Determinants of cognitive ageing and dementia

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Thesis submitted for the Degree of Doctor of Philosophy

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I, Pamela Almeida-Meza, confirm that the work presented in this thesis is my own. Where information has been derived by other sources, I confirm that this has been indicated in the thesis.

Signature: Date: 24 May 2023

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Abstract

Background: Sociobehavioural determinants of cognitive reserve (CR), such as education, verbal ability, occupation, and leisure, have been found to be beneficial to older age cognitive health, but more evidence is needed to understand the pathways involved and the relationship between CR, cognitive function, brain reserve (BR), and dementia risk.

Methods: CR theory (1) was tested with moderation models utilising the Cognitive Reserve Index (CRI) (2) and verbal ability, in the associations between childhood cognition or brain markers and older age cognitive function in three cohort studies (NSHD, Insight 46 and UK Biobank, Chapters 4 to 6). The association between leisure engagement and dementia incidence was explored in one cohort study (ELSA, Chapter 7).

Results: CR modifies cognitive ability, whereby for individuals with lower childhood cognitive ability, higher CR scores predict higher later-life cognitive function. Across studies, the CR markers were consistently associated with older age cognitive function, independently of childhood cognition and brain markers, but their contribution to BR was less clear (Chapter 5). Furthermore, the moderating role of CR was inconsistent; CR modified the association between brain markers and cognitive function in Insight 46 (Chapter 5), but this was not replicated in UK Biobank (Chapter 6). Finally, leisure engagement showed a consistent association with cognitive function and BR and modified the association between these two variables (Chapters 4 to 6). The ELSA study suggested that for married individuals, intellectual leisure engagement was associated with a reduced incidence of dementia (Chapter 7).

Conclusions: The observational evidence from this thesis adds to the growing evidence for the multiple pathways through which various sociobehavioural determinants are associated

with older-age cognitive function and dementia. The findings can inform public policy and design effective interventions to prevent cognitive ageing and dementia.

Impact statement

The key contribution of this thesis is the identification and assessment of various sociobehavioural determinants that are associated with cognitive function and dementia risk in older age, and the exploration of some of the pathways through which they operate, including cognitive reserve. This research provided insights into how sociobehavioural factors (e.g., education, verbal ability, occupation, leisure) can contribute to cognitive health in older adults and the importance of cognitive reserve on cognitive functioning and dementia risk. These analyses were conducted in three British cohorts of ageing to ensure the robustness of the findings. The results of this thesis can inform the development of interventions aimed at promoting healthy cognitive ageing and preventing dementia and are relevant to clinical practice and public health policy.

Two chapters of this thesis have been published in peer-reviewed scientific journals: the *Journal of Alzheimer's Disease* in 2021 and *Neurology* in 2022. Both publications received a large amount of media coverage, resulting in over 200 news stories in a wide variety of outlets including the Daily Mail, Physician's Weekly, and i News. Furthermore, since its publication the article in the *Journal of Alzheimer's Disease* has been cited 14 times, and the Neurology article was published alongside an Editorial by Schnaider Beeri and D'Abreu (3), which commented favourably on the findings and highlighted the importance of lifelong lifestyle choices and interventions to prevent cognitive decline in older adults. Additionally, the findings from this thesis were disseminated as posters and oral presentations at several national and international conferences including the Gerontological Society of America in November 2020, the Society for Social Medicine Annual Scientific Meeting in September 2020, and the Alzheimer's Association International Conference in July 2020.

In accordance with the Open Science principles, the new data created for this thesis – the Cognitive Reserve Index based on Nucci et al., 2012 Cognitive Reserve Index questionnaire (CRIq) (2) – were made publicly available via the UK Biobank platform on April 2023.

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List of abbreviations

Aβ Amyloid beta

ACE-III Addenbrooke's Cognitive Examination III

AD Alzheimer's dementia

ADNI Alzheimer's Disease Neuroimaging Initiative

APOE Apolipoprotein E

BDNF Brain-derived neurotrophic factor

BM Brain maintenance

BR Rain reserve

CES-D Centre for Epidemiologic Studies Depression Scale

CR Cognitive Reserve

CRI Cognitive Reserve Index

CRIq Cognitive Reserve Index questionnaire

CR/RANN Cognitive Reserve/Reference Ability Neural Network Study

DLB Dementia with Lewy Bodies

ELSA English Longitudinal Study of Ageing

FINGER Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

FRS Framingham Heart Study cardiovascular risk scores

FTD Frontotemporal dementia

GHQ-28 General Health Questionnaire - 28

HRS Health and Retirement Study

IQCODE Informant Questionnaire on Cognitive Decline in the Elderly

LEQ Lifetime of Experiences Questionnaire

LBC Lothian Birth Cohorts

MCI Mild cognitive impairment

MI Multiple imputations

MMSE Mini-Mental State Examination

MRC Medical Research Council

MRI Magnetic resonance imaging

NART National Adult Reading Test

NIA National Institute of Aging

NSHD National Survey of Health and Development

PACC Preclinical Alzheimer Cognitive Composite

PET Positron emission tomography

RCT Randomised controlled trial

ROIs Regions of interest

ROSMAP Religious Orders Study and the Rush Memory and Ageing Project

SEP Socioeconomic position

SHR Sub-hazard ratio

SNPs Single-nucleotide polymorphism

TILDA The Irish Longitudinal Study of Ageing

TIV Total intracranial volume

TDI Townsend deprivation index

TDP-43 Transactive-response DNA-binding protein 43

UK United Kingdom

US United States of North America

VaD Vascular dementia

VETSA Vietnam Era Twin Study of Ageing

WHO World Health Organization

WMH White matter hyperintensities

WMHV White matter hyperintensity volumes

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Chapter 1. Introduction

1.1 Population ageing and the global burden of dementia

Over the past few decades, the age structure of the population has been transformed worldwide by the unprecedented increase in life expectancy and reduction in birth rates. Around 8.5% of the world's population is over the age of 65, with a substantial number of people reaching their ninth or even tenth decade (4). Furthermore, in most parts of the world, the fertility rate has decreased significantly and is expected to continue to decline (5). In the United Kingdom (UK), the total fertility rate for England and Wales has been declining steadily across all age groups, being its lowest ever recorded in 2020 (6). Consequently, people over the age of 65 have outnumbered children under the age of 5 (7), and by 2050 individuals aged 65 and older will represent 16.7% of the world's population (4). Specifically, projections of the age structure of the UK estimate that by 2043 there will be 3 million people aged 85 years and older (Figure 1).

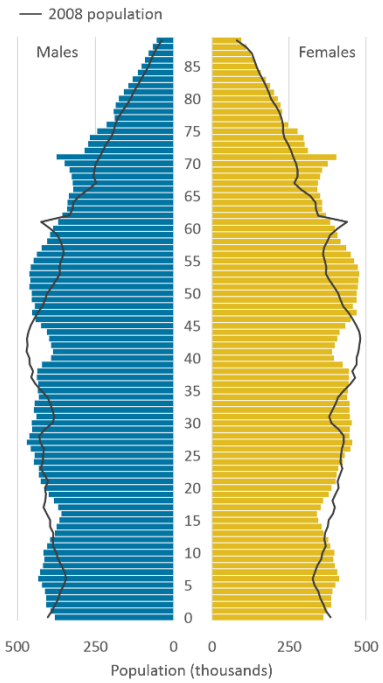


Figure 1 Population pyramid for the UK, mid-2018, single year of age 0 to 89
Source: Office for National Statistics, National Records

The increase in life expectancy and population ageing has partly resulted from improvements in health care and public health initiatives for early detection and delayed onset of non-communicable diseases, directly reducing mortality rates in adulthood (8). However, cognitive impairment and dementia continue to represent the main drivers of disability and dependency related to ageing, as well as increased mortality at a global level, carrying a high personal, financial, and societal burden. Hence, as the proportion of the ageing population increases, so does the global prevalence of dementia, with deleterious consequences for society.

In the early 2000s, it was estimated that 24 million people had dementia worldwide (9), while current estimates suggest that over 50 million people are living with dementia (10). In the UK, it is estimated that one in 11 people over the age of 65 are living with dementia

(11). By 2050 it is estimated that globally around 131.5 to 152.8 million people will be diagnosed with this disease (8,12,13). Furthermore, as the number of dementia diagnoses increases, so do the associated costs of medical and residential care. Worldwide, the estimated annual cost of dementia is above $1.3 trillion and is expected to rise to $2.8 trillion by 2050 (14). In 2010 dementia was considered the most costly brain disorder in the UK, representing £18.5 million per annum, surpassing the cost of psychotic disorders, mood disorders, and addiction (15). Furthermore, in 2019 the total cost of dementia in the UK amount to £34.7 billion, from which health care costs account for 14%, unpaid care account for 40%, and social care account for 45% (16).

Despite these dire global projections for the prevalence of dementia and its social and economic consequences, some evidence has suggested that the age-specific incidence of dementia might be decreasing in high-income countries (17–20). Changes in exposure to potential developmental, lifestyle and cardiovascular risk factors appear to have increased the age of onset of dementia and thus, deferred it to older age (18,21–24). However, estimates have also suggested that the absolute number of people living with dementia will continue increasing over time (25–27). A study investigating cohort trends in cognitive function across 7 decades of birth cohorts in the Health and Retirement Study (HRS) (from 1890 to 1959) found that cognitive function has improved for the first generations (born between 1890 to 1947) but has significantly declined for newer generations (born between 1948 to 1959) (28), potentially due to lower household wealth, increased loneliness and psychiatric problems, and cardiovascular risk factors for the youngest cohorts (28). Hence, despite some studies suggesting that the incidence and prevalence of dementia may stabilise (29–31) the disease burden is still expected to increase over time (32). Data

modelling of the UK suggests that by 2040, 1.2 million people will be living with the disease, representing a 57% increase in the number of people with dementia from 2016 (32).

Cognitive impairment and dementia are associated with increased risk of disability, health care costs, and reduced quality of life for the elderly population. In 2022 Dementia and Alzheimer's disease were identified as the leading cause of death in England, with 95 deaths per 100,000 people. In 2016 it was estimated that the total disability-adjusted life years for mild cognitive impairment (MCI) and dementia was 1,295 per 100,000, with an expected rise to 9,501 per 100,000 in 2065, providing evidence for the current and projected disease burden of dementia (33). Furthermore, after the onset of dementia, survival ranges between 1.1 and 10 years depending on age, gender, dementia subtype, and severity stages, with older and male individuals having the shortest survival (34,35). Current estimates suggest that for individuals over the age of 80, dementia is considered responsible for 10.4% of the global number of years of life lost and years lived with disability (35,36). Therefore, dementia represents one of the most disabling and burdensome health issues worldwide, with years of life lost and death being the dominant consequences of the disease (36).

1.2 Individual differences in cognitive ageing and dementia risk

Despite cognitive decline and dementia being among the most feared aspects of ageing (37), epidemiological research has led to the consensus that dementia is not a normal part of ageing and is potentially preventable (38). At least 30 to 40% of the variability in dementia risk is dependent on non-genetic influences, and the environment is considered to play a crucial role in modulating the risk (38–40). Furthermore, there is great heterogeneity in the cognitive function of older people. Even among those who develop dementia, there is a

large variance in the pattern of clinical progression (41), which might be related to exposure and accumulation of risk and protective factors across the life course (42).

