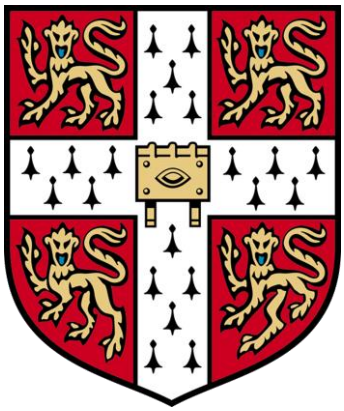
The Epidemiology of Cognitive Function In a Community Based Population. The EPIC-Norfolk Study



Shabina Anwar Hayat

Darwin College
University of Cambridge

This dissertation is submitted for the degree of

Doctor of Philosophy

May 2020

Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text and acknowledgment. Parts of the work described in this thesis have been published or presented elsewhere as indicated clearly in the beginning of the relevant chapter or in the text. The dissertation is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution.

This thesis was undertaken in the Department of Public Health and Primary Care in Cambridge under the supervision of Professors Carol Brayne and Kay-Tee Khaw. The dissertation length does not exceed the 60,000 words limit stipulated by the School of Clinical Medicine.

Summary

The Epidemiology of Cognitive Function in a Community Based Population. The EPIC-Norfolk Study

PhD dissertation by Shabina A. Hayat

Although age is the strongest known risk factor, not all people who reach old age develop dementia before they die. Recommendations on potentially modifiable risk factors for the prevention of dementia are based on evidence that is, at best, moderate in strength. There are major calls to strengthen the evidence on potentially modifiable risk factors of dementia.

The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) is a prospective population study of 25 639 men and women aged 40–79 years first recruited in 1993-1997, who attended a health examination. Subsequent follow-ups have involved self-report of health and lifestyle and further health examinations. Cognitive measures (7 tests assessing a range of domains) were introduced as part of a third health examination between 2006 and 2011 (including data from a pilot phase 2004–2006) and are available on 8585 individuals. Almost complete follow-up for disease outcomes, including dementia and mortality, has been established via linkage to health records.

Education was strongly associated with cognitive function for all abilities tested. Cross-sectional and prospective analyses showed those who were physically inactive during work, were less likely to have poor cognition (bottom tenth percentile of a composite cognition score); Odds Ratio (OR) = 0.68 (95% Confidence Interval or CI 0.54, 0.86 P=0.001). In contrast, inactivity during leisure time was associated with increased risk of poor performance in the cross-sectional analyses, although this association was not observed in the prospective analyses. Poor cognition was independently associated with higher risk of all-cause mortality and predictive of incident dementia. Associations were observed for the composite score (global cognition) as well as specific cognitive abilities. Poor cognition in four or more tests was associated with ten-fold increased risk of developing dementia compared with those who did not perform poorly in any test OR=10.82 (95% CI 6.85, 17.10 P<0.001). Addition of each cognitive measure strengthened prediction models of dementia further, Area under the curve (AUC) = 0.85 (95% CI 0.82, 0.87 P<0.001), with the single test for episodic memory having the strongest influence.

Routinely collected health records are increasingly encouraged and used for epidemiological research for dementia outcome ascertainment. The linkage of the cohort to diverse routine records enabled comparison of these data sources. I provide evidence for the need of a more consensus-based approach to the methods of data collection, coding and interpretation of health data across all sources examined (hospital inpatient, mortality and mental health services datasets).

In summary, the findings from this dissertation suggest the relationships between lifestyle factors, poor cognition and dementia are complex. For stronger evidence, future studies need to account for characteristics of the sample population and for the test used to measure cognition. Furthermore, there is a need for a more nuanced approach to the way the exposure of interest as well as dementia outcomes are measured and to adequately address the issue of potential confounding.

FOR MY BELOVED PARENTS (MAMA AND BABA)

Acknowledgments

I would like to offer my sincerest thanks to both my supervisors, Professors Kay-Tee Khaw and Carol Brayne who have supported and guided me throughout the course of my PhD. They were encouraging, inspirational and always available for advice and guidance whenever I needed it. I am indebted to Professor Khaw who has always been so supportive throughout my career at EPIC-Norfolk and for encouraging me to do this PhD. She has been there every step of the way, offering her time and guidance even after her retirement, for which I will be forever grateful. I am extremely grateful to Professor Brayne who has shown such kindness and patience and has always believed in me. I am also grateful to the late Professor Sheila Bingham whose recommendation, changed the course of my career. It has been a privilege to have worked with such strong and inspirational women, who have been excellent role models as well as leaders in their field.

I would like to thank each and every member of the EPIC-Norfolk team, both in the research team based in Cambridge and the clinic team in Norwich who were more like family members than colleagues. In particular, I would like to thank Nichola Dalzell who played a key role in the set up and running of the 3HC and assisted me with the dementia case ascertainment. Nicola has not only been a brilliant and reliable colleague, but a wonderful friend and support for many years. I would also like to Professor Paul Foster for his encouragement and his friendship. A special thanks to Jen, Tori, Anthony, Ali Reza, Phyo, Yue and all the other EPIC PhD students I had the pleasure to work with. A big thanks also to Ailsa, Daksha, Steph, Nicole, Neha, Marleen (particularly for her help with SPSS), Angela and Carolyn for all their hard work as well as their support and friendship.

I am particularly grateful to Robert Luben who has been a colleague, friend and a fellow PhD. I am thankful for his help in every aspect of this PhD, from making sense of the datasets through to his insightful comments in the manuscripts we co-authored. I will always cherish the times we spent together, first running the EPIC-Norfolk study and then completing our PhDs together. It has been a great journey with a very good friend.

I would like to thank my lovely family for their prayers and positive encouragement, especially my ‘sisters’ Baji Tahira, Nasreen (Nushie), Naheed (Nani), Samina (Mina), as well as Nomaan (Nomi), Reema, Zahira, Sharah, Sufyan, Aliya and my dearest Rohma. Also, my wonderful friends Shahzia, Jas, Shamsa and Robina who have always been there for me. I want to say a special thanks to my brother Anjum (bhai) and sister Shahina (Tina) who are so much than just my siblings. They have supported me, encouraged me to study further and always had so much faith in me. I am proud to be their sister.

I would also like to thank my dearest Rahil and Zayna (my first babies), and my lovely Umar and Farah for all their love and support.

I want to thank my husband Nasir for his caring support, especially during the Covid-19 lockdown period. I could not have done this without him. I would also like to say a big thank you to my lovely son Yusuf, who would quietly close the door whilst I was studying, so that I would not be disturbed and a special thanks to my beautiful daughter Yasmin whose comforting words and special hugs have got me through some stressful times. I will always be grateful for the love she has given me.

I am grateful for the prayers of my loving father-in-law, who was so proud that I was a scientist, and my brother-in-law, Rafiq Hayat for his continuous encouragement. Finally, I give thanks for my beloved parents, who sadly left this world too soon. They taught me to always be willing to learn, work hard and persevere, regardless of how difficult the task may be and to them I dedicate this thesis.

EPIC-Norfolk Research Team (2004–2018)

Contributors

Principal Investigators: Nick Day, Kay-Tee Khaw, Sheila Bingham, Nicholas J. Wareham
Carol Brayne (Cognition component)

Study design and management: Robert Luben, Nichola Dalzell

Data management: Robert Luben, Amit Bhaniani, Serena Anuj, Caroline Brechin, Neha Shah and Connie Tang

Research assistants: Nicole Llewellyn Stephanie Moore, Elliott Grigg

Study administration / assistants Daksha Parmer, Sandra Owen, Rachel Webb

Clinical Team

Senior EPIC Research Nurses: Anna McVittie, Peta Kerrigan, Karen Banks-Dunnell

EPIC Research Nurses: Karen Smith, Josephine Fillery, Susan Allen, Anne Lazar, Jilly Gourlay, Mark Francis, Brian Emeney, Jayne Taylor, Mary Graydon, Jenny Jagger, Joy Blackburn, Judith Gowlett, Maureen Stuart, Lisa Davies

EPIC clinic study assistants: Cristina Bouchcinsky, James Lawton, Sue Harvey
Staff Training (Cognition): Linda Barnes (MRC CFAS)
PhD Support: Marleen Lentjes, Angela Mulligan, Fiona Matthews, Richard Merrick, Simon White, Sarah Asad

Participant Involvement: As part of the research process, the EPIC-Norfolk team actively promoted the involvement of participants. A participants' advisory panel. (EPAP: EPIC Participant Advisory Panel) advised on various aspects of the study and gave their views on potential future projects. Although, the panel did not contribute to the work used in this thesis, I am very grateful for the support of the panel members. I was closely involved in the running of this advisory group during my time as the Research Manager/Coordinator for the EPIC-Norfolk Study from inception of EPAP in 2010 until December 2018.

Supporting Publications

Hayat, S.A., Luben R, Wareham N, Khaw K.T, Brayne C (*2020*). Cross-sectional and prospective relationship between occupational and leisure time inactivity and cognitive function in an ageing population. The European Prospective Investigation into Cancer and Nutrition in Norfolk (EPIC-Norfolk) Study. International Journal of Epidemiology, 2020, 1–15

Hayat, S. A., Luben, R., Dalzell, N., Moore, S., Hogervorst, E., Matthews, F. E., Khaw, K.T. (2018). Understanding the relationship between cognition and death: a within cohort examination of cognitive measures and mortality. Eur J Epidemiol, 33(11), 1049-1062.

Hayat, S. A., Luben, R., Dalzell, N., Moore, S., Anuj, S., Matthews, F. E., Khaw, K.T. (2016). Cross Sectional Associations between Socio-Demographic Factors and Cognitive Performance in an Older British Population: The European Investigation of Cancer in Norfolk (EPIC-Norfolk) Study. *PLoS One*, *11*(12), e0166779.

Hayat, S. A., Luben, R., Moore, S., Dalzell, N., Bhaniani, A., Anuj, S. Brayne, C. Khaw, K.T (2014). Cognitive function in a general population of men and women: a cross sectional study in the European Investigation of Cancer-Norfolk cohort (EPIC-Norfolk). *BMC Geriatr*, *14*, 142.

Hayat, S. A., Luben, R., Keevil, V., Moore, S., Dalzell, N., Bhaniani, A., Khawaja, A, Foster, P, Brayne C Khaw, K.T (2014). Cohort Profile: A prospective cohort study of objective physical and cognitive capability and visual health in an ageing population of men and women in Norfolk (EPIC-Norfolk 3). *International Journal of Epidemiology*, *43*(4), 1063-1072.

Conferences

Society for Social Medicine & Population Health 2020 virtual meeting
Poster presentation (Thursday 10th September 2020)
Title: Performance on different cognitive tests predict future dementia: fifteen years of follow-up in a British cohort study.

Alzheimer's Research UK, Research Conference 2019 (Harrogate, UK)
Oral Presentation and Abstract (Monday 18th March 2019)
Title: The association of inactivity/sedentary behaviour during occupational and leisure time and cognitive performance: Findings from a British prospective cohort study.

Abbreviations

6-CIT, 6-item Cognitive Impairment Test

A Level, Advanced Level

ACE or ACE-R, Addenbrooke's Cognitive Examination, or ACE (Revised version)

CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test

CI, Confidence Interval

DDR, Dementia diagnosis rate

DSM V, Diagnostic and Statistical Manual of Mental Disorders (fifth edition)

EPIC-Norfolk, European Investigation into Cancer in Norfolk

Freq, Frequency

FTMS, First Trial Memory Score (outcome measure for CANTAB-PAL)

GP, General Practitioner

GPCOG, General Practitioner Assessment of Cognition

HSCIC, Health and Social Care Information Centre

HVLT, Hopkins Verbal Learning Test

HR, Hazard ratio

ICD -10, International Classification of Diseases (10th revision)

MCI, Mild Cognitive Impairment

MHLDDS, Mental Health and Learning Disabilities Data Set

MHMDS, Mental Health Minimum Data Set

MHSDS, Mental Health Services Data Set

MMSE, Mini Mental State Exam

MRC-CFAS, Medical Research Council Cognitive Function and Ageing Study

N, Number

NART, National Adult Reading Test (Short-NART, shortened version)

NHS, National Health Service

NSFT, Norfolk and Suffolk Foundation Trust

O Level, Ordinary Level

OR, Odds ratio

PW-Accuracy Accuracy Score, for the letter cancellation task

QOF, Quality and Outcomes Framework

RCGP, Royal College of General Practitioners

SD, Standard deviation

SF-EMSE, Shortened version (Short form) of the Extended Mental State Exam

VST, Visual Sensitivity Test

Table of Contents

List of Tables

List of Figures

List of Boxes

Personal contribution

My personal contributions to the EPIC-Norfolk Study and the work presented in this thesis include:

1. Study design, overall management and set up of the third health examination phase of the EPIC-Norfolk Study (3HC), and continued management until December 2018
2. Writing of all the SOPs and training of staff over the 8 year period of the of the 3HC in particular with regards to the cognition battery
3. Involved with all aspects on data cleaning for the cognitive measures
4. Working with collaborators to modify the tests to allow them to be used in an epidemiological setting (i.e. shortening of test time, selection of outcome measures and recording of data)
5. Prioritising testing of participants to maximise ascertainment of cognitive data
6. Dementia case ascertainment from GP practices between 2016-2018
7. Responsibility for all research governance for EPIC-Norfolk since 2002-2018
8. Lead applicant for acquiring the NHS Digital data for health and mortality endpoints, including the mental health dataset
9. Designing and conducting all analyses presented in this thesis.

I am indebted to my colleagues at EPIC-Norfolk who have assisted me with running the study and collecting the data used in this thesis. I have made clear where I have not conducted the work myself, this includes parts of data collection and aspects of data cleaning, although I was involved in the overall decision making for these areas. With published work, while I wrote the publication as the main author, the co-authors did contribute suggestions and comments for manuscripts, including where necessary, refining the analytical plan. All authors saw and approved the final manuscript submitted for publication. Where I have included work of my colleagues, I refer to as ‘we’ in the thesis.

Chapter 1: Introduction

1.1 Summary

In this Chapter, I present the current state of knowledge of the epidemiology of the broad spectrum of cognitive ageing including cognitive impairment and dementia in an ageing population. This chapter is a critical evaluation of the recent literature of the established risk factors of cognition across a continuum of cognitive function. The purpose is to identify the gaps in the understanding and interpretation of previous research that will be addressed by this thesis. The main aims and objectives of the thesis are also presented at the end of this chapter.

For this (Appendix 1) and subsequent chapters, an electronic search was performed using Pub Med to try to find evidence on age related differences in cognitive function and on the broader subject of cognitive ageing. Although a systematic review was not conducted for this thesis, the search on existing evidence for each chapter was comprehensive to examine what is known on the subject area and identify what is not known, unclear or limitations from previous studies. Where available, reviews on cognition and each exposure or outcome were examined. Manual searches involving the scanning of reference lists of articles to identify further articles were also carried out. Searches were focused on older adults.

1.2 Background

There are nearly 12 million people in the UK who are aged 65 or over and this number continues to rise. It is expected that, in 50 years, there will be an additional 8.6 million people aged 65 years and over – that is roughly equivalent to the population of London. [1] The increasing number of older individuals in the population is leading to a projected increase in numbers with chronic disease and disability, conditions strongly associated with ageing. Cognitive impairment and dementia are particular concerns and have a major impact on the quality of life and independence of an individual. Cognitive impairment and dementia are age-related conditions that have huge implications, both, as a human and an economic cost to society. [2] Though decline in cognitive function is associated with ageing and memory complaints in the elderly are common, cognitive impairment and dementia are not an inevitable part of ageing. [3] There is a wide range of cognitive capability seen within the older population [4] and cognitive impairment itself is a broad term. Cognitive impairment relates to impairment in one or multiple cognitive domains based on objectively measured performance. Dementia is a syndrome characterised by impairment in these domains, sufficiently severe to interfere with daily functioning. This thesis deals with cognitive function and impairment across a range of abilities.

1.2.1 Dementia: a global health challenge

Dementia is said to be the leading cause of dependence and disability worldwide [5] and described as the greatest challenge of our time. [6] Approximately 47 million people are currently living with dementia, costing £26.3 billion in UK alone, [7] with numbers of individuals with dementia and costs set to rise as life expectancy increases. [5] The value of preventing or delaying dementia onset is far greater than that of early detection or treatment to prevent further decline. [8]

In December 2013, Canada, France, Germany, Italy, Japan, Russia, the United Kingdom and the United States (the G8 nations) established the World Dementia Council (WDC), consisting of experts from across disciplines to provide global advocacy and leadership on key dementia challenges. [9] This is one of the many initiatives across the world to improve lives of those living with dementia. There is growing evidence that the prevalence of dementia is declining in high-income countries, [10] providing some hope of the possibility in preventing or delaying dementia. [11] Research has focused primarily on the impaired states, after the condition has developed, with less focus on prevention.

However, the body of research in prevention is growing. [11] There is emerging evidence that public health interventions might, if implemented effectively, contribute to delaying the onset and reducing the future number of people who have cognitive impairment and dementia. Postponing dementia onset by only one year could reduce dementia cases globally by nine million in 2050. [12] A number of reports including those from the National Academies of Sciences, Engineering, and Medicine and the Lancet Commission on Dementia Prevention, Intervention and Care, [6,11,13] have been published on the available evidence for recommendations on future public health strategies on how to best manage or prevent cognitive decline, impairment and dementia. With no treatment available for the commonly expressed dementia syndromes, there is an increasing interest in the potential role of modifiable factors in preventing or delaying the onset of dementia.

1.3 Cognitive assessment

There are many assessment tools available for assessing cognition, [14–18] for both study and diagnostic purposes. Tests have been developed to assess different abilities and across different settings, and their utility vary across populations they are used in. [19] Performance on tests is influenced by demographic factors, such as age, gender and education level. [20] Further limitations for assessing cognition described in the literature include low levels of accuracy for detecting mild impairment. [21–23] Many studies have been limited either by small cognitive batteries assessing few cognitive domains or using tools such as the widely used Mini-Mental State Examination [24] (MMSE) which is known to be less sensitive to milder levels of cognitive dysfunction. [14,25] This heterogeneity

makes comparisons across studies difficult. [26] It is necessary to evaluate the utility of tests and to identify tests that are sensitive to early changes in cognition as well as able to capture the complexities of real-world tasks. [26]

Current policies do not support screening for future dementia among apparently healthy individuals. This is due to the lack of certainty of the clinical outcome and effective interventions, with potential for more harm than good.[6] However, neuropsychological testing has been shown to be a useful addition to prediction models of dementia in prospective cohort studies. [27,28] These dementia risk models are all currently within the research settings only. The purpose of such models is to classify individuals into different risk categories and in particular, identify those with high risk. [27] Further evidence and evaluating risk in different populations has been called for. [29] The predictive accuracy of such models have been reported as acceptable among different cohorts, [27] some better at ruling out those at lower risk than identifying the higher risk individuals. [30]

1.4 Cognitive ageing is a continuum

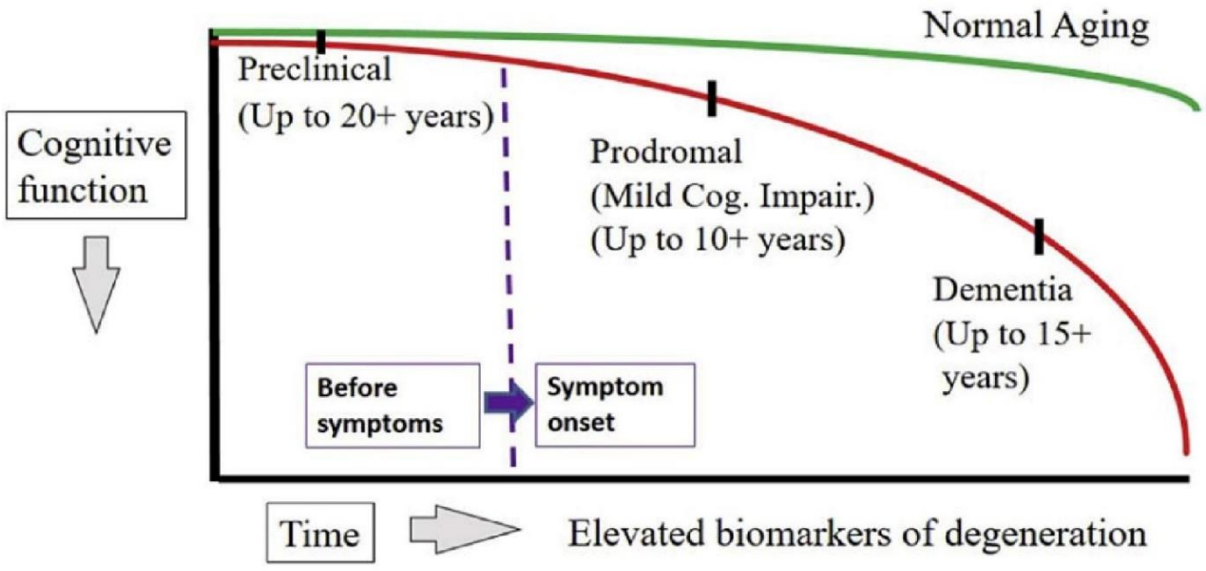
Cognitive ageing describes change in cognitive function as people age. However, cognitive ageing is complex and it is still unclear why there is such heterogeneity in the cognitive performance observed in the older population. [31] It is necessary to consider the continuum of cognitive ageing including the dementia syndromes rather than the distinct disease states. This decline is a result of a combination of lifestyle, biological, genetic and environmental factors, which puts some individuals on the course of cognitive impairment and possible dementia and others on a course of healthy cognitive ageing.[32] There is a wide spectrum of cognitive ability from 'normal' to severe dementia. [33–35] The need to understand the mechanisms of cognitive ageing and the factors contributing to differences observed in individuals is not a new debate. [36,37] **Figure 1.1** Is a diagrammatic representation of decline across this spectrum.

In addition to the difficulty in separating the pathological from the non-pathological, [36] there is also complexity and inconsistency by which cognitive domains are assessed. There is a plethora of tests used in research to measure cognition, making it difficult to compare across studies. Each of these tests measure a slightly different aspect of cognition, with varying cut-off thresholds, and many tests not validated in the populations for which they are intended to be used. [16] Furthermore, older adults are likely to have a range of co-morbidities, sensory losses, or to be taking medication that may impair cognition that may impact their cognitive performance, making it even more difficult to define cognitive ageing.

Differences in age-related decline form a continuum and not discrete groups of diseased states. Cognitive decline in absolute terms is difficult to determine. This is because decline has to be in relation to a prior level of function, which in most cases, particularly in research studies examining cognition, is not available. Also, similar levels of brain pathology can present very different levels of performance, [33,37] including individuals showing no apparent decline, yet presenting with considerable pathology in their brains [37] (discussed further below under 'Subtypes of dementia').

Although the progression of dementia is on a continuum, in practicality, the stages of dementia have to be clinically defined and categories have been introduced such as mild cognitive impairment, which align somewhere between normal cognitive ageing and dementia. The earliest clinical stages are characterised by noticeable memory lapses, but do not affect the individual's ability to carry out activities of daily living. [38] Individuals need more assistance in their daily life as the dementia progresses to the more moderate and severe stages which may involve further memory loss, confusion, possible personality and behavioural changes and eventually death. [39]

Figure 1.1: The disease spectrum from 'normal' cognition to severe dementia (Alzheimer's Disease).



(Source: Gale et al., Journal of Medicine 2018) [40]

1.4.1 Normal cognitive ageing

Increasing age is associated with lower performance on cognitive tasks. The effect of age on general cognitive function has been shown to be apparent from the age of 45 years onwards. [41] Understanding the wider implications of age related decline and not just in terms of impairment is extremely important, because this wider ranging decline impacts the majority of older individuals.[26] It is necessary to have insight to the variability observed in this group of individuals usually categorised

as ‘normal’. Normal ageing is not a precise term, as it does not accurately reflect the range of variation observed in older individuals. One generally used definition of ‘normal’ is the absence of disease; [42] which is not appropriate to use in older individuals who are likely to have a number of co-morbid conditions, impairments and disabilities.

It is therefore more fitting to refer to what is ‘typical function’, which would include comorbidities, and some decline with increasing age, but not to the extent that significantly influences cognitive function. However, even this definition, which relies on a notion of what is construed to be average for a particular age group, is not particularly useful as this varies substantially in different populations. [43,44] There is a huge amount of inter-individual and intra-individual variability amongst older adults. That is, not only are there differences in ability across age-groups, but the trajectory of decline vary across the different cognitive functions. [45] Some aspects of cognition decline, whilst others may remain stable or improve at different time points. In general, older individuals do not perform as well as those younger, however, there is huge variability, amongst older individuals, with some cognitively performing as well, or even out-performing their younger counterparts.[26] Various studies have examined this heterogeneity in older people, but many are restricted in the domains they assessed or the characteristics and age range of their sample population.

1.4.2 Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is described as the transitional stage between normal ageing and early dementia in the literature, recognised as a separate clinical condition. [46] Individuals with MCI are said to have cognitive impairment but not sufficiently severe to constitute dementia. The scope of MCI has changed from its earlier version of focus on memory impairment only, [47] broadening to include impairment in other cognitive domains. [48] MCI has attracted particular interest, because although this cognitive impairment is not severe enough to meet the clinical criteria of dementia, an individual with MCI has been reported to have an increased risk of dementia. [49] This suggests that many individuals with MCI are actually in a pre-dementia phase of the disease. [50] However, using MCI as a milder form of cognitive impairment and pre-dementia to try to identify early mechanisms that trigger dementia has been complicated. This is because not all MCI converts to dementia, [49,51] making it a very unstable and heterogeneous state. [52] Other reasons for inconsistencies across studies reporting on MCI are similar to those reported above, that is variation in the characteristics of the population assessed, inconsistency in the operational criteria for MCI, insufficient of follow-up time, and the nature of the assessment tools. Further more robust studies are needed to examine early stages of decline. [53]

1.4.3 Subtypes of dementia

Dementia is an umbrella term and is best described as a syndrome than a specific disease. It describes the symptoms that occur when the brain is affected by certain diseases or conditions. Dementia can result from a number of distinct diseases and disorders with different aetiologies and pathophysiologies that cause damage to the brain. Even within the same disease, there is considerable heterogeneity in terms of symptoms and disease trajectories. [54] Primary dementias include Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD),where decline in cognitive abilities is mostly due to an underlying neurodegenerative process and not a direct result of a specific aetiology. [55] Secondary dementias are those caused by, or closely related to an underlying disease such or condition, such as infection with the Human Immunodeficiency Virus, Parkinson's disease (PD) head injury, stroke, thyroid disorders or vitamin B12 deficiency. Table 1.1 is an overview of the more commonly reported characteristics of the main dementia subtypes, although it is important to highlight, most dementia, is predominantly associated with mixed pathologies. [56]

Individuals will exhibit different symptoms, depending on the type and stage of their particular dementia and which part of the brain is affected by the disease process. These symptoms will change with time as the diseases progress to involve different areas of the brain. Different types of dementia tend to target particular parts of the brain, as presented in **Figure 1.2**, though clinical symptoms do not strictly reflect a specific aetiology, [54] and the figure's pathological and clinical presentations should be interpreted with caution. Ageing is associated with many chronic diseases, some that affect the brain and influence cognition. People with dementia and MCI present with mixed neuropathologies, [57] and these comorbid pathologies are said to account for as many if not more dementia than AD. Furthermore, neuropathologies of the common causes of dementia [AD, VaD and DLB) have been reported to be present in the brains of older persons without dementia. [58] This complexity is a combination of mixed dementia pathologies and the influence of cognitive or neural reserve. [57]

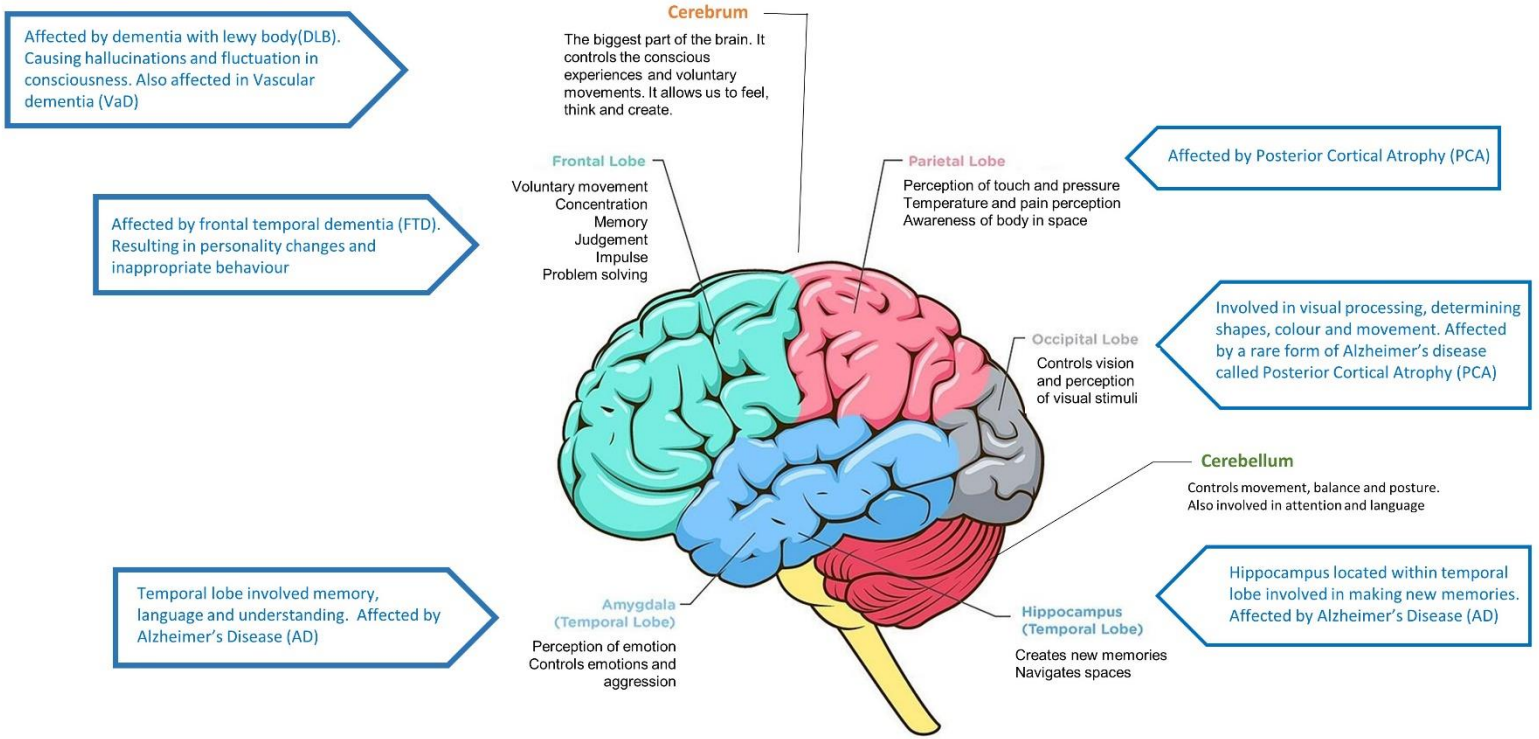
Treating dementia as a single entity at a population level is considered to be appropriate for policy development and also many risk factors are shared, particularly for AD and VaD. Using this approach of a broader classification also improves external validity. [59] Many studies involve individuals who are already identified clinically in cognitive decline, with fewer studies involving the healthy and cognitively unimpaired. Understanding cognition in older people, not only in terms of impairment, but across the spectrum, including that of high cognitive function is important.

Table 1.1: Overview of the Clinical Characteristics of the main dementia subtypes

Dementia subtype	**Clinical Symptoms** [60]
Alzheimer's disease (AD)	Short-term memory impairment in early stage; other domains may also be affected (e.g. problem solving, finding words, making decisions). Insidious onset and slow progressive decline.
Vascular dementia (VaD)	Usually correlated with cerebrovascular disease (stroke, lacunar infarcts) and atherosclerotic comorbidities (diabetes, hypertension, coronary heart disease) • Mild memory impairment in early stage • Impaired judgement • Possible gait difficulties and falls (depending on the extent of the stroke) • Sudden or gradual onset
Mixed dementia	The abnormal protein deposits associated with Alzheimer's disease coexist with blood vessel problems linked to vascular dementia. Also seen are AD related changes in the brain along with Lewy bodies. Individuals with mixed dementia may have brain changes linked to all three AD, VaD and DLB.
Dementia with Lewy bodies (DLB)	Confusion, Poor executive function and visual hallucinations in early stage; deficits on tests designed to examine visual perception. Motor alterations (as in PD) are absent in DLB. Fluctuating cognition associated with parkinsonism.
Frontotemporal dementia (FTD)	More prominent personality changes (disinhibition) and behavioural disturbances (apathy, aggression, agitation with less memory impairment in early stage).
Parkinson's dementia (PD)	Up to 80% of patients with Parkinson's disease progress to dementia. Motor alteration including tremor, rigidity, bradykinesia and changes in gait. Dementia similar to that of LBD or AD.
Other dementias	Dementia can be the result of varied and different pathophysiologic processes affecting the brain, with slight variation in clinical presentations depending on the underlying cause.

Modified from Duong et al., (2017) [60]

Figure 1.2: Parts of the brain affected by different dementia syndromes



Source: Image modified from: Dementia—What part of the brain is under attack [61]

This page is intentionally left blank

1.5 Cognitive Reserve

The concept of cognitive reserve has been proposed to account for the discrepancy between the degree of brain damage or pathology and its clinical manifestations. [62] It is now known that about a third of older persons without dementia or MCI meet pathologic criteria for AD, suggesting that many people are able to maintain excellent cognition despite the accumulation of brain pathology. [57] What allows some people to be more resilient to cognitive impairment than others is unclear, but it is understood that cognitive reserve may be mediated in many different ways. [63] It is also considered to account for social and leisure engagement as well as for cognitive functioning. [64] Cognitive reserve is a hypothetical construct, and therefore cannot be measured directly. Proxy indicators of cognitive reserve include educational attainment, occupational achievement, and intelligence. Education is probably the most widely used indicator of cognitive reserve. [65] However, other factors that are closely related to education such as social economic status (SES), occupation and childhood education and parental SES as well as lifestyle exposures have been associated with reserve. [66,67] Clearer understanding of cognitive reserve and its relationship with different factors is important, if we are to develop interventions to slow cognitive ageing or reduce the risk of dementia.

1.6 Characterisation of cognitive abilities

Cognitive ability covers a number of domains, which together form the basis of cognitive function. As yet, there does not appear to be an agreement on the classification of the cognitive domains or which abilities are most important in testing cognitive decline and importantly, which predict future adverse health outcomes. The leading theoretical model for conceptualising cognitive abilities splits cognition in to two categories, 'fluid' and 'crystallised' abilities. [68] Fluid abilities include abilities such as recall, learning, problem solving, encoding and recognition and crystallised ability is regarded as knowledge gained over time (such as vocabulary and general knowledge). In general, fluid mental abilities have been shown to decline with age, occurring from as early as middle age, [37] whilst crystallised abilities remain fairly stable well into later life. [69–71] Mental function can be assessed in terms of both global and domain specific function. [69] It is stating the obvious that cognitive abilities are central to carrying out everyday activities, living independently and for general health and wellbeing, but understanding the components and determinants may help us better understand how best to maintain abilities in later life.

Distinguishing between cognitive abilities is important because they play different roles and are influenced by age to varying degrees. However, measuring these abilities is complicated because they are not clearly distinct from one another. One cognitive ability may have an impact on the performance

of another, or different abilities work in conjunction to execute a given function. There is lack of agreement between a particular tests and its assumed cognitive domain. [72] **Figure 1.3** shows some of the abilities mentioned in the literature and, as mentioned previously, considered to be important in assessing cognitive performance. Individuals can have impairment in one cognitive domain but perform well in another or a number of cognitive deficits can occur concurrently. There is increasing evidence of substantial variability in cognitive abilities within individuals, [73] but the role of this variability within different domains is not clearly understood. [74] Where studies have examined cognitive abilities in more detail, studies are restricted such as just including women [74] or those of older age groups. [21,72,74,75]

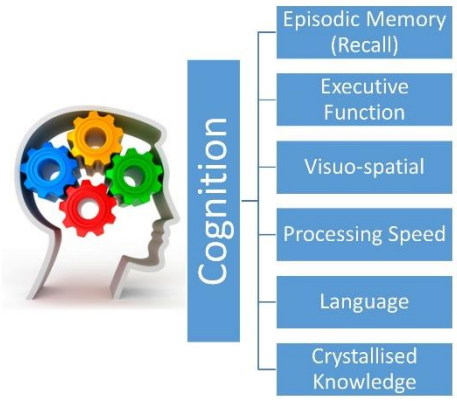
Dementia is characterised by severe deficits mainly within the fluid cognitive abilities, which worsen and affect more domains as the disease progresses. [76] Dementia for most, has a long prodromal period, whereby individuals who go onto develop dementia, exhibit cognitive deficits many years before any symptoms or receiving a clinical diagnosis. [77] Variability across tasks may also indicate neurological dysfunction. [73] Greater variability across different cognitive domains has been associated with poorer performance and dementia, [78] and has been said to be a good predictor of cognitive impairment over and above the mean level of performance in cognitive tasks. [79] Furthermore, there is also evidence of more pervasive cognitive deficits across domains in earlier stages of decline, and not just memory alone. [80–82]

Studies have reported on different cognitive tests to assess cognitive deficits related to dementia. [83] Although current policy does not support screening [6] neuropsychological assessment is central to the diagnosis of dementia and identifying individuals who may be in a prodromal phase dementia. Studies have varied considerably in terms of the cognitive domain assessed, length of follow-up, or the characteristics of the population, all making it difficult to compare the predictive accuracy of these tests. [27]

Not everyone with MCI or mild cognitive dysfunction, is in the preclinical phase of the disease, but there has been increasing perception of a need to identify tools that can separate accurately those who will remain stable from those who will progress to dementia. While several studies have reported the ability of cognitive tests to predict the onset of dementia in the short term, few have studied this phenomenon for a period of more than 10 years. [84] Further risk assessment across different populations using existing and new assessment tools is recommended to get further insight to the validity of neuropsychological tests. [27] Characterising assessment tools across different cognitive abilities and examining how these tools are influenced by the population characteristics is important. We need further insight into the utility of assessment tools that have been previously validated in

predicting dementia. Most studies have examined these models in later life, with very few able to examine mid-life predictors.

Figure 1.3: Some cognitive abilities used in assessing cognitive function



1.7 Definitions and Classification Systems

There are two main diagnostic classification systems that are used for the clinical diagnosis of dementia. The World Health Organisation's (WHO) International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, currently as the fifth edition (DSM 5). [59] In addition to these two classification systems, there are other recognised systems that have been specifically developed for diagnosis of Alzheimer's and vascular dementia respectively. These are: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) and the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS–AIREN). In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) convened to update the NINCDS-ADRDA criteria for AD and all cause dementia [85] to include the asymptomatic, minimally symptomatic, and dementia phases of AD, [86] as well as incorporating the available information from clinical, imaging, and laboratory assessments. [85] Although there is considerable compatibility between the systems, there is no clear formally agreed definition and because the criteria are set based on clinical judgement, there can be variability in classifying an individual depending on the system used. The classification system used by hospital codes in the UK is the WHO's ICD-10, which will be discussed in this thesis. Further details of the other classification systems will not be discussed.

1.8 Dementia ascertainment using medical record Linkage in UK.

To examine associations of dementia with risk factors robustly and accurately, studies need to involve a representative sample followed up long term. One high quality study is the Medical Research Council Cognitive Function and Ageing Study (CFAS).[87,88] A particular strength of CFAS is the use of a study algorithmic approach to diagnose dementia, which gives consistency across area and time. [88] However not all population studies are able to use this approach. Furthermore, one of the main known limitations of longitudinal studies is attrition and loss to active follow-up, in particular of those who are sick, frailer and older. Therefore, medical records are an important resource for dementia ascertainment allowing a more complete follow up of individuals in a cohort, reducing risk of bias.

In the UK, the National Health Service (NHS) allows hospital usage free at the point of delivery for all UK residents and so will hold medical records on the whole population. This presents an ideal opportunity for well-characterised cohort studies to strengthen their ability to investigate the role of risk factors for different health outcomes, including dementia, through record linkage. Administrative health databases in the UK contain clinical data coded using the ICD-10 classification system. Routinely collected NHS databases in England include Hospital Episode Statistics, (HES) and mortality data that can be linked using their unique NHS number and date of birth via NHS Digital. The linked hospital records contain coded diagnostic information for all inpatient and day-case admissions. [89]

Dementia diagnoses are also held in national mental healthcare data, which are held in separate datasets from HES and mortality data. These different datasets are described in further detail in Chapter 7. However, these databases are primarily for administrative purposes, and research purposes are secondary use of these data. It is therefore important to examine these databases carefully to get a better understanding of the underlying nature of these data to allow accurate case ascertainment. Not all individuals with dementia may have a hospital admission with a diagnosis of dementia. Nevertheless, while the sensitivity of hospital records to identify dementia cases is uncertain, as long as appropriate codes are used, the specificity of routinely collected healthcare data to identify disease cases is very high.[90]

In general practice, clinical information is recorded using a 'Read Code' system developed by Royal College of General Practitioners (RCGP) representatives from England, Northern Ireland, Scotland and Wales and is maintained and updated by NHS Digital. This coding system is different yet again to the others listed above, but can, largely, be mapped to ICD or DSM codes, this is then mapped to the nearest read code equivalent when transferred to GP records. Linking to GP records is not always possible as described in detail later (Chapter 8). Most studies therefore use HES or mortality data. There is also variability and discrepancy in identification of dementia across these data sources. [90]

Rates of dementia will vary depending on the definition of dementia used, which varies across coding and disease classification In addition to this inconsistency across systems, changes in policy and practice has raised concerns over the accuracy and completeness of dementia recording in health care records, [91,92] which differ not only at general practice level but geographically across the UK. [93,94] Although there have been two large scaled cohort studies comparing dementia ascertainment across data sources, these studies have their limitations, including that they have fewer dementia cases due to the age profile of the cohort. [91,95] Medical records are a major source of case ascertainment for epidemiological studies examining relationship of different risk and protective factors of dementia. [91,96] Scrutiny of these methods across different populations and geographical areas is necessary in order to understand the strengths and weaknesses of using routinely collected records in research.

1.9 Assessing cognitive performance in older populations

A diagnosis of dementia is made only after a comprehensive assessment, [97] and will depend on the classification system used. Therefore, the criteria for defining impairment can vary and be inconsistent. Cognitive impairment ranges from mild to severe. Dementia is typically diagnosed when the impairment in cognitive function has become severe enough to compromise the functions of every-day life, and this of course will vary from one individual to the next. There may be a decline in the ability to judge, think, plan and organise, or a significant change in behaviour in terms of emotional responsibility, irritability, or loss of social skills.

A diagnostic assessment for cognitive impairment involves a number of steps. This includes history taking, cognitive assessment, physical and laboratory examination and a review of medication, all factors that may have an adverse effect on cognition. [16,19]. The Mini Mental State Examination (MMSE) is probably the most frequently used test for diagnostic purposes [18], however, more recently a number of alternatives are being used by practitioners such as the 6-item Cognitive Impairment Test (6-CIT), Addenbrooke's Cognitive Examination (ACE, or the revised version ACE-R) and the General Practitioner Assessment of Cognition (GPCOG) to name a few. Table 1.2 shows the main domains assessed, the maximum possible score and the cut-off indicating impairment for each test. Even in clinical practice, there are no commonly agreed cut-offs and the recommendation is that the cut-points should be adjusted to account for factors, such as age and education [25] or the setting in which the test is administered. [98] There has been much debate over the issue of screening for dementia [16,99] and one of the reasons for arguing against screening, other than the lack of available treatment and cause of anxiety to an individual are the concerns over the validity and utility of the available tests.

Table 1.2. Common assessment tools used in clinical practice

Test	Domains Tested	Max Score	Cut-off score (indicating impairment)
6-CIT	Orientation, attention and memory	28	8 /28 or 10/28 for severe impairment*
MMSE	Global measure of cognition (memory attention, registration, language visuospatial, praxis, verbal fluency executive function	30	24/30 or 23/30 for severe impairment 27/30 for higher educated individuals
ACE-R	Attention/orientation, memory, verbal fluency, language and visuospatial abilities	100	88/100 or 82/100 in hospital or clinic setting
GPCOG	GPCOG-Patient Component: Cognitive assessment of orientation, memory and visuospatial abilities Informant component: Assessment of functional abilities in activities of daily life	9 (Patient) 8 (Informant)	4/9 on GPCOG-Patient Cog and 3/8 on GPCOG-Informant

* Higher score reflects poorer performance

In terms of research settings, the number of tests is too vast to list. It is broadly accepted that cognitive abilities can be measured in both general and specific terms, and different assessment tools have been used across studies reporting both on domain specific and global cognition. Most studies report on global cognition, with much fewer reporting domain specific results. Even those testing different domains, report either using composite scores or z- scores. As yet, there does not appear to be an agreement on the classification of the cognitive domains and there is still a lack of consensus on which abilities are the most important in testing cognitive decline. [69] Using common metrics such as z-scores may facilitate comparison of scores across different measures; however, these standards have their limitations. Using a composite score results in loss of information on the separate abilities and z-scores assume a normal distribution and are usually standardised by age. However in terms of maintaining cognition, generally of greater interest, is the absolute level of function regardless of age.

Numerous dementia risk models have been developed, and currently are confined within research settings only. The purpose of such models is to classify individuals into different risk categories and in particular, identify those with high risk. [27] Further evidence and evaluating risk in different populations has been called for. [29] Neuropsychological measures are key measures included in prediction models of dementia in addition to age. [27,28] Greater variability and impairment across different cognitive domains has also been associated with poorer performance and dementia. [78]

Despite a great deal of research and debate, it remains unclear as to whether we should consider any impairment in absolute terms or relative to age and education. Furthermore, cut-points predicting disease or impact on function and what level requires action will be different for different individuals and across different populations. Socioeconomic and demographic variation among populations can result in a given score of a test to have different implications in different samples. [44,100] A test score

suggesting poor performance or even impairment in a given population could be typical scores in a poorly educated but unimpaired community sample. [44] This problem has been addressed in studies by deriving cut-off scores from the population itself, [101] defining performance at a predetermined percentile of the population sample as "impaired". Therefore, cognitive ageing is not easily defined by a clear thresholds on cognitive tests, as many factors such as, occupation, education, as well as health, may influence test performance and norms. [26] There is a need to question what is important to measure when assessing cognitive function.

1.10 Cognitive Epidemiology

Understanding how cognitive function is associated with disease and health outcomes, as well as identifying potentially modifiable environmental determinants of cognitive health in mid to later life is important and may help inform clinical and public health interventions. [102] Studying determinants and risk factors of cognitive impairment and dementia is paramount to gain insight into the mechanisms relating to cognitive impairment and dementia. By influencing these factors, it is hoped that the course of the disease can be modified. [103] In this section, I briefly discuss the main factors investigated in cognitive epidemiology research.

1.10.1 Risk factors for cognitive impairment

Dementia is a multifactorial disorder, resulting from a lifetime exposure of protective and risk factors. As reducing risk of dementia as well as promoting good cognitive health in older people are both important in terms of public health, then having in-depth knowledge of these different factors, and how they may reduce or increase an individual's risk of developing dementia is necessary. By studying these risk factors in a meaningful way, we can have a better understanding of the mechanisms leading to dementia as well as shedding light on whether these factors could differentially influence or confound cognitive measures depending on the properties of a particular test.

1.10.1.1 Non-modifiable factors

Age itself is the strongest risk factor for cognitive impairment and dementia [36] which of course is not modifiable. [59] Also non-modifiable are genetic risk factors, of which the most established risk factor, particularly for AD is the apoliprotein E (ApoE) gene. [54] ApoE presents in three allelic forms (e2, e3, and e4), of which the e4 allele is a recognised risk factor faster cognitive decline [104] and dementia.[54]

Women have been reported as having higher dementia rates, however, this difference has generally been accounted for as women have longer life expectancy than men. As age is the greatest risk factor for dementia, the lifetime risk of dementia is greater for women, but the exact differences in risk factors remain unclear and might vary across populations. [105] Studies generally adjust for sex, but few have actually examined sex differences in risk factors for dementia. Some factors have been reported to confer greater risk for men, such as hyperlipidemia and myocardial infarction with depression for women. The distribution and prevalence of major risk factors between the sexes and age groups vary, and further work is needed to identify how these risk factors differ in men and women. [106]

1.10.1.2 Modifiable factors

The concept of prevention being better than cure, [6] in the absence of any substantial progress on the latter, [6] underpins the growing interest in the role of modifiable risk factors for cognitive impairment and dementia, a number of which have been reported. Socioeconomic factors have been examined in detail, and shown to be strong correlates of cognition, with associations persisting throughout life. [107] Education has been identified as the strongest and most consistent protective factor for dementia, [108] and as mentioned previously, is commonly used as a proxy measure for cognitive reserve. [65,109] Studies have also suggested that dietary, such as adherence to a Mediterranean diet, and lifestyle factors such as physical activity are associated with cognitive function, [110] although for both the evidence is considered to be incomplete. Physical inactivity (independent of physical activity), has been found to be risk factor for major health conditions, [111] including cognitive impairment. [112], but the neuroprotective effect of physical activity has not been consistently shown. [113]

Many modifiable risk factors for dementia are mostly related to cardiovascular disease (CVD) risk factors (diabetes, hypertension and obesity). Managing the known risk factors for CVD such as, diabetes, hypertension, mid-life obesity, physical inactivity and smoking to reduce dementia risk, are widely accepted. [9,114] Depression is another factor associated with increased risk for dementia,

[115] although longer prospective investigations present a more mixed picture. [116] It is unclear if depression is a risk factor, a feature of the preclinical phase of dementia, or an associated comorbidity with a common cause. It is quite possibly a combination of all three. Other factors that are not so well established, but have been proposed as to influence dementia risk include body fat distribution, especially abdominal fatness (central obesity), as reflected by waist circumference or waist-to-hip ratio (WHR) [117] and poor lung function. [118] Management of hearing loss and social isolation have also been included in the list.

1.10.2 Cognitive performance as predictors of mortality

Poor cognitive performance has been reported to predict increased mortality risk. [39,119,120] A number of hypotheses have been presented. [121] One hypothesis is that higher education and social class are both related to better health and to improved cognition and so all three are associated with better health and lower mortality. The second hypothesis suggests cognitive function has an indirect effect on mortality, mediated through social and behavioural lifestyle differences, such as healthy eating, stopping smoking and exercise, which in turn affect mortality. A third hypothesis is that cognitive ability may be a proxy indicator of deficient brain development that is correlated with later adulthood illness or as a marker for general bodily integrity. [122]

The relationship between cognition and mortality is complex despite being consistently reported. [123] Better cognitive ability is said to be an indicator of a well-functioning body influenced by genetic as well as early and later life biological and environmental factors. This includes the integrity of the brain and the efficiency of information processing, which has been suggested to be more strongly related to mortality than other cognitive abilities.[124,125] Even though many cohort studies have shown robust associations between cognition and mortality, there still remains ambiguity on understanding this relationship and as yet no pathway or mechanism has been postulated. Variation in methodologies has resulted in inconsistencies across studies and there are no clear explanations of the mechanisms involved. The question of whether poor cognitive function is merely a marker for general decline or plays a causative role in death remains unanswered. Further clarity on this complex relationship is needed. Studies examining association of milder cognitive dysfunction and mortality have been inconsistent. [39,119]

1.10.3 Cognitive performance as predictors of dementia

Neuropsychological testing provides information on the nature and extent of cognitive deficits There is also evidence of more pervasive cognitive deficits across domains in earlier stages of decline, and

not just memory alone. It is important to be able to identify how impairment across a range of different cognitive abilities are related to health outcomes, particularly death and dementia.

1.11 Gaps identified in the literature

Despite the huge efforts and investment in research in cognitive ageing and dementia, there is still a further need to strengthen the evidence on potentially modifiable risk factors of cognitive impairment and dementia. Many protective and risk factors cluster together, making it hard at times to interpret the data. The variability observed in the literature can be explained, in part by health status, education, socioeconomic factors and genetics, but is also likely to be due to heterogeneity in methodologies across studies. The review of the literature has identified a number of gaps that have not been adequately addressed in the previous literature and will shape the specific aims and objectives of this thesis.

Although many studies have shown cognitive function to be hugely variable in older people, many studies are restricted in the domains they assessed, reporting mainly on global cognition, or limiting to memory. It is necessary to examine a wide range of abilities. Studies have also been limited in the age range of the study population involving only older individuals, [87,88] or with population sample recruited from clinical settings, [123] who may have other co-morbidities. There are studies that are restricted in terms of including either only men, [126,127]. Women [95] or limited in the socio-economic range. [126,128] All these limitations have the potential to not only introduce bias and confounding, or reduce generalisability of the findings, but also make it difficult to compare across studies. It is extremely important to disentangle confounding caused by methodological variation.

Smaller studies are unable to account for a wide range of covariates, limiting the ability to detect the associations and control for potential confounders. [129] Given the complexity, any associations and the selection of covariates need careful consideration. Failure for adequate adjustment for covariates leads to residual confounding. Furthermore, lack of detailed examination of both the way exposure and outcome variables are measured can also mask the true nature of relationships. It is important to use a nuanced approached where possible to examine these factors, adjusting for a range of co-variates without losing power to tease out the true relationship, which may be some of the reasons as to why previous studies have been inconsistent in their findings.

In terms of modifiable factors, education and physical activity are of particular interest, as they both could either exert direct effects on brain structure, improving vascularisation and contributing to building cognitive reserve. For physical activity, there is already the mantra, what is good for the heart, is good for the brain. However, the evidence on physical activity is inconclusive, [11] and studies with

longer follow-up suggest that a lower risk of dementia in physically active people may be attributable to reverse causation. [113] Educated people typically have lower risk of cardiovascular disease and engage in healthier behaviours; therefore education is important not only as a determinant, but also as a confounder in many of these studies. It is important to gain further insight into this complex relationship of different domains of physical activity in a long prospective cohort across a wider socio-economic range.

A number of studies have shown the relationship between cognition and mortality, [121,130–133] for both global and domain specific measures. [121,131] However, the evidence for association at milder levels is mixed. [119,134,135] It would be of interest to explore whether this relationship extends beyond to include poor performance, even before any evidence of impairment, which would impact more individuals in an ageing population. For studies examining cognitive measures predicting dementia, there are limitations in terms of the range of cognitive tests and short follow-up time. Examining these in individuals free of cognitive impairment or dementia at the time of cognitive testing and across a wider age range merits further investigation.

Finally, the use of health records as a measure of dementia outcomes in medical research and for policy tracking has become an increasingly important resource for dementia ascertainment. Whilst the availability of data provides opportunities for powerful and efficient research, these data sources are prone to inconsistency, misclassification and influenced by change in dementia practice and policy. Researchers should be aware of the strengths and limitations of the secondary use of health records used within their studies and report on the influence of these factors on the accuracy of their findings.

1.12 Overview of setting: The EPIC-Norfolk Study

The European Prospective Investigation into Cancer (EPIC) is a 10-country collaborative study in which EPIC-Norfolk is one of the UK centres, designed to investigate the aetiology of major chronic diseases. [136] EPIC-Norfolk recruited and examined 25 639 men and women resident in East Anglia (aged 40–79 years), between 1993 and 1997 at baseline. The EPIC collaboration was set up to examine the dietary determinants of cancer, but the remit in the EPIC-Norfolk cohort was broadened from the outset to include determinants of other health conditions and chronic diseases disability and death in middle and later life. [137] Recruitment was via general practices in the city of Norwich and the surrounding small towns and rural areas; detailed methods have been published. [137,138] As virtually all residents in the UK are registered with a general practitioner through the National Health Service, general practice lists serve as population registers.

Cognitive assessment was introduces as part of the third health examination (3HC) between 2006 and 2011, with a brief pilot phase between 2004 and 2006. [138] Epidemiological studies, such as EPIC-Norfolk provide data to define impairment based on function of normal ranges within healthy populations. Recruitment for EPIC-Norfolk was via general practices, and participants were included only from those practices that agreed to participate. Of the 77,630 individuals invited to take part in the study, 30,445 (39%) responded and 25,639 (33%) attended the baseline examination. For the third health examination, 18,380 from the original cohort were invited, of which 8,623 (47%) took part. Although the study team tried to maximise participation by facilitating travel, and accommodating participants through flexible clinic hours, this would have been limited due to funding and practical reasons.

For a study to be representative of a population, there needs to be a high participation rate from the whole population, or a random subset of the population. Those who did not take part would be more likely to be older, frailer and cognitively impaired. While the original participants in the EPIC-Norfolk study were largely comparable in characteristics to the those in the Health Survey for England, those returning for the third health examination were survivors and more likely to be healthy and have the capacity to participate so without obvious dementia. Though the EPIC-Norfolk participants are likely to represent a healthier subset of the older UK population, there was still good representation from men and women, across a wide age range, education and social class and cognitive ability. These limitations are addressed in individual chapters of this thesis.

1.13 Potential to study the epidemiology of cognitive function in EPIC-Norfolk

The likely selection of healthier individuals participating in EPIC-Norfolk make it difficult to generalise from the findings to estimate and quantify the prevalence of the cognitive impairment and the burden of dementia in the UK. However, examining and understanding associations of risk factors with cognitive function and dementia within in this cohort can potentially shed light on underlying aetiological mechanisms which may inform future policies. There will of course be some limitations and biases introduced in the analyses presented in this thesis. However, these will be highlighted in the specific chapters, including where possible, the bias introduced by non-participation. The impact of missing data, specific to individual analyses is addressed in each chapter separately.

1.14 Aims and objectives

This thesis attempts to address some of these specific gaps as highlighted in the literature review, using a cohort, with no overt cognitive impairment at the time of testing, providing further insight to the methodological differences and variability presented in other studies. A major focus of this thesis is

the question of what is important to measure when assessing cognitive function and to gain understanding of the utility of these tests in predicting outcomes such as mortality and dementia. By characterising the assessment tools, which has been limited in the literature, and knowing how best to measure cognition across the spectrum, we can gain a better understanding of cognitive function and impairment.

The **overall aim** of this thesis was to obtain an understanding of factors associated with cognitive function in later life and to address the knowledge gaps with the aim to add to the emerging body of evidence of prevention and delay of cognitive impairment and dementia.

The well-characterised nature of the EPIC-Norfolk cohort, and long follow-up allows for a more detailed approach to examine potential confounders, that other studies may not have addressed adequately. This study is well-placed, not only to identify factors associated with poor cognition but also factors associated with maintaining abilities in older age. EPIC-Norfolk is an excellent platform to investigate cognitive function across a broad spectrum of abilities in men and women, across levels of education, social class and other lifestyle factors.

The **specific objectives** of this thesis are:

1. To describe the rationale and methods for introducing cognitive measures in the EPIC-Norfolk Study, giving outline of study design, and key findings (Chapter 2).

2. To present descriptive statistics and distributions of cognitive performance across a range of cognitive domains in this cohort of men and women in mid to later life. To operationalise cognitive dysfunction across different cognitive abilities in individuals who are clinically cognitively unimpaired (Chapter 3).

3. To examine associations of socio-demographic variables and cognition and provide further insight as to how cognitive assessment tool relate specifically to age, sex, social class and education (Chapter 4).

4. To examine the relationship (both cross-sectional and prospective) between physical inactivity during work and leisure time and cognitive performance (Chapter 5).

5. To explore the reported increased risk of mortality associated with cognitive dysfunction and dementia, by examining whether relationship can be observed at lesser levels of poor cognition, and whether this varies across cognitive domains (Chapter 6).

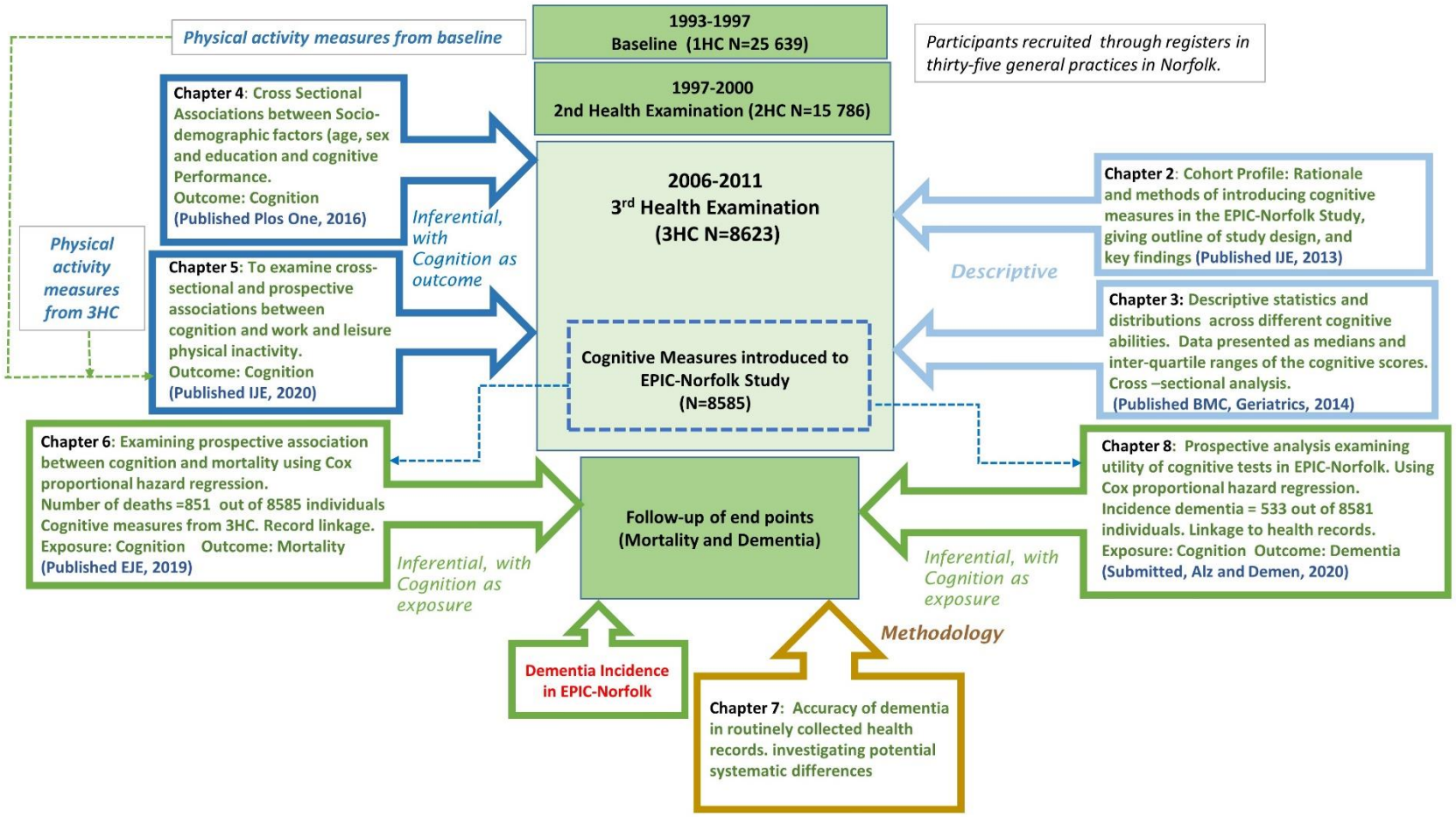
6. To examine the recording of dementia diagnosis in routinely collected health records, the impact of incomplete or inaccurate recording, and how variation across sources may influence analysis and interpretation of associations (Chapter 7).

7. To examine the utility of the cognitive tests used in EPIC-Norfolk to predict dementia and also examine whether the extent of impairment across different cognitive tasks enhances the predictive power over and above the level of individual cognitive test performance alone (Chapter 8).

1.15. Study Design

The study design is summarised in **Figure 1.4**, presenting the selection of the study population, size of the analytical sample, primary exposures and outcomes of interest and methodology for each of the analyses described and published work from this thesis.

Figure 1.4: Flow Chart of the study design of EPIC-Norfolk, summarising the description of each analytical sample used for the chapters and publications in this thesis.



Chapter 2: Methods (Cohort Profile)

The work presented in this Chapter has been published:

Hayat, S. A., Luben, R., Keevil, V. et al., (2014). Cohort Profile: A prospective cohort study of objective physical and cognitive capability and visual health in an ageing population of men and women in Norfolk (EPIC-Norfolk 3). International Journal of Epidemiology, **43**(4), 1063-1072.

2.1 Summary

This chapter will expand on information presented in the previous chapter on the background, rationale and methods used to measure cognitive function in the EPIC-Norfolk cohort as well as the other covariates used in the analyses. This chapter also provides details on the characteristics of the participants and the level of attrition within the study caused by various reasons (i.e. death or poor health), that may be considered a potential bias in the analyses carried out in subsequent chapters of this thesis.

2.2 Introduction

Substantial data already exist on dementia and cognitive impairment, mainly in the older population using a wide range of instruments, each with merits and limitations assessing different aspects or stages of cognition. There is a need for assessment in a wider age range from mid to later life that will allow accurate measure of a broad range of ability and domains, with an optimal balance between sensitivity and specificity in the settings in which these tools are applied. EPIC-Norfolk has had a particular focus on characterizing exposures in terms of modifiable lifestyle factors. One of the key priorities of this study has been to develop, improve and gain further insight into exposure measurement and to characterise participants extensively in terms of their lifestyle, physiological, metabolic and genetic profiles. The specific aim of this chapter is to describe in detail, the assessment tools used to measure cognitive function, the selection of covariates, descriptions of the main exposure and outcome measures and the characteristics of the participants selected in order to address the proposed research question in this thesis.

2.3 Ethical Permission and Research Approvals

Ethical approval for EPIC-Norfolk core study (Baseline) was provided by the Norwich District Health Authority ethics committee (Rec Ref: 98NC01). EPIC-Norfolk 3HC, the baseline for cognitive measures, was approved by the Norfolk Local Research Ethics Committee (05/Q0101/191) and East Norfolk and Waveney NHS Research Governance Committee (2005EC07L). Participants gave signed informed consent at both baseline and then subsequently at the 3HC to cover new measures that were not present in previous health examinations. This study was conducted in compliance with the principles expressed in the Declaration of Helsinki and the Research Governance Framework for Health and Social Care.

Section 251 (S.251) of the NHS Act 2006 allows the common law duty of confidentiality to be set aside in specific circumstances where anonymised information is not sufficient and where patient consent

is not practicable. EPIC-Norfolk S.251 approval to allow access to medical records and complete follow up of participants. In more recent phases, explicit signed consent to link to medical records has been given by participants attending health examinations.

Section 251 Application number 059:
https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/confidentiality-advisory-group-registers/

2.4 Settings and population

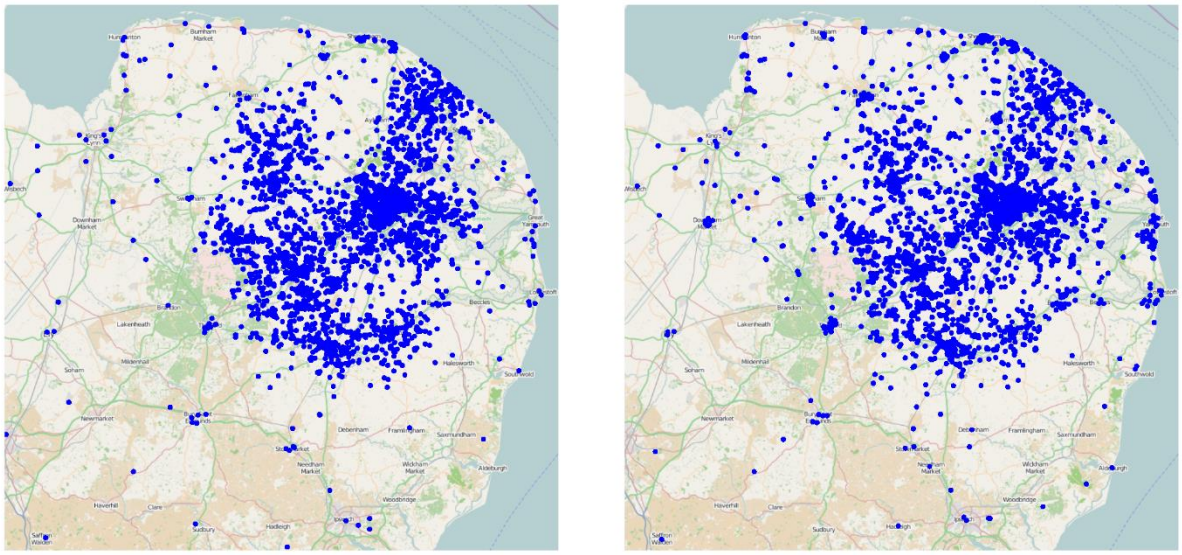
The European Prospective Investigation into Cancer and Nutrition (EPIC) project is an international collaboration across ten European countries (France, Germany, Greece, Italy, The Netherlands, Spain, United Kingdom, Sweden, Denmark and Norway). This well-established cohort was initiated in 1989–1990, recruited of 519 978 participants (366 521 women and 153 457 men), mainly aged 35–70 years at baseline. [136,139] EPIC was originally designed to investigate the role of nutrition in cancer aetiology, but the study has grown to include other medical conditions such as cardiovascular disease, diabetes and Parkinson's. [140]

The work in this thesis is based on the data collected in EPIC-Norfolk, one of the two centres from the United Kingdom of this ten-country collaboration. Although EPIC-Norfolk started as a diet and cancer study, its remit was widened from inception to include investigation of major determinants of chronic disease, disability and death in middle and later life and lifestyle exposures other than just diet. [137] The study location comprises of the city of Norwich and its surrounding small towns and rural areas (**Figure 2.1**). This area was chosen on the basis of low level of outward migration and the practical advantage of being served by one major district general hospital at the time, which would facilitate end-point ascertainment through linkage to hospital-based records.

