-0.66, 0.40)	-0.11 (-0.66, 0.44)	-0.00 (-0.51, 0.51)	-0.09 (-0.61, 0.43)	-0.07 (-0.61, 0.48)	-0.27 (-0.82, 0.27)	-0.27 (-0.83, 0.29)	-0.24 (-0.81, 0.34)
APOE ε4 (non-carrier)	-0.99 (-1.49, -0.48)	-0.99 (-1.51, -0.47)	-1.09 (-1.63, -0.55)	-0.95 (-1.46, -0.44)	-0.96 (-1.48, -0.45)	-1.06 (-1.60, -0.53)	-0.94 (-1.45, -0.43)	-0.95 (-1.47, -0.43)	-1.0 (-1.59, -0.52)	-0.91 (-1.42, -0.39)	-0.93 (-1.45, -0.41)	-1.03 (-1.57, -0.49)
Age acceleration by Sex interaction term	0.02 (-0.05, 0.10)	-	-	0.01 (-0.07, 0.10)	-	-	0.04 (-0.03, 0.12)	-	-	0.06 (-0.08, 0.20)	-	-
Smoker (never)	-	0.79 (0.29, 1.30)	0.79 (0.27, 1.32)	-	0.79 (0.29, 1.30)	0.79 (0.27, 1.32)	-	0.80 (0.30, 1.31)	0.80 (0.28, 1.33)	-	0.57 (0.02, 1.12)	0.58 (0.02, 1.16)
History of hypertension	-	-	-0.43 (-0.99, 0.10)	-	-	-0.42 (-0.97, 0.12)	-	-	-0.42 (-0.98, 0.11)	-	-	-0.47 (-1.02, 0.07)

History of diabetes	-	-	0.31 (-1.02, 1.44)	-	-	0.31 (-1.02, 1.43)	-	-	0.31 (-1.02, 1.44)	-	-	0.27 (-1.07, 1.40)
History of cardiovascular or cerebrovascular disease	-	-	-0.33 (-0.95, 0.26)	-	-	-0.34 (-0.96, 0.25)	-	-	-0.33 (-0.95, 0.26)	-	-	-0.33 (-0.95, 0.26)

Additional file 3: Table S2. Competing risk regression models for components of AgeAccelGrim

	Component of AgeAccelGrim							
	DNAm ADM	**DNAm B2M**	**DNAm CystatinC**	**DNAm GDF15**	**DNAm Leptin**	**DNAm PAI1**	**DNAm TIMP1**	**DNAm PACKYRS**
Component of AgeAccelGrim	0.99 (0.98, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.97 (0.95, 0.99)
Sex (female)	1.33 (0.82, 2.16)	1.10 (0.72, 1.70)	1.07 (0.68, 1.69)	1.07 (0.69, 1.66)	0.86 (0.39, 1.89)	1.13 (0.72, 1.77)	1.04 (0.67, 1.61)	0.94 (0.60, 1.47)
APOE ε4 (non-carrier)	0.43 (0.28, 0.65)	0.43 (0.28, 0.65)	0.43 (0.28, 0.66)	0.44 (0.29, 0.67)	0.43 (0.28, 0.66)	0.43 (0.28, 0.65)	0.44 (0.29, 0.67)	0.46 (0.30, 0.70)

Additional file 4: Table S3. Logistic regression models for components of AgeAccelGrim