Health is a life-long process, and therefore, the determinants of cognitive ageing can be tracked across the whole life course, with important risk factors having their effect very early in life (43). In the face of an ageing population and increased longevity, understanding cognitive ageing and dementia's modifiable risk factors is a global priority. Therefore, this PhD project aims to investigate the pathways through which various sociobehavioural variables are directly and indirectly associated with older-age cognitive function and dementia.

Chapter 2. Literature review

2.1 Cognitive ageing

Cognitive function is an important determinant of quality of life and the ability to maintain independence in old age. However, even among cognitively healthy individuals, it is recognised that ageing is associated with a normative decline in working memory abilities, which in turn affects other cognitive domains such as information processing, executive function, comprehension, problem-solving and learning (44,45). A study investigating the age-related effects on verbal and visuospatial working memory in 880 individuals aged 15 to 80 years found evidence suggesting that working memory performance declines gradually across the adult life course, starting as early as age 35, worsening with advancing age, and becoming especially noticeable and significant for 60 to 70 year-olds (46). Similarly, verbal fluency and episodic memory have also been found to decline along with age, occurring at a faster pace beyond age 70 (47). Episodic memory in particular has been identified as having the highest predictive accuracy from progression to dementia (48). Furthermore, evidence from the Lothian Birth Cohorts (LBC) has suggested that once cognitive decline becomes apparent for some domains, a general decline in all abilities is likely to follow (49,50). The clinical hallmark of dementia is a consistent pattern of decline in cognitive function which is severe enough to interfere with a person's daily functioning and independence, particularly when associated with neurodegeneration in medial temporal lobe structures, which are essential for normal memory function (51) (see Chapter 2.2 'Dementia').

Even though a gradual decline in cognitive function is correlated with normal ageing (i.e., in the absence of severe diseases or dementia), ageing does not affect individuals uniformly, making it challenging to estimate typical trajectories of late-life decline. Some cognitively

healthy older adults have been shown to have stable cognitive performance for up to 15 years – even into the ninth decade of life (52). Furthermore, a study following 1,010 older individuals for up to 24 years suggested that late-life adverse cognitive outcomes reflect non-normative pathologic processes that lead to brain deterioration (53). In line with this, Boyle and her team suggested a novel indicator of brain health, the "cognitive clock", which showed that cognitive age is a better predictor of brain health than chronological age (54). Furthermore, the concept of "successful cognitive ageing" and the term "Super Agers" have been used to describe a sub-set of older individuals who preserve their cognitive abilities until later in life, demonstrating similar memory abilities and processing speed to younger adults (55–59). These findings suggest that for some individuals, the brain maintains neuroplasticity and the ability for resilience in older age (see section 2.3.5 'Reserve'). Thus far, it is considered that person-specific engagement in psychosocial, health, and lifestyle-related factors could potentially be associated with superior cognitive abilities among older people.

2.2 Dementia

Late-onset dementia refers to various neurodegenerative conditions diagnosed in people over the age of 65, inducing cognitive (i.e., memory loss, thinking impairment), psychological (i.e., disturbances of mood, behaviour, and personality), and functional (i.e., self-care, managing finances, and using transportation) symptoms (60,61) which are severe enough to interfere with daily functioning and independence. Individuals with dementia may present varying types of symptoms, which in turn can differ considerably in severity. Different pathologies have been found to cause dementia, with the most common being Alzheimer's disease (50 to 75%), vascular dementia (VaD, 20%), dementia with Lewy bodies

(DLB, 10 to 15%) and frontotemporal dementia (FTD, 2%) (12,62,63). Although it is important to consider that not all individuals presenting these pathologies develop the clinical manifestation of dementia (see section 2.3.5 'Reserve'). Therefore, here and throughout the term Alzheimer's disease will be used to refer to the neuropathological changes associated with the disease, whereas the term Alzheimer's dementia (AD) will be used to refer to the clinical manifestation commonly associated with Alzheimer's disease.

The classification of MCI is conceptualised as a transitional stage between normal ageing and dementia, characterised by cognitive decline in the absence of functional impairment and often representing a prodromal form of dementia (64,65). Some individuals with MCI might remain stable or even return to their cognitive baseline (66), while others, particularly those with primary memory deficits, are considered to be at increased risk of developing dementia, with an estimated conversion rate of 10 to 15% per year (67).

Several theories have been proposed to explain the development and progression of dementia. Some of the most prominent theories are the amyloid-cascade hypothesis, cholinergic hypothesis, vascular hypothesis, inflammation and immune system dysregulation hypothesis, and oxidative stress hypothesis. Dementia is a complex condition with multiple underlying factors, and therefore, these hypotheses are not mutually exclusive. This thesis will focus on the amyloid-cascade hypothesis and vascular hypotheses (see section 2.2.1.'Dementia biomarkers for a description of each).

Cortical proteins play a key role in molecular functions and biological processes of the brain; however, when these proteins misfold and accumulate in the brain, they lead to network breakdown, neuronal loss, and reduction of cerebral volume, all of which constitute the underlying brain changes associated with neurodegenerative diseases such as AD and FTD

(68). Therefore, dementia types are defined by the type of protein and the site and size of the accumulation (68). The amyloid hypothesis proposes that the key feature of AD is the deposition of amyloid-β (Aβ) (eventually hardens into neuritic plaques), which in turn leads to the deposition of pathologic tau (tau tangles or neurofibrillary tangles), and results in the progressive degeneration of the medial temporal lobe and limbic structures (69–71). On the other hand, FTD has been associated with transactive response DNA-binding protein 43 (TDP-43) and abnormally phosphorylated tau protein (Pick bodies), which contribute to the degeneration of the frontal and anterior temporal lobes (71). Conversely, VaD is considered a heterogeneous group of non-AD involving large and small cerebral arteries resulting from ischemic, haemorrhagic, anoxic, or hypoxic brain damage (71,72).

Most dementias have a long pre-symptomatic phase, during which molecular pathology gradually accumulates, leading to brain damage, which becomes self-perpetuated once established. For AD, there is substantial evidence that Aβ and tau begin to accumulate up to two decades before the onset of dementia symptoms (73–75), and hence, a clinical diagnosis of dementia is not required for a post-mortem pathologic diagnosis of Alzheimer's disease (71). Therefore, a "preclinical stage" of AD, a neuro-pathological state defined by the presence of Aβ and neurofibrillary tangles, has been proposed for the clinical trajectory of dementia (73,76). As shown in Figure 2, the pathological process of dementia and its clinical symptomatology is conceptualised as a continuum, with preclinical dementia preceding MCI, which then leads to the different severity stages of dementia (mild, moderate, and severe) (see section 2.2.1.1 'Amyloid, tau, and neuronal injury' for a description of the pathological process indicating the presence and severity of dementia) (77). After diagnosis of dementia, the average survival has been estimated to range between one and 10 years, depending on age, gender, dementia type and severity (35).

Furthermore, a recent overview of the evidence suggested that the MCI to mild dementia stages last three to four years, while moderate and severe stages last one to two years, with the duration of the disease stage shortening with advancing age (78). However, accurate estimates of disease duration across different stages of dementia have been hindered by heterogeneous reporting in the literature, which is accounted for study setting and dementia type (78).

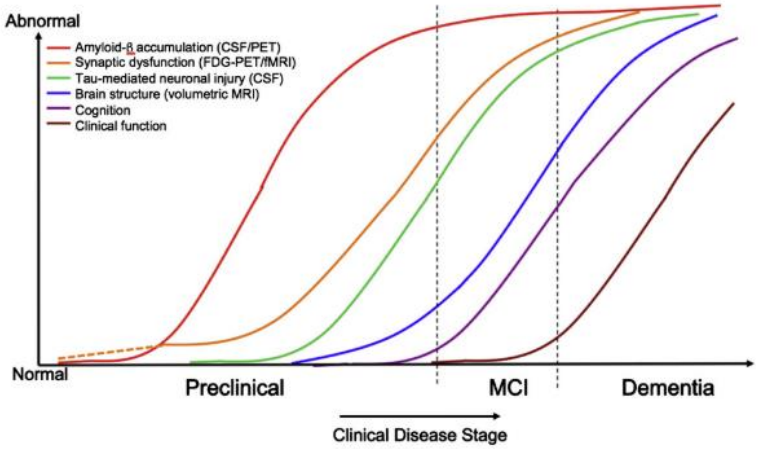


Figure 2 Dynamic biomarkers of AD expanded to explain the preclinical phase.
Source: Sperling et al., 2011

The different dementias are clinically heterogeneous disorders influenced by diverse risk factors. AD and FTD have been strongly linked with genes that encode specific proteins: the apolipoprotein E (APOE) gene for Aβ peptide in AD and the microtubule-associated protein tau and transmembrane protein 106B genes for tau protein in FTD, with carriers of specific alleles being at increased risk of protein accumulation leading to AD or FTD, but not of vascular pathologies associated with VaD (68,71). On the other hand, vascular risk factors, such as abdominal obesity, insulin resistance, hypertension, and dyslipidaemia, are well-

known factors for VaD (79,80). Vascular lesions have been found to contribute to the development of vascular dementia but not with progression to AD specifically (81).

Despite the differences in risk factors and associated pathologies, the boundaries between dementia subtypes are diffuse, with different dementias having common underlying neuropathology (82,83). After death, approximately 46% to 77% of the brains of people with AD have plaques and tangles, plus small vessel disease and other neuropathologies (84–88) (Figures 3 to 5). In line with this, two recent studies, one carried out with 391 deceased older adults from the Religious Orders Study and the Rush Memory and Aging Project (ROSMAP) and the other with 375 deceased older adults from the University of Kentucky Alzheimer's Disease Centre Brain Bank, found that half the sample had three or more conditions (e.g., Alzheimer's disease, microinfarcts, arteriolosclerosis, atherosclerosis, gross infracts, cerebral amyloid angiopathy, hippocampal sclerosis, and Lewy bodies) (88) and that 20% of the sample presented quadruple misfolded proteins (tau neurofibrillary tangles, Aβ, α-synuclein, and TDP-43). Furthermore, almost 40% presented three concurrent proteinopathies (89). Based on this evidence, the term dementia is currently attributed to a host of neuropathologic conditions that can coexist in the brain (76,90,91).

Due to the lack of clear differential diagnostic criteria and the neuropathologic comorbidity of the pathologies, in 2010, Richards and Brayne proposed that dementia represents a diffuse clinical syndrome representing a gradual accumulation of various pathologies arising from multiple related risk factors over the life course (Figure 4) (92). Recent evidence supporting this theory has led to the recognition of AD as a multifactorial disorder associated with a spectrum of neuropathologies (76). Due to their complex multifactorial

aetiology, the pathological mechanisms underlying some forms of dementia remain unclear, and research continues to focus on understanding the factors that modulate its risk (93).