2.4.1 Recruitment of participants to the study

In total 77 630 men and women then aged 40–79 years were invited to take part EPIC-Norfolk at baseline between 1993 and 1997 through registers in thirty-five general practices in Norfolk. The standard protocols of the health examination have been published. [137] Specific details of the measures used in this dissertation are as summarised below.

Figure 2.1: A map of Norfolk representing the distribution of participants soon in 2000 and in 2014, showing little change in migration over the course of the study.



2000 2014

2.4.2 Baseline Health Examination

At the baseline health examination, trained nurses took anthropometric measurements on individuals who were wearing light clothing and no shoes. Height was measured to the nearest millimeter using a free-standing stadiometer, and weight was measured to the nearest 0.1kilogram (using digital scales, Tanita). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. A D-loop non-stretch fiberglass tape was used for the circumference measures. Waist circumference was measured at the smallest circumference between the ribs and the iliac crest to the nearest 0.1 cm while the participant was standing with the abdomen relaxed, at the end of a normal expiration. Waist circumference was defined as the minimum circumference at the natural waistline between the lower rib margin and the iliac crest. Hip circumference was defined as the maximum circumference between iliac crest and the crotch. Waist:hip ratio (WHR) was calculated as hip circumference/waist circumference.

Lung function was measured by forced expiratory volume in one second (FEV1) using an electronic handheld turbine spirometer (Micro Medical Ltd, Rochester, United Kingdom), with the higher of two consecutive expirations recorded after a practice blow. Calibration was performed regularly on a weekly basis to ensure the accuracy and precision of both equipment and personnel. Although measures of both FEV1 and forced vital capacity (FVC) were taken, only FEV1 is reported here. Blood pressure was measured by using an Accutorr non-invasive oscillometric blood pressure monitor

(Datascope Medical, Huntingdon, United Kingdom) after the participant had been seated for 5 min. The mean of two systolic readings was used in the analyses.

Nurses also took non-fasting blood samples in plain and citrate bottles. Serum concentrations of total cholesterol, were measured on fresh samples with the RA 1000 (Bayer Diagnostics, Basingstoke). Plasma vitamin C levels were measured from blood drawn into citrate bottles. The blood was stored overnight in a dark box in a refrigerator at 4–7°C and then spun at 2,100g for 15 min at 4°C. Plasma was stabilized in a standardized volume of metaphosphoric acid and then stored at 270°C. The plasma vitamin C level was estimated using a fluorometric assay within 1 week of sampling (12). The coefficient of variation was 5.6% at the lower end of the range (mean 33.2 µmol/l) and 4.6% at the upper end of the range (mean 102.3 µmol/l).

2.4.2.1 Health and Lifestyle Questionnaire

A health and lifestyle questionnaire (HLQ) was posted to the participants for self-completion, which they either returned by free-post or returned at the health examination. The health and lifestyle questionnaire has a common format across the EPIC cohorts. Sociodemographic, health and lifestyle data were collected from the HLQ.

2.4.2.2 Covariates from questionnaire

Marital status was categorised as 'married' or 'single' (combining single, separated, divorced and widowed categories). Education (the highest level attained) was categorised into three groups (i) No qualification (not completing school up to the age of 16), (ii) Completion of school up to the age of 16 or up to the age of 18 and finally (iii) those obtaining an education to graduate level (those who obtained a degree or equivalent) or above.

Social class, for men was coded using current occupation except if participants reported as being unemployed in which case their partner's social class was used. Last employment was used for men who were retired. Unemployed men without partners were unclassified. Social class in women was based on their partner's social class except when the partner's social class was unclassified or missing, or they had no partner in which case social class was based on their own occupation. An unemployed woman without a partner was coded as unclassified. Social class was classified according to the Registrar General's occupation-based classification scheme into five main categories. [141]. Social class I consists of professionals, class II includes managerial and technical occupations, class III is subdivided into non-manual and manual skilled workers (III non-manual and III manual), class IV consists of partly skilled workers, and class V comprises unskilled manual workers.

Smoking history was derived from yes/no responses to the questions “Have you ever smoked as much as one cigarette a day for as long as a year?” and “Do you smoke cigarettes now?” Alcohol consumption was derived from the question “How many alcoholic drinks do you have each week?” with four separate categories of drinks. Total alcohol consumption was estimated as the total units of drinks consumed in a week. For these analyses, a moderate drinker was defined as someone who drank one or more units a week (that is, not a non-drinker) but not more than 14 units a week. Participants were categorised by smoking status as current, former, and never smokers, and alcohol consumption was computed as units per week.

Total (habitual) physical activity was assessed using two questions (Appendix 2). The first referred to usual occupational physical activity (over a period of one year), classified into four categories: sedentary or inactive, standing, physical work and heavy manual work. The second question was on the amount of time spent in hours per week in both winter and summer, on cycling and other physical exercise from which the average time spent daily in leisure-time activity per day was calculated. A simple four-category physical activity index was derived based on the level of activity from occupational and leisure components (Appendix 3). The questionnaire was validated as a measure of physical activity energy expenditure against individually calibrated heart rate monitoring. [142] The physical activity index has previously reported to predict total mortality, cardiovascular disease incidence [143] and stroke. [144]

Medical history was ascertained with the question “Has a doctor ever told you that you have any of the following?” followed by a list of conditions that included heart attack, stroke, diabetes, depression requiring treatment, pulmonary disease, asthma and cancer. Hearing problems were ascertained from yes/no response to the question “Do you have any problems with your hearing?”

2.4.3 Recruitment to the Third Health Examination phase (3HC)

Invitations to the third health examination (3HC) phase of EPIC-Norfolk (also called EPIC-Norfolk 3) included a follow-up health and lifestyle questionnaire (HLQ, follow IV). Participants were asked to send their response on ‘Participation Form’ indicating their preference of timings and returning their completed HLQ in a freepost envelope. Those not attending could also give a reason for their refusal. Every endeavour was made to facilitate participation, including providing transport for the less abled participants wanting to attend the health examination. The order of GP practices approached for EPIC-Norfolk 3HC was based on geographical location and distance from the clinic in the Regional Centre (Norwich). Practices were approached two at a time, one at close proximity to the clinic (city practice) and one further afield (rural area). Funding constraints led to the exclusion of 4 of the original 35 GP

practices from follow up. As a result of not including these practices, 1906 eligible participants were not approached for EPIC-Norfolk 3HC. Recruitment to EPIC-Norfolk 3HC is summarised in **Figure 2.2**.

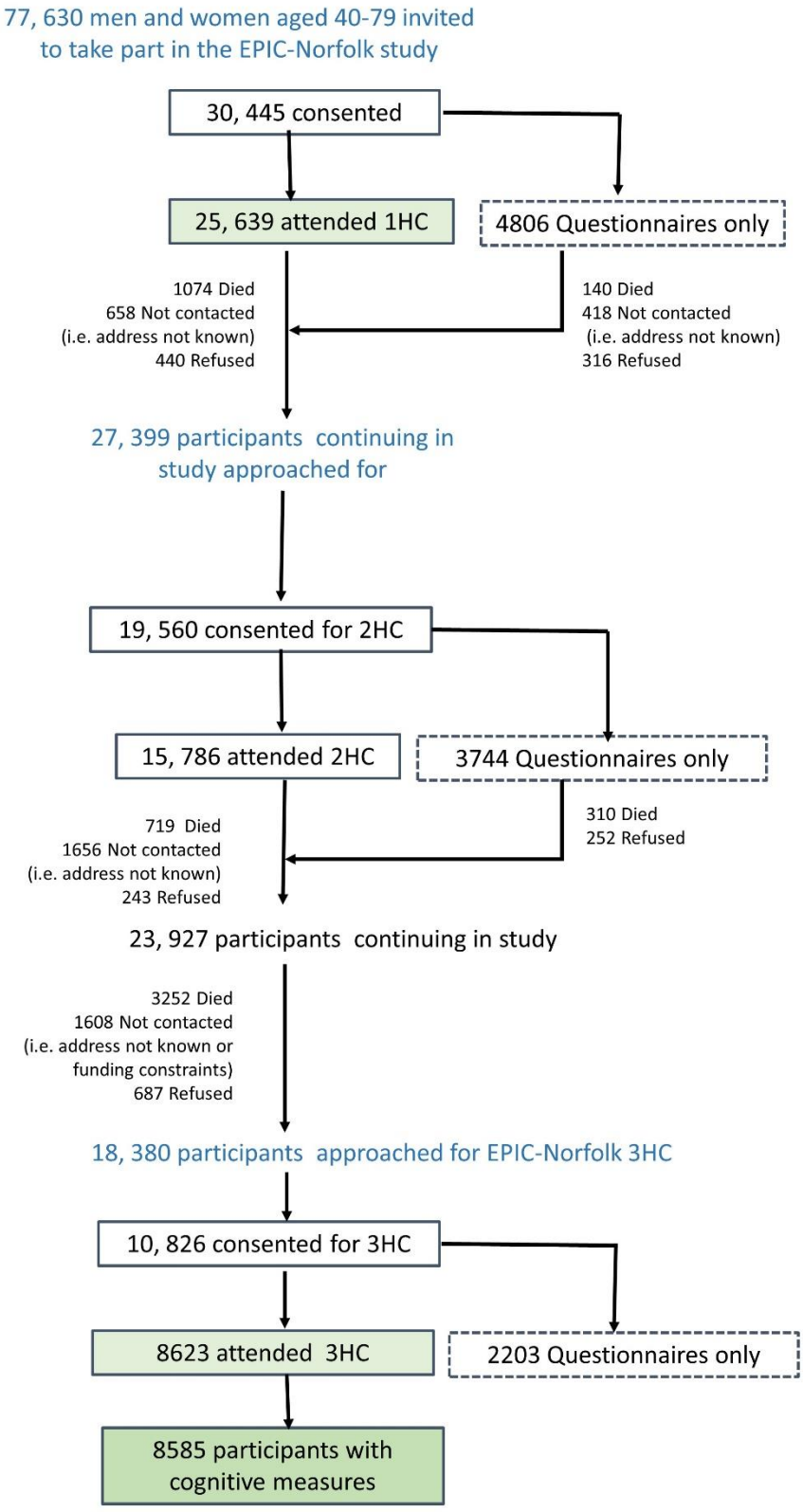
2.4.4 EPIC-Norfolk 3HC Pilot Study

EPIC-Norfolk 3HC was piloted using one of the collaborating GP practices for over 18 months between 2004–2006. This pilot demonstrated willingness of participants to travel a significant distance (15 miles in this case) to take part. The pilot indicated the feasibility of including new measures as well as measures collected in previous examinations and estimate of response rate from the cohort. The results of the pilot were used to make modifications to the protocol where necessary, to allow some of the tests more suitable to an epidemiological setting.

2.4.5 Follow-up

There have been five health check phases since the start of the study. A diagrammatic representation of the timeline is given in **Figure 2.3** of the different phases over the past 25 years of the study and the level of participation at each stage. The inclusion criteria for invitation to each health examination is to include all participants (funding permitting) who consented at baseline, after excluding those who had died or previously requested no further approaches. Record linkage to participant data at NHS-Digital, the national provider of data on health (mainly from National Health Service) and social care in England, ensured participant contact information was up to date. In addition to health examinations, participants have also been invited to complete health and lifestyle questionnaires (HLQ), food frequency questionnaires, seven-day food diaries, health and life experiences (HLEQ) and physical activity questionnaires at regular intervals in between health examinations. Other than the HLQ from baseline (1HC) and third health examination phase (3HC), questionnaires and health examination measures from the other time-points have not been used in this thesis. This is highlighted in **Figure 2.3** using a darker font.

Figure 2.2: A flow chart of participant recruitment for EPIC-Norfolk 3HC.



Modified from Hayat et al., IJE (2014)

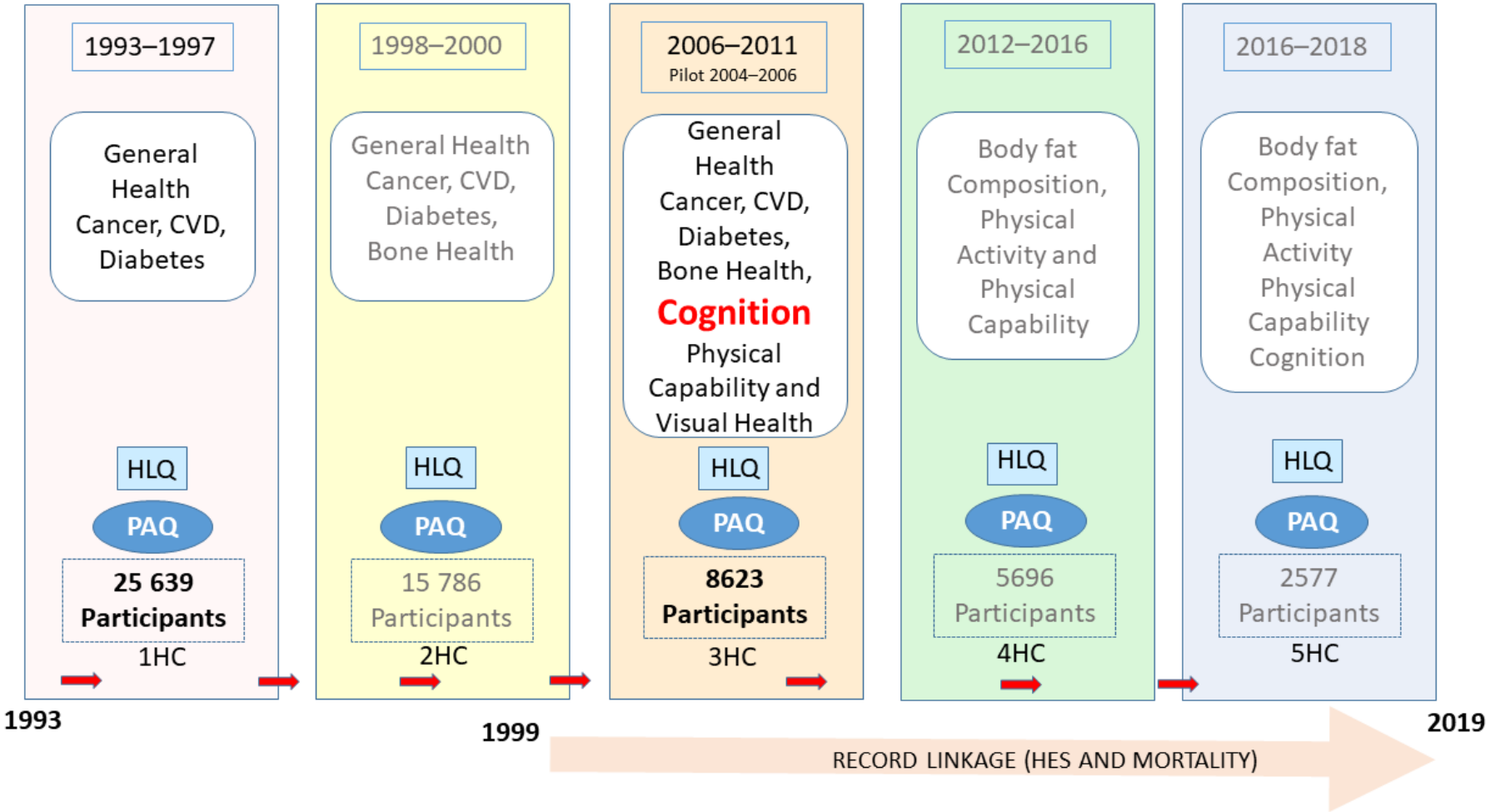
Participants have been passively followed up for mortality and other health end-points through medical record linkage. Further details of the specific data used for each analysis are provided in the relevant chapters. A description of record linkage and the different data sources used for dementia diagnosis is given below with further details in Chapter 8. Cognitive measures were introduced to EPIC at the third health examination phase (3HC) between 2006-2011 with a brief pilot phase between 2004–2006. All cognitive measures used in this thesis are from this time point. Repeat measures of cognition were taken at the 5th health examination (2016-2018), although these measures were not available at the time of writing this dissertation.

2.4.6 EPIC-Norfolk -Third Health Examination

The three main areas of investigation for the third health examination phase EPIC-Norfolk (3HC), also called EPIC-Norfolk 3, [138] were visual health, cognition and physical capability. Other aspects of ageing that were included were skin ageing and physical activity. Measures from the previous health examinations were also repeated. These included anthropometry (height, weight, waist circumference, hip circumference), blood pressure, heel-bone ultrasound, impedance/body fat percentage, ankle brachial pressure, lung function and blood sampling. The 3HC lasted between 150-180 minutes, with the cognition component lasting approximately 40 minutes depending on the ability of the participant. Detailed guidelines for scoring (as summarised in Appendix 4) were also provided. The cognition battery was conducted approximately half through the appointment. This was so that sufficient time had elapsed for the nurse administering the test to establish a rapport with the participant, but not too long into the appointment where the participant may have become anxious or tired, which could then have a possible effect on their performance.

Though EPIC-Norfolk 3HC ran over 7 years (including the pilot), the administration of the health examination remained unchanged with staff tightly following a standardised protocol for test administration and scoring, adhering to a script for some for a standard verbal response ensuring consistency and accuracy minimizing variation, differences in interpretation and reducing subjectivity. The protocol also included guidance on how to encourage participants without giving feedback. The EPIC-Norfolk 3HC protocol and cohort profile have been published. [138] Full lists of the measurements available from 3HC including repeated measures, are detailed in Boxes 2.1 and 2.2.

Figure 2.3: Timeline of the EPIC-Norfolk Study over 25 years of follow-up (Data used only 1HC and 3HC highlighted with a darker font)



Box 2.1: Self-report data collected from questionnaires at EPIC-Norfolk 3HC

Health and Lifestyle Questionnaire (Follow-Up IV)
Socio-demographic
Employment status
Self-rated Health and diagnosis (including vision and hearing)
Social networks and support, Leisure activities and Hobbies
Activities of daily living
Falls
Medication
Smoking and alcohol (*Alcohol intake measure of unit per week was calculated from number of drinks consumed per day over 7 days which was different from baseline which was calculated from total number of drinks consumed over 7 days).
*Self-perceived wealth and economic status

Health and Life Experiences Questionnaire (HLEQ)
Psychosocial Measures
*Widespread Pain using the Manchester Coding System
Social life
Loneliness
Anxiety and depression
Mood status
Health
Daily activities, lifetime events,
Childhood experiences personal beliefs

Physical Activity Questionnaire (EPAQ2) and perception of local environment
*Self- report on physical activity behaviours in three domains: activity at home, work and recreation. Also, using Geographical Information Systems (GIS) with Neighbourhood Environment Walkability Scale, (NEWS) to observe how environmental factors play a role in determining behaviour
*Skin Ageing
*Self- report on exposure to UV sunlight (lifetime and previous year)
*Skin reaction to sunlight exposure
*Tanning (including attitude towards UV exposure)
*Use of sun protection/skin care
*Natural hair colour (at age 20 and current)

Dietary Data
7Day Food Diary and FFQ

*New measures in EPIC-Norfolk 3HC (not applied at previous phases).

Box 2.2: New and repeat objective measures applied at the third health examination (3HC)

Venous Blood Sample	Biomarkers included full blood count (platelets, total white blood count, neutrophils, basophils, eosinophils, monocytes, lymphocytes, total red blood cell count); Mean corpuscular volume - MCV Hematocrit (HCT) haemoglobin (Hb); glycated haemoglobin (HbA1C); Lipid profile (Total cholesterol, HDL LDL Triglyceride); vitamin C; creatinine; albumin; and C-reactive protein. Serum, plasma and whole blood also stored for future biochemical profiling and DNA extraction.
Anthropometric measures	Standing height (Stadiometer, Chasmores, UK), weight, waist and hip circumference.
Impedance /body fat	Body fat percentage measured using TANITA TBF-300 MA Body Composition Analyser (Tanita UK, Ltd., Yiewsley, UK).
Physiological Function	Brachial pressure and heart rate measured with Accutorr PlusTM automatic sphygmomanometer blood pressure monitor (Datascope Medical, Huntingdon, United Kingdom). Also measured was *Ankle Brachial Pressures using the mini Dopplex D990 Doppler Pen with Ultrasonic Doppler flow detector (Huntleigh Healthcare, UK) and respiratory function using a portable spirometer (Micro Medical, United Kingdom).
Ultrasound measurements of the calcaneus	Attenuation of broadband ultrasound(dB/MHz) and speed of sound (m/s) were measured twice on each foot with CUBA clinical instrument (McCue Ultrasonics, Winchester).
*Skin Ageing	Digital Images of skin on face and hands.
*Cognitive Assessment	Retrospective and prospective memory, attention and calculation, registration, new learning, language, executive function, reading ability and Visuospatial /constructional ability.
*Functional Capability	Gait speed, balance, chair stands, one leg stand (for participants under age 70), grip strength using a Smedley's Dynamometer (Scandidact, Kvistgaard, Denmark).
*Objective Measure of Physical Activity	Physical Activity using a commercial accelerometer, the GT1M (Actigraph, Florida, USA).
*Eye Examination	Visual acuity (VA) using the LogMAR visual acuity chart 1 (Precision Vision, LaSalle, IL, USA), intraocular pressure (IOP) using an AT555 Non-Contact Tonometer (Reichert, New York, USA) and later using the Ocular Response Analyzer (ORA, Reichert, New York, USA), axial length and anterior chamber depth using IOLMaster, (Carl Zeiss Meditech Ltd, Welwyn Garden City, UK), retinal nerve fibre layer thickness (GDx VCC, Zeiss, Dublin, CA, USA. Threshold visual field analysis was done with the Humphrey field analyser (Carl Zeiss Meditech Ltd, Welwyn Garden City, UK), optic nerve head topography determined using the HRT II (Heidelberg Retina Tomograph, Heidelberg Engineering, Heidelberg, Germany), Colour fundus photography of optic disc and macula using a Topcon non-mydriatic retinal camera TRC-NW6S non-mydriatic retinal camera and IMAGEnet Telemedicine System (Topcon Corporation, Tokyo, Japan) with a 10 megapixel Nikon D80 camera (Nikon Corporation, Tokyo, Japan).
Medication	Confirmation of medication by nurse using repeat prescription slips.

Source: Hayat et al. (2014)

2.4.7 Objective Cognitive Measures in EPIC-Norfolk 3HC

The Cognition battery used in EPIC-Norfolk consisted of seven tests assessing both global function and specific cognitive abilities. These tests were chosen on the basis that they are validated tests, assessing a range of cognitive domains and had been shown to be sensitive to the early changes of decline, and associated with function and health outcomes. The cognitive tests used in EPIC-Norfolk are described below. It is important to highlight that whilst the score of each test purports to assess the performance of a single 'main' ability, the score reflects a range of other abilities that are being utilised. Each test assesses more than the one single ability (as shown in Fig 2.4) and to execute a task successfully, abilities work in conjunction not independently of each other. In this thesis, I have used the main ability of each test, however for the visual sensitivity test (VST), there were two separate outcome measures that were available later in the thesis. Chapters 3 and 4 only include one measure from this test, whereas the remaining chapters include both, giving a total of 8 different abilities assessed.

Short Form Extended Mental State Exam (SF-EMSE)

The Extended Mental State Exam (EMSE) [22] extends the widely used Mini Mental State Exam (MMSE), [145] a test known for its limitations, [14,25] in particular in higher functioning individuals. [22]. The original EMSE consists of 47 items from the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) interview schedule [146,147] as well as items recommended in the report from the MRC Alzheimer's Disease Workshop held in 1987. [148]. EPIC-Norfolk used a modified shorter version of this test consisting of 11 selected items assessing functioning at the higher end of the ability range. Using items from the SF-EMSE, a full-scale MMSE score could also be ascertained by assuming an almost perfect performance on the excluded items in a highly functioning population. [149] The 'full derived' MMSE score allows the comparison of the other components of the battery using the SF-MMSE scores as a validated and recognised standard.

Attention and Visual Search (Letter Cancellation)

The letter cancellation task [150] assesses attention, mental processing and speed. The task involved a visual search of a set of random letters printed in a grid like format consisting of 26 rows and 30 columns with the aim of crossing out as many of the 72 possible target letters (P and W) within one minute. There are two outcome measures in this task, the first is for speed which is total numbers of letters searched in the allocated time and the second is the accuracy score (the outcome measure that was used in this thesis), which is number of correctly identified target letters minus all potential target letters missed up to the point scanned by participant.

Hopkins Verbal Learning Test (HVLT)

The HVLT [151] is a short reliable test of verbal recall and recognition. [152–154] The test consists of a 12-item word list, from three semantic categories, ('precious stones', 'human shelter' and 'animals with four legs'). Participants were presented with the word list on a computer screen and asked to memorise the words. The computer program was timed with an interval of 1 second between each word presentation. At the end of the presentation the participant was asked to recall as many of the words as they could. The list was shown a further two times. Correctly recalled words were recorded. A score for each trial and the total recall score (maximum of 36) was noted. Any incorrect words mentioned were also documented, and although not used in here, are available for future analysis. Here, the total HVLT score was used as the outcome measure.

Cambridge Neuropsychological Test Automated Battery: Paired Associates Learning (CANTAB-PAL).

The Paired Associates Learning test (CANTAB-PAL), tests episodic memory and new learning and has shown to be a sensitive tool as a determinant of memory deficit in the early stages of dementia. [155–158] Participants were presented with six white boxes (and then eight at the final stage) on a touch screen, opening sequentially to display 1,2,3,6 and then 8 abstract visual patterns. Immediately after the final test pattern was displayed, one of the patterns was displayed in the middle of the screen and the participant was required to touch the box where that pattern was located on the screen. The task consisted of eight stages and up to ten presentations after which the task terminated. There are a number of outcome measures in CANTAB-PAL, all which have to be analysed with reference to the PAL stages completed measure. The outcome measure used here was the 'first trial memory score' (FTMS), the number of patterns correctly associated to their locations in the first attempt summed across the stages completed. Details on the other outcome measures and the justification to use FTMS is given in the scoring criteria in Appendix 4.

Visual Sensitivity Test (Reaction Time)

The Visual Sensitivity Test (VST) [159] assesses disturbance of the magnocellular pathway and consists of two parts: In the first part, a triangle appears at random on the screen and the participant had to press the space bar on the computer as soon as the triangle was seen. In the second part, the screen is full of constantly moving dots, from which a triangle forms at a random point on the screen. The test required the participant to press the space bar when the triangle became apparent, with the triangle gradually becoming more obvious with time, and so increasing the probability of detection over time. The VST gave 70 measures per participant, with the final reading value (used in analyses) being the average of these measures. The majority of analyses in this these uses both stages of the test as

separate outcome measure of reaction time (in milliseconds), VST-Simple and VST-Complex reaction times respectively. Timings were recorded and stored automatically under the participant's unique study number.

The National Adult Reading Test (NART)

The National Adult Reading Test (NART) [160] shown to correlate with pre-morbid intelligence and general cognitive ability [161,162]. The NART uses the assumption that the level of reading ability is closely related to general intellectual level and is a more objective measure of pre-morbid ability than using demographic variables such as years of education and socio-economic status. [162] The NART is widely accepted and commonly used though it is known to have limitations, particularly in the less educated. [163] As the words in the NART do not follow the standard (British) grapheme-phoneme rules, the test requires the participant to recognise the word in its written form, as decoding the word would result in an incorrect pronunciation. The NART thus gives an implicit measure of the individual's knowledge of the English vocabulary. This test provides a measure of reading ability or prior crystallised intelligence, when assessing level of cognition for an individual both in absolute terms and relative to others within their age range.

Participant were presented with 50 irregular words of varying difficulty on a computer screen. Here, the short NART protocol [164] was used from which a full NART score was derived using an algorithm based on the performance on the first half of the test (Appendix 4). Only those individuals scoring between 21-25 on the first half of the test, proceeded to the full NART of 50 words. The outcome was an error score, so a higher score indicated lower performance. There have been some reservations regarding the practical utility of the short NART, but its accuracy, at the time of the 3HC was shown to be almost equivalent to the full-length NART. [165]

Prospective Memory

This is a test for the memory for future intentions, previously suggested to be sensitive to early stages of cognitive decline. [166,167] Participants were asked to remember to carry out an explicit instruction at a specified point later in the appointment. This was to seal and initial an envelope when it was handed back to the participant after completing a previous task. Responses were scored on whether both, one or none of the actions were completed when the envelope was handed to them. For the purpose of the analysis here, participants were defined as being 'successful' if they carried out at least one correct action without having to be prompted.

This page is intentionally left blank

Figure 2.4: Cognitive abilities assessed by each test used in the EPC-Norfolk, 2006–2011 (including data from the pilot phase 2004–2006).

Test (Outcome Measure)	Cognitive Abilities/Domains (as reported in literature)							Cognitive Ability/Domains (with score) as reported						
SF-EMSE (Global Cognition)	Language	Registration	Retrospective Memory	Attention (Calclation)	Visuospatial	Verbal Fluency	Executive Function	Language (7)	Registration (3)	Retrospective Memory (12)	Attention (calculation) (5)	Visuo-spatial (1)	Verbal Fluency (5)	Exec. Function (4)
HVLT Total Recall Score	Language		Retrospective (Verbal Episodic) Memory		Verbal Learning		Executive Function	Retrospective Memory [Verbal Episodic Memory (36)]						
CANTAB-PAL FTMS	Retrospective (Non-verbal Episodic) Memory				Visuospatial Function			Retrospective Memory [Non-Verbal Episodic Memory (26)]						
Event and Time Based Task	Prospective Memory				Retrospective Memory			Prospective Memory (2)						
Letter Cancellation (PW Accuracy)	Executive Function		Attention		Processing Speed		Visuospatial Function	Attention (72)						
NART (Error Score)	Language (Comprehension)				Intelligence			Intelligence (50)						
VST (Reaction Time in milliseconds)	Visuospatial Function				Processing Speed			Processing Speed (Reaction time in milliseconds)						

2.4.8 EPIC-Cognition battery scores and data cleaning

The scoring (and where necessary, details on the criteria) applied to each item on the components of EPIC- Cognition battery are given in Appendix 4.

2.4.9 Ascertainment of endpoints

Almost complete follow-up for disease outcomes in EPIC-Norfolk has been established via linkage to routinely collected National Health Service (NHS) databases in England (Hospital Episode Statistics, HES) and mortality data for all participants using their unique NHS number and date of birth. The linked hospital records contain coded diagnostic information for all inpatient and day-case admissions. [89] To maximise dementia ascertainment, EPIC-Norfolk also obtained national mental healthcare data from three separate mental health data releases covering different time periods. These were Mental Health Minimum Data Set (MHMDS), Mental Health and Learning Disabilities Data Set (MHLDDS) and the Mental Health Services Data Set (MHSDS), which contain record-level data about individuals in contact with mental health services including memory clinics.

The MHMDS, MHLDDS and MHSDS incorporates mental health data (including dementia), over the follow-up periods, 2009-2014, 2015-2016 and 2017-2018 respectively. Each subsequent release was wider in scope than the previous version. These datasets contained mainly service-level breakdowns that were not applicable here with little additional diagnostic information. The latest release, MHSDS was the widest and most complex dataset which contained substantially more diagnostic information. Limited GP data have also been used in this thesis. Further details of record linkage and the datasets are given Chapter 7.

2.5 Analyses

Measuring performance against the distribution of cognitive scores within a population to define abnormality, particularly where the data are not normally distributed has been described previously, [44,168] and to derive cut-off scores for community studies from the population under investigation to be a reasonable methodology to adopt. [169] The data for most of the tests in EPIC-Norfolk, were not normally distributed and the prevalence of dementia and cognitive impairment using accepted standard diagnostic criteria is low in the cohort. [170] It was therefore necessary to establish operational criteria for cognitive dysfunction specific to this population. [170] Due to the distribution and non-linear response observed in all the analyses in this thesis, associations were examined using approximate percentile cut-offs rather than the continuous cognitive score. Details on how

participants were defined into categories of performance are given in the separate chapters. For most analyses in this thesis, poor performance on any test was defined as obtaining a score less than a cut-off point corresponding to the 10th percentile of the population distribution in each of the cognitive tests individually. For prospective memory, where participants either succeeded or failed the task, those failing were assigned to the poor performance group and those succeeding, to the standard level. Associations with cognitive function, mortality and dementia were examined using different methodologies as described in the separate chapters.

To address the limitation of multiple testing, a composite score (EPIC-COGComp) was also created for some of the analyses. EPIC-COGComp represents general cognition and a wider range of cognitive domains underlying all the cognitive functions assessed. A categorical variable was created for EPIC-COGComp score as with the individual tests. Details of how associations were assessed are given in the individual chapters and in Appendix 5.

2.5.1 Missing data and extreme outliers

If a cognitive test was abandoned or the participant refused to continue, the participant was scored on what had been completed and the data included in the analysis. Reasons for refusal were recorded to differentiate those participants who refused or failed to complete as a result of a technical fault or ran out of time, from those who refused because they expressed anxiety or difficulty with the task. Those who refused prior to starting a test or those who said no to a test component were assigned as missing data. Any participant identification number that could not be accurately assigned to a known individual was also removed from the final analysis as were any implausible values. Specific details on missing data are given in the separate chapters.

2.5.2 Reporting on results

Participants scoring low on any of the cognition tests were not referred for further assessment, nor were results reported to their GP. This was indicated on the participant information sheet (PIS) sent to the participant in the invitation pack. Clinically relevant results from other parts of the health examination such as for raised blood pressure, lipid profile and the eye examination were referred to GP Practices for further follow-up.

2.6 Participant Characteristics and Attrition

Of the 77 630 approached to take part in EPIC-Norfolk, 30 445 consented and completed a health questionnaire, of which 42% of all women agreed to take part as compared to 36% of all men. It is difficult to compare characteristics between responders and non-responders as limited data are available on non-responders, other than non-responders were more likely to be men and younger. All ages were well represented for both men and women in the EPIC-Norfolk cohort including those who were 70 years or older. The cohort was 99.7% White Caucasian, with fewer smokers than the general UK population. [137] The cohort was similar to the national population samples studied in the Health Survey of England, in terms of anthropometry, serum lipids and blood pressure. Of those who consented, 25 639 (84%) attended a health examination at baseline (1HC). These participants were within the age range 40–79 years.

Table 2.1: Age and sex distribution of responders and non-responders at baseline (1993–1997).

Age-Band (Years)	Responders 39.0 % (N=30, 445)	Non responders 61.0 % (N=47, 185)
Men 48.7% (37, 825)	36.2 (13 700)	63.8 (24 125)
≤ 44	4.3 (587)	6.5 (1572)
45-49	16.7 (2287)	21.0 (5061)
50-54	15.9 (2178)	18.2 (4385)
55-59	15.2 (2075)	15.1 (3649)
60-64	15.6 (2142)	13.1 (3165)
65-69	15.4 (2112)	11.8 (2848)
≥ 70	16.9 (2319)	14.3 (3445)
Women 51.3% (39, 805)	42.1 (16 745)	57.9 (23 060)
≤ 44	4.6 (778)	6.2 (1422)
45-49	18.4 (3084)	18.7 (4304)
50-54	16.1 (2699)	16.1 (3717)
55-59	15.1 (2523)	13.8 (3189)
60-64	14.8 (2482)	13.0 (3009)
65-69	14.9 (2492)	13.4 (3080)
≥ 70	16.1 (2687)	18.8 (4339)

To examine attrition in the cohort, the baseline characteristics of those who attended both the 1HC and EPIC-Norfolk 3HC were then compared with the 17, 789 participants who attended the 1HC only (Table 2.2). The proportions of men and women were similar, with women comprising 55.3% of the group attending both baseline and follow-up health examinations and 54.5% of those attending the baseline health examination only (P=0.2). Those who returned to take part in EPIC-Norfolk 3HC were, at the time of the first health examination, more likely to be younger, taller and have lower weight, lower blood pressure and lower cholesterol concentrations. They were also more likely to be educated to at least to O-level standard or equivalent (i.e. leaving school with exams at 16 years of age), to have a higher socioeconomic status, to have never smoked and to have been more physically active. Responders to EPIC-Norfolk 3HC were also more likely to drink more alcohol at baseline than those who did not respond.

Table 2.2 shows that the patterns seen in the baseline characteristics were the same in both men and women. Although, as might be expected, those attending EPIC-Norfolk 3HC were healthier and of higher education and socioeconomic status at baseline compared with those not attending, the cohort still represents a diverse population with a wide socio- economic distribution and range of lifestyle factors of interest, such as physical activity and obesity. Those invited for the 3HC (N=18 382) but did not attend, were also compared to those who actually attended to give further insight to the characteristics of those used in the various analyses in this thesis. Those who were invited and did not attend, were more likely to be older, with higher self-reported heart attack, stroke and diabetes prevalence. Non-attenders were also more likely to have no qualifications and be in the lower socio-economic groups (Table 2.3).

Table 2.2: Baseline characteristics of participants in EPIC-Norfolk. Participants who attended health examinations in both the first and third phases of EPIC-Norfolk (3HC + 1HC) are compared to those who were examined in the first phase only (Baseline, 1HC).

	Men			Women		
Variable	3HC+ 1HC (N=3615)	1HC only (N=7992)	P-value	3HC + 1HC (N=4495)	1HC only (N=9537)	P-value
Mean (SD)[a]						
Age (years)	56.6 (7.9)	61.0 (9.5)	<0.001	55.2 (7.8)	60.7 (9.5)	<0.001
Height (cm)	174.9 (6.5)	173.6 (6.7)	<0.001	162.1 (6.0)	160.4 (6.3)	<0.001
Body Mass Index (kg/m^2)	26.1 (3.0)	26.7 (3.4)	<0.001	25.5 (4.1)	26.6 (4.4)	<0.001
Systolic Blood Pressure (mmHg)	134.2(16.3)	138.9 (18.1)	<0.001	129.4 (17.1)	136.0 (19.4)	<0.001
Total Cholesterol (mmol/L)	6.0 (1.1)	6.1 (1.1)	0.01	6.1 (1.1)	6.4 (1.2)	<0.001
Frequency, % (N)[b]						
Education						
No qualification	22.0 (795)	34.3 (2739)	<0.001	29.5 (1327)	48.2 (4593)	<0.001
Any Qualifications	78.0 (2819)	65.7 (5245)	<0.001	70.5 (3167)	51.8 (4936)	<0.001
Social Class (% Non-manual)	65.0 (2333)	55.4 (4324)	<0.001	67.5 (3001)	58.5 (5393)	<0.001
Smoking						
Current	8.7 (313)	13.8 (1092)		8.8 (392)	12.6 (1187)	
Ex-smoker	49.7 (1792)	56.7 (4492)	<0.001	30.3 (1354)	33.2 (3123)	<0.001
Never	41.6 (1498)	29.5 (2339)		61.0 (2729)	54.2 (5108)	
Physical Activity						
Inactive	23.1 (834)	34.4 (2752)		20.3 (914)	35.3 (3363)	
Mod. Inactive	26.1 (945)	24.0 (1913)	<0.001	33.2 (1493)	31.5 (3000)	<0.001
Mod. active	25.0 (905)	22.0 (1755)		26.0 (1168)	20.4 (1948)	
Active	25.8 (931)	19.7 (1571)		20.5 (920)	12.9 (1226)	
Median (IQR)[c]						
Alcohol Intake (Units/ week)	7.0 (2.5, 14.5)	6.0 (2.0, 14.0)	<0.001	2.5 (1.0, 7.5)	2.0 (0.5, 6.0)	<0.001

Note: Groups were compared using unpaired student's t-test[a], chi square[b] and Mann Whitney[c] tests as appropriate.

Abbreviations: 1HC: First Health examination; 3HC: Third Health examination; Mod, moderately; SD= Standard Deviation; IQR= Inter-Quartile Range; kg: kilogram; cm: centimetres; mmHg: millimetres of mercury; mmol/L: millimoles/Litre; %: frequency; N: number; I-IIINM: social class I-III Non-Manual

Table 2.3: Characteristics of individuals with a cognitive test measure compared to those who either did not attend or had no cognitive test measure.

	Total Invited (N=18, 382)		
	Attenders, with cog score (N=8585)	Non attenders (N=9797)*	P-Value
Characteristics at Baseline			
Mean (SD)			
Age	55.7 (7.8)	58.9 (9.3)	<0.001
Frequencies, % (N)			
% men	44.7 (3841)	42.0 (4117)	<0.001
Level of education			
No Qualification	26.2 (2251)	45.1 (4414)	<0.001
O or A level	56.1 (4521)	46.2 (4521)	
Graduate Level or above	17.6 (1513)	8.7 (856)	
Social Class			
Professional	8.8 (748)	4.9 (468)	<0.001
Managerial	41.1 (3498)	30.1 (2867)	
Skilled Non-Manual	16.0 (1364)	17.1 (1635)	
Skilled Manual	20.6 (1748)	26.8 (2555)	
Semi-Skilled	11.2 (950)	16.3 (1550)	
Non-Skilled	2.3 (197)	4.8 (459)	
Alcohol (Units/week)			
0	8.9 (763)	15.5 (2263)	<0.001
≤ 14 Units	75.2 (6426)	71.6 (6912)	
> 14 Units	15.8 (1353)	12.8 (1239)	
Smoking Status			
Never	52.2 (4463)	45.0 (4365)	<0.001
Former	38.9 (3329)	41.0 (3971)	
Current	8.9 (760)	14.0 (1361)	
Co-morbidities			
Heart attack	1.5 (128)	2.6 (251)	<0.001
Stroke	0.6 (50)	1.0 (99)	0.001
Cancer	4.4 (374)	4.4 (426)	1.00
Diabetes	1.0 (85)	2.2 (218)	<0.001
Depression	14.6 (1250)	14.3 (1398)	0.6

(* includes 38 who attended but had no cognition score). Abbreviations: A, Advanced; N, Number; O, Ordinary; SD, standard deviation

2.7 EPIC-Norfolk Study overview

There are over 25 years of longitudinal data on this well-characterised cohort of men and women from Norfolk, first seen at baseline between 1993–97 when they were aged 40–79 years. The remit of EPIC-Norfolk has broadened over the years to include other aspects of ageing including cognition and dementia. A major strength of the EPIC-Norfolk study is the availability of longitudinal exposure and health outcome data from baseline to the present. This cohort provides the opportunity to examine the trajectory of functioning in the general population and in particular the determinants of high as well as poor performance.

From the 1HC onwards, emphasis has always been placed on using validated instruments and objective biomarkers to measure exposures including diet and physical activity. This has been extended to include cognitive measures that were introduced to EPIC-Norfolk as part of the third health examination phase. Reviewing the utility of the various cognitive tests for use in an epidemiological setting is part of this thesis and will be discussed further in Chapter 3.

Most large cohort studies have to rely on linkage with death records to obtain mortality by cause, and on self- reported questionnaires for non-fatal health outcomes which are limited by response rates and subjective recall. The EPIC-Norfolk cohort has been followed up by medical record linkage since 1999, first by linking to local hospital and disease registers, and more recently via NHS-Digital. This allows complete case ascertainment which would otherwise not be possible.

The main limitations of the study are those that concern all cohort studies, in particular healthy volunteer bias and attrition. As one would expect, individuals would be less likely to participate in either the baseline or subsequent follow-up examinations if they were seriously ill, disabled or had major cognitive or visual impairment. In EPIC-Norfolk third health examination, there was likely to be selective truncation of individuals from the cohort at the lower end of the distribution of functional performance and some loss of frailer members of the cohort, but there remains a large range of performance and health to examine determinants of healthy ageing. Furthermore, the availability of baseline characteristics and mortality, and follow-up of the original cohort, enable characterisation of both those who have and those who have not participated in follow-up examinations. The characteristics of those included in the analyses and those who are not, are examined in each chapter.

Chapter 3: Descriptive Epidemiology

The work presented in this Chapter has been published:

Hayat, S. A., Luben, R., Moore, S., Dalzell, N., et al., (2014). Cognitive function in a general population of men and women: a cross sectional study in the European Investigation of Cancer-Norfolk cohort (EPIC-Norfolk). BMC Geriatr, 14, 142. doi:10.1186/14712318-14-142

3.1 Summary

This chapter details the distribution of cognitive function in different cognitive domains by age and sex and compare the utility of a number of assessment tests in EPIC-Norfolk. A total of 8623 participants attended the third health examination with cognitive test measures available on 8585 individuals. The cognitive test battery comprised of seven validated tests including: a shortened version of the Extended Mental State Exam (SF-EMSE); letter cancellation task; Hopkins Verbal Learning Test (HVLT); Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test (CANTAB-PAL); Visual Sensitivity Test (VST); Shortened version of the National Adult Reading Test (Short-NART) and a task to test for prospective memory. Descriptive data are presented for this cohort of men and women in mid to later life.

There were no overt reports of cognitive impairment in EPIC-Norfolk participants at time of cognitive testing. Increasing age was generally associated with declining mean cognitive function with the exception of Short-NART, where there did not seem to be any strong association with age. Although the test scores generally decline across age groups (with the widest variation seen in the oldest age group), there was a range of capability from poor to high performance in each age band, with some participants from the oldest age group outperforming their younger counterparts. Some sex differences were also observed. These variations may provide insights into the determinants of cognitive function in later life.

3.2 Introduction

A broad range of cognitive capability is observed in the older population [171] as well as substantial inter-individual heterogeneity in rates of decline. [71] The range encompasses high cognitive functioning even in the very old, [75] mild cognitive impairment (MCI), through to dementia at the other end of the spectrum. Substantial data already exist on dementia and cognitive impairment, mainly in the older population, from using a wide range of instruments, each with merits and limitations that assess different aspects or stages of cognition. Episodic memory deficits have been shown in a number of studies to be associated with the strongest and most persistent risk of cognitive decline [129,172] and are the most common and earliest complaints in MCI. [173] However deficits in other cognitive domains can also occur, some early on, including attention, executive functioning, prospective memory, semantic memory, verbal ability, visuospatial skills, attention and processing speed.[174–176]

There is a need for assessments to cover a broad range of ability and domains, have an optimal balance between sensitivity and specificity with high positive predictive value in the settings in which they are applied. Population-specific normative values for cognition are necessary. This not only allows for comparison of cognitive performance of those presenting in a clinical setting, [177] but may assist to identify early indicators of decline. However, before we are able to advise guidelines and policies on health, we need to gain better insight into the ageing process in the general population and the range of functions in both domain specific and global cognition.

The primary aim of this chapter is to present data from a general population of men and women without overt cognitive impairment using a comprehensive cognitive test battery assessing a range of function including memory (retrospective and prospective), executive function, attention, calculation, registration, language, praxis, abstract thinking, processing and new learning. The secondary aim is to explore the comparability of the different tests and their use in a community setting.

3.3 Methods

3.3.1. Participants and measurements

Participant recruitment and an overview of the EPIC-Norfolk methods have been described earlier in Chapter 2. This includes a detailed description of the cognition battery. Specific methods for the work presented in this chapter are given here.

3.3.2 Covariates

Smoking status, mental activities, employment status and hobbies were obtained from responses from the health questionnaire completed near the time of 3HC. Participants were asked to report on type and frequency of mental activities with the question 'Please indicate when you take part in any of the following activities' followed by the following options: (1) Listening to radio; (2) Reading newspaper; (3) Reading magazines; (4) Reading books; (5) Playing games such as cards, chess; (6) Crosswords and (7) Puzzles. A mental activity score was calculated by assigning 1 point for an individual who reported doing a particular activity once a year or less up to 5 points if they did the activity every day. In total there were seven activities (listening to the radio, reading the newspaper, reading magazines, reading books, playing games such as cards or chess, crosswords and puzzles). The minimum score possible was 7 and the maximum was 35. Those with missing data were excluded from the analysis.

Education level was obtained from baseline questionnaire and dichotomised: The first category was leaving school with no formal qualification (less than O level or equivalent, or leaving school before the age of 16). The second category consisted of those leaving school with at least some qualification. This group combined those attaining O-level or equivalent (completing school to the age of 16), A-level or equivalent (completing schooling to the age of 18 years) and those obtaining a degree or equivalent.

3.4 Analysis

The outcome measures of six of the test components were continuous. The prospective memory variable measure was dichotomised into 'successful' and 'unsuccessful'. The descriptive data (using the original untransformed scores of the continuous variables) are presented as medians and inter-quartile ranges as the cognitive scores in majority of the tests were not normally distributed. For the SF-EMSE Items, letter cancellation (Accuracy Score), HVLT, and CANTAB-PAL (FTMS), a higher score indicated better performance. For the outcome measure for VST (reaction time) and NART (Short NART-Error Score), a higher score indicated poorer performance. Cross sectional data are presented by age and sex and by age, sex and MMSE Category. For further insight, a graphical representation of the scores using a range of percentiles (1^{st}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} and 99^{th}) by age group and sex are also given. Statistical analysis for this chapter was performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

3.5 Results

Of the 8623 participants attending the 3HC, 45% (n=3861) were men and 55% (n=4762) were women. Cognitive data were available on 8585 individuals. Over 90% of those with cognitive data completing or attempting six or all the tests in the battery. The CANTAB-PAL and VST had slightly lower completion rate (at 86.5% and 83% respectively), partly due to a technical computer failure, resulting in loss of data on 150 participants. Table 3.1 summarises the cognitive domains covered by each of the tests used in this study and the number of participants completing each test component.

Men and women were equally likely to complete the tests, with 6011 (69.7%) participants attempting all the components of cognitive battery and only 850 participants (less than 10%) of those taking part attempting or completing five components or fewer. Those completing all the components were slightly younger (mean age 68.8 compared to 70.9 years in men and 67.4 compared to 69.8 years in women), and were more likely to be either in paid employment or actively taking part in regular social networks when compared those who did not complete all the tests. More men had left school with qualifications than women (77.8% compared to 70.3%), although more women participated in regular social activities (68.5% for women compared to 59.5% for men). Women also reported more mental stimulating activities in their leisure time (with mean mental activity score of 23.2 in women as compared to 21.1 for men).

Distributions for cognitive function (by each test component and stratified by sex) are presented in **Figure 3.1**. The SF-EMSE distribution had a negative skew but did not have the same strong ceiling effect as the SF-MMSE scores in this cohort (distribution not shown), with 2298 (27%) of participants scoring the maximum SF- MMSE score of 29 as compared to only 2.4% (n=200) scoring the maximum EMSE score of 37. The data for letter cancellation (PW Accuracy) and HVLT Total Score were both approximately normal distributed, as was the distribution for FTMS (other than a peak at score 0, which suggests that a high proportion of participants were unable to achieve a correct response immediately). The data for reaction time of the VST were highly positively skewed (as a result of a few extreme, but genuine slow responders).

For the short NART, there was a peak at the error score of 24, followed by alternating peaks and troughs in data giving a 'comb-like' distribution. This pattern in the distribution is as a result of the short NART algorithm (as described Appendix 4). The peaks in the distribution can be attributed to those assigned an error score by the algorithm, artificially inflating the scores at these points. The greatest peak (and the starting point of this comb effect of the data) was seen to occur at the cut-off point of score of 20 (giving a full NART error of 24), which was the point where participants with this score or lower, did not continue with the second half of the test.

Figure 3.1: Distribution of scores (of continuous cognition variables) in men and women in EPIC-Norfolk

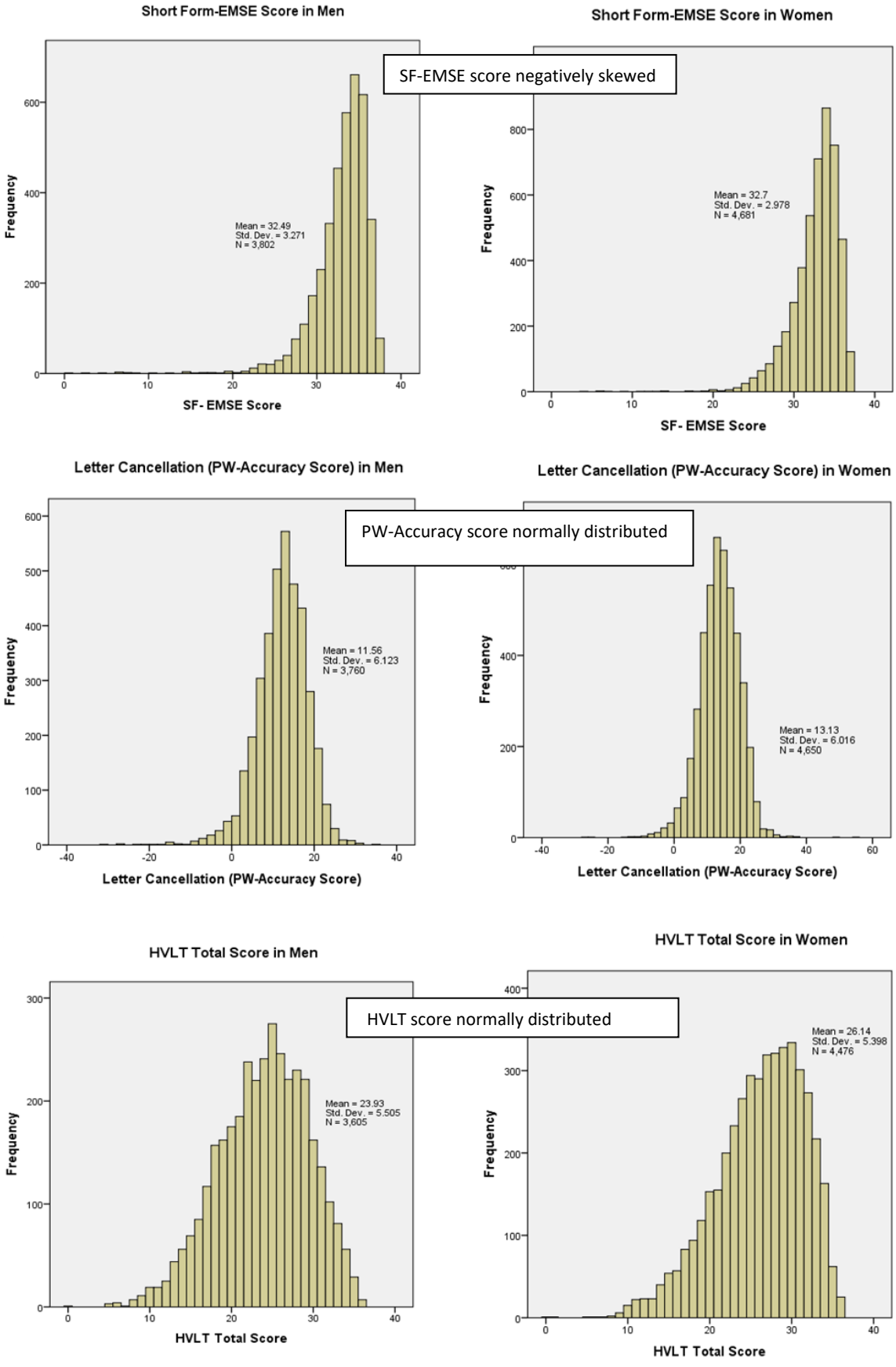


Figure 3.1: Continued

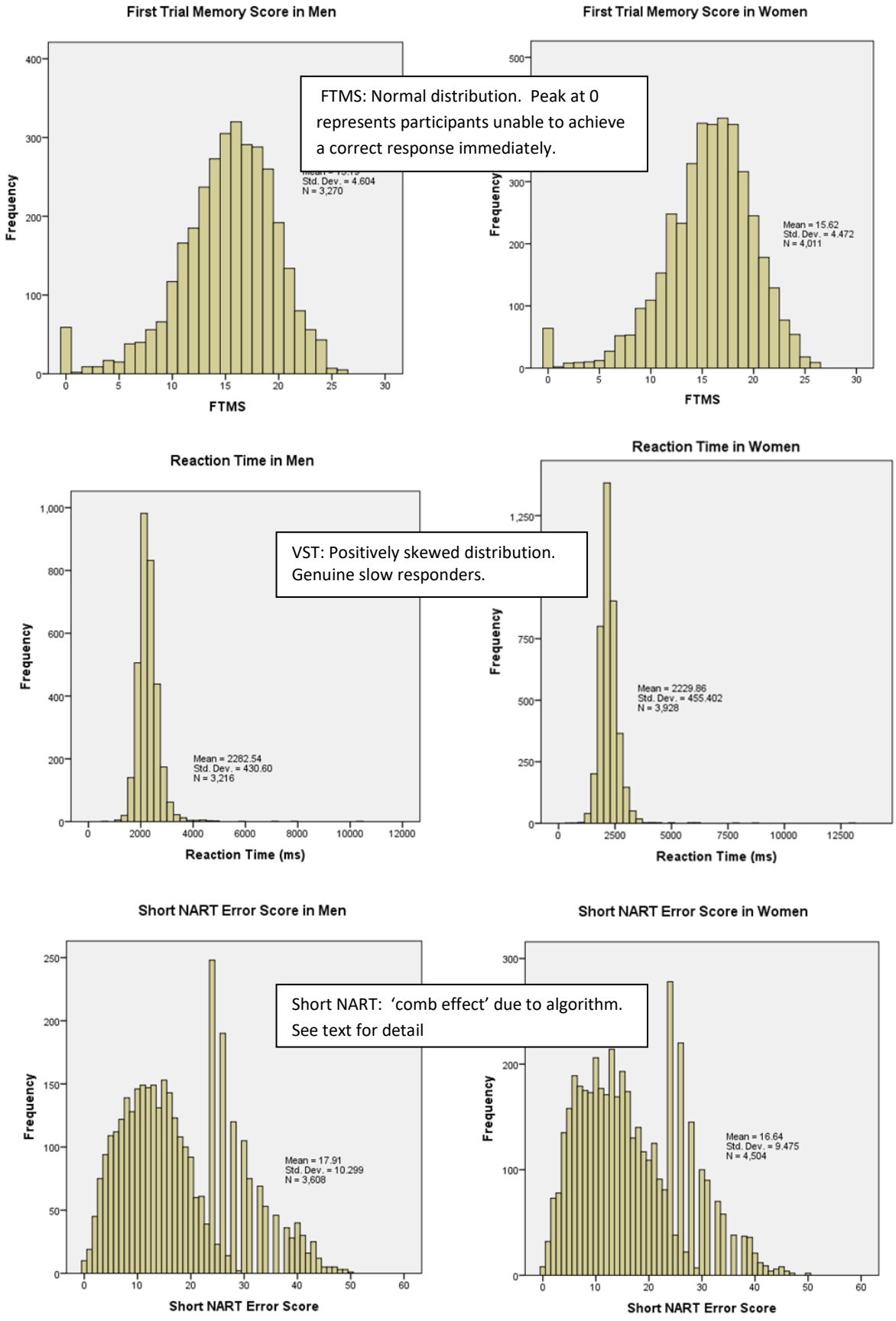


Table 3.1: Summary of test components of the EPIC-Norfolk cognition battery and number of participants attempting all or part of each component.

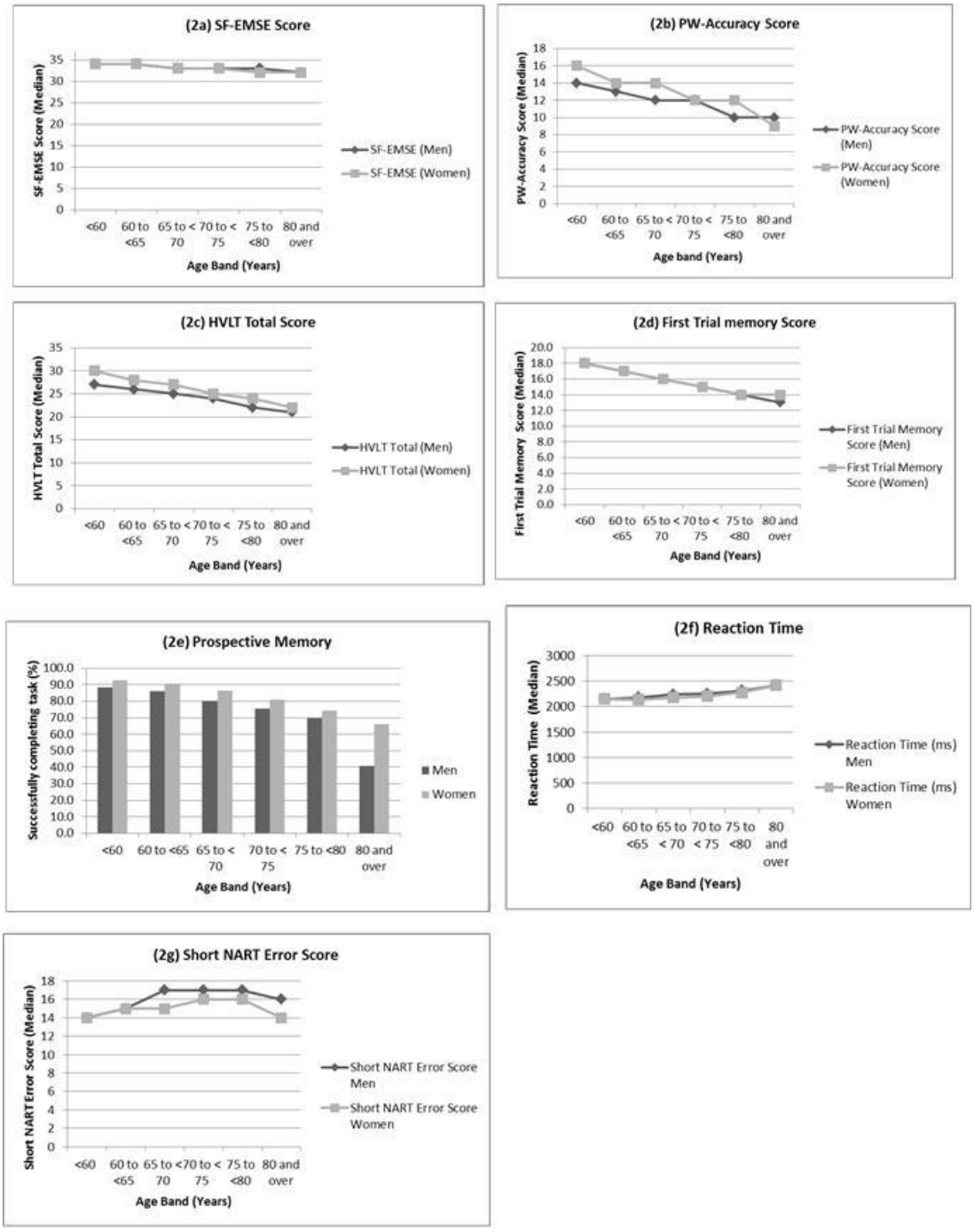
Cognitive Test	Cognitive Domain	Outcome Measure* (Maximum possible test score)	Number of Participants attempted/completed test component
Short Form-Extended Mental State Exam (SF-EMSE)	Global measure of cognition from MMSE to assess domains for retrospective memory (immediate and delayed), attention and calculation, registration, verbal registration, language (object naming/sentence), visual and constructional skills, praxis. Added items for Memory (extension on retrospective memory), praxis, verbal fluency (animal naming), language (writing to dictation) and abstract thinking.	SF-EMSE Score (37)	98% (8483)
Letter Cancellation Task	Executive function - covering visual search, attention, mental and processing speed)	Accurately identified target letters in one minute (72)	97.5% (8410)
Hopkins Verbal Learning Test (HVLT)	Recognition/learning and episodic memory	Total HVLT Score - Total of correctly identified target words over 3 trials (36)	93.7% (8081)
CANTAB®-Paired Associate Learning (CANTAB-PAL)	Episodic memory and new learning/Visuospatial	First Trial Memory Score (26)	86.5% (7281)
Visual Sensitivity Test (VST)	Visuospatial (magnocellular pathway)	Reaction Time in milliseconds	83% (7144)
National Adult Reading Test (NART)	Proxy Measure of IQ - Pre-morbid Intelligence	Short NART Error Score - 50 minus the number of correctly pronounced words from list (50)	94.1% (8112)
Time and Event Based Task	Prospective memory	Success vs Failure	97% (8403)

*Frequencies for only one outcome measure (as used in this thesis) given in this summary table.

The median scores of each of the test components were plotted with age in men and women as shown in **Figure 3.2** (3.2a–3.2g). The data presented here are cross-sectional, showing the association of scores with age group. **Figure 3.2** showing median scores declining with age. The proportion of participants successfully completing the prospective memory task lowers with increased age group. In the case of the VST (**Figure 3.2f**), the median reaction time increases with age group. The short NART error score showed an increase with age initially, remains steady then a slight reduction in the oldest group (**Figure 3.2g**). In almost all tests, women generally performed better than men.

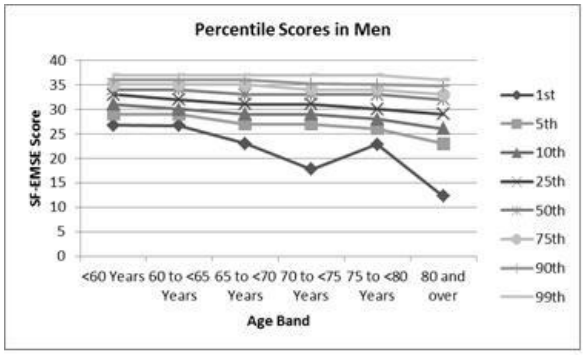
The data were further characterised by calculating percentile scores plotted by age group. **Figure 3.3** shows lower scores with increasing age. For higher percentiles, scores remain reasonably stable across age groups, but the spread and variation in scores becoming greater across each age group, with the lowest percentile having markedly lower performance. The variation in scores was least for the SF-EMSE compared to the other tests in the battery. For reaction time and short NART error score, the 99th percentile indicated the poorest performers. The short NART error score exhibited widest variation across age and even some improvement in scores in the oldest age groups.

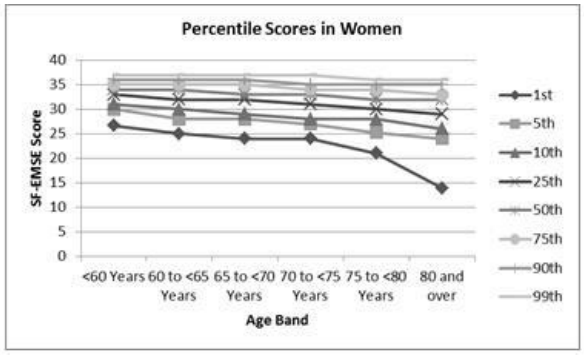
Figure 3.2: Cognitive performance with age in men and women in the EPIC-Norfolk 3HC cohort.

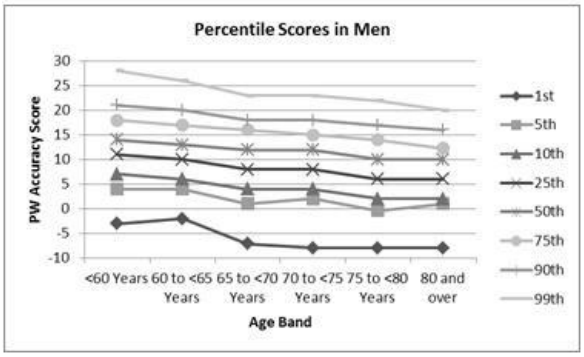


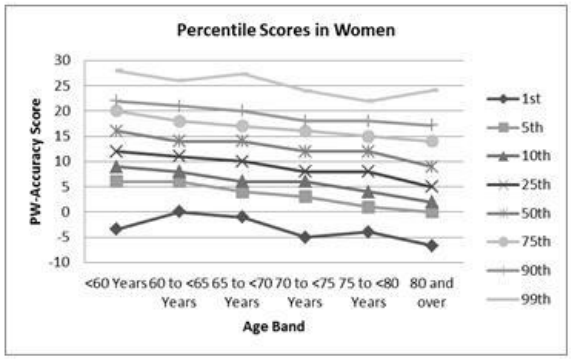
Scores (median values) as shown in **Figures 3.2a-3.2d** are test scores where higher scores correspond to better performance and scores in **Figures 3.2 f and 3.2g** are reaction time and error score respectively, where a higher score indicates poorer performance. **Figure 3.2e** is shown as a percentage of participants successfully completing prospective memory task.