	Component of AgeAccelGrim							
	DNAm ADM	**DNAm B2M**	**DNAm CystatinC**	**DNAm GDF15**	**DNAm Leptin**	**DNAm PAI1**	**DNAm TIMP1**	**DNAm PACKYRS**
Component of AgeAccelGrim	-0.01 (-0.02, 0.00)	-1.39 (-3.85, 9.33)	-6.94 (-1.80, 3.44)	-0.00 (-0.00, 0.00)	3.88 (-6.45, 0.00)	1.39 (-1.94, 2.09)	-0.00 (-0.00, 0.00)	-0.04 (-0.06, -0.01)
Sex (female)	0.29 (-0.27, 0.86)	7.11 (-4.26, 5.79)	3.54 (-4.67, 5.47)	0.03 (-0.47, 0.54)	-1.95 (-1.07, 0.68)	9.58 (-0.42, 0.62)	-0.03 (-0.54, 0.49)	-0.12 (-0.64, 0.41)
APOE ε4 (non-carrier)	-0.97 (-1.48, -0.46)	-9.69 (-1.47, -4.63)	-9.70 (-1.48, -4.64)	-0.95 (-1.45, -0.44)	-9.58 (-1.46, -0.45)	-9.71 (-1.48, -0.47)	-0.96 (-1.46, -0.45)	-0.89 (-1.40, -0.38)

Additional file 5: Table S4. Pearson correlations for epigenetic age acceleration measures in LBC1921

	IEAA	EEAA	AgeAccelGrim	AgeAccelPheno
IEAA	1	0.394*	0.259*	0.403*
EEAA	0.394*	1	0.439*	0.424*
AgeAccelGrim	0.259*	0.439*	1	0.416*
AgeAccelPheno	0.403*	0.424*	0.416*	1

*Note. n=383. *Correlation is significant at the 0.01 level (2-tailed)*

Appendix 5. Supplementary material to Section 7.2

Supplementary material for:

Sibbett, RA et al. Does incipient dementia explain normal cognitive decline determinants? Lothian birth cohort 1921. *Psychology and Aging* 2018

Contents

Supplementary File A: Supplementary Tables

Note: This supplementary file contains seven tables that display the complete results for each main analysis, as described in the main text.

Table S1. *Main Analysis and Terminal Decline Analysis Results for APOE ε4 (paper 1)*

	Main Sensitivity Results			Terminal Decline Results		
	F	**Significance**	**Effect Size (η_p^2)**	**F**	**Significance**	**Effect Size (η_p^2)**
Age 11 IQ	239.4	<0.001	0.40	200.47	<0.001	0.396
Sex	4.76	0.03	0.013	2.63	0.106	0.009
***APOE* ε4**	4.27	0.039	0.012	1.30	0.255	0.004
***APOE* ε4*Sex**	0.001	0.98	<0.001	0.417	0.519	0.001

Table S2. *Main Analysis and Terminal Decline Analysis Results for APOE ε4 (Paper 2)*

		Main Sensitivity Results			Terminal Decline Results		
	Dependent Variable	**F**	**Significance**	**Effect Size (η_p^2)**	**F**	**Significance**	**Effect Size (η_p^2)**
***APOE* ε4 Carrier**	Verbal Fluency score- age 79	0.19	0.664	0.001	0.59	0.443	0.002
	Ravens Matrices score- age 79	3.57	0.060	0.010	1.89	0.170	0.006
	Logical Memory score- age 79	8.16	0.005	0.022	2.95	0.087	0.010
Sex	Verbal Fluency score- age 79	0.52	0.470	0.001	0.04	0.845	<0.001
	Ravens Matrices score- age 79	10.92	0.001	0.030	2.41	0.122	0.008
	Logical Memory score- age 79	1.23	0.268	0.003	3.20	0.075	0.010
Age 11 IQ	Verbal Fluency score- age 79	26.49	<0.001	0.069	21.62	<0.001	0.066
	Ravens Matrices score- age 79	85.49	<0.001	0.194	69.31	<0.001	0.186
	Logical Memory score- age 79	30.38	<0.001	0.079	24.95	<0.001	0.076

Table S3. *Main Analysis and Terminal Decline Analysis Results for Smoking*

	Main Sensitivity Results			Terminal Decline Results		
	F	**Significance**	**Effect Size (η_p^2)**	**F**	**Significance**	**Effect Size (η_p^2)**
Age 11 IQ	231.09	<0.001	0.391	191.49	<0.001	0.383
Sex	3.12	0.078	0.009	1.89	0.170	0.006
Smoker	3.67	0.026	0.020	1.97	0.141	0.013
Smoker*Sex	1.38	0.252	0.008	1.46	0.235	0.009