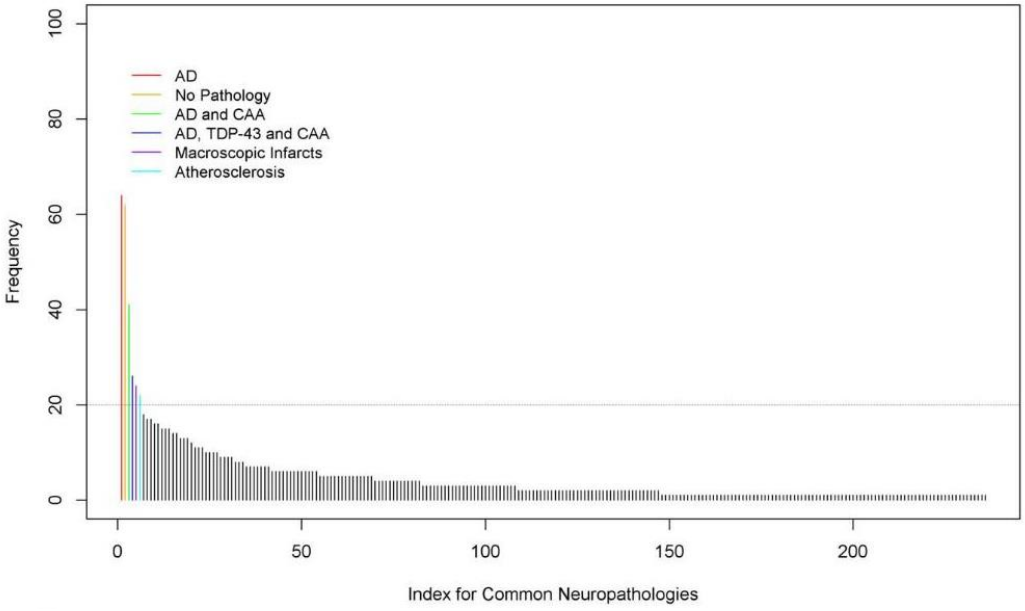


Figure 3 Frequencies of observed combinations of neuropathologies.
Each bar corresponds to a single combination (236 possible combinations)
AD= Alzheimer's disease, CAA=cerebral amyloid angiopathy
Source: Boyle & Wilson et al., 2018

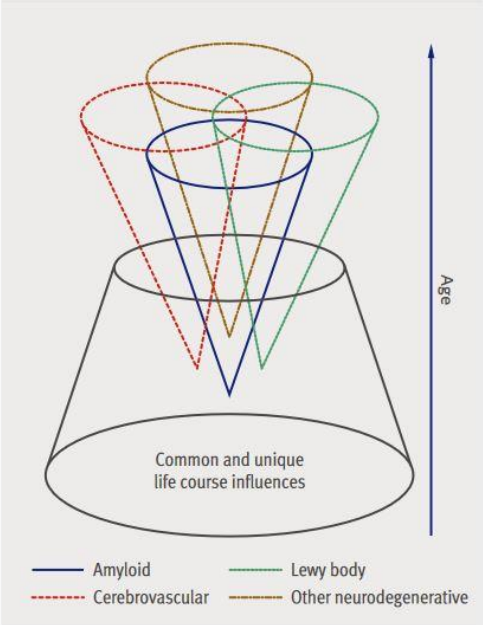


Figure 4 Dementia as a diffuse multiform syndrome.
Source: Richards & Brayne, 2010

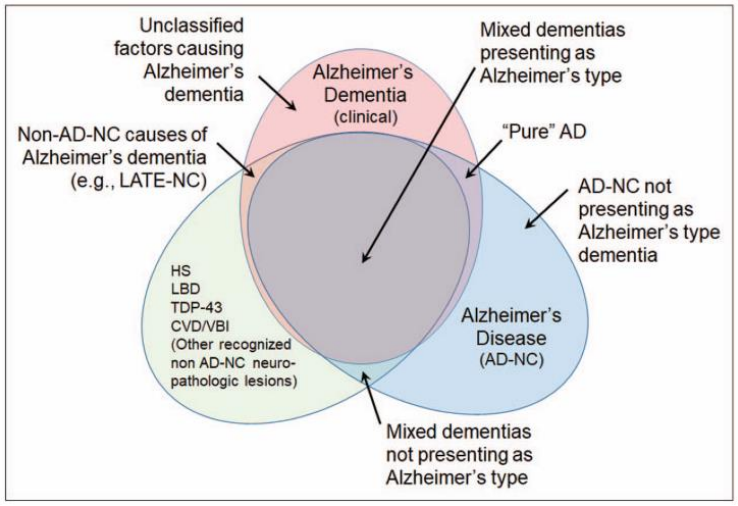


Figure 5 Overlaps between neuropathologies.
AD, Alzheimer's disease; AD-NC, Alzheimer's neuropathologic change; CVD, cardiovascular disease; HS, hippocampal sclerosis; LBD, Lewy body disease; transactive response DNA-binding protein 43, TDP-43; VBI, vascular brain injury
Source: Mehta & Schneider, 2021

2.2.1 Dementia biomarkers

The underlying pathologic processes of dementia can be documented in vivo through biomarkers such as abnormal protein accumulation and neurodegeneration (i.e., total brain volume, hippocampal volume, and white matter hyperintensities [WMH]), which constitute some of the key neuropathologic features of AD and VaD (94). These measures of brain disease have been identified to account for approximately 50% of the variance in memory performance (95,96). Furthermore, the risk of dementia can also be accounted for by genetic factors.

2.2.1.1 Amyloid, tau, and neuronal injury

Aβ [A], tau [T], and neurodegeneration [N] [AT(N)] constitute the backbone of the biomarker system proposed by the US National Institute of Ageing (NIA) and Alzheimer's Association Research Framework of Alzheimer's Disease (97). The presence of these neuropathology markers indicates the presence and severity of AD. As mentioned in section 2.2, 'Dementia', over time, abnormal Aβ and tau spread through the brain, often resulting in neurodegeneration and leading to the characteristic progression of AD symptomatology (98).

The presence of Aβ and tau proteins can be assessed in living individuals by analysing cerebrospinal fluid and plasma (99–102) or in the brain by injecting radiotracers that bind to the proteins and performing molecular imaging techniques such as positron emission tomography (PET) (103–105). According to the Modified Braak and Braak neurofibrillary pathology scheme, the distribution and severity of synaptic degeneration can be described in six stages: the initial stages (I & II), where specific structures of the medial temporal lobe (transentorhinal and entorhinal cortices) are affected, the intermediate stages (III & IV)

where the hippocampus and limbic structures are affected, and the late stages of the disease (V & VI), where areas of the neocortex are involved (68,69,106).

The amyloid-cascade hypothesis proposes that Aβ accumulation is the etiological factor that drives tau pathology, which in turn results in grey matter loss and consequent memory impairment (70,107). Longitudinal evidence using neuroimaging data from the Harvard Aging Brain Study and the Alzheimer's Disease Neuroimaging Initiative (ADNI) supported this sequential order of the biomarkers, where it was found that baseline Aβ burden was associated with the slope of tau accumulation, which in turn led to reduced cortical thickness, ultimately resulting in cognitive decline (108). However, mouse models have suggested that the toxicity of Aβ depends on the presence of tau and have, in part, led to the hypothesis that tau pathology might be the key initiating factor for AD, particularly for sporadic AD, with some evidence that it precedes the appearance of Aβ plaques (76,109–111). In light of this, the AT(N) system acknowledges an uncertain relationship between Aβ, tau, and disease symptoms (97). Nevertheless, neuroimaging results from several studies have consistently found an association between higher values of these two proteins and poorer cognitive performance, suggesting support for their deleterious effect on neurodegeneration and cognition in older adults (104,107,112,113).

In terms of neurodegeneration, structural imaging techniques such as magnetic resonance imaging (MRI) are used to detect in vivo brain atrophy. Regions of interest (ROIs) and volumes of interest have been informative to identify the neuroimaging phenotypes associated with MCI and AD. In particular, medial temporal atrophy and hippocampal atrophy are considered the most useful biomarkers to detect the progression of AD dementia (114). Findings from ADNI provided support for this theory, showing that

neurodegeneration of the hippocampus is the most robust predictor for imminent conversion from MCI to AD (115). However, a recent systematic review which included 14 studies investigating the association between biomarkers and their association with clinical progression to MCI or AD, suggested that both Aβ and tau profiles are strongly associated with clinical progression, with less conclusive results from structural biomarkers (i.e., brain volume, cortical volume, and WMH) (116).

2.2.1.2 Vascular biomarkers

Cerebral vascular disease is common in older adults, with data showing that microinfarcts are common in up to 64% of ageing brains (117–120). Furthermore, 80% of patients diagnosed with AD with no previous indication of mixed dementia have evidence of vascular pathology at autopsy (121). Hence, cardiovascular risk factors, such as hypertension and hypercholesterolemia, are recognised as the main contributors to the pathophysiology of AD, positioning cardiovascular diseases as pathogenic and establishing the 'vascular hypothesis of Alzheimer's disease' (76,122–124).

Autopsy-based evidence from ROSMAP studies has provided sound evidence for the contribution of cerebral vessel pathology, measured through large and small vessel disease, to the risk of AD and lower performance in most cognitive domains (125). Additionally, evidence from the two cohorts in ROSMAP has suggested that eleven cortical proteins previously identified as implicated in AD were also associated with non-AD neurodegenerative and cerebrovascular conditions (88). Therefore, it has been suggested that vascular biomarkers should be included in the AT(N) biomarker system to better characterise and understand the contributions of vascular dysfunction to cognitive impairment in AD (122).

Cerebral small vessel disease can manifest as WMH, which can be detected on MRI (126). A systematic review and meta-analysis carried out with data from prospective longitudinal studies that used MRI indicated that WMH burden is consistently associated with an increased risk of cognitive decline, particularly in VaD and is also present in AD (127). Furthermore, a recent study using data from the Multimodal Neuroimaging in Early Alzheimer's Disease cohort found evidence suggesting that WMH contribute to lower cognition in AD, independently of Aβ deposition, cortical atrophy, and hippocampal atrophy (128). It has been suggested that demyelination, axonal loss of vascular integrity, and blood-brain barrier breakage represent some of the major underlying pathologies of WMH (129). Furthermore, previous findings have suggested that vascular risk factors, such as hypertension, obesity, diabetes, and smoking, as well as education and occupation, play an important role in the development of WMH (130,131).

2.2.1.3 Genetic biomarkers

Twin studies have shown that at least 58 to 79% of the risk for AD can be accounted for by hereditable factors (132), and genome-wide association studies have identified thousands of genetic variants that may contribute to the risk of dementia, particularly AD (133). A meta-analysis of genome-wide association studies including 31 cohorts found a significant association between cognitive function and four genes, TOMM40, APOE, ABCG1 and MEF2C, previously associated with Alzheimer's disease (134). To date, the e4 allele of the APOE gene is the best-known variant associated with the risk of AD (135,136). APOE is a major cholesterol carrier that supports important processes ensuring brain health, including the proteolytic clearance of Aβ from the brain – with the e4 allele showing less efficiency during this task (137).

In humans, APOE is associated with three alleles: the e4 allele (frequency of 13.7%), which increases the risk of AD and cerebral amyloid angiopathy as compared to those with the e3 allele (frequency of 77.9%), and the e2 allele (frequency of 8.4%) which decreases the risk of the disease (138,139). The presence of at least one APOE e4 allele has been associated with the presence of multiple proteinopathies, which include tau, Aβ, α-synuclein, and TDP-43 (89,140). Thus, for individuals with one e4 allele, the risk of AD is estimated to be three times higher, while for individuals with both copies, the risk has been estimated to range between nine to 13 times higher (141,142).