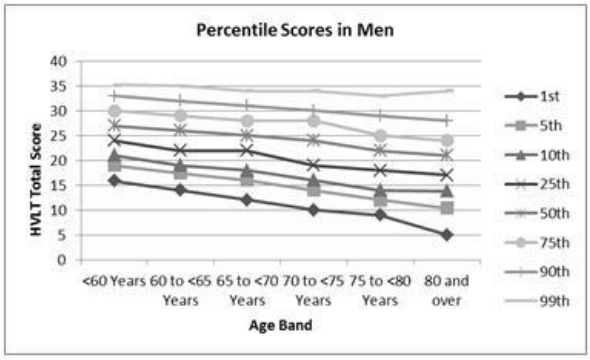
Figure 3.3: Cross-sectional percentile levels of scores by age group in EPIC-Norfolk men and women

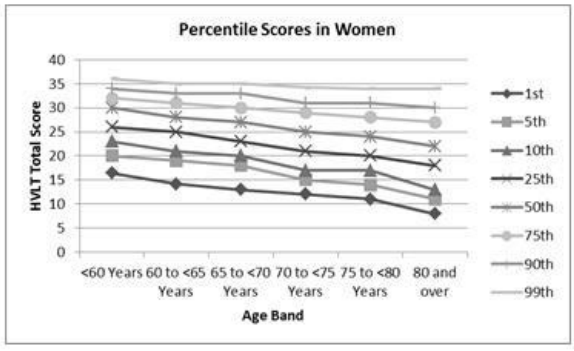


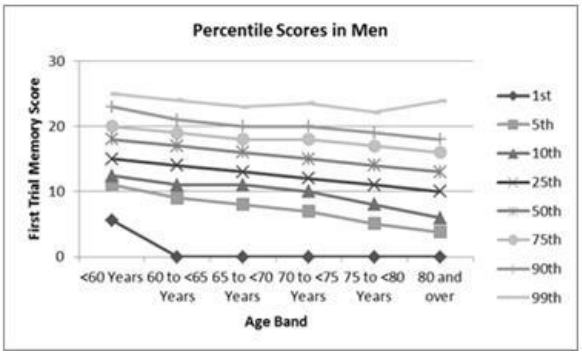












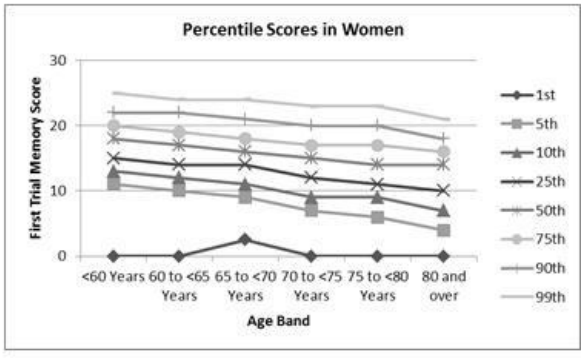
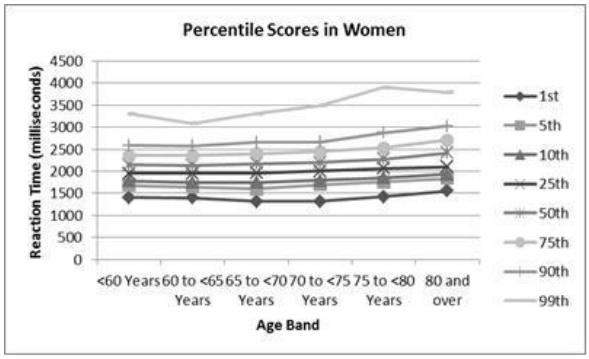
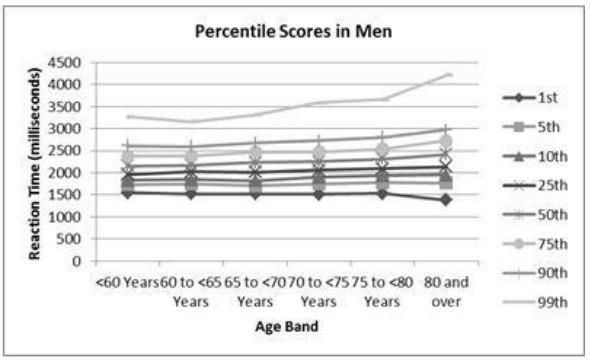
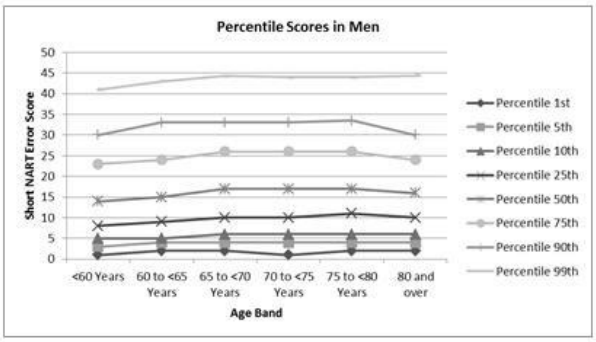
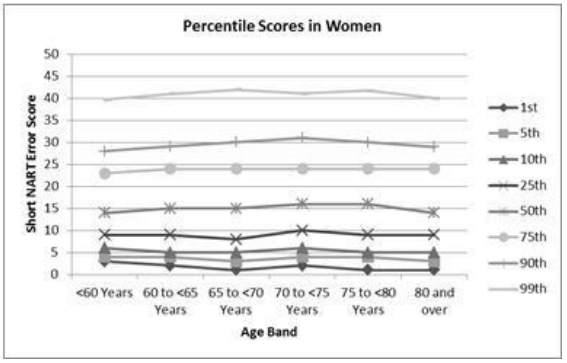


Figure 3.3 Continued









A graphical presentation of percentile scores plotted against age-group (cross-sectional) showing performance from the highest to the lowest percentile scores in the six tests with continuous scores.

The measures from each test component were compared to the MMSE, which is widely used in both research and clinical settings, despite its limitations. [178] The accepted cut off score of less than or equal to 23 as indicating presence of cognitive impairment has evolved from research findings,[25] although higher cut-offs have been used. [18,179] In this high functioning cohort, there were very few individuals with a score of ≤23; therefore the cut off used here for poorest performance was based on the 10th percentile score of 24. A modified form of the MMSE (SF-MMSE) was used, with its derived full MMSE score [149] creating three categories based on the distribution of SF-MMSE scores in the study population. The first category was defined as ≤ 24), the third category was defined at the highest SF-MMSE scores (28–29) and the middle category was created using the remaining scores of 25–27.

Tables 3.2 and 3.3 shows the distribution of all the tests in cognitive battery across the three SF-MMSE categories in men and women respectively. The general pattern for all the test components were similar with the scores of the continuous test variables improving across SF-MMSE categories. For the prospective memory test, the proportion of participants successfully completing the task also increased across the three SF-MMSE categories. Again, scores in women were slightly higher than men. There was still a range of performance seen across all three SF-MMSE categories.

The top performing 2298 participants who performed perfectly on the SF-MMSE (achieving a maximum possible score of 29), also included participants who were amongst the poor performers (with scores in the bottom 10^{th} percentile) for the other components. These findings were still valid for the top 25% and for the top 10% of the SF-EMSE performers (Table 3.4), although the numbers were increasingly lower than those seen with the top SF-MMSE scores.

Spearman's rank correlation coefficients were calculated (Table 3.5) to investigate the strength of relationship between each of the tests used in EPIC-Norfolk cognitive battery. The correlations were moderate to weak for most tests with HVLT having stronger associations with the other tests, such as with SF-EMSE (r=0.49) followed by FTMS (r=0.38) and short NART (r=-0.38). This inverse association was as a result of the NART Error scale, with larger number representing poor performance.

Table 3.2: Distribution of Cognition Test Component Scores by MMSE Cut off score in men

Test	MMSE Score ≤ 24				MMSE Score 25–27				MMSE Score 28–29			
	Freq. N	Mean (SD)	Median (IQR)	Range	Freq. N	Mean (SD)	Median (IQR)	Range	Freq. N	Mean (SD)	Median (IQR)	Range
SF-EMSE	240	25.2 (5.4)	27 (24, 28)	0, 32	1489	31.3 (2.2)	32 (30, 33)	17, 35	2073	34.2 (1.6)	34 (33, 35)	26, 37
P-W Acc Score	222	6. 5 (7.9)	8 (3, 12)	-28, 20	1474	10.5 (5.9)	11 (7, 14)	-23, 31	2064	12.8 (5.6)	13 (10, 17)	-31, 34
HVLT	209	19.1 (5.9)	19 (15, 23)	0, 33	1391	22.4 (5.3)	23 (19, 26)	5, 35	1980	25.5 (4.9)	26 (22, 29)	7, 36
FTMS	195	11.9 (4.9)	13 (9, 15)	0, 23	1258	14.3 (4.6)	15 (12, 18)	0, 26	1794	16.2 (4.2)	17 (14, 19)	0, 26
VST (ms)	190	237 (733)	2263 (2063, 2509)	1239, 10489	1222	2310 (427)	2260 (2056, 2506)	567, 7148	1777	2253 (382)	2214 (2025, 2442)	1232, 7838
Short-NART	200	25. 2 (11.1)	26 (17, 33)	2, 50	1394	20.1 (10.4)	19 (12, 26)	0, 49	1985	15.6 (9.4)	14 (8, 22)	0, 49
Prospective Memory (%)	217		55%		1470		73%		2063		84%	

Table 3.3: Distribution of Cognition Test Component Scores by MMSE Cut off score in women

Test	MMSE Score ≤ 24				MMSE Score 25–27				MMSE Score 28–29			
	Freq. N	Mean (SD)	Median (IQR)	Range	Freq. N	Mean (SD)	Median (IQR)	Range	Freq. N	Mean (SD)	Median (IQR)	Range
SF-EMSE	390	26.8 (3.8)	28 (26, 29)	4, 32	1718	31.5 (2.0)	32 (30, 33)	20, 35	2573	34.4 (1.5)	35 (34, 35)	24, 37
P-W Acc Score	375	9.3 (6.4)	10 (6 13)	-16, 35	1710	12.3 (5.8)	12 (9, 16)	-28, 32	2565	14. 3 (5.8)	14 (11, 18)	-26, 54
HVLT	352	21. 1 (6.0)	22 (17, 25)	5, 36	1612	24.6 (5.3)	25 (21, 29)	0, 36	2467	27.9 (4.5)	29 (25, 31)	10, 36
FTMS	325	13.2 (4.5)	13 (11, 17)	0, 24	1433	14.8 (4.6)	15 (12, 18)	0, 26	2212	16.6 (4.1)	17 (14, 19)	0, 26
VST (ms)	302	2393 (825)	2294 (2076, 2538)	459, 12869	1408	2259 (447)	2216 (2004, 2466)	1054, 7973	2167	2184 (374)	2156 (1965, 2374)	710, 8695
Short-NART	358	24.3 (10.4)	24 (16, 31)	2, 50	1616	18.6 (9.4)	18 (11, 26)	0, 47	2487	14.3 (8.4)	13 (8, 20)	0, 45
Prospective Memory (%)	379		64%		1707		79%		2567		90%	

Table 3.4: Distribution of scores in participants with near perfect MMSE and EMSE Scores

	(A)Top MMSE Score of 29				**(B) Top 25% EMSE Score (≥35)**				**(C) Top 10% EMSE Score (≥ 36)**			
	Men		Women		Men		Women		Men		Women	
	N*	Frequency % (N)	N*	Frequency % (N)	N*	Frequency % (N)	N*	Frequency % (N)	N*	Frequency % (N)	N*	Frequency % (N)
P-W Accuracy Score (10th percentile <= 5)	1006	8.2 (82)	1286	5.3 (68)	1034	5.5 (57)	1336	4.2 (56)	418	2.9 (12)	569	3.1 (18)
HVLT (10th percentile <=18)	962	6.7 (64)	1238	2.4 (30)	998	4.6 (46)	1285	1.1 (14)	404	1.5 (6)	568	0.5 (3)
FTMS (10th percentile <= 10)	870	6.2 (54)	1122	4.2 (47)	895	5.1 (46)	1149	3.6 (41)	360	5.3 (19)	514	2.5 (13)
VST (10th percentile >=2702 ms)	874	7.8 (68)	1100	5.4 (59)	904	7.1 (64)	1131	4.6 (52)	366	5.2 (19)	509	4.5 (23)
Short NART Error Score (10th percentile >=31)	964	5.9 (57)	1252	2.6 (33)	1006	4.0 (40)	1308	1.7 (22)	409	1.7 (7)	577	1.2 (7)

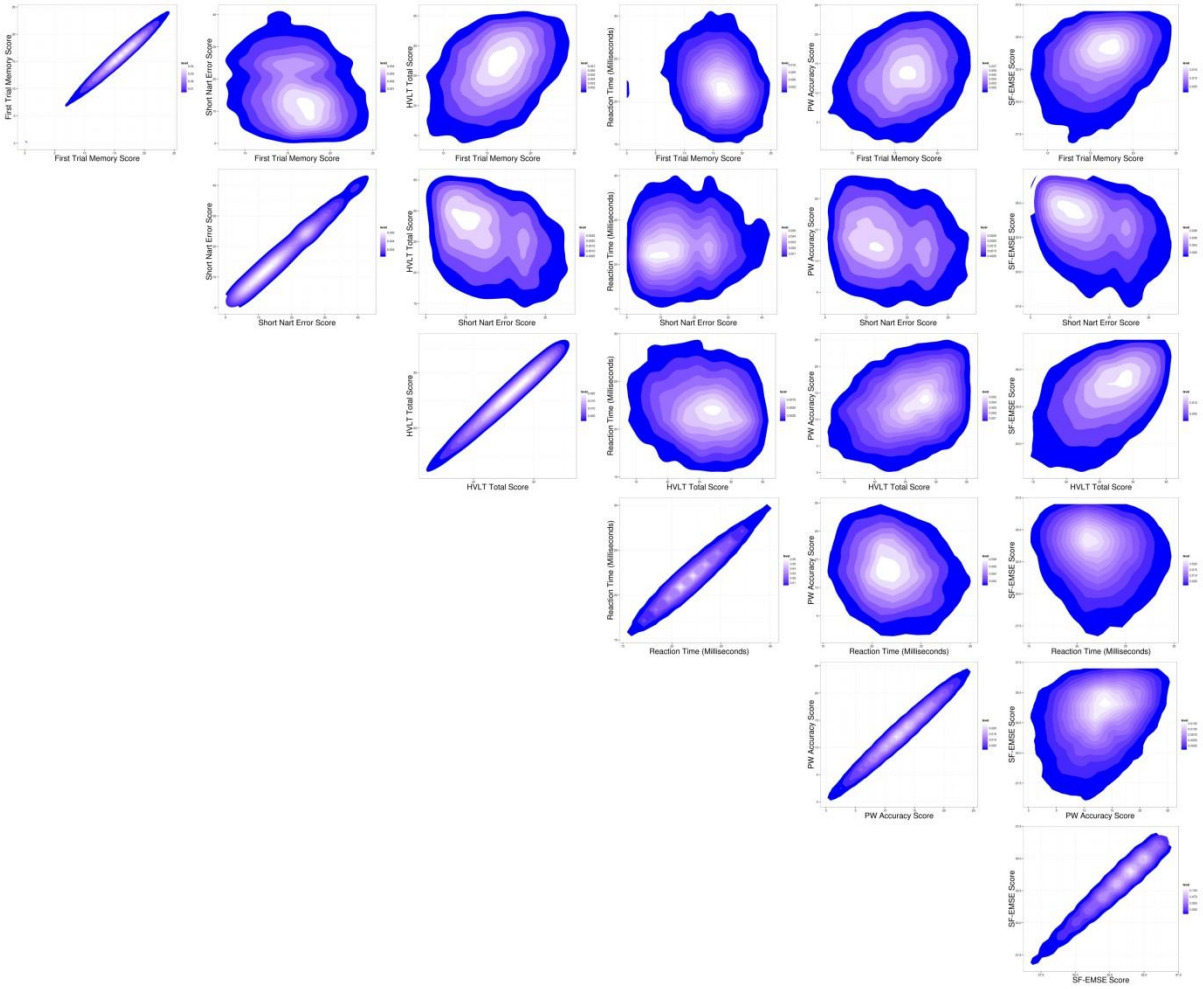
Participants achieving (A) Perfect MMSE Score of 29 (B) Top 25% SF-EMSE score and (C) Top 10% SF-EMSE score and scoring in bottom 10th percentile of other cognition tests
N*: Total Number of Participants with both test scores available
N: Number of participants in the bottom 10^{th} percentile

Table 3.5: Spearman's correlation coefficient between the test components of the EPIC-Norfolk Cognition Battery

	SF-EMSE	PW Accuracy	HVLT	FTMS	Prospective memory	VST
PW-Accuracy	0.33					
HVLT	0.49	0.33				
FTMS	0.34	0.26	0.38			
Prospective memory	0.26	0.19	0.23	0.21		
VST	-0.16	-0.17	-0.17	-0.17	-0.09	
NART	-0.38	-0.21	-0.34	-0.21	-0.13	0.06

To illustrate the relationship of the tests further, the distribution of the scores were plotted as contour plots (**Figure 3.4**). The contours represent strength of correlation between scores of the tests. There seemed to be some undefined spread for each test, however there was a systematic pattern seen in all the plots, with some of the test pairs showing a better relationship than others. The general direction of the plot and the peak of overlap of scores seem to appear in areas where one would expect, however with most of the plots what is seen at best is a moderate relationship between these tests.

Figure 3.4: Contour plots to show relationship of data from EPIC-Norfolk cognition battery



Legend: The contours represent the strength of the relationship between the scores (continuous) of the test components. The first plot in each row shows the outcome measure variable of each individual test plotted against itself depicting the perfect positively linear association. Subsequent plots showing the relationship with one of the other tests. Some test pairs showing a better relationship than others. The peak (white area) representing the region with greatest density of scores, centres at different points for each test pair combination.

3.6 Discussion

In this chapter, cross-sectional findings are presented on cognitive function profiles across a range of domains using previously validated instruments in men and women in EPIC-Norfolk 3HC (age 48-92 years). Despite the EPIC-Norfolk cognitive battery being relatively long, it was well tolerated by this general study population. Individuals can have impairment in one cognitive domain but perform well in another or a number of cognitive deficits can occur concurrently. There is increasing evidence of substantial variability in cognitive abilities within individuals. Hilborn et al., (2009) termed this variability in performance across different tasks within an individual as 'dispersion'. It is important to gain a better understanding of the dispersion displayed by healthy individuals in order to allow accurate clinical judgment on unhealthy or abnormal dispersion. [73]

Previous studies have shown that a variety of cognitive deficits are associated with preclinical stages of different types of dementias and that decline can occur in a number of cognitive domains, even before any of the clinical criteria of early stages of cognitive decline are met. [21,180] These findings are consistent with previous studies that have shown variability and dispersion across different cognitive domains in older people. [73,181] Further investigation is necessary to confirm whether the differences observed across the domains provide any meaningful indicators of cognitive performance over time.

The frequency distribution and data from the pilot (where the full NART was used for 300 participants) indicate that the short NART equation does not hold in this cohort. The aim of the short- NART was to lessen participant load and anxiety, however in an assessment such as the one in this study; participants were as likely to be anxious for any of the other components. The pilot data show that participants who obtained a score of 20 (n=82) for the first half of NART obtained a mean score of 7.9 (SD=3.7) for the second half, which is better than the algorithm prediction.

As with previous studies [182,183] age was also found to be inversely associated with the complete range of cognitive function being tested with the exception of NART, where there did not seem to be any strong association between the short NART score and age. This confirms previous findings that NART is a good measure of pre-morbidity [161,162] and that age has little or no effect on NART performance in the absence of early dementia. [184]

Differences in abilities across gender and age categories were observed. These may have arisen because of age and sex differences in education status. Although education was not investigated in detail here, the sample includes individuals leaving school with and without qualifications in all age groups analysed. There was also a finding seen in EPIC-Norfolk that has not been noted in other studies,

where women perform better than men across all the test components in all age groups, and even though more men than women reported leaving school with some qualification, this suggests that educational status might not explain these sex differences seen. Women gave reports of more social and mentally stimulating activities in their spare time, both linked to better cognitive performance at older age. [185]

Percentile scores from this cross-sectional data (**Figure 3.3**) show that the greatest decline in all test components is seen in poor performers across all the age groups. This graphical presentation can be used to compare scores or estimate age and sex adjusted scores across the different domains investigated here. Individuals scoring below the 25th percentile could be considered as cognitively impaired for that domain and require further investigation.

The MMSE's lack of ability to assess individual domains and its poor sensitivity to mild cognitive impairments are frequently cited limitations. [25] This is because most healthy individuals can successfully answer most of the test items. Even though more demanding tests are available, [14,15,22] the MMSE still remains the most widely used and cited test of global cognition. The psychometric qualities and utility of the other tests used in the battery were compared with the SF-MMSE to provide a baseline for future studies as a comparator with other studies. The MMSE, being a global measure of cognition contains items that test the same domains of memory function as the other components of cognitive battery. As expected, a positive direction with increased SF-MMSE score category was observed across all tests, however, there was still a range of scores (capability) within each of the SF-MMSE categories.

On further investigation of participants obtaining the maximum score of 29 on the SF-MMSE, we found in the range of 6-8% of men and 2-5% of women also scored in the bottom 10th percentile of the other tests (Table 3.4). On examining those individuals who obtained the top 25% and further in the top 10% SF-EMSE scores, there were still participants in poorest performers (10th percentile) of the other tests, although the figures were reduced. Those scoring in the bottom 10th percentile tended to be older than those with scores above the 10th percentile for all the tests apart from the Short NART. The number of participants scoring the maximum possible score of 37 on the SF-EMSE was small (n=200). No individuals scored in the bottom 10th percentile of the other tests other than one person who scored in the lowest 10th percentile for the NART. We show that obtaining a perfect score on the MMSE does not indicate absence of impairment, thus confirming previous findings for the need to supplement the MMSE in cognitive testing, [25] particularly in a normal to high functioning population.

The limited reliability and validity of the MMSE in a general population has been attributed to the restricted range of MMSE. The EMSE has been shown to be sensitive across a range of performance, to avoid the ceiling effect and that (even in its short form as it has been used here), the EMSE provides extended coverage of cognitive domains (extending on attention, memory, processing and executive function).

Spearman's rank correlation (Table 3.5) show correlations are moderate to weak for most tests with HVLT having the strongest associations with other test components especially with FTMS and NART. This is not surprising, as HVLT, FTMS and NART assess similar cognitive sub domains of memory and language, however the moderate degree of correlation is somewhat counterintuitive, as we would expect this to be higher. The contour plots (**Figure 3.4**) depict the spread of scores (and area of overlap) indicating that with some association, there is also some non-systematic scatter of scores suggesting that these tests may be assessing different aspects of cognitive function.

As part of the work carried out by myself and colleagues at EPIC-Norfolk, we addressed some practical and methodological issues with regards to minimising variability and subjectivity that can be introduced at any part of administration, scoring or cleaning of the data. Detailed description of the methods are given in the publication [170] and how we standardised protocols for use in an epidemiological setting to ensure accuracy and consistency. Having these methods standardised and documented is also extremely important to allow comparability and potential harmonisation of data with other studies. The other advantage of this study over previous studies is that it has been conducted in a large well characterised cohort of men and women with good representation from a very wide age range, which has been a limiting factor in some previous studies. [126,186]

There is likely to be some loss of the more cognitively impaired, the oldest and frailest participants, there remains a wide range of performance and health across the whole age span of interest (from mid–life to over 90 years) represented in EPIC-Norfolk 3HC. The other limitation is that this is a cross-sectional study and so although age differences and between person effects can be observed, within person differences or age related changes cannot, as longitudinal data are required. Finally, and very importantly, in this particular investigation, the potential effects of education were not taken into account. Education is a known strong predictor of cognitive function [187–189] and on the rates of decline. [190] The purpose of this chapter was to present the descriptive data on this cohort. The relationship of education and other factors to cognitive performance is explored in Chapter 4.

Everyday activities in the real world are complex, requiring independence, planning, organisation, sequencing and judgement and have been shown to be a significant predictor of functional status. [191] Therefore, assessing cognitive function in a range of domains such as executive functions, planning, flexibility, abstract thinking, semantic memory as well as episodic memory is vital. The EPIC-Norfolk Cognition battery is a comprehensive battery of accurate and well-tolerated tests that provide evidence of cognitive function in a number of cognitive domains that have previously been reported to be involved in much earlier stages of decline. Though there is reduction in performance across age, there is also a great deal of heterogeneity in older individuals. In the subsequent chapters, I provide further insight to this variability individuals across the cognitive domain assessed. Careful consideration should be given to the purpose for using a particular test (including whether the aim is to obtain global or domain specific measure, time availability and target population) when selecting an assessment tool for cognitive function.

Chapter 4: Socio-demographic Factors and Cognitive Performance

The work presented in this Chapter has been published:

Hayat, S. A., Luben, R., Dalzell, N., Moore, S., Anuj, S., Matthews, F. E., Wareham N, Brayne C, and Khaw, K–T,. (2016). Cross Sectional Associations between Socio-Demographic Factors and Cognitive Performance in an Older British Population: The European Investigation of Cancer in Norfolk (EPIC-Norfolk) Study. *PLoS One*, *11*(12), e0166779

4.1 Summary

Cognition covers a range of abilities, such as memory, response time, language and different tests cover specific or generic aspects, however differences between the measures may be observed within the same individuals. In this Chapter, the association of sociodemographic factors, age, sex and education were examined for the different cognitive domains covered by the seven cognitive tests used in EPIC-Norfolk 3HC. Cognitive measures were available on 8584 men and women for these analyses.

Though age, sex, education and social class were all independently associated with cognitive performance in multivariable analysis, the magnitude of these associations differed across the different cognitive tests. Increasing age was associated with increased risk of a poor performance score in all of the tests, except for the National Adult Reading Test (NART), an assessment of crystallized intelligence. Compared to women, men were more likely to have had poor performance for verbal episodic memory, Odds Ratio, OR = 1.99 (95% Confidence Interval, 95% CI 1.72, 2.31), attention OR=1.62, (95% CI 1.39, 1.88) and prospective memory OR=1.46, (95% CI 1.29, 1.64); however, no sex difference was observed for global cognition, OR= 1.07 (95% CI 0.93, 1.24). The association with education was strongest for NART, and weakest for processing speed. The varying relationships seen across different tests may help explain discrepancies in results reported in the current literature and provides insights into influences on cognitive performance in later life.

4.2 Introduction

Cognitive ability covers a range of domains, which together form the basis of cognitive function. These domains include recall, learning, understanding, encoding and recognition, most of which require prior knowledge and experience. Measuring cognitive abilities is not straightforward because they are not clearly distinct from one another. One ability may have an impact on the performance of another, or different abilities work in conjunction to execute a function, thus making selection of cognitive tests and the interpretation of results difficult.

There is a growing interest in the heterogeneity of cognitive performance observed in the ageing population (1) and what might constitute ‘normal cognitive ageing’. Certain abilities such as memory, spatial ability and processing speed have been observed to decline more readily than others such as comprehension and vocabulary which tend to remain stable for longer [69,71]. Some suggest that decline in mental speed contributes to the decline seen in other abilities [43,192]. Studies have also indicated that decline occurs at global and at domain specific level [21,81,174,193] and so both should be tested.

The difficulties and limitations associated with assessment of cognitive function as a result of the variability in cognitive testing and methodologies restricting cross study comparisons are well known [16,19]. Although a plethora of cognitive assessment tools exist, test performances vary depending on the populations in which they are being used [19]. Low levels of accuracy for detecting mild impairment, demographic biases and a lack of an agreed battery of tests appropriate for use in different situations, all add to the complexities [16].

There does not appear to be an agreement on the classification of the cognitive domains and there is a lack of consensus on which abilities are most important in testing cognitive decline [69]. The aim of this analysis was to gain further insight into how performance on a range of widely used cognitive assessment tools may relate to the socio-demographic factors, age, sex, social class and education.

4.3 Methods

4.3.1. Participants and measurements

An overview of the EPIC-Norfolk 3HC methods has been described in Chapter 2. Specific methods for the work presented in this chapter are given here.

4.3.2 Covariates

The covariates used in this analysis are as follows. Education based on the highest qualification attained and social class were taken from baseline questionnaire. These variables have been described in Chapter 2. Age (at the time of cognitive testing) was categorised into 5 year age bands. Information on marital status was obtained from the health questionnaire completed near the time of the health examination. Very few participants reported being separated (less than one percent), so this category was combined with the divorced group giving four categories; married, single, widowed and divorced or separated.

4.4 Analysis

Poor performance was defined as described in Chapter 2, using a cut-off corresponding to the 10th percentile of the population distribution in each of the cognitive tests individually. It was not possible to define a cut-point with 10% of the population distribution for the prospective memory task as 19% of the population failed the task and therefore this was used as the lower cut-point. Participants were then classified into two groups based on the cut-off for each of the tests.

Associations of age, sex, marital status, education and social class with the different cognitive tests were assessed using multivariable logistic regression modelling. Marital status, education and social class were grouped as follows: Marital status into Married and Single (combining, Single, separated, divorced and widowed categories); Social Class into Non manual (combining classes I, II and III non-manual) and manual classes (combining manual classes III manual, IV and V); Education was re-categorized into three groups ; No qualification (less than obtaining an O level or equivalent or not completing school up to the age of 16), Completion of school up to the age of 16 or up to the age of 18 (by combining the two categories of attaining 'O' level or equivalent and 'A' level or equivalent) and finally those obtaining education to graduate level (those with a degree or equivalent) or above.

Obtaining a score less than a cut-off point corresponding to the 10th percentile of the population distribution (or failing the prospective memory task) was first examined by univariate analysis, using the chi-square test to observe differences between the groups for each socio- demographic variable. The associations between each variable and being in the poor performance group were assessed using logistic regression analysis adjusting for co-variates; age (per 5 years), sex (women being the reference group), marital status (being married as the reference group), educational level (no qualification being the reference group for the three level education variable, and with qualifications being the reference group for the dichotomised education variable) and social class (non-manual, as the reference group) where social class was examined using both the "conventional" method using a woman's partner's occupation, as well as personal measures according to a woman's own occupation.

Data were further examined stratified into two age groups at age 65 years (those under age 65 and those 65 years and older). Age was also included in a model as a continuous variable and the unstandardised (Beta) coefficient were examined to compare differences in terms of chronological years of age for education level (comparing those with no qualifications with those completing school to the age of 16 or 18 and secondly, those with no qualifications with those educated to graduate level).

To examine difference in poor cognitive performance for age depending on education level, a further model was run, which included the interaction term age group (< 65 and those ≥65 years) x education (entered as the dichotomized variable, no qualification compared to those with any qualification). Tests showing a significant interaction between age group and education (no qualification compared to those with any qualification), were then stratified to examine the magnitude of differences in associations for these two age groups. Although intelligence and education are said to be correlated, [194] it was not assumed that the test for crystallised intelligence, NART, was measuring the same exposure. As a secondary analysis, associations were examined by further adjusting for the NART Error

Score. All P values reported are 2-sided. Statistical analyses for this chapter were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Missing data in cognitive tests

To explore the effect of missing data, a sensitivity analysis was carried out only in individuals with complete data on all seven cognitive tests and the specified covariates (n = 5727).

4.5 Results

Of the 8623 participants attending the third examination, cognitive data were available on 8585 men and women. At the time of writing this chapter, the data were available on 8584 individuals and seven cognition measures rather than eight, which are presented in the results here. Table 4.1 presents descriptive data showing the characteristics of the men and women in the EPIC-Norfolk cohort 3 for these 8584 individuals and **Figure 4.1** shows the distribution of the EPIC-Norfolk participants with poor cognitive performance across the seven cognitive tests. Subsequent chapters refer to 8585 individuals and eight cognitive measures (reason for this discrepancy is explained in Chapter 2). This is a higher functioning cohort, with over 50% of participants not in the poor performing group for any test. Less than 10% of the cohort had a poor performance score in three or more tests. Tables 4. 2a-c present the distribution of poor cognitive performance by socio-demographic variable (age, sex, marital status, education and social class) in each of the tests. Tables 4.3 and 4.4 show associations adjusted for age only and the covariates age, sex, education and social class respectively.

Figure 4.1: Distribution of participants in the poor performance group across the seven cognitive measures individually grouped in the EPIC-Norfolk Cognition Battery.

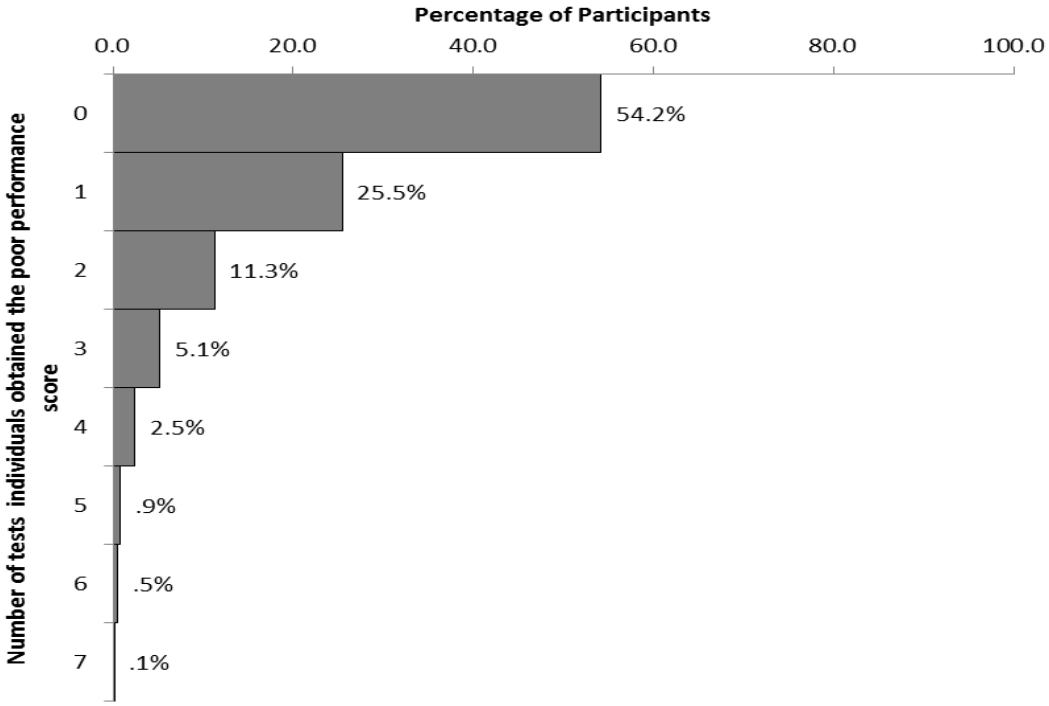


Table 4.1: Characteristics of the 8584 individuals with available cognitive measures participating in EPIC-Norfolk (2006–2011), including pilot data (2004–2006).

	Men (N=3840)		Women (N=4744)	
Mean Age (SD)	69.4	(8.1)	68.1	(8.0)
Frequency % (N)				
Age Band (Years)				
<60	10.3	(397)	14.0	(665)
60–64	22.7	(871)	26.4	(1252)
65–69	20.9	(802)	20.8	(985)
70–74	19.8	(760)	17.4	(825)
75–-790	15.4	(591)	12.9	(613)
≥ 80 years	10.9	(419)	8.5	(404)
Marital status				
Single	3.1	(116)	4.0	(184)
Married	86.6	(3244)	71.5	(3314)
Widowed	6.2	(234)	16.3	(754)
Separated or Divorced	4.0	(152)	8.3	(386)
Education				
Degree Level	20.1	(772)	15.6	(741)
A level and equivalent	48.0	(1844)	41.1	(1951)
O Level and equivalent	9.8	(377)	13.6	(647)
No Qualifications	22.0	(846)	29.6	(1404)
Social Class				
Professional	9.5	(364)	8.2	(384)
Managerial	42.7	(1628)	39.8	(1869)
Skilled Non Manual	12.2	(466)	19.1	(898)
Skilled Manual	22.7	(865)	18.8	(883)
Semi-Skilled Manual	11.0	(418)	11.3	(532)
Non-skilled	1.9	(72)	2.7	(125)
Mean Cognitive Test Score (SD)				
SF-EMSE	32.5	(3.2)	32.7	(3.0)
HVLT	23.9	(5.5)	26.1	(5.4)
FTMS	15.2	(4.6)	15.6	(4.5)
PW-Accuracy	11.6	(6.1)	13.1	(6.0)
VST, Reaction Time (ms)	2282.5	(430.6)	2229.9	(455.4)
Short NART Error Score	17.9	(10.3)	16.6	(9.5)
Frequency % (N) Prospective Memory (Successful)	77.7 (2912)		84.1 (3915)	

Abbreviations: A Level, Advanced Level; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test; FTMS, First Trial Memory Score; HVLT, Hopkins Verbal Learning Test; ms. milliseconds; NART, National Adult Reading Test; N, Number; O Level, Ordinary Level; SF-EMSE; Shortened version (Short form) of the Extended Mental State Exam; SD, Standard deviation; VST, Visual Sensitivity Test

Table 4.2a: Distribution of participants in the bottom tenth percentile in each cognitive test by socio-demographic variables (age).

	SF-EMSE		HVLT		FTMS		PW-Accuracy		Prosp. Mem		VST		Short-NART	
	Freq. (N)	Freq, % Score <=29 (N)	Freq. (N)	Freq, % Score <=18 (N)	Freq. (N)	Freq, %Score<= 10 (N)	Freq. (N)	Freq, % Score <=5 (N)	Freq. (N)	Freq, % failed (N)	Freq. (N)	Freq, % Time >= 2702.46 ms (N)	Freq. (N)	Freq, % Score>=31 (N)
All	8483	12.9 (1092)	8081	12.9 (1042)	7281	11.9 (870)	8410	10.9 (915)	8403	18.8 (1576)	7144	10.0 (714)	8112	(10.5) 849
Age-Band														
<60	1055	4.6 (49)	1022	2.9 (30)	959	4.1 (39)	1048	4.9 (51)	1049	8.8 (92)	890	6.6 (59)	999	8.0 (80)
60—64	2105	7.6 (159)	2061	5.7 (118)	1877	6.7 (125)	2098	6.0 (125)	2095	11.7 (246)	1846	6.1 (112)	2062	9.5 (196)
65—69	1767	11.3 (200)	1700	8.6 (146)	1529	8.9 (136)	1756	9.6 (169)	1751	16.3 (286)	1522	8.1 (124)	1716	11.7 (201)
70—74	1572	14.1 (221)	1496	17.6 (263)	1339	14.2 (190)	1563	11.6 (181)	1558	21.6 (336)	1323	9.7 (128)	1508	11.9 (180)
75—79	1183	20.6 (244)	1109	23.2 (257)	985	21.0 (207)	1170	17.4 (203)	1170	27.8 (325)	996	14.3 (142)	1107	11.8 (131)
≥ 80	801	27.3 (219)	693	32.9 (228)	592	29.2 (173)	775	24.0 (186)	780	37.3 (291)	567	26.3 (149)	720	8.5 (61)
		p<0.001		p<0.001		p<0.001		p<0.001		p<0.001		p<0.001		p<0.001

P-value for trends across the groups using the chi-square test

Abbreviations for tables 4.2a-4.2c: A Level, Advanced Level; Freq, frequency; FTMS, First Trial Memory Score (outcome measure for CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test) ; HVLT, Hopkins Verbal Learning Test; Ms, millisecond; NART, National Adult Reading Test; N, Number; O Level, Ordinary Level; SF-EMSE:, PW-Accuracy (Accuracy Score, for the letter cancellation task) Shortened version (Short form) of the Extended Mental State Exam; VST, Visual sensitivity test

Table 4.2b: Distribution of participants in the bottom tenth percentile in each cognitive test by socio-demographic variables (sex and marital status).

	SF-EMSE		HVLT		FTMS		PW-Accuracy		Prosp. Mem		VST		Short-NART	
	Freq (N)	Freq, % Score <=29 (N)	Freq. (N)	Freq, % Score <=18 (N)	Freq. (N)	Freq, %Score<=10 (N)	Freq. (N)	Freq, % Score <=5 (N)	Freq. (N)	Freq, % failed (N)	Freq. (N)	Freq, % Time >= 2702.46 ms (N)	Freq. (N)	Freq, % Score>=31 (N)
Sex														
Women	4681	12.4 (580)	4476	9.5 (424)	4011	11.0 (442)	4650	8.8 (409)	4653	15.9 (738)	3928	9.3 (364)	4504	8.8 (397)
Men	3802	13.5 (512)	3605	17.1 (618)	3270	13.1 (428)	3760	13.5 (506)	3750	22.3 (838)	3216	10.9 (350)	3608	12.5 (452)
		p=0.14		p<0.001		p=0.007		p<0.001		p<0.001		p=0.02		p<0.001
Marital status														
Single	295	14.2 (42)	282	12.4 (35)	251	19.9 (50)	291	12.0 (35)	239	18.4 (54)	241	11.6 (28)	283	9.5 (27)
Married	6494	12.0 (777)	6225	12.3 (766)	5620	10.6 (597)	6445	9.9 (638)	6439	17.8 (1149)	5499	9.5 (521)	6244	10.5 (656)
Widowed	964	17.9 (173)	883	18.7 (165)	786	19.1 (150)	948	17.2 (163)	948	25.7 (244)	779	14.4 (112)	895	10.4 (93)
Separated or Divorced	533	12.8 (68)	499	8.6 (43)	445	8.3 (37)	530	10.0 (53)	529	16.3 (86)	450	7.6 (34)	503	8.0 (40)
		p<0.001		p<0.001		p<0.001		p<0.001		p<0.001		p<0.001		p=0.3

Table 4.2c: Distribution of participants in the bottom tenth percentile in each cognitive test by socio-demographic variables (social class and education).

	SF-EMSE		HVLT		FTMS		PW-Accuracy		Prosp. Mem		VST		Short-NART	
	Freq. (N)	Freq, % Score <=29 (N)	Freq. (N)	Freq, % Score <=18 (N)	Freq. (N)	Freq, %Score <=10 (N)	Freq. (N)	Freq, % Score <=5 (N)	Freq. (N)	Freq, % failed (N)	Freq. (N)	Freq, % Time >= 2702.46 ms (N)	Freq. (N)	Freq, % Score >=31 (N)
Education														
Degree Level	1491	4.9 (73)	1415	5.0 (71)	1283	6.7 (86)	1484	6.8 (101)	1484	13.2 (196)	1264	7.7 (97)	1447	1.0 (15)
A level and equivalent	3749	11.4 (429)	3596	12.5 (449)	3233	10.9 (352)	3719	11.1 (412)	3720	18.0 (668)	3195	9.2 (295)	3604	8.0 (289)
O Level and equivalent	1019	7.5 (76)	976	7.9 (77)	895	9.7 (87)	1013	5.9 (60)	1011	16.1 (163)	870	8.5 (74)	966	4.3 (42)
No Qualifications	2222	23.0 (512)	2092	21.2 (443)	1868	18.4 (344)	2192	15.6 (341)	2186	25.0 (547)	1813	13.7 (248)	2093	24.0 (502)
		p<0.001		p<0.001		p<0.001		p<0.001		p<0.001		p<0.001		p<0.001
Social Class														
Professional	734	7.9 (58)	694	8.5 (59)	649	8.5 (55)	728	7.6 (55)	727	14.0 (102)	646	9.0 (58)	709	2.1 (15)
Managerial	3445	9.9 (342)	3306	10.2 (336)	2957	10.7 (316)	3416	9.1 (312)	3416	17.7 (603)	2893	9.2 (266)	3311	5.7 (188)
Skilled Non Manual	1350	11.0 (149)	1286	13.1 (168)	1139	12.3 (140)	1342	10.6 (142)	1342	17.4 (233)	1145	10.0 (114)	1301	7.1 (92)
Skilled Manual	1736	16.8 (291)	1644	16.2 (267)	1493	12.5 (187)	1722	13.2 (228)	1715	22.0 (377)	1453	10.2 (148)	1633	20.3 (332)
Semi-Skilled Manual	943	20.4 (192)	893	18.3 (163)	811	16.3 (132)	932	13.9 (130)	932	21.8 (203)	782	11.5 (90)	900	17.9 (161)
Non-skilled	196	24.5 (48)	185	22.2 (41)	165	18.2 (30)	193	15.5 (30)	194	21.1 (41)	157	15.3 (24)	178	28.7 (51)
		p<0.001		p<0.001		p<0.001		p<0.001		p<0.001		p<0.08		p<0.001

Table 4.3: Age adjusted Odds ratios for poor performance (defined as obtaining a score less than a cut-off point corresponding to the 10th Percentile of the population distribution) for each test in the cognition battery used in EPIC-Norfolk.

	SF-EMSE Global function		**HVLT Verbal episodic memory**		**FTMS Non-verbal episodic memory**		**PW-Accuracy**		**Prospective Memory**		**VST Reaction Time Processing Speed**		**NART Error Score Intelligence**	
	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)
Sex (Men)	1.00	(0.88,1.14) p=1.00	1.86	(1.62, 2.13) p<0.001	1.09	(0.94, 1.26) p=0.3	1.49	(1.30, 1.72) p<0.001	1.42	(1.27, 1.59) P<0.001	1.10	(0.94, 1.29) p=0.2	1.47	(1.28-1.70) P<0.001
Marital status (Single)*	1.03	(0.89, 1.21) p=0.7	0.81	(0.69, 0.96) p=0.01	1.19	(1.00, 1.41) p=0.05	1.17	(0.99-1.37) p=0.07	0.99	(0.86, 1.13) p=0.9	1.01	(0.84,1.22) p=0.9	0.87	(0.72-1.04) p=0.1
Social Class (Manual)*	2.25	(1.97, 2.57) p<0.001	2.04	(1.77-2.34) p<0.001	1.48	(1.27, 1.72) p=0.01	1.65	(1.43, 1.90) p<0.001	1.44	(1.28, 1.62) p<0.001	1.24	(1.05, 1.46) p=0.01	4.3	3.70-5.00 p<0.001
Education, O/A level*	0.46	(0.40, 0.52) p<0.001	0.59	(0.51, 0.69) p<0.001	0.62	(0.53, 0.73) p<0.001	0.70	(060, 0.82) p<0.001	0.74	(0.65, 0.84) p<0.001	0.74	(0.62, 0.89) p=0.002	0.72	(0.61, 0.86) p<0.001
Education, Graduate level*	0.20	(0.16, 0.26) p<0.001	0.24	(0.19, 0.32) p<0.001	0.39	(0.30, 0.51) p=0.001	0.48	(0.38, 0.61) p<0.001	0.55	(0.46, 0.66) p<0.001	0.64	(0.50, 0.82) p<0.001	0.03	(0.02, 0.05) p<0.001

* Reference categories: women; married; non-manual; no qualifications

Abbreviations: CI, Confidence Interval; FTMS, First Trial Memory Score (outcome measure for CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test); HVLT, Hopkins Verbal Learning Test; N, Number; NART, National Adult Reading Test; Odds Ratio, OR; PW-Accuracy (Accuracy Score, for the letter cancellation task) SF-EMSE, Shortened version (Short form) of the Extended Mental State Exam; SD, Standard deviation, VST, Visual Sensitivity Test

Table 4.4. Odds ratios for poor performance (defined as obtaining a score less than a cut-off point corresponding to the 10th Percentile of the population distribution) for each test in the cognition battery used in EPIC-Norfolk, adjusted for covariates (age, sex, marital Status, education and social class).

	SF-EMSE Global function		**HVLT Verbal episodic memory**		**FTMS Non-verbal episodic memory**		**PW-Accuracy**		**Prospective Memory**		**VST Reaction Time Processing Speed**		**NART Error Score Intelligence**	
	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)	OR	95% CI (p value)
Number of Participants included in analysis	8208		7817		7036		8138		8403		6902		7846	
Age (per 5 year increase)	1.43	(1.37, 1.50) (*P*<0.001)	1.68	(1.60, 1.77) (*P*<0.001)	1.50	(1.42, 1.58) (*P*<0.001)	1.38	(1.32, 1.45) (*P*<0.001)	1.38	(1.33, 1.43) (*P*<0.001)	1.37	(1.30, 1.45) (*P*<0.001)	0.96	(0.91, 1.01) (*P*=0.09)
Sex (Men)*	1.07	(0.93, 1.24) (*P*=0.3)	1.99	(1.72, 2.31 (*P*<0.001)	1.17	(1.00, 1.36) (*P*=0.06)	1.62	(1.39, 1.88) (*P*<0.001)	1.46	(1.29, 1.64) (*P*<0.001)	1.16	(0.98, 1.37) (*P*=0.08)	1.77	(1.51, 2.08) (*P*<0.001)
Marital status (Single)*	1.08	(0.92, 1.28) (*P*=0.3)	0.99	(0.83,1.19) (*P*=0.9)	1.26	(1.05, 1.50) (*P*=0.01)	1.35	(1.14, 1.61) (*P*=0.001)	1.11	(0.96, 1.27) (*P*=0.2)	1.04	(0.85, 1.27) (*P*=0.7)	1.04	(0.85, 1.27) (*P*=0.7)
Social Class (Manual)*	1.68	(1.45, 1.94) (*P*<0.001)	1.52	(1.31, 1.77) (*P*<0.001)	1.24	(1.06, 1.46) (*P*=0.01)	1.42	(1.22, 1.66) (*P*<0.001)	1.25	(1.10, 1.42) (*P*=0.001)	1.10	(0.92, 1.31) (*P*=0.3)	2.63	(2.23, 3.09) (*P*<0.001)
Education, O/A level*	0.5	(0.43, 0.58) (*P*<0.001)	0.59	(0.51, 0.69) (*P*<0.001)	0.65	(0.55, 0.77) (*P*<0.001)	0.72	(0.62, 0.85) (*P*<0.001)	0.74	(0.65, 0.84) (*P*<0.001)	0.74	(0.62, 0.89) (*P*=0.002)	0.27	(0.23, 0.32) (*P*<0.001)
Education, Graduate level*	0.25	(0.19, 0.33) (*P*<0.001)	0.26	(0.20, 0.35) (*P*<0.001)	0.43	(0.33, 0.57) (*P*=0.001)	0.54	(0.41, 0.69) (*P*<0.001)	0.56	(0.46, 0.69) (*P*<0.001)	0.67	(0.51, 0.88) (*P*=0.004)	0.05	(0.03, 0.08) (*P*<0.001)

* Reference categories: women; married; non-manual; no qualifications

Abbreviations: CI, Confidence Interval; FTMS, First Trial Memory Score (outcome measure for CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test); HVLT, Hopkins Verbal Learning Test; N, Number; NART, National Adult Reading Test; Odds Ratio, OR; PW-Accuracy (Accuracy Score, for the letter cancellation task) SF-EMSE, Shortened version (Short form) of the Extended Mental State Exam; SD, Standard deviation, VST, Visual Sensitivity Test

Table 4.4 indicates that increasing age was associated with being in the poor performance group for all tests, except the NART error score (intelligence) for which there was no significant trend with age in the multivariable model, Odds Ratio (OR)= 0.96 (95% Confidence Interval (CI) 0.91, 1.01 *P*=0.09). The strongest association was observed for HVLT OR = 1.68 (95% CI 1.60, 1.77) *P*<0.001)) followed by FTMS OR = 1.50 (95% CI 1.42, 1.58 *P*<0.001), both testing for episodic memory. The OR observed for the tests for the other domains were more comparable to each other.

Stratifying data by age group (<65 and ≥65 years of age)

When the data were stratified into the two age groups (<65 years and ≥65 years), the most striking difference in association between the age groups was observed for the VST for both age and sex, where for the under 65 group, there was no association between age and poor performance, OR= 0.9 (95% CI 0.75, 1.15 P=0.5) or for sex, OR= 0.99 (95% CI 0.71, 1.37 P=0.9), but statistically significant associations observed in the 65+ years age group for age, OR= 1.52 (95% CI 1.40, 1.66 P<0.001) and sex OR= 1.23 (95% CI 1.01, 1.50 P=0.04). The results for the stratified analyses are shown in Table 4.5.

Sex

There were noticeable differences in the odds ratios for gender across the different tests. Men were more likely to be in the poor performance group for HVLT, PW-Accuracy, the prospective memory task and NART. Weaker, but not statistically significant associations were observed for FTMS and VST. There were no differences observed between men and women for SF-EMSE.

Marital status

Marital status was significantly associated with cognitive performance for FTMS and PW-Accuracy, with poor performance more likely in single than married individuals. The other tests showed no evidence of associations with marital status.

Education

More education was strongly associated with decreased poor performance across all the tests. However, the strength of association varied from one test to another, with NART being most strongly associated, particularly at graduate level.

Education was examined as a dichotomized variable (so that the ORs for education were directly comparable with the other covariates). This time comparing no qualification with any qualification (combining 'O', 'A' and degree level), and using the qualification group as the reference, the OR

observed were; SF-EMSE OR=2.22 (95% CI 1.92, 2.56*P*<0.001); HVLT OR=1.89 (95% CI 1.62, 2.20 *P*<0.001); FTMS OR=1.63 (95% CI 1.38, 1.93 *P*<0.001); Prospective memory OR=1.42 (95% CI 1.24, 1.62*P*<0.001); PW-Accuracy OR=1.45 (95% CI 1.23, 1.70 *P*<0.001); VST OR=1.37 (95% CI 1.14, 1.65 *P*=0.001) and NART 4.31 (95% CI 3.66, 5.08 *P*<0.001). Again, any qualification compared to no qualification having the strongest association for the NART.

Using the unstandardized regression coefficients (from the model adjusting for covariates in table 3), we observed that the likelihood of being in the poor performance group for those with an education up to 'O' or 'A' level compared to having no qualification was equivalent to being just over 5 years younger for HVLT, FTMS, PW-Accuracy, prospective memory task, and VST. Comparing those at graduate level to no qualification, the risk was equivalent to being almost 10 years younger for most of the tests and 13 years younger for the HVLT. For the SF-EMSE, those with O/A level qualifications compared to those with no qualifications was equivalent to being 9.9 years younger and those educated to graduate level was equivalent to 19.6 years younger.

There was significant interaction between education (no qualification compared to those with any qualification) for HVLT (p=0.01) and FTMS (p=0.01) but not for SF-EMSE, PW-Accuracy, prospective memory, VST or NART. On stratifying the data for both HVLT and FTMS (complete data not shown), the associations were stronger with education for the under 65 age group for HVLT, OR= 3.42 (95% CI 2.35, 4.99 P<0.001) than for the ≥65 year age group OR= 1.94 (95% CI 1.65, 2.28 P<0.001); and for FTMS, the under 65 age group OR= 2.50 (95% CI 1.73, 3.62 P<0.001) and ≥65 year age group OR= 1.66 (95% CI 1.39, 1.99 P<0.001). This can be seen in the associations observed for education in the age group stratified data (Table 4.5), particularly for education to O/A level (completing education to 16 or 18 years) for HVLT and FTMS. Associations were considerably stronger for the <65 years age group as compared to the ≥65 years for both these tests. The association with education did not differ greatly in the two age groups for the remaining tests.

Table 4.5: Odds ratios for poor performance stratified by those over and under 65 years in the EPIC-Norfolk Cohort.

	SF-EMSE		HVLT		FTMS		PW-Accuracy		Prosp. Mem		VST (Reaction Time)		Short-NART	
<65 Years Poor performance (N)	3071 (199)		2997 (142)		2754 (154)		3057 (170)		3055 (330)		2658 (162)		2975 (260)	
≥ 65 Years Poor performance (N)	5137 (832)		4820 (857)		4282 (670)		5081 (702)		5078 (1185)		4244 (520)		4871 (546)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age (per 5 Years)														
<65 Years	1.46	(1.16, 1.86) P=0.02	1.74	(1.29, 2.35) p<0.001	1.53	(1.16, 2.00) P=0.002	1.24	(0.80, 1.56) P=0.08	1.31	(1.10, 1.56) P=0.003	0.9	(0.75, 1.15) p=0.5	0.99	(0.82, 1.20) P=0.9
≥ 65 Years	1.44	(1.34, 1.54) p<0.001	1.69	(1.58, 1.82) p<0.001	1.52	(1.41, 1.64) p<0.001	1.37	(1.28, 1.47) p<0.001	1.39	(1.31, 1.48) p<0.001	1.52	1.40, 1.66 p<0.001)	0.88	(0.80, 0.96) P=0.03
Sex (Men)														
<65 Years	1.28	(0.95, 1.73) P=0.8	2.13	(1.50, 3.02) p<0.001	1.36	(0.97, 1.90) p=0.2	1.79	(1.30, 2.45) p<0.001)	1.59	(1.26, 2.01) p<0.001)	0.99	(0.71, 1.37) P=0.9	2.00	(1.51, 2.63) p<0.001
≥65 Years	1.02	(0.87, 1.20) P=0.1	1.96	(1.66, 2.31) p<0.001	1.11	(0.93, 1.33) p=0.08	1.57	(1.33, 1.87) p<0.001	1.41	(1.23, 1.62) p<0.001	1.23	(1.01, 1.50) P=0.04	1.68	(1.37, 2.04) p<0.001
Marital status (Single)														
<65 Years	1.14	(0.76, 1.70) p=0.5	1.38	(0.87, 2.18) p=0.2	1.78	(1.19, 2.67) p=0.01	1.11	(0.72, 1.71) p=0.08	1.17	(0.85, , 1.61) P=0.3	0.74	(0.45, 1.21) P=0.2	1.14	(0.79, 1.66) P=0.5
≥ 65 Years	1.06	(0.89, 1.27) p=0.5	0.95	(0.78, 1.15) p=0.6	1.15	(0.94, 1.40) p=0.2	1.40	(1.16, 1.69) p=0.001	1.08	(0.92, 1.26) p=0.4	1.08	(0.86, 1.35) p=0.5	1.03	(0.81, 1.31) p=0.8

Table 4.5: Continued

	SF-EMSE		HVLT		FTMS		PW-Accuracy		Prosp. Mem		VST (Reaction Time)		Short-NART	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Social Class (Manual)														
<65 Years	1.71	(1.25, 2.34) p=0.001	1.14	(0.79, 1.64) p=0.5	1.44	1.01, 2.05 p=0.05	1.45	1.03, 2.03 p=0.03	1.41	(1.09, 1.81) p=0.01	1.17	(0.83, 1.66) p=0.4	1.91	(1.44, 2.54) p<0.001
≥65 Years	1.67	(1.42, 1.96) P<0.001	1.60	(1.35, 1.89) p<0.001	1.18	(0.98, 1.43) p=0.08	1.42	(1.19, 1.69) p<0.001	1.20	(1.04, 1.39) P=0.02	1.10	(0.89, 1.35) P=0.4	3.01	(2.46, 3.67) p<0.001
Education (O/A level)														
<65 Years	0.46	(0.33, 0.63) p<0.001	0.34	(0.23, 0.50) p<0.001	0.44	(0.30, 0.63) p<0.001)	0.71	(0.49, 1.04) p=0.08	0.71	(0.54, 0.95) p=0.02	0.73	(0.49, 1.08) p=0.1	0.21	(0.16, 0.28) p<0.001
≥65 Years	0.51	(0.43, 0.60) p<0.001	0.66	(0.55, 0.78) p<0.001	0.72	(0.60, 0.87) p=0.01	0.73	(0.61, 0.87) p=0.001	0.74	(0.64, 0.86) p<0.001	0.75	(0.60, 0.92) p=0.01	0.31	(0.25, 0.37) p<0.001
Education (Graduate)														
<65 Years	0.20	(0.11, 0.36) p<0.001	0.14	(0.07, 0.28) p<0.001	0.30	(0.16, 0.54) p<0.001)	0.52	(0.30, 0.91) p=0.02	0.50	(0.33, 0.76) p=0.001	0.62	(0.36, 1.07) p=0.09	0.05	(0.02, 0.10) p<0.001
≥65 Years	0.27	(0.19, 0.36) p<0.001	0.29	(0.22, 0.40) p<0.001	0.47	(0.35, 0.64) p<0.001	0.54	(0.40, 0.72) p<0.001	0.59	(0.47, 0.74) p<0.001)	0.69	(0.50, 0.94) p=0.02	0.04	(0.02,0.09) p<0.001

Abbreviations: A Level, Advanced Level; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test; CI, Confidence Interval, FTMS, First Trial Memory Score; HVLT, Hopkins Verbal Learning Test; NART, National Adult Reading Test; N, Number; O Level, Ordinary Level; OR, Odds ratio, SF-EMSE:, Shortened version (Short form) of the Extended Mental State Exam; SD, Standard deviation; VST, Visual Sensitivity Test

Social Class

Manual social class was independently associated with poor performance for all the tests apart from VST. On repeating the model but using individuals' own social class or occupation rather than the 'conventional' method, the associations observed were slightly stronger, however, there were no qualitative differences observed in the relationship. The data for both measures of social class are shown in Table 4.6.

Adjustment for NART

When the models were additionally adjusted for the NART error score as a secondary analysis (Table 4.7), the odds were attenuated, but a higher likelihood of poor performance per 5 year increase in age was still observed for all remaining tests. The relationship observed for SF-EMSE reversed, with men 27% less likely to be in the poor performance group than women OR=0.83, (95% CI 0.71, 0.97) *P*=0.02. Little change seen was observed in the associations for any of the tests for marital status.

Associations with education at both 'O' or 'A' level and at graduate level were attenuated but still observed for SF-EMSE and FTMS after adjusting for NART. Graduate level education remained inversely associated with for poor cognitive performance. Associations were no longer significant for education and PW-Accuracy or the prospective memory task, For HVLT, associations with education were observed at graduate level but not at 'O' and 'A' level. For VST, associations were only observed for those completing school to 'O' and 'A' level but did not remain at graduate level. For social class, additionally adjusting for NART substantially attenuated associations, with just SF-EMSE still statistically significant association.

Missing data in cognitive tests

The results from the sensitivity analysis carried out only on individuals with complete data on all tests were similar to earlier results presented. The sensitivity analyses are shown in Tables 4.8 and 4.9.

Table 4.6: Odds ratios for poor performance (defined as obtaining a score less than a cut-off point corresponding to the 10th Percentile of the population distribution adjusted for all covariates using 'conventional' method using partner's occupation/social class for women in analysis (as presented in Table 4.3) and individuals' own occupation/social class.

	SF-EMSE		HVLT		FTMS		PW-Accuracy		Prospective Memory		VST		Short-NART	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Number of Participants		8208		7817		7036		8138		8403		6902		7846
Based on partner social class (Manual)*	1.68	(1.45, 1.94) p<0.001	1.52	(1.31, 1.77) p<0.001	1.24	(1.06, 1.46) p=0.01	1.42	(1.22, 1.66) p<0.001	1.25	(1.10, 1.42) p=0.001	1.10	(0.92, 1.31) p=0.3	2.63	(2.23, 3.09) p<0.001
Number of Participants		8043		7659		6889		7976		7970		6760		7689
Based on individual's social class (Manual)	1.98	(1.70, 2.30) p<0.001	1.69	(1.45,1.98) p<0.001	1.44	(1.22, 1.71) p<0.001	1.46	(1.24, 1.72) p<0.001	1.50	(1.31, 1.71) p<0.001	1.05	(0.87, 1.27) p=0.6	2.97	(2.52, 3.50) p<0.001

[†] Odds ratio – as presented in Table 4.3 * Reference category: Non-manual

Abbreviations: A Level, Advanced Level; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test; CI, Confidence Interval, FTMS, First Trial Memory Score; HVLT, Hopkins Verbal Learning Test; NART, National Adult Reading Test; N, Number; O Level, Ordinary Level; UO, Odds ratio, SF-EMSE:, Shortened version (Short form) of the Extended Mental State Exam; SD, Standard deviation; VST, Visual Sensitivity Test

Table 4.7: Odds Ratios for poor performance (defined as obtaining a score less than a cut-off point corresponding to the 10th Percentile of the population distribution) for each test in the cognition battery used in EPIC-Norfolk 3HC, adjusted for covariates, age, sex, marital status, social class, education and NART Error Score.

	SF-EMSE		HVLT		FTMS		PW-Accuracy		Prospective Memory		VST	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Number of Participants included in analysis		7778		7598		6711		7742		7731		6714
Age (per 5 year increase)	1.51	(1.43, 1.59) p<0.001	1.75	(1.66, 1.84) p<0.001	1.51	(1.43, 1.59) p<0.001	1.41	(1.34, 1.48) p<0.001	1.39	(1.34, 1.45) p<0.001	1.38	(1.31, 1.46) p<0.001
Sex (Men) *	0.83	(0.71, 0.97) p=0.02	1.78	(1.52, 2.07) p<0.001	1.08	(0.92, 1.27) p=0.4	1.52	(1.29, 1.78) p<0.001	1.37	(1.21, 1.55) p<0.001	1.14	(0.96, 1.36) p=0.1
Marital status (Single)*	1.02	(0.85, 1.22) p=0.9	1.00	(0.83, 1.20) p=1.00	1.23	(1.02, 1.49) p= 0.03	1.31	(1.09, 1.57) p=0.004	1.10	(0.95, 1.28) p=0.2	1.03	(0.84, 1.26) p=0.8
Social Class (Manual)*	1.19	(1.02, 1.40) p=0.03	1.17	(0.99, 1.37) p=0.06	1.05	(0.88, 1.25) p=0.6	1.12	(0.94, 132) p=0.2	1.09	(0.95, 1.24) p=0.2	1.12	(0.92, 1.34) P=0.3
Education, O/A level*	0.77	(0.65, 0.91) p=0.02	0.87	(0.73, 1.03) p=0.1	0.82	(0.68, 0.98) P=0.03	0.97	(0.81, 1.16) p=0.7	0.89	(0.77, 1.02) P=0.1	0.79	(0.64, 0.97) p=0.02
Education, graduate level*	0.70	(0.51, 0.96) P=0.03	0.54	(0.39, 0.74) p<0.001	0.66	(0.49, 0.90) p=0.01	0.97	(0.72, 1.29) p=0.8	0.83	(0.66, 1.04) P=0.10	0.79	(0.58, 1.07) p=0.1
NART Error Score	1.07	(1.06, 1.08) p<0.001	1.06	(1.05, 1.07) p<0.001	1.04	(1.02, 1.04) p<0.001	1.05	(1.04, 1.04) p<0.001	1.03	(1.02, 1.04) p<0.001	1.01	(1.00, 1.02) p=0.3

*Reference Categories women, married, non-manual and no qualifications

Abbreviations: A Level, Advanced Level; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test; CI, Confidence Interval, FTMS, First Trial Memory Score; HVLT, Hopkins Verbal Learning Test; NART, National Adult Reading Test; N, Number; O Level, Ordinary Level; UO, Odds ratio, SF-EMSE:, Shortened version (Short form) of the Extended Mental State Exam; SD, Standard deviation; VST, Visual Sensitivity Test

Table 4.8: Sensitivity analysis with Odds ratios for poor performance (defined as obtaining a score less than a cut-off point corresponding to the 10th Percentile of the population distribution adjusted for covariates (age, sex, marital status, social class and education) for the 5727 participants with complete data on all seven cognitive tests.

	SF-EMSE		HVLT		FTMS		PW-Accuracy		Prospective Memory		VST		Short-NART	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age (per 5 years)	1.43	(1.34, 1.52) p<0.001	1.65	(1.55, 1.76) p<0.001	1.49	(1.40, 1.58) p<0.001	1.37	(1.29, 1.45) p<0.001	1.40	(1.33, 1.45) p<0.001	1.34	(1.26, 1.42) p<0.001	1.00	(0.90, 1.02) p=0.2
Sex (Men)*	0.93	(0.78, 1.11) P=0.5	1.94	(1.62, 2.32) p<0.001	1.16	0.97, 1.39 p=0.1	1.63	(1.35, 1.96) p<0.001	1.39	(1.21, 1.61) p<0.001	1.18	(0.97, 1.42) p=0.09	1.71	(1.42, 2.07) p<0.001
Marital status (Single)*	1.04	(0.83, 1.29) p=0.7	0.95	(0.76, 1.18) p=0.6	1.16	(0.94, 1.44) p=0.2	1.34	(1.08, 1.66) p=0.01	1.03	(0.86, 1.22) p=0.8	1.09	(0.87, 1.37) p=0.4	0.95	(0.74, 1.21) p=0.7
Social Class (Manual)*	1.65	(1.37, 1.98) p<0.001	1.56	(1.30, 1.87) p<0.001	1.26	(1.05, 1.52) p=0.02	1.44	(1.19, 1.75) p<0.001	1.21	(1.04, 1.41) p=0.01	1.13	(0.92, 1.38) p=0.3	2.59	(2.14, 3.15) p<0.001
Education , O/A level*	0.52	(0.43, 0.62) p<0.001	0.62	(0.51, 0.75) p<0.001	0.65	(0.53, 0.78) p<0.001	0.69	(0.57, 0.85) p<0.001	0.72	(0.61, 0.85) p<0.001	0.77	(0.62, 0.95) p=0.02	0.26	(0.22, 0.32) p<0.001
Education, Graduate *	0.23	(0.16, 0.33) p<0.001	0.23	(0.16, 0.34) p<0.001	0.35	(0.26, 0.50) p<0.001	0.50	(0.36, 0.69) p<0.001	0.54	(0.42, 0.68) p<0.001	0.74	(0.54, 1.00) p=0.05	0.04	(0.02, 0.07) p<0.001

*Reference Categories women, married, non-manual and no qualifications

Abbreviations: A Level, Advanced Level; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test; CI, Confidence Interval, FTMS, First Trial Memory Score; HVLT, Hopkins Verbal Learning Test; NART, National Adult Reading Test; N, Number; O Level, Ordinary Level; UO, Odds ratio, SF-EMSE:, Shortened version (Short form) of the Extended Mental State Exam; SD, Standard deviation; VST, Visual Sensitivity Test

Table 4.9: Sensitivity analysis with Odds ratios for poor performance (defined as obtaining a score less than a cut-off point corresponding to the 10th Percentile of the population distribution adjusted for covariates (age, sex, marital Status, social class and education) and NART Error Score for the 5727 participants with complete data on the seven cognitive tests.

	SF-EMSE		HVLT		FTMS		PW-Accuracy		Prospective Memory		VST	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age (per 5 years)	1.48	(1.39-1.57) p<0.001	1.71	(1.60-1.82) p<0.001	1.51	(1.42-1.60) p<0.001	1.39	(1.31-1.48) p<0.001	1.41	(1.35-1.48) p<0.001	1.34	(1.26-1.43) p<0.001
Sex (Men)	0.79	(0.65, 0.95) p=0.01	1.74	(1.45, 2.10) p<0.001	1.09	(0.91,-1.31) p=0.3	1.50	(1.24-1.81) p<0.001	1.31	(1.13-1.51) p<0.001	1.16	(0.96-1.41) p=0.1
Marital status (Single)	1.06	(0.85-1.32) p=0.6	0.96	(0.77, 1.20) p=0.7	1.18	(0.95-1.45) p=0.1	1.36	(1.10-1.69) p=0.01	1.04	(0.87-1.24) p=0.7	1.10	(0.87-1.38) p=0.4
Social Class (Manual)	1.25	(1.03, 1.51) p=0.03	1.20	(0.99, 1.46) p= 0.06	1.11	(0.91-1.34) p=0.3	1.20	(0.98-1.47) p=0.07	1.06	(0.90-1.24) p=0.5	1.09	(0.89-1.35) p=0.4
Education, O/A level*	0.79	(065, 0.97) p=0.02	0.88	(072, 1.07) p=0.2	0.79	(0.64, 0.96) p=0.02	0.90	(0.72, 1.11) p=0.3	0.88	(0.74, 1.05) p=0.1	0.81	(0.64, 1.01) p=0.06
Education, Graduate level*	0.58	(0.39, 0.87) p=0.01	0.49	(0.33, 0.72) p<0.001	0.53	(0.37, 0.76) p=0.01	0.86	(0.60, 1.22) p=0.4	0.81	(0.62, 1.06) p=0.1	0.81	(0.58, 1.14) p=0.2
NART Error Score	1.07	(1.06, 1.08) p<0.001	1.06	1.05, 1.07 p<0.001	1.03	(1.02, 1.04) p<0.001	1.04	(1.03, 1.05) p<0.001	1.03	(1.02, 1.04) p<0.001	1.01	1.00, 1.02 p=0.2

*Reference Categories women, married, non-manual and no qualifications

Abbreviations: A Level, Advanced Level; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test; CI, Confidence Interval, FTMS, First Trial Memory Score; HVLT, Hopkins Verbal Learning Test; NART, National Adult Reading Test; N, Number; O Level, Ordinary Level; UO, Odds ratio, SF-EMSE:, Shortened version (Short form) of the Extended Mental State Exam; SD, Standard deviation; VST, Visual Sensitivity Test.