Table S4. *Main Analysis and Terminal Decline Analysis Results for Vitamin B-12*

		Main Sensitivity Results				Terminal Decline Results			
Model	**Variable**	**Beta**	**Beta SE**	**Standardised Beta**	**Significance**	**Beta**	**Beta SE**	**Standardised Beta**	**Significance**
Model 1	Age 11 IQ	0.585	0.045	0.584	<0.001	-	-	-	-
	B-12*	1.771	0.642	0.124	0.006	-	-	-	-
Model 2	Age 11 IQ	0.612	0.045	0.611	<0.001	0.569	0.046	0.609	<0.001
	Sex	-3.257	1.272	-0.115	0.011	-2.825	1.285	-0.108	0.029
	APOE ε4 status	1.884	1.505	0.056	0.211	0.394	1.553	0.012	0.800
	Smoking status	1.428	0.995	0.065	0.152	1.220	1.022	0.059	0.234
	Statin use	4.238	2.517	0.080	0.093	3.513	2.599	0.070	0.178
	Total number of drugs	-0.947	0.281	-0.159	0.001	-1.072	0.284	-0.194	<0.001
	B-12*	1.535	0.624	0.110	0.014	1.127	0.631	0.087	0.075

Note. *Standardised as z-scores

Table S5. *Main Analysis and Terminal Decline Analysis Results for Physical Fitness*

	Main Sensitivity Results					Terminal Decline Results				
	R^2 change	**Beta**	**Beta SE**	**Standardised Beta**	**Significance**	**R^2 change**	**Beta**	**Beta SE**	**Standardised Beta**	**Significance**
Age 11 IQ	0.383	0.549	0.042	0.559	<0.001	0.385	0.534	0.044	0.558	<0.001
Fitness trait	0.047	2.976	0.559	0.209	<0.001	0.048	2.851	0.602	0.203	<0.001
Social class	0.18	-2.285	0.726	-0.136	0.002	0.013	-1.913	0.763	-0.116	0.013
Sex	0.08	-2.535	1.135	-0.088	0.026	0.007	-2.335	1.170	-0.085	0.047

Note. Smoking status and *APOE* ε4 carrier status did not enter the model (p>0.05).

Table S6. *Multivariable Linear Regression Results: All main variables and Age 79 IQ Scores*

	R^2 change	Beta	Beta SE	Standardised Beta	Significance
Age 11 IQ	0.342	0.562	0.043	0.563	<0.001
Fitness trait	0.058	3.658	0.620	0.255	<0.001
Vitamin B-12*	0.021	2.507	0.735	0.147	0.001
Sex	0.013	-3.284	1.226	-0.115	0.008

Note. *Vitamin B-12 standardised as z-scores. Smoking status and *APOE* ε4 carrier status did not enter the model (p>0.05).

Table S7. *Multivariate General Linear Modelling Results: All Main Variables and Verbal Fluency, Raven's Matrices and Logical Memory Test Scores*

	Dependent Variable	F	Significance	Partial Eta Squared
***APOE* ε4 Status**	Verbal Fluency score- age 79	0.44	0.506	0.001
	Ravens Matrices score – age 79	1.85	0.175	0.006
	Logical Memory score- age 79	5.47	0.020	0.018
Sex	Verbal Fluency score- age 79	0.32	0.575	0.001
	Ravens Matrices score – age 79	13.27	<0.001	0.042
	Logical Memory score- age 79	1.15	0.284	0.004
Age 11 IQ	Verbal Fluency score- age 79	18.96	<0.001	0.059
	Ravens Matrices score – age 79	66.79	<0.001	0.182
	Logical Memory score- age 79	21.35	<0.001	0.066
Smoking Status	Verbal Fluency score- age 79	0.50	0.609	0.003
	Ravens Matrices score – age 79	0.84	0.432	0.006
	Logical Memory score- age 79	0.48	0.617	0.003
Vitamin B-12*	Verbal Fluency score- age 79	0.38	0.539	0.001
	Ravens Matrices score – age 79	3.82	0.052	0.013
	Logical Memory score- age 79	0.878	0.349	0.003
Fitness	Verbal Fluency score- age 79	12.28	0.001	0.039
	Ravens Matrices score – age 79	17.98	<0.001	0.056
	Logical Memory score- age 79	0.24	0.627	0.001