Since APOE is involved in the transport of cholesterol and other lipids between cellular structures, APOE e4 carriers have also been found to be more likely to develop other conditions such as cardiovascular disease and diabetes (139,143,144), themselves risk factors for dementia, as noted. In terms of neuropathology, previous evidence has suggested that the expression of APOE e4 is associated with cerebrovascular abnormalities and contributes to the breakage of the blood-brain barrier, one of the causes of WMH (145–149). Furthermore, investigations into the association between WMH and APOE have suggested a moderated mediation in the link between high blood pressure and cognitive function, whereby APOE e4 contributes to worse cognitive functioning by interacting with blood pressure to affect cerebrovascular health (150).

Evidence has suggested that APOE e4 relates to normal, not just pathological, cognitive ageing (49) with a meta-analysis examining the role of APOE e4 in normal ageing suggesting that e4 carriers performed worse in global cognition, episodic memory, and executive functioning (151). Furthermore, longitudinal evidence from the LBC identified APOE e4 as the most important factor determining cognitive decline, even after adjusting for other

important risk factors such as childhood cognitive ability, education, SEP, lifestyle, and health (152). And for individuals in the early stages of AD, the presence of the e4 allele has been found to influence the rate of cognitive decline more significantly (153). Therefore, APOE e4 is considered a key genetic risk factor for cognitive decline and dementia.

2.2.2 Dementia risk factors and prevention

2.2.2.1 Non-modifiable risk factors

Biological and genetic factors play a central role in the risk of developing dementia (132). Advancing age remains one of the greatest known risk factors for dementia, with its prevalence increasing rapidly from about 2-3% among those aged 70-75 years to 20-25% among those aged 85 years and older (9). For individuals over the age of 65, the prevalence of dementia roughly doubles every 5 years (9,154).

Furthermore, despite recent evidence suggesting that men have higher vascular risk than women (42), epidemiological studies have found that for women, cardiovascular conditions have stronger associations with cognitive decline and that the prevalence of all-type dementia is higher than for men (12,155). Furthermore, females present greater severity of neuropsychiatric symptoms (depression, aberrant motor behaviour, and psychiatric symptoms) associated with AD, and in the presence of neuropathology, they are more susceptible to the clinical manifestations of the disease (12,156,157). Research has also suggested that due to their longer life expectancy, females with dementia tend to have more prolonged survival than males, and thus, lose more years of their remaining life span (33,35,158).

As presented in section 2.2.1.3 ‘Genetic biomarkers’, the e4 allele of the APOE gene is the best-known genetic risk factor for AD. However, genes appear to have a relatively small

impact on the risk for late-onset dementia compared to the early onset of AD or 'familial' disease (159). A recent study carried out with 3,874 participants from the Chicago Health and Ageing Project found evidence suggesting that APOE e4 carriers had a faster cognitive decline than non-carriers, but that adherence to a healthy lifestyle was associated with a slower cognitive decline regardless of genetic risk (160). Hence, the effect of APOE e4 on cognitive function has been found to be influenced by other risk factors, such as sex, age, education, depression, and cardiovascular health (161–164).

2.2.2.2 Modifiable risk factors

As presented in section 2.2 'Dementia', the dementias are clinically heterogeneous and might result from complex interactions of non-modifiable risk factors with underlying pathologies as well as lifestyle and environmental factors across the life course (165). A systematic review of reviews carried out in 2019, which included 91 articles reporting meta-analyses, found that low education, diabetes, smoking, depression, mid-life obesity, high homocysteine levels, hypertension, arterial fibrillation, hearing loss, and social engagement are associated with increased risk of dementia (166). Furthermore, the study found that physical activity, fish consumption, light alcohol consumption, antihypertensives and statin use are associated with a reduced risk of dementia (166). More recently, a 2020 meta-analysis of observational studies and randomised controlled trials (RCT) added to the literature by identifying additional risk factors such as low cognitive activity, stress, cerebrovascular disease, and head trauma, which had strong evidence for increasing AD risk, and other risk factors such as weight loss in late-life, sleep, frailty, and low vitamin C which had moderate evidence (167). Correspondingly, the 2020 *Lancet* Commission agreed on 12 life course risk factors which were found to account for up to 40% of worldwide dementias: low education, hearing loss, head injury, hypertension, excessive alcohol consumption,

obesity, smoking, depression, social isolation, physical inactivity, air pollution, and diabetes (39) (Figure 6).

To further support the idea that dementia is largely preventable, the decline of age-specific incidence of dementia in high-income countries is suspected to be driven by prevention policies aimed at reducing chronic diseases (23,168). The evidence suggests that over the past three decades, changes in exposure to cardiovascular risk factors have been paralleled with a progressive decline in the incidence of dementia, particularly for highly educated individuals (22,169). In general, socioeconomic factors, such as low educational attainment, have been associated with a high risk of obesity, diabetes, hypertension, and dyslipidaemia, all of which are associated with VaD and AD (72). Economically disadvantaged populations are considered to be generally at increased risk of poor management of health conditions due to a lack of access to the services or necessary resources and knowledge to maintain good health (170).

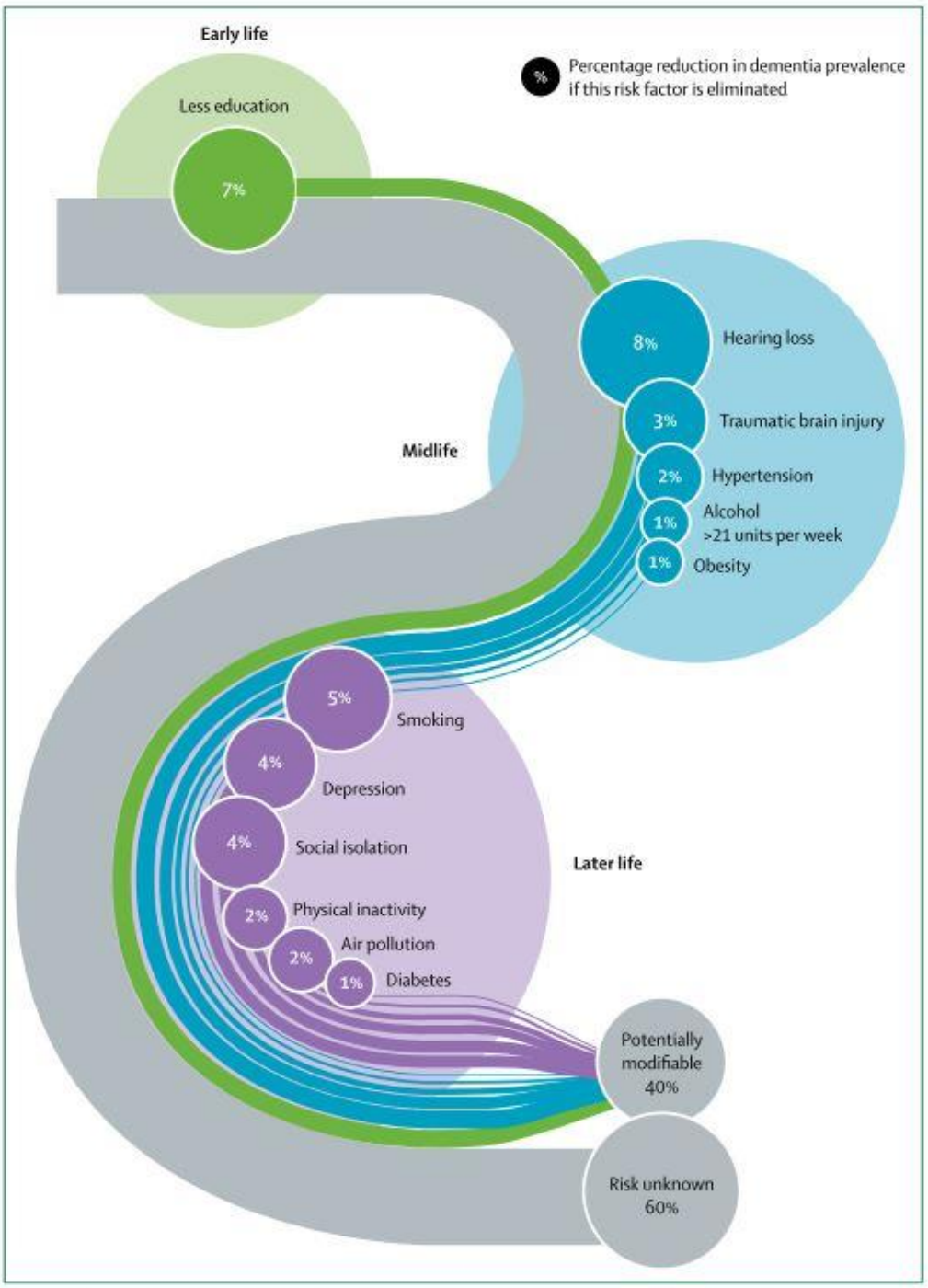


Figure 6 Population attributable fraction of potentially modifiable risk factors for dementia
Source: Livingston et al., 2020

2.3 Life course determinants of cognitive ageing and dementia

2.3.1 Childhood cognitive ability

Different domains of cognitive functioning, such as attention and concentration, memory, executive functioning, processing speed, and language, correlate substantially and are considered to contribute to general cognitive ability, which represents a key output of brain function and an important indicator of brain health (171,172). Individual differences in cognitive abilities are usually measured by assessing the subdomains of each ability using neuropsychological tests.

Childhood and adolescence represent important periods for the consolidation of cognitive health (173,174), and therefore they are proposed to represent important early determinants of cognitive ageing (43). Such a hypothesis presents cognitive ability as a minimum threshold that acts as a necessary, yet not sufficient, condition for educational and vocational success and the accumulation of cognitive reserve (see section 2.3.5 'Reserve') (175). This is in line with Crystal and Shea's model of cumulative advantage, which describes processes by which effects of early advantages can persist into late life, with the economic effects of early advantages often being magnified over the life course (176). Supporting this, evidence from the Vietnam Era Twin Study of Ageing (VETSA) has suggested that there is substantial stability in cognitive ability from ages 20 to 62 years, showing a correlation ranging between 0.73 to 0.85 (177).

Evidence from the UK Birth cohorts has provided sound support for the stability of cognitive ability across the life course, showing a consistent association between childhood cognitive ability and later-life cognition. Data from the LBC have shown that childhood cognitive ability, assessed at age 11, is the strongest predictor of late-life cognitive ability and is

associated with cognitive trajectories at the end of life, as well as the incidence of late-onset dementia (178–180). Similarly, a more recent study using data from the 1932 Scottish Mental Survey cohort found that, for individuals in the lowest cognitive ability groups, childhood mental ability assessed at age 11 was associated with dementia risk 54 years later (181). Furthermore, in the National Survey of Health and Development (NSHD) or British 1946 Birth Cohort Study, it was found that cognitive decline between ages 43 and 53 was partly explained by childhood cognitive ability and that this was independent of other determinants of cognitive ageing such as education and occupation (182).

Childhood cognitive ability has been consistently associated with the state of brain structure in older age. Evidence from several studies carried out with the LBC has found associations between cognitive ability at age 11 and cortical thickness, WMH, and VaD (180,183,184). Evidence from 869 participants from the 1972-73 Dunedin Birth Cohort found that worse cognitive function and brain health at age three were associated with more advanced brain age in midlife (185). Similarly, evidence from four prospective cohort studies (Stratifying Resilience and Depression Longitudinal Study, the Dutch Famine Birth Cohort, the LBC, and the Simpson's Cohort), which combined data from nearly 2,000 participants, showed that higher childhood cognitive ability is associated with lower WMH, fewer infarcts and lacunes, and lower total small vessel disease burden five to eight decades later, independently of education and childhood socioeconomic position (SEP) (186). These findings support the lifelong association between cognitive ability and brain health and might be explained by the association between lower cognitive ability and lifestyle choices that might increase the risk of vascular diseases and AD (187,188).