4.6 Discussion

This chapter presents the results of the association of age, sex, education, social class and (as a secondary analysis), crystallized intelligence on different cognitive abilities using a range of assessment tools in a healthy population of older men and women. We observed that the relationship of sociodemographic factors with cognitive function does depend on the assessment tool used.

Older age was found to be associated with poor performance in all of the cognitive tests (abilities), except with the NART score (crystallized intelligence), confirming in this larger study that age has little or no association with NART performance [184]. The greatest age-related differences were observed for HVLT (verbal episodic memory). Episodic memory deficits have been reported to be associated with strongest and most persistent risk of cognitive decline [129,172] and are the most common and earliest complaints. These findings are consistent with previous work, here presented in terms of poorer performance observed in multiple domains across age [71,81,195] and stability observed in crystallized intelligence, or knowledge that is learned and acquired over years which has shown to be more resistant to the effect of age.[163,164,196]

Men were significantly more likely to be poor performers compared to women for HVLT, PW-Accuracy (attention), prospective memory and in NART. The sex differences were greatest for HVLT. In contrast, there was no significant sex difference for SF-EMSE (global function). Differences in men and women have been shown across various domains, [197] and these findings were consistent with other studies. [198] Dementia can be considered as the extreme of poor cognitive performance. Though the overall prevalence of dementia is reported as higher in women, [199] this could be explained by a higher proportion of older women in the general population. Findings from large population-based studies report no sex differences in the rates of dementia up to high age [200–202] with higher rates only observed in women compared to men in the oldest old. [202] The higher prevalence of dementia observed in women may be due to the fact that age is the strongest risk factor for dementia and women make up the majority of the older population due to their increased life expectancy relative to men. No significant differences between men and women were observed for VST (processing speed), although previous studies have found men to perform better. [203] This could be partly explained in the composition of the test, which relies on the accurate recognition of a triangle shape as well as speed. Hence accuracy (performed better by women) and reaction time or processing speed (performed better by men), when combined, result in men and women shown to be performing similarly.

As shown previously, [126] education and social class were independently associated with cognitive performance. This was observed across all the domains even when adjusting for age and the other covariates. Although associations were strengthened when assigning social class to women using their own social class, we found no qualitative differences in associations from this and the 'conventional' method and the prediction of poor performance in all the tests.

When estimating the potential impact of education on the age-related likelihood of poor performance, this was noticeable for the SF-EMSE test for global cognition, where the risk of being in the poor performance group for those with an education up to 'O' and 'A' level compared to no qualification was equivalent to being almost 10 years younger and at graduate level compared to no qualification, this difference was even greater, with the risk equivalent to being almost 20 years younger.

We also found that the influence of education was stronger in younger age group (<65 years) than in ≥65 year age group. Not having qualifications in those <65 years was associated with greater risk of being in the poor performance group compared to people aged 65 and over. Plausible explanations for this difference include the likelihood that other factors such as co morbidities common in older people could have a greater influence on cognitive performance in older people.

NART, as would be expected, showed the greatest association with education, however when controlling for the NART, associations were substantially attenuated but still observed for the SF-EMSE and FTMS for the levels of education examined. The change of direction of the association observed for SF-EMSE and sex after adjusting for NART may be because men performed worse than women on the NART and this was observed in the change in association on adjusting for NART.

Education was associated with a lowered risk of poor performance for HVLT at graduate level but not at 'O' and 'A' level in the fully adjusted model. Associations were no longer present for PW-Accuracy and little for prospective memory. Education and Intelligence (of which NART is a proxy measure), even though known closely related variables, are not perfectly correlated, and cannot be substituted for each other. [194] These findings support this and indicate that whatever NART assesses, whether it is a surrogate for prior ability including childhood intelligence or a composite indicator of education; adjusting for NART has a material influence on the independent association of social class and education on cognitive performance measures. Though NART does not completely remove association in all the tests here, it is an important exposure to consider and reasonable to adjust for when analysing cognitive function.

Another noteworthy point is that tests put forward as measuring similar domains, such as FTMS and HVLT; both measures of episodic memory (one verbal and one non-verbal), showed quite different relationships, particularly for sex, with men showing greater likelihood of poor performance for HVLT

than the FTMS. One possible explanation is that tasks requiring verbal and semantic knowledge are considered to be more cognitively demanding, requiring greater self-initiation and encoding than non-verbal tasks such as the FTMS of the CANTAB-PAL. [81,204] This observation, as well as that seen for processing speed, highlights the complex nature for assessing cognitive function, because different abilities do not work in isolation. As for others, [72] the EPIC-Norfolk tests showed no clear pattern of the underlying cognitive domains being assessed. Each test actually assesses more than the one ability (as shown in **Figure 2.2**, Chapter 2) and to execute a task successfully, abilities work in conjunction and not independently of each other. While the score focuses on the performance of a single 'main' ability, it actually reflects a range of other abilities that are being utilised.

There are a number of strengths to this study. The data are collected from a single large population with individuals being assessed under the same conditions. This reduces the variation in methodology seen in other studies that have combined data from various sources. We also examined ability separately across a wider range covering six domains including a test for global function and not restricted to a few domains, just episodic memory or simply global cognitive function as in many studies. Furthermore, we assessed differences in performance at individual test level rather than as aggregated test scores which allowed us to observe differences even in those tests intending to measure the same ability.

A limitation of this investigation is that it was not possible to test for other risk factors for poor performance in particular comorbidities, all which influence cognitive performance. The main focus of this paper was on differences across assessment tools. This study is cross-sectional, and reflects a more 'healthy profile' as it consists of survivors and those who attend the health examination and get tested.

Summary of Chapter

- Education and social class were independently associated with cognitive performance across all domains even after adjusting for age and the other covariates.
- Older age was found to be associated with poor performance in all of the cognitive tests (abilities), except with the NART score (crystallised cognition).
- Sex differences were observed for some tests.
- The risk of poor global cognitive function for those with O/A level qualifications compared to those with no qualifications was equivalent to being almost 9.9 years younger and those educated to graduate level was equivalent to 19.6 years younger.
- The Influence of education varied by age group. Not having qualifications in those <65 years was associated with greater risk of being in the poor performance group compared to people aged 65 and over.

Chapter 5: Physical Inactivity and Cognitive Performance

The work presented in this Chapter has been published:

Hayat, S. A., Luben, R Wareham, N, Khaw K-T and Brayne C (2020). Cross-sectional and prospective relationship between occupational and leisure time inactivity and cognitive function in an ageing population. The European Prospective Investigation into Cancer and Nutrition in Norfolk (EPIC-Norfolk) Study. International Journal of Epidemiology, 2020, 1–15

5.1 Summary

The current evidence for higher physical activity and better cognitive function and lower risk of dementia is strong but not conclusive. More robust evidence is needed to inform public health policy and practice. This chapter provides further insight to discrepancies observed across studies, reporting on habitual inactivity including that during work. As part of this investigation, I examined cross-sectional and prospective relationships of physical inactivity during leisure and occupation time, measured at two time points, with cognitive performance using a validated physical activity index in the 8585 EPIC-Norfolk participants with cognition data from EPIC-Norfolk. Associations were examined using multinomial logistic regression adjusting for socio-demographic and health variables as well total habitual physical activity.

Inactivity during work was inversely associated with poor cognitive performance (bottom tenth percentile of a composite cognition score), Odds Ratio (OR) = 0.68 (95% Confidence Interval (CI) 054, 0.86) P=0.001. Results were similar cross-sectionally; OR = 0.65 (95% CI 0.45, 0.93) P=0.02. Manual workers had increased risk of poor performance compared to those with an occupation classified as inactive. Inactivity during leisure time was associated with increased risk of poor performance in the cross-sectional analyses only.

Associations between physical inactivity and cognitive function differ depending on whether activity is measured during work or leisure. Findings from this cohort, which represents a wide socio-economic range, suggest that the relationship between inactivity and cognition is strongly confounded by education, social class and occupation. Physical activity during leisure may be protective for poor cognition, but work related physical activity is not protective. This suggests the need to have a greater understanding of the mechanisms and confounding underlying these paradoxical findings.

5.2 Introduction

Physical inactivity and sedentary behaviour (independent of physical activity), have been reported to be risk factors for major health conditions, [111] including cognitive impairment. [112] The available evidence for future public health strategies on how to best manage or prevent cognitive decline, impairment and dementia has shown physical activity to be predominantly, but not consistently, beneficial, with mixed evidence from observational studies. [113,205,206] The reasons for these discrepancies are unclear, [11] but may be partly due to the heterogeneity and limitations in the methodologies across studies. This includes differences in follow up time, [207] low power with insufficient sample size, differences in population characteristics [208–210] and the variability in the

way the exposure (physical activity) and the outcome (cognition) are measured and defined across studies.

Most studies have focused on moderate and severe cognitive impairment including dementia with far less on the relationship of physical activity and milder cognitive dysfunction. Cross-sectional studies with short follow-up times, cannot distinguish causal effects from reverse causation, and confounding is an issue highlighted as a limitation in observational studies. [206,207] Experimental studies examining the influence structured physical activity on enhancing cognitive function have also been inconsistent. [211] Studies cited in the literature have differed in methodology, but have predominantly used leisure time activity, [113,207] with few examining work-based physical activity. [205,206] Although leisure time activity has been associated with better cognition, [208] work-related physical activity has shown no relationship, [205] or even the contrary, with lower socio-economic groups and manual occupations with higher physical activity showing greater risk of dementia and cognitive impairment. [206,212] To advise on public health strategies for maintaining cognition in later life for all in society, we need a better understanding of discrepancies in the existing evidence base.

This chapter sets out to examine the cross-sectional and prospective relationship between physical inactivity and cognitive performance (both in terms of poor and high performance), in older men and women from a wide range of socio-economic background and education. Findings are presented on habitual inactivity including work and leisure time, using a simple pragmatic validated physical activity scale.

5.3 Methods

5.3.1 Participants and measurements

An overview of the EPIC-Norfolk 3HC methods have been described in Chapter 2. Specific methods for the work presented in this chapter are given here.

5.3.2 Assessment of cognition

For this analysis, the EPIC-Norfolk cognition battery, as described in Chapter 2. However, in this investigation, two separate outcome measures were available at the time of this chapter for the Visual Sensitivity Test (VST), a test for processing speed. These were VST-simple and VST-complex and are analysed here as separate measures. As a result, here, we report on eight separate cognitive measures rather than seven as reported in Chapter 4.

5.3.3 Assessment of Physical Activity

Total (habitual) physical activity was assessed as described in Chapter 2 using the two questions as described in Appendix 2. A four-category physical activity index was derived based on the level of activity during occupation and leisure time (Appendix 3).

5.3.4 Covariates

Education (the highest level attained) and social class were derived from the baseline questionnaire and analysed as described in Chapter 2. Briefly, education was categorised into three groups (i) No qualification (not completing school to age 16), (ii) Completing school to age 16 or 18 years ('O' or 'A' level) and (iii) educated to graduate level (a degree or equivalent) or above. Social class was analysed as separate categories for the univariate analysis, but then subsequently as the dichotomous variable ''non-manual'' and ''manual''. Self-report of smoking status and alcohol intake (units/week) were obtained from questionnaires from baseline and close to the time of cognitive testing (3HC). Alcohol units were categorised into three groups: 0 Units, 1-14 Units and more than 14 Units. Age (at baseline) was categorised into 5-year age bands.

5.4 Analysis

Descriptive analysis of cognitive scores by physical activity category revealed a non-linear relationship. Associations were therefore again examined using approximate percentile cut-offs rather than the continuous cognition score. For this chapter, participants were classified into three groups based on their scores, creating a 3-level categorical variable for each of the eight cognitive measures individually. The lowest level (1) corresponded to poor performance, as described in Chapter 2using the 10th percentile of the population distribution. The highest level (3) corresponded to high performance (defined as obtaining a score greater than a cut-off point corresponding to approximately the 90th percentile of the population distribution). The remaining consisted of those within the 11^{th}-89^{th} percentile, the standard level (2). For prospective memory, those failing were assigned to the poor performance group and those succeeding, to the standard level. In this investigation, we also included the composite score, representing general cognition underlying all the cognitive functions assessed. A 3-level categorical variable was created for EPIC-COGComp for poor, high and standard group level as for the cognitive measures individually as described in Appendix 5.

The physical activity index was examined in three different ways. Firstly, the four point index was use to examine the characteristics of the population across the four categories of physical activity both at baseline and at the 3HC. Secondly, we examined the association with cognition by dichotomising the

index into 'inactive' and 'active'. Finally, we additionally examined the association using the dichotomised index for occupation and leisure time components separately.

Associations between cognition (poor and high performance) and physical inactivity at the time of cognitive testing at 3HC (cross-sectional), and at baseline (prospective), were examined using multinomial logistic regression. **Figure 5.1** is a timeline of the study, presenting the two time points used in the analyses. Associations were assessed adjusting for age at time of cognitive testing (per 5 years) and sex (models 1), adding education and social class (models 2), extending the models to include prevalent disease (models 3), and finally, adjusting further for total habitual activity (Models 4) in the separate work and leisure analyses. Education, social class, physical activity, smoking and prevalent disease were all treated as categorical variables in the analysis and age per 5 years entered as continuous.

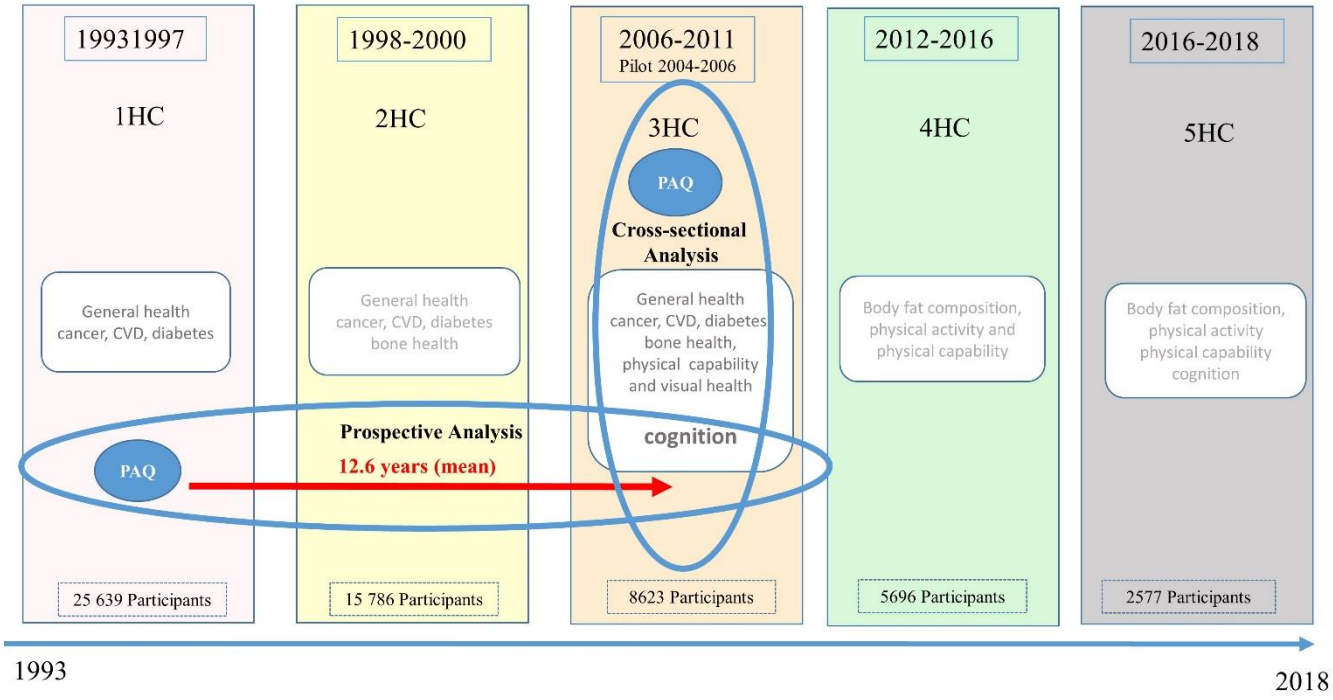
We also examined possible interaction with education and work-related activity and stratified by education group before calculating adjusted odd ratios for work and leisure. Sensitivity analyses were conducted (i) by assigning participants with missing data to the poor performance group and (ii) by grouping participants in approximate quartiles (rather three levels) of cognition scores.

5.5 Results

From baseline to time of cognitive testing (3HC), the mean follow-up time was 12.6 years (SD=2.0). There were 8585 participants with cognitive measures, resulting in 8501 participants in the cross-sectional and 8585 in the prospective analyses respectively. There were slightly fewer in the cross-sectional analyses due to some missing physical activity data. Those invited for the 3HC (N=18, 382) but did not attend, were more likely to be older, with higher self-reported heart attack, stroke and diabetes prevalence. Non-attenders were also more likely to have no qualifications and be in the lower socio-economic groups (Table 5.1).

Tables 5.2 and 5.3 show the characteristics (unadjusted) of the participants by habitual physical activity category for men and women at baseline and the 3HC respectively. At baseline, for men, a greater proportion of the moderately inactive and inactive were educated to graduate level and were from higher socio-economic groups. They were also more current smokers compared to those in the other levels of activity. For women, the inactive groups had fewer individuals in the higher educated and socio-economic groups, although as with men, more current smokers. Inactive individuals (for both men and women) were more likely to be older with men reporting higher rates of diabetes and women having higher rates of depression. At 3HC (Table 5.3), majority of individuals reported to be retired from their main occupation and were more likely to be inactive. Inactive men and women had higher rates of heart attack and stroke and more were non-drinkers and current smokers. There were no clear differences between level of physical activity (for baseline or 3HC) and score for any of the cognitive tests.

Figure 5.1: Simplified diagrammatic Timeline showing the two time points of the cross-sectional and prospective analyses



Legend: Timeline of the EPIC-Norfolk study showing the five health check phases over 25 years, the main area of interest for each phase and the number of participants recruited to study at that time-point. Cognitive measures from Third Health Check (3HC) were used in this analysis. Physical activity measures were taken from baseline (1HC- for prospective analysis) and at 3HC (for cross-sectional analysis).

Abbreviations: 1HC, First Health Check; 2HC, Second Health Check; 3HC, Third Health Check; 4HC, Fourth Health Check; 5HC, Fifth Health Check; PAQ, Physical activity Questionnaire.

Table 5.1: Characteristics of individuals by those invited, attended 3HC with a cognitive test measure compared to those who either did not attend 3HC (including the pilot) or had no cognitive test measure.

	Total Invited (N=18,382)		
	Attenders, with cog score(N=8585)	Non-attenders (N=9797)*	P-Value
Characteristics at Baseline			
Mean (SD)			
Age	55.7 (7.8)	58.9 (9.3)	<0.001
Frequencies, % (N)			
% men	44.7 (3841)	42.0 (4117)	<0.001
Level of education			
No Qualification	26.2 (2251)	45.1 (4414)	<0.001
O or A level	56.1 (4521)	46.2 (4521)	
Graduate Level or above	17.6 (1513)	8.7 (856)	
Social Class			
Professional	8.8 (748)	4.9 (468)	<0.001
Managerial	41.1 (3498)	30.1 (2867)	
Skilled Non-Manual	16.0 (1364)	17.1 (1635)	
Skilled Manual	20.6 (1748)	26.8 (2555)	
Semi-Skilled	11.2 (950)	16.3 (1550)	
Non-Skilled	2.3 (197)	4.8 (459)	
Alcohol (Units/week)			
0	8.9(763)	15.5 (2263)	<0.001
≤ 14 Units	75.2 (6426)	71.6 (6912)	
> 14 Units	15.8 (1353)	12.8 (1239)	
Smoking Status			
Never	52.2 (4463)	45.0(4365)	<0.001
Former	38.9 (3329)	41.0 (3971)	
Current	8.9 (760)	14.0 (1361)	
Co-morbidities			
Heart attack	1.5 (128)	2.6 (251)	<0.001
Stroke	0.6 (50)	1.0 (99)	0.001
Cancer	4.4 (374)	4.4 (426)	1.00
Diabetes	1.0 (85)	2.2 (218)	<0.001
Depression	14.6 (1250)	14.3 (1398)	0.6

P- Value Using Anova or chi sq

* includes 38 who attended but had no cognition score). Abbreviations: A, Advanced; N, Number; O, Ordinary; SD, standard deviation

Table 5.2: Baseline (1993–1997) characteristics of the 8585 EPIC-Norfolk men and women with cognitive data collected at 3HC (2006–2011, including data from pilot 2004–2006) by level of physical activity.

	Level of Activity as reported at Baseline by Men					
Characteristics at Baseline	**ALL N=3841**	**Inactive N=880**	**Moderately inactive N=1001**	**Moderately active N=973**	**Active N=987**	**P-Value**
Mean (SD)						
Age	56.4 (7.9)	58.1 (8.0)	56.3 (8.0)	56.1 (7.7)	55.1 (7.5)	<0.001
Frequencies, % (N)						
Level of education						
No Qualification	22.1 (847)	22.9 (201)	19.2 (192)	19.9 (194)	26.3 (260)	<0.001
O or A level	57.8 (2221)	59.5 (523)	52.5 (526)	60.4 (588)	59.2 (584)	
Graduate level	20.1 (772)	17.6 (155)	28.3 (283)	19.6 (191)	14.5 (143)	
Social Class						
Professional	9.5 (364)	11.1 (97)	14.6 (145)	7.7 (74)	4.9 (48)	<0.001
Managerial	42.7 (1629)	47.0 (411)	47.6 (473)	42.3 (408)	34.4 (337)	
Skilled Non-Manual	12.2 (466)	16.2 (142)	15.8 (157)	9.9 (96)	7.2 (71)	
Skilled Manual	22.7 (865)	14.4 (126)	13.1 (130)	27.4 (264)	35.2 (345)	
Semi-Skilled	11.0 (418)	9.8 (86)	7.8 (78)	10.8 (104)	15.3 (150)	
Non-Skilled	1.9 (72)	1.5 (13)	1.1 (11)	2.0 (19)	3.0 (29)	
Co-morbidities						
Heart attack	2.6 (101)	3.6 (32)	2.4 (24)	2.6 (25)	2.0 (20)	0.2
Stroke	0.7 (27)	0.8 (7)	0.9 (9)	0.9 (9)	0.2 (2)	0.2
Cancer	2.8 (106)	2.5 (22)	2.6 (26)	3.9 (38)	2.0 (20)	0.07
Diabetes	1.4 (54)	2.3 (20)	1.4 (14)	1.8 (18)	0.2 (2)	0.001
Depression	8.6 (329)	9.2 (81)	9.5 (95)	8.0 (78)	7.6 (75)	0.4
Alcohol (Units/week)						
0	5.9 (227)	5.7 (50)	5.0 (50)	6.7 (65)	6.3 (62)	0.2
≤ 14 Units	68.3 (2614)	71.1 (619)	67.4 (672)	68.3 (663)	66.9 (660)	
> 14 Units	25.7 (984)	23.2 (202)	27.6 (275)	25.0 (243)	26.8 (264)	
Smoking Status						
Never	41.4 (1586)	36.9 (324)	44.6 (445)	41.0 (397)	42.6 (420)	0.04
Former	49.6 (19.1)	53.0 (465)	47.4 (473)	49.5 (480)	49.0 (483)	
Current	8.9 (342)	10.0 (88)	8.0 (80)	9.5 (92)	8.3 (82)	
	Mean Cognitive Test Score at 3HC (SD)					
SF-EMSE	32.5 (3.3)	32.2 (3.7)	32.9 (2.8)	32.6 (3.4)	32.3 (3.4)	<0.001
HVLT	23.9 (5.6)	23.6 (5.8)	24.2 (5.7)	23.9 (5.6)	23.7 (5.4)	0.1
PAL- FTMS	15.4 (4.3)	15.3 (4.3)	15.4 (4.5)	15.6 (4.2)	15.2 (4.3)	0.3
PW-Accuracy	12.3 (5.6)	12.3 (6.0)	12.7 (5.9)	12.4 (6.1)	12.0 (6.3)	0.08
VST-simple[ǂ]	657.7 (161.6)	658.8 (175.2)	656.4 (161.9)	654.9 (151.1)	661.0 (158.8)	0.9
VST-Complex[ǂ]	2227.5 (422.9)	2267.8 (499.4)	2235.5 (440.4)	2200.7 (375.4)	2210.1 (369.2)	0.01
Short-NART[ǂ]	17.9 (10.3)	16.4 (10.0)	16.2 (9.8)	18.6 (10.3)	20.3 (10.5)	<0.001
Comp. Score	7.7 (1.8)	7.7 (1.8)	7.8 (1.8)	7.7 (1.8)	7.4 (1.8)	0.001
Pros. Mem % failed (N)	22.3 (838)	20.6 (176)	21.6 (211)	23.0(219)	24.1 (232)	0.3

Table 5.2: Continued…

Characteristics at Baseline	ALL	Level of Activity as reported at Baseline by Women: Inactive	Moderately inactive	Moderately active	Active	P-Value
	N=4744	N=976	N=1577	N=1230	N=961	
Mean (SD)						
Age	55.1 (7.7)	56.9 (8.2)	55.4 (7.9)	54.4 (7.4)	53.8 (7.1)	<0.001
Frequencies, % (N)						
Level of education						
No Qualification	29.6 (1404)	31.5 (307)	28.2 (445)	29.4 (362)	30.2 (290)	<0.001
O or A level	54.8 (2598)	56.8 (554)	55.5 (876)	51.5 (634)	55.6 (534)	
Graduate Level or above	15.6 (741)	11.7 (114)	16.2 (256)	19.0 (234)	14.3 (137)	
Social Class						
Professional	8.2 (384)	5.6 (54)	9.0 (141)	9.2 (112)	8.1 (77)	<0.001
Managerial	39.8 (1869)	35.5 (342)	41.1 (642)	41.93 (511)	39.5 (374)	
Skilled Non-Manual	19.1 (898)	23.5 (226)	20.4 (319)	17.3 (211)	15.0 (142)	
Skilled Manual	18.8 (883)	21.2(204)	17.7 (277)	17.0 (207)	20.6 (195)	
Semi-Skilled	11.3 (532)	11.0 (106)	10.1 (158)	11.6 (141)	13.4 (127)	
Non-Skilled	2.7 (125)	3.2 (31)	1.5 (24)	3.0 (37)	3.5 (33)	
Co-morbidities						
Heart attack	0.6 (27)	0.4 (4)	0.6 (9)	0.6 (7)	0.7 (7)	0.8
Stroke	0.5 (23)	0.7 (7)	0.5 (8)	0.4 (5)	0.3 (3)	0.6
Cancer	5.7 (268)	6.8 (66)	5.2 (82)	5.7 (70)	5.2 (50)	0.4
Diabetes	0.7 (31)	0.5 (5)	0.9 (14)	0.4 (5)	0.7 (7)	0.4
Depression	19.5 (921)	22.7 (221)	19.4 (305)	18.1 (222)	18.0 (173)	0.03
Alcohol (Units/week)						
0	11.4 (536)	13.6 (131)	10.2 (160)	10.4(128)	12.2 (117)	0.1
≤ 14 Units	80.8 (3812)	78.9 (758)	82.0 (1288)	81.0 (993)	80.5 (773)	
> 14 Units	7.8 (369)	7.5 (72)	7.8 (122)	8.6 (105)	7.3 (70)	
Smoking Status						
Never	60.9 (2877)	58.0 (563)	60.4 (947)	63.2 (774)	61.9 (593)	0.02
Former	30.2 (1428)	30.9 (300)	30.8 (483)	28.1 (344)	31.4 (301)	
Current	8.9 (418)	11.1 (108)	8.9 (139)	8.7 (107)	6.7 (64)	
Mean Cognitive Test Score at 3HC (SD)						
SF-EMSE	32.7 (3.0)	32.6 (3.1)	32.7 (3.1)	32.8 (2.8)	32.6 (3.0)	0.2
HVLT	26.04 (5.5)	25.7 (5.9)	26.1 (5.6)	26.4 (5.3)	25.9 (5.3)	0.04
PAL- FTMS	15.8 (4.2)	15.7 (4.2)	15.8 (4.3)	15.9 (4.2)	15.8 (4.2)	0.6
PW-Accuracy	13.8 (5.9)	13.4 (6.3)	14.0 (5.8)	14.0 (5.9)	13.8 (5.8)	0.08
**VST-simple ǂ	668.7 (169.9)	690.3 (212.0)	662.1 (155.7)	663.3 (148.5)	664.6 (168.5)	0.001
**VST-Complex ǂ	2172.3 (432.5)	2205.4 (481.4)	2163.7 (455.5)	2173.3 (403.1)	2151.3 (371.2)	0.07
Short-NART ǂ	16.6 (9.5)	16.8 (9.7)	16.1 (9.2)	16.4 (9.4)	17.6 (9.6)	0.001
Composite score	8.1 (1.8)	8.0 (2.0)	8.2 (1.8)	8.1 (1.8)	8.0 (1.7)	0.3
Pros. Mem % failed (N)	15.9 (738)	16.1 (154)	15.6 (241)	15.5 (187)	16.5 (156)	0.9

Abbreviations: A, Advanced level, HVLT, Hopkins Verbal Learning Test; N, Number; NART, National Adult Reading Test O, Ordinary; PAL-FTMS, Paired Associates Learning, First Trial Memory Score; Pros. Mem, Prospective Memory; SD, standard deviation; SF-EMSE, Short Form Extended mental state exam; VST, Visual Sensitivity Test.

** Reaction time measure in milliseconds ǂHigher Short NART scores indicate lower performance.

Table 5.3: Characteristics of EPIC-Norfolk men (N=3786*) and women (N=4680*) at time of cognitive testing (3HC Phase, 2006-2011, including data from pilot 2004–2006) by level of physical activity.

	Men					
	ALL	**Inactive**	**Moderately inactive**	**Moderately active**	**Active**	**P-Value**
	N=3841*	**N=1410**	**N=952**	**N=712**	**N=712**	
Mean (SD)						
Age	69.4(8.1)	72.0 (7.9)	69.2 (7.9)	67.4 (7.8)	66.4 (7.3)	0.01
Frequencies, % (N)						
Retired from main occupation	75.9 (2842)	81.7 (701)	77.1 (749)	76.5 (727)	69.0 (665)	<0.001
Co-morbidities						
Heart attack	5.2 (198)	7.1 (100)	4.1 (39)	4.2 (30)	3.5 (25)	<0.001
Stroke	3.0 (116)	4.7 (66)	2.2 (21)	2.1 (15)	1.5 (11)	<0.001
Cancer	7.2 (276)	7.5 (106)	7.8 (74)	6.7 (48)	6.2 (44)	0.6
Diabetes	3.9 (151)	5.2 (74)	3.0 (29)	4.1 (29)	2.4(17)	0.01
Depression	14.0 (536)	13.1 (185)	15.9 (151)	14.5 (103)	12.4(88)	0.2
Alcohol (Units/week)						
0	22.2 (824)	27.3 (375)	18.5 (173)	20.5 (144)	18.9 (132)	
≤ 14 Units	59.2 (2193)	55.6 (764)	62.6 (585)	60.6 (425)	59.9 (419)	<0.001
> 14 Units	18.6 (690)	17.0 (234)	18.8 (176)	18.8 (132)	21.2 (148)	
Current Smokers % (n)	4.2 (158)	4.8 (68)	3.9 (37)	3.2 (23)	4.2 (30)	0.3
Mean Cognitive Test Score (SD)						
SF-EMSE	32.5 (3.3)	32.0 (3.7)	32.9 (3.0)	32.8 (2.9)	32.7 (2.8)	<0.001
HVLT	23.9 (5.6)	23.0 (5.8)	24.3 (5.6)	24.5 (5.4)	24.5 (5.1)	<0.001
PAL- FTMS	15.4 (4.3)	14.7 (4.4)	15.6 (4.3)	16.1 (4.1)	15.8 (4.1)	<0.001
PW-Accuracy	12.3 (6.1)	11.9 (6.0)	12.7 (6.2)	12.6 (6.2)	12.5 (6.2)	0.003
**VST-simple ǂ	657.7 (161.6)	667.9 (172.7)	660.7 (178.0)	645.6 (121.9)	646.9 (151.8)	0.01
**VST-Complex ǂ	2227.7 (422.9)	2267.2 (431.6)	2230.4 (462.7)	2192.3 (350.6)	2191.1 (414.3)	<0.001
Short-NART ǂ	17.9 (10.3)	18.0 (10.4)	16.2 (10.1)	18.1 (10.0)	19.7 (10.5)	<0.001
Composite Score	7.7 (1.8)	7.3 (1.8)	7.9 (1.8)	7.8 (1.8)	7.8 (1.6)	<0.001
Pros. Mem % failed (N)	22.3 (838)	24.7 (337)	21.7 (202)	19.8 (139)	20.7 (145)	0.04

Table 5.3: Continued …

	Women					
	ALL N=4744*	**Inactive N=1739**	**Moderately inactive N=1509**	**Moderately active N=792**	**Active N=640**	**P-Value**
Mean (SD)						
Age	68.1 (8.0)	70.8 (8.2)	67.2 (7.5)	66.0 (7.4)	65.3 (7.3)	<0.001
Frequencies, % (N)						
Retired from main occupation	78.8 (3549)	84.1 (788)	79.0 (1180)	76.8 (899)	75.7 (682)	<0.001
Co-morbidities						
Heart attack	2.0 (93)	3.1 (54)	1.8 (27)	0.8 (6)	0.9 (6)	<0.001
Stroke	1.4 (66)	2.1 (37)	1.3 (19)	0.9 (7)	0.5 (3)	0.01
Cancer	11.1 (528)	12.5 (217)	10.7 (161)	9.1 (72)	10.6 (68)	0.07
Diabetes	2.3 (109)	2.9 (50)	1.9 (29)	1.8 (14)	2.3 (15)	0.2
Depression	28.0 (1328)	29.0 (504)	27.4 (414)	30.2 (239)	23.6 (151)	0.03
Alcohol (Units/week)						
0	36.0 (1638)	43.1 (731)	31.7 (465)	30.4 (234)	33.3 (208)	<0.001
≤ 14 Units	58.5 (2664)	52.4 (889)	62.4 (914)	62.5 (481)	60.8 (380)	
> 14 Units	5.6 (253)	4.4 (75)	5.9 (86)	7.1 (55)	5.9 (37)	
Current Smokers % (n)	4.5 (212)	5.8 (100)	3.4 (51)	4.2 (33)	4.4 (28)	0.01
Mean Cognitive Test Score (SD)						
SF-EMSE	32.7 (3.0)	32.2 (3.2)	33.0 (2.8)	33.0 (3.0)	32.8 (2.7)	<0.001
HVLT	26.0 (5.5)	25.0 (5.9)	26.7 (5.3)	26.6 (5.1)	26.8 (5.0)	<0.001
PAL- FTMS	15.8 (4.2)	15.3 (4.3)	16.1 (4.2)	16.1 (4.1)	16.1 (4.2)	<0.001
PW-Accuracy	13.8 (5.9)	13.0 (6.1)	14.5 (5.8)	14.3 (5.7)	14.2 (5.8)	<0.001
**VST-simple‡	668.7 (169.9)	685.6 (189.4)	661.6 (172.0)	660.1 (152.5)	651.4 (122.3)	<0.001
**VST-Complex‡	2172.3 (432.5)	2208.1 (444.4)	2159.6 (469.6)	2136.1 (385.6)	2149.4 (361.4)	0.001
NART ‡	16.6 (9.5)	17.2 (9.5)	15.7 (9.4)	16.2 (9.5)	17.5 (9.4)	<0.001
Composite Score	8.1 (1.8)	7.3 (1.8)	7.9 (1.8)	7.8 (1.8)	7.8 (1.6)	<0.001
Pros. Mem % failed (N)	15.6 (738)	19.3 (327)	12.5 (185)	16.0 (125)	14.5 (91)	<0.001

*****Total does not match due to missing data

Abbreviations: A, Advanced level, HVLT, Hopkins Verbal Learning Test; N, Number; NART, National Adult Reading Test O, Ordinary; PAL-FTMS, Paired Associates Learning, First Trial Memory Score; Pros. Mem, Prospective Memory SF-EMSE, Short Form Extended mental state exam; VST, Visual Sensitivity Test;

** Reaction time measure in milliseconds ‡ Higher Short-NART scores indicate lower performance

Table 5.4 shows associations of habitual inactivity cross-sectionally and prospectively, across individual cognitive tests (assessing a range of domains) and the composite score. After controlling for age and sex, most attenuation occurred for the bottom 10th percentile, with some after adjusting for education and social class. Further adjustments for other co-variables, made little difference to the point estimates. Apart from the NART, where education and social class strengthened the association with cognition, there was little change across the models for the top 10th percentile for the other tests.

For most tests, there was little or no relationship between habitual inactivity and cognition. However, being inactive was positively associated with poor performance for VST-complex both in cross-sectional and possibly also in the prospective analyses OR=1.20 (95% CI 1.02, 1.42 P=0.03); OR=1.20 (95% CI 0.99, 1.44 P=0.06) respectively. Inactive participants were also less likely to perform poorly in the prospective analysis for the prospective memory task OR=0.79 (95% CI 0.69, 0.91 P=0.001).

Physical inactivity increased the likelihood of high performance for the tests HVLT OR=1.23 (95% CI 1.04, 1.47 P=0.02) and NART OR=1.37 (95% CI 1.14, 1.65 P=0.001), but only for the prospective analyses. For VST-Simple, those inactive at 3HC were less likely to be high performers. No associations were observed for poor performance. For the composite score, inactivity was associated with increased risk of poor performance cross-sectionally, and a possible decreased risk prospectively. For practicality, only the composite score was used to examine the relationship with work and leisure separately. Table 5.5 shows these associations in men and women with further adjustment for total habitual activity (Models 4).

Leisure inactivity seemed to increase risk of poor performance, cross-sectionally OR=1.27 (95% CI 1.00, 1.61 P=0.05). For high performance, no relationship was observed cross-sectionally, but a possible inverse relationship was observed for the prospective analyses. There seemed to be some indication of an increased risk with poor performance for inactivity in men cross-sectionally and decrease in being in the top performance prospectively. No clear relationship was observed for women.

Table 5.4: Association (prospective and cross-sectional) between physical inactivity and cognitive performance for eight cognitive measures separately and composite score for participants taking part in EPIC-Norfolk, 2006–2011 (including Data from the Pilot Phase 2004–2006).

	Model 1					Model 2					Model 3				
Inactive vs Active*	**REF****	**Bottom 10th PCTILE**		**Top 10th PCTILE**		**Bottom 10th PCTILE**		**Top 10th PCTILE**			**Bottom 10th PCTILE**		**Top 10th PCTILE**	
	OR	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**N**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
SF-EMSE														
Cross-sec.(N=8368)	1.00	1.20	(1.04, 1.37) P=0.01	0.82	(0.71, 0.96) P=0.01	1.08	(0.94, 1.24) P=0.3	0.90	(0.77, 1.05) P=0.2	8289	1.08	(0.94, 1.24) P=0.3	0.90	(0.77, 1.05) P=0.2
Prospective (N=8483)	1.00	0.99	(0.85, 1.16) P=0.9	1.06	(0.90, 1.25) P=0.5	0.96	(0.82, 1.13) P=0.6	1.08	(0.91, 1.28) P=0.4	8356	0.96	(0.81, 1.12) P=0.6	1.06	(0.90, 1.26) P=0.5
HVLT														
Cross-sec.(N=8028)	1.00	1.19	(1.02, 1.39) P=0.03	0.83	(0.71, 0.97) P=0.02	1.12	(0.95, 1.31) P=0.2	0.93	(0.79, 1.09) P=0.4	7954	1.10	(0.94, 1.30) P=0.2	0.93	(0.79. 1.10) P=0.3
Prospective (N=8138)	1.00	1.09	(0.92, 1.30) P=0.3	1.20	(1.02, 1.42) P=0.03	1.08	(0.90, 1.29) P=0.4	1.25	(1.06, 1.49) P=0.01	8020	1.07	(0.90, 1.28) P=0.4	1.23	(1.04, 1.47) P=0.02
PAL- FTMS														
Cross-sec.(N=7352)	1.00	1.24	(1.06, 1.45) P=0.01	0.97	(0.82, 1.14) P=0.7	1.16	(0.99, 1.36) P=0.07	1.02	(0.86, 1.21) P=0.8	7283	1.16	(0.99, 1.36) P=0.07	1.01	(0.85, 1.19) P=0.9
Prospective (N=7461)	1.00	0.86	(0.71, 1.03) P=0.09	0.96	(0.80, 1.16) P=0.7	0.85	(0.70, 1.02) P=0.08	0.97	(0.81, 1.18) P=0.8	7352	0.84	(0.70, 1.02) P=0.07	0.96	(0.79, 1.16) P=0.7
PW-Accuracy														
Cross-sec.(N= 8296)	1.00	1.03	(0.89, 1.19) P=0.7	0.93	(0.79, 1.10) P=0.4	0.99	(0.85, 1.14) P=0.9	0.96	(0.82, 1.13) P=0.6	8219	0.97	(0.84, 1.13) P=0.7	0.98	(0.83, 1.16) P=0.8
Prospective (N=8410)	1.00	0.98	(0.83, 1.15) P=0.8	1.09	(0.91, 1.30) P=0.4	0.99	(0.84, 1.17) P=0.9	1.10	(0.92, 1.32) P=0.3	8285	0.99	(0.84, 1.17) P=0.9	1.14	(0.95, 1.36) P=0.2
VST-simple (Reaction Time, ms)														
Cross-sec.(N=7067)	1.00	1.06	(0.90, 1.25) P=0.5	0.77	(0.64, 0.92) P=0.004	0.99	(0.84, 1.18) P=0.9	0.77	(0.64, 0.92) P=0.004	6999	0.99	(0.84, 1.18) P=0.9	0.76	(0.64, 0.92) P=0.004
Prospective (N=7171)	1.00	1.06	(0.88, 1.28) P=0.5	1.00	(0.82, 1.21) P=0.9	1.05	(0.87, 1.27) P=0.6	0.99	(0.81, 1.21) P= 0.9	7062	1.04	(0.86, 1.26) P=0.7	0.99	(0.81, 1.20) P=0.9

Table 5.4 continued…

		Model 1				Model 2					Model 3			
Inactive vs Active *	**REF** OR**	**Bottom 10th PCTILE**		**Top 10th PCTILE**		**Bottom 10th PCTILE**		**Top 10th PCTILE**			**Bottom 10th PCTILE**		**Top 10th PCTILE**	
	OR	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**		**OR**	**(95% CI)**	**OR**	**(95% CI)**
VST-Complex (Reaction Time, ms)														
Cross-sec.(N=7067)	1.00	1.25	(1.06, 1.48)	0.94	(0.79, 1.11)	1.22	(1.03, 1.44)	0.93	(0.78, 0.1.10)	6999	1.20	(1.02, 1.42)	0.93	(0.78, 1.11)
		P=0.01		P=0.5		P=0.02		P=0.4			P=0.03		P=0.4	
Prospective (N= 7171)	1.00	1.22	(1.02, 1.46)	1.02	(0.84, 1.23)	1.23	(1.02, 1.45)	1.01	(0.84, 1.23)	7062	1.20	(0.99, 1.44)	1.01	(0.83, 1.22)
		P=0.03		P=0.9		P=0.03		P=0.9			P=0.06		P=1.00	
NART														
Cross-sec.(N=8002)	1.00	1.03	(0.88, 1.20)	0.84	(0.72, 0.98)	0.89	(0.76, 1.05)	1.06	(0.89, 1.25)	7922	0.89	(0.75, 1.05)	1.07	(0.90, 1.26)
		P=0.7		P=0.03		P=0.2		P=0.5			P=0.2		P=0.5	
Prospective (N=8112)	1.00	0.87	(0.72, 1.04)	1.18	(1.00, 1.40)	0.88	(0.73, 1.07)	1.38	(1.15, 1.66)	8000	0.88	(0.72, 1.06)	1.37	(1.14, 1.65)
		P=0.1		P=0.05		P=0.2		P=0.001			P=0.2		P=0.001	
Composite Score														
Cross-sec.(N=6061)	1.00	1.28	(1.11, 1.47)	0.83	(0.70, 0.97)	1.18	(1.02, 1.37)	0.91	(0.77, 1.07)	6002	1.17	(1.01, 1.36)	0.91	0.77, 1.07)
		P=0.001		P=0.02		P=0.03		P=0.3			P=0.04		P=0.3	
Prospective (N=6152)	1.00	0.87	(0.74, 1.02)	1.13	(0.95,1.34)	0.86	(0.72, 1.02)	1.18	(0.98, 1.41)	6057	0.85	(0.71, 1.01)	1.15	(0.96, 1.38)
		P=0.1		P='0.2		P=0.08		P=0.08			P=0.07		P=0.1	
	REF***	**Fail**				**Fail**					**Fail**			
Pros. Mem**		**OR**	**(95% CI)**			**OR**	**(95% CI)**				**OR**	**(95% CI)**		
Cross-sec. (N=8290)	1.00	1.03	(0.91, 1.16)			1.03	(0.91, 1.16)			8213	0.98	(0.87, 1.11)		
		P=0.6				P=0.6					P=0.8			
Prospective (N=8403)	1.00	0.81	(0.70, 0.93)			0.8	(0.69, 0.92)			8278	0.79	(0.69, 0.91)		
		P=0.003				P=0.001					P=0.001			

Model 1: Adjusted age per 5 years increase (at time of cognitive testing) and sex Model 2: Adjusted age per 5 years increase (at time of cognitive testing, or 3HC), sex , education (at 3 levels, 1/no qualifications, 2/O and A level and 3/degree and above) social class (at two levels, manual and non-manual) Model 3: Adjusted age per 5 years increase (at time of cognitive testing at 3HC , sex education (at 3 levels, 1/no qualifications, 2/O and A level and 3/degree and above from baseline) social class (at two levels, manual and non-manual from baseline) prevalent disease (at baseline and at 3HC) and smoking (at two level, smokers vs non-smokers, at baseline and at 3HC); Abbreviations: A, Advanced level, Cross-sec., Cross-sectional analysis; HVLT, Hopkins Verbal Learning Test; ms, milliseconds; N, Number; NART, National Adult Reading Test O, Ordinary; PAL-FTMS, Paired Associates Learning, First Trial Memory Score; PCTILE, Percentile; Pros. Mem, Prospective Memory; SF-EMSE, Short Form Extended mental state exam; VST, Visual Sensitivity Test; Reference categories are active*; 11th-89th** percentile and success*** group respectively).

Table 5.5: Association between physical inactivity (leisure and occupation time separately) with cognition (using composite score only) in the EPIC-Norfolk Cohort (including pilot data) for men and women combined as well as separately.

Inactive vs Active*	Model 3							Model 4**						
	REF**	Bottom 10th PCTILE			Top 10th PCTILE			REF**	Bottom 10th PCTILE			Top 10th PCTILE		
	OR	OR	(95% CI)	P-Value	OR	(95% CI)	P-Value	OR	OR	(95% CI)	P-Value	OR	(95% CI)	P-Value
Leisure Activity Only (ALL)														
Cross-Sec. (N=6002)	1.00	1.24	(1.07, 1.43)	0.004	0.95	(0.82, 1.12)	0.6	1.00	1.27	(1.00, 1.61)	0.05	1.07	(0.83, 1.36)	0.6
Prospective (N= 6057)	1.00	1.01	(0.88, 1.17)	0.9	0.96	(0.82, 1.12)	0.6	1.00	1.14	(0.96, 1.36)	0.1	0.81	(0.66, 1.00)	0.05
Men														
Cross-Sec. (N=2693)	1.00	1.34	(1.09, 1.64)	0.01	1.09	(0.85, 1.40)	0.5	1.00	1.35	(1.00, 1.82)	0.05	1.31	(0.91, 1.88)	0.2
Prospective (N=2725)	1.00	0.97	(0.80, 1.18)	0.8	0.79	(0.61, 1.01)	0.06	1.00	1.17	(0.93, 1.48)	0.2	0.60	(0.42, 0.87)	0.01
Women														
Cross-Sec. (N=3309)	1.00	1.13	(0.92, 1.39)	0.3	0.87	(0.72, 1.07)	0.2	1.00	1.14	(0.77, 1.71)	0.5	0.91	(0.65, 1.27)	0.6
Prospective (N=3332)	1.00	1.04	(0.84, 1.28)	0.7	1.08	(0.89, 1.32)	0.5	1.00	1.05	(0.81, 1.37)	0.7	0.95	(0.73, 1.23)	0.7
Work Activity Only (ALL)														
Cross-Sec. (N= 2756)[‡]	1.00	0.65	(0.50, 0.85)	0.002	1.21	(0.99, 1.48)	0.06	1.00	0.65	(0.45, 0.93)	0.02	1.19	(0.95, 1.50)	0.1
Prospective (N= 5020)	1.00	0.66	(0.55, 0.79)	<0.001	1.21	(1.03, 1.43)	0.02	1.00	0.68	(0.54, 0.86)	0.001	1.16	(0.96, 1.40)	0.1
Men														
Cross-Sec. (N=1388)	1.00	0.75	(0.52, 1.06)	0.1	1.31	(0.95, 1.80)	0.1	1.00	0.70	(0.43, 1.13)	0.1	1.39	(0.97, 2.00)	0.08
Prospective (N=2275)	1.00	0.70	(0.54, 0.91)	0.01	1.21	(0.92, 1.61)	0.2	1.00	0.77	(0.56, 1.07)	0.1	1.27	(0.93, 1.73)	0.1
Women														
Cross-Sec. (N=1368)	1.00	0.53	(0.34, 0.82)	0.004	1.18	(0.91, 1.53)	0.2	1.00	0.59	(0.33, 1.04)	0.07	1.10	(0.81, 1.50)	0.5
Prospective (N=2745)	1.00	0.63	(0.47, 0.83)	0.001	1.20	(0.98, 1.47)	0.08	1.00	0.59	(0.41, 0.84)	0.004	1.08	(0.85, 1.37)	0.5

Model 3: Adjusted age per 5 years increase (at time of cognitive testing, or 3HC) , sex education (at 3 levels, 1/no qualifications, 2/O and A level and 3/degree and above from baseline) social class (at two levels, manual and non-manual from baseline) prevalent disease (at baseline and time of cog testing, 3HC) and smoking (at two level, smokers vs non-smokers, all co-variates measures entered from baseline and at 3HC separately.

(Reference categories are active* and 11th-89th** percentile group respectively)

Abbreviations: Cross-sect: Cross-sectional, N, number; OR, Odds ratio PCTILE, percentile; **Model 4: As in model 3 with further adjustment for total physical activity as categorical variables.

In contrast to leisure time, inactivity during work was associated with lower risk of poor performance with little difference observed in the cross-sectional and prospective analyses. In relation to high performance, the relationship was stronger for men, with a possible increased likelihood of high performance observed for inactive working men, but not for inactive working women (Table 5.5).

Figure 5.2 is a visual representation of the relationship between inactivity and cognitive performance for total habitual, as well as leisure and work time activity separately, at the two time points (men and women combined). **Figure 5.3** shows that increased work related physical activity (as reported at baseline), was associated with increased risk of poor performance with manual workers having a greater risk of poor performance than those with physically inactive occupations; OR=2.70 (95%CI 1.76, 4.16 P<0.001).

No significant interaction was observed with education and work related activity either cross-sectionally (bottom and top 10th percentile P=0.4 and P=0.9 respectively) or prospectively (bottom and top 10th P=0.6 and P=0.5 respectively). However, those with no qualifications were less likely to be inactive at work and more likely to be inactive at leisure (Table 5.6).

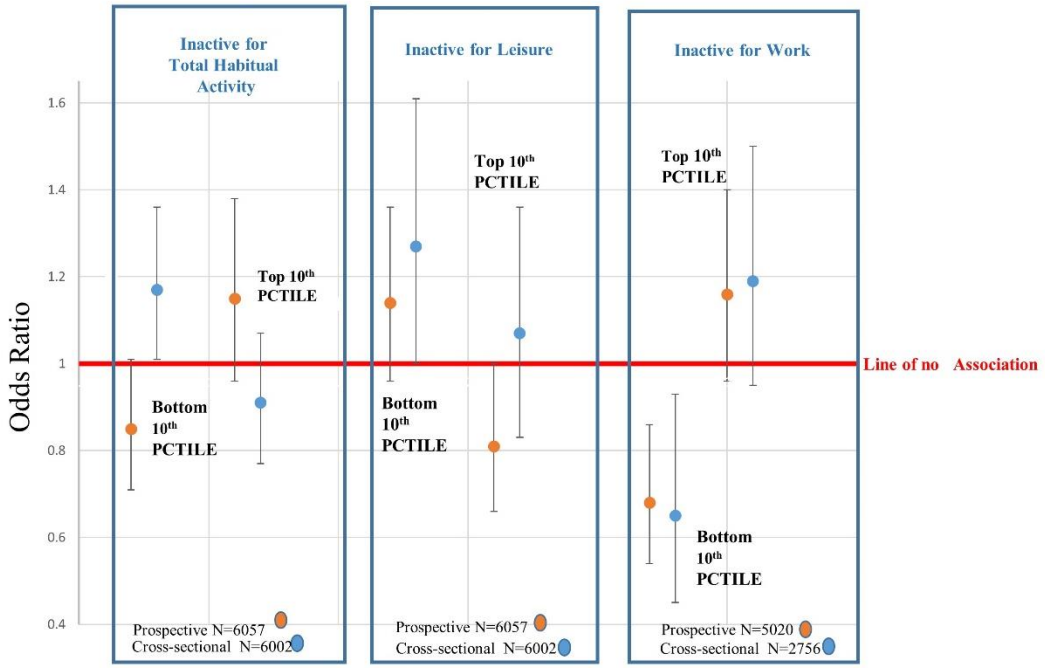
Table 5.6: Distribution of inactivity during leisure and work by education level (cross-sectional and prospective analysis).

	Frequencies, % (N)		
	No Qualifications	**Any Qualifications**	**P-Value**
Cross-sectional			
Inactive at work (N=1675)	25.7 (183)	48.3 (1492)	<0.001
Inactive at leisure (N=4098)	58.0 (1282)	45.0 (2816)	<0.001
Prospective			
Inactive at work at baseline (N=2742)	22.6 (372)	44.3 (2370)	<0.001
Inactive at leisure (N=3661)	50.6 (1138)	39.8 (2523)	<0.001

Due to the strong influence of education on cognition, data were stratified by education groups ('No Qualifications' and 'With Qualifications'). Adjusted odd ratios in each group for both work and leisure are presented in Table 5.7. On stratification, results indicate that being inactive at work reduced risk of poor performance for both those with and without qualifications. Furthermore, those remaining in an inactive job at the time of cognitive testing increased their probability of being in the top tenth percentile OR= 1.29 (95%CI 1.02, 1.62 P=0.03). The risk for poor performance increased for those inactive for leisure, particularly for those 'with qualifications' OR= 1.35 (95%CI 1.00, 1.81 P=0.05).

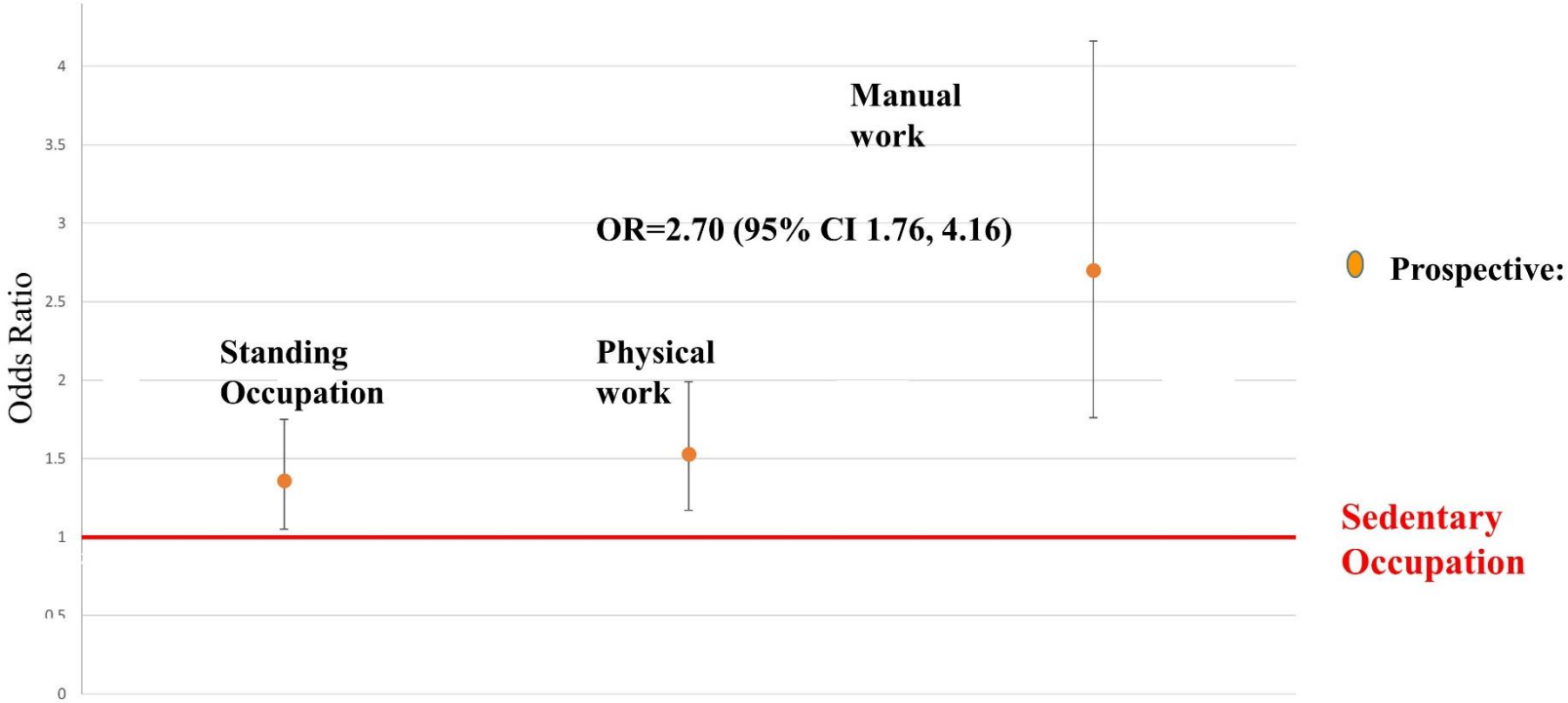
In the first sensitivity analysis, imputing poor performance for missing data made little difference to the odds ratio (Table 5.8), suggesting that the missing data do not reduce the representativeness of the sample. The second analyses based on approximate quartiles of cognitive scores shows a threshold relationship with physical inactivity (Table 5.9). Using groups of approximate quartiles (Table 5.10), the associations for most of the tests, were similar to those observed in the main analyses (Table 5.4). There was little or no association between habitual inactivity and cognition. Changing the grouping made little difference on the overall findings. Given that this study is in apparently healthy older adults, the more stringent cut-off as used in the main analysis is more appropriate.

Figure 5.2: Diagrammatic representation of the cross-sectional and prospective relationship between poor cognition and inactivity for (1) habitual (total), (2) for leisure and (3) for work.



Diagrammatic representation of the relationship between inactivity and cognitive performance for total habitual, as well as leisure and work time activity separately, at the two time points (men and women combined). The relationship between inactivity and cognition is clearer with the separation of work and leisure time activity. Inactive at leisure is associated with increased risk of poor cognition, whereas inactive at work, is associated with a lower risk of poor cognition

Figure 5.3: Relationship between poor cognition and increasing level of work related physical activity as reported at baseline.



Increasing work related activity has a greater risk of poor performance for those in manual work having almost three times higher risk of poor performance than those with a sedentary job
Abbreviations: CI, Confidence Interval; OR, Odds ratio

Table 5.7: Association between physical activity (leisure and occupational separately) and cognitive performance (using composite score) in the EPIC-Norfolk 3HC Cohort (2006–2010), including pilot data (2004–2006) stratified by education.

Inactive vs Active*	No Qualifications							With Qualifications						
	Inactive, % (N)	Bottom 10th PCTILE			Top 10th PCTILE			Inactive, % (N)	Bottom 10th PCTILE			Top 10th PCTILE		
		OR	(95% CI)	P-Value	OR	(95% CI)	P-Value		OR	(95% CI)	P-Value	OR	(95% CI)	P-Value
Leisure Activity														
Cross-sectional (N=6002)	56.5 (831)	1.17	(0.79, 1.73)	0.4	1.30	(0.61, 2.76)	0.5	43.9 (1988)	1.35	(1.00, 1.81)	0.05	0.94	(0.73, 1.22)	0.7
Prospective (N=6057)	49.8 (743)	1.17	(0.79, 1.73)	0.4	1.30	(0.61, 2.76)	0.5	40.4 (1842)	1.35	(1.00, 1.81)	0.05	0.94	(0.73, 1.22)	0.7
Work Activity														
Cross-sectional (N=2756)	16.7 (81)	0.57	(0.22, 1.47)	0.2	1.22	(0.37, 3.99)	0.7	48.6 (1104)	0.64	(0.43, 0.94)	0.02	1.29	(1.02, 1.62)	0.03
Prospective (N=5020)	23.5 (263)	0.57	(0.35, 0.93)	0.02	1.00	(0.45, 2.18)	1.00	44.8 (1747)	0.71	(0.54, 0.94)	0.02	1.17	(0.97, 1.42)	0.1

*Active=reference category ǂ 11-89 PCTILE =reference category

Table 5.8: Sensitivity Analysis I -Association between physical activity (leisure and occupation time separately) with cognition (using composite score only) in the EPIC-Norfolk Cohort by including those with missing data as being in poor performance group for each test.

	Model 3							Model 4***						
Inactive vs Active*	**REF****		**Bottom 10th PCTILE**			**Top 10th PCTILE**		**REF ****		**Bottom 10th PCTILE**			**Top 10th PCTILE**	
	OR	**OR**	**(95% CI)**	**P-Value**	**OR**	**(95% CI)**	**P-Value**	**OR**	**OR**	**(95% CI)**	**P-Value**	**OR**	**(95% CI)**	**P-Value**
Leisure Activity Only														
Cross-Sec (N=8386)	1.00	1.17	(1.01, 1.36)	0.03	0.92	(0.79, 1.06)	0.2	1.00	1.23	(0.97, 1.58)	0.1	0.95	(0.75, 1.20)	0.6
Prospective (N= 8457)	1.00	1.05	(0.91, 1.21)	0.5	1.03	(0.89, 1.20)	0.6	1.00	1.06	(0.89, 1.27)	0.5	0.87	(0.71, 1.06)	0.2
Work Activity Only														
Cross-Sec (N=3769)	1.00	0.74	(0.56, 0.97)	0.03	1.29	(1.07, 1.56)	0.01	1.00	0.64	(0.43, 0.94)	0.02	1.28	(1.03, 1.59)	0.02
Prospective (N= 6892)	1.00	0.72	(0.60, 0.88)	0.001	1.26	(1.08, 1.47)	0.003	1.00	0.66	(0.51, 0.85)	0.001	1.18	(0.99, 1.40)	0.07
Total activity														
Cross-Sec (N=8386)	1.00	1.11	(0.96, 1.29)	0.1	0.91	(0.78, 1.07)	0.3							
Prospective (N= 8457)	1.00	1.02	(0.87, 1.21)	0.7	1.23	(1.03, 1.46)	0.02							

Model 3: Adjusted age per 5 years increase (at time of cognitive testing, or 3HC), sex, education (at 3 levels, 1/no qualifications, 2/O and A level and 3/degree and above from baseline) social class (at two levels, manual and non-manual from baseline) prevalent disease (at baseline and time of cog testing, 3HC) and smoking (at two level, smokers vs non-smokers, all co-variates measures entered from baseline and at 3HC separately
(Reference categories are active* and 11^{th}-89^{th}** percentile group respectively)
***Model 4: As in model 3 with further adjustment for total physical activity as categorical variable

Table 5.9: Sensitivity Analysis II showing age and sex adjusted association by approximate quartile group

		Model 1		
		OR	**(95% CI)**	**P-Value**
	Freq, N			
Cross-sectional				
SF-EMSE	**8368**			
G1	2261	1.44	(1.21, 1.70)	<0.001
G2	2252	1.18	(1.00, 1.40)	0.05
G3	2863	1.16	(0.99, 1.37)	0.07
G4	992	1.00		
Prospective				
SF-EMSE	**8483**			
G1	2305	0.94	(0.78, 1.14)	0.6
G2	2276	0.91	(0.76, 1.10)	0.3
G3	2898	0.97	(0.81, 1.16)	0.7
G4	1004	1.00		
Cross-sectional				
HVLT	8028			
G1	1998	1.35	(1.17, 1.56)	<0.001
G2	2482	1.21	(1.05, 1.38)	0.01
G3	1621	1.09	(0.94, 1.26)	0.3
G4	1927	1.00		
Prospective				
HVLT	**8138**			
G1	2036	0.91	(0.77, 1.07)	0.2
G2	2514	0.87	(0.75, 1.01)	0.07
G3	1640	0.88	(0.75, 1.04)	0.1
G4	1948	1.00		
Cross-sectional				
FTMS	**7352**			
G1	2030	1.18	(1.00, 1.38)	0.05
G2	2067	1.11	(0.95, 1.29)	0.2
G3	1984	1.05	(0.90, 1.23)	0.6
G4	1271	1.00		
Prospective				
FTMS	**7461**			
G1	2074	0.87	(0.72, 1.04)	0.1
G2	2093	0.93	(0.83, 1.18)	0.9
G3	2012	1.03	(0.87, 1.23)	0.7
G4	1282	1.00		
Cross-sectional				
PW_Acc	**8296**			
G1	2071	1.05	(0.92, 1.21)	0.5
G2	2198	1.02	(0.89, 1.17)	0.8
G3	2131	1.02	(0.89, 1.17)	0.8
G4	1896	1.00		
Prospective				
PW_Acc	**8410**			
G1	2105	0.92	(0.78, 1.08)	0.3
G2	2229	1.01	(0.87, 1.18)	0.9
G3	2154	1.05	(0.90, 1.22)	0.6
G4	1922	1.00		

Table 5.9: Continued…

		Model 1		
		OR	(95% CI)	P-Value
	Freq, N			
Cross-sectional				
VST-Simple	**7067**			
G1	1765	1.20	(1.04, 1.39)	0.01
G2	1768	1.09	(0.94, 1.26)	0.3
G3	1776	1.13	(0.98, 1.30)	0.1
G4	1758	1.00		
Prospective				
VST-Simple	**7171**			
G1	1790	1.14	(0.97, 1.34)	0.1
G2	1795	0.99	(0.84, 1.16)	0.9
G3	1795	1.04	(0.88, 1.22)	0.6
G4	1791	1.00		
Cross-sectional				
VST-Complex	**7067**			
G1	1767	1.13	(0.98, 1.31)	0.1
G2	1768	1.06	(0.92, 1.22)	0.5
G3	1768	0.95	(0.83, 1.10)	0.5
G4	1764	1.00		
Prospective				
VST-Complex	**7171**			
G1	1792	1.14	(0.97, 1.34)	0.1
G2	1793	0.99	(0.84, 1.16)	0.9
G3	1794	1.07	(0.91, 1.25)	0.4
G4	1792	1.00		
Cross-sectional				
NART	**8002**			
G1	1803	1.10	(0.96, 1.26)	0.2
G2	2183	1.24	(1.09, 1.41)	0.001
G3	1973	1.10	(0.96, 1.26)	0.2
G4	2043	1.00		
Prospective				
NART	**8112**			
G1	1835	0.77	(0.66, 1.90)	0.001
G2	2219	0.82	(0.71, 0.95)	0.01
G3	2005	0.86	(0.74, 0.99)	0.04
G4	2053	1.00		
Cross-sectional				
Composite Score*	**6061**			
G1	1782	1.37	(1.17, 1.61)	<0.001
G2	1356	1.12	(0.94, 1.32)	0.2
G3	1461	1.12	(0.95, 1.31)	0.2
G4	1462	1.00		
Prospective				
Composite Score*	**6152**			
G1	1820	0.84	(0.70, 1.01)	0.07
G2	1374	0.93	(0.77, 1.12)	0.4
G3	1481	1.05	(0.88, 1.26)	0.6
G4	1477	1.00		

*See Appendix 5 below for details on how the composite score for the above approximate quartile group was created.