Note. *Vitamin B-12 standardised as z-scores

Supplementary File B: Risk Factor and Dementia Interactions

Following each of the main individual analyses, we completed a subsequent analysis in which participants with probable dementia or no dementia were included. We excluded participants with possible dementia. Forming a between-groups variable (dementia or no dementia), we included an interaction term with the risk factor (e.g. dementia status*smoking status) to determine whether the effect of the risk factor varied as a function of the dementia group.

APOE ε4 Paper 1: Moray House Test (MHT) score as outcome.(Ian J. Deary et al., 2002)

When we included those participants without dementia (n=363) and those with probable dementia (n=101)—a future diagnosis of probable dementia was associated with a lower standardised MHT score at age 79 ($F_{1,456}$=8.13, p=0.005, η_p^2=0.018). The *APOE* ε4 carrier status by dementia status interaction was not significant ($F_{1,456}$=1.10, p=0.30, η_p^2=0.002), demonstrating that the effect of *APOE* ε4 was not significantly different between the two dementia groups. The mean MHT score (standardised) at age 79 (95% CI) for *APOE* ε4 carriers was 96.47 (92.88, 100.06) for those with dementia and 98.89 (96.43, 101.35) for those without dementia. The mean MHT score at age 79 for *APOE* ε4 non-carriers was 96.48 (93.70, 99.27) for those with dementia and 101.73 (100.43, 103.03) for those without dementia.

APOE ε4 Paper 2: Logical Memory, Raven's Matrices, and verbal fluency as outcomes.(I. Deary, Whiteman, Pattie, & Starr, 2004)

When the analysis was repeated with the inclusion of probable dementia cases, a future diagnosis of dementia was found to contribute to Raven's Matrices ($F_{1,454}$= 8.24, p=0.004, η_p^2 =0.018) and Logical Memory test scores ($F_{1,454}$= 5.65, p=0.018, η_p^2 =0.012) at age 79. The *APOE* ε4 carrier status by dementia status interaction was

associated with Raven's Matrices test score at age 79 ($F_{1,454}$= 7.75, p=0.006, η_p^2 =0.017) but not Logical Memory ($F_{1,454}$=0.49, p=0.484, η_p^2 =0.001) or Verbal Fluency test scores ($F_{1,454}$= 0.20, p=0.66, η_p^2=<0.001). The effect of *APOE* ε4 on Raven's Matrices test score was therefore different between those who developed dementia and those who did not, but no difference was noted for Logical Memory or Verbal Fluency. The mean (95% CI) Raven's Matrices test score for *APOE* ε4 carriers was 30.84 (29.19, 32.49) for those without dementia and 30.79 (28.45, 33.12) for those who developed dementia. For noncarriers, the mean test score was 32.65 (31.77, 33.53) for those without dementia and 27.58 (25.71, 29.45) for those who developed dementia.

Smoking

Repeating the main analysis with the inclusion of participants who developed probable dementia (n=100) and participants who remained dementia free (n=367), we found that dementia was associated with age 79 IQ ($F_{1,457}$=6.60, p=0.01, η_p^2 =0.014). The smoking status by dementia status interaction was not associated with age 79 IQ ($F_{2,457}$=0.513, p=0.599, η_p^2 =0.002). The effect of smoking was not therefore significantly different between the dementia groups. For those without dementia, the estimated marginal mean scores (95% CI) were 96.25 (92.24, 100.25) for current smokers, 101.28 (99.72, 102.85) for ex-smokers and 102.29 (100.43, 104.14) for never-smokers. For those who developed probable dementia, the mean scores were 87.40 (74.87, 99.24) for current smokers, 97.61 (94.28, 100.93) for ex-smokers and 96.53 (93.51, 99.54) for never-smokers.