There is substantial consensus that cognitive ability is greatly heritable, with genes accounting for half of its variance (189–191) and its heritability increasing throughout the lifespan, starting at 20% in infancy and reaching 60% to 80% in older age (171,192,193). However, the quick rise in IQ scores over the past few generations, known as the Flynn effect, and evidence from adoption studies have shown that the environment plays a crucial role in the development of cognitive ability and that this role is independent of genetics (171,194). A longitudinal study of 1,288 twins found that genetic factors contribute to stability in general cognitive ability, while environmental differences between members of a twin pair are responsible for change over time up to age 62 (177). Supporting the role of the environment on cognitive function, a recent study carried out using data from 4,553 participants from the English Longitudinal Study of Ageing (ELSA) found that a literate environment in the childhood home may have lasting direct effects on memory function in later life (195). Furthermore, a meta-analysis assessing the impact of education on cognitive function suggested that during early life, education promotes increases in cognitive abilities (196). Furthermore, data from a longitudinal twin study also suggested that the genetic and environmental contributions to educational attainment differ by levels of cognitive ability, whereby for individuals with lower cognitive ability, the environment plays a more important role in predicting educational attainment, whereas genetics predict educational attainment more strongly for individuals with high cognitive ability (197). Hence, it is not yet clear to what extent other factors such as the environment and lifestyle, modify the association between early-life cognitive ability and cognitive decline and dementia (198).

2.3.1.1 Crystalised cognitive abilities

Cognitive abilities have different trends of development and age-related decline. Abilities with an extensive knowledge base, or crystallised abilities (e.g., verbal abilities [vocabulary,

lexical-semantic knowledge, verbal comprehension, and discourse processing] and general knowledge), reflect reasoning based on the acquired information and tend to remain stable or even increase as people age (199,200). In contrast, abilities that reflect the efficiency of processing at the time of assessment, referred to as fluid abilities (e.g., memory, executive functioning, attention, visuospatial abilities, cognitive flexibility, and reasoning), start to decline earlier and are therefore thought to be more sensitive to age and morbidity (42,201–204).

Crystallised cognitive ability is considered a reliable and stable entity, predicting educational and social outcomes as well as health and mortality (177,205–207). Crystallised cognitive abilities are commonly measured using vocabulary and general knowledge assessments. Numerous high-quality epidemiological studies link verbal ability in early life and cognitive functioning in adulthood and older age. Evidence from the Nun Study, a study based on a religious order of nuns in the United States, showed that the idea density and grammatical complexity portrayed in the autobiographies that 93 novices wrote at age 22 predicted better patterns of cognitive ageing 58 years later (208). Furthermore, a neuropathological investigation conducted on 14 participants who died during the study period showed that low linguistic ability in early life was associated with more AD pathology (208).

Crystallised cognitive abilities have been associated with better memory function and executive control (199,209,210), even after controlling for AD neuropathology in cognitively healthy and cognitively impaired older adults (211–213). Thus, older individuals tend to perform better in domains that rely on gathering knowledge from previous experiences (204,214). It is theorised that as individuals age, the experiences associated with the acquisition of new verbal skills as well as the opportunities to use previously learned ones

(204,214), enhance memory traces and may change the organisation of the brain, reducing the risk of cognitive decline (209). Furthermore, crystallised cognitive abilities may reflect the quality, benefit, or outcomes of educational attainment as well as wider academic and cognitive experiences accumulated across life (211). In sum, crystallised cognitive abilities have been succinctly defined as abilities reflecting "the product of experience, both cultural and educational, in interaction with fluid intelligence; people with higher levels of fluid intelligence will generally amass learnt information faster, allowing higher crystallized intelligence" (200).

2.3.2 Education

The association between education and cognitive function or dementia has been widely studied, with epidemiological investigations supporting the association since the early 1900s and providing evidence that education has a protective effect on general cognition, even in the face of multiple measures of brain burden (215–218). Some recent studies have even suggested that individuals with higher educational attainment have a greater chance of reversion from MCI to normal cognition (219) and that even a few years of formal education might contribute to reducing dementia risk (24,220–224). One study estimated that each extra year of education delays the onset of cognitive decline by a year (218).

Furthermore, two recent studies investigating the extent to which education accounts for cohort differences in cognitive function found support for the idea that increasing educational opportunities decrease the risk of cognitive impairment in later life. Both studies found that when participants reached an older age, those born later (after 1947) had better cognitive scores than the older cohort (before 1932) and had a significantly lower prevalence of MCI (25% vs 10%) (225,226). Hence, education has been theorised to delay

the onset of cognitive decline, reduce the risk of dementia, and contribute to cognitive reserve (see section 2.3.5 'Reserve'), as well as provide a protective effect against the accumulation of pathology arising from life-long environmental factors, particularly for vascular brain disease (222).

The contribution of education to cognitive ability through adulthood and older life has also been captured by life course studies. Data from the British 1946 birth cohort found that educational attainment in early adulthood was significantly associated with higher verbal ability, memory, and fluency in late midlife (227). Furthermore, a comparison of the contribution of childhood social class, childhood cognition, education, and occupation to adult literacy between the British 1946 and 1958 Birth Cohorts found a more substantial effect of schooling on midlife literacy for the younger cohort (228). The authors argued that the change in pattern in the association between education and literacy in these two cohorts might have resulted from the effects of change in education policy during 1972 when the UK Government raised the minimum school leaving age from 15 to 16 (228). Furthermore, two path analyses using data from the 1946 British Birth Cohort found that education has an important contribution to cognition in midlife and directly into older life cognition, even after accounting for childhood SEP and childhood cognition (229,230). The combined evidence of these studies has provided strong evidence for the effect of formal education and life-long learning on cognitive ability and the risk of dementia (23).

Various mechanisms have been proposed to explain how education influences cognitive ability and dementia risk. For instance, the association between education and dementia could be partly attributable to compensatory strategies that delay the detection of the disease (221), suggesting that a greater burden of AD is required for educated individuals to

develop the clinical symptoms of dementia (231,232). Other potential mechanisms involve education's association with general cognitive ability, neurodegeneration, and cardiovascular disease. Longitudinal findings from the Origins of Variance in the Old-Old: Octogenarian Twins study showed that education was positively associated with the level of performance on crystallised cognitive abilities, even at the time of dementia diagnosis (233). Education might also directly improve other cognitive skills, such as semantic memory and executive functioning, which, complemented by continuing mental activity throughout the life course, could mitigate the rate of decline associated with age and the development of dementia (216,234,235). To illustrate this, a large longitudinal study using data from 10 countries of the Survey of Health, Ageing, and Retirement in Europe found that more educated individuals performed better in memory when compared to those who were less educated (236). In terms of neuropathology, there is some evidence suggesting that low education is associated with cerebral small vessel diseases (e.g., microbleeds) and a reduction of total brain volume (186). Furthermore, higher educational attainment has been found to modify how people process cognitive tasks and enhance synaptic density in the neocortex (237,238).

Additionally, two theories have been proposed to further explain how education is generally associated with better outcomes, including a reduced risk of dementia. On the one hand, the social capital theory argues that education exposes individuals to institutional resources and endows them with productivity-enhancing skills while socialising them to achievement and expanding their social network (239). On the other hand, signalling theory argues that education acts merely as a signal, conferring credentials that employers use to select people into the labour force (240). These theories might be complementary and help explain how

education may further reduce dementia incidence through the maintenance of self-efficacy, social integration, and preservation of active mental life (92,241).

Since educational attainment is both determined by and an indicator of an individual's social position relative to other members of society, education has often been used as a proxy for SEP. Previous research has suggested that a major part of the effect of education on older age cognition is indirect, through education's contribution to adult SEP (242). Therefore, part of the association between education and dementia might be explained by SEP itself (243), particularly since it influences access to other factors associated with cognition, such as occupation, social network, leisure engagement, health behaviours, etc. (242). However, large-scale, longitudinal studies have also shown that the association between educational attainment and dementia incidence remain significant when other measures of SEP, such as occupation or wealth, are controlled for (235,243,244). Furthermore, education and SEP have been argued to occupy different temporal spaces in the life course and to represent different aspects of social circumstances (242,245–247). Thus, the advantage conveyed by education to cognitive function cannot be reduced to SEP. Education appears to influence older age cognitive ability through multiple direct and indirect pathways, highlighting its relevance as a life course predictor of cognitive ageing.

2.3.3 Occupation

Occupation is thought to represent an important indicator of middle-aged cognitive stimulation. Several longitudinal studies have found various aspects of work activity and the work environment to be inversely associated with cognitive function and dementia. For example, when compared to white-collar occupations, manual occupations have been associated with an increased risk of dementia, with agricultural work showing 46% greater

odds of developing the disease (248,249). Furthermore, cross-sectional evidence from HRS has suggested that higher mental and social work demands, and lower physical work demands, relate to better cognitive function in adulthood (250). Similarly, findings from the Whitehall II study indicated that higher employment grade, measured in the order of increasing salary, was associated with better verbal memory (251). Other studies have assessed occupational complexity using the Dictionary of Occupational Titles classification, which focuses on three dimensions: interacting with data (e.g., from comparing to synthesizing), people (e.g., from taking instructions to mentoring), or things (e.g., from handling to setting up) (252). Studies investigating the long-term effects of work complexity on cognitive function or dementia have suggested that complexity with data and people are associated with better cognitive performance in later life (253–259). Furthermore, Nationwide Danish data (N=1,210,720) suggested that higher occupation-based SEP partly mitigate the risk of dementia associated with lower educational attainment (260). Similarly, a recent multicohort study of over 100,000 participants found that cognitive stimulation in the workplace, indexed through job demands and job control, was associated with lower dementia risk and that this association was independent of educational attainment, cardiometabolic diseases, and the competing risk of death (261).

A systematic review of 14 studies concluded that there is evidence for an association between complex occupations interacting with people and data and lower dementia risk (262). However, a more recent systematic review examining 34 studies found inconclusive results for the association between work activity and dementia risk (215). Despite the bulk of evidence suggesting an association between occupation and cognitive function or dementia risk, the inconsistency between the systematic reviews might be caused by the different measures individual studies use to assess occupation (259,263,264), and thus

studies are needed to identify what aspects of occupation are associated with improved cognitive function in older age.

There are numerous mechanistic pathways that might explain the association between occupation and cognitive ability. In terms of adaptability, the brain appears to be susceptible to neuroplastic changes and neuromodulation in response to occupational demands, facilitating the development of cognitive skills and the generation and maintenance of efficient cognitive networks (265–267). A classic example of this is the evidence from MRIs on licensed London taxi drivers, whose professional demands depend on navigational skills, showing significantly increased grey matter volume in the right and left hippocampi, reflecting an improvement in visuospatial performance, which was linearly associated with years of learning (268). Furthermore, higher occupational status is related to economic security, access to resources, and less likelihood of exposure to adverse factors associated with low-status occupation (269–272). Generally, individuals with lower SEP, which is usually measured based on occupational class, are exposed to deficient social conditions, such as inadequate housing and sanitation, and other risk factors, such as low social status and deprived neighbourhoods, while also possessing fewer resources to manage these circumstances, and thus promoting behaviours that are detrimental to health (273). The association between socioeconomic disparities and health outcomes has been widely studied and is well established, with a lower SEP being associated with cardiovascular diseases and dementia (270–272,274,275).