Table 5.10: Sensitivity Analysis III showing association between physical inactivity using groups of approximate quartiles

Inactive*	Model 3			Model 4		
	OR	(95% CI)	P-Value	OR	(95% CI)	P-Value
Leisure Activity Only						
(ALL- men and women combined)						
Cross-sectional (N=6002)						
G1 (N=1758)	1.15	(0.98, 1.36)	0.09	1.08	(0.82, 1.41)	0.6
G2 (N=1349)	1.07	(0.91, 1.26)	0.4	1.18	(0.91, 1.52)	0.2
G3 (N=1442))	1.06	(0.90, 1.23)	0.5	1.02	(0.79, 1.31)	0.9
G4 (N=1453)	1.00			1.00		
Prospective (N=6057)						
G1 (N=1776)	1.07	(0.91, 1.27)	0.5	1.28	(1.04, 1.58)	0.02
G2 (N=1363)	1.02	(0.87, 1.20)	0.8	1.10	(0.89, 1.36)	0.4
G3 (N=1456)	1.09	(0.93, 1.27)	0.3	1.10	(0.89, 1.34)	0.4
G4 (N=1462)	1.00			1.00		
Work Activity Only						
Cross-sectional (N=2756)						
G1 (N=590)	0.49	(0.38, 0.63)	<0.001	0.45	(0.33, 0.63)	<0.001
G2 (N=588)	0.70	(0.55, 0.88)	0.002	0.71	(0.54, 0.94)	0.02
G3 (N=716)	0.91	(0.74, 1.12)	0.4	0.86	(0.67, 1.09)	0.2
G4 (N=862)	1.00			1.00		
Prospective (N=5020)						
G1 (N=1338)	0.57	(0.47, 0.69)	<0.001	0.59	(0.47, 0.74)	<0.001
G2 (N=1091)	0.74	(0.62, 0.89)	0.001	0.74	(0.60, 0.91)	0.01
G3 (N=1271)	0.94	(0.80, 1.11)	0.5	0.94	(0.77, 1.13)	0.5
G4 (N=1320)	1.00			1.00		

*(Reference group=Active)

5.6 Discussion

This analysis of cognition in a mid-life population derived cohort reveals a differential in association between cognition and inactivity during work and leisure. Work related physical activity does not protect against poor cognitive performance. Those reporting an inactive occupation had a lower future risk of poor cognition and were more likely to have higher performance in cognitive tests in later life, a finding most obvious in men.

One limitation of this study is of healthy volunteer bias and lower representation of the poor cognition group. Nevertheless, EPIC-Norfolk still includes a wide range of individuals in terms of social class, education, age and cognitive ability and both men and women as in the general population. [213] Another limitation is the inability to control for other early life indicators such as prior intelligence, early childhood factors, family social economic status and parental education, which are known determinants of cognitive function, [214] but were not available in this cohort.

The use of a self-report measure of physical activity may be criticised as prone to recall biases, and not accurate as an objective measure. This index was derived based on self-reported classification of the level of certain leisure activities and the type of work participants typically did. We did not quantify the level of inactivity. However this index has been validated and shown to predict cardiovascular disease and mortality.[215] Its greatest advantage is its simplicity and usability in different settings. Finally, due to the nature of design of the study as an observational study, adjusting for the unequal distribution of the potential confounders is always limited and there may be residual confounding.

The principal strength of this study is the in-depth exploration of particular types of physical activity and the relationship with cognitive function. Differential associations between work and leisure time inactivity were observed. Varying distribution of these activities in populations, or as in this study, at different time points, may influence associations observed. This has not been explored previously. We also report differences across socio-demographic factors. Other cohorts have been limited in their breadth of sociodemographic factors, with either insufficient [206] or over-representation of more educated, 'white collar' or affluent individuals. [113,216]

Physical inactivity during leisure time was more strongly associated with poor performance for men in the cross-sectional analysis and the inverse relationship between inactivity during work was stronger in women. However, in terms of high performance, occupational inactivity was stronger for men only. The reasons for this may well reflect the use of partner's occupation for classifying women's social class. A woman classified by her partner's manual social class may not necessarily have the same

physical activity patterns as her partner, although, this could be further evidence of confounding by social class.

Unlike others studies, we observed little evidence of reverse causation. [113,205,206,208] The differential relationship between inactivity and cognitive function was only revealed by stratifying the components of the physical activity index into work and leisure time activity, something not done previously. Studies reporting reverse causation as a potential bias, have used moderate and severe cognitive impairment including dementia [113,205,206,208] as the outcome measure, with less interest in the milder cognitive dysfunction. Cognitive impairment and dementia have a long prodromal period resulting in individuals having reduced physical activity, and more likely to be lost to follow up.

These results are consistent with other studies, showing a positive relationship with poor cognition and leisure time inactivity [208,217,218] and work-related activity, [206] with increasing physical work of manual workers having a greater risk of poor performance. We also found a physically inactive job (typically a desk job) reduces the risk of poor cognition irrespective of education. This may be because a desk job is likely to be more cognitively demanding than a manual occupation and strengthens the findings of confounding by education, occupation and social class. The observations for leisure activity also provide further evidence of confounding by differential leisure time pursuits according to education and social class.

A number of issues have been addressed in response to reports calling for stronger evidence on physical activity for preventing cognitive decline, impairment and dementia. [11,219] Despite adjusting for a range of co-factors including education, social class and health, other studies have not been able to adequately address the issue of residual confounding. We conclude that the relationship between inactivity and cognition is complex and risk factors are not independent of each other. Though promoting physical activity can do no harm, policy makers must be transparent about the evidence and the limitations of confounding before embarking on any health promotion strategies so not to lose public support by giving mixed messages.

Further studies are needed, in particular, on inequalities across socio-economic groups and the impact of lower education, poor quality work (shortage of beneficial physical and mental stimulation), particularly for manual labour, and the lack of opportunity and space to be physically active for leisure. All these are key drivers that provide fewer opportunities to build cognitive reserve to protect for cognitive impairment and dementia in later life. [212] Future studies should use methods that clearly

discriminate between work and leisure, and be more specific on the nature of inactivity with good representation across socio-economic groups.

Summary of Chapter

- For most tests, there was little or no relationship between total (habitual) inactivity and cognition.
- Leisure inactivity seemed to increase risk of poor performance, cross-sectionally (OR=1.27 (95% CI 1.00, 1.61 P=0.05), but no association observed prospectively.
- In contrast to leisure time, inactivity during work was associated with lower risk of poor performance (observed in both cross-sectional and prospective analyses).
- Those with no qualifications were less likely to be inactive at work and more likely to be inactive at leisure.
- Increased work related physical activity (as reported at baseline), was associated with increased risk of poor performance with manual workers having a greater risk of poor performance than those with physically inactive occupations; OR=2.70 (95%CI 1.76, 4.16 P<0.001).

Chapter 6: Cognitive Performance and Mortality

The work presented in this Chapter has been published:

Hayat, S. A., Luben, R., Dalzell, N., Moore, S., Hogervorst, E., Matthews, F. E., Khaw, K.T. (2018). Understanding the relationship between cognition and death: a within cohort examination of cognitive measures and mortality. Eur J Epidemiol, 33(11), 1049-1062.

6.1 Summary

Despite several studies demonstrating an independent and inverse association between cognition and mortality, the nature of this association still remains unclear. In this chapter, associations of cognition and mortality were examined after accounting for sociodemographic, health and lifestyle factors, again exploring both the test and population characteristics that may influence this relationship.

Participants with cognition data from 3HC were followed up until 2016 for mortality. The relationship between individual cognitive tests and the global cognition composite score (EPIC-COGComp) and mortality was examined as was whether the ability in predicting mortality differed by population characteristics. Risk of death was estimated using Cox proportional hazard regression models including sociodemographic, lifestyle and health variables, and self-reported comorbidities, as covariates in the models.

Poor cognitive performance (bottom quartile of combined cognition score) was associated with higher risk of mortality, Hazard Ratio= 1.32 (95% Confidence Interval 1.09, 1.60); individual cognitive tests varied in their mortality associations and also performed differently in middle-age and older age groups. Poor cognitive performance is independently associated with higher mortality. This association is observed for global cognition and for specific cognitive abilities. Associations varied depending on the cognitive test (and domain) as well as population characteristics, namely age and education.

6.2 Introduction

Studies have shown increased risk of mortality with dementia [134,220,221] and cognitive impairment. [39,119,120] However, in an ageing population, understanding the nature of this relationship across the continuum may provide insight into the different trajectories of decline. Poor cognitive function or mild impairment has also been shown to be independently associated with subsequent mortality, [121,130,181,222] both when measured globally and by specific cognitive domain. [121,131,223] It is important to investigate whether less severe cognitive dysfunction or poor cognition has a higher mortality risk, not only because it precedes cognitive impairment and dementia, [33–35] but also because it is likely to affect more individuals than those with impaired cognition and dementia as defined using accepted criteria. Studies examining association of milder cognitive difficulties with impending death have shown to be inconsistent. [39,119,224]

Associations between cognition and mortality have been reported in late, [132,225] and at mid-life. Cross study comparisons are difficult due to differences in methodologies used. These include: inconsistencies in accounting for covariates that are associated with both cognitive function and mortality; [130,131,226,227]using different cognitive tests; the use of selected groups, such as older

individuals, [228–231] or clinical patients, [123] both of which are more likely to have co-existing morbidities. This has resulted in studies reporting different associations with mortality. [131,133,223,232] The earlier hypotheses of terminal cognitive effects being greater in middle age and younger old and diminishing in later life have been refuted [130] and shown to continue to exist into oldest age, studies examining these age related differences in community dwelling older individuals have been limited.

The main aim of this chapter was to investigate how specific cognitive abilities differ in predicting mortality comparing this to a global cognition score after controlling for a range of known sociodemographic, health and lifestyle factors. We also examine the influence of the characteristics of the population tested on this relationship, namely age and education.

6.3 Methods

6.3.1 Participants and measurements

An overview of the EPIC-Norfolk 3HC methods have been described in Chapter 2. Specific methods for the work presented in this chapter are given here.

6.3.2 Assessment of cognition

For this analysis, the EPIC-Norfolk cognition battery, as described in Chapter 2. Again, as in Chapter 5, both the available outcome measures VST-simple and VST-complex were included in the analyses as separate measures.

6.3.3 Covariates

Covariates from both baseline and at time of cognitive testing were used. Weight from the 3HC was measured to the nearest 0.1kg (using digital scales, Tanita) and height was measured with a stadiometer (Chasmores, UK) to the nearest 0.1 cm to calculate body mass index (BMI: weight (in kilograms) divided by height (in meters squared)). Education (the highest level attained) and social class were obtained from the baseline questionnaire. Education was categorised into three groups (i) No qualification (not completing school up to the age of 16), (ii) Completion of school up to the age of 16 or up to the age of 18 and finally (iii) those obtaining an education to graduate level (those who obtained a degree or equivalent) or above. Social class was dichotomised, into ‘non manual’ and ‘manual’ class. Self-report of smoking status (current, former or never smoker) and alcohol intake (Units/Week) were obtained from health and lifestyle questionnaire administered at the time of the

clinic appointment. Alcohol units were categorised into three groups: 0 Units, 1-14 Units and more than 14 Units.

Physical activity index from the time of cognitive testing (at the 3HC) was used here as described in Chapter 2 and Appendices 2 and 3. Age (at 3HC) was categorized into 5-year age bands. History of heart-attack, stroke, cancer, diabetes and depression were established using self-report of a range of conditions from health and life style follow up questionnaire from the nearest point of the 3HC.

6.3.4 Mortality

Participants were followed up from the date of the cognitive examination until the date of their death or end of 31 March 2016, an average of 7.1 years. The cohort is linked to the NHS Central Register (NHS Digital) for health and the Office of National Statistics (UK) for death certification.

6.3.5 Missing cognition data

A number of sensitivity analyses were conducted to explore the effect of missing data. Hazard ratios were examined by assigning participants with missing data to either the poor performance or to the reference category. Hazard ratios also examined for individuals with data on all eight cognitive measures and the specified covariates (n = 5971) and compared to those with complete missing data of any of the eight cognitive measures as well as those not attending the health examination.

6.4 Analysis

Previously, poor performance was defined as obtaining a score less than a cut-off point corresponding to approximately the 10th percentile of the population distribution in each of the eight cognitive measures individually. Here, in order to have sufficient power for the analyses, the 25th percentile of the population distribution was used. Participants were classified into two groups based on the cut-off scores for each of the tests. For prospective memory, as with previous analyses, poor performance was defined as those failing the task.

The composite score was created as detailed Appendix 5. For this chapter, EPIC-the composite score was created from the individual cognitive test and participants classified in two groups for the continuous composite score in the same way as the scores were for the individual test, based on groups of approximate quartiles. Briefly, for each of the individual cognition tests, a score of ‘0’ or ‘1’ was assigned based on whether the individual was in the ‘poor performance’ or ‘good performance or reference’ group for each of the eight cognitive outcome measures individually. The composite score was calculated as a sum of the score based on the performance group for all eight cognition test

outcomes (range= 0-8). The approximate bottom quartile for the composite score, was used to define poor performance for 'g'.

Preliminary examination across groups of approximate quartiles (due to the non- parametric distribution) did not show a linear relationship with mortality for all the cognitive tests (Table 6.1). There seemed to be a more threshold response, with the lowest (approximate quartile) group having greater mortality than the other groups.

The risk of death was estimated as a hazard ratio with 95 percent confidence interval (95%CI) for each of the cognitive tests in separate Cox proportional hazard regression models. The independent association of poor performance with mortality was assessed by first adjusting for age (per 5 years, treated as a continuous variable) and sex (models 1), then including education and social class (models 2) and finally extending the models to include other health variables (smoking, BMI, physical activity) and comorbidities (models 3).

Education, social class, physical activity and smoking were all treated as categorical variables in the analysis, as was co-morbidity (as present or not). Low and high BMI have stronger association with mortality than the intermediate groups (Table 6.2), however initial exploratory analyses showed little difference in hazard ratio when BMI was entered as a categorical (as low, normal, overweight and obese groups) or as a continuous variable. Therefore, BMI was entered in the model as a continuous variable to improve sensitivity of the analysis. The cognitive score was entered as a dichotomised variable based on the description above (poor performance or not). Including alcohol did not change the associations observed and so to reduce degrees of freedom and to increase stability of the models, we did not include alcohol in the final analysis.

Table 6.1: Age and sex adjusted association with mortality across performance group (approximate quartile) for each cognitive test for participants taking part in EPIC-Norfolk, 2006-2011 (including Data from the Pilot Phase 2004–2006).

		Deaths in each group	Age and sex adjusted model		
	Range of score or time	ǂ Freq, % (N)	HR	(95% CI)	P-Value
SF-EMSE					
G1 (N=2305)	0-31	14.6 (337)	1.23	(0.92, 1.66)	0.2
G2 (N= 2276)	32-33	9.6 (219)	1.03	(0.76, 1.39)	0.9
G3 (N=2898)	34-35	7.6 (219)	1.02	(0.75, 1.37)	0.9
G4 (N=1004)*	36-37	5.4 (54)	1.00		
		p=<0.001			
HVLT					
G1 (N=2037)	0-22	15.1 (308)	1.22	(0.97, 1.53)	0.09
G2 (N=2514)	23-26	9.7 (243)	1.11	(0.88, 1.39)	0.4
G3 (N=1640)	27-29	6.0 (99)	0.80	(0.61, 1.05)	0.1
G4 (N=1948)*	30-36	5.9 (114)	1.00		
		p=<0.001			
FTMS					
G1 (N=2074)	0-13	14.3 (296)	1.08	(0.84, 1.41)	0.5
G2 (N=2093)	14-16	9.2 (192)	0.94	(0.71, 1.22)	0.6
G3 (N=2012)	17-18	7.4 (148)	0.90	(0.68, 1.19)	0.5
G4 (N=1282)*	19-26	5.9 (76)	1.00		
		p=<0.001			
PW-Accuracy					
G1 (N=2337)	-31, 9	15.0 (351)	1.57	(1.24, 1.97)	<0.001
G2 (N=1872)	10-12	9.9 (185)	1.28	(1.00, 1.63)	0.05
G3 (N=2144)	13-16	8.0 (172)	1.22	(0.95, 1.57)	0.1
G4 (N=2057)*	17-54	4.9 (100)	1.00		
		p=<0.001			

Table 6.1: Continued

			Age and sex adjusted model		
	Range of score/time	[i] Deaths in each group, % (N)	HR	(95% CI)	P-Value
VST_Simple (ms)					
G1 (N=1788)	694.11-4078.32	12.4 (222)	1.30	(1.03, 1.63)	0.03
G2 (N=1786)	623.79-694.00	9.5 (169)	1.11	(0.87, 1.40)	0.4
G3 (N=1783)	579.15-623.75	7.3 (131)	0.99	(0.77, 1.27)	0.9
G4 (N=1787)*	453.11-579.11	6.4 (115)	1.00		
		p=<0.001			
VST_Complex (ms)					
G1 (N=1786)	2387.29-11 825.88	13.8 (247)	1.30	(1.04, 1.63)	0.02
G2 (N=1786)	2157.80-2387.16	8.3 (149)	1.06	(0.83, 1.35)	0.6
G3 (N=1786)	1955.37-2157.64	7.1 (126)	0.99	(0.77, 1.28)	0.9
G4 (N=1786)*	458.90-1955.31	6.4 (115)	1.00		
		p=<0.001			
Short-NART					
G1 (N=1835)	25-50	9.6 (176)	0.91	(0.74, 1.12)	0.4
G2 (N=2219)	16-24	9.2 (205)	0.91	(0.75, 1.11)	0.3
G3 (N=2005)	10-15	8.8 (177)	0.91	(0.74, 1.11)	0.3
G4 (N=2053)*	0-9	9.3 (191)	1.00		
		p=0.8			

[i]P values by T test or Chi sq for proportion

G1-G4 are approximate quartile, with G1 being the lowest approximate quartile and G4, the highest. *Reference group (G4)

Abbreviations: CI, Confidence interval HVLT, Hopkins Verbal Learning Test, ms, milliseconds; : N, Number; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; ; Pros. Mem, Prospective memory; PW-Acc, PW-Accuracy, SD, Standard deviation; SF-EMSE, Short Form Extended Mental State Exam; Sh-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

Table 6.2: Distribution of deaths by body mass index (BMI) category

		Deaths	Age and Sex adjusted		
	Freq	Freq, % (N)	HR	(95% CI)	P-Value
>20-25 kg/m2 (Normal)	2854	8.8 (250)	1.00		
<=20 kg/m2 (Low)	216	15.7 (34)	2.17	(1.51, 3.11)	<0.001
>25-30 kg/m2 (Overweight)	3890	9.7 (379)	0.94	(0.80, 1.10)	0.4
>30 kg/m2 (Obese)	1643	11.4 (187)	1.32	(1.09, 1.59)	0.004
		*P=0.001			

In addition, the interaction terms 1/ age group (≤ 65 and those >65 years x each cognition test as the dichotomized variable) and 2/ education group (Qualifications and No Qualifications x each cognition test as the dichotomized variable) were included to examine if age or education group contributed to performance for each test. Due to the strong influence of age and education on both cognition and mortality, the data were also stratified into age and education groups and adjusted hazard ratios calculated in each group. Stratification not only allows the examination of possible interaction, but examining the consistency of association in the different groups, permits the exploration of further potential confounding.

Spearman's rank correlation coefficients were calculated using the continuous score for each of the individual tests, to examine the strength of relationship between each of the tests (as shown previously in Chapter 3). The final analysis (model 4) mutually adjusted for all eight cognitive measures (entered as dichotomised variables as described above). Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA), with the level of significance set at 0.05.

6.5 Results

After a maximum of 11.5 years of follow up (with an average of 7.1 years), there were 861 deaths in the 8623 participants taking part in EPIC-Norfolk 3HC. There were 849 deaths observed in the 8585 participants who had a cognitive tests measure (9.9% of the EPIC-Norfolk 3HC cohort). **Figure 6.1** summarises participation level at each phase and the selection of the analytical sample for this study.

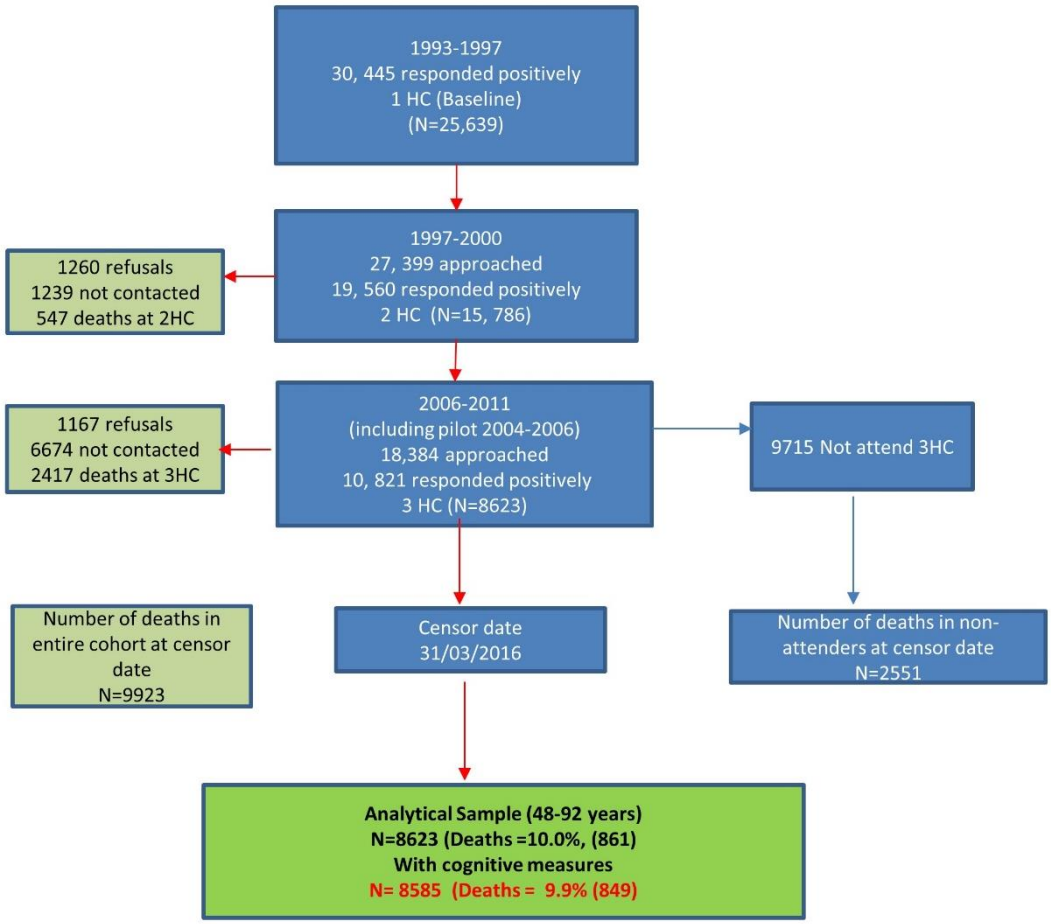
Table 6.3 shows the means and proportions of the variables included in this analysis by survival status. There were significant differences between the two groups for almost all the variables examined. Those who died, were older, more likely to be men, have no qualifications, be physically inactive, to

be non-drinkers, less likely to have been never smokers, and a higher proportion reported prevalent disease. Of the 8585 participants with cognitive data, 6128 participants had data for all the cognitive tests with 2457 having some of the test measures and 38 participants having none. These 38 participants were not included in the main analysis.

Compared to those with incomplete or no data, those having attempted all the tests were younger, had higher average scores for all the tests, reported less co-morbidity, were less likely to be physically inactive, have no qualifications and be non-drinkers (Table 6.4). The age and sex adjusted hazard ratios for mortality for those who attended the health check and those who were invited but did not attend were examined. Using the group who had attended 3HC and had data on all 8 tests as reference, the mortality risk were as follows: with data on 1-7 tests, HR=1.23 (95%CI 1.07, 1.41 P= 0.004); attended 3HC, but with no cog data HR=1.71 (95%CI 0.96, 3.03 P= 0.07) and for those who were invited but did not attend 3HC, HR=2.33 (95%CI 2.11, 2.56 P= <0.001).

Table 6.5 shows the results of the Cox proportional hazards analyses for all the tests separately and for the composite score. For the age and sex adjusted models, there was an increased risk of mortality in those obtaining a poor performance score as compared to those who did not for each of the cognitive tests apart from the Short-NART. Additional adjustment for education and social class made little difference to the hazard ratios, as did the additional adjustment for co-variates (smoking, body mass index, physical activity) and comorbidities (models 3). Although the magnitude of the association varied slightly across the different tests, the PW-Accuracy test showed the strongest association, and was comparable to the association observed for the composite score.

Figure 6.1 Selection of participants from EPIC-Norfolk 3HC (including the pilot phase) for all-cause mortality, followed up until March 2016.



Source: Hayat et al., EJE, 2018 [233]

In the sensitivity analysis, imputing missing into the poor performance made little difference to the hazard ratios (with slightly strengthening associations for some), but attenuating considerably for most of the tests including the composite score when 'missings' were assigned to the reference category (Table 6.6). Thus indicating that the 'missings' were likely to be in the poor performance group. Further sensitivity analyses, to compare those with measures on all eight tests, with those with seven tests or less, showed associations that were similar to those seen in the whole cohort analysis. Associations were statistically significant and stronger for participants with data on all eight tests, and considerably attenuated for those with data on seven tests or less. In the latter group, associations were observed for PW-Accuracy, VST complex and prospective memory, although not to significance. There was little or no association for the remaining tests for those with incomplete data (Table 6.7).

No significant interaction was observed with age group (≤65 vs >65 years) and any of the cognitive test (data not shown) and for education, only significant for HVLT (P=0.03) but none of the other tests. On stratification, there seem to be some age group differences, with significant and stronger associations observed for the composite score, HVLT, PW-Accuracy and VST-Complex (Table 6.8) in the middle-age group. Weaker and mostly significant associations observed for composite and for all the other tests, except short-NART in the older age group. Stratifying by education group, associations with mortality were observed in the 'no qualifications' sub group for all tests apart from HVLT and weak but not significant for NART. Only weak (or no) association were observed in the 'with qualifications' sub group for all tests with strongest association observed for HVLT, PW-Accuracy and the composite score. (Table 6.8). The confidence intervals overlapped in both the age and education sub-groups.

Table 6.3: Characteristics by survival status of 8585 participants with cognitive measures in the Third Health Check Phase of the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk 3HC) Study, 2006-2011 (including pilot data, 2004–2006). Participants followed up until 31 March 2016.

		Dead		**Alive**	
		n=849		**n=7736**	**P-Value**
Mean (SD)					
Age	75.6	(7.7)	67.9	(7.7)	<0.001
Body Mass Index (Kgs/M^2)	27.1	(4.6)	26.8	(4.3)	0.8
Cognitive Test Score					
SF-EMSE	31.4	(4.1)	32.7	(3.0)	<0.001
HVLT	22.6	(6.3)	25.3	(5.5)	<0.001
PAL- FTMS	14.0	(4.8)	15.8	(4.2)	<0.001
PW-Accuracy	10.1	(6.4)	12.7	(6.0)	<0.001
VST-simple (Reaction Time, ms)	711.01	(211.3)	659.4	(160.7)	<0.001
VST-Complex (Reaction Time, ms)	2320.9	(520.9)	2184.3	(417.03)	<0.001
Short-NART	17.4	(10.2)	17.2	(9.8)	0.5
Prospective Memory % failed (n)	30.3	(246)	17.5	(1330)	<0.001
Co-morbidity, % (n)					
Heart attack	9.9	(84)	2.7	(207)	<0.001
Stroke	5.7	(48)	1.7	(134)	<0.001
Cancer	15.8	(134)	8.7	(670)	<0.001
Diabetes	5.7	(48)	2.7	(212)	<0.001
Depression	11.5	(98)	8.3	(642)	0.001
Sex, % men (n)	57.4	(487)	43.4	(3354)	<0.001
***Education, % No qualifications (n)**	33.5	(284)	25. 4	(1967)	<0.001
***Social Class, % Manual (n)**	31.0	(261)	34.4	(2634)	0.05
***Physical Activity, % Inactive (n)**	56.8	(471)	35.1	(2678)	<0.001
Smoking Status, % (n)					
Current	5.5	(36)	4.3	(334)	
Former	56.0	(366)	45.1	(3527)	<0.001
Never	38.4	(251)	50.6	(3952)	
Alcohol Intake, % (n)					
0 Units	34.1	(275)	29.3	(2187)	
1-14 Units/week	53.8	(343)	59.3	(4419)	0.01
>14 Units per week	11.6	(94)	11.4)	(849	

P values by T test or Chi square for proportion
Abbreviations: HVLT, Hopkins Verbal Learning Test, ms, milliseconds; : N, Number; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; PW-Acc, PW-Accuracy, SD, Standard deviation; SF-EMSE, Short Form Extended Mental State Exam; Short-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test.

* Reference categories: With Qualifications; Non-manual and Active (respectively).

Table 6.4: Comparison of Characteristics of 6128 participants of the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk) Study with all 8 cognitive measures and those with incomplete or no data.

	All 8 tests (N=6128)		1-7 Tests (N=2457)		No Cog Data (N=38)		P-Value
Mean (SD)							
Age	68.0	(7.7)	70.4	(8.6)	73.9	(9.4)	<0.001
Body Mass Index (Kgs/M²)	26.8	(4.3)	26.9	(4.4)	27.4	(4.7)	0.5
Cognitive Test Score							
SF-EMSE	32.9	(2.7)	32.0	(4.0)	-		<0.001
HVLT	25.3	(5.5)	24.4	(6.1)	-		<0.001
PAL- FTMS	15.8	(4.2)	14.9	(4.7)	-		<0.001
PW-Accuracy	12.6	(6.1)	11.9	(6.1)	-		<0.001
VST-Simple	660 .6	(147.6)	684.0	(251.4)	-		<0.001
VST-Complex	2186.8	(394.6)	2255.0	(592.7)	-		<0.001
Short-NART	17.2	(9.8)	17.4	(10.1)	-		0.4
Pros. Mem % failed (n)	18.2	(1117)	20.2	(459)	-		0.04
Percent % (N)							
Sex, men	44.8	(2747)	44.5	(1094)	52.6	(20)	0.6
*Education, No qualifications	24.6	(1510)	30.2	(741)	47.4	(18)	<0.001
*Social Class, Manual	33.5	(2035)	35.3	(860)	28.9	(11)	0.2
*Physical Activity, Inactive	35.9	(2168)	40.4	(981)	60.0	(21)	<0.001
Co-morbidity							
Heart attack	3.0	(186)	4.3	(105)	5.3	(2)	0.01
Stroke	1.8	(113)	2.8	(69)	7.9	(3)	0.001
Cancer	9.1	(559)	10.0	(245)	10.5	(4)	0.5
Diabetes	2.9	(179)	3.3	(81)	5.3	(2)	0.5
Depression	21.8	(1336)	21.5	(528)	31.6	(12)	0.3
Mortality, Dead	6.7	(410)	10.6	(261)	31.6	(12)	<0.001
Smoking, Current	4.4	(263)	4.4	(107)	5.7	(2)	0.9
Alcohol Intake Units/week							
0	28.1	(1657)	34.0	(805)	36.4	(12)	
1-14	60.5	(3566)	54.6	(1291)	57.6	(19)	<0.001
>14	11.4	(674)	11.4	(269)	6.1	(2)	

Hazard ratios (Age and Sex adjusted)

8 Tests	1-7 Tests		0 Tests		Non-Attenders	
HR	HR	95% CI	HR	95% CI	HR	95% CI
1.00 (Ref)	1.23 p= 0.004	(1.07. 1.41)	1.71 p=0.07	(0.96, 3.03)	2.33 p=<0.001	(2.11, 2.56)

P values by Anova, T test or Chi sq for proportion Reference categories: Any qualifications, Non-manual and Active

Abbreviations: HVLT, Hopkins Verbal Learning Test, ms, milliseconds; : N, Number; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; Pros. Mem, Prospective memory task; PW-Acc, PW-Accuracy, SD, Standard deviation; SF-EMSE, Short Form Extended Mental State Exam; Short-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

Table 6.5: Association between poor performance and mortality for eight cognitive measures separately in the EPIC-Norfolk Cohort (2006–2010), including pilot data (2004–2006) over 11 years of follow up.

				Model 1			Model 2				Model 3			
	* Range	N	Frequency Mortality % (n)	HR	95% CI	P-Value	N	HR	95% CI	P-Value	N	HR	95% CI	P-Value
SF-EMSE		**8483**					**8402**				**8273**			
Good	32,37	6178	8.0 (492)	1.00				1.00				1.00		
Poor	0, 31	2305	14.6 (337)	1.21	1.05, 1.39	0.01		1.22	1.05, 1.41	0.01		1.17	1.00, 1.36	0.05
			p<0.001											
HVLT		**8139**					**8063**				**7944**			
Good	22, 36	6102	7.5 (456)	1.00				1.00				1.00		
Poor	0, 21	2037	15.1(308)	1.21	1.04, 1.41	0.01		1.21	1.03, 1.41	0.02		1.19	1.01, 1.40	0.03
			p<0.001											
PAL-FTMS		**7461**					**7390**				**7273**			
Good	14, 26	5387	7.7 (416)	1.00				1.00				1.00		
Poor	0, 13	2074	14.3 (296)	1.16	1.00, 1.36	0.05		1.16	1.00, 1.36	0.06		1.18	1.01, 1.38	0.04
			p<0.001											
PW-Acc		**8410**					**8331**				**8205**			
Good	10, 54	6073	7.5 (457)	1.00				1.00				1.00		
Poor	-31, 9	2337	15.0 (351)	1.31	1.14, 1.52	P<0.001		1.33	1.15, 1.54	P<0.001		1.33	1.15, 1.54	P<0.001
			p<0.001											

Table 6.5: Continued

				Model 1			Model 2				Model 3			
	*** Range**	**N**	**Frequency Mortality % (n)**	**HR**	**95% CI**	**P-Value**	**N**	**HR**	**95% CI**	**P-Value**	**N**	**HR**	**95% CI**	**P-Value**
VST- Simple		**7144**					**7074**				**6963**			
Good	453.1, 694.0	5356	7.7 (415)	1.00				1.00				1.00		
Poor	694.1, 4078.3	1788	12.4 (222) p<0.001	1.25	1.06, 1.48	0.01		1.23	1.04, 1.46	0.02		1.22	1.03, 1.45	0.02
VST-complex		**7144**					**7074**				**6963**			
Good	458.8, 7291.1	5358	7.3 (390)	1.00				1.00				1.00		
Poor	849.2, 11825.8	1786	13.8 (247) p<0.001	1.28	1.08, 1.50	0.004		1.28	1.08, 1.51	0.003		1.26	1.07, 1.50	0.01
Short-NART		**8112**					**8030**				**7907**			
Good	0, 24	6277	9.1 (573)	1.00				1.00	0.85, 1.29			1.00		
Poor	25, 50	1835	9.6 (176) p=0.6	0.98	0.82, 1.16	0.8		0.97	0.81, 1.16	0.7		0.97	0.80, 1.17	0.7
Prospective Memory		**8403**					**8324**				**8199**			
Success		6827	8.3 (567)	1.00				1.00				1.00		
Failure		1576	15.6 (246) p<0.001	1.25	1.08, 1.46	0.004		1.25	1.07, 1.46	0.01		1.27	1.08, 1.49	0.003
Composite Score		**6128**					**6067**				**5971**			
Good	6, 8	4237	6.3 (267)	1.00				1.00				1.00		
Poor	0, 5	1891	13.5 (255) p<0.001	1.27	1.06, 1.53	0.01		1.26	1.04, 1.52	0.02		1.31	1.09, 1.60	0.01

Models 1 adjusted for age and sex; Models 2 adjusted for age, sex, education and social class; Models 3 adjusted for age, sex, education and social class, smoking, body mass index (bmi), physical activity and prevalent disease.

Abbreviations: CI, Confidence interval; HVLT, Hopkins Verbal Learning Test, N, Number; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; PW-Acc, PW-Accuracy, SF-EMSE, Short Form Extended Mental State Exam; Short-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test *Range of score (or in case of VST, reaction time in milliseconds)

Table 6.6: Sensitivity analysis to examine the impact of missing data on association of poor performance with mortality for each cognition score separately and the composite score after adjusting for age, sex, education and social class, smoking, body mass index (BMI), physical activity and prevalent disease. Hazard ratio for risk of death shown for (1) those with no missing values (2) missing values included as poor performers (3) missing values included in the reference (good) performers.

	Original (excluding missing values)				Missing values imputed as poor performers (811/8368)			Missing values imputed as good performers (811/8368)		
	n/N	**HR**	**(95% CI)**	**P-Value**	**HR**	**(95% CI)**	**P-Value**	**HR**	**(95% CI)**	**P-Value**
SF-EMSE	**795/8273**									
Good		1.00			1.00			1.00		
Poor		1.17	(1.01, 1.36)	0.04	1.17	(1.01, 1.36)	0.04	1.16	(1.00, 1.35)	0.05
HVLT	**735/7944**									
Good		1.00			1.00			1.00		
Poor		1.19	(1.01, 1.40)	0.03	1.20	(1.04, 1.39)	0.01	1.13	(0.97, 1.31)	0.1
PAL-FTMS	**685/ 7273**									
Good		1.00			1.00			1.00		
Poor		1.18	(1.01, 1.38)	0.04	1.22	(1.05, 1.42)	0.01	1.13	(0.97, 1.32)	0.1
PW-Acc	**778/ 8205**									
Good		1.00			1.00			1.00		
Poor		1.33	(1.15, 1.54)	<0.001	1.34	(1.16, 1.54)	<0.001	1.30	(1.12, 1.50)	<0.001
VST-Simple	**613/6963**									
Good		1.00			1.00			1.00		
Poor		1.23	(1.03, 1.45)	0.02	1.31	(1.13, 1.51	<0.001	1.12	(0.96, 1.31)	0.2
VST-Complex	**613/ 6963**									
Good		1.00			1.00			1.00		
Poor		1.26	(1.07, 1.50)	0.01	1.28	(1.12, 1.48)	0.001	1.11	(0.94, 1.30)	0.2

Table 6.6: Continued

		Original (excluding missing values)			Missing values imputed as poor performers (811/8368)			Missing values imputed as good performers (811/8368)		
	n/N	**HR**	**(95% CI)**	**P-Value**	**HR**	**(95% CI)**	**P-Value**	**HR**	**(95% CI)**	**P-Value**
Short-NART	**718/ 7907**									
Good		1.00			1.00			1.00		
Poor		0.98	(0.81, 1.18)	0.8	1.04	(0.89, 1.22)	0.6	0.95	(0.79, 1.14)	0.6
Pros. Mem	**784/ 8199**									
Good		1.00			1.00			1.00		
Poor		1.27	(1.08, 1.49)	0.003	1.23	(1.06, 1.44)	0.01	1.26	(1.08, 1.48)	0.004
EPIC-Cog Comp	**504/ 5971**									
Good		1.00			1.00			1.00		
Poor		1.32	(1.09, 1.60)	0.01	1.38	(1.19, 1.61)	<0.001	1.16	(1.00, 1.35)	0.05

Abbreviations: CI, Confidence interval; EPIC- COGComp, Composite score (a summary score based on the performance group using data from all eight cognition test outcomes); Freq, Frequency; HVLT, Hopkins Verbal Learning Test; Mort., Mortality; N, Number in the analyses, n, number of deaths; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; PW-Acc, PW-Accuracy, SF-EMSE, Short Form Extended Mental State Exam; Short-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

Table 6.7: Hazard ratios (95% CI), adjusted for age, sex, education and social class, smoking, body mass index (BMI), physical activity and prevalent disease by individual cognitive tests, for participants with all 8 cognitive measures and those with incomplete data (on 1-7 tests).

	Data with all 8 tests (n=5971)			Data on 1-7 tests (N=Varies according to test)*		
	HR	**(95% CI)**	**P-Value**	**HR**	**(95% CI)**	**P-Value**
SF-EMSE						
Good	1.00					
Poor	1.31	(1.08, 1.58)	0.01	0.98	(0.76, 1.24)	0.8
HVLT						
Good	1.00					
Poor	1.23	(1.02, 1.50)	0.04	1.06	(0.79, 1.41)	0.7
PAL FTMS						
Good	1.00					
Poor	1.24	(1.03, 1.49)	0.02	1.01	(0.73, 1.35)	0.9
PW-Acc						
Good	1.00					
Poor	1.37	(1.14, 1.65)	0.001	1.26	(098, 1.62)	0.07
VST-Simple						
Good	1.00					
Poor	1.31	(1.08, 1.58)	0.01	0.85	(0.56, 1.29)	0.4
VST-Complex						
Good	1.00					
Poor	1.29	(1.07, 1.56)	0.01	1.14	(0.76, 1.70)	0.5
Short-NART						
Good	1.00					
Poor	1.01	(0.81, 1.26)	0.9	0.92	(0.63, 1.34)	0.7
Pros. Mem						
Good	1.00					
Poor	1.31	(1.07, 1.59)	0.01	1.23	(0.94, 1.61)	0.1

*N Varies according to test

SF-EMSE N= 2302

HVLT N= 1973

PAL-FTMS N=1302

PW_Acc N=2234

VST= 992

Sh-NART N=1936

Pros. Mem= 2228

Abbreviations: HVLT, Hopkins Verbal Learning Test, ms, milliseconds; : N, Number; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; PW-Acc, PW-Accuracy, Pros. Mem; Prospective memory task; SD, Standard deviation; SF-EMSE, Short Form Extended Mental State Exam; Sh-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

The data were also tested for reverse causality, which is to examine whether the associations observed were as a result of those with disease pathology (and being closer to death) also having lower cognition. The analyses (model 3) were repeated for each of the tests individually and the composite score by excluding individuals who died within three years of follow-up after cognitive testing (N=229). At population level, the results of the reduced sample did not show evidence of reverse causality with hazard ratios barely changing.

Exclusions of deaths within three years of the cognitive test and then stratifying the data by age group showed a different result from the original stratified analyses. The hazard ratios in the older-age group showed little change (Table 6.10). However the same was not observed for the middle-age group with variations in their prediction of mortality across the different tests. The association for most of the tests were attenuated (and due to small number, were no longer significant). The greatest (and significant) increase in association for the middle-age group was observed for HVLT HR= 2.19 (95% CI 1.20, 4.00). Association were also strengthened for prospective memory. The greatest differences observed across the two age-groups were also seen in HVLT and prospective memory (and remained, though to a lesser degree for composite score). The age group differences observed without exclusion of deaths, no longer remained for PW-Accuracy and VST-Complex.

Correlations between the different cognitive tests were weak to modest, as discussed previously (Table 3.5, Chapter 3) with the strongest between the HVLT (verbal episodic memory) and SF-EMSE (global cognition), r=0.48 and the weakest between the VST-Complex and Short-NART r= 0.06. Therefore, collinearity was not considered to be an issue when including all cognitive measures in the final model. The PW-Accuracy test remained the strongest independent predictor of mortality after mutually adjusting for all the other cognitive abilities (Table 6.11)

Table 6.8: Association of poor performance and mortality, stratified by age group (equal to or younger than 65 years and over 65 years) in the eight cognitive measures separately and the combined composite cognition score.

	Age ≤ 65 Years				Age > 65 Years			
Test	**n/N**	**HR**	**(95% CI)**	**P-Value**	**n/N**	**HR**	**(95% CI)**	**P-Value**
SF-EMSE	95/3102	1.19	(0.72, 1.97)	0.5	700/5171	1.17	(1.00, 1.37)	0.05
HVLT	96/3048	1.74	(1.05,2.87)	0.03	639/4896	1.15	(0.97, 1.36)	0.1
PAL-FTMS	91/2843	1.15	(0.68, 1.92)	0.6	594/4430	1.18	(1.00, 1.39)	0.05
PW-Accuracy	95/3088	1.60	(1.01, 2.54)	0.04	683/5117	1.29	(1.10, 1.50)	0.001
VST-Simple	83/2683	1.11	(0.64, 1.92)	0.7	530/4280	1.25	(1.05, 1.50)	0.01
VST-Complex	83/2683	1.68	(1.02, 2.75)	0.04	530/4280	1.23	(1.03, 1.47)	0.02
Short- NART	90/3005	0.80	(0.46, 1.39)	0.4	628/4902	0.99	(0.81, 1.22)	0.9
Pros. Mem	95/3086	1.27	(0.70, 2.30)	0.4	689/5113	1.26	(1.07, 1.49)	0.01
EPIC-COGComp	74/2383	1.76	(1.03, 3.02)	0.04	431/3590	1.28	(1.04, 1.56)	0.02

Abbreviations: CI, Confidence interval; EPIC-COGComp , EPIC-Cognition composite score; HVLT, Hopkins Verbal Learning Test, N, Number included in the analysis; n, number of deaths, PAL-FTMS, Paired Associated Learning, First Trial Memory Score; ; Pros. Mem, Prospective memory; PW-Acc, PW-Accuracy, SF-EMSE, Short Form Extended Mental State Exam; Short-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

Table 6.9: Association of poor performance and mortality, stratified by education group (With Qualification and No Qualifications) in the eight cognitive measures separately and the combined composite cognition score.

	With Qualifications			P-Value	No Qualifications			P-Value
Test	**n/N**	**HR**	**(95% CI)**		**n/N**	**HR**	**95% CI**	
SF-EMSE	526/6117	1.12	(0.92, 1.36)	0.2	269/2156	1.25	(0.97, 1.60)	0.08
HVLT	487/5896	1.33	(1.09, 1.62)	0.01	248/2048	0.99	(0.76, 1.28)	0.9
PAL-FTMS	450/5422	1.06	(0.87, 1.30)	0.6	235/1851	1.43	(1.10, 1.86)	0.01
PW-Accuracy	517/6079	1.31	(1.09, 1.57)	0.004	261/2126	1.41	(1.09, 1.81)	0.01
VST-Simple	411/5205	1.15	(0.93, 1.43)	0.2	202/1758	1.37	(1.03, 1.83)	0.03
VST-Complex	411/5205	1.12	(0.91, 1.39)	0.3	202/1758	1.61	(1.20, 2.15)	0.001
Short- NART	480/5879	0.84	(0.63, 1.11)	0.2	238/2028	1.14	(0.87, 1.49)	0.3
Prosp. Mem	521/6078	1.19	(0.97, 1.46)	0.1	263/2121	1.41	(1.09, 1.83)	0.01
EPIC-COG Comp	342/4508	1.27	(1.00, 1.60)	0.05	162/1463	1.46	(1.03, 2.07)	0.04

Abbreviations: CI, Confidence interval; EPIC-COG Comp, EPIC-Cognition Composite score; HVLT, Hopkins Verbal Learning Test, N, Number included in the analysis; n, number of deaths, PAL-FTMS, Paired Associated Learning, First Trial Memory Score; ; Pros. Mem, Prospective memory; PW-Acc, PW-Accuracy, SF-EMSE, Short Form Extended Mental State Exam; Short-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

Table 6.10: Association between poor performance and mortality for eight cognitive measures separately (Model 3) stratified by age group (≤65 vs > 65 years) after excluding 229 individuals who died within 3 years of cognitive testing.

	Age <=65 Years				Age > 65 Years			
Test	**n/N**	**HR**	**(95% CI)**	**P-Value**	**n/N**	**HR**	**(95% CI)**	**P-Value**
SF-EMSE	65/30722	0.89	(0.47, 1.71)	0.5	521/4992	1.15	(0.96, 1.38)	0.1
HVLT	65/3017	2.19	(1.20, 4.00)	0.01	481/4992	1.22	(1.01, 1.48)	0.04
PAL-FTMS	62/2814	1.05	(0. 55, 2.01)	0.9	455/4291	1.27	(1.05, 1.53)	0.02
PW-Accuracy	65/3058	1.29	(0.72, 2.32)	0.4	509/ 4943	1.27	(1.06, 1.52)	0.01
VST-Simple	52/2652	0.92	(0.44, 1.91)	0.7	398/4148	1.30	(1.06, 1.60)	0.01
VST-Complex	52/2652	1.30	(0.66, 2.56)	0.5	398/4148	1.30	(1.06, 1.59)	0.01
Short- NART	59/2974	0.87	(0.45, 1.71)	0.7	465/4739	0.87	(0. 68, 1.11)	0.3
Pros. Mem	65/3056	1.63	(0.84, 3.2)	0.2	512/4936	1.29	(1.07, 1.57)	0.01
EPIC-COG Comp	46/2355	1.55	(0.76, 3.15)	0.2	331/3490	1.34	(1.07, 1.69)	0.02

Abbreviations: CI, Confidence interval; EPIC-COG Comp, Composite score; HVLT, Hopkins Verbal Learning Test, N, Number included in the analysis; n, number of deaths, PAL-FTMS, Paired Associated Learning, First Trial Memory Score; ; Pros. Mem, Prospective memory; PW-Acc, PW-Accuracy, SF-EMSE, Short Form Extended Mental State Exam; Short-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

Table 6.11: Poor performance as a predictor of mortality using the eight cognitive measures separately as measured in the EPIC-Norfolk 3HC after adjusting for all co-variates and mutually adjusting for all other cognitive measures (Model 4)

		N = 5971 (504 events)	
Test	**HR**	**(95% CI)**	**P-Value**
SF-EMSE	1.17	(0.95, 1.43)	0.1
HVLT	1.07	(0.87, 1.32)	0.5
PAL- FTMS	1.11	(0.91, 1.34)	0.3
PW-Accuracy	1.27	(1.05, 1.54)	0.02
VST-Simple	1.18	(0.97, 1.43)	0.1
VST-Complex	1.19	(0.98, 1.44)	0.08
Short-NART	0.90	(0.72, 1.13)	0.4
Pros. Mem.	1.18	(0.96, 1.45)	0.1

Abbreviations: CI, Confidence interval; HVLT, Hopkins Verbal Learning Test, N, Number included in the analysis; n, number of deaths, PAL-FTMS, Paired Associated Learning, First Trial Memory Score; Pros. Mem, Prospective memory; PW-Acc, PW-Accuracy, SF-EMSE, Short Form Extended Mental State Exam; NART, National Adult Reading Test; VST, Visual Sensitivity Test

6.6 Discussion

Key findings from this chapter show poor cognitive performance to be independently associated with higher mortality over an average of seven years of follow-up. Greater mortality was observed in the lowest (approximate quartile) group, showing the association to be a threshold effect similar to previous reports [168] rather than a gradient across the range of ability. Associations were not only observed for global cognitive function (using the composite score), but also for the individual tests covering a number of abilities or domains [170]. These associations remained after adjusting for sociodemographic, a range of lifestyle and health variables, including prevalent disease. Associations were not observed for the Short-NART. This was expected as accumulated knowledge is known to be more stable than other cognitive abilities until later life. [69,71]

This study confirms the robust relationship between cognition and mortality, [121,130–133] and that the ability to predict mortality not only exists for global cognition, but also across several cognitive domains. [121,131] This is to varying degrees, with some specific abilities to be more powerful predictors than others. Population characteristics, particularly age and education also influenced the relationship and the predictive value of each test. Cognitive impairment, even at mild levels increases the risk of mortality. [134] Unlike previous reports of no association of mild impairment and mortality,

[135] this study has shown this relationship extends beyond to include poor performance, even before any evidence of impairment.

There are three possible explanations for the observed increased associations with mortality; (1)poor performance, which is on the trajectory of cognitive decline, is an early indicator of dementia, which reduces survival time (2) cognition is not related, but the association is confounded by disease pathology (reverse causality) which is having a negative impact on cognition and increasing mortality; (3) poor cognition is having an indirect impact by those with lower cognition unable to engage in appropriate lifestyle and health behaviours, such as healthy diet, being physically active and not smoking. Also having poorer health literacy which may hinder the recognition of signs and symptoms of disease, seek medical attention and follow prescribed medication regimes. It is unclear which of the three possibilities could be in operation, it could be either or all three.

On initial analyses by age group, associations between cognitive test performance and survival were stronger in individuals who were in the middle-age group than those who were over 65 years. However, this may be an artefact of a recognised methodological issue. [130] The majority of the survivors in middle-age group are expected to survive many years beyond the census date, whereas survivors in the older age group (being chronologically closer to death, be frailer, have more co-morbidities and disabilities) are more likely to die soon after the census date. Therefore, there are less differences between the cognitive scores of those who die shortly on either side of the census date in the older group, and the differences between deceased and survivors become more obscure. This incomplete investigation of the effects of survival duration in studies is a known restriction of the survival analysis methods. [130]

There was little evidence of reverse causality at population level in the EPIC-Norfolk cohort when excluding individuals who died within three years of the health examination. Excluding these individuals also removed the differences initially observed by age group, confirming that associations are not restricted to middle age, but continue into older age. [130] However, there was the strengthening of the hazard ratios for HVLT and prospective memory and mortality in the middle-age group, not seen in the older age group. This indicates that dysfunction of memory (both episodic and prospective) is far more detrimental in terms of survival in middle age than it is in later life. These findings concur with those from the Whitehall Study that also showed memory to better predict risk of mortality in midlife. [234]

The other observation to highlight is the variation in the VST measures across the age groups. This shows that the two measures may be assessing different abilities. The measures of VST-Simple may be

a reflection of overall frailty, slowing of simple responses and indicative of accelerated physical ageing in the older age group, and is not as sensitive to normal cognitive ageing and in situations of reasonable motor speed. The reduced differential between the age groups for PW-Accuracy and VST-Complex, after excluding those who died within 3 years indicate the greater significance of processing speed in proximity to death than to chronological age. These functions are known to be affected by physiologic functioning strongly predict mortality. [124]

Investigations in mortality by cause are required to examine these results in more detail. To examine the question of the of different pathologies, is beyond the scope of this paper, as this requires information on cause specific mortalities across the different domains assessed by the EPIC-Norfolk Cognition Battery. In the case of all-cause mortality, individual cognitive domains are generally comparable to the composite score though there are some individual variations. [226]

With regards to education, being in the poor performance group (in general) had a greater disadvantage in terms of survival for the 'no qualifications' group than it did for the 'with qualifications' group. This was observed for the composite score and the individual tests (although not significant for SF-EMSE and NART). The association was not observed in the HVLT, a test of verbal episodic memory, that requires semantic knowledge. [151] Even though social class was adjusted for, it can be speculated, that education adds some advantage to survival that is beyond socio-economic status. These results are line with previous findings, [119] that better cognition does not give the survival advantage in circumstances of better socio-economic conditions as it does in lower socio-economic conditions. Having said that, the overall influence was seen in both education groups, providing further support of the independent relationship cognition and mortality.

In the EPIC-Norfolk population with no overt symptoms of cognitive impairment, this work has shown that the relationship between cognition and mortality exists along the continuum to include poor cognitive performance and that this association is not restricted to the disease states of cognitive impairment and dementia. Although memory deficits are the most common precursors to dementia, prospective memory, processing speed and executive function have also been shown to be strong indicators of decline and mortality. [81,235] This study adds further evidence to the importance of these measures as predictors of mortality in this relatively high functioning population.

Correlations between the cognitive tests were not high, suggesting that they measure different abilities. However, cognitive abilities do not work in isolation or independently of each other, with any given test making demands on a range of abilities. A single test cannot give a pure measure of a single cognitive ability, [235] thus making it difficult to isolate the true contribution of the single measure

being reported. Assessing cognition across domains provides detail to the size and nature of the relationship with mortality.

A relatively large proportion of deaths in the middle age group occurred within 3 years. This may be a reflection of the health of the participants attending the health examination. The younger attendees attending the health examination, may have been available due to ill health stopping them from working or other activities, and older participants were the more able and fitter survivors able to attend the clinic. Both groups may therefore be slightly different from their peers in the general population. The mortality rate in the under 65 group was very small, and would need further numbers to see if the associations observed in this age group are robust.

Having highlighted the limitation of the participants in EPIC-Norfolk as healthier individuals, the cohort still includes a wide age range from mid to later life, is representative of both men and women and covers a broad range of socio-economic and education levels. Conducting this study in this healthier population has the advantage of less confounding from co-morbidities, a limitation in other studies of older or from selected clinical groups. These cognitive measures were part of a wider, comprehensive health examination (maximum length 3 hours). Those who were slower, less able and possibly less healthy individuals had less chance to complete all tests within the limited appointment time. This is further strengthened as associations were observed in healthier individuals with data on all 8 measures, but not in those completing fewer tests, also indicating that conducting this analysis in a less healthy cohort may not have shown similar associations. Various methods have been used to deal with the issue of confounding, including stratification, multi-variate adjustment and excluding people who died within three years of the cognitive test and found associations between cognition and mortality to remain. Nevertheless, residual confounding by other known and unknown risk factors may still be present.

Inconsistencies across studies may also be due to the heterogeneity in methodologies, in terms of assessment tools and the sample population. If tests purporting to measure the same ability are tapping into different cognitive and sensory abilities, they cannot be measuring the exact same construct. Adding to this complexity is the variation in the rate of decline across the abilities, each with different influence on performance and subsequently on the outcome measured.

One single test did not stand out as being the best predictor for mortality; however, we do not agree that individual cognitive domains are no better predictors than more general cognitive scores. [226] Using this argument for the sake of brevity is too simplistic. The test for general cognition (SF-EMSE), testing a number of domains, did not perform as well as the composite score which was a combination

of all the tests of the battery, or even some of the other tests measuring fewer abilities. By combining all tests and presenting as a single standardised score and not considering the separate abilities (as some studies have done), may result in missing on vital information that may then hinder interpretation.

These findings support the conclusion that cognitive function is independently associated with death. However, it is important to give due consideration to the characteristics of the sample population and psychometric properties of the assessment tools when interpreting results.

Summary of Chapter

- Poor cognitive performance was independently associated with higher mortality over an average of seven years of follow-up.
- The relationship between poor cognition and mortality exists for global cognition and across separate abilities, with some specific abilities to be more powerful predictors than others.
- Measuring cognitive domains separately gives more insight than a global measure.
- Those with 'no qualifications' had a greater disadvantage in terms of survival.
- Poor performance was associated with higher mortality across several domains and independently of common chronic diseases. These associations varied not only in magnitude across domains but also differed between older and middle-aged participants.
- Different cognitive tests tap into a range cognitive and sensory abilities to perform a given task. Therefore, psychometric properties of tests should be given due consideration when interpreting results.

Chapter 7: Accuracy of Dementia Recording

Paper in progress: Hayat SA, Luben R, Khaw K.T, Brayne C: Accuracy of dementia outcomes from linkage to medical health records. A detailed examination of NHS data sources to ascertain dementia in a British cohort in Norfolk.

7.1 Summary

The use of health records as a measure of dementia outcomes in medical research and for policy tracking has become an increasingly important resource for dementia ascertainment. Here we examine the variability in recording of dementia outcomes in different service settings. This chapter presents findings from EPIC-Norfolk linkage to medical records. Dementia diagnosis was ascertained from secondary care National Health Service (NHS) data sources. Primary care records for a sub-set of the cohort were also reviewed. Characteristics of individuals with a dementia diagnoses from the different data sources were examined. Risk of receiving a dementia diagnosis were estimated using Cox proportional hazard models adjusting for socio-demographic variables. There were 2699 participants receiving a dementia diagnosis in one or more of the data sources examined. There was limited concordance across the NHS-Digital data sources. Discrepancies were also observed with primary care records for a sub-set of the cohort and report on potential linkage-related selection bias.

Using record linkage from diverse settings reveals differences in dementia diagnosis, suggesting that different people are identified via varying routes within the NHS. This Chapter presents potential linkage related selection biases in primary and secondary care data sources. With the expansion of using routinely-collected health data, researchers should be aware and report on the limitations and challenges as well as associated biases of individual data sources.

7.2 Introduction

There has been an exponential increase in the secondary use of health records for research across the world in the last decade. [236] In the United Kingdom (UK), the potential value of using health care data led to the launch of the Farr Institute of Health Informatics in 2013, and its successor Health Data Research UK (HDR-UK) in 2018, with the vision to improve population health, address health inequalities, and to drive efficient service provision. [237] Linkage to medical records has also been increasingly used to examine dementia causes and outcomes. Researchers employ different methods to examine databases to ascertain dementia diagnoses. These include diagnostic and Quality and Outcomes Framework (QOF) codes, reviewing free text and searching for prescriptions for dementia defining drugs.[238] Whilst the availability of data provides opportunities for powerful and efficient research, it also presents some challenges and limitations, in particular, in relation to dementia-related outcomes.[238]

In the UK, the National Health Service (NHS) holds data on all hospital admissions by condition. This potentially allows for ascertainment of dementia from routine data sources for cohort studies. To date, mortality and Hospital Episode Statistics (HES) data have been the main sources of health records for

case ascertainment for epidemiological studies. [91,95,238] These data are coded using the International Classification of Diseases version 10 (ICD-10) which are mainly diagnostic codes. However, using these sources alone seriously underestimates the number of dementia cases as most dementia patients will not require hospitalisation for their dementia nor will they have dementia as a cause of death recorded on their death certificate. [95]

General practitioners maintain primary care records, which include information, not only for diagnoses, but also for administrative purposes, including details of specialist referrals such as to memory clinics. Diagnosis of dementia is usually initiated in a primary care setting, based on patient symptoms or caregivers' concerns, [239] therefore GP records, in theory, should be a more complete source for dementia case ascertainment. The coding system used in primary care is different from the ICD system used in secondary care and death registration. This coding system uses Read Codes, and codes for dementia, in particular, are numerous, complex and prone to coding error and misclassification. [94] The use of multiple systems across different settings and unfamiliar codes adds to the confusion and lack of clarity. [94]

There is no national system for collecting or sharing primary care data [240] and from the available literature, the linking of cohorts to GP data in the UK appears to be limited. [90,95,241] Clinical Practice Research Datalink (CPRD) is a primary care database of anonymised medical records from general practitioners that is widely used in epidemiological research. However, CPRD has its limitations, including variability in the quality of data which are not primarily for the purpose of research and not accurately accounting for 'missingness' of data; [242] as only individuals attending their general practice are recorded. Furthermore, CPRD is only available for a limited number of practices.

Epidemiological studies depend on accurate, reliable and relevant information from data sources if they are to be useful for risk, natural history studies as well as estimates of prevalence and incidence of health conditions. Whilst these opportunities for access to a wide range of data has hugely increased the potential of research of dementia – it also presents challenges and uncertainties in the strengths, limitations and the potential biases of these data sets. One main limitation is the impact of incomplete or inaccurate recording of dementia which can affect analysis and interpretation of results. [243] Researchers should be aware of the strengths and limitations of data sources used for research and the accuracy of results should be interpreted and reported subject to these caveats. [244]

Dementia ascertainment is complex in primary and secondary care settings [94,96] as well on death certification,[245] with poor reporting underestimating dementia in the population. [246] There is substantial heterogeneity in the methods for case-ascertainment in dementia literature, [247] with studies

applying different criteria for ascertainment. [91] Further adding to the complexity is the variations in dementia reporting across regions in UK. [91,93,248] As a result, data sources are prone to inconsistency, misclassification and influenced by change in dementia practice and policy, [248] such as those summarised in Box 7.1 below. Currently, no data source has been recognised as the 'gold standard'. [238]

A number of cohort studies have reported on use of electronic records for dementia outcomes. [90,95] These large quantitative studies may be limited in terms of generalisability. If routine data are to be used to address measurement of dementia outcomes, it is of value to examine how these data sources behave in other populations. EPIC Norfolk provides an opportunity to test whether there are systematic differences and potential biases in such approaches.

The aim of this investigation was to describe the procedures to gain further understanding of the accuracy of coding for dementia and dementia related outcomes across different data sources, namely HES, mortality data and the recently available mental health dataset. We examine whether there is a differential in estimating dementia across the different data sources. We provide novel insight into the mental health dataset and further compare secondary and primary records using GP records in a sub-population of the EPIC-Norfolk cohort.

Box 7.1: Increased awareness of dementia through changes policy for public and practitioners

2006: Introduction of dementia to Quality of Framework (QOF) registers. QOF rewards GP Practices for the provision of quality care and helps to standardise improvements in the delivery of primary medical services. Participation in QOF is voluntary

2009: The 2009 National Dementia Strategy was introduced to increase the public and professional awareness and understanding of dementia. Also, the dementia prevalence indicator to the Quality Outcomes Framework was introduced in primary care

2011: Changes to coding practice. For mortality coding, deaths previously coded with an underlying cause of unspecified cerebrovascular disease were reclassified as vascular dementia

2012: The Dementia Challenge was launched in March 2012 by Prime Minister, David Cameron. This programme superseded the national strategy from 2009 – focus was on three main areas: bringing about improvements in health and care, creating dementia friendly communities and improving research

2013: The Dementia Commissioning for Quality and Innovation (CQUIN) was introduced (to encourage practitioners to identify those who potentially have dementia in a secondary care setting

2014: Mortality coding revised - dementia coded as the underlying cause of death

2015: Prime Minister launched his Challenge on Dementia 2020, which set out to build on the achievements of the Prime Minister's Challenge on Dementia 2012–2015

7.3 Methods

7.3.1 Participants and measurements

All participants with baseline measure were included in this analysis as described in chapter 2

7.3.2 Covariates

Education (the highest level attained) and social class were obtained from the baseline questionnaire. Education was categorised into three groups (i) No qualification (not completing school up to the age of 16), (ii) Completion of school up to the age of 16 or up to the age of 18 and finally (iii) those obtaining an education to graduate level (those who obtained a degree or equivalent) or above. Age at baseline and (where available), age at time of dementia diagnosis was used.

Social class was classified according to the Registrar General's occupation-based classification scheme into five main categories. [141] Social class I consists of professionals, class II includes managerial and technical occupations, class III is subdivided into non-manual and manual skilled workers (III non-manual and III manual), class IV consists of partly skilled workers, and class V comprises unskilled manual workers.

7.3.3 Dementia ascertainment and diagnostic codes in hospital and death records

Virtually complete follow-up for cohort for mortality and hospital admissions in EPIC-Norfolk has been established via linkage to routinely collected National Health Service (NHS) databases in England (Hospital Episode Statistics, HES) and for mortality data for all participants using their unique NHS number and date of birth. Although mortality data are provided by the Office for National Statistics (ONS), data linkage to the EPIC-Norfolk cohort for NHS and mortality data was carried out by NHS Digital, a statutory body in England, permitted to receive identifiable patient data for linkage. Linked hospital records contain coded diagnostic information for all inpatient and day-case admissions. [89]

We also obtained national mental healthcare data, which contain record-level data about individuals in contact with mental health services including memory clinics. There were three iterations of the mental health data covering different time periods. These were Mental Health Minimum Data Set (MHMDS), Mental Health and Learning Disabilities Data Set (MHLDDS) and the Mental Health Services Data Set (MHSDS). The MHMDS, MHLDDS and MHSDS incorporates mental health data (including dementia), over the follow-up periods, 2009-2014, 2015-2016 and 2017-2018 respectively.

Participants with incident dementia were defined as those free of dementia at the time of enrolment to the study, but identified with a dementia diagnosis subsequently. Individuals were followed from the date of consent, until the earliest date of a dementia diagnosis or date of death in or after 1996 when formal follow up by health records began in EPIC-Norfolk. Here, dementia from HES records, death certificate or the mental health data was defined as any of the diagnostic code as listed in Table 7.1. For HES, mortality and the mental health data, ICD 10 codes were used. To maximise the outcome data, we focused on all-cause rather than cause-specific dementia. Cases were defined as 'definite' 'probable' or 'possible' dementia, and only the 'definite dementia' cases were included in the analyses. The sub type of dementia was not analysed separately. Data were used from the NHS Digital (HES, mental health and mortality datasets) both individually and all three combined. Participants with no reports of death or dementia were censored on 31st December 2018. **Figure 7.1** is a diagrammatic representation of selection of participants and record linkage in the EPIC-Norfolk cohort.

7.3.4 Dementia case ascertainment through GP records

For a sub-group of the EPIC-Norfolk cohort, we compared the NHS Digital datasets of secondary care to primary care data or GP records. The protocol was based on a 'clean up' exercise [94] that has been recommended by clinical commissioning groups to improve dementia diagnosis in practices. [249] We employed Read codes (also included Table 7.1) which have been identified as being those most commonly used in making a dementia or dementia related diagnoses. [94]

Case ascertainment from GP records was carried out in three phases. Firstly, twenty-six of the GP practices collaborating with EPIC-Norfolk were contacted to participate. Practices who agreed, were provided with a detailed protocol and a list of patients on their register who were also participants in the study. Practice managers were provided with name, NHS numbers and date of birth under a secure password protected system to identify the correct individuals from their patient database. The practice ran searches to generate lists of patients (EPIC-Norfolk participants only) who may have dementia or dementia related condition, or have been prescribed dementia defining medication, Donepezil, Galantamine, Rivastigimine or Memantine.

Due to the variability in coding systems and the use of Read codes across practices, [94] GP practices were asked to include any other dementia Read codes they routinely used. Data were returned via the secure system. Practices were also asked to complete a simple questionnaire. The full protocol and sample questionnaire are available on request. Practices were advised to take advantage of this exercise by comparing results of the search against their Quality of Framework (QOF) [248] dementia register to check for discrepancies to improve their dementia diagnosis rates. [94]

In the second phase, cases identified from GP records were cross-checked with the NHS Digital data, and the level of agreement between the data sources was examined. Participants with a definite diagnosis in secondary care, but not indicated in the GP data were further reviewed in the third and final, case confirmation phase. Here, discrepant records were individually reviewed by the researchers (SAH and NJD). **Figure 7.2** shows the timeline for recruitment of practices and data capture for dementia for the GP case ascertainment. Initial case ascertainment from GPs was conducted between 2016-2017 and NHS Digital data were up to 31st March 2018, with case confirmation in GP records up to 20th December 2018.

7.4 Analysis

Definite dementia cases were defined as having one or more of the ICD-10, (or for the GP records) Read code, for dementia. Age and sex-specific rates for all-cause dementia and mortality were calculated for the entire cohort. The number and proportion of participants with a diagnosis of dementia from the three NHS Digital data sources separately and combined were explored. Differences in socio-demographic characteristics (age at recruitment, sex, education and social class) of dementia cases across the three NHS Digital datasets were examined.