Vitamin B-12

When we include only those participants with probable dementia (n=101) or no dementia (n=367), there was no significant association between the interaction term (dementia and vitamin B-12) and age 79 IQ ($S\beta$=-0.030, p=0.463). Future probable dementia was shown to be associated with age 79 IQ ($S\beta$=-0.141, p<0.001).

Physical Fitness

Including in the analysis only those with probable dementia (n=97) or no dementia (n=359) – the interaction variable between dementia and fitness did not enter the model ($p>0.05$). Future probable dementia was again associated with age 79 IQ ($S\beta$=-0.14, $p<0.001$, R^2=0.021).

References

Deary, I. J., Whiteman, M. C., Pattie, A., Starr, J. M., Hayward, C., Wright, A. F., . . . Whalley, L. J. (2002). Cognitive change and the APOE epsilon 4 allele. Nature, 418, 932–932. https://doi.org/10.1038/418932a

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Appendix 6. Abbreviations

£	Pound Sterling
AD	Alzheimer's Disease
ADM	Adrenomedullin
AgeAccelGrim	Age acceleration measure based on GrimAge procedure
AgeAccelPheno	Age acceleration measure based on PhenoAge procedure
APA	American Psychiatric Association
APOE	Apolipoprotein E
APP	Amyloid precursor protein
B2M	Beta-2 microglobulin
BBC	British Broadcasting Corporation
BBSRC	UK Biotechnology and Biological Sciences Research Council
BMI	Body mass index
BP	Blood Pressure
CC75C	Cambridge City over-75s Cohort
CHI	Community health index
CpG	Cytosine and guanine separated by only one phosphate group
CPRD	Clinical Practice Research Database
CRR	Competing risk regression
CSF	Cerebrospinal fluid
CSO	Chief Scientist Office
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic Acid
DNAm	DNA methylation
DNAm GrimAge	A DNA methylation-based measure of epigenetic age
DNAm PhenoAge	A DNA methylation-based measure of epigenetic age
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-V	Diagnostic and Statistical Manual of Mental Disorders- version 5
EEAA	Extrinsic epigenetic age acceleration
FEV_1	Forced expiratory volume in 1 second
GDF-15	Growth differentiation factor 15

GPRD	General Practice Research Database
HAA	Hospital Activity Analysis
HADS	Hospital anxiety and depression scale
HDRUK	Health Data Research United Kingdom
HR	Hazard Ratio
ICD	International Classification of Diseases
ICD 9 or 10	International Classification of Diseases version 9 or 10
IEAA	Intrinsic epigenetic age acceleration
IQ	Intelligence quotient
ISD	Information Services Division
LBC1921	Lothian Birth Cohort 1921
LPA	Lasting Power of Attorney
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MHE	Mental Health Enquiry
MHT	Moray House Test
MRC	Medical Research Council UK
MRC CFAS Study	Medical Research Council Cognitive Function and Ageing
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological and Communicative Disorders and Stroke and Association pour la Recherché at l'Enseignement en Neurosciences
NLSAA	Nottingham Longitudinal Study of Activity and Ageing
ONS	Office for National Statistics
OR	Odds Ratio
PACKYRS	Smoking pack years
PAI-1	Plasma activator-inhibitor 1
PCR	Polymerase chain reaction
PET	Positron emission tomography (scan)

PiMS	Patient Information Management System (electronic patient record system)
SBP	Systolic blood pressure
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SMS1932	Scottish Mental Surveys 1932
SPICE-PC	Scottish Programme for Improving Clinical Effectiveness – Primary Care
THIN	The Health Improvement Network
TIMP-1	Tissue inhibitor metalloproteinase 1
Trak	TrakCare (electronic hospital patient records)
UK	United Kingdom
UK DRI	United Kingdom Dementia Research Institute
UN	United Nations
US$	American Dollars
USA	United States of America
VD	Vascular dementia
WHO	World Health Organisation
WISE	Women Cognitive Impairment Study of Exceptional Aging
95% CI	Ninety-five percent confidence interval