2.3.3.1 Retirement

Another important aspect linked to work that might be associated with dementia risk is retirement. The transition from the labour force into retirement involves essential changes

in cognitive demands, potentially influencing cognitive function (276). Previous research has suggested that later retirement age is associated with delayed age of onset of AD, providing support for the hypothesis that later retirement is protective against dementia (277). However, the findings from systematic reviews on the association between retirement and cognitive function are mixed, with evidence from seven studies suggesting that the association between retirement and decline in crystallised and fluid abilities appears to be affected by the characteristics of the job, but concluding that more research is needed to clarify the association and the mechanisms behind the associations (278). Yet, of the studies included in this systematic review, only one controlled for engagement in leisure activities after retirement. The study was carried out using data from the Whitehall II study and found that retirees were more likely to engage in leisure activities than those who remained in employment (279). However, the analysis also suggested that an increase in participation in leisure after retirement did not suppress the negative association between retirement and a change in cognitive test scores (279). Nevertheless, a recent investigation using HRS data found that the negative association between retirement and cognition was attenuated by engagement in mental leisure activities but not by physical, social, or household leisure activities (280). Furthermore, a literature review on the impact of retirement on cognitive function suggested that people retiring from jobs that are not cognitively stimulating might benefit most from retirement since it offers the time and opportunity to engage in cognitively stimulating activities (281). Thus, the results of these studies seem to point to a potential interaction between work complexity and leisure activities during retirement, suggesting that the direction and strength of the association between retirement and cognitive ability or dementia might depend on the characteristics of the occupation and participation in leisure activities after retirement (188,282).

2.3.4 Leisure

Leisure time activities are described as pursuits outside of work or chores, the purpose of which is enjoyment or wellbeing (283). Research has suggested that engagement in physical, intellectual, and social leisure activities has an essential role in maintaining brain health and real-world functioning, contributing to healthy physical and cognitive ageing and thus, reducing dementia risk (284–289). Furthermore, people appear to engage in different types of leisure according to age, gender, and marital status (290,291). Since physical function tends to decrease with age, the choices of physical activities older individuals can engage in also decrease (292). Therefore, it has been suggested that participation in physical activities decreases with age for both genders (290). In contrast, intellectual and social activities show more stability and even an increased engagement for females (290) and married individuals (293).

Evidence from a twin study found that greater midlife engagement in a variety of leisure activities was associated with a 26% risk reduction for dementia onset, and large longitudinal studies have found a lower incidence of dementia ranging between 33 to 52% for those who engage in various leisure activities (255,287,294,295). Furthermore, recent findings from the Kungsholmen Project in Sweden indicated that the risk of dementia progressively declined with cumulative exposure to reserve-enhancing latent factors during early (education, SEP, work complexity), adult (job demands, decision latitude, work complexity), and later life (physical, mental, and social activity) (296). The study also found that when the life factors were mutually adjusted, the factor representing late-life leisure activities showed a stronger inverse association with dementia in comparison to earlier life and adulthood activities, which included educational and occupational components (296). This finding was corroborated by a study carried out with autopsied cases from the Rush

Memory and Aging project, which found that leisure activities in mid- and late-life were more important than education in offsetting the negative association between neuropathology and cognitive function (297). Furthermore, the contribution of leisure to cognitive ageing has been recognised by two systematic reviews, each exploring 15 and 25 cohort studies on leisure activity and their association with dementia risk, which concluded that engagement in social, mental, and physical activities could have protective effects against dementia diagnosis (285,298).

Two recent large longitudinal studies argued that a reduction in leisure activity participation is not associated with reduced dementia risk but rather an indication of prodromal dementia, proposing that there may be a reverse directionality bias when interpreting previous leisure activity and dementia findings (267,299). On one hand, cognitive decline during older age is an insidious process that often leads to dementia (see section 2.2 'Dementia'); therefore, reduced engagement in leisure activities might be due to the prodromal symptoms of dementia rather than a risk factor for the disease. On the other hand, the benefits of leisure activity engagement on brain health and cognitive function are likely to be nuanced and multifactorial. Cognitive decline in older life can have various causes, including genetic vulnerability, physical inactivity, and chronic conditions, such as depression and cardiovascular disease, each associated with different risk and protective factors, which might be modified by lifestyle choices (300–303). Furthermore, it is possible that lifelong participation in leisure activity may reflect the use of cognitive abilities, indicating above-average cognition (304). However, two studies using data from the LBC 1921 and NSHD birth cohorts found that, after controlling for childhood cognitive ability, engagement in intellectual and social leisure activities in midlife was associated with higher cognitive ability while engaging in physical activity was associated with less cognitive decline

(187,305) supporting leisure engagement independent association with better cognitive abilities during older age.

The research on leisure activity engagement has also suggested possible pathways for their association with cognitive function and dementia risk reduction. Intellectual and social activities might have a dual protective role in the brain by contributing to cognitive reserve (266,287) (see section 2.3.5 'Reserve') as well as increasing synaptogenesis, promoting cardiovascular health, and enhancing the brain's vasculature (306,307). Supporting this theory, previous research has found that leisure activities promote brain health (larger total brain volume, higher grey matter volume, higher quality of white matter tracts, and fewer WMH) and better cognitive performance (308–310).

2.3.4.1 Cognitive activities

Cognitive leisure activities are activities that are enjoyable and produce intellectual stimulation (e.g., activities related to arts, reading, writing, playing board games, etc.). Neurobiological evidence has suggested that cognitive stimulation elicits various plastic responses in the adult brain, including neurogenesis and improved learning (311). According to the disuse, or "use-it-or-lose-it" hypothesis, keeping mentally active is needed to maintain cognitive function and prevent cognitive decline and the onset of dementia (203). Similarly, according to the cognitive reserve hypothesis (see section 2.3.5 'Reserve'), engagement in cognitive leisure activities contributes to more efficacious, flexible, and adaptive neuronal communication.

Intellectually stimulating activities, such as playing a musical instrument, have been previously associated with a reduced risk of dementia, independently of other risk factors such as sex, education, and physical activity (312). Longitudinal studies have suggested that

engagement in intellectual leisure activities is associated with a reduced incidence of Alzheimer's disease, with those who are cognitively less engaged being 2.6 times more likely to develop Alzheimer's disease, independently of past cognitive ability, life course SEP, physical activity, and baseline cognitive function (313,314). Furthermore, time spent engaging in cognitive activities has been associated with greater cortical and subcortical brain volumes (total cortex, temporal and occipital lobes, thalamus, caudate, hippocampus and amygdala) (315) and intervention studies have suggested that engagement in cognitive leisure activities (e.g., arts, writing, board games, reading, handcrafts, crossword puzzle, and learning computer skills) is associated with improvement in cognition across multiple cognitive domains, including working memory (292). In accordance with these findings, evidence from systematic reviews and meta-analyses has consistently reported a positive association between participation in cognitive leisure activities and a reduction of the risk of dementia and cognitive impairment, as well as improved cognitive test performance (316–318).

2.3.4.2 Social activities

Large longitudinal studies have found that different aspects of socialisation, such as social support, frequency of contact with relatives or friends, size of the network, quality of relationships, and social participation, are related to better cognitive performance and reduced risk of dementia (319–326), even for disadvantaged populations (327). A recent longitudinal study investigating the association between patterns of social engagement and conversion from MCI to dementia found that increased engagement and more variety of social engagement (e.g., volunteering, educational courses, nonreligious organisation, meeting up, talking on the phone) were associated with lower risk of conversion to dementia, even after controlling for cognitive and physical activities (328). Furthermore, a

systematic review and meta-analysis, which included 19 longitudinal studies investigating the association between social relationship factors and dementia, indicated that factors that represent lack of social interaction, such as low social participation, less frequent social contact, and loneliness, were associated with incident dementia (329).

The coronavirus pandemic of 2019 highlighted that, as a social species, social participation and interactions are crucial for human wellbeing throughout life, particularly promoting physical and mental health. Social network structure has been argued to operate at a behavioural level by providing social support, social influence, social engagement and attachment, and access to resources and material goods (330). Moreover, possible mechanisms such as effects on inflammatory and immune processes, reduced vascular disease risk, and lower risk of depression, as well as an increased cognitive reserve through mental stimulation, have been proposed in the contribution of social engagement to reduced risk of age-related cognitive decline and dementia (331,332). However, as dementia progresses, individuals might be less able to engage socially, posting the possibility of reverse directionality bias in the association between social engagement and dementia. Nevertheless, recent findings have suggested that lower cognitive functioning is associated with reduced diversity of social networks, but not with the quality of social relations which tend to remain unchanged (322).

Due to the heterogeneity of terms used to measure social participation, there is no consensus over which measures of social activity are the most important (see Figure 7 for glossary of terms). A recent scoping study defined social participation as “a person’s involvement in activities providing interactions with others in community life and important shared spaces, evolving according to available time and resources, and based on the societal

context and what individuals want and is meaningful to them", and concluded that a single definition may facilitate the study of socialisation in older age (333). Furthermore, it has been argued that different social factors dynamically coexist, and thus, the question of whether and how various social factors contribute to cognitive health requires more comprehensive approaches that capture multiple aspects of socialisation simultaneously (304).

Term	Definition
Social participation	Engagement of individuals in social leisure activities (focusing on activities undertaken with other people), contact with social networks and their satisfaction with this participation.
Social activity engagement	Taking part in leisure activities within the communities in which people live, including activities undertaken with other people that are social, physical and mentally stimulating[145,146].
Social contact	A quantitative measure relating to visiting or communicating with relatives, friends and acquaintances, usually but not necessarily as a recreational activity; and not encompassing qualitative aspects of satisfaction with social contact.
Social network	The web of social relationships that surround an individual and the characteristics of those ties[145,146].
Social isolation	The inadequate quality and quantity of social relations with other people at different levels of human interaction (individual, group, community and the larger social environment)[147].
Social interaction	The quality of the verbal and nonverbal behaviors that are exercised between an individual and others in their surroundings.
Loneliness	A subjective unpleasant experience that occurs when a person's network of social relationships is deficient in quality[148].
Social support	The exchange of resources is intended to enhance the well-being of the recipient, including emotional and instrumental support[149].

Figure 7 Glossary of terms realting to social participation
Source: Sommerlad et al., 2023

2.3.4.3 Physical activities

A wealth of data indicates that physical activity has a positive impact on brain health. Physical activity has been associated with preserved brain volume and prevention of shrinkage of brain regions associated with memory (e.g., hippocampus), thus protecting the structure and function of the brain (334,335). Furthermore, a robust cerebrovascular response to aerobic exercise has been shown to modify the association between Aβ deposition and early indicators of cognitive executive dysfunction, such as response inhibition (336). Research has also suggested that exercise supports existing cerebral blood vessels and increases the growth of new ones, providing a prime environment for old and new neurons to thrive (337,338). Exercise has also been suggested to improve immune function, and in particular, to counteract neuroinflammatory changes related to ageing and even to modulate neuroinflammation in AD (339,340).