Cox proportional-hazards models were used to compare the association of socio-demographic factors and risk of a dementia diagnosis across these data sources, with mutual adjustment all the co-variates. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Table 7.1: ICD 10 and Read codes used in EPIC-Norfolk to search for 'Definite' dementia cases

Read codes	ctv3_codes	Read Code Description	ICD Code	ICD Description
Eu00	**Eu00**	Dementia in Alzheimer's disease	**F00**	Dementia in Alzheimer's disease
			G30	Alzheimer's disease
Eu000		Dementia in Alzheimer's disease with early onset	**F00.0**	Dementia in Alzheimer's disease with early onset
			G30.0	
Eu001	**X0030**	Dementia in Alzheimer's disease with late onset	**F00.1**	Dementia in Alzheimer disease with late onset
			G30.1	
	XaIKC	Alzheimer's disease with late onset		
Eu002	**Eu002**	Dementia in Alzheimer's disease, atypical or mixed type	**F00.2**	Dementia in Alzheimer disease, atypical or mixed type
			G30.8	Other Alzheimer's disease
F110		Dementia in Alzheimer's disease, unspecified	**F00.9**	Dementia in Alzheimer's disease, unspecified
			G30.9	
Eu01	**XE1Xs**	Vascular dementia	**F01**	Vascular dementia
			F01.0	Vascular dementia of acute onset
Eu011	**Xa0IH**	Multi-infarct dementia	**F01.1**	Multi-infarct dementia
Eu012	**X003T**	Subcortical vascular dementia	**F01.2**	Subcortical vascular dementia
Eu01y	**Eu01y**	Other vascular dementia	**F01.8**	Other vascular dementia
Eu01z	**Eu01z**	Vascular dementia, unspecified	**F01.9**	Vascular dementia, unspecified
			F02	Dementia in other diseases classified elsewhere
Eu020	**X0034**	Picks Disease (Read)/Frontotemporal dementia includes Picks Disease and progressive isolated aphasia(CTv3)	**F02.0**	Dementia in Pick's disease
			F02.1	Dementia in Creutzfeldt-Jakob disease
			F02.2	Dementia in Huntington's disease
Eu023	**Eu023**	Dementia in Parkinson's disease	**F02.3**	Dementia in Parkinson's disease
			F02.8	Dementia in other specified diseases classified elsewhere

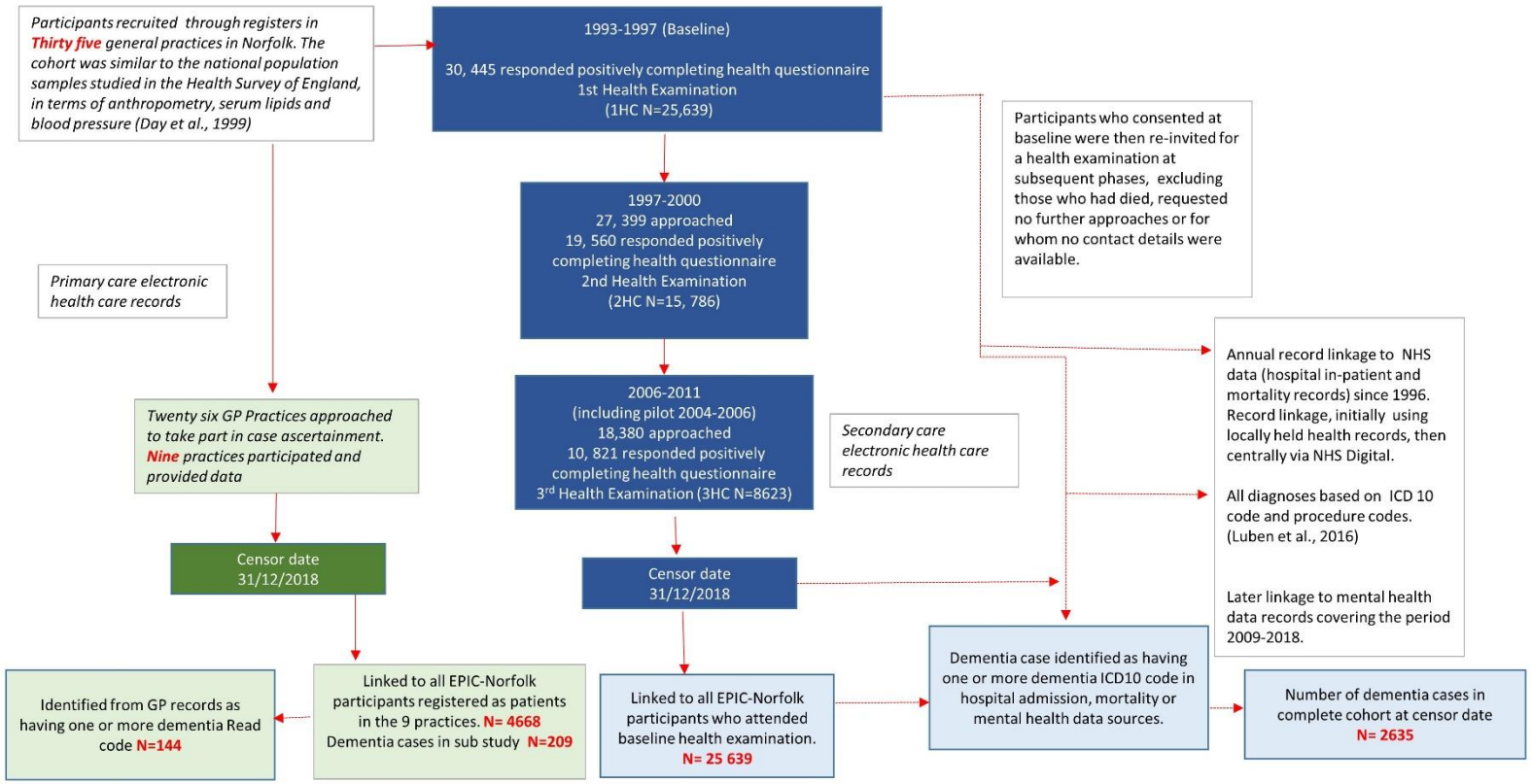
Table 7.1: Continued…

Eu02y	**X0034**	Dementia in other diseases specified elsewhere (Read)/Frontotemporal dementia includes Pick's Disease and progressive isolated aphasia		
			G31.0	Frontotemporal dementia
Eu025	**X003A**	Lewy body dementia	**G31.8**	Other specified degenerative diseases of nervous system Grey-matter degeneration [Alpers] Lewy body(ies)(dementia)(disease) Subacute necrotizing encephalopathy [Leigh]
	XaKyY	Lewy body dementia		
Eu02z	**XE1Z6**	Unspecified dementia	**F03**	Unspecified dementia
			F05.1	Delirium superimposed on dementia
	X002w	Dementia		
	X00R2	Senile dementia		
1461	**1461**	History of dementia		
Eu107 **Eu10711** **E012** **E0120**	**Xa25J**	Alcoholic dementia	**F10.7**	Residual and late-onset psychotic disorder: Includes Alcoholic dementia NOS Chronic alcoholic brain syndrome Dementia and other milder forms of persisting impairment of cognitive functions

Anti-Dementia Medications

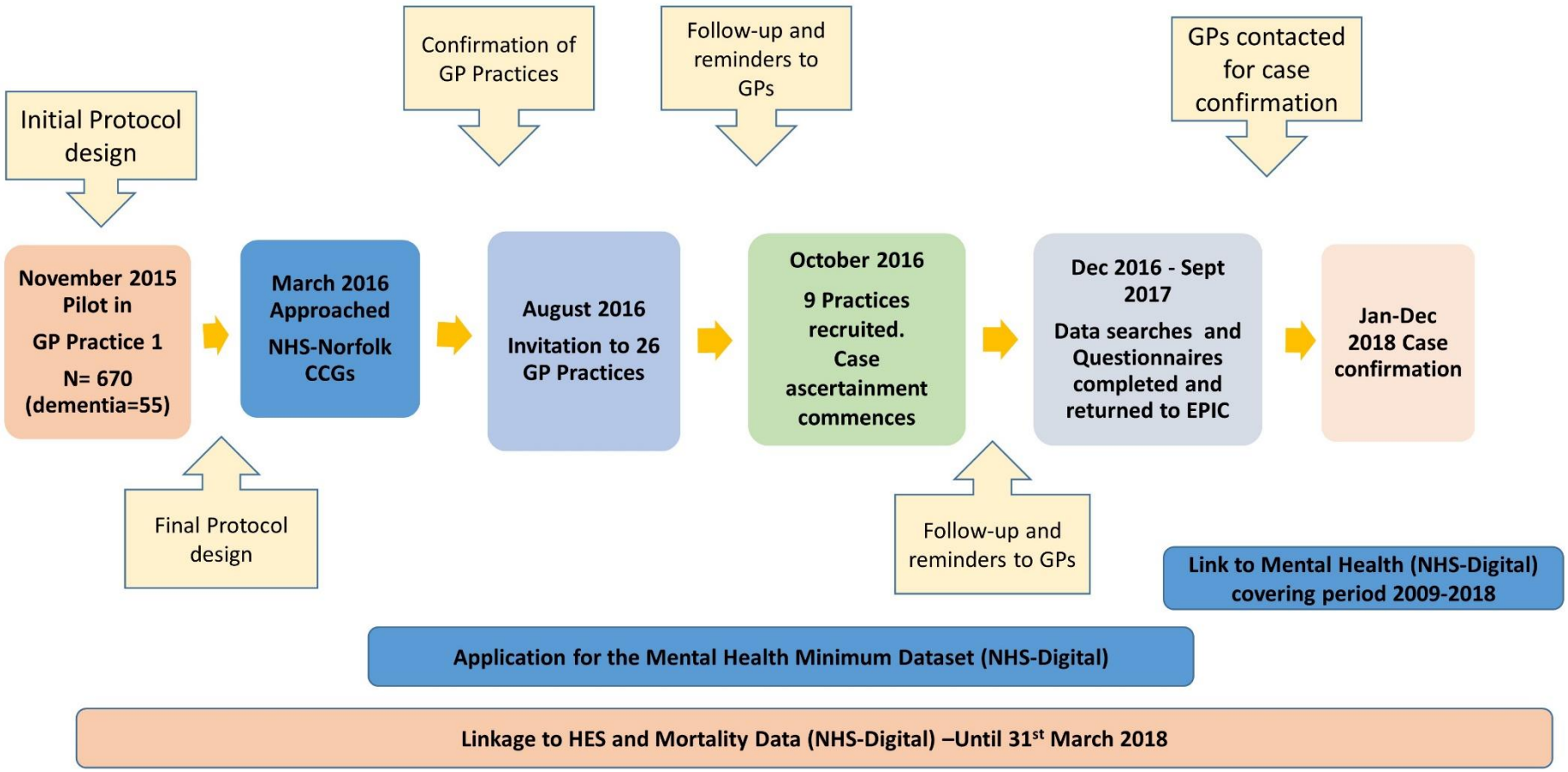
- Donepezil (Aricept®Aricept Evess®)
- Galantamine (Reminyl®, Reminyl® XL)
- Rivastigimine (Exelon)
- Memantine hydrochloride

Figure 7.1: Flow diagram of selection of EPIC-Norfolk participants for record linkage.



Key: Dotted lines represent passive follow-up and solid lines represent direct contact with GP Practice or participants

Figure 7.2: Timeline of recruitment and data capture for dementia case ascertainment from GP Practices in the EPIC-Norfolk cohort.



7.5 Results

There were 2635 cases of dementia identified from the cohort of 25,639 individuals at the censor date of 31st December 2018 after 25.8 years of follow-up. The youngest age of entry to the study at baseline was just below 40 and the oldest age of the participant at the censor date was 101 years. Out of the 2298 individuals with data on age of diagnosis, the minimum age of diagnosis was 54 years and maximum was 99 years. **Figure 7.3** shows the relationship between age and number of dementia diagnosed. Table 7.2 shows the sex- and age-specific cumulative incidence of dementia and deaths in the cohort. Increasing age was associated with increasing rates of dementia and death. This table reflects the higher mortality in men which results in higher absolute numbers and of dementia cases in women.

Figure 7.3: Scatter plot of age of diagnosis by age at baseline.

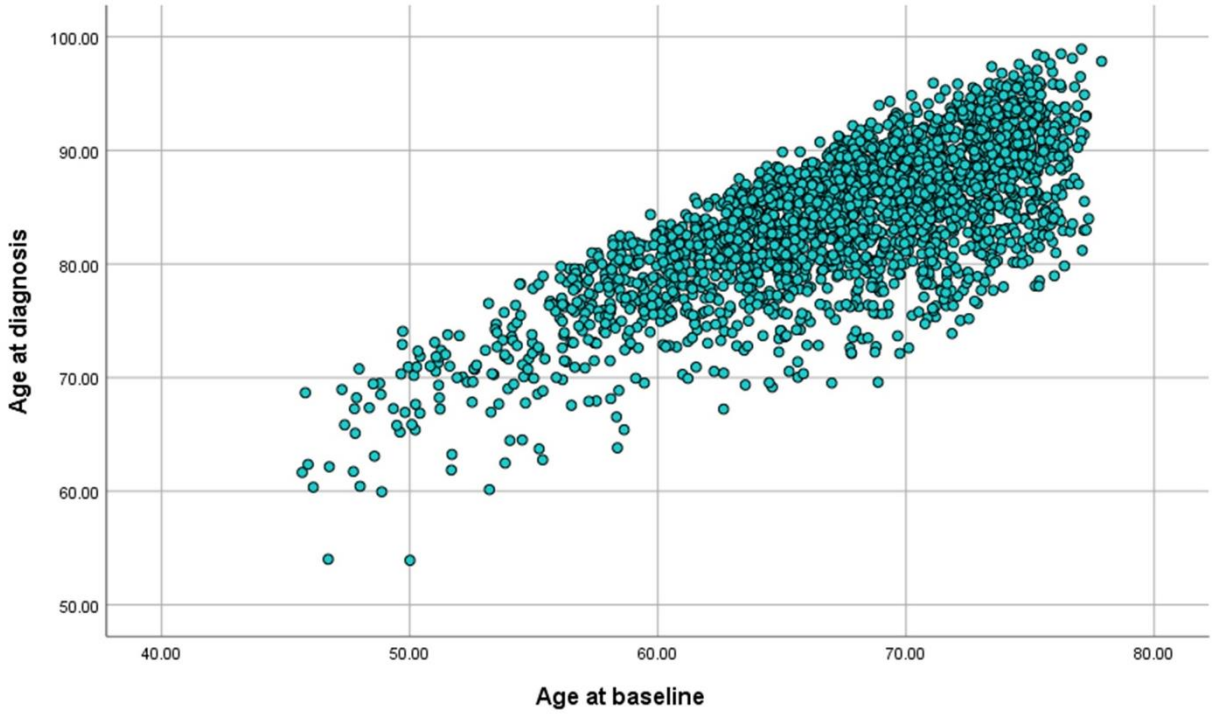


Table 7.2: Age and sex specific proportions of dementia and death in EPIC-Norfolk from 1996 until 31st December 2018 using all 3 secondary care data sources provided by NHS Digital.

Age Band at baseline	Median age	Freq (N)	% with dementia (N)	% Died (N)	P-Value
Men (N=11 607)					
<=59 Years	51.6	5915	3.2 (190)	17.4 (1028)	
60-64 Years	62.5	1848	12.3 (228)	46.7 (863)	
65-69 Years	67.5	1890	15.6 (294)	72.0 (1361)	<0.001
70-74 Years	72.5	1579	17.3 (273)	89.9(1420)	
>75 years	75.7	375	14.9 (56)	95.7 (359)	
Women (N=14032)					
<=59 Years	51.3	7656	3.1 (234)	11.9 (909)	
60-64 Years	62.6	2118	15.0 (318)	36.9 (782)	
65-69 Years	67.4	2103	23.2 (488)	55.4 (1166)	<0.001
70-74 Years	72.4	1766	27.5 (486)	80.4 (1419)	
>75 years	75.8	389	28.8 (112)	90.7 (353)	
ALL (N=25 639)					
<=59 Years	51.5	13571	3.0 (412)	14.3 (1937)	
60-64 Years	62.6	3966	13.5 (536)	41.5 (1645)	
65-69 Years	67.5	3993	19.3 (769)	63.3(2527)	<0.001
70-74 Years	72.5	3345	22.8 (750)	84.7 (2839)	
>75 years	75.7	764	22.0 (168)	93.2 (712)	

NHS Digital Data Sources: Hospital Episode Statistics (HES), mortality and mental health datasets

P values by Chi sq for proportion

On comparing characteristics across the different data sources, there were no differences in terms of sex and socio-demographic profiles (Table 7.3), other than those from the mortality dataset were older. The majority of dementia cases were identified from HES, followed by mortality, with the least number identified from the mental health dataset. The distribution of dementia cases across the three NHS Digital data sources is shown in **Figure 7.4**. This figure shows very little overlap between all three datasets, with varying degree of overlap between across the different datasets. In terms of socio-demographic factors predicting dementia, associations were similar across the three data sources (Table 7.3). Age was a stronger predictor in mortality dataset and weakest in the mental health data. Having qualifications had a lower risk of future dementia, as expected, this was observed for mortality and HES data but not for the mental health dataset, most likely due to the smaller numbers.

The mental health datasets included recorded observations and mainly administrative data such as mental health reviews, care programmes and pathways that include contacts with mental health care professionals (both in hospitals and in outpatient clinics and the community) as well as diagnostics and treatment codes. The service-level breakdown of the metal health data was not applicable here, as there was little additional diagnostic information. The latest release, MHSDS (2017-2018) appeared to be the most complex dataset, covering mental healthcare more comprehensively and containing diagnostic ICD10 codes that were limited in the previous years.

Table 7.3: Comparison of characteristics of 'definite dementia' cases identified from the three data sources separately and combined.

	HES DATASET		MH DATASET		MORTALITY. DATASET		All 3 Data sources HES/MH/ MORTALITY		P-value
	Definite dementia N=2157		Definite dementia N=727		Definite dementia N=1276		Definite dementia N=2635		
Socio-demographic Mean (SD)									
Age at Baseline	66.9	(6.3)	64.1	(6.5)	67.9	(5.9)	66.7	(6.5)	<0.001
Age at Diagnosis	83.7	(6.5)	82.7	(6.8)	84.6	(6.4)	83.8	(6.5)	<0.001
Sex, % women (n)	59.8	(1290)	59.7	(434)	60.5	(772)	60.5	(1594)	0.9
Education, % (n)									
No qualifications	49.1	(1057)	45.3	(329)	50.4	(641)	48.4	(1274)	0.5
O/ A level Standard	41.9	(903)	45.3	(329)	41.4	(527)	42.6	(1120)	
Graduate Level	9.0	(194)	9.4	(68)	8.2	(105)	9.0	(238)	
Social Class, % (n)									
Professional	6.3	(132)	5.6	(42)	6.0	(74)	6.3	(162)	0.7
Managerial	33.6	(702)	32.0	(240)	34.0	(421)	33.9	(866)	
Skilled Non-Manual	20.5	(428)	21.1	(158)	21.7	(268)	20.5	(523)	
Skilled Manual	21.2	(442)	21.4	(160)	20.5	(253)	21.3	(544)	
Semi-Skilled	14.1	(295)	17.2	(129)	13.6	(168)	14.2	(362)	
Non-Skilled	4.2	(88)	2.7	(20)	4.3	(53)	3.8	(98)	

Abbreviations: HES, Hospital Episode Statistics; MH, Mental Health

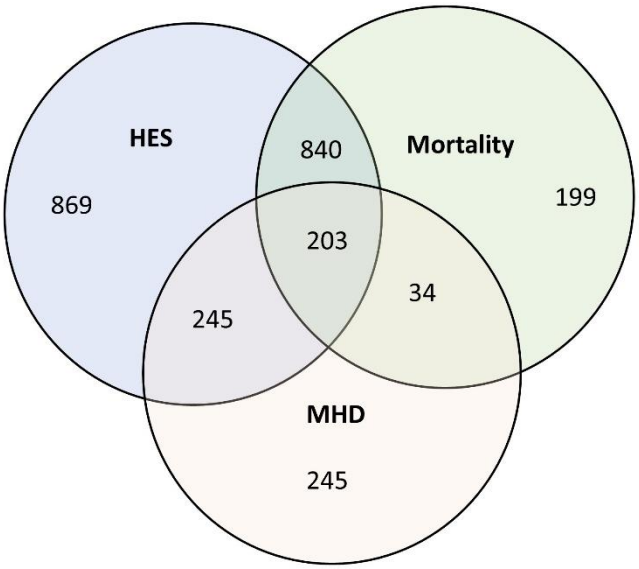
Table 7.4: Association of sociodemographic factors and dementia in the EPIC-Norfolk Cohort in the three data sources combined and individually, mutually adjusted for age, sex, education and social class.

	All 3 data sources (Dementia=2555)			HES dataset only (Dementia=2087)			MH dataset only (Dementia=715))			Mortality dataset only (Dementia=1229)		
Factor	HR	95% CI	P-Value	HR	95% CI	P-Value	HR	95% CI	P-Value	HR	95% CI	P-Value
Age per 5 years	2.19	(2.13, 2.26)	<0.001	2.23	(2.16, 2.31)	<0.001	1.80	(1.71, 1.89)	<0.001	2.57	(2.46, 2.69)	<0.001
Sex (Men)	0.98	(0.91, 1.06)	0.6	1.01	(0.92, 1.10)	0.9	1.03	(0.88, 1.20)	0.7	1.08	(0.96, 1.21)	0.2
Education (With qualifications)	0.87	(0.80, 0.95)	0.002	0.87	(0.79, 0.95)	0.002	0.91	(0.78, 1.07)	0.2	0.84	(0.74, 0.94)	0.003
Social Class (Non-manual)	0.99	(0.91, 1.08)	0.8	0.98	(0.89, 1.07)	0.7	0.93	(0.79, 1.09)	0.4	1.03	(0.91, 1.16)	0.7

*Reference categories: women, no qualifications, manual

Abbreviations: HES, Hospital Episode Statistics; MH, Mental Health

Figure 7.4: Distribution of cases (N=2635) across the three main data sources from NHS Digital followed up until 31st December 2018.



For the sub-study involving validation with GP records, out of the 26 practices that were contacted, 14 agreed to participate, 6 declined and 6 gave no response. Of the 14 that agreed, 8 practices completed the questionnaire and 9 provided data. There were no criteria for selecting a practice for this validation, other than they were EPIC-Norfolk practices. There was a mix of rural and city practices, classified as urban or town and fringe areas, [250] although the majority of the practices ultimately submitting data were city-based. In this sub-population, 4.4% (209 cases) were dementia cases identified from HES, mental health data, mortality and the GP records compared to 10.1% cumulative incidence in the rest of the cohort.

However, this sub-population of 4668 participants were younger, more likely to be women, and of higher education and social class when compared to the rest of the cohort (Table 7.5). Out of the 209 cases, 57 were found in both secondary and primary care data and 87 were in primary care records only. In this small study, almost all the practices reported to use Read codes and not free text and all reported their dementia cases to be confirmed through secondary referral. Five out of the eight practices reported on discrepancy with their QOF registers. The summarised responses to the questionnaire from GPs are given in **Figure 7.5**. Participants who were prescribed one of the four dementia drugs (N=57), also had a Read code of a definite dementia diagnosis. There were no cases identified from drugs alone.

Table 7.5: Comparison of socio-demographic characteristics between sub-population (N=4668) and rest of EPIC-Norfolk cohort with baseline measures.

	Cohort		GP Sub-cohort		P-Value
	N=21 537**		N=4668		
Socio-demographic					
Mean (SD)					
Age at Baseline	59.8	(9.5)	56.1	(7.9)	<0.001
Age at dementia diagnosis	83.8	(6.5)	84.5	(6.6)	0.1
Sex, % women (n)	54.3	(11 688)	57.1	(2344)	0.001
Education, % (n)					
No qualifications	37.9	(8165)	31.4	(1289)	<0.001
O/ A level Standard	49.8	(10 723)	52.5	(2154)	
Graduate Level	12.2	(2630)	16.0	(658)	
Social Class, % (n)					
Professional	6.7	(1401)	8.7	(353)	<0.001
Managerial	36.4	(7659)	37.1	(1497)	
Skilled Non-Manual	16.8	(3533)	15.0	(606)	
Skilled Manual	23.1	(4855)	22.7	(917)	
Semi-Skilled	13.6	(2854)	12.6	(507)	
Non-Skilled	3.5	(727)	3.9	(158)	

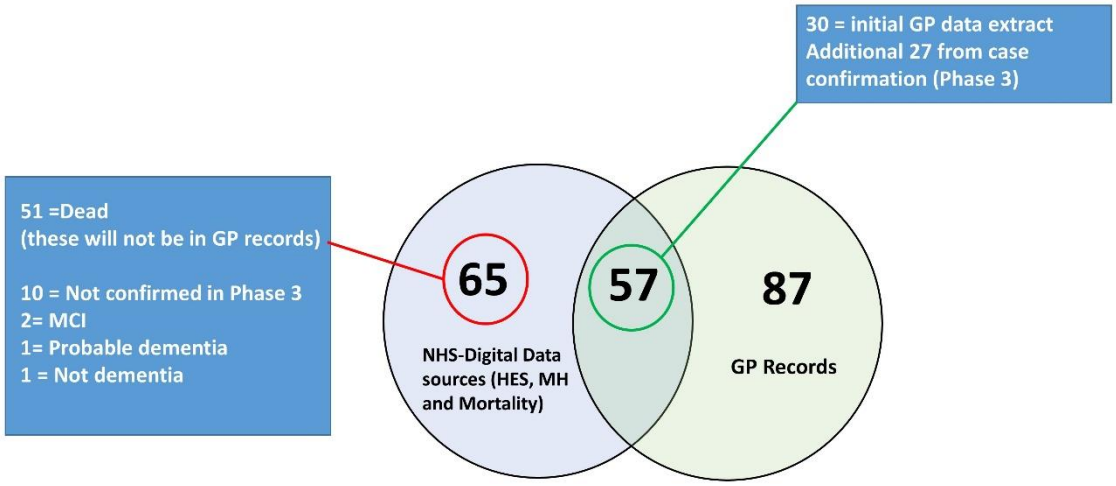
Figure 7.5: Summary of responses from qualitative questionnaires collaborating Practices providing GP data.

Results from Questionnaire: **8/10** GP Practices returned a completed questionnaire

Used both Read Code and Medication code for searches	7
Included other dementia codes not on the list in protocol	4
Information provided as Read Code plus free text (free text not available)	6 (0 with free text only)
Practice experiencing difficulties with Dementia Read Codes	6=NO 1= YES 1=NR
In House Cognitive Testing carried out by Practice	7 =YES
Reason for patient cognitive testing/referral to memory clinic	Patient concern 7=YES 1=Not Able GP Judgement 6=YES 1=NO 1=Not Able Opportunistic testing 6 =YES 1= Not Able
How is a confirmed dementia diagnosis made	Following 2^{0} referral =8 includes GP Judgement = 4
How is this information (1) received and (2) entered into GP database	(1) Free text =8 (1 also included ICD code) (2) Read code= 7 (1 uses FT, ICD and Read)
All cases from search already included on QOF register	3= YES 5=NO
Discrepancy between results on QOF register and from the read code search	5=YES 3 =NO

There were 65 participants who had a definite dementia diagnosis in the secondary care records, but not in their GP records. For the majority (51 cases), the reason for absence from GP systems was because the participant had died, and the dementia diagnoses had come from mortality records. Once a patient is deceased their information is removed from the GP system. For the remaining (N=14), 3 participants had an MCI or probable dementia code, and for 10 participants, we were unable to confirm diagnosis. This could be because they had died recently, or had moved to another practice, in which case their records would no longer be available by the GP. One patient had no indication of any dementia or dementia related condition. Another important point to highlight, that of the 57 cases that were in both the secondary and primary data sources, just over half were available from the initial GP data extract, with the other 27 missed by the practices. These were only obtained with further detailed review of individual records by the researchers. These cases would not have been included if the extra confirmation phase had not been a part of the study design. Distribution of dementia cases across primary and secondary care datasets are shown in **Figure 7.6.**

Figure 7.6: Distribution of cases (N=209) identified from primary and secondary care in sub-population of EPIC-Norfolk participants (N=4668)



.

7.6 Discussion

This study shows dementia is recorded across different data sources and although there is some concordance across these sources, this is limited. As a result, we have shown that using a single data source would underestimate dementia numbers and to use multiple sources is the best approach to maximize dementia ascertainment from routinely collected health records. [238] The most widely used data sources by studies are HES and mortality records, [91] each with limitations and both underestimate the burden of dementia. [96,238,251] Dementia is not always the primary cause of death and so may not be included on the death certificate, [251] and underreporting in hospital records is also a known problem. [252] In this relatively small study, we also show the limitations apply to GP records. Medication for dementia drugs provided no additional cases, even though this is another potential source. [238] For all sources to be useful for research, dementia diagnoses has to be documented accurately recorded which is not always the case and also varies across regions. [93]

Medical records allow virtually complete follow-up, for research; [28] however, the limitations in terms of accuracy, completeness of dementia recording [91,92] and underestimation of cases are well recognised. As with other studies, [90,95,238] we also interpreted the absence of a dementia diagnosis code as absence of the dementia, although this may not necessarily be the case. Even though using medical records is less sensitive to making a study diagnosis, specificity in all these data sources is likely to be high, as a clinical diagnosis, particularly in primary care records is usually made after referral to a specialist. [253] One major limitation of this study is that all the medical records for the entire cohort were not inspected, and so likely to have missed more, which would have reduced sensitivity. Furthermore, milder cases that have not been identified would have been missed. Misclassification will have some impact on association, the level of importance of this will depend on the purpose of the study. Under-ascertainment is inevitable and should be taken into account when making prevalence estimations.

Another limitation is that the competing risk of death was not accounted for, which will be high in this ageing population. Although the proportion of deaths by age in men and women were presented. Individuals are likely to die as a result of old age and other comorbidities before a diagnosis of dementia. In the Cox regression models, these individuals would have been censored and considered ‘at risk’ when in fact they should not be. However, to account for the competing risk for death, death has to be a discrete event from dementia, and given that dementia from mortality records was included, this overlap does not allow for competing risk of death to be estimated here.

Using simple socio-demographic factors to examine associations, including the most common and strongest risk factor, age, small differences were observed, across the main two data sources, with

some difference in the mental health dataset. However, there is the potential for these differences to be greater due to missing data, particularly for more complex factors than those examined here. Therefore, associations with unrecorded dementia cases in a data source could yield different study results. Studies have highlighted regional variation in rates of diagnosis and reliability of existing data. [238] We have demonstrated that this heterogeneity exists even in a single geographical region.

I have described the relatively newer mental health datasets from NHS Digital, which do not seem to be widely used as the other data sources and have not been described previously. These datasets are complex, with information on individuals (from referral to final discharge) who have been in contact with secondary mental health services. Each subsequent release of the mental health data was wider in scope than the previous version. The mental health dataset for the final year of follow-up (MHSDS) had the greatest number of dementia cases than all earlier iterations of this dataset from previous years. It is unclear as to why this sharp increase in diagnosis codes occurs. It may be as a result of change in the coding practice in mental health services, or the way these data are extracted to include diagnoses as well as service codes.

The mental health dataset has huge potential to provide more accurate estimate of true dementia in the population in the UK. As shown here, there are a number of potential pitfalls in dementia ascertainment. Not all individuals with dementia will have a hospital or death record, and despite the expectation, GP records are not a complete source for dementia. [94] However, the mental health dataset has the potential to provide additional cases, of those not only presenting to GPs and hospitals, but those individuals living in the broader community. This dataset will need further reviewing for future work.

We were unable to examine primary care records via databases such as CPRD, as it is currently not possible to link to primary care in EPIC-Norfolk in this way. As we had to make direct contact with practices and rely on them to extract the data, we were restricted, for practical reasons, to link to a subset only. The protocol was time and labour intensive, although the main purpose of the sub-study was to provide some insight of the degree of agreement between primary and secondary records, which has been shown to be good in other large cohort studies. [90,95] However, in this study, we did not observe the same level of concordance, with a proportion of individuals in secondary care without a record in primary, even though the primary care records were scrutinised up to one year after follow up period in secondary care records. This discrepancy was mainly due to individuals who had died and GP live databases do not hold records on the deceased. This protocol demonstrates how under-reporting by GP practices, may influence studies using databases such as CPRD to under estimate proportion of dementia cases. [254]

As with the UK Biobank study, [90] we also found significant proportion of dementia cases in primary care records, that were not in hospital or mortality records. In EPIC-Norfolk this figure was 42% compared to 52% in UK Biobank. The lower rate is reflective of the older age of the EPIC-Norfolk cohort. However, it also shows that even with an older cohort, there are still cases found in primary care, that would be otherwise missed if researchers are using HES and mortality data alone.

The UK Biobank study was based on the Scottish arm of the study only and did not include other geographical areas covered by UK Biobank. Scotland has some of the best linkable health service datasets in the world, in part due to the adoption in the 1970s of a centrally maintained unique identifier allocated to all GP registered patients. Data quality is generally considered to be high and centralisation of data, both GP and secondary care, making the data more accessible to research. This position is not currently shared by the other countries of UK, although may change in the near future with the establishment of HDRUK. [237] Another large cohort study, the Million Women Study, also found NHS hospital admission data to agree with primary care records, [95] however, this study only consisted of women, and also like UK Biobank, participants were younger.

The study in the sub-population of the EPIC-Norfolk cohort has highlighted a number of key issues. The first is the potential level of 'missingness' as reported previously; [242] if we had relied on the initial data extract provided by the practices, we would have missed just under half the dementia cases. Even though the diagnosis was present in the records, the information was not provided by the practice. The second point to highlight is the bias introduced in the sub-population. It is clear from the characteristics and dementia rates, that this sub-population is different from the overall EPIC-Norfolk cohort. There were no specific criteria set in approaching practices; however, the practices that responded were mainly city practices, and the patient-base in these practices was younger, more educated and of higher social class.

It is likely that the practices that responded were more proactive in taking part in research. As a result, introducing a selection bias. This bias is clearly reflected in the dementia rates, which was 10% in the EPIC-Norfolk cohort overall, compared to 4% in the sub-set from the nine GP practices taking part. Databases such as CPRD are extremely powerful data sources, but are not representative of all practices in the UK based on geography and size, [242] and HES and mortality also rely on data that has been provided by practices. Errors in documenting or missing information can lead to biased results and so the data available for research should be used and interpreted with caution.

Recently there have been changes to coding within primary care with the introduction of new codes SNOMED CT.[255] This new coding system to replace Read codes and eventually also be used in secondary care is meant to provide clarity and consistency across primary and secondary care.

However the implementation of this will take several years and the impact of this is yet unknown. There is also potential in the mental health data that includes other service related codes that could be utilised for further insight into the level of cognitive impairment in the community. There are a number of administrative codes that relate to low, moderate and severe cognitive impairment. This information could be used to supplement the diagnostic information and could be useful in ascertaining milder forms of impairment and dementia. This study could also be further strengthened by linking to primary care database such as CPRD,[242] to allow for more complete record linkage of the cohort. However, as shown in this study, it is not necessary that diagnoses within research databases are a true reflection of dementia cases known to the actual general practices. [238]

Record linkage is a powerful tool to improve the accuracy and completeness of dementia ascertainment for public health research purposes. Currently there are inconsistencies in the methodologies and challenges in using these data that were not collected for the purpose of research. The results of this work suggest that in UK, record linkage with hospital admission, mortality and primary care data provide the ability to identify dementia cases for epidemiologic analyses of risk factors within a cohort. However, the generalisability and reliability of these data for incidence and prevalence rates is more challenging due to variability in ascertainment and diagnostic criteria which may differ over time and in different populations. Researchers analysing linked datasets in most cased, will not have all the information necessary to assess the impact of error on their results. Researchers must be fully aware of the strengths and limitations of the data sources they use and be transparent in reporting on how these reflect on the accuracy of their findings.

Summary of Chapter

- At the censor date of 31st December 2018 after 25.8 years of follow-up, there were 2635 cases of dementia identified from the EPIC-Norfolk cohort recruited at baseline.
- The age range of EPIC-Norfolk participants with a dementia diagnosis was 54-99 years.
- Dementia is recorded in different data sources, concordance across these sources, is limited.
- Using multiple sources is the best approach to maximize dementia ascertainment from routinely collected health records.
- Small differences in socio-demographic factors were seen across the main two data sources, HES and mortality, with some difference in the mental health dataset.
- The relatively newer mental health datasets from NHS Digital, warrants further scrutiny.

Chapter 8: Cognitive Predictors of Dementia

The work presented in this Chapter is to be submitted to Alzheimer's and Dementia (April 2020):

Hayat SA, Luben R, Khaw K, Brayne C: Cognitive performance as a predictor of incident dementia in a British prospective cohort study with over 15 years of follow-up.

8.1 Summary

Studies have shown impairment in multiple cognitive domains several years before a clinical diagnosis of dementia. This chapter examines the utility of the cognitive battery used in EPIC-Norfolk as well as a composite global score, to predict dementia, ascertained using health record linkage in 8581 of the participants individuals over 15 years follow-up (2004-2019). Risk of dementia was estimated using Cox proportional hazard models adjusting for sociodemographic, lifestyle and health variables, evaluating discriminative accuracy of the models by analysing receiver operating characteristic (ROC) curves.

Poor cognition was predictive of incident dementia, even after adjustment for co-variates. Those with a poor performance score for global cognition (bottom 10%) were almost four times as likely to get a dementia diagnosis than those who performed well Hazard Ratio (HR)=3.51 (95%CI 2.61, 4.71 p<0.001). Associations were observed for specific as well as global cognitive abilities. The test for episodic (verbal) memory outperformed other tests and was comparable to global cognition scores. Poor cognition in four or more tests was associated with 10-fold increased risk of developing dementia compared to those not performing poorly in any test HR=10.82 (95% CI 6.85, 17.10 p<0.001). Cognitive measures strengthen prediction models of dementia (Area under the curve (AUC) = 0.85 (95%CI 0.82, 0.87 p<0.001).

This investigation provides further insight on poor cognition predicting future dementia. This association was observed for global cognition and specific abilities, particularly for verbal episodic memory. Deficits across multiple domains predict dementia over and above individual test scores.

8.2 Introduction

Dementia for most has a long prodromal period, whereby individuals who go onto develop dementia, exhibit cognitive deficits many years before any symptoms or receiving a clinical diagnosis. [77] Though difficult to discriminate dementia in its early stages from normal cognitive ageing, [74,256,257] there is evidence from large cohort studies that, in general, those who develop dementia after follow-up had exhibited poorer cognitive performance relative to those who did not develop dementia although this has not translated into accurate individual risk prediction. [81] The risks exist both at a global and domain specific level, [174,258] including episodic memory, executive functioning, verbal ability, visuospatial skill, attention, and processing speed. [259,260] The predictive accuracy of dementia prediction models have been reported as variable among different cohorts. [27]

The purpose of this chapter is to examine the predictive utility of a range of cognitive tests (both global and domain specific) for dementia in a population of relatively healthy men and women prior to a clinical diagnosis. Also examined, is whether the extent of impairment across different cognitive tasks enhances the predictive power over and above the level of individual cognitive test performance alone.

8.3 Methods

8.3.1 Participants and measurements

In this analysis, participants with cognitive measures taken at 3HC were included. Details of the methods of collecting the measures are described in Chapter 2. All cognitive measures of the individual tests and the composite score were used.

8.3.2 Covariates

Education (highest level attained) and social class were obtained from the baseline (1993-1997) questionnaire. Education was categorised into three groups (i) No qualification (not completing school up to the age of 16), (ii) Completion of school up to the age of 16 or up to the age of 18 and finally (iii) those obtaining an education to graduate level (those who obtained a degree or equivalent) or above. Social class was dichotomised, into 'non manual' and 'manual' class. Age was categorized into 5-year age bands.

Other co-variates included in analysis (weight and height to calculate BMI, lung function, blood pressure, plasma vitamin C levels was estimated using a fluorometric assay. Self-report of smoking status (current, former or never smoker) and alcohol intake (Units/Week) were obtained from health and lifestyle questionnaire administered at the time of the clinic appointment. Alcohol units were categorised into 3 groups: 0 Units, 1-14 Units and more than 14 Units. Habitual physical activity was dichotomised into 'physically inactive' and 'any physical activity' Medical history of heart-attack, stroke, cancer, diabetes, hypertension, chronic obstructive pulmonary disease (COPD), depression; and memory and hearing problems, were established from health and life style follow up questionnaire. Details for all co-variates are decribed in Chapter 2.

8.3.3 Dementia ascertainment and diagnostic codes

Almost complete follow-up for disease outcomes in EPIC-Norfolk has been established via linkage to routinely collected National Health Service (NHS) databases in England (Hospital Episode Statistics, HES) and mortality data for all participants using their unique NHS number and date of birth. The linked hospital records contain coded diagnostic information for all inpatient and day-case admissions. [89] To maximise dementia ascertainment, the national mental healthcare data were also included.

Incident dementias were defined as those people without any formal record of dementia in medical records at the time of enrolment to the study, but identified with a dementia diagnosis through routine records subsequently. Participants were followed up from the date of consent at baseline until the first date of a dementia diagnosis, date of death or censoring with neither at 31st March 2019 Using the diagnostic codes for dementia as defined in Chapter 7, as any of the ICD-10 codes as listed in Table 7.1. We used cases with a definite clinical diagnosis from any cause. The sub types of dementia were not analysed separately.

8.4 Analyses

Associations were examined using approximate percentile cut-offs rather than the continuous cognitive score. Poor performance for this chapter was defined as obtaining a score less than a cut-off point corresponding to approximately the 10th percentile of the population distribution in each of the eight cognitive measures individually. As described previously (and in Appendix 5), participants were classified into two groups based on the cut-off scores for each of the tests. For prospective memory, poor performance was defined as those failing the task. The composite score was also included in the analysis. Participants were classified in two groups for the continuous composite score in the same way as the scores were for the individual tests described above. Details as decribed in Appendix 5.

The risk of a 'definite dementia' diagnosis was estimated as a hazard ratio with 95 percent confidence interval (95%CI) for each of the cognitive tests in separate Cox proportional hazard regression models. Age (at time of cognitive testing), and multivariable-adjusted models were additionally constructed to estimate dementia risk. The models were as follows:

Model 1: Socio-demographic factors (Age, per 5 years, sex, education and social class)

Model 2: Socio-demographic and lifestyle (smoking, physical activity and alcohol)

Model 3: Socioeconomic, lifestyle and biological factors (cholesterol, systolic blood pressure, body mass index (BMI), waist hip ratio (WHR), lung function, measured by forced expiratory volume in one second (FEV1) and plasma vitamin C) and prevalent disease.

Education, Social class, physical activity and smoking were all treated as categorical variables in the analysis, as was co-morbidity (as present or not). Exploratory analyses showed little difference in hazard ratio when BMI was entered as a categorical (as low, normal, overweight and obese groups) or as a continuous variable (data not shown), therefore, BMI was entered in the model as a continuous variable to improve sensitivity of the analysis. The cognitive score was entered as a dichotomised variable based on the description above (poor performance or not).

The distribution of participants with poor cognitive performance across the eight cognitive measures were categorised based on the number of tests with a poor performance score as follows: A/ 4-8 tests; B/ 2-3 tests; C/1 test D/ 0 tests (Reference category). Associations were examined with the number of tests included as a categorical variable in in the multivariate adjusted model (Model 3), and then additionally adjusted for each cognitive tests.

The accuracy in predicting future dementia was examined by first generating predicted probabilities from multiple logistic regression. These were then used to plot a receiver operating characteristic curve to derive the area under the curve (AUC). The predictor variables included models examined by ROC were:

A/ Age, sex and education (Basic model, as reported previously [28])

B/ Multi-variable adjusted model (including socioeconomic, lifestyle, biological factors and prevalent disease (Model 3)

C/ Variables as in Model 3, further adjusted for composite score (using the dichotomous variable of the composite)

D/ Variables as in Model 3, further adjusted for 'number of tests with poor performance' (using the 4-level variable for number of tests, as described above).

8.4.1 Missing data

The impact of missing data was examined by assigning participants with missing data to 1/ the poor performance group and then 2/ to the reference group to examine the impact on hazard ratios. Hazard ratios were examined for individuals with data on all eight cognitive tests and the specified covariates (N=6151) and compared to those with missing data of any of the eight cognitive measures as well as those not attending the health examination.

8.4.2 Sensitivity analyses

For the sensitivity analyses, participants were first grouped into approximate quartiles of cognition scores (rather the tenth percentile as a cut-off), to investigate potential difference in association with change of the percentile defining poor function. In the second sensitivity analysis, participants who had died or were diagnosed with dementia in the first five years of follow-up, were excluded to test for potential reverse causation bias.

8.5 Results

Of the 8623 individuals who took part in the 3HC, 8585 had cognitive measures with a total of 537 with a dementia diagnosis (based on the ICD codes as in Table 7.1) after a maximum of 14.8 years of follow up (mean 9.6, median 9.8 years). Four of these participants were excluded from the analyses as they received their dementia diagnosis before cognitive assessment resulting in a total of 533 dementia cases in the final analytical sample of 8581 men and women who were aged 48-92 at the time of their cognitive assessment. **Figure 8.1** summarises the participation level at each phase of the study from baseline and the selection of the analytical sample. The total number of incident dementia in EPIC-Norfolk participants from the 25, 639 individuals who attended the baseline health check at the censor date was 3187.

Table 8.1 shows the means and proportions of the variables included in this analysis by dementia status. Those with dementia, were more likely to be older, have no qualifications, more likely to be physically inactive, non-drinkers or smokers and have higher blood pressure. They were also more likely to have reported suffering from stroke, hypertension, diabetes, memory and hearing problems. Those with subsequent dementia scored lower on all the cognition tests at the 3HC, except the short-NART. Of the 8581 participants with cognitive data, 6152 participants had data for all the cognitive tests with 2391 having some of the test measures and 38 participants having none. In the healthier cohort, over half the participants did not exhibit poor performance in any of the eight cognitive measures, 26.1% exhibited poor performance in one test; 17.1% in 2-3 tests and 4.8% in 4-8 tests (**Figure 8.2**). This figure is similar to **Figure 4.1** (Chapter 4). This is repeated here as it includes the updated numbers across eight measures rather than the seven measures as used in the eariler chapters of this thesis.

Figure 8.1: Selection of study participants in the EPIC-Norfolk third health check (including pilot phase 2004–2006) for all-cause 'definite' dementia, followed until 31 March 2019.

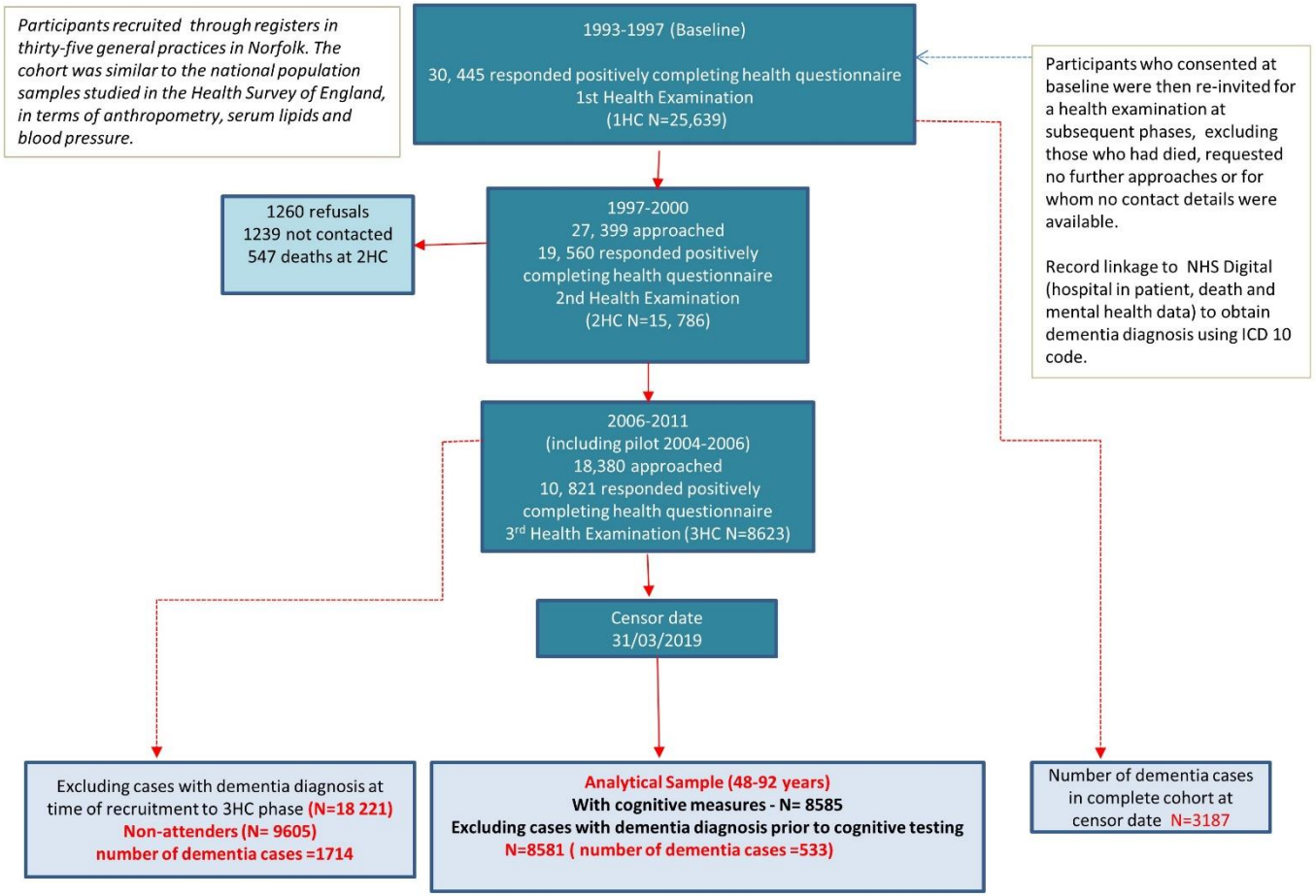


Table 8.1: Characteristics by dementia status of 8581 participants with cognitive measures in the Third Health Check Phase of the European Prospective Investigation of Cancer in Norfolk Study, 2006-2011 (including pilot data, 2004–2006). Participants followed up until 31 March 2019.

	Definite dementia		**No dementia**		
	N=537		**N=8048**		**P-Value**
Socio-demographic					
Mean (SD)					
Age	76.3	(6.2)	68.2	(7.9)	<0.001
Sex, % women (n)	50.3	(266)	55.6	(4476)	0.02
Marital status, % married (n)	69.8	(353)	78.8	(6204)	<0.001
Education, % (n)					
No qualifications	34.0	(180)	25.7	(2068)	
O/ A level Standard	51.0	(270)	56.5	(4548)	<0.001
Graduate Level	14.9	(79)	17.8	(1434)	
Social Class, % (n)					
Professional	7.8	(41)	8.9	(707)	0.5
Managerial	41.7	(220)	41.1	(3278)	
Skilled Non-Manual	17.3	(91)	16.0	(1272)	
Skilled Manual	18.8	(99)	20.7	(1647)	
Semi-Skilled	12.7	(67)	11.1	(883)	
*Retired	76.3	(5904)	95.8	(483)	<0.001
Non-Skilled	1.7	(9)	2.3	(187)	
Lifestyle					
Physically Inactive, % (n)	46.2	(237)	36.6	(2909)	<0.001
Smoking Status, % (n)					
Current	3.3	(17)	4.4	(353)	
Former	52.6	(270)	45.5	(3620)	0.01
Never	44.1	(226)	50.0	(3976)	
Alcohol Intake, % (n)					
0 Units	36.4	(180)	29.4	(2281)	
1-14 Units/week	54.1	(268)	59.1	(4586)	0.004
>14 Units per week	9.5	(47)	11.5	(896)	
Take part in regular social activities	66.7	(171)	64.4	(2830)	0.3
Biological/Physiological, mean (SD)					
Body Mass Index (Kgs/M^2)	26.7	(4.2)	26.8	(4.3)	0.4
Waist hip ratio	0.91	(0.08)	0.89	(0.08)	0.003
Total cholesterol in mmol/L	5.1	(1.17)	5.4	(1.1)	<0.001
Systolic blood pressure, mmHg	138.5	(18.0)	136.0	(16.2)	0.001
Plasma vitamin C in umol/L	60.5	(22.4)	63.2	(22.3)	0.02
FEV (mL)	2.18	(0.7)	2.46	(0.7)	<0.001

Abbreviations: FEV, forced expiratory volume; umol/L, micromoles per litre; mml/L, milliomoles per litre; mL, millilitres; mmHg: millimetres of mercury; *From main occupation at time of cognitive testing

Table 8.1: Continued…

	Definite dementia N=533		No dementia N=8048		P-Value
Prevalent disease **Co-morbidity, self-report Yes% (n)**					
Heart attack	4.0	(21)	3.4	(270)	0.5
Hypertension	37.8	(200)	24.8	(2000)	<0.001
Stroke	4.5	(24)	2.0	(158)	<0.001
Cancer	10.2	(54)	9.3	(750)	0.5
Diabetes	6.8	(36)	2.8	(224)	<0.001
Depression	18.9	(100)	21.9	(1762)	0.1
COPD	9.3	(49)	8.1	(653)	0.4
Memory problems	7.4	(39)	1.9	(152)	<0.001
Hearing problems	41.2	(218)	31.0	(2498)	<0.001
Cognitive Test Score, Mean (SD)					
SF-EMSE	29.8	(4.4)	32.8	(2.9)	<0.001
HVLT	20.0	(6.4)	25.4	(5.5)	<0.001
FTMS	12.7	(4.7)	15.8	(4.2)	<0.001
PW-Accuracy	9.7	(6.6)	13.4	(5.9)	<0.001
VST-simple	722.0	(224.6)	660.2	(161.4)	<0.001
VST-Complex	2378.0	(500.0)	2185.9	(421.7)	<0.001
Short-NART Error	17.4	(10.0)	17.2	(9.9)	0.7
Success Frequency % (N)					
Prospective memory	82.8	(6537)	57.5	(289)	<0.001

P values by T test or Chi square for proportion

Abbreviations: COPD, chronic obstructive pulmonary disease HVLT, Hopkins Verbal Learning Test, L, litre; umol, micromoles; mm, millimoles, ms, milliseconds; : N, Number; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; ; Pros. Mem, Prospective memory; PW-Acc, PW-Accuracy, SD, Standard deviation; SF-EMSE, Short Form Extended Mental State Exam; Sh-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

Hazard ratios for dementia, adjusted for age (at the time of the invitation to the 3HC) per 5 years, sex, education and social class for those who attended the health check and those who were invited but did not attend (N=9605) were examined. Using the group who had attended 3HC and had data on all 8 tests as reference, the dementia risk (adjusted for age, sex, education and social class) were as follows: with data on 5-7 tests, HR=1.12 (95%CI 0.93, 1.35 P= 0.2); 1-4 tests HR=1.38 (95%CI 0.95, 2.00 P= 0.1); attended 3HC, but with no cognition data HR=2.35 (95%CI 1.21, 4.57 P= 0.01) and for those who were invited for the 3HC but did not attend HR=1.83 (95%CI 1.61, 2.08 P= <0.001). Data shown in Table 8.2.

Figure 8.2: Distribution of poor performance across the eight measures in the EPIC-Norfolk cohort

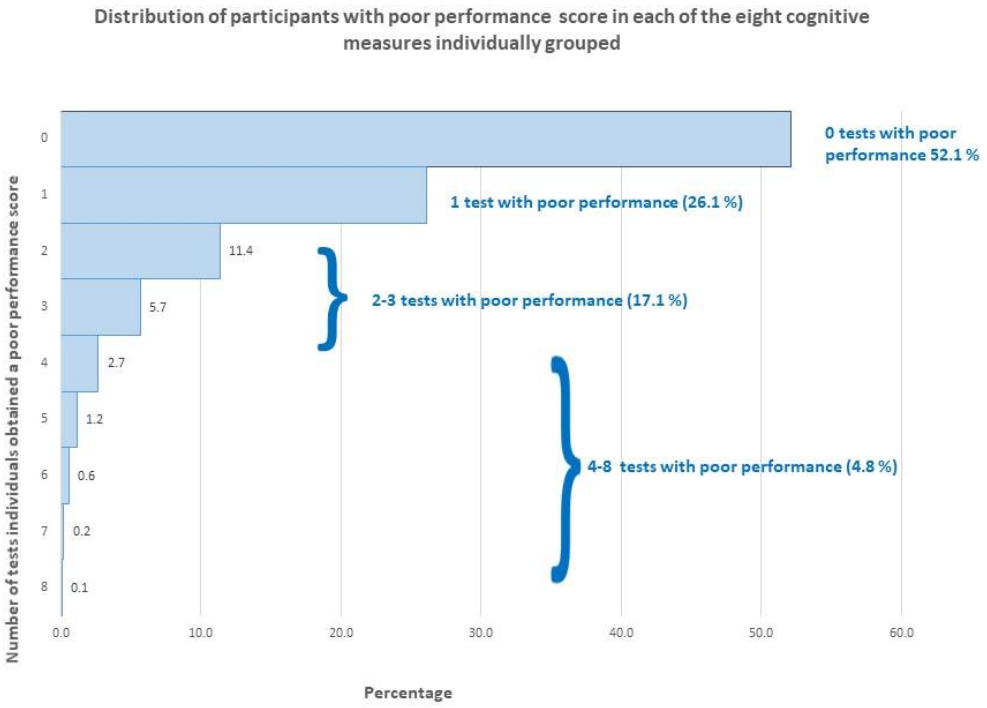


Table 8.2: Hazard ratios for dementia risk for those who attended the health examination and completed some cognitive tests and for those who were invited but did not attend, adjusted for age (at the time of the invitation to the 3HC) per 5 years, sex, education and social class.

			Attended 3HC				**Invited but did not attend 3HC**	
8 Tests	5-7 Tests		1-4 tests		0 Tests			
HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
1.00 (Ref)	1.12	(0.93, 1.35)	1.38	(0.95, 2.00)	2.35	(1.21, 4.57)	1.83	(1.61, 2.08)
	p= 0.2		p=0.1		p=0.01		p=<0.001	

Table 8.3: Association of cognitive performance (using the bottom 10th percentile as cut-off for poor performance) and dementia across the eight cognitive measures separately and a combined composite score as measured in the EPIC-Norfolk Cohort (2006–2010), including pilot data (2004–2006).

		Model 1				Model 2				Model 3			
Test, Freq (N)	**Frequency Dementia % (N)***	**Dementia (N)**	**HR**	**95% CI**	**P-Value**	**Dementia (N)**	**HR**	**95% CI**	**P-Value**	**Dementia (N)**	**HR**	**95% CI**	**P-Value**
SF-EMSE (8479)		**521**				**519**				**351**			
Poor	18.4 (201)		3.09	(2.58, 3.70)	<0.001		3.20	(2.67, 3.87)	<0.001		3.16	(2.51, 3.98)	<0.001
Good	4.3 (320)		1.00				1.00				1.00		
	P<0.001												
HVLT (8135)		**485**				**484**				**333**			
Poor	21.2 (175)		3.45	(2.84, 4.18)	<0.001		3.56	(2.93, 4.34)	<0.001		3.12	(2.44, 4.00)	<0.001
Good	4.2 (310)		1.00				1.00				1.00		
	P<0.001												
FTMS (7459)		**437**				**436**				**289**			
Poor	15.4 (126)		2.06	(1.66, 2.55)	<0.001		2.05	(1.66, 2.55)	<0.001		2.11	(1.61, 2.78)	<0.001
Good	4.7 (311)		1.00				1.00				1.00		
	P<0.001												
PW-Acc (8406)		**510**				**508**				**343**			
Poor	13.7 (133)		1.79	(1.47,2.19)	<0.001		1.82	(1.49, 2.23)	<0.001		1.78	(1.39, 2.28)	<0.001
Good	5.1 (377)		1.00				1.00				1.00		
	P<0.001												
VST- Simple (7169)		**413**				**412**				**289**			
Poor	11.9 (85)		1.77	(1.39, 2.25)	<0.001		1.80	(1.41, 2.29)	<0.001		1.78	(1.33, 2.38)	<0.001
Good	5.1 (328)		1.00				1.00				1.00		
	P<0.001												

Table 8.3: Continued…

		Model 1				Model 2				Model 3			
Test, Freq (N)	**Frequency Dementia % (N)***	**Dementia (N)**	**HR**	**95% CI**	**P-Value**	**Dementia (N)**	**HR**	**95% CI**	**P-Value**	**Dementia (N)**	**HR**	**95% CI**	**P-Value**
VST-complex (7169)		**413**				**412**				**289**			
Poor	14.8 (106)		2.15	(1.72, 2.69)	<0.001		2.17	(1.73, 2.72)	<0.001		2.18	(1.65, 2.86)	<0.001
Good	4.8 (307)		1.00				1.00				1.00		
	P<0.001												
NART Errors (8109)		**474**				**472**				**330**			
Poor	6.5 (55)		1.10	(0.83, 1.46)	0.4		1.10	(0.83, 1.46)	0.5		1.07	(0.73, 1.56)	0.7
Good	5.8 (419)		1.00				1.00				1.00		
	P=0.5												
Prospec. Memory (8400)		**507**				**505**				**341**			
Failure (1574)	13.7 (216)		2.37	(1.98, 2.84)	<0.001		2.37	(1.97, 2.84)	<0.001		2.36	(1.89, 2.95)	<0.001
Success (6826)	4.3 (291)		1.00				1.00				1.00		
	P<0.001												
Composite score (6151)		**334**				**333**				**230**			
Poor	19.4 (124)		3.50	(2.75, 4.35)	<0.001		3.71	(2.93, 4.70)	<0.001		3.51	(2.61, 4.71)	<0.001
Good	3.8 (210)		1.00				1.00				1.00		
	P<0.001												

Model 1: Socio-demographic (Age, per 5 years, sex, education and social class) factors

Model 2: Socio-demographic and lifestyle (smoking, physical activity and alcohol) factors

Model 3: Socioeconomic, lifestyle and biological (cholesterol, systolic blood pressure, BMI, WHR, FEV and plasma vitamin C) factors and prevalent disease

Abbreviations: HVLT, Hopkins Verbal Learning Test, ms, milliseconds; : N, Number; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; ; Pros. Mem, Prospective memory; PW-Acc, PW-Accuracy, SD, Standard deviation; SF-EMSE, Short Form Extended Mental State Exam; Sh-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test.

Table 8.3 shows the results of the Cox proportional hazards analysis for all the tests separately and for the composite score. For the age and sex adjusted models, there was an increased risk of dementia in those obtaining a poor performance score as compared to those who did not for each of the cognitive tests apart from the Short-NART. Further adjustments for education and social class (Model 2) and then for co-variates; smoking, body mass index, physical activity and comorbidities (Model 3), made little difference to the hazard ratios. The magnitude of the association varied slightly across tests, with the association with the composite as the strongest. Of the individual tests, the HVLT, a test for verbal episodic memory was comparable to the association observed for global cognition.

Imputing individuals with missing data into either the poor performance or reference group, slightly attenuated the hazard ratios (Table 8.4), but remained similar to those presented in the main table (Table 8.3). Missings added to the poor performance group showed greater attenuation of the hazard ratio, this is possibly because most of these individuals were unlikely to be poor performers. The analyses based on quartiles of cognitive performance (Table 8.5) showed a threshold association, mainly for the bottom two quartiles for most tests. Therefore using the more stringent cut-off in this cohort of healthier and higher functioning individuals is appropriate. Repeating the multivariable analysis after excluding individuals who died or received a dementia diagnosis within five years of follow-up after cognitive testing (Number of dementia cases=426), resulted in slight attenuation of the hazard ratios (Table 8.6). Associations based on the level of dysfunction across the cognitive abilities, showed a steep linear increase in risk of dementia, as the numbers of abilities with poor performance increased (Table 8.7).

Compared to those who did not have a poor performance score in any test, poor performance in one test doubled the risk of dementia, in 2-3 tests had a four-fold increase and those with poor performance in 4-8 tests (which was in just under 5% of the sample) had over a ten-fold increased risk of dementia, HR=10.82 (95%CI 6.85, 17.1 P=.001). Those with poor cognition in 4-8 tests showed more variability across domains than those with poor cognition in fewer domains. Controlling for each of the cognitive test as well as the composite score made little difference to the associations, as shown diagrammatically in **Figure 8.3** (with the data presented in Table 8.8), however, adjusting for HVLT (episodic memory) did attenuate the associate more than the other cognitive measures. Those who with poor performance in 4-8 tests were more likely to be older, have no qualifications, have higher reporting rate of heart attack, hypertension, stroke, diabetes, memory and hearing problems. The mean score for all the cognition tests were substantially lower for this group, including a higher NART error score. (Table 8.9).

Table 8.4: Sensitivity analysis to examine the impact of missing data on association of poor performance with dementia for each cognition score separately and the composite score

	No Missing Values (Model 3)			'Missings' assigned to 'poor performance' group (Model 3) Dementia N=362			'Missings' assigned to 'reference' group (Model 3), Dementia N=362		
Test	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**
SF-EMSE									
Poor	3.16	(2.51, 3.98)	<0.001	3.08	(2.46, 3.85)	<0.001	3.08	(2.45, 3.86)	<0.001
Good	1.00			1.00			1.00		
HVLT									
Poor	3.12	(2.44, 4.00)	<0.001	2.41	(1.92, 3.03)	<0.001	2.92	(2.30, 3.71)	<0.001
Good	1.00			1.00			1.00		
FTMS									
Poor	2.11	(1.61, 2.78)	<0.001	1.87	(1.50, 2.34)	<0.001	1.85	(1.43, 2.39)	<0.001
Good	1.00			1.00			1.00		
PW-Acc									
Poor	1.78	(1.39, 2.28)	<0.001	1.83	(1.45, 2.31)	<0.001	1.72	(1.34, 2.20)	<0.001
Good	1.00			1.00			1.00		
VST- Simple									
Poor	1.78	(1.33, 2.38)	<0.001	1.37	(1.10, 1.71)	<0.001	1.67	(1.26,2.21)	<0.001
Good	1.00			1.00			1.00		
VST-complex									
Poor	2.18	(1.65, 2.86)	<0.001	1.58	(1.28, 1.97)		2.05	(1.58, 2.67)	<0.001
Good	1.00			1.00			1.00		
NART Errors									
Poor	1.07	(0.73, 1.56)	0.7	1.08	(0.82, 1.43)	0.6	1.00	(0.69, 1.45)	0.9
Good	1.00			1.00			1.00		
Prospec. Memory									
Failure	2.36	(1.89, 2.95)	<0.001	2.38	(1.92, 2.95)	<0.001	2.22	(1.79, 2.76)	<0.001
Success	1.00			1.00			1.00		
Composite score									
Poor	3.51	(2.61, 4.71)	<0.001	2.58		<0.001	2.95	(2.33,3.73)	<0.001
Good	1.00			1.00	(2.04, 3.26)				

*Using Model 3 from the main analysis (adjusted for Socioeconomic, lifestyle and biological factors and prevalent disease). Hazard ratio for risk of dementia shown for (1) those with no missing values (2) missing values included as poor performers (3) missing values included in the reference (good) performers.

Abbreviations: HVLT, Hopkins Verbal Learning Test, ms, milliseconds; : N, Number; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; ; Pros. Mem, Prospective memory; PW-Acc, PW-Accuracy, SD, Standard deviation; SF-EMSE, Short Form Extended Mental State Exam; Sh-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

Table 8.5: Association of cognitive test score (by approximate quartile) and dementia across the eight cognitive measures separately and a combined composite score as measured in the EPIC-Norfolk Cohort (2006–2010), including pilot data (2004–2006) and followed up over average of 9.6 years, after adjustment for covariates.

		Model 1				Model 2				Model 3			
Test, Freq (N)	**Freq Dementia % (N)***	**Freq Dementia N**	**HR**	**95% CI**	**P-Value**	**Freq Dementia (N)**	**HR**	**95% CI**	**P-Value**	**Freq Dementia (N)**	**HR**	**95% CI**	**P-Value**
SF-EMSE (8479)		**521**				**519**				**351**			
Q1 (2302)	13.2 (304)		3.57	(2.21, 5.78)	<0.001		3.82	(2.35, 6.20)	<0.001		4.18	(2.30, 7.61)	<0.001
Q2 (2276)	5.5 (126)		1.77	(1.08, 2.92)	0.03		1.84	(1.12, 3.02)	0.02		2.00	(1.09, 3.69)	0.03
Q3 (2897)	2.5 (73)		0.99	(0.56, 1.66)	0.9		1.01	(0.61, 1.70)	0.9		0.99	(0.52, 1.86)	1.00
Q4 (1004)	1.8 (18)		1.00				1.00				1.00		
	P<0.001												
HVLT (8135)		**485**				**484**				**333**			
Q1 (2034)	14.0 (285)		4.33	(3.02, 6.21)	<0.001		4.63	(3.21, 6.68)	<0.001		4.14	(2.65 6.47)	<0.001
Q2 (2514)	4.3 (109)		1.70	(1.16, 2.49)	0.001		1.75	(1.19, 2.56)	0.004		1.74	(1.10, 2.75)	0.02
Q3 (1640)	3.4 (55)		1.46	(0.96, 2.22)	0.08		1.47	(0.96, 2.24)	0.07		1.52	(0.92, 2.49)	0.1
Q4 (1947)	1.8 (36)		1.00				1.00				1.00		
	P<0.001												
PAL-FTMS (7459)		**437**				**436**				**289**			
Q1 (2073)	10.7 (221)		3.03	(1.92, 4.77)	<0.001		3.05	(1.93, 4.82)	<0.001		4.14	(2.22,7.75)	<0.001
Q2 (2093)	5.8 (121)		2.12	(1.33, 3.39)	0.002		2.13	(1.34, 3.40)	0.001		2.83	(1.50, 5.34)	0.001
Q3 (2012)	3.7 (74)		1.59	(0.98, 2.59)	0.06		1.62	(0.99, 2.63)	0.05		2.31	(1.20, 4.44)	0.04
Q4 (1281)	1.6 (21)		1.00				1.00				1.00		
	P<0.001												
PW-Acc (8406)		**510**				**508**				**343**			
Q1 (2103)	11.5 (241)		2.42	(1.77, 3.32)	<0.001		2.43	(1.77, 3.34)	<0.001		2.75	(1.83, 4.15)	<0.001
Q2 (2229)	6.5 (144)		1.54	(1.11, 2.14)	0.01		1.55	(1.12, 2.16)	0.01		1.81	(1.18, 2.75)	0.01
Q3 (2153)	3.5 (76)		1.04	(0.72, 1.49)	0.8		1.03	(0.72, 1.48)	0.9		1.28	(0.81, 2.01)	0.3
Q4 (1921)	2.6 (49)		1.00				1.00				1.00		
	P<0.001												

Table 8.5: Continued…

		Model 1				Model 2				Model 3			
	Frequency Dementia % (n)	Freq Dementia N	HR	95% CI	P-Value	Freq Dementia N	HR	95% CI	P-Value	Freq Dementia N	HR	95% CI	P-Value
VST- Simple (7169)		**413**				**412**				**289**			
Q1 (1789)	8.9 (159)		1.47	(1.10, 1.96)	0.01		1.45	(1.09, 1.94)	0.01		1.33	(0.94, 1.87)	0.1
Q2 (1795)	5.5 (99)		1.04	(0.76, 1.41)	0.8		1.02	(0.75, 1.40)	0.9		0.94	(0.65, 1.37)	0.8
Q3 (1794)	4.8 (87)		1.03	(0.75, 1.42)	0.9		1.05	(0.77, 1.45)	0.8		1.05	(0.72, 1.53)	0.8
Q4 (1791)	3.8 (68)		1.00				1.00				1.00		
	P<0.001												
VST-complex (7169)		**413**				**412**				**289**			
Q1 (1791)	9.9 (177)		1.59	(1.20, 2.11)	0.01		1.61	(1.21, 2.13)	0.001		1.41	(1.01, 1.98)	0.04
Q2 (1793)	5.1 (92)		1.11	(0.81, 1.52)	0.5		1.11	(0.81, 1.52)	0.5		1.03	(0.71, 1.48)	0.9
Q3 (1793)	4.2 (75)		1.01	(0.73, 1.40)	1.0		1.01	(0.73, 1.40)	1.0		0.91	(0.62, 1.35)	0.6
Q4 (1792)	3.9 (69)		1.00				1.00				1.00		
	P<0.001												
NART Errors (8109)		**474**				**472**				**330**			
Q1 (1835)	6.2 (114)		0.93	(0.72, 1.19)	0.6		0.94	(0.70, 1.25)	0.7		0.85	(0.59, 1.21)	0.4
Q2 (2218)	5.9 (130)		0.89	(0.70, 1.14)	0.4		0.91	(0.70, 1.18)	0.5		0.86	(0.63, 1.18)	0.4
Q3 (2003)	5.2 (104)		0.80	(0.62, 1.04)	0.1		0.80	(0.62, 1.04)	0.1		0.83	(0.61, 1.13)	0.3
Q4 (2053)	6.1 (126)		1.00				1.00				1.00		
Composite score (6151)	P=0.5												
Composite score (6151)		**334**				**333**				**230**			
Q1 (1845)	10.8 (200)		3.82	(2.41, 6.06)	<0.001		4.16	(2.60, 6.66)	<0.001		4.87	(2.68, 8.85)	<0.001
Q2 (1368)	5.2 (71)		2.17	(1.33, 3.55)	0.002		2.22	(1.35, 3.64)	0.002		2.58	(1.38, 4.82)	0.003
Q3 (1401)	3.0 (42)		1.59	(0.94, 2.69)	0.08		1.62	(0.96, 2.75)	0.07		1.97	(1.02, 3.78)	0.04
Q4 (1537)	1.4 (21)		1.00				1.00				1.00		
	P<0.001												
Prospec. Memory (8400)		**507**				**505**				**341**			
Failure (1574)	13.7 (216)		2.37	(1.98, 2.84)	<0.001		2.37	(1.97, 2.84)	<0.001		2.36	(1.89, 2.95)	<0.001
Success (6826)	4.3 (291)		1.00				1.00				1.00		
	P<0.001												

Table 8.6: Sensitivity Analysis showing association with dementia after excluding individuals who died or were diagnosed with dementia within 5 years of cognitive testing (N=426 dementia cases).

		Excluding death and dementia cases within 5 years*		
Test, Frequency (N)	**Dementia (N)**	**HR**	**95% CI**	**P-Value**
SF-EMSE (7760)	**288**			
Poor		2.63	(2.02, 3.41)	<0.001
Good		1.00		
HVLT (7482)	**277**			
Poor		2.8	(2.14, 3.72)	<0.001
Good		1.00		
FTMS (6856)	**240**			
Poor		1.80	(1.32, 2.46)	<0.001
Good		1.00		
PW-Acc (7707)	**283**			
Poor		1.54	(1.16, 2.05)	0.002
Good		1.00		
VST- Simple (6594)	**236**			
Poor		1.66	(1.18, 2.31)	0.003
Good		1.00		
VST-complex (6594)	**238**			
Poor		1.61	(1.16, 2.24)	0.01
Good		1.00		
NART Errors (7074)	**273**			
Poor		1.03	(0.68, 1.57)	0.9
Good		1.00		
Prospective Memory (7696)	**283**			
Failure (1574)		2.25	(1.76, 2.87)	<0.001
Success (6826)		1.00		
Composite score (5673)	**189**			
Poor		2.94	(2.11, 4.11)	<0.001
Good		1.00		

Table 8.7: Association between number of tests with a poor performance score and dementia, adjusting for all the co-variates (Model 3) and excluding those with dementia prior to attending the 3HC (N= 4485).

		Model 3		
Number of tests where participants obtained a poor performance score	**Freq Dementia (N)**	**HR**	**95% CI**	**P-Value**
	230			
0 (N=2365)		1.00		
1 (N=1184)		2.18	(1.45,3.27)	<0.001
2-3 (N=745)		4.30	(2.90, 6.39)	<0.001
4-8 (N=200)		10.82	(6.85, 17.1)	<0.001

Figure 8.3: Diagrammatic representation of association between level of poor cognition and risk of dementia, controlling for each of the cognitive test.

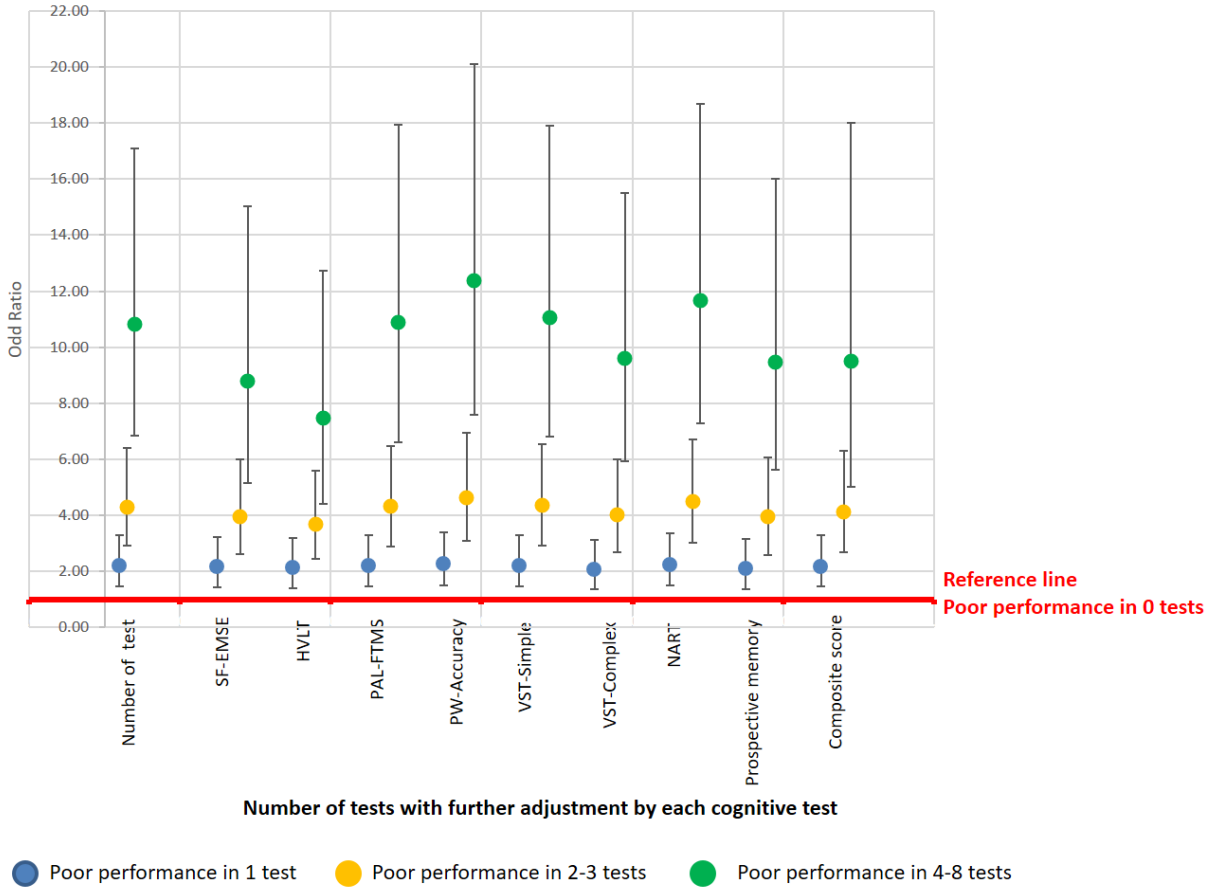


Table 8.8: Association of the number of cognitive tests and dementia with adjustment for co-variates (Model 3) and then additional adjustment for individual cognitive tests and composite score.

		Model 3 (with no adjustment for any cog measure)			Model 3 and further adjusted for SF-EMSE			Model 3 and further adjusted for HVLT			Model 3 and further adjusted for FTMS			Model 3 and further adjusted for PW_Acc		
Number of tests where participants obtained a poor performance score	**Freq Dementia (N)**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**
	321															
0 (N=3138)		1.00			1.00						1.00			1.00		
1 (N=1567)		2.06	(1.47, 2.89)	<0.001	2.01	(1.43, 2.82)	<0.001	1.96	(1.40, 2.76)	<0.001	2.07	(1.47, 2.91)	<0.001	2.12	(1.51, 2.98)	<0.001
2-3 (N=1011)		3.69	(2.65, 5.14)	<0.001	3.34	(2.36, 4.73)	<0.001	2.98	(2.09, 4.23)	<0.001	3.76	(2.68, 5.29)	<0.001	4.00	(2.85, 5.62)	<0.001
4-8 (N=279)		9.15	(6.27, 13.37)	<0.001	7.20	(4.59, 11.30)	<0.001	5.54	(3.54, 8.68)	<0.001	9.52	(6.28, 14.43)	<0.001	10.44	(6.90, 15.58)	<0.001

Table 8.8: continued…

		Model 3 and further adjusted for VST-Simple			Model 3 and further adjusted for VST-Complex			NART			Model 3 and further adjusted for PM_S			Model 3 and further adjusted for Composite Score		
Number of tests where participants obtained a poor performance score	**Freq Dementia (N)**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-Value**
	321															
0 (N=3138)		1.00			1.00			1.00			1.00			1.00		
1 (N=1567)		2.08	(1.48, 2.92)	<0.001	1.97	(1.40, 2.78)	<0.001	2.10	(1.50, 2.95)	<0.001	1.96	(1.38, 2.77)	<0.001	2.06	(1.47, 2.89)	<0.001
2-3 (N=1011)		3.77	(2.68, 5.29)	<0.001	3.50	(2.50, 4.91)	<0.001	3.88	(2.78, 5.42)	<0.001	3.39	(2.37, 4.85)	<0.001	3.23	(2.24, 4.67)	<0.001
4-8 (N=279)		9.48	(6.35, 14.15)	<0.001	8.36	(5.62, 12.44)	<0.001	10.11	(6.81, 15.01)	<0.001	7.95	(5.12, 12.34)	<0.001	6.45	(3.78, 11.02)	<0.001

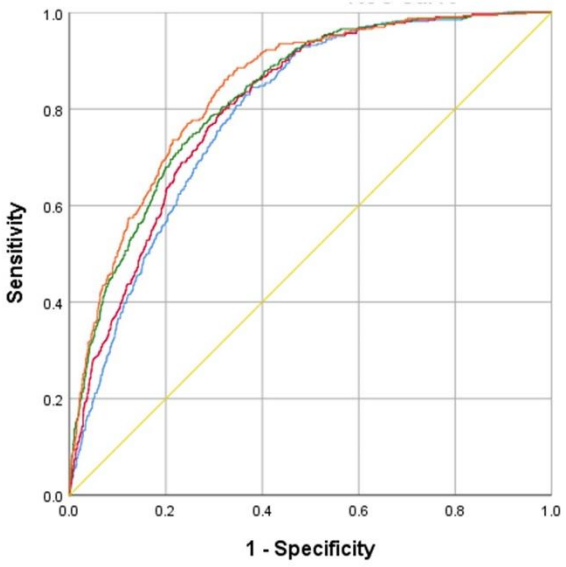
Table 8.9: Comparison of characteristics of individuals in the poor performance group across the eight cognitive measure.

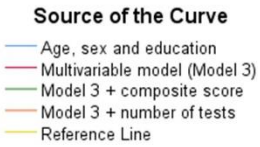
	0 tests	1 test	2-3 tests	4-8 tests	P-Value
Socio-demographic					
Mean (SD)					
Age	65.9 (7.1)	68.8 (7.5)	71.4 (7.6)	74.5 (7.1)	<0.001
Sex, % women (N)	58.9 (1888)	54.7 (879)	47.1 (495)	46.4 (134)	<0.001
Education as reported at baseline % (N)					
No qualifications	15.2 (489)	28.1 (451)	40.6 (426)	52.8 (152)	
O/ A level Standard	60.7 (1947)	56.4 (906)	51.2 (537)	43.8 (126)	<0.001
Graduate Level	24.0 (771)	15.5 (249)	8.2 (86)	3.5 (10)	
Prevalent disease					
Co-morbidity, self report Yes% (N)					
Heart attack	2.4 (77)	3.1 (49)	4.4 (46)	5.5 (16)	0.001
Hypertension	24.2 (777)	23.0 (369)	28.5 (299)	29.1 (84)	0.003
Stroke	1.3 (41)	1.8 (29)	2.4 (25)	7.3 (21)	<0.001
Cancer	8.7 (278)	8.9 (143)	11.0 (115)	8.7 (25)	0.2
Diabetes	2.5 (81)	2.7 (44)	3.4 (36)	6.2 (18)	0.003
Depression	22.6 (725)	21.9 (352)	18.9 (198)	22.1 (64)	0.1
COPD	8.5 (273)	8.3 (134)	6.7 (70)	5.9 (17)	0.1
self-report mem. Problem	0.9 (28)	1.6 (25)	3.7 (39)	12.1 (35)	<0.001
Hearing Problems	28.9 (928)	32.3 (518)	33.2 (349)	38.4 (111)	0.001
Cognitive Test Score, Mean (SD)					
SF-EMSE	34.0 (1.7)	32.9 (2.2)	30.9 (2.8)	27.6 (3.2)	<0.001
HVLT	27.4 (4.2)	25.1 (4.9)	21.5 (5.4)	16.3 (5.3)	<0.001
PAL- FTMS	17.8 (3.2)	15.5 (3.9)	13.3 (4.3)	9.9 (4.4)	<0.001
PW-Accuracy	15.6 (4.7)	12.8 (5.7)	9.4 (6.3)	5.8 (6.1)	<0.001
VST-simple, reaction time	615.1 (66.3)	670.87 (141.8)	732.6 (196.3)	844.5 (294.2)	<0.001
VST-Complex, reaction time	2082.9 (269.8)	2223.9 (377.3)	2338.5 (488.1)	2600.0 (691.2)	<0.001
Short-NART Error	13.8 (7.4)	18.1 (9.8)	23.1 (10.6)	27.9 (10.9)	<0.001
Success Frequency % (N)					
Prospective memory	100 (3207)	72.5 (1165)	56.4 (592)	23.5 (68)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease HVLT, Hopkins Verbal Learning Test, N, Number; PAL-FTMS, Paired Associated Learning, First Trial Memory Score; ; Pros. Mem, Prospective memory; PW-Acc, PW-Accuracy, SD, Standard deviation; SF-EMSE, Short Form Extended Mental State Exam; Short-NART, Short National Adult Reading Test; VST, Visual Sensitivity Test

The ROC curves in **Figure 8.4** show the accuracy of the models presented in this study. Age most powerful factor even under 5 year bands. The AUC successively improved marginally from the basic model with addition of the covariates (Model 3), further with cognitive measure (shown here with the composite score); with the greatest predictive power of the final model which included 'number of tests'.Multiple logistic regression was used to generate predicted probabilities for three models (1) adjusted for age, sex and education (2) the multivariate model with all co-variates (Model 3) excluding the cognitive test and (3) Model 3 plus cognitive performance for each of the tests and the composite score using both quartile and tenth percentile cut-offs. AUC values for these models for the individual tests (with the odds ratios from the multiple logistic regression used to generate the predicted probabilities) are presented in Tables 8.10 and 8.11 respectively.

Figure 8.4: ROC curves for the prediction of incident dementia according to (1) age, sex, and education (2) with additionally adjusted for co-variates included in Model 3 (3) Model 3 + composite score (4) Model 3+ number of tests.





	AUC	95% CI	P-value
Age, sex, education	0.79	(0.77, 0.82)	<0.001
Model 3	0.81	(0.78, 0.83)	<0.001
Model 3+ Composite score	0.83	(0.81, 0.86)	<0.001
Model 3+ number of tests	0.85	(0.82, 0.87)	<0.001

Table 8.10: Odds ratios (with 95%CI) of definite dementia diagnosis based on risk factors included (1) age, sex and education and (2) the fully adjusted and the multi-variate adjusted model (Model 3) as used in the cox regression as used in the main analysis. Also presenting AUC values as created from the predicted probabilities from multiple logistic regression.

Risk factor	OR	95% CI	P-Value	AUC	95%CI	P-Value
Minimally adjusted model N=8579				0.79	(0.77, 0.80)	<0.001
Age per 5 years	1.92	(1.81, 2.05)	<0.001			
Sex (Men)	1.07	(0.89, 1.29)	0.5			
Education (No Qualifications)	1.11	(0.91, 1.35)	0.3			
Model 3 (Multi-variate model) N=8382				0.80	(0.78, 0.81)	<0.001
Age per 5 years	1.94	(1.80, 2.08)	<0.001			
Sex (Men)	1.04	(0.86, 1.27)	0.7			
Education (No Qualifications)	1.12	(0.91, 1.38)	0.3			
Social class (Manual)	1.04	(0.84, 1.28)	0.7			
Smoking (current)	1.37	(0.83, 2.27)	0.2			
Physical activity (Inactive)	0.83	(0.69, 1.01)	0.07			
Co-morbidity, self-report Yes% (n)						
Heart attack	0.53	(0.32, 0.88)	0.01			
Hypertension	1.35	(1.11, 1.64)	0.003			
Stroke	1.41	(0.85, 2.33)	0.2			
Cancer	0.80	(0.58, 1.09)	0.2			
Diabetes	1.85	(1.24, 2.77)	0.002			
Depression	1.16	(0.91, 1.47)	0.2			
COPD	1.11	(0.80, 1.53)	0.6			
Memory problems	2.25	(1.52, 3.34)	<0.001			
Hearing Problems	1.04	(0.86, 1.27)	0.7			

Abbreviations: COPD, chronic obstructive pulmonary disease; OR, Odds Ratio

Table 8.11: Odds ratios (with 95%CI) of dementia from the multiple logistic regression of the multi-variate model (Model 3) with additional adjustment for the eight cognitive measure, composite score and number of tests. Both quartile and tenth percentile cut-offs shown with corresponding AUC values for each model.

Test, Freq (N)	HR	95% CI	P-Value	AUC	95%CI	P-Value
SF-EMSE (8285)						
Quartiles				0.82	(0.80, 0.84)	<0.001
Q1 (2231)	3.97	(2.41, 6.55)	<0.001			
Q2 (2234)	1.93	(1.15, 3.22)	0.01			
Q3 (2835)	1.05	(0.62, 1.78)	0.9			
Q4 (985)	1.00					
10th PCTILE				0.82	(0.80, 0.83)	<0.001
Poor	3.14	(2.53, 3.89)	<0.001			
Good	1.00					
HVLT (7951)						
Quartiles				0.82	(0.80, 0.84)	<0.001
Q1 (1977)	3.92	(2.68, 5.73)	<0.001			
Q2 (2459)	1.66	(1.12, 2.46)	0.001			
Q3 (1612)	1.43	(0.93, 2.22)	0.1			
Q4 (1903)	1.00					
10th PCTILE				0.82	(0.80, 0.84)	<0.001
Poor	3.49	(2.78, 4.39)	<0.001			
Good	1.00					
FTMS (7281)						
Quartiles				0.81	(0.79, 0.83)	<0.001
Q1 (2005)	3.07	(1.91, 4.92)	<0.001			
Q2 (2053)	2.23	(1.38, 3.62)	0.001			
Q3 (1962)	1.81	(1.10, 2.98)	0.02			
Q4 (1261)	1.00					
10th PCTILE				0.81	(0.79, 0.83)	<0.001
Poor	1.98	(1.54, 2.54)	<0.001			
Good	1.00					
PW-Acc (8215)						
Quartiles				0.81	(0.79, 0.82)	<0.001
Q1 (2040)	2.31	(1.65, 3.25)	<0.001			
Q2 (2174)	1.55	(1.10, 2.21)	0.01			
Q3 (2120)	1.04	(0.71, 1.52)	0.8			
Q4 (1881)	1.00					
10th PCTILE				0.81	(0.79, 0.82)	<0.001
Poor	1.79	(1.42, 2.26)	<0.001			
Good	1.00					

Table 8.11: continued….

	Based on Model 3					
	HR	**95% CI**	**P-Value**	**AUC**	**95%CI**	**P-Value**
VST- Simple (6997)						
Quartiles				0.80	(0.78, 0.82)	<0.001
Q1 (1738)	1.52	(1.11, 2.08)	0.01			
Q2 (1754)	1.04	(0.75, 1.46)	0.8			
Q3 (1756)	1.17	(0.83, 1.65)	0.4			
Q4 (1749)	1.00					
10th PCTILE				0.80	(0.79, 0.82)	<0.001
Poor	1.74	(1.32, 2.29)	<0.001			
Good	1.00					
VST-complex (6997)						
Quartiles				0.80	(0.79, 0.82)	<0.001
Q1 (1740)	1.52	(1.12, 2.06)	0.01			
Q2 (1755)	1.03	(0.74, 1.44)	0.9			
Q3 (1751)	0.92	(0.65, 1.30)	0.6			
Q4 (1751)	1.00					
10th PCTILE				0.81	(0.79, 0.83)	<0.001
Poor	2.17	(1.67, 2.82)	<0.001			
Good	1.00					
NART Errors (8109)						
Quartiles				0.80	(0.78, 0.82)	<0.001
Q1 (1782)	0.94	(0.68, 1.28)	0.7			
Q2 (2154)	0.84	(0.63, 1.12)	0.4			
Q3 (1956)	0.81	(0.61, 1.07)	0.1			
Q4 (2027)	1.00					
10th PCTILE				0.80	(0.78, 0.82)	<0.001
Poor	0.94	(0.68, 1.28)	0.7			
Good	1.00					
Composite score (6151)						
Quartiles				0.82	(0.80, 0.84)	<0.001
Q1 (1786)	4.01	(2.47, 6.53)	<0.001			
Q2 (1336)	2.24	(1.34, 3.74)	0.002			
Q3 (1370)	1.70	(0.99, 2.91)	0.06			
Q4 (1509)	1.00					
10th PCTILE				0.83	(0.81, 0.85)	<0.001
Poor	3.64	(2.76, 4.80)	<0.001			
Good	1.00					
Pros. Memory (8210)				0.81	(0.80, 0.83)	<0.001
Failure (1531)	2.37	(1.98, 2.84)	<0.001			
Success (6679)	1.00					
Number of tests				0.84	(0.82, 0.86)	<0.001
4-8 (N=279)	8.79	(5.77, 13.39)	<0.001			
2-3 (N=1011)	3.82	(2.70, 5.40)	<0.001			
1 (N=1567)	2.04	(2.70, 5.40)	<0.001			
0 (N=3138)	1.00	(1.44, 2.90)	<0.001			

8.6 Discussion

This work presents findings on the value of a range of cognitive tests and their individual predicted risk of dementia in this cohort of individuals mid-late life. Dementia is associated with lower cognitive function many years before the recognised onset of the disease, [77,81] with preclinical disease on a continuum from completely asymptomatic individuals. [33] This chapter reports on eight simple cognitive tests that accurately predict an average of a decade before the onset of dementia. The more pervasive and greater the variability, the higher the risk of dementia. Presented here is additional evidence on the utility of a range of cognitive tests and the predicted risk of dementia in individuals free of dementia at the time of cognitive testing. Impairment in multiple domains, independently predicted risk of dementia over and above performance score of individual tests or a composite score. Poor cognition in four or more tests is associated with a ten-fold increased risk of developing dementia compared to those not performing poorly in any test. The addition of cognition score (using just the composite score AUC=0.83), improved the multivariable adjusted model alone (AUC=0.81), and including the number of tests with impaired cognition, improved the model even further (AUC=0.85). These findings are comparable to other studies of risk prediction models. [27,28]

There are a number of limitations to this work. The first as discussed previously, is the issue of healthy volunteer bias. However, there is a wide representation of individuals in terms of age, education, social class and both men and women as in the general population. [213] As the focus of the 3HC was on aspects of ageing, it could be said that participants had concerns on their cognition. However, this seems unlikely as the majority of individuals scored well and the differences between the impaired group and the reference group were large.

Those who did not attend this interview but had given permission to track medical records had 83% higher risk of dementia than those who attended and did all eight cognitive test (HR=1.83 (95%CI 1.61, 2.08 P= <0.001)). The use of a self-report measure of many of the factors may also be criticised as prone to recall biases or not accurate as an objective measure. Conducting this study in this healthier population has the advantage of less confounding from co-morbidities. Although a wide range of factors were adjusted for, due to the nature of an observational study, residual confounding cannot be excluded.

Using medical records allows a more complete follow-up, limiting attrition as a bias and is widely used method in epidemiological research. [28] The downside of this is the dependence on medical records, prone to inconsistencies across time, with changes in policy and practice raising concerns over the accuracy and changing completeness of dementia recording. [91,92] Also, as highlighted previously in Chapter 7, medical records are known to underestimate the number of individuals with dementia, as

not all individuals receive a formal diagnosis. Nevertheless, even though less sensitive, medical record diagnosis is likely to be highly specific such that when an individual has a diagnosis or death certification with dementia recorded this is highly likely to be accurate. [92]

Although adjudication may increase sensitivity, in a large cohort study, misclassification of relatively few positive cases as non-cases will have little impact on the overall association. Ascertainment was maximised by using a broad definition of 'any definite dementia' from a range of data sources. Any methodological changes (such as those for dementia mortality), are likely to have little impact on the overall rates for dementia. Using 'definite dementia' as the outcome, is also a limitation, as it could be missing milder forms of cognitive dysfunction. There was minimal change in association when removing those with a dementia diagnosis or who had died within 5 years of cognitive testing. However, reverse causation cannot be ruled out due the long preclinical phase of dementia. [243] Further follow-up time is needed, although determining temporality for dementia will always be challenging. Also, having a wide age range at baseline, it is possible to observe the different influence of factors and how their relationship varied with dementia as midlife or later life exposures.

The cognition assessment in EPIC-Norfolk was a comprehensive battery covering a wide range of domains. These results are comparable to the predictive values reported in previous studies, [27] including those recently reported by UK Biobank. [28] However, this study goes beyond the predictive accuracy of cognitive test score alone, and demonstrates the added value of including the level of impairment as measured across multiple domains.

Substantial cognitive changes occur with healthy ageing. Previous studies have shown that there are milder or pre-symptomatic stages of dementia, not limited to memory. [80,82] This work confirms these findings in this larger cohort with a wider age range. It is quite possible to misclassify milder symptoms or asymptomatic without memory concerns as normal cognitive aging. These findings also clearly show the magnitude of the predictive accuracy of a wide range of cognitive tests from the same cohort, with some tests predicting better than others. In particular, this work shows that tests of processing speed are not as powerful as the other tests. These points are important to consider in future work.

It is extremely important to disentangle confounding caused by methodological variation to understand who are at greatest risk. Here, the risk predicted was ten-fold greater in those with pervasive impairment, however the confidence intervals for this group were wide due to smaller size of this group. This gives some uncertainty of the true magnitude of the increased risk. Other cohort

studies examining dementia risk should consider impairment across multiple domains in their prediction models to examine the association within their settings.

Even with a ten-fold increased risk of dementia in those with more pervasive impairments, the findings do not support future screening or use of predictive modelling for diagnostic use for dementia and agree with recommendations of the USPSTF. [261] Predictive modelling will always result in a considerable number of false positives and is very much a research tool at present. It does however, provide the necessary insight to factors that either increase or decrease risk of dementia. Detecting the earliest phases of impairment across cognitive domains, could inform the design of trials of preventive or modifying interventions [6] and identify target populations greatest at risk who can then also be included in such trials.

Summary of Chapter

- There were 537 participants with a dementia diagnosis in EPIC-Norfolk with a maximum of 14.8 years of follow up (median 9.8 years).
- Poor cognition was predictive of incident dementia across all abilities, even after adjustment for co-variates.
- Compared to those who did not have a poor performance score in any test, poor performance in one test doubled the risk of dementia.
- Those with a poor performance score for global cognition (bottom 10%) were almost four times as likely to get a dementia diagnosis than those who performed well HR=3.51 (95%CI 2.61, 4.71 p<0.001).
- Cognitive measures strengthen prediction models of dementia AUC = 0.83 (95%CI 0.81, 0.85 p<0.001).

Chapter 9: Discussion

9.1 Summary of findings

This thesis explores the relationship of a number of non-modifiable and modifiable factors and cognition across a range of function and cognitive abilities. A major focus of this work was to get a better understanding and insight to heterogeneity in cognitive performance observed in older people and to identify what influences are important to consider when assessing cognitive function in an ageing population. This dissertation presents a number of key findings on cognitive function from EPIC-Norfolk, a 25-year prospective cohort study that are presented in Box 9.1, adding to existing evidence from previous epidemiological studies on cognitive function and dementia. Heterogeneity in population characteristics, differences in methodologies and inadequate control of confounding are contributing to the inconsistencies observed across studies investigating relationship modifiable risk factors and cognitive impairment and dementia. It is important to disentangle confounding by methodological variation to have a clearer understanding of these associations.

The European Prospective Investigation into Cancer in Norfolk is a prospective population study of 25 639 men and women aged 40–79 years when recruited in 1993–1997 and followed up to the present. The infrastructure of this study was used to examine the epidemiology of cognitive function in this middle aged and older general population. Most studies of cognitive function hitherto have been based in older populations, or in selected groups such as occupational cohorts. In a 2006–2011 at a follow up examination 8585 men and women from the cohort undertook a range of cognitive tests. Individuals were cognitively unimpaired at time of testing. The cohort has been followed up through record linkage with routine health records to ascertain dementia endpoints.

In the first part of the thesis, I examine the descriptive epidemiology of cognitive function in this population to provide further insight into the relationship with various demographic and lifestyle factors. Cognitive function profiles are presented across a range of domains using previously validated assessment tools in this cohort of men and women in mid to later life. In general, cognition declines with age but there is a wide range of capability from poor to high performance across each age band, with some participants from the oldest age group outperforming their younger counterparts. I addressed a number of issues relating to the variability and heterogeneity of cognitive function observed in older people and provide further insight into the potential reasons for the inconsistencies reported in the current literature. In the second part of the thesis, I explore the prospective relationship between cognitive function and subsequent mortality and incident dementia.

Box 9.1: Summary of key findings from this thesis

Confirmation of previous findings

- Variability, heterogeneity and dispersion exists for the range of cognitive domains assessed. There is a wide variation in cognitive performance in the EPIC-Norfolk cohort.
- With fewer studies involving the healthy and cognitively unimpaired, this thesis adds to the understanding not only in terms of impairment, but across the spectrum, including that of high cognitive function.
- This work addresses the question of what is important to measure when assessing cognitive function using a broad range of cognitive measures.
- The EMSE is able to differentiate between individuals at the high end of the ability range in this general functioning population. Even a small number of additional items can extend the higher end of performance range.
- Unlike for the MMSE, those in the highest performance group of the short-form EMSE were not in the poor performance group of the other tests, demonstrating the greater discriminative ability of the EMSE (even in the shortened form).
- This thesis details the psychometric qualities and utility of a range of validated tests using, as a comparator, the widely used MMMSE test, known for its ceiling effects. Those with the highest possible MMSE score could potentially be in the poor performance group of another cognitive test.

New findings (Methodological)

- The short-NART equation for predicting the full NART score, is not as reliable in a more general population as it was in the elderly population it was originally tested on.
- A recommendation from this investigation is to lower the cut-off even further so that there is no need to use the algorithm for the short-NART.

Influence of socio-economic factors

- The relationship of socio-demographic factors with performance varies according to the cognitive test. These differences are observed even across different tests purporting to test the same ability.
- Education is strongly associated with cognitive function across all the abilities. However, this association varies considerably across abilities. Not having qualifications in those <65 years is associated with greater risk of being in the poor performance group. For the SF-EMSE, comparing those with an education up to 'O' or 'A' level compared to those with no qualification, is equivalent to those almost 10 years younger and for those at graduate level, the likelihood is equivalent to those younger by nearly 20 years.

Box 9.1: continued

Novel findings for physical activity

- This thesis presents novel evidence on physical activity during work and leisure time from individuals across a wide range of socio-economic background and education, showing that this relationship is complex.
- Inconsistencies in the literature on physical activity and cognitive function may be attributable to studies not addressing residual confounding by education adequately.
- Physical inactivity during work is inversely associated with poor cognitive performance. Manual workers had almost three times increased risk of poor performance compared to those with an occupation classified as inactive.

Insight to characterisation of dementia outcomes

- Present differences of all-cause dementia incidence as ascertained across major data sources used in epidemiological research. There is a lack of consistency in dementia ascertainment from different routinely collected health records.
- The work presents new insight into the more recent mental health services dataset.
- This thesis highlights potential reasons for discrepancies across the different data sources. There is need to develop a more consensus approach to methods of data collection, coding and interpretation of routinely collected health data.

Cognitive predictors of mortality and dementia

- Poor cognition is independently associated with higher risk of all-cause mortality
- The relationship with mortality varies across cognitive abilities.
- Poor cognition has a greater disadvantage in terms of survival for those with no qualifications.
- Poor cognition predicts incident dementia. This association was observed for those in the bottom 10% of the composite score HR=3.51 (95%CI 2.74, 4.48 p<0.001) as well as for the specific cognitive abilities.
- Although associations vary across abilities, poor performance in the test for verbal episodic memory is particularly good in predicting dementia. Cognitive measures strengthen prediction models of dementia AUC = 0.83 (95%CI 0.81, 0.85 p<0.001).
- Impairment in multiple domains, independently predicts risk of dementia over and above the performance score of individual tests or a composite score.
- The more pervasive and greater the variability, the higher the risk of dementia. Poor cognition in four or more tests is associated with a ten-fold increased risk of developing dementia compared to those not performing poorly in any test.

9.2 Strengths and Limitations

9.2.1. Strengths

The setting of the EPIC-Norfolk has allowed the exploration of cognitive function from earlier stages of decline, a time-point of great interest in terms of identifying early indicators cognitive impairment and dementia. The large sample size, longer follow up, wider age range, large number of co-variates, characterisation of exposure and the detailed measure of cognition has identified the implications of confounding on associations that has not been clear in previous studies. This clearly demonstrates that variation in methods for measuring and characterising the exposure will give different associations for addressing the same research question.

The emphasis of EPIC-Norfolk has always been the development and use of better epidemiological assessment tools for diet, physical activity and now this has extended to include cognition. The other strengths include the large sample size, and the long follow up from baseline of over 25 years and up to 15 years from cognitive testing to time of time of follow-up for dementia outcomes. Although the cohort is not ethnically diverse, the population at baseline was similar to the national population samples studied in the Health Survey of England, in terms of anthropometry, serum lipids and blood pressure. [137] Furthermore, unlike other studies that are more restrictive in age, sex or based on specialised groups such as occupations cohorts that may not represent the general population, the EPIC-Norfolk cohort comprises both men and women, covers a broad range in age, education and social class.

Even in this relatively well-functioning group that underwent cognitive testing, [138] there was a wide range of cognitive performance across all cognitive domains. The use of an extensive battery was also an advantage allowing assessment across a broad range of abilities. With the availability of longitudinal exposure and health outcome data from baseline to the present, this cohort provides the ideal opportunity to examine the trajectory of functioning in the general population and across a wide range of cognitive function, to allow examination of correlates of high as well as poor performance.

9.2.2. Limitations

The main limitation is healthy volunteer bias and attrition. Those who attended the 3HC were healthier and younger individuals, with older, frailer and cognitively impaired individuals more likely to be lost to follow-up. The less frail cognitively impaired will be less likely to attend, as discussed in Chapter 3, and this would result in selective truncation of individuals from the lower cognitive performance. However, despite this, there was still a broad range of ability observed across a wide age range. The

baseline characteristics available on the individuals from the first health examination allowed comparisons and some characterisation of those who did not attend the third health examination who had cognitive measures. Nevertheless, irrespective of whether individuals attended subsequent examinations, the whole cohort from baseline had complete follow-up using health record linkage.

Although an extensive cognition battery was used to measure cognition, EPIC-Norfolk was not primarily a study of cognitive function at baseline, and the measures of cognition were incorporated at a subsequent examination. However, the compliance rate for the cognitive measures was exceptionally high, where out of the 8623 individuals who attended the 3HC, 8585 had a cognitive test measure. The other limitation is that, although this study incorporates over 25 years of follow up, cognitive measures were not introduced until the third health examination phase, which took place 10 years from baseline. Furthermore, cognitive measures from only one time-point were used, so the work here is not presented in terms of decline in function, but as a level of performance compared to the rest of the population.

Use of percentile scores rather than continuous score, which would be more statistically robust could also be criticised. Methodology varies across studies which use different cut-offs to define cognitive performance. In this cohort, with no overt cognitive impairment, I have previously shown that the cognitive scores are not normally distributed, [170] and in the descriptive analysis of scores revealed a non-linear relationship which is why the associations were examined using approximate percentile cut-offs. Given that this study is in relatively healthy older adults, I chose in most of the analyses a more stringent cut-off (10th percentile), even though the more stringent cut-off will still include individuals who do not have cognitive impairment or dementia. Nevertheless, the bottom tenth percentile corresponds more closely to impairment and dementia prevalence rates which has been reported in the Dementia UK update report as 7.1% [262] based on findings from the MRC Cognitive Function and Ageing Study II. [263]

9.2.3 Missing data

On the whole, EPIC-Norfolk participants were very compliant, and there was little missing data, particularly for the cognition data where only 38 participants out of the 8623 who attended the 3HC phase had no cognitive measures. The characteristics of these 38 individuals are provided in the relevant chapters. Study samples in the analyses varied across the thesis due to information on co-variates. Each chapter includes complete case analysis but also includes sensitivity analyses, to demonstrate clearly that 'missingness' was random and did not change associations. As mentioned above, the compliance for the cognition tests were good and there was complete follow-up through

medical health records for dementia and mortality outcomes. The issue of missing data in health records is well recognised, however, the impact of this potential bias is addressed in this thesis in Chapter 7.

9.2.4 Multiple testing

Multiple testing across different cognitive test means statistically significant association could be observed by chance. I did not do Bonferroni adjustments to estimate significant P values as assessment of associations rely on judgements in any case. However, one of the main aims of this work was to examine and compare associations across different cognitive domains separately. To address this point, I also included a composite score representing global cognition (beyond that which is measured by the SF-EMSE test). There is the issue of multiple testing across different hypotheses and chance associations cannot be entirely ruled out as in any other study.

9.2.5 Residual confounding, reverse causation and over-adjustment

EPIC-Norfolk wide range of data available allowing control for a wide range of factors, but since adjustment can never be complete for many reasons including measurement of variables, residual confounding cannot be entirely ruled out. This is particularly so for education which is a major potential confounder for other observed associations. Another limitation is the inability to control for other early life indicators such as family social economic status and parental education, which are established determinants of cognitive function, [214] but were not available in this cohort. These factors are known to be associated with cognition as well as dementia and mortality. [222,264,265]

To address the issue of reverse causation, sensitivity analyses were conducted, removing cases of those who had died or had a dementia diagnosis within 3-5 years. Despite this, reverse causation may still bias the observation as dementia has such a long preclinical phase. Conducting this study in this healthier population has the advantage of less confounding from co-morbidities. Although we adjusted for a much wider range of factors, confounding may still bias these results. Pre-existing health conditions were based on self-report, which are prone to recall bias

Association with cognition is complex – pathways are not clear and so could have over-adjusted for some variables. Co-variates were added to models based on the literature. For cognition and dementia over-adjustment is less likely as shown in models, once adjusted for age and education, associations were not very different with further adjustments. All the models were shown in each chapter.

9.3 Interpretation of findings

There is both the political and public will to invest in dementia research and gain a better understanding of mechanisms leading to disease. [266] However, before we can investigate or advise on prevention strategies or for modifying the course of dementia, it is crucial to disentangle the existing evidence and gain insight into why to variations and inconsistencies are observed across studies. There is no doubt that age is the biggest risk factor for dementia [36] and that is supported by this work. The additional contribution of other risk factors will be limited in relation to age, but they are still important. The evidence from observational studies on a range of factors that could contribute to delaying the onset and reducing the future number of people who have cognitive impairment and dementia [6,11,13] is supported by the work presented here.

Despite the increase in dementia research, the evidence for most of these factors is still inconclusive and the reasons are not clear. [11,26] It is important to ascertain whether this is due real differences in the distribution of predisposing factors or due to differences in methodologies, including limitations in the way either the exposure or outcome is measured. [103] These inconsistencies make it difficult to compare findings across studies. In this thesis, I have used the data collected in the EPIC-Norfolk cohort, to try and to explore and provide further explanation for the differences that have been reported in other studies. This involved examining the accuracy of study-specific methodology, characteristics of the population and setting as well as the exposure and outcome in terms of cognition and dementia.

I have examined association of potentially modifiable factors such as education, social class and physical activity with cognition across the continuum from mild cognitive dysfunction through to the other end of the spectrum of a clinical diagnosis of dementia. Although education is a well-established protective factor for cognition, I have shown here, that the strength of this association varies according to the cognitive tests used. Higher level of education is known to be associated with better cognition and lower risk of dementia. It is also associated with a healthier lifestyle, which may well to be part of the explanation. Also presented in this thesis, is a novel perspective to an existing problem of confounding and I suggest more precise assessment methods that are able to discriminate between physical inactivity during work and leisure, and are more specific on the nature of inactivity for future studies. Furthermore, education attainment, which is a complex construct, needs to be given further consideration that other studies may not be accurately accounting for. Inconsistencies in the literature may be attributable to studies not addressing residual confounding by education adequately.

Dementia remains a clinical diagnosis, despite the increased knowledge in biomarkers and that dementia is a syndrome that occurs on a continuum with a long pre-clinical phase. Diagnosis is usually

made using various recognised classification systems and research studies use one or more of these definitions to operationalise dementia as an outcome. Another methodological issue highlighted from the work of this thesis is the need for more accurate and consistent recording of dementia in health records. Rates of dementia will vary depending on the definition of dementia which is based on coding and disease classification. Inconsistency across systems result in inaccuracies and incomplete dementia recording in health care records, [91,92] which are a major source of case ascertainment for epidemiological studies examining relationship of different risk and protective factors of dementia. [91,96] It is necessary to be aware of the shortcomings of these data sources when studies report on their findings. [238] This work highlights methodological limitations that may contribute to the variability and dementia ascertainment across different settings. It is paramount to have robust methods to provide the reliable and consistent evidence that is required to better inform future health policies.

9.4 In context of other work

There are many high quality prospective cohort studies that are investigating different aspects to enhance our understanding of ageing, cognitive impairment and dementia. [88,123,126,128,129] Each with strengths and limitations, adding to the difficulties to compare across studies. Some of these studies were specifically set up to study cognition, [88] but many added cognitive measures later in the course of the study. The availability of a range of risk factors, have allowed detailed exploration of a range of factors from mid to later life and their association with cognition and dementia. [90,95,119,126,128]

EPIC-Norfolk is such a study where cognitive measures were introduced at a later stage and cannot be considered to be representative of the older population of UK. The EPIC-Norfolk cohort is deeply characterised with a wide range of both phenotypic and genetic data of which only selected factors were used as exposure and as co-variates. This presents a rich resource of a wide range of factors from mid to later life that can be used to compare with other studies similar in nature examining cognition. The fact that EPIC-Norfolk participants did not have any overt cognitive impairment at the time of cognitive testing, also offers excellent opportunity in providing a wider window to assess the earlier indicators of cognitive dysfunction, often missed by cohorts of older individuals in later life.

9.5 Public Health Implications

Prevention or delaying dementia onset is a public health priority. [266] Given the scale of the numbers of individuals, even a modest delay in the onset of dementia could have a major impact on public health, with significant cost savings and considerable benefits to the health and wellbeing of

individuals. There is no shortage of evidence for recommendations on future public health strategies on how to best manage or prevent cognitive decline, impairment and dementia. The evidence is said repeatedly to be strong but inconclusive. [11] The aim of this thesis was to try and examine the reasons for theses inconsistencies. The relationship between risk factors and cognition is complex, not only in how these factors interact and cluster together, but also how these risk factors vary over time. This may be a reason why it has not been possible to translate the available evidence into proper prevention or intervention strategies.

Developing and strengthening public health strategies that would enable the delay in onset of dementia is vitally important and with no doubt, will bring huge benefits for an ageing society. Targeting modifiable factors such as lifestyle, health and social-economic factors is a sensible approach. However, care needs to be taken as to how this health message is promoted. Findings for the differential relationship between inactivity at work and leisure and cognition, demonstrates this point. The conclusion from these analyses was that although promoting physical activity can do no harm, we must be aware of the limitations of confounding before embarking on any health promotion strategies so not to lose public support by giving mixed messages.

Cognitive tests used in EPIC-Norfolk predicted future dementia up to a decade before the onset as defined clinically. The aim would not be to use such models as a screening tool to identify individuals with dementia, however detecting the earliest phases of impairment across cognitive domains, could inform the design of trials of preventive or modifying interventions [6] and identify target populations greatest at risk who can then also be included in such trials.

9.6. Implications for future work

As highlighted by the Lancet report, [6] there is a growing interest in modifiable risk factors in the prevention or delay of dementia. One key finding from this work on physical activity could be extended to include objective measure of physical activity that were available from the time of cognitive testing. These data current need further validation using the physical activity questionnaire. However, using objective measures of physical activity would provide a more accurate measure of inactivity to examine associations in further detail. We could also examine sedentary behaviour, which is different from inactivity.

It would also be useful to examine the other main modifiable risk factors of dementia, diabetes, midlife hypertension, midlife obesity and depression that have been highlighted in the Lancet report. Of particular interest is depression, which has also shown to be associated with increased risk for dementia, [115] although longer prospective investigations does not show the same relationship. [116]

EPIC-Norfolk has detailed measures of emotional health, work strain, social support and personal dispositions. These data will provide further insight to this relationship over a period of twenty-five years. Some dementia risk factors linked to health disparities or social inequalities, which have not been examined in this thesis, but could be an extension to this work. Due to time constraints, I was unable to explore the relationship with social networks and mental activity in detail. It would be possible to examine the above factors with social and leisure activities to add to existing evidence for a better understanding of the influence of such activities to wellbeing and better cognitive function in later life. [64]

The other area of work which will be of particular interest is the exploration of the new mental health data that were used in this thesis have had very limited use by other studies. There is a need for a deeper understanding of these data to be able to exploit the databases to maximise the information from these sources. The mental health data offer the potential to ascertain dementia cases not only from GPs, hospital and death records, but those individuals living in the broader community diagnosed by memory clinics. As the field of dementia research increases use of routinely collected health records, it is important for experts across disciplines, including clinicians, data curators and researchers to work together to develop methods for consistent and accurate data capture with less subjective input and influence by practice and policy changes. With additional follow-up time, there will be more individuals in EPIC-Norfolk with dementia and dementia related syndromes that can be examined in detail with, other factors. This work led to the incorporation of childhood factors in the most recent health check, which will be available in the future.

Despite the expansion in dementia research, establishing causal relationship between risk factors and outcomes is still a major challenge. Randomised controlled trials (RCTs) are the gold standard in evidence generation but are unlikely to be as effective in testing interventions or causal factors for dementia related syndromes. This is because of the complex and multifaceted nature of cognitive impairment and dementia, and the insidious onset of these conditions. Furthermore, the biggest risk factor, age, comes with frailty, reduced functional health and co-morbidities, all adding to the complexity, that cannot be teased out by RCTs that are designed to test single-intervention at a time.

Although the focus of research has turned heavily to data and linkage to health records, my thoughts resulting from this work is that this resource must be addressed with caution and although will be a great asset to dementia research, it should only supplement the evidence-base. Despite the shortcomings of observational studies that have been highlighted such as confounding and biases, I believe longitudinal population-based cohort studies have much to contribute to future dementia research. The UK has many excellent cohort studies with vast amount of data, biological samples and

expertise gathered over many years. With future development on potential biomarkers, stored samples can be used to analyse potential early indicators of decline. Only in these large cohorts with long follow-up time can the more complex interactions of potential risk factors and their temporal relationship with cognitive impairment and dementia be examined. A more collaborative approach across these cohorts is needed. We need to gain further insight into the characteristics of the cognitive tests and harmonise their measures to allow better understanding across their different populations, and a clearer overall picture. It is not sufficient to merely report associations, but important to try to elucidate what could be the underlying mechanisms that are involved and how this could translate to preventing or delaying the onset of dementia.

Dissertation at a glance

What is already known on this topic?
There is an increasing interest in the potential role of modifiable factors in preventing or delaying the onset of dementia. Despite the extensive research in this area, the available evidence is mixed and inconclusive and further research is needed.

Reasons for discrepancies across studies are unclear but may be partly due to variability in methodologies and inconsistencies making it difficult to interpret and compare findings. It is crucial to disentangle the existing evidence and gain insight to variation observed across studies and investigate whether this is due real differences in the distribution of predisposing factors or due to differences in methodologies.

What this study adds.
This dissertation presents a number of key findings on cognitive function from EPIC-Norfolk, a 25-year prospective cohort study.

Though age, sex, education and social class were all independently associated with cognitive performance across all abilities, the magnitude of these associations differed across the different cognitive tests.

The varying relationships seen across different tests may help explain discrepancies in results reported in the current literature and provides insights into influences on cognitive performance in later life.

Measuring cognitive domains separately gives more insight than a global measure. Different cognitive tests tap into a range cognitive and sensory abilities to perform a given task. Therefore, psychometric properties of tests should be given due consideration when interpreting results.

To our knowledge, this prospective study is the first to investigate habitual physical inactivity during leisure and work time (combined and separately) from individuals from a wide range of socio-economic background and education. Those with an inactive job had a lower risk of poor cognition. Manual workers had almost three times increased risk of poor performance compared to those with an occupation classified as inactive.

With up to 15 years of follow-up, poor performance exhibited across a wider range of cognitive abilities is shown to increase the risk of dementia. These results suggest that a more variable cognitive profile may signify poorer cognitive health.

Appendices

Appendix 1

Literature Review Search Strategy (overall :

Search ((((((((((cognitive function) OR cognit*) OR cognition) OR cognitive abilities) OR cognitive abilities)) AND (((variation) OR variability) OR differences)) AND (((((age) OR aging population) OR ageing population) OR older adults) OR age related))) AND ((((abilities) OR domains) OR global function) OR specific))) AND ((((((((((((mortality) OR death) OR health) OR function) OR cognitive impairment) OR dementia) OR cardiovascualr) OR CVD) OR cancer) OR depression) OR obesity) OR bmi) OR diabetes) OR chronic disease) identified 4727 citations. Limiting the search to articles published in English, based on human research and restricting the age group to 'middle aged' and Aged '45 years +' reducing the number to 2308 citations, and further limiting to when including the search terms AND (((assessment*) OR test*), to include articles reporting on assessment tools.

Appendix 2

Work and Leisure time components of the EPIC Physical activity questions from which total physical activity score derived

1. We would like to know the type and amount of physical activity involved in your work. Please tick what best corresponds to your present activities from the following four possibilities:

☐ Sedentary occupation - You spend most of your time sitting (such as in an office)

☐ Standing occupation - You spend most of your time standing or walking. However, your work does not require intense physical efforts (e.g. shop assistant, hairdresser, guard, etc.)

☐ Physical work - This involves some physical effort including handling of heavy objects and use of tools (e.g. plumber, cleaner, nurse, sports instructor, electrician, carpenter, etc.)

☐ Heavy manual work - This involves very vigorous physical activity including handling of very heavy objects (e.g. docker, miner, bricklayer, construction worker, etc.)

2. In a typical week during the past 12 months, how many hours did you spend on each of the following activities? (Put '0' if none) Cycling, including cycling to work and during leisure time

In summer _____ hours per week

In winter _____ hours per week

Other physical exercise such as keep fit, aerobics, swimming, jogging

In summer _____ hours per week

In winter _____ hours per week

Hours per day of recreational activity computed from [(mean of summer and winter hours per week cycling) + (mean of summer and winter hours per week other physical exercise)]/7.

Appendix 3

The four levels of the index are as follows:

(1) Inactive (a sedentary job and no recreational activity)

(2) Moderately inactive (a sedentary job with, 0.5 h recreational activity per day or standing job with no recreational activity)

(3) Moderately active (sedentary job with 0.5–1 h recreational activity per day, or standing job with, 0.5 h recreational activity per day, or physical job with no recreational activity)

(4) Active (sedentary job with 1h recreational activity per day, or standing job with 1h recreational activity per day, or physical job with at least some recreational activity, or heavy manual job).

Appendix 4

EPIC-Cognition (EPIC-COG) Battery Scores and Data Cleaning

The scoring (and where necessary, details on the criteria) applied to each item on the components of EPIC- Cognition Battery (EPIC-COG) are given here. All the raw data collected have been kept in the original form. Data entered by the nurse was captured immediately on an electronic Case Report form (eCRF). Pen and paper tests were recorded directly on a paper copy of the CRF identified with the participant's unique study number. This information has been included as supplementary material and published. [170]

Any changes made to data (as part of the data cleaning process) were made at the analysis library level with any assumptions and subsequent actions (i.e. what changes were made, who made the change, why and how that change was made) clearly documented. Reasons for refusal were recorded to differentiate those participants who refused or failed to complete as a result of a technical fault or ran out of time, from those who refused because they expressed anxiety or difficulty with the task. Those who refused prior to starting a test or those who said no to a test component were assigned as missing data.

1/ Short Form- Mini Mental State Exam (SF-MMSE)

These 11 items make up the SF-MMSE, giving a possible maximum score of 15 and are part of the wider Short Form Extended Mental State Exam (SF-EMSE), administered as the first test of the EPIC-COG battery.

Scoring Criteria: Participants completing and or attempting any part of the SF-MMSE were included in the analysis, scoring '0' on the sections not completed. Incomplete data would also include the added codes (as described above for reasons for refusal) indicating specific reason for the incomplete data. A derived full MMSE Score can be obtained by using the following simple algorithm: SF-MMSE Score +14 (giving a possible maximum score of 29). This work has been published. [149]

Domain: Language

Max Possible Score = 2

	Correct	Incorrect
Pencil……	|_1_|	|_0 |
Wristwatch……..	|_1_|	|_0_|

Domain: Registration

Max Possible Score = 3	Named on first try	Not named on first try
Apple……	|_1_|	|_0_|
Table……	|_1_|	|_0_|
Penny……	|_1_|	|_0_|

Domain: Retrospective Memory

Max Possible Score = 3

	Recalled	Not Recalled
Apple……	|_1_|	|_0_|
Table……	|_1_|	|_0_|
Penny……	|_1_|	|_0_|

Serial Sevens

Domain: Attention (Calculation)

Max Possible Score = 5

Scoring criteria specific to this item: The main section containing missing data for the SF-MMSE is for the Serial Sevens. For this specific item, if a participant gave at least one answer (correctly or incorrectly) then all other scores were marked as 1 or 0 (non-missing). If there was an answer followed by a refusal then again all subsequent scores were also marked as 1 or 0 (non-missing). The nurse would indicate specific reason for an incomplete Serial 7 score.

Correct		Incorrect	
1st answer is correct	|_1_|	1st answer is incorrect	|_0_|
2nd answer is correct	|_1_|	2nd answer is incorrect	|_0_|
3rd answer is correct	|_1_|	3rd answer is incorrect	|_0_|
4th answer is correct	|_1_|	4th answer is incorrect	|_0_|
5th answer is correct	|_1_|	5th answer is incorrect	|_0_|

Domain: Language

Max Possible Score = 1

Data entry Code: Correct |_1_| Incorrect |_0__| Inapplicable |___| Refused |___|

Scoring criteria specific to this item: Spelling, grammar, punctuation and capitalisation were not important.

The sentence had to have a subject (real or implied), a verb (showing an action or state of being) and had to convey a meaning that made sense. Imperative sentences, where the subject was implied, such as 'Help' or 'Go away' were considered to be acceptable. For consistency and accuracy in scoring, although the subject could be real or implied, but the verb could NOT be missing nor could it be implied for the sentence to be correct. Further details (and examples) for clarifying these criteria were included in the protocol.

In summary, to score a point, the sentence:

- must make sense
- be complete and not fragmented
- include a subject (real or implied), and it should be quite clear as to who/what the subject is that the participant was referring to
- include a verb, and the verb had to be clearly stated and not be implied

Verification: All sentences were reviewed first by a member of the clinic team, then by a member of the research team based in Cambridge (who were not involved in the data collection) and checked against the above criteria. If there was a disagreement on whether a sentence was correct or not, the final decision was made by consensus.

Praxis -Copying 2 inter-locking pentagons

Domain: Visuo-spatial

Max Possible Score = 1

The participant was asked to copy a picture of a pentagon onto the paper copy of the CRF under the original drawing. The drawing was done freehand. If the drawing was not attempted (and there was no reason given for refusal), it was marked as incorrect.

Correct |_1_|Incorrect |_0_|

Scoring Criteria specific to this item: The two figures had to have both five sides and intersect to give a four sided figure in the middle. Both shapes did not have to be exactly the same, but needed to be relatively similar in shape and size to one another and all 10 angles needed to be relatively preserved The lines drawn by the participant had to be solid and although they did not have to completely join, most of them should have done so. Furthermore, all the lines had to be straight and not curved, tremor and rotation of the figures could be ignored.

If the participant did more than one drawing, they were asked to cross out the figure they did NOT want to use. If this step was missed and there were two drawings, only the best drawing was scored at the final verification step.

2/ Additional Items forming the Extended Mental State Examination (EMSE)

The remaining 15 item of the EMSE add a further possible score of 22 to the SF-MMSE score of 15 (Maximum score =37). The majority of the analyses in this thesis use the complete SF-EMSE score. The SF-MMSE score was used in a limited number of analyses as a validated and recognised standard, to compare the other components of the EPIC Cognition battery.

Scoring Criteria: As with the first 11 items, participants completing and or attempting any part of the SF-EMSE were included in the analysis, scoring '0' on the sections not completed. Incomplete data would also include the added codes on refusal) indicating specific reason for the incomplete data such as refusal from the participants.

Extension on Expression/Naming

Domain: Language

Max Possible Score = 2

Correct Incorrect

(1) Keys…….. |_1_| |_0_|

(2) Envelope……. |_1_| |_0_|

Animals named in 1 minute

Domain: Verbal Fluency

Max Possible Score = 5

Scoring Criteria specific to this item: Nurses entered the numbers of animals named in one minute (this raw score is available from the dataset). Any duplications were corrected by the clinic staff (at the first checking stage) The raw score was then converted to a derived score ranging from 0-5 as in the original EMSE test used in CFAS (derived scores for numbers of animals named as shown in Table A4.1table below)

Table A4.1: Derived Scores for the Animal Naming (Executive Function) item of EMSE

Numbers of animals named	Derived Score
0	0
1-8	1
9-16	2
17-24	3
25-32	4
33+	5

Extension on Recall

Domain: Retrospective Memory

Possible Score = 4

	Recalled	Not recalled
(3) Pencil……	|_1_|	|_0_|
(4) Wristwatch…….	|_1_|	|_0_|
(5) Keys……	|_1_|	|_0_|
(6) Envelope……	|_1_|	|_0_|

(7) **Extension on Language (Writing address to dictation)**

Address on Envelope

Domain: Language

Max Possible Score = 2

Scoring Criteria specific to this item: Every envelope submitted was checked at the clinic and then again by a member of the research team at Cambridge. Criterion was whether the letter would reach the right person and destination (spelling and neatness were not important). If it would, and the letter was addressed in the standard format (address at the front, middle of envelope), then it was marked as correct (score of 2 points). If the letter had all the information written correctly, and therefore, in a real scenario, the letter would reach destination, but the address was not written in a standard way (all on one line, address written at the back etc.), then that was 'poor but acceptable' and given a score of 1. If it did not have the correct information, or was missing (and other items of the EMSE were not missing), then that was scored as Incorrect (Score of 0).

Correct: |_2_| **Poor but acceptable:** |_1_| **Incorrect** |_0_|

Abstract and Concrete Thinking

Naming like objects

Domain: Executive function

Possible Score = 4

Scoring Criteria specific to this item: All responses were checked for by the Cambridge research team and entered into the database and analysed on the basis of frequencies of the different responses given by participants. An answer was considered to be 'Abstract' , if the answer was the most specific category that both items fell into. If the answer was where the category was too broad, or described

characteristics that answer was 'Concrete' and an 'Incorrect' answer was anything that was not stating the category, no answer given or where participant highlighted the differences between the two items. A final judgement was made (and when necessary agreed by consensus) on all responses entered on the eCRF.

For the Apple/Banana Similarity Item, there was only one correct 'Abstract' answer and this was 'fruit'. Examples of responses scored as 'Concrete' (describing characteristics, or category too broad) included 'food', 'eat them both' or 'grow on trees', 'has peel' or 'skins' or 'healthy food'. Examples of incorrect response include' They are not the same or not similar, 'pear', 'long and round'

The abstract answer for the Boat/Car similarity item was a little more complicated and responses from the cohort varied considerably. Abstract responses included 'modes of travel' 'or 'conveyance', 'you travel/ ride in them both. Concrete answers included responses such as 'mechanical', 'both have engines', 'both carry passengers/people' or 'used for leisure' and incorrect responses included 'one on water/sea, other on land', 'road and river' 'sailing and motoring'.

(8) **Apple and banana**

Abstract Answer (Fruit)	|_2_|
Concrete Answer (Food, grow, have peel)	|_1_|
Incorrect	|_0_|

(9) **Boat and car**

Abstract Answer (Both vehicles/ modes of transport	|_2_|
Concrete Answer (Have seats/motorized)	|_1_|
Incorrect	|_0_|

Recall of name and Address

Domain: Retrospective memory

Max Possible Score = 5

	Recalled	Not recalled
(10)John……	|_1_|	|_0_|
(11)Brown……	|_1_|	|_0_|
(12)42……	|_1_|	|_0_|
(13)West Street…….	|_1_|	|_0_|
(14)Bedford…….	|_1_|	|_0_|

3/ Letter cancellation Task

Attention, visual search and Mental Speed

Max possible Score = 72

Scoring Criteria: The following three variables are the raw data calculated and recorded by the nurse:

1/Target letters (PW)- number of target letters (P's and W's) correctly identified (target_pw)

2/ Line stopped – the line that the participant stopped on after 1 minute (pw-line)

3/ Column stopped – the column that the participant stopped on (pw_col)

From the data above, the following **derived** variables that are used in the analysis can be calculated

1/PW Accuracy — No. of PW correctly identified minus targets missed (pw_acc) up to the point reached

2/ PW Speed = No. of cells covered/No. of cells on the "pw" worksheet i.e.960

The outcome variable PW Accuracy has been used for this test in this thesis

4/ Hopkins Verbal Learning Test

Maximum possible is 36.

Scoring criteria: The words were checked on the eCRF as the participant correctly recalled each word. The software program automatically tallied the number of checks for each trial and the nurse manually entered the score. Those boxes not checked indicated that the participants had not recalled that word in that particular trial. The tally and the score had to be present for each trial and had to match to verify that the score was correctly entered by the nurse. If a participant did not attempt (or refused) the entire test, then a comment had to be entered to identify those participants who didn't do the test (missing data) as compared to those who scored 0 on a trial.

If Trial 1 had a score for 'Total' and there was no score for Trial 2/3 (nor a comment or refusal), then after checking the paper record, that data was considered to be incomplete (and so assigned as missing data)

If Trial 1 had no score entered but had a score for Trial 2 and 3, then after checking the paper records, the final decision was to consider the test as completed, with the score for Trial 1 score = 0

5/ CANTAB Paired Associates Learning (CANTAB-PAL) Test.

The CANTAB-PAL data was recorded and stored automatically under the participant study identifier. The data includes a number of outcome measures, such as PAL total errors; PAL total errors (adjusted); PAL First trial memory score, PAL Stages completed; PAL Stages completed on first trial all available in the analysis library. Also recorded was whether the participant refused this test completely and/or if the test had been aborted and if so, at what stage of the test. All this data is available for analysis. In this thesis, the PAL First trial memory score (the number of patterns correctly located after the first trial) was the outcome measure used for this test. The First trial memory score indicates immediate ability to store visual information.

6/ Visual Sensitivity Test (VST)

This electronic data was automatically collected and stored in files with the participant's unique study identifier as the participant completed the test. The visual sensitivity data includes a number of measures, although the outcome measure used for analysis is reaction time (measured in milliseconds). There were a large number of measures per participant (approximately 70), and the final reaction time used for analysis was the average value of all these measures. The two main derived outcome measures used were VST-simple and VST complex as described in Chapter 2.

Data cleaning was done in a number of stages. Firstly, software program checked and excluded any participants whose visual sensitivity was not in its correct form or whose study identifier was not recognised. Secondly, the largest time value was identified for each person. Then using the remaining (all except the largest time) measures, a mean and standard deviation was defined. Any record where the largest time value was greater than the mean plus 8 standard deviations was excluded (this was to remove any extreme outliers from the data from individual participant's repeat measures). The average reaction time was then calculated from the remaining measures and this value was used as the final reaction time for the analysis library.

7/ National Adult Reading Test (NART)

Maximum possible (Error Score) is 50.

The NART Test Manual, second edition (Nelson, 1982) provides a pronunciation guide to assist with scoring. A more detailed pronunciation guide was developed in-house, highlighting variations that were acceptable (taking the regional Norfolk accent into account) and by also providing the 'common incorrect' answers which were presented by the EPIC-Norfolk cohort. This was also to assist those administering the test to discriminate what was correct and what – even though quite commonly used,

clearly incorrect. The detailed guide is given below. Those administering tests were also provided with a sound recording of the words so that they could refresh their memories whenever necessary, and were given ongoing training throughout the year.

Recordings (stored as mp3 files) of the test were made so that scores could be checked after the participant had completed the appointment if it was required. Any difficulty with reading, visual or hearing impairment or understanding of the instructions, were noted on the eCRF and if necessary the test was aborted. If the data was incomplete, as in words missing from recordings (and no explanation for this noted on the eCRF) and the equation from the SHORT-NART protocol could not be applied, then this data was assigned as missing data.

Scoring Criteria: Each correctly pronounced word was given a score of 1. Incorrectly pronounced. When the participant reached the half way mark, the nurse could then decide if the test was to be continued or not depending on the score achieved in the first half. If a participant pronounced a word correctly and then 'corrected themselves' with an incorrect pronunciation, they were asked to choose a final answer. Scores were based on the final answer given. In summary, the error score (50 minus the total number correct) remained as was if the participants NART error score was between 0-11. For participants scoring between 12 and 20, a conversion (as shown in Table A4.2) was used to compute the Full NART Error Score. Participants scoring 21 or more were allowed to continue with full NART and the error score calculated as shown below. This is described in detail elsewhere. [163]

Table A4.2: Conversion table for the Short NART error score

Short NART correct score	Conversion to Full NART error score
0-11	As in full NART (50 minus correct)
12	38
13	36
14	34
15	33
16	31
17	30
18	28
19	26
20	24
21+	As in full NART (50 minus correct)

Beardsall and Brayne (1990)

8/ Prospective Memory

Max Possible Score = 2

Scoring Criteria: To obtain the highest score of 2, the participant had to carry out both actions without being prompted by the nurse. If there was any variation, or the nurse was uncertain of a particular response, then this information was included in the eCRF. The research team at Cambridge then made the final judgment on the score. If the participant carried out an extra action (i.e. put the pen in the envelope, wrote full name, or wrote something extra such as the date), they still scored the maximum 2 points. Where there was some variation, a judgment was made if they would receive the points, for example, the participant put a cross at the back, or initialled inside before sealing, or initialled front of the envelope – in these particular situations, the participant still scored 2.