The association between physical activity and brain health has been argued to be mediated by neural growth factors. Brain-derived neurotrophic factor (BDNF) is a protein found in high concentration in the central nervous system, and it has been implicated in neural development and functioning, including neurogenesis, dendritic growth, and long-term potentiation of neurons (341). A meta-analysis that included 29 individual studies examining the effect of exercise on BDNF found support for this association, showing that acute and regular exercise have a significant impact on BDNF and suggesting that regular exercise intensifies the magnitude of these effects (342). Moreover, physical activity has been found to improve vascular function and might improve cerebral blood circulation. A systematic review of 24 longitudinal studies found a significant association between physical exercise and a reduced risk of developing VaD (343).

Despite the accumulating evidence from individual studies showing that physical activity appears to be associated with a lower risk of dementia (305,344–347), even for individuals meeting the criteria for MCI (348), to date, epidemiological studies have provided mixed evidence on the association between physical activity and dementia risk. Evidence from two meta-analyses which included prospective cohort studies showed a clear association between physical activity engagement and cognitive function (349,350). In contrast, evidence from 10,308 participants with a mean follow-up of 28 years from the Whitehall II cohort suggested no association between physical activity and cognitive decline or dementia (351). And, a more recent meta-analysis which accounted for reverse directionality bias found no association between physical activity and dementia (352).

Apathy and behavioural inhibition are commonly observed in the preclinical stages of dementia, which can start years before the manifestation of symptoms. Hence, it has been argued that physical inactivity, instead of constituting a risk factor, might result from prodromal dementia, highlighting once more the issue of reverse causality bias in the investigation of leisure activity engagement and dementia risk (353).

2.3.5 Reserve

The rate of cognitive decline associated with dementia is heterogeneous among older adults. Some individuals show greater cognitive decline, while others show sustained cognitive abilities or a slower cognitive decline during the disease course of dementia (354,355). Furthermore, it is common to find a dissociation between brain pathology and its expected clinical features. Despite maintaining cognitive integrity before death, 70% of people have post-mortem evidence of varying degrees of plaques and tangles (73,356), and around 20% to 40% have sufficient neuropathology to meet the criteria of Alzheimer's

disease, cerebrovascular disease, and Lewy body disease (85,208,357–364). For individuals with no cognitive impairment at death, post-mortem neuropathology consistent with Alzheimer's disease is so common that it is often referred to as asymptomatic Alzheimer's disease (84,357). Furthermore, on average, around 41% of the variability in cognitive decline can be explained by age-related neuropathologies, suggesting that other factors may also impact cognitive function in older age (84,95,365).

The concept of reserve is a theoretical framework used to describe differences in developmental trajectories and in ageing (366). Physiologic reserve, which describes a system's resilience or ability to maintain function despite damage from injury or disease, is considered a multidimensional construct involving physical, psychological, and social aspects of health (367,368). Thus, to explain the individual heterogeneity in cognitive decline and to account for the non-linearity between neuropathology and its clinical presentation, several investigators proposed three complementary models of reserve: brain reserve (BR), cognitive reserve (CR), and brain maintenance (BM) (221,238,369,370), as well as related terms such as resilience and compensation.

Evidence for the concept of reserve started accumulating as early as the early 1900s, supporting the idea that after sustaining an injury, the brain can utilise the remaining brain tissue to take over functions from the affected brain regions (371). Over the past decade, reserve and its related terms have become important terms for aging-related research to explain individual differences in susceptibility to cognitive impairment in the presence of brain changes, and thus, there have been several efforts to develop consensual conceptual and operational definitions. See Table 1 for individual studies and definitions.

One of the first reviews aiming to define CR, BR, and compensation was that of Stern in 2002 (265). Stern based the definition on his observations and the previous work of Katzman and Satz who proposed the concepts of reserve, threshold theory and BR capacity (221,358,369). Additional terms, such as BM (370), have also been included and adopted to later reviews and sub-terms for CR, such as neural reserve and neural compensation, were added (372). Furthermore, later reviews included important updates to the terms. For instance, BR went from being considered a static construct to being conceptualised as a dynamic one, which could be modified in response to experience via neurogenesis and neural plasticity (373). Other reviews have been published which have suggested different terminology as well as definitions, suggesting, for instance, that the distinction between CR and BR is unnecessary given that cognition depends on the brain (374–376). In 2019 the US NIA sponsored the Reserve and Resilience Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Ageing and Dementia led by Stern, which aimed to develop consensus definitions and research guidelines for CR and related concepts (377). During the autumn of 2019, the Collaboratory held the first Workshop on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia, during which various investigators presented their research, further demonstrating the wide variety of definitions used to conceptualise and measure reserve. In 2019, Pettigrew and Soldan published a comprehensive summary of the reserve, resilience, and related terms used to date. The authors found variation in the terminology and approach to measuring reserve but suggested that "all models seem to agree that certain lifetime experiences, in combination or interaction with genetic factors, can positively or negatively impact (a) brain health and (b) the ability of the brain to cope with ageing and pathology. The models also appear to agree that as pathology levels or age-related brain changes increase, the ability of the brain

to cope with these changes decreases" (378). This thesis focuses on the life course determinants of cognitive ageing and dementia, accounting, when possible, for their contribution through BR and CR. The definitions and research approaches will be informed using the latest reviews and updates on the topic (1,379).

Table 1 Published reviews and commentaries defining reserve and related concepts.

Stern, 2002 (265)	Brain reserve	"Amount of damage that can be sustained before reaching a threshold for clinical expression". "The threshold model revolves around the construct of BR capacity (Satz et al., 2011)". "While BR capacity is a hypothetical construct, concrete examples might include brain size or synapse count". "The model presupposes that there is a critical threshold of BR capacity. Once the threshold is passed, specific clinical or functional deficits emerge".	
	Cognitive Reserve	"The ability to optimise or maximise performance through differential recruitment of brain networks, which perhaps reflect the use of alternate cognitive strategies. CR is present in both healthy individuals and those with brain damage and is reflected in the modulation of the same brain networks. The definition encompasses two possibilities, differences in recruitment of the same network, and differential ability to recruit alternative networks".	
	Compensation	"The term CR can be limited to the variability seen in non-brain damaged individuals, which distinguishes it from compensation, which might be reserved for a specific response to brain damage". "Compensation is not simply a response to difficulty and implies an attempt to maximise performance in the face of brain damage by using brain structures or networks not engaged when the brain is not damaged".	
Stern, 2009 (373)	Brain reserve	"Individual differences in the brain itself allow some people to cope better than others with brain pathology". "These differences can be quantitative, such as larger brain, more neurons, or synapses. In addition, life experience can influence brain anatomy via neurogenesis, angiogenesis, promoting resistance to apoptosis, and up-regulating compounds that promote neural plasticity".	
	Cognitive reserve	"Individual differences in how people process tasks allow some to cope better than others with brain pathology. The possible neural implementation of CR can be subdivided into neural reserve and neural compensation":	
		Neural reserve	"Inter-individual variability – perhaps in the form of differing efficiency, capacity, or flexibility – in the brain networks or cognitive paradigms that underlie task performance in the healthy brain. An individual whose networks are more efficient, have greater capacity, or are more flexible might be more capable of coping with the disruption imposed by brain pathology".
		Neural compensation	"Inter-individual variability in the ability to compensate for brain pathology's disruption of standard processing networks by using brain structures or networks not normally used by individuals with intact brains. This compensation may help maintain or improve performance".

Tucker & Stern, 2011 (380)	Brain reserve	“BR refers to quantitative measures such as brain size or neuronal count. According to this model, there is some threshold at which clinical deficits will become apparent and those individuals with more BR require more pathology to reach that threshold”. “It is a quantitative model: a given brain injury will affect everyone in the same way and brain injuries across the lifespan sum together”.		
	Cognitive reserve	“Refers to how flexibly and efficiently one can make use of available BR. In terms of the cognitive processes involved, CR may operate by allowing for more flexible strategy usage, an ability thought to be captured by executive function tasks”. “CR is theorised to manifest as neural reserve or neural compensation”.		
		Neural reserve	“In the absence of pathology, neural reserve allows young healthy individuals with higher CR to process tasks more efficiently, and with greater capacity”.	
		Neural compensation	“Refers to the use of alternate brain regions not normally seen in healthy young adults to compensate for deficits in primary avenues for successful task performance. It is sometimes, but not necessarily, associated with better performance”.	
Nyberg et al., 2012 (370)	Brain reserve	“Individual differences in the brain itself allow some people to cope better than others with brain pathology. These differences can be quantitative, such as larger brain, more neurons, or synapses. In addition, life experience can influence brain anatomy via neurogenesis, angiogenesis, promoting resistance to apoptosis, and up-regulating compounds that promote neural plasticity (Stern, 2009)”.		
	Cognitive reserve	“Individual differences in how people process tasks allow some to cope better than others with brain pathology. The possible neural implementation of CR can be subdivided into neural reserve and neural compensation (Stern, 2009)”.		
	Brain maintenance	“Individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related cognitive decline. Preserved chemistry, structure, and function”.		
Barulli & Stern, 2013 (372)	Brain reserve	“Differences in brain size and other quantitative aspects of the brain that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insult”.		
	Cognitive reserve	“Differences in cognitive processes as a function of lifetime intellectual activities and other environmental factors that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insult”.		
		Neural reserve	“One proposed neural basis of CR that involves cognitive networks used by unimpaired individuals. Individual differences in network efficiency/capacity or the use of alternative strategies may provide reserve against the impact of brain changes”.	
			Efficiency	“The degree to which a task-related brain network must become activated to accomplish a given task”.

			Capacity	"The degree to which a task-related brain network can be activated maximally to keep performing a task even in the face of increasing demands".
		Neural compensation	"One proposed neural basis CR involving the utilization of alternative networks not typically used by healthy individuals to maintain or improve cognitive performance".	
	Brain maintenance	"Lifestyle factors give an individual protection from the development of pathology itself, as opposed to protection given against the manifestation of harmful cognitive decline in the presence of increasing pathologic burden".		
Cabeza et al., 2018 (374)	Reserve	"We believe that reserve should be defined as a cumulative improvement, due to genetic and/or environmental factors, of neural resources that mitigates the effects of neural decline caused by ageing or age-related diseases". "Given that cognition depends on the brain, we believe that this distinction is somewhat artificial and prefer to use only the term reserve".		
	Maintenance	"We propose that the term maintenance be used to refer to the preservation of neural resources, which entails ongoing repair and replenishment of the brain in response to damage incurred at the cellular and molecular levels owing to wear and tear".		
	Compensation	"We propose that the term compensation should be used to refer to the cognition-enhancing recruitment of neural resources in response to relatively high cognitive demand". "Our definition of compensation is not limited to healthy and pathological ageing; it also applies to the cognition-enhancing recruitment of resources in response to task demands in other age groups and other forms of pathology". "We believe that it is necessary to distinguish between three different mechanisms or forms of compensation: compensation by upregulation, selection, and reorganisation".		
		Upregulation	"Enhancement of cognitive performance by boosting a neural process in response to task demands"	
		Selection	"Recruitment, by older adults, of neural circuitry associated with cognitive processes that are available to but not engaged by young adults under the same objective task conditions".	
		Reorganisation	"When older adults use a neural mechanism to respond to ageing-induced losses that is not available to younger individuals".	
Arenaza-Urquijo & Vemuri, 2018 (381)	Brain resistance	"Avoiding pathology, i.e., remaining cognitively normal with low Alzheimer's disease pathology. The act of resisting, opposing, or withstanding. Resistance to AD will thus imply avoiding the appearance of Alzheimer's disease".		

		Includes: neuroprotection, BM, neural efficiency, and CR (neural reserve)	
		Neuroprotection	"Maintenance of neuronal integrity against internal or external insults".
		Brain maintenance	"Preservation of brain structure (neuroprotection), preservation of task-related networks, along with the absence of significant pathologies"
		Neural reserve	"Emphasizes strategies used when coping with task demands that can be identified in the absence of pathologic changes".
	Brain resilience	"Coping with pathology, i.e., remaining cognitively normal despite substantial Alzheimer's Disease pathology. Resilience denotes the ability to cope in the face of adversity. Thus, resilience to AD may represent an individual's ability to sustain a better-than-expected cognitive performance in relation to the degree of AD pathology". "Includes: compensation, metabolism maintenance, structure maintenance, BR (threshold model), CR (neural compensation)".	
		Compensation	"Refers to strategies used to compensate for cognitive decline and thus counteract the changes that occur during aging or pathology".
		Cognitive reserve	"Includes the notion of neural compensation to refer to an active response implying the use of new or alternate brain networks after pathology has affected those networks typically utilised".
		Brain reserve	"The threshold model posits that there is a specific cut-off that sets the amount of brain change that can be sustained before reaching a threshold for clinical symptoms"
Montine et al., 2019 (382)	Resistance	"Inferred from an observed absence or lower level of dementia-associated brain injury, relative to an expected greater frequency or severity based on age, genetic factors, or other characteristics of the individual".	
	Resilience	"Inferred from an observed level of cognitive functioning higher than expected in the face of demonstrated brain injury".	
		Apparent	"Specific lesion type without consideration of common co-morbidities".
		Essential	"Achieved once comprehensive assessment of brain lesions associated with dementia is carried out"
	Reserve	"Measured or inferred as either brain structural and/or psychological pre-morbid capacity. Measures of reserve capacity must have been estimated prior to the development of brain injury".	
Stern & Barulli, 2019 (383)	Brain reserve	"The hypothesis is that a physically larger brain provides reserve capacity which protects the individual from the negative effects of aging and disease on brain function". "Major factor explaining threshold differences in the onset of clinical symptoms or the expression of impaired test performance after acquired brain injury".	

		"Although the concept of BR capacity could be operationally defined and measured in terms of overall brain size or specific anatomical functional relations, it is treated initially as a hypothetical construct that is related to adaptive behaviour. It is further assumed that two psychosocial factors, namely, general intelligence and educational level, represent indirect, albeit imprecise, measures of this construct (Satz et al., 2011)".	
	Cognitive reserve	"The relationships between the numerous lifetime exposure factors can lead to a brain that is much more resilient with respect to the presence of damage and pathology, and knowledge of how many factors are present in an individual's life is useful to predict to a given level of pathology".	
	Brain maintenance	"Individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related cognitive decline. Preserved chemistry, structure, and function (Nyberg et al., 2012)".	
Pettigrew & Soldan, 2019 (378)	Resilience	Brain reserve	"Refers to the structural characteristics of the brain at a given point in time and may protect against age and disease-related brain changes by impacting the threshold at which cognitive or functional decline emerge".
		Cognitive reserve	"Adaptability that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult (Stern et al., 2019)".
		Brain maintenance	"The process of maintaining or perhaps enhancing the brain through lifetime experiences and their interaction with genetic factors (Nyberg et al., 2012)".
	Brain resistance	"The brain processes underlying the ability to better resist pathology and is measured by absent or lower than expected AD pathology levels. (Similar to concept of BM) (Arenaza-Urquijo & Vemuri, 2018)".	
	Brain resilience	"Brain resilience is defined as the ability to cope with AD pathology and is measured by better-than-expected cognitive performance, brain structure, or function given some level of AD pathology (overlaps with CR) (Arenaza-Urquijo & Vemuri, 2018)".	
	Reserve	"Refers to the improvement of brain anatomic or physiologic processes involved in cognition (such as the efficiency or capacity of neural processes) above current levels; thereby attenuating the effects of age- or disease-related brain changes (Cabeza et al., 2018)".	
	Maintenance	"Refers to the preservation of the processes over time through ongoing cellular, molecular, and systems-level repair and plasticity (Cabeza et al., 2018)".	
	Compensation	"Defined as the recruitment of neural processes in response to high cognitive demand that enhances cognitive performance (Cabeza et al., 2018)".	

	"Despite the different terminology and approaches to measuring reserve, all models seem to agree that certain lifetime experiences, in combination or interaction with genetic factors, can positively or negatively impact (a) brain health and (b) the ability of the brain to cope with aging and pathology. The models also appear to agree that as pathology levels or age-related brain changes increase, the ability of the brain to cope with these changes' decreases".			
Stern et al., 2020 (384)	Resilience	Brain reserve	"Commonly conceived as neurobiological capital (numbers of neurons, synapses, etc.). BR implies that individual variation in the structural characteristics of the brain allows some people to better cope with brain aging and pathology than others before clinical or cognitive changes emerge". "The status of the brain at any point in time".	
		Cognitive reserve	"Refers to the adaptability (i.e., efficiency, capacity, flexibility) of cognitive processes that helps to explain differential susceptibility by cognitive abilities or day-to-day function to brain aging, pathology, or insult. At the brain level, CR is proposed to be supported by more adaptable functional brain processes".	
			Efficiency	"Can be defined as the degree to which a given task-related brain network must become activated to accomplish a given task. A more efficient network will show less activation to produce the same (or better) level of performance".
			Capacity	"Can be defined as the maximum degree to which a task-related brain network can be activated to keep performing a task in the face of increasing demands".
			Flexibility	"The behavioural implication of flexibility is that an individual with higher CR may have more varied solution strategies available. This might be reflected by the ability to utilize alternate networks during task performance that result in more successful performance".
		Brain maintenance	"Reduced development over time of age-related brain changes and pathology based on genetics or lifestyle. It reflects the fundamental notion that the brain is modifiable based on experience". "BR and BM are fundamentally related concepts. It remains an open question as to whether in fact they the same concept are viewed at different timescales. Better BM could thus sustain higher BR".	
Collaboratory, 2022 (385)	Resilience	"General term that subsumes any concept that relates to the capacity of the brain to maintain cognition and function with aging and disease".		

		Brain reserve	"Used to reflect the neurobiological status of the brain (numbers of neurons, synapses, etc.) at any point in time. It does not involve active adaptation of functional cognitive processes in the presence of injury or disease as does CR".
		Cognitive reserve	"Is a property of the brain that allows for cognitive performance that is better than expected given the decree of life course related brain changes and brain injury or disease".
		Brain maintenance	"Refers to the relative absence of changes in neural resources or neuropathologic change over time as a determinant of preserved cognition in older age".
Kremen et al., 2022 (379)	Reserve	Cognitive reserve	"An individual's total or overall cognitive resources".
		Brain reserve	"An individuals total neural resources or neurobiological capital".
	Maintenance	Cognitive maintenance and maintenance of cognitive reserve	"The degree to which cognitive decline over time is minimised. Maintenance of CR simply refers to maintenance with respect to CR specifically (i.e., overall cognitive ability); it highlights the fact that CR can change over time".
		Brain maintenance	"The relative absence of deterioration over time in brain structure and function".
	Resilience	Cognitive resilience	"The ability to maintain cognitive performance in the face of adverse brain-related change, measured pathology, or other risk factors for cognitive decline".
		Brain resilience	"Brain structure or function that is better maintained given factors that cause, or increase risk for, adverse brain changes".
		Resistance	"Avoiding cognitive decline or brain pathology despite adverse factors. Resistance is a subcategory of resilience because resistance against one risk factor necessarily means resilience against some other factor".
Stern et al., 2023 (1)	Resilience	"General term that subsumes any concept that relates to the capacity of the brain to maintain cognition and function with aging and disease. There can be substantial variability in the mechanisms underlying resilience these can be CR, BM, BR".	
		Brain reserve	"Used to reflect the neurobiological status of the brain (numbers of neurons, synapses, etc.) at any point in time. It does not involve active adaptation of functional cognitive processes in the presence of injury or disease".
		Cognitive reserve	"Property of the brain that allows for cognitive performance that is better than expected given the degree of life course related brain changes and brain injury or disease". "Property of the brain refers to multiple potential mechanisms including molecular, cellular, and network levels. The working hypothesis is that these mechanisms help

			cope with or compensate for brain changes and the consequences of brain injury or disease". "These mechanisms can be characterised via biological or cognitive-experimental approaches". "Better than expected cognitive performance refers to differences ideally measured longitudinally". "It can be influenced by multiple genetic and environmental factors, operating at various points or continuously across the lifespan".
		Brain maintenance	"Relative absence of changes in neural resources or neuropathologic change over time as a determinant of preserved cognition in older age. It can be influenced by multiple genetic and environmental factors operating at various points across the lifespan".

2.3.5.1 Brain reserve, resilience, and maintenance

BR refers to the neurobiological status of the brain, or neurobiological capital, at any point in time and does not involve active adaptation to injury or disease (1). BM refers to the absence of deterioration in brain structure and function and the degree to which genetic and lifestyle factors protect against the development of neuropathology over time (1,379). Additionally, the term brain resilience was recently suggested by Kremen and colleagues, referring to "brain structure or function that is better maintained given factors that cause, or increase the risk for, adverse brain changes" (379,384).

The BR model proposes that differences in brain structure or quantitative aspects of the brain, such as brain size, cranial circumference, and synaptic density, are responsible for individual differences in the tolerance to brain pathology burden (284). Supporting this theory, various studies have found that the prevalence or incidence of clinical dementia is lower for individuals with initially larger and heavier brains, while those who develop the disease show less clinical expression (41,358,386,387). According to BR theory, genetic, developmental, nutritional, and environmental factors contribute to the development of the brain's structural integrity, as well as to BM and resilience (1). A longitudinal cross-cohort study using 7,002 MRI scans found that higher cognitive ability in younger age was associated with cortical thickness via BR and BM mechanisms and that these associations were independent of education (388). Furthermore, cognitive engagement, physical activity, and a healthy diet could stimulate neuroplasticity by improving neurotrophic signalling, neurogenesis, antioxidant defence in the brain, and maintaining brain and cognitive function (389). Supporting this, evidence from 2,413 Chinese and 19,822 British participants suggested that modifiable lifestyle factors such as diet, physical activity, smoking, alcohol

consumption and body mass index are associated with larger total brain volumes, and grey matter, as well as smaller WMH burden (390).

Evidence from various prospective cohort studies has suggested that childhood cognitive ability is associated with brain cortex volume, WMH, infarcts and lacunes, and total small vessel disease five to eight decades later, representing an important risk factor for VaD (183–186). A recent systematic review and meta-analysis of 18 studies found support for the association between lifestyle factors and brain markers, suggesting that cognitive and social leisure activities are associated with white matter volume and white matter lesions, as well as regional grey matter volume (391). In particular, white matter abnormalities have been associated with lifestyle factors related to cardiovascular risk (392–395). Furthermore, evidence from 431 participants from VETSA suggested that an unfavourable lifestyle (measured through smoking behaviour, alcohol consumption, social engagement, physical activity, and diet) was associated with advanced brain ageing only for individuals with lower cognitive ability during early adulthood, suggesting a moderating role of lifestyle factors in the association between early cognitive ability and brain ageing (396).

2.3.5.1.1 OPERATIONAL DEFINITIONS