Where there was missing data, the nurse was able to specify reasons (Unable or Refused) for this specific item.

Possible Scores were as follows:

Seal/Initial envelope…

Seals and writes own name without prompt	|_2_|
One action without prompt, one with	|_1_|
One action without prompt only	|_1_|
One action only (with prompt)	|_0_|
No correct action	|_0_|

NART Pronunciation Guide

Word	Pronunciation I	Detailed Pronunciation II	Unacceptable Answers
chord	körd	cord - *ch* as *c* as in *cat*	chord - *ch* as in *chair*
ache	āk	ayhk - long *a* as in *ape* and *ch* as *c* as in *cat*	ache - *a* as in *ah* or *ch* as in *chair*
depot	dep'ō	**dep**-oh, **deep**-oh - *t* is silent	de-**pot** - *t* not silent, as in *pot*
aisle	īl	iyl - *ai* as long *i* not as in *air*, *s* is silent	**aye**-sle, **iye**-sle, iyls - pronouncing the *s*
bouquet	bōōk'a, bōōk'ā, bōkā'	**boo**-kay, **boh**-kay, boh-**kay** - stress on either syllable, *t* is silent	boo-**ket, boh**-keht, banquet - pronouncing the *t*
psalm	säm	sahm - *p* is silent	palms, p-**sahms** - pronouncing the *p*
capon	kā'pn	**kay**-pon	**cap**-on, cah-**pone**
deny	di-nī	dih-**niy**	**deh**-nee
nausea	nö'si-ə, nö'zhə	**naw**-zee-uh, **naw**-zhuh	**naw-see** - 1 syllable
debt	det	det - *b* is silent	**deb**-it
courteous	kûrt'yəs	**kur**-tee-us - *cour* as is *curtain*	**core**-tee-us - *cour* as in *core*
rarefy	rār'-i-fī	**rair**-i-fiy - 3 syllables	**rare**-fee, **rare**-fye - 2 syllables

Word	Pronunciation I	Detailed Pronunciation II	Unacceptable Answers
equivocal	i-kwiv'ə-kl	i-**kwiv**-i-kul	eqwi-**vo**-cal - like the word *vocal*
naive	nä-ēv	na-**eev** - pronouncing the *a* and *i* separately	nave - 1 syllable
catacomb	kat'ə-kōōm	**kat**-uh-koom - like the word *tomb* with a silent b	**cata-**comb - like the word comb or pronouncing the b
gaoled	jāld	jailed	**gay**-old, gold - like the work *goaled*
thyme	tīm	time	thime, theme - *th* as in thought or their
heir	ār	air - *h* is silent	hair, hear - pronouncing the *h*
radix	rā'diks	**ray**-diks - long *a* as in *ape*	**rah-**dix - *ra* as in *ran* or *rob*
assignate	as'-ig-nāt	**ass**-ig-nate - *a* is not silent, the second *a* is long	**ass-i-nate, ass-ig-net -** not pronouncing the g as in assign
hiatus	hī-ā'təs	hiy-**ay**-tus - emphasis on long a, pronouncing both *i* and and *a*	hi-**at**-us, **hee**-at-us, **hiy**-tus, **hay**-shus
subtle	sut'l	**suht**-l - *b* is silent, **suh**-el (regional pronunciation)	su**b**-tel - pronouncing the *b*
procreate	prō'kri- āt	**proh**-kree-ate - long *o*, like the word *create*	**prah**-create, **pro**-creet
gist	jist	jist - *g* as in *ginger*	**g**ist - *g* as in *goat*

Word	Pronunciation I	Detailed Pronunciation II	Unacceptable Answers
gouge	gowj	gowj - *gou* as in *gown*, second *g* as *j*	gooje, goje, gorge, gowg
superfluous	sōō-pûr'floo-əs, sū-pûr'floo-əs	soo-**pur**-floo-us - emphasis on per	super-**floo**-us, super-**flur**-us - like the word *super*
simile	sim'i-li	**sim**-i-lee - 3 syllables	smile, **sim**-mile - like the words *smile* or *mile*
banal	bən-al'	ba-**naal** - emphasis on *a* as in *ah*	**bay**-nal, **ban**-el - long *a* as in *ape* or emphasis on first syllable
cellist	chel'ist	**chel**-ist - *c* as *ch* as in *chair*	**sell**-ist - *c* as *s* as in *sell*
facade	fa-säd'	fa-**sahd** - *c* as *s* as in *sell* and second *a* as in *ah*	fa-**kade**, fa-**sade** - *c* as in *cat* or long *a* as in *ape*
zealot	zel'ət	**zel**-uht - *eal* as *el* as in *elder*	**zee**-lot - *eal* with long *e* as in *real*
drachm	dram	dram - *ch* is silent	**dra**-kum, **drak**-ma - pronouncing the *ch*
aeon	ē'on	**ee**-on - *a* is silent and *e* is long as in *eve*	**aye**-on - pronouncing the *a* rather than the *e*
placebo	plə-sē'bō	pla-**see**-boh - emphasis on *ce* with a long *e* as in *eve*	**place**-bo, **pla**-see-boo - like the word *place*
abstemious	ab-stē'mi'əs	ab-**stee**-mee-us - emphasis on long *e* as in *steam*	ab-**stem**-ious - short *e* as in *stem*

Word	Pronunciation I	Detailed Pronunciation II	Unacceptable Answers
detente	dā-tãt	day-**tahnt** - first *e* as long *a* as in *ape*, second *e* as short *a* as in *ah*, last *e* is silent	**dee**-tent, de-**ten**-tee - pronouncing any of the *e*s with an *e* sound
idyll	id'il, id'əl	**id**-ill - short *i* as in *in*	**iye**-dle - long *i* as in *island*
puerperal	pū-ûr'pər-əl	poo-**er**-per-al, pyoo-**ur**-per-al - 4 syllables	pur-**per**-il, **pur**-per-al - *puer* like the word *purr* or *peral* like the word *peril*
aver	ə-vûr'	a-**vur** - emphasis on *ver*	**ave**-ur, **av**-ur - *av* as in *wave* or emphasis on the *a*
gauche	gōsh	gohsh - gau like the word *go*, *che* pronounced as *sh*	gawch, gowsh - *gau* as in *gown* or *ch* as in *chair*
topiary	tō'pi-ə-ri	**toh**-pee-er-ee - emphasis on *to* like the word *toe*	**top**-pee-ary, toh-**pie**-er-ree - *top* like the word *top* or emphasis not on first syllable eg. toh–**pi**-ar-ree
leviathan	le-vī'-ə-thən	le-**viy**-e-thun - emphasis on *vi* with long *i*	**levy**-ay-than - *levi* like the word *levy*, long first *a*

Word	Pronunciation I	Detailed Pronunciation II	Unacceptable Answers
beatify	bi-at'i'fi	bee-**at**-i-fiy - 4 syllables, long *e* like the word *be* and emphasis on *at* like the word *at*	**beet**-i-fie, b**eet**-fee, beautify - 3 syllables, *beat* like the word *beet*
prelate	prel'it	**prel**-it - emphasis on short *e* as in *eh*	**pree**-late, pre-**late** - long first *e*, *late* like the word *late*
sidereal	sī-dē'ri-əl	siy-**deer**-ee-ul - *i* and both *e*s pronounced long	**side**-real, sid-eh-**real** -short *i* as in *Sid* or *real* like the word *real*
demesne	di-mān', di-mēn'	dih-**mane**, dih-**meen** - *s* is silent	de-**mes**-nee, de-**mence** - pronouncing the *s*
syncope	sing'kə-pē	**sing**-kuh-pee, **sin**-kuh-pee - 3 syllables, *co* as in *cone* and *pe* like the word *pea*	**sing**-kope, **sine**-kope - 2 syllables, cope like the word cope
labile	lā'bīl	**lay**-bile - long *a* as in *ape*, *bile* like the word *bile*	lah-**bile**, lah-**beel**, **lab**-i-lee - *a* as in *ah*
campanile	kam-pan-ē'lā , kam-pan-ē'lē	kam-pan-**ee**-lee, kam-pan-**ee**-lay, kam-pan-**eel**	**kam**-pan-nile - pronounced like the river Nile

Appendix 5

Creating the cognition composite score from the EPIC-Norfolk Cognition Battery (EPIC-COGComp) Method

A composite score (EPIC-COGComp) representing all the abilities covered in the EPIC-Norfolk Cognition Battery was included in some of the analyses in this dissertation. For each of the individual cognition test (as listed in Table A5.1, with the predominant abilities assessed by each test), a composite score that was then either split into three (Chapter 5) or two groups (Chapters 6 and 8), based on the cut-off point corresponding to a percentile of the population distribution in each of the eight cognitive outcome measures individually. Participants were allocated to a group based on their individual score as described below:

In **Chapter 5,** EPIC-COGComp was created as a **3-category** variable using the bottom tenth percentile as a cut-off Participants were classified as follows:

Poor Performance: Participants were classified to this group if they obtained a score less than a cut-off point corresponding to approximately the 10th percentile of the population distribution. Poor performance was assigned a score of 0.

High Performance: Participants were classified to this group if they obtained a score above a cut-off point corresponding to approximately the 90th percentile of the population distribution. High performance was assigned a score of 2

Standard Performance: All remaining participants not within the bottom or top tenth percentile groups were classified to this group. Standard performance was assigned a score of 1

For prospective memory, where participants, as previously, those failing the task were classified to the poor performance group and assigned a score of '0' and those who were successful were assigned a score of '1'.

The EPIC-COGComp composite score was calculated as a sum of the score based on the performance group for all eight cognition test outcomes. However, as this composite was categorised into 3 groups and included high performance, the score range was 0-15). The lowest score was 0, (being in the poor performance group for all 8 cognitive test outcomes (only 4 participants in the cohort had a score of 0). The highest score in the cohort was 14, with no participant attaining the top score of 15 (that is, being in the high performance group for all 8 cognitive test outcomes).

A three–level categorical variable of the EPIC-COGComp score was then created from the continuous score using the bottom 10th percentile (obtaining a score of 6 or below), top 10th percentile (obtaining a score of 10 or above) and those with scores between 7-9 in the standard performance group.

In **Chapter 6,** EPIC-COGComp was created as a **2-category** variable, this time the cut-off was using the (approximate) 25th percentile as a cut-off. Participants were classified as follows:

Poor Performance: Participants were classified to this group if they obtained a score less than a cut-off point corresponding to approximately the 25th percentile of the population distribution. Poor performance was assigned a score of '0'

Good/Standard Performance: Participants were classified to this group if they obtained a score above a cut-off point greater than the 25th percentile of the population distribution. Good performance was assigned a score of 1.

Prospective memory success or failure was treated as above.

The EPIC-COGComp composite score was then calculated as a sum of the score based on the performance group for the eight cognition tests. For this analyses, the lowest possible score was 0 (being in the poor performance group for all 8 cognitive test outcomes) and the highest was 8, (being in the standard performance group for all 8 cognitive test outcomes).

The dichotomised variable of the EPIC-COGComp score was included in the analyses in the exact same way as the individual tests scores, with the approximate bottom quartile (or in this case, obtaining a score of 5 or below) defining poor performance for global cognition.

In **Chapter 8,** EPIC-COGComp was using the 10th percentile as a cut-off to create a **2-category** variable and the and the prospective memory success or failure was treated as previously. The EPIC-COGComp composite score was then calculated as a sum of the score based on the performance group for the eight cognition tests (range again, was 0-8).

Missing Data

As the EPIC-COGComp, composite score relies on a score for all eight cognitive tests, it was only possible to examine associations with mortality for those with a score on all 8 outcomes, reducing the analysis to only 6128 participants. To maximise use of the data, two variants of the composite score were created to include all the available cognitive measures. The first variant (EPIC-COGComp0) was generated by imputing a score of 0 (assigning individuals to the 'poor performance group') for any test with a missing value and the second variant (EPIC-COGComp1) was generated by imputing a score of

1 (assigning individuals to the 'good performance or reference group') for any test with a missing value. The range for both variants were also 0-8 or 0-15 for the two and three category composite score respectively. These variants were used in the sensitivity analyses as described in the relevant chapters.

Table A5.1: List of the individual cognitive tests used in the EPIC-Norfolk 3HC

	Name and outcome measure	**Predominant ability measured by test**
1	A shortened version of the Extended Mental State Exam (SF-EMSE)	Global function
2	Hopkins Verbal Learning Test (HVLT)	Verbal episodic memory (Immediate total recall of three trials
3	Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Test	Non-verbal episodic memory
4	Letter Cancellation Task	Attention
5	Event and Time Based Task	Prospective memory
6 7	Visual Sensitivity Test (VST) (1) VST-Simple (2) VST-Complex	Simple and complex visual processing speed
8	Shortened version of the National Adult Reading Test (Sh-NART)	Reading ability and crystallised intelligence

References

[1] Age UK. Factsheet: Later life in the United Kingdom. 2019.

[2] Brayne C, Matthews FE, McGee M, Jagger C. Health and ill-health in the older population in England and Wales. The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Age Ageing 2001;30:53–62.

[3] Rapp PR, Amaral DG. Individual differences in the cognitive and neurobiological consequences of normal aging. Trends Neurosci 1992;15:340–5.

[4] O'Connor PJ. Normative data: their definition, interpretation, and importance for primary care physicians. Fam Med 1990;22:307–11.

[5] Prince M, Albanese E, Guerchet M, Prina M. World Alzheimer report 2014 dementia and risk reduction: an analysis of protective and modifiable factors. 2014.

[6] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673–734. https://doi.org/10.1016/S0140-6736(17)31363-6.

[7] Lewis F, Schaffer SK, Sussex J, O'Neill P, Cockcroft L. Consulting report for Alzheimer's Research UK : The trajectory of dementia in the UK – making a difference. 2014.

[8] Jorm AF, Korten AE, Henderson AS. The prevalence of dementia: A quantitative integration of the literature. Acta Psychiatr Scand 1987;76:465–79. https://doi.org/10.1111/j.1600-0447.1987.tb02906.x.

[9] Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's Dement 2015;11:718–26. https://doi.org/10.1016/j.jalz.2015.05.016.

[10] Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimer's Res Ther 2016;8. https://doi.org/10.1186/s13195-016-0188-8.

[11] The National Academies of Sciences. Preventing Cognitive Decline and Dementia: A Way Forward. Washington (DC): The National Academies Press; 2017. https://doi.org/10.17226/24782.

[12] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. Lancet Neurol 2014;13:788–94. https://doi.org/10.1016/S1474-4422(14)70136-X.

[13] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819–28. https://doi.org/10.1016/S1474-4422(11)70072-2.

[14] Teng E L and Chui H C. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987;43:314–8.

[15] Nasreddine ZS, Phillips N, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9. https://doi.org/10.1111/j.1532-5415.2005.53221.x.

[16] Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry 2007;78:790–9. https://doi.org/10.1136/jnnp.2006.095414.

[17] Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. QJM 2007;100:469–84. https://doi.org/10.1093/qjmed/hcm051.

[18] Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: An update. Int J Geriatr Psychiatry 2010;25:111–20. https://doi.org/10.1002/gps.2306.

[19] Dangour AD, Allen E. Do omega-3 fats boost brain function in adults? Are we any closer to an answer? Am J Clin Nutr 2013;97:909–10. https://doi.org/10.3945/ajcn.113.061168.

[20] Ozer S, Young J, Champ C, Burke M. A systematic review of the diagnostic test accuracy of brief cognitive tests to detect amnestic mild cognitive impairment. Int J Geriatr Psychiatry 2016;31:1139–50. https://doi.org/10.1002/GPS.4444.

[21] Cullum S, Huppert FA, McGee M, Dening T, Ahmed A, Paykel ES, et al. Decline across different domains of cognitive function in normal ageing: results of a longitudinal population-based study using CAMCOG. Int J Geriatr Psychiatry 2000;15:853–62. https://doi.org/10.1002/1099-1166(200009)15:9<853::AID-GPS211>3.0.CO;2-T [pii].

[22] Huppert F, Cabelli ST, Matthews FE. Brief cognitive assessment in a UK population sample — distributional properties and the relationship between the MMSE and an extended mental state examination. BMC Geriatr 2005;5:7. https://doi.org/10.1186/1471-2318-5-7.

[23] Friedman TW, Yelland GW, Robinson SR. Subtle cognitive impairment in elders with Mini-Mental State Examination scores within the “normal” range. Int J Geriatr Psychiatry 2012;27:463–71. https://doi.org/10.1002/gps.2736.

[24] Folstein S, Mchugh P. Mini-Mental State : A Practical Method for Grading the Cognitive State of Patients for the Clinician. Int J Geriatr Psychiatry 1998;13:285–94. https://doi.org/10.1002/(SICI)1099-1166(199805)13:5<285::AID-GPS753>3.0.CO;2-V.

[25] Tombaugh TN, McIntyre NJ, Tombaugh T N MNJ, Tombaugh TN MN. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922–35.

[26] Institute of Medicine of the National Acadamies. Cognitive Aging: Progress in Understanding and Opportunities for Action. Washington, DC: National Academic Press; 2015.

[27] Hou X, Feng L, Zhang C, Cao X, Tan L, Yu J-T. Models for predicting risk of dementia: a systematic review. J Neurol Neurosurg Psychiatry 2019;90:373–9. https://doi.org/10.1136/jnnp-2018-318212.

[28] Calvin CM, Wilkinson T, Starr JM, Sudlow C, Hagenaars SP, Harris SE, et al. Predicting incident dementia 3-8 years after brief cognitive tests in the UK Biobank prospective study of 500,000 people. Alzheimer’s Dement 2019;15:1546–57. https://doi.org/10.1016/j.jalz.2019.07.014.

[29] Warren-Gash C. Dementia risk prediction models - What do policy makers need to know? Cambridge, UK: 2019.

[30] Walters K, Hardoon S, Petersen I, Iliffe S, Omar RZ, Nazareth I, et al. Predicting dementia risk in primary care: Development and validation of the Dementia Risk Score using routinely collected data. BMC Med 2016;14:1–12. https://doi.org/10.1186/s12916-016-0549-y.

[31] Weaver Cargin J, Collie A, Masters C, Maruff P. The nature of cognitive complaints in healthy older adults with and without objective memory decline. J Clin Exp Neuropsychol 2008;30:245–57.

[32] National Institute on Aging. U.S. Department of Health and Human Services. Alzheimer's Disease: Unraveling the Mystery. Silver Spring, MD: 2008.

[33] Brayne C, Calloway P. Normal Ageing, Impaired Cognitive Function and Senile Dementia of the Alzheimer's type: A Continuum. Lancet 1988;1:1265–7.

[34] Collie A, Maruff P, Shafiq-Antonacci R, Smith M, Hallup M, Schofield PR, et al. Memory decline in healthy older people: implications for identifying mild cognitive impairment. Neurology 2001;56:1533–8. https://doi.org/10.1212/WNL.56.11.1533.

[35] Cargin JW, Maruff P, Collie A, Shafiq-Antonacci R, Masters C. Decline in verbal memory in non-demented older adults. J Clin Exp Neuropsychol 2007;29:706–18. https://doi.org/10.1080/13825580600954256.

[36] Brayne C. The elephant in the room — healthy brains in later life, epidemiology and public health. Nat Rev Neurosci 2007;8:233–9.

[37] Deary IJ, Corley J, Gow AJ, Harris SE, Houlihan LM, Marioni RE, et al. Age-associated cognitive decline. Br Med Bull 2009;92:135–52. https://doi.org/10.1093/bmb/ldp033.

[38] Ritchie K. Mild cognitive impairment: an epidemiological perspective. Dialogues Clin Neurosci - 2004;6:401–8.

[39] Kelman HR, Thomas C, Kennedy GJ, Cheng J. Cognitive impairment and mortality in older community residents. Am J Public Health 1994;84:1255–60. https://doi.org/10.2105/AJPH.84.8.1255.

[40] Gale SA, Acar D, Daffner KR. Dementia. Am J Med 2018;131:1161–9. https://doi.org/10.1016/j.amjmed.2018.01.022.

[41] Hoogendam YY, Hofman A, Van Der Geest JN, Van Der Lugt A, Ikram MA. Patterns of cognitive function in aging: The Rotterdam Study. Eur J Epidemiol 2014;29:133–40. https://doi.org/10.1007/s10654-014-9885-4.

[42] Petersen RC, Smith GE, Waring S, Ivnik R, Kokmen E, Tangelos E. Aging , Memory , and Mild Cognitive Impairment 1997;9:65–9.

[43] Salthouse T. What and When of Cognitive Aging. Curr Dir Psychol Sci 2004;13:140–4.

[44] Cullen B, Fahy S, Cunningham CJ, Coen RF, Bruce I, Greene E, et al. Screening for dementia in an Irish community sample using MMSE: a comparison of norm-adjusted versus fixed cut-points. Int J Geriatr Psychiatry 2005;20:371–6. https://doi.org/10.1002/gps.1291.

[45] Cloutier S, Chertkow H, Kergoat MJ, Gauthier S, Belleville S. Patterns of cognitive decline prior to dementia in persons with mild cognitive impairment. J Alzheimer's Dis 2015;47:901–13. https://doi.org/10.3233/JAD-142910.

[46] Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–94.

[47] Petersen RC, Smith GE, Stephen W, Ivnik RJ, Tangalos EG, Kokmen E. Mild Cognitive Impairment Characterization and Outcome. Arch Neurol 1999;56:303–9.

[48] Artero S, Petersen R, Touchon J, Ritchie K. Revised criteria for mild cognitive impairment: validation within a longitudinal population study. Dement Geriatr Cogn Disord 2006;22:465–70. https://doi.org/10.1159/000096287.

[49] Bennett DA, Wilson RS, Schneider J, Evans DA, Beckett L, Aggarwal NT, et al. Natural history of mild cognitive impairment in older persons. Neurology 2002;59:198–205. https://doi.org/N/A.

[50] Petersen RC, Knopman DS, Boeve BF, Yonas E, Ivnik RJ, Smith GE, et al. Mild cognitive impairment: Ten years later. Arch Neurol 2009;66:1447–55. https://doi.org/10.1001/archneurol.2009.266.Mild.

[51] Ganguli M, Dodge HH, Shen C, DeKosky ST. Mild cognitive impairment, amnestic type: An epidemiologic study. Neurology 2004;63:115–21. https://doi.org/10.1212/01.WNL.0000132523.27540.81.

[52] Petersen RC. Mild cognitive impairment. N Engl J Med 2011;364:2227–34. https://doi.org/10.1056/NEJMcp0910237.

[53] Petersen R, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med 2014;275:214–28. https://doi.org/10.1111/joim.12190.Mild.

[54] Ryan J, Fransquet P, Wrigglesworth J, Lacaze P. Phenotypic Heterogeneity in Dementia: A Challenge for Epidemiology and Biomarker Studies. Front Public Heal 2018;6:4–9. https://doi.org/10.3389/fpubh.2018.00181.

[55] Risk reduction of cognitive decline and dementia: WHO Guidelines. Geneva: 2019.

[56] Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: Attributable-risks at death in the medical research council cognitive function and ageing study. PLoS Med 2009;6. https://doi.org/10.1371/journal.pmed.1000180.

[57] Bennett DA. Mixed pathologies and neural reserve: Implications of complexity for Alzheimer disease drug discovery. PLoS Med 2017;14. https://doi.org/10.1371/journal.pmed.1002256.

[58] Boyle PA, Yu L, Wilson RS, Schneider JA, Bennett DA. Relation of neuropathology with cognitive decline among older persons without dementia. Front Aging Neurosci 2013;5:1–8. https://doi.org/10.3389/fnagi.2013.00050.

[59] Ritchie CW, Terrera GM, Quinn TJ. Dementia trials and dementia tribulations: methodological and analytical challenges in dementia research. Alzheimers Res Ther 2015;7:31. https://doi.org/10.1186/s13195-015-0113-6.

[60] Duong S, Patel T, Chang F. Dementia: What pharmacists need to know. Can Pharm J 2017;150:118–29. https://doi.org/10.1177/1715163517690745.

[61] Source Figure 1.2. Image of the Brain n.d. https://hub.permobil.com/blog/dementia-what-part-of-the-brain-is-under-attack.

[62] Arenaza-Urquijo EM, Wirth M, Chételat G. Cognitive reserve and lifestyle: Moving towards preclinical Alzheimer's disease. Front Aging Neurosci 2015;7:1–12. https://doi.org/10.3389/fnagi.2015.00134.

[63] Stern Y. Cognitive Reserve. Neuropsychologia 2009;47:2015–28. https://doi.org/10.1016/B978-0-12-804766-8.00011-X.

[64] McHugh Power J, Tang J, Lawlor B, Kenny RA, Kee F. Mediators of the relationship between social activities and cognitive function among older Irish adults: results from the Irish longitudinal study on ageing. Aging Ment Heal 2018;22:129–34.

https://doi.org/10.1080/13607863.2016.1233935.

[65] Tucker-Drob EM, Johnson KE, Jones RN. The cognitive reserve hypothesis: a longitudinal examination of age-associated declines in reasoning and processing speed. Dev Psychol 2009;45:431–46. https://doi.org/10.1037/a0014012.

[66] Scarmeas N, Stern Y. Cognitive reserve and lifestyle. J Clin Exp Neuropsychol 2003;25:625–33. https://doi.org/10.1076/jcen.25.5.625.14576.

[67] Clare L, Wu Y, Teale JC, Macleod C, Matthews F, Brayne C, et al. Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: A cross-sectional study. PLOS Med 2017;14:e1002259. https://doi.org/10.1371/journal.pmed.1002259.

[68] Horn JL, Cattell RB. Age differences in fluid and crystallized intelligence. Acta Psychol (Amst) 1967;26:107–29. https://doi.org/10.1016/0001-6918(67)90011-X.

[69] Deary IJ, Batty GD. Cognitive epidemiology. J Epidemiol Community Health 2007;61:378–84.

[70] Morse CK. Does variability increase with age? An archival study of cognitive measures. Psychol Aging 1993;8:156–64. https://doi.org/10.1037/0882-7974.8.2.156.

[71] Wilson RS, Beckett L, Barnes LL, Schneider J, Bach J, Evans D, et al. Individual differences in rates of change in cognitive abilities of older persons. Psychol Aging 2002;17:179–93.

[72] Coen RF, Robertson DA, Kenny RA, King-Kallimanis BL. Strengths and Limitations of the MoCA for Assessing Cognitive Functioning. J Geriatr Psychiatry Neurol 2016;29:18–24. https://doi.org/10.1177/0891988715598236.

[73] Hilborn J V, Strauss E, Hultsch DF, Hunter MA, Hilborn J V, Strauss E, et al. Intraindividual variability across cognitive domains : Investigation of dispersion levels and performance profiles in older adults Intraindividual variability across cognitive domains : profiles in older adults. J Clin Exp Neuropsychol 2009;31:412–24. https://doi.org/10.1080/13803390802232659.

[74] Vaughan L, Leng I, Dagenbach D, Resnick SM, Rapp SR, Jennings JM, et al. Intraindividual variability in domain-specific cognition and risk of mild cognitive impairment and dementia. Curr Gerontol Geriatr Res 2013. https://doi.org/10.1155/2013/495793.

[75] Berkman LF, Seeman TE, Albert M, Blazer D, Kahn R, Mohs R, et al. High, usual and impaired functioning in community-dwelling older men and women: findings from the MacArthur Foundation Research Network on Successful Aging. J Clin Epidemiol 1993;46:1129–40.

[76] Bastin C, Salmon E. Early neuropsychological detection of Alzheimer's disease. Eur J Clin Nutr 2014;68:1192–9. https://doi.org/10.1038/ejcn.2014.176.

[77] Small BJ, Mobly JL, Laukka EJ, Jones S, Bäckman L. Cognitive deficits in preclinical Alzheimer's disease. Acta Neurol Scand Suppl 2003;107:29–33. https://doi.org/10.1034/j.1600-0404.107.s179.6.x.

[78] Halliday D, Stawski R, Cerino E, DeCarlo C, Grewal K, MacDonald S. Intraindividual Variability across Neuropsychological Tests: Dispersion and Disengaged Lifestyle Increase Risk for Alzheimer's Disease. J Intell 2018;6:12. https://doi.org/doi:10.3390/jintelligence6010012.

[79] Rapp MA, Schnaider-Beeri M, Sano M, Silverman JM, Haroutunian V. Cross-domain variability of cognitive performance in very old nursing home residents and community dwellers:

Relationship to functional status. Gerontology 2005;51:206–12. https://doi.org/10.1159/000083995.

[80] Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of Alzheimer disease: A 22-year prospective study of the Framingham cohort. Arch Neurol 2000;57:808–13. https://doi.org/10.1001/archneur.57.6.808.

[81] Bäckman L, Jones S, Berger A, Laukka EJ, Small BJ. Multiple cognitive deficits during the transition to Alzheimer's disease. J Intern Med 2004;256:195–204. https://doi.org/10.1111/j.1365-2796.2004.01386.x.

[82] Kramer JH, Nelson A, Johnson JK, Yaffe K, Glenn S, Rosen HJ, et al. Multiple cognitive deficits in amnestic mild cognitive impairment. Dement Geriatr Cogn Disord 2006;22:306–11. https://doi.org/10.1159/000095303.

[83] Belleville S, Fouquet C, Hudon C, Zomahoun HTV, Croteau J. Neuropsychological Measures that Predict Progression from Mild Cognitive Impairment to Alzheimer's type dementia in Older Adults: a Systematic Review and Meta-Analysis. Neuropsychol Rev 2017;27:328–53. https://doi.org/10.1007/s11065-017-9361-5.

[84] Cervilla J, Prince M, Joels S, Lovestene S, Mann A. Premorbid cognitive testing predicts the onset of dementia and Alzheimer's disease better than and independently of APOE genotype. J Neurol Neurosurg Psychiatry 2004;75:1100–6. https://doi.org/10.1136/jnnp.2003.028076.

[85] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011;7:263–9. https://doi.org/10.1016/j.jalz.2011.03.005.

[86] Cummings J. Alzheimer's disease diagnostic criteria: Practical applications. Alzheimer's Res Ther 2012;4. https://doi.org/10.1186/alzrt138.

[87] Cognitive function and dementia in six areas of England and Wales: the distribution of MMSE and prevalence of GMS organicity level in the MRC CFA Study. Psychol Med 1998;28:319–35. https://doi.org/10.1017/S0033291797006272.

[88] Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: Results of the cognitive function and ageing study i and II. Lancet 2013;382:1405–12. https://doi.org/10.1016/S0140-6736(13)61570-6.

[89] Luben R, Hayat S, Wareham N, Khaw KTT. Predicting admissions and time spent in hospital over a decade in a population-based record linkage study: the EPIC-Norfolk cohort. BMJ Open 2016;6. https://doi.org/10.1136/bmjopen-2015-009461.

[90] Wilkinson T, Schnier C, Bush K, Rannikmäe K, Henshall DE, Lerpiniere C, et al. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. Eur J Epidemiol 2019;34:557–65. https://doi.org/10.1007/s10654-019-00499-1.

[91] Wilkinson T, Ly A, Schnier C, Rannikmäe K, Bush K, Brayne C, et al. Identifying dementia cases with routinely collected health data: A systematic review. Alzheimer's Dement 2018;14:1038–51. https://doi.org/10.1016/J.JALZ.2018.02.016.

[92] Gao L, Calloway R, Zhao E, Brayne C, Matthews FE. Accuracy of death certification of dementia

in population-based samples of older people: Analysis over time. Age Ageing 2018;47:589–94. https://doi.org/10.1093/ageing/afy068.

[93] Fox M, Fox C, Cruickshank W, Penhale B, Poland F, Steel. Understanding the dementia diagnosis gap in Norfolk and Suffolk: A survey of general practitioners. Qual Prim Care 2014;22:101–7.

[94] Russell P, Banerjee S, Watt J, Adleman R, Agoe B, Burnie N, et al. Improving the identification of people with dementia in primary care: evaluation of the impact of primary care dementia coding guidance on identified prevalence. BMJ Open 2013;3:e004023. https://doi.org/10.1136/bmjopen-2013-004023.

[95] Brown A, Kirichek O, Balkwill A, Reeves G, Beral V, Sudlow C, et al. Comparison of dementia recorded in routinely collected hospital admission data in England with dementia recorded in primary care. Emerg Themes Epidemiol 2016;13:1–9. https://doi.org/10.1186/s12982-016-0053-z.

[96] Sommerlad A, Perera G, Singh-Manoux A, Lewis G, Stewart R, Livingston G. Accuracy of general hospital dementia diagnoses in England: Sensitivity, specificity, and predictors of diagnostic accuracy 2008–2016. Alzheimer's Dement 2018;14:933–43. https://doi.org/10.1016/j.jalz.2018.02.012.

[97] NICE Clinical guidlines 42. Dementia. Supporting people with dementia and their carers in health and social care. NICE; 2006.

[98] Velayudhan L, Ryu S, Raczek M, Philpot M, Lindesay J, Critchfield M, et al. Review of brief cognitive tests for patients with suspected. Int Psychogeriatr 2014;26:1247–62. https://doi.org/10.1017/S1041610214000416.

[99] Brunet MD, McCartney M, Heath I, Tomlinson J, Gordon P, Cosgrove J, et al. There is no evidence base for proposed dementia screening. Bmj 2012;345:e8588–e8588. https://doi.org/10.1136/bmj.e8588.

[100] Crum R, Anthony J, Bassett S, Folstein MF. Population based norms for mini-mental state examination. JAMA 1993;269:2386–91.

[101] Ganguli M, Snitz BE, Lee CW, Vanderbilt J, Saxton JA, Chang CCH. Age and education effects and norms on a cognitive test battery from a population-based cohort: The Monongahela-Youghiogheny Healthy Aging Team. Aging Ment Heal 2010;14:100–7. https://doi.org/10.1080/13607860903071014.

[102] Crous-Bou M, Minguillón C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: From risk factors to early intervention. Alzheimer's Res Ther 2017;9:1–9. https://doi.org/10.1186/s13195-017-0297-z.

[103] Van Der Flier WM, Scheltens P. Epidemiology and risk factors of dementia. J Neurol Neurosurg Psychiatry 2005;76:v2–7. https://doi.org/10.1136/jnnp.2005.082867.

[104] Huppert F, Wilcock G. Ageing, cognition and dementia. Age Ageing 1997;26:20–3. https://doi.org/10.1097/01.AOG.0000138804.50006.7e.

[105] Mielke MM. Sex and Gender Differences in Alzheimer's Disease Dementia. Psychiatr Times 2018;35:14–7.

[106] Azad NA, Al Bugami M, Loy-English I. Gender differences in dementia risk factors. Gend Med

2007;4:120–9. https://doi.org/10.1016/S1550-8579(07)80026-X.

[107] Kuh D, Karunananthan S, Bergman H, Cooper R. A life-course approach to healthy ageing: Maintaining physical capability. Proc Nutr Soc 2014;73:237–48. https://doi.org/10.1017/S0029665113003923.

[108] Cadar D, Lassale C, Davies H, Llewellyn DJ, Batty GD, Steptoe A. Individual and area-based socioeconomic factors associated with dementia incidence in England: Evidence from a 12-year follow-up in the English longitudinal study of ageing. JAMA Psychiatry 2018;75:723–32. https://doi.org/10.1001/jamapsychiatry.2018.1012.

[109] Jones RN, Manly J, Glymour M, Rentz D, Jefferson AL, Stern Y. Conceptual and Measurement Challenges in Research on Cognitive Reserve. J Int Neuropsychol Soc 2011;17:593–601. https://doi.org/10.1038/jid.2014.371.

[110] Nijholt W, Jager-Wittenaar H, Visser M, Van Der Schans CP, Hobbelen JSM. Are a healthy diet and physical activity synergistically associated with cognitive functioning in older adults? J Nutr Health Aging 2016;20:525–32. https://doi.org/10.1007/s12603-015-0610-0.

[111] I-Min Lee, MBBS, ScD, Eric J Shiroma, MSc, Felipe Lobelo, MD, PhD, Pekka Puska, MD, Working Group* Steven N Blair, PED, and Peter T Katzmarzyk P for the LPAS. Impact of Physical Inactivity on the World's Major Non- Communicable Diseases. Lancet 2012;380:219–29. https://doi.org/10.1016/S0140-6736(12)61031-9.

[112] Falck RS, Landry GJ, Best JR, Davis J, Liu-Ambrose T. Examining Relationships of Physical Activity and Sedentary Behaviour With Cognitive Function Among Older Adults With Mild Cognitive Impairment: a Cross-Sectional Study. Alzheimer's Dement 2017;13:P865–6. https://doi.org/10.1016/j.jalz.2017.06.1231.

[113] Sabia S, Dugravot A, Dartigues J-F, Abell J, Elbaz A, Kivimäki M, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. Bmj 2017;357:j2709. https://doi.org/10.1136/bmj.j2709.

[114] Larson EB, Yaffe K, Langa KM. New Insights into the Dementia Epidemic. N Engl j Med 2013;12:2275–7. https://doi.org/doi:10.1056/NEJMp1311405. New.

[115] Mirza SS, Wolters FJ, Swanson ScD SA, Hofman A, Tiemeier H, Saeed Mirza S, et al. 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. The Lancet Psychiatry 2016. https://doi.org/10.1016/S2215-0366(16)00097-3.

[116] Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, et al. Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. JAMA Psychiatry 2017;74:712–8. https://doi.org/10.1001/jamapsychiatry.2017.0660.

[117] Cereda E, Sansone V, Meola G, Malavazos AE. Increased visceral adipose tissue rather than BMI as a risk factor for dementia. Age Ageing 2007;36:488–91. https://doi.org/10.1093/ageing/afm096.

[118] Lutsey PL, Chen N, Mirabelli MC, Lakshminarayan K, Knopman DS, Vossel KA, et al. Impaired lung function, lung disease, and risk of incident dementia. Am J Respir Crit Care Med 2019;199:1385–96. https://doi.org/10.1164/rccm.201807-1220OC.

[119] Liu IY, LaCroix AZ, White LR, Kittner SJ, Wolf PA. Cognitive impairment and mortality: a study of possible confounders. Am J Epidemiol 1990;132:136–43.

[120] Frisoni GB, Fratiglioni L, Fastbom J, Viitanen M, Winblad B. Mortality in Nondemented Subjects with Cognitive Impairment : The Influence of Health-related Factors 1999;150:1031–44.

[121] Shipley BA, Der G, Taylor MD, Deary IJ. Cognition and mortality from the major causes of death: the Health and Lifestyle Survey. J Psychosom Res 2008;65:143–52. https://doi.org/10.1016/j.jpsychores.2008.02.017.

[122] Deary IJ. Looking for "system integrity" in cognitive epidemiology. Gerontology 2012;58:545–53. https://doi.org/10.1159/000341157.

[123] Anstey KJ, Mack HA, Von Sanden C. The relationship between cognition and mortality in patients with stroke, coronary heart disease, or cancer. Eur Psychol 2006;11:182–95. https://doi.org/10.1027/1016-9040.11.3.182.

[124] Deary IJ, Der G. Reaction time explains IQ' s association with death. Psychol Sci 2005;16:64–9. https://doi.org/10.1111/j.0956-7976.2005.00781.x.

[125] Roberts B a., Der G, Deary IJ, Batty GD. Reaction time and established risk factors for total and cardiovascular disease mortality: Comparison of effect estimates in the follow-up of a large, UK-wide, general-population based survey. Intelligence 2009;37:561–6. https://doi.org/10.1016/j.intell.2009.02.001.

[126] Gallacher JEJ, Elwood PC, Hopkinson C, Rabbitt PM, Stollery BT, Sweetnam PM, et al. Cognitive function in the Caerphilly study: Associations with age, social class, education and mood. Eur J Epidemiol 1999;15:161–9. https://doi.org/10.1023/A:1007576324313.

[127] Elwood PC, Pickering J, Bayer A, Gallacher JEJ. Vascular disease and cognitive function in older men in the Caerphilly cohort. Age Ageing 2002;31:43–8.

[128] Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. BMJ 2012;344:d7622. https://doi.org/10.1136/bmj.d7622.

[129] Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Mild cognitive impairment in different functional domains and incident Alzheimer's disease. J Neurol Neurosurg Psychiatry 2005;76:1479–84. https://doi.org/10.1136/jnnp.2004.053561.

[130] Rabbitt P, Watson P, Donlan C, Mc Innes L, Horan M, Pendleton N, et al. Effects of death within 11 years on cognitive performance in old age. Psychol Aging 2002;17:468–81. https://doi.org/10.1037/0882-7974.17.3.468.

[131] Smits CH, Deeg DJ, Kriegsman DM, Schmand B. Cognitive functioning and health as determinants of mortality in an older population. Am J Epidemiol 1999;150:978–86. https://doi.org/10.1093/oxfordjournals.aje.a010107.

[132] Bäckman L, MacDonald SWS. Death and cognition: Synthesis and outlook. Eur Psychol 2006;11:224–35. https://doi.org/10.1027/1016-9040.11.3.224.

[133] Pavlik VN, de Moraes SA, Szklo M, Knopman D, Mosley TH, Hyman D. Relation between Cognitive Function and Mortality in Middle-aged Adults: The Atherosclerosis Risk in Communities Study. Am J Epidemiol 2003;157:327–34. https://doi.org/10.1093/aje/kwf209.

[134] Saz P, Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. Int J Geriatr Psychiatry

2001;16:751–61.

[135] Bassuk SS, Wypij D, Berkman LF. Cognitive impairment and mortality in the community-dwelling elderly. Am J Epidemiol 2000;151:676–88. https://doi.org/10.1093/oxfordjournals.aje.a010262.

[136] Riboli E, Kaaks R. The EPIC Project : Rationale and Study Design. Int J Epidemiol 1997;26:8–10.

[137] Day N, Oakes S, Luben R, Khaw K-T, Bingham S, Welch A, et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. Br J Cancer 1999;80:95–103.

[138] Hayat SA, Luben R, Keevil VL, Moore S, Dalzell N, Bhaniani A, et al. Cohort profile: A prospective cohort study of objective physical and cognitive capability and visual health in an ageing population of men and women in Norfolk (EPIC-Norfolk 3). Int J Epidemiol 2014;43:1063–72. https://doi.org/10.1093/ije/dyt086.

[139] Riboli E. Nutrition and cancer: background and rationale of the European Prospective Investigation into Cancer and Nutrition (EPIC). Ann Oncol 1992;3:783–91.

[140] Gallo V, Brayne C, Forsgren L, Barker RA, Petersson J, Hansson O, et al. Parkinson's Disease Case Ascertainment in the EPIC Cohort: The NeuroEPIC4PD Study. Neurodegener Dis 2015;15:331–8. https://doi.org/10.1159/000381857.

[141] Shohaimi S, Welch A, Bingham S, Luben R, Day N, Wareham N, et al. Residential area deprivation predicts fruit and vegetable consumption independently of individual educational level and occupational social class: a cross sectional population study in the Norfolk cohort of the European Prospective Investigation into Canc. J Epidemiol Community Health 2004;58:686–91. https://doi.org/10.1136/jech.2003.008490.

[142] Wareham NJ, Jakes RW, Rennie KL, Mitchell J, Hennings S, Day NE. Validity and repeatability of the EPIC-Norfolk Physical Activity Questionnaire. Int J Epidemiol 2002;31:168–74. https://doi.org/10.1093/ije/31.1.168.

[143] Khaw K. Work and leisure time physical activity assessed using a simple, pragmatic, validated questionnaire and incident cardiovascular disease and all-cause mortality in men and women: The European Prospective Investigation into Cancer in Norfolk prospective pop. Int J Epidemiol 2006;35:1034–43. https://doi.org/10.1093/ije/dyl079.

[144] Myint P, Luben R, Wareham N, Welch A, Bingham S, E DN, et al. Combined Work and Leisure Physical Activity and Risk of Stroke in Men and Women in the European Prospective Investigation into Cancer-Norfolk Prospective Population Study. Neuroepidemiology 2006;27:122–9.

[145] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[146] Roth M, Tym E, Mountjoy CQ. CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry 1986;149:698–709. https://doi.org/10.1192/bjp.149.6.698.

[147] Roth M, Huppert FA, Mountjoy CQ, Tym E. The Cambridge examination for mental disorders of the elderly – revised schedule. Cambridge, UK: Cambridge University Press; 1998.

[148] Medical Research Council. Report from the MRC Alzheimer's Disease Workshop. 1987.

[149] Matthews FE, Stephan B, Khaw K-T, Hayat S, Luben R, Bhaniani A, et al. Full-scale scores of the Mini Mental State Examination can be generated from an abbreviated version. J Clin Epidemiol 2011;64:1005–13. https://doi.org/10.1016/j.jclinepi.2010.11.014.

[150] Richards M, Kuh D, Hardy R, Wadsworth MEJ. Lifetime cognitive function and timing of the natural menopause. Neurology 1999;53:308–14. https://doi.org/10.1212/wnl.53.2.308.

[151] Brandt J. The hopkins verbal learning test: Development of a new memory test with six equivalent forms. Clin Neuropsychol 1991;5:125–42. https://doi.org/10.1080/13854049108403297.

[152] De Jager C, Hogervorst E, Combrinck M, Budge MM. Sensitivity and specificity of neuropsychological tests for mild cognitive impairment , vascular cognitive impairment and Alzheimer ' s disease. Psychol Med 2003;33:1039–50. https://doi.org/10.1017/S0033291703008031.

[153] Frank RM, Byrne GJ. The clinical utility of the Hopkins Verbal Learning Test as a screening test for mild dementia. Int J Geriatr Psychiatry 2000;15:317–24. https://doi.org/10.1002/(SICI)1099-1166(200004)15:4<317::AID-GPS116>3.0.CO;2-7 [pii].

[154] Hogervorst E, Lapuerta P, Swales K. The Hopkins Verbal Learning Test and Screening for Dementia 2002:13–20.

[155] Fowler K S; Saling, M M,;Conway, EL, Semple, J M, Louis WJ. Paired Associates Performance in the early detection of DAT. J Int Neuropsychol Soc 2002;8:58–71.

[156] Fowler KS, Saling MM, Conway EL, Louis WJ, Semple JM. Computerized delayed matching to sample and paired associate performance in the early detection of dementia. Appl Neuropsychol 1995;2:72–8. https://doi.org/10.1207/s15324826an0202_4.

[157] Swainson R, Hodges JR, Galton CJ, Semple J, Michael A, Dunn BD, et al. Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. Dement Geriatr Cogn Disord 2001;12:265–80. https://doi.org/10.1159/000051269.

[158] Blackwell AD, Sahakian BJ, Vesey R, Semple JM, Robbins TW, Hodges JR. Detecting dementia: Novel neuropsychological markers of preclinical Alzheimer's disease. Dement Geriatr Cogn Disord 2004;17:42–8. https://doi.org/10.1159/000074081.

[159] Kirby E, Bandelow S, Hogervorst E. Visual impairment in Alzheimer's disease: a critical review. J Alzheimers Dis 2010;21:15–34. https://doi.org/10.3233/JAD-2010-080785.

[160] Nelson HE, Willison J. The revised national adult reading test – Test manual 1991.

[161] Crawford JR, Parker DM, Stewart LE, Besson JA, Lacey G. Prediction of WAIS IQ with the National Adult Reading Test: Cross-validation and extension. Br J Clin Psychol 1989;28:267–73. https://doi.org/10.1111/j.2044-8260.1989.tb01376.x.

[162] Crawford JR, Deary IJ, Starr J, Whalley LJ. The NART as an index of prior intellectual functioning: a retrospective validity study covering a 66-year interval. Psychol Med 2001;31:451–8. https://doi.org/10.1017/S0033291701003634.

[163] Brayne C, Beardsall L. Estimation of verbal intelligence in an elderly community: An epidemiological study using NART. Br J Clin Psychol 1990;29:217–23.

[164] Beardsall L, Brayne C. Estimation of verbal intelligence in an elderly community: A prediction

analysis using a shortened NART. Br J Clin Psychol 1990;29:83–90.

[165] Crawford JR, Parker DM, Allan KM, Jack AM, Morrison FM. The Short NART: cross-validation, relationship to IQ and some practical considerations. Br J Clin Psychol 1991;30 (Pt 3):223–9.

[166] Huppert F, Beardsall L. Prospective memory impairment as an early indicator of dementia. J Clin Exp Neuropsychol 1993;15:805–21. https://doi.org/10.1080/01688639308402597.

[167] Huppert F, Johnson T, Nickson J. High Prevalence of Prospective Memory Impairment in the Elderly and in Early-stage Dementia : Findings from a Population-based Study. Appl Cogn Psychol 2000;14:S63–81. https://doi.org/10.1002/acp.771.

[168] Kuh D, Richards M, Hardy R, Butterworth S, Wadsworth MEJ. Childhood cognitive ability and deaths up until middle age : a post-war birth cohort study 2004;33:408–13. https://doi.org/10.1093/ije/dyh043.

[169] Ganguli M, Belle S, Ratcliff G, Seaberg E, Huff FJ, Von der Porten K, et al. Sensitivity and specificity for dementia of population-based criteria for cognitive impairment: The MoVIES project. Journals Gerontol 1993;48:152–61. https://doi.org/10.1093/geronj/48.4.M152.

[170] Hayat SA, Luben R, Moore S, Dalzell N, Bhaniani A, Anuj S, et al. Cognitive function in a general population of men and women: a cross sectional study in the European Investigation of Cancer-Norfolk cohort (EPIC-Norfolk). BMC Geriatr 2014;14:142. https://doi.org/10.1186/1471-2318-14-142.

[171] O'Connor DW. Memory complaints and impairment in 55 normal depressed and demented elderly persons identified in a community survey. Arch Gen Psychiatry 1990;47:224–7.

[172] de Jager CA, Schrijnemaekers A-CMC, Honey TEM, Budge MM. Detection of MCI in the clinic: evaluation of the sensitivity and specificity of a computerised test battery, the Hopkins Verbal Learning Test and the MMSE. Age Ageing 2009;38:455–60.

[173] Petersen RC, Doody R, Kurz a, Mohs RC, Morris JC, Rabins P V, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–92.

[174] Tucker-Drob EM. Global and domain-specific changes in cognition throughout adulthood. Dev Psychol 2011;47:331–43. https://doi.org/10.1037/a0021361.

[175] Ylikoski R. Heterogeneity of cognitive profiles in aging: Successful aging, normal aging, and individuals at risk for cognitive decline. Eur J Neurol 1999;6:645–52. https://doi.org/10.1046/j.1468-1331.1999.660645.x.

[176] Perry RJ, Watson P, Hodges JR. The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. Neuropsychologia 2000;38:252–71. https://doi.org/10.1016/S0028-3932(99)00079-2.

[177] Kenny RA, Coen RF, Frewen J, Donoghue O, Cronin H, Savva GM. Normative values of cognitive and physical function in older adults: findings from the Irish Longitudinal Study on Ageing. J Am Geriatr Soc 2013;61 Suppl 2:S279-90. https://doi.org/10.1111/jgs.12195.

[178] Spencer RJ, Wendell CR, Giggey PP, Katzel LI, Lefkowitz DM, Siegel EL, et al. Psychometric limitations of the mini-mental state examination among nondemented older adults: an evaluation of neurocognitive and magnetic resonance imaging correlates. Exp Aging Res 2013;39:382–97. https://doi.org/10.1080/0361073X.2013.808109.

[179] Lacy M, Kaemmerer T, Czipri S. Standardized Mini-Mental State Examination Scores and Verbal Memory Performance at a Memory Center: Implications for Cognitive Screening. Am J Alzheimers Dis Other Demen 2014. https://doi.org/10.1177/1533317514539378.

[180] Weaver Cargin J, Maruff P, Collie A, Masters C. Mild memory impairment in healthy older adults is distinct from normal aging. Brain Cogn 2006;60:146–55. https://doi.org/10.1016/j.bandc.2005.10.004.

[181] Christensen H, Mackinnon A, Korten A, Jorm AF, Henderson AS, Jacomb P, et al. An analysis of diversity in the cognitive performance of elderly community dwellers: individual differences in change scores as a function of age. Psychol Aging 1999;14:365–79.

[182] White L, Katzman R, Losonczy K, Salive M, Wallace R, Berkman L, et al. Association of education with incidence of cognitive impairment in three established populations for epidemiologic studies of the elderly. J Clin Epidemiol 1994;47:363–74. https://doi.org/10.1016/0895-4356(94)90157-0.

[183] Brayne C, Gill C, Paykel ES, Huppert F, O'Connor DW. Cognitive decline in an elderly population-a two wave study of change. Psychol Med 1995;25:673–83.

[184] Crawford JR, Stewart LE, Garthwaite PH, Parker DM, Besson JA. The relationship between demographic variables and NART performance in normal subjects. Br J Clin Psychol 1988;27 (Pt 2):181–2.

[185] Valenzuela MJ, Sachdev P. Assessment of complex mental activity across the lifespan: development of the Lifetime of Experiences Questionnaire (LEQ). Psychol Med 2007;37:1015–25. https://doi.org/10.1017/S003329170600938X.

[186] Fleming J, Zhao E, O'Connor DW, Pollitt P, Brayne C. Cohort profile: The Cambridge City over-75s Cohort (CC75C). Int J Epidemiol 2007;36:40–6. https://doi.org/10.1093/ije/dyl293.

[187] Jagger C, Matthews R, Melzer D, Matthews F, Brayne C. Educational differences in the dynamics of disability incidence, recovery and mortality: Findings from the MRC Cognitive Function and Ageing Study (MRC CFAS). Int J Epidemiol 2007;36:358–65. https://doi.org/10.1093/ije/dyl307.

[188] Matthews FE, Chatfield M, Brayne C. An investigation of whether factors associated with short-term attrition change or persist over ten years: data from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). BMC Public Health 2006;6:185. https://doi.org/10.1186/1471-2458-6-185.

[189] Brayne C, Calloway P. The association of education and socioeconomic status with the mini mental state examination and the clinical diagnosis of dementia in elderly people. Age Ageing 1990;19:91–6. https://doi.org/10.1093/ageing/19.2.91.

[190] Barnett JH, Hachinski V, Blackwell AD. Cognitive health begins at conception: addressing dementia as a lifelong and preventable condition. BMC Med 2013;11:246. https://doi.org/10.1186/1741-7015-11-246.

[191] Bell-McGinty S, Podell K, Franzen M, Baird AD, Williams MJ. Standard measures of executive function in predicting instrumental activities of daily living in older adults. Int J Geriatr Psychiatry 2002;17:828–34. https://doi.org/10.1002/gps.646.

[192] Salthouse T. The processing-speed theory of adult age differences in cognition. Psychol Rev 1996;103:403–28. https://doi.org/10.1037//0033-295X.103.3.403.

[193] Williams JG, Huppert F, Matthews FE, Nickson J. Performance and normative values of a concise neuropsychological test (CAMCOG) in an elderly population sample. Int J Geriatr Psychiatry 2003;18:631–44. https://doi.org/10.1002/gps.886.

[194] Deary IJ, Johnson W. Intelligence and education: Causal perceptions drive analytic processes and therefore conclusions. Int J Epidemiol 2010;39:1362–9. https://doi.org/10.1093/ije/dyq072.

[195] Salthouse T, Ferrer-Caja E. What needs to be explained to account for age-related effects on multiple cognitive variables? Psychol Aging 2003;18:91–110. https://doi.org/10.1037/0882-7974.18.1.91.

[196] Nelson HE, McKenna P. The use of current reading ability in the assessment of dementia. Br J Soc Clin Psychol 1975;14:259–67.

[197] Gerstorf D, Herlitz A, Smith J. Stability of sex differences in cognition in advanced old age: the role of education and attrition. J Gerontol B Psychol Sci Soc Sci 2006;61:P245–9.

[198] Meinz EJ, Salthouse T. Is age kinder to females than to males? Psychon Bull Rev 1998;5:56–70. https://doi.org/10.3758/BF03209457.

[199] Alzheimer's Association. 2012 Alzheimer's disease facts and figures. Alzheimers Dement 2012;8:131–68.

[200] Hofman A, Rocca WA, Brayne C, Breteler MMB, Clarke M, Cooper B, et al. The Prevalence of Dementia in Europe: A Collaborative Study of 1980–1990 Findings. Int J Epidemiol 1991;20:736–48. https://doi.org/10.1093/ije/20.3.736.

[201] Ruitenberg A, Ott A, Van Swieten JC, Hofman A, Breteler MMB. Incidence of dementia: Does gender make a difference? Neurobiol Aging 2001;22:575–80. https://doi.org/10.1016/S0197-4580(01)00231-7.

[202] Bamford SM, Walker T. Women and dementia - Not forgotten. Maturitas 2012;73:121–6. https://doi.org/10.1016/j.maturitas.2012.06.013.

[203] Der G, Deary IJ. Age and sex differences in reaction time in adulthood: Results from the United Kingdom Health and Lifestyle Survey: Correction. Psychol Aging 2009;24:229. https://doi.org/10.1037/a0015515.

[204] Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ. Paired associate performance in the early detection of DAT. J Int Neuropsychol Soc 2002;8:58–71.

[205] Rovio S, Kåreholt I, Viitanen M, Winblad B, Tuomilehto J, Soininen H, et al. Work-related physical activity and the risk of dementia and Alzheimer's disease. Int J Geriatr Psychiatry 2007;22:874–82. https://doi.org/10.1002/gps.1755.

[206] Morgan GS, Gallacher J, Bayer A, Fish M, Ebrahim S, Ben-Shlomo Y. Physical activity in middle-age and dementia in later life: Findings from a prospective cohort of men in caerphilly, South Wales and a meta-analysis. J Alzheimer's Dis 2012;31:569–80. https://doi.org/10.3233/JAD-2012-112171.

[207] Hamer M, Muniz Terrera G, Demakakos P. Physical activity and trajectories in cognitive function: English Longitudinal Study of Ageing. J Epidemiol Community Health 2018:jech-2017-210228. https://doi.org/10.1136/jech-2017-210228.

[208] Rovio S, Kåreholt I, Helkala E, Viitanen M, Winblad B, Tuomilehto J, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 2005;4:705–11. https://doi.org/10.1016/S1474-4422(05).

[209] Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, et al. Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. J Intern Med 2011;269:107–17. https://doi.org/10.1111/j.1365-2796.2010.02281.x.

[210] Blondell SJ, Hammersley-Mather R, Veerman J. Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC Public Health 2014;14:1–12. https://doi.org/10.1186/1471-2458-14-510.

[211] Angevaren M, Aufdemkampe G, Verhaar HJJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev 2008:CD005381. https://doi.org/10.1002/14651858.CD005381.pub3.

[212] Daly S, Allen J. Inequalities in mental health, cognitive impairment and dementia among older people. 2016.

[213] Hayat SA, Luben R, Dalzell N, Moore S, Anuj S, Matthews FE, et al. Cross Sectional Associations between Socio-Demographic Factors and Cognitive Performance in an Older British Population: The European Investigation of Cancer in Norfolk (EPIC-Norfolk) Study. PLoS One 2016;11:e0166779. https://doi.org/10.1371/journal.pone.0166779.

[214] Greenfield EA, Moorman SM. Childhood Socioeconomic Status and Later Life Cognition: Evidence From the Wisconsin Longitudinal Study. J Aging Heal 2019;31:1589–615. https://doi.org/10.1177/0898264318783489.

[215] Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2003;6:407–13. https://doi.org/10.1079/PHN2002439.

[216] Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants with Those of the General Population. Am J Epidemiol 2017;186:1026–34. https://doi.org/10.1093/aje/kwx246.

[217] Singh-Manoux A, Hillsdon M, Brunner E, Marmot M. Effects of physical activity on cognitive functioning in middle age: Evidence from the whitehall II prospective cohort study. Am J Public Health 2005;95:2252–8. https://doi.org/10.2105/AJPH.2004.055574.

[218] Middleton L, Barnes D, Lui L, Yaffe K. Physical Activity Over the Life Course and its Association with Cognitive Performance and Impairment in Old Age. J Am Geriatr Soc 2010;58:1322–6. https://doi.org/10.1111/j.1532-5415.2010.02903.x.Physical.

[219] Davies R. Gill Livingston: transforming dementia prevention and care. Lancet 2017;390:2619. https://doi.org/10.1016/S0140-6736(17)31913-X.

[220] Sachs GA, Carter R, Holtz LR, Smith F, Stump TE, Tu W. Cognitive Impairment : An Independent Predictor of Excess Mortality. A cohort study. Ann Intern Med 2011;155:300–8.

[221] Ojagbemi A, Bello T, Gureje O. Cognitive Reserve, Incident Dementia, and Associated Mortality in the Ibadan Study of Ageing. J Am Geriatr Soc 2016;64:590–5.

https://doi.org/10.1111/jgs.14015.Cognitive.

[222] Batty GD, Deary IJ, Gottfredson LS. Premorbid (early life) IQ and Later Mortality Risk: Systematic Review. Ann Epidemiol 2007;17:278–88. https://doi.org/10.1016/j.annepidem.2006.07.010.

[223] Peng TC, Chen WL, Wu LW, Chen YJ, Liaw FY, Wang GC, et al. The Effect of Neurobehavioral Test Performance on the All-Cause Mortality among US Population. Biomed Res Int 2016;2016. https://doi.org/10.1155/2016/5927289.

[224] Gale CR, Martyn CN, Cooper C. Cognitive impairment and mortality in a cohort of elderly people. BMJ 1996;312:608–11.

[225] Small BJ, Bäckman L. Time to Death and Cognitive Performance. Curr Dir Psychol Sci 1999;8:168–72.

[226] Gallacher J, Bayer A, Dunstan F, Yarnell J, Elwood P, Ben-Shlomo Y. Can we understand why cognitive function predicts mortality? Results from the Caerphilly Prospective Study (CaPS). Intelligence 2009;37:535–44. https://doi.org/10.1016/j.intell.2009.02.004.

[227] Batty GD, Deary IJ, Zaninotto P. Original Contribution Association of Cognitive Function With Cause-Specific Mortality in Middle and Older Age : Follow-up of Participants in the English Longitudinal Study of Ageing. Am J Epidemiol 2016;183:183–90. https://doi.org/10.1093/aje/kwv139.

[228] Small BJ, Bäckman L. Cognitive correlates of mortality: Evidence from a population-based sample of very old adults. Psychol Aging 1997;12:309–13. https://doi.org/10.1037/0882-7974.12.2.309.

[229] Neale R, Brayne C, Johnson AL. Cognition and survival: an exploration in a large multicentre study of the population aged 65 years and over. Int J Epidemiol 2001;30:1383–8. https://doi.org/10.1093/ije/30.6.1383.

[230] Connors MH, Sachdev PS, Kochan NA, Xu J, Draper B, Brodaty H. Cognition and mortality in older people: the Sydney Memory and Ageing Study. Age Ageing 2015;44:1049–54. https://doi.org/10.1093/ageing/afv139.

[231] Luck T, Roehr S, Jessen F, Villringer A, Angermeyer MC, Riedel-Heller SG. Mortality in Individuals with Subjective Cognitive Decline: Results of the Leipzig Longitudinal Study of the Aged (LEILA75). J Alzheimer's Dis 2015;48:S33–42. https://doi.org/10.3233/JAD-150090.

[232] Ghisletta P, McArdle JJ, Lindenberger U. Longitudinal cognition-survival relations in old and very old age: 13-year data from the Berlin aging study. Eur Psychol 2006;11:204–23. https://doi.org/10.1027/1016-9040.11.3.204.

[233] Hayat SA, Luben R, Dalzell N, Moore S, Hogervorst E, Matthews FE, et al. Understanding the relationship between cognition and death: a within cohort examination of cognitive measures and mortality. Eur J Epidemiol 2018;0123456789. https://doi.org/10.1007/s10654-018-0439-z.

[234] Sabia S, Guéguen A, Marmot MG, Shipley MJ, Ankri J, Singh-Manoux A. Does cognition predict mortality in midlife? Results from the Whitehall II cohort study. Neurobiol Aging 2010;31:688–95. https://doi.org/10.1016/j.neurobiolaging.2008.05.007.

[235] Swan GE, Carmelli D, LaRue A. Performance on the digit symbol substitution test and 5-year

mortality in the Western Collaborative Group Study. Am J Epidemiol 1995;141:32–40.

[236] Casey JA, Schwartz BS, Stewart WF, Adler NE. Using Electronic Health Records for Population Health Research: A Review of Methods and Applications. Annu Rev Public Health 2016;37:61–81. https://doi.org/10.1146/annurev-publhealth-032315-021353.

[237] Ford E, Boyd A, Bowles JKF, Havard A, Aldridge RW, Curcin V, et al. Our data, our society, our health: A vision for inclusive and transparent health data science in the United Kingdom and beyond. Learn Heal Syst 2019;3:e10191. https://doi.org/10.1002/lrh2.10191.

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

[239] Brayne C, Fox C. Dementia Screening in Primary Care. Public Health 2007;298:2409–11.

[240] UK Biobank. Primary Care Linked Data :Companion Document 2019:1–24. https://www.ukbiobank.ac.uk.

[241] Cornish RP, Henderson J, Boyd AW, Granell R, Van Staa T, Macleod J. Validating childhood asthma in an epidemiological study using linked electronic patient records. BMJ Open 2014;4:1–6. https://doi.org/10.1136/bmjopen-2014-005345.

[242] Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, Staa T van, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827–36. https://doi.org/10.1093/ije/dyv098.

[243] Weuve J, Proust-Lima C, Power MC, Gross AL, Hofer SM, Thiébaut R, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research 2015;11:1098–109. https://doi.org/10.1016/j.jalz.2015.06.1885.

[244] Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLOS Med 2015;12:e1001885. https://doi.org/10.1371/journal.pmed.1001885.

[245] Perera G, Broadbent M, Callard F, Chang C-K, Downs J, Dutta R, et al. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. BMJ Open 2016;6:e008721. https://doi.org/10.1136/bmjopen-2015-008721.

[246] Romero JP, Benito-León J, Louis ED, Bermejo-Pareja F. Under reporting of dementia deaths on death certificates: A systematic review of population-based cohort studies. J Alzheimer's Dis 2014;41:213–21. https://doi.org/10.3233/JAD-132765.

[247] Global Burden of Diseases (GBD) 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016 a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:88–106. https://doi.org/10.1016/S1474-4422(18)30403-4.

[248] Mukadam N, Livingston G, Rantell K, Rickman S. Diagnostic rates and treatment of dementia before and after launch of a national dementia policy: An observational study using English national databases. BMJ Open 2014;4:1–8. https://doi.org/10.1136/bmjopen-2013-004119.

[249] London Clinical Networks. "Coding clean-up " Exercise Guidance to GPs to improve dementia

coding , and raise diagnosis rates: A step by step approach. London, UK: n.d.

[250] British Household Panel Survey, waves 1-17 (1991-2008) User Documentation: Rural-Urban Indicator (URIND) Rural-Urban Indicator. 2008.

[251] Perera G, Stewart R, Higginson IJ, Sleeman KE. Reporting of clinically diagnosed dementia on death certificates: Retrospective cohort study. Age Ageing 2016;45:667–72. https://doi.org/10.1093/ageing/afw077.

[252] Crowther GJE, Bennett MI, Holmes JD. How well are the diagnosis and symptoms of dementia recorded in older patients admitted to hospital? Age Ageing 2017;46:112–8. https://doi.org/10.1093/ageing/afw169.

[253] Ford E, Greenslade N, Paudyal P, Bremner S, Smith HE, Banerjee S, et al. Predicting dementia from primary care records: A systematic review and meta-analysis 2018. https://doi.org/10.1371/journal.pone.0194735.

[254] Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. Lancet Public Heal 2017;2:e149–56. https://doi.org/10.1016/S2468-2667(17)30031-2.

[255] NHS Digital. SNOMED CT: A clinical vocabulary for electronic health records n.d. https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct.

[256] Singh-Manoux A, Kivimäki M. The importance of cognitive ageing for understanding dementia. Age (Omaha) 2010;32:509–12. https://doi.org/10.1007/s11357-010-9147-7.

[257] Bäckman L. Memory and cognition in preclinical dementia: What we know and what we do not know. Can J Psychiatry 2008;53:354–60. https://doi.org/10.1177/070674370805300604.

[258] Johnson DK, Storandt M, Morris JC, Langford ZD, Galvin JE. Cognitive profiles in dementia Alzheimer disease vs healthy brain aging. Neurology 2008;71:1783–9. https://doi.org/10.1212/01.wnl.0000335972.35970.70.

[259] Bäckman L, Laukka EJ, Wahlin A, Small BJ, Fratiglioni L. Influences of preclinical dementia and impending death on the magnitude of age-related cognitive deficits. Psychol Aging 2002;17:435–42. https://doi.org/10.1037/0882-7974.17.3.435.

[260] Rapp MA, Reischies FM. Attention and executive control predict Alzheimer disease in late life: Results from the Berlin Aging Study (BASE). Am J Geriatr Psychiatry 2005;13:134–41. https://doi.org/10.1097/00019442-200502000-00007.

[261] Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, et al. Screening for Cognitive Impairment in Older Adults. US Preventive Services Task Force Recommendation Statement. JAMA 2020;323:800. https://doi.org/10.1001/jama.2020.0435.

[262] Report commisioned by Alzheimer's Society. Dementia UK Update. Second Edition. London, UK: 2014.

[263] Norton S, Matthews FE, Brayne C. A commentary on studies presenting projections of the future prevalence of dementia. BMC Public Health 2013;13. https://doi.org/10.1186/1471-2458-13-1.

[264] Gow AJ, Johnson W, Pattie A, Whiteman MC, Starr J, Deary IJ. Mental ability in childhood and

cognitive aging. Gerontology 2008;54:177–86. https://doi.org/10.1159/000118098.

[265] Deary IJ, Gow AJ, Taylor MD, Corley J, Brett C, Wilson V, et al. The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. BMC Geriatr 2007;7:28. https://doi.org/10.1186/1471-2318-7-28.

[266] Frankish H, Horton R. Prevention and management of dementia: a priority for public health. Lancet 2017;390:2614–5. https://doi.org/10.1016/S0140-6736(17)31756-7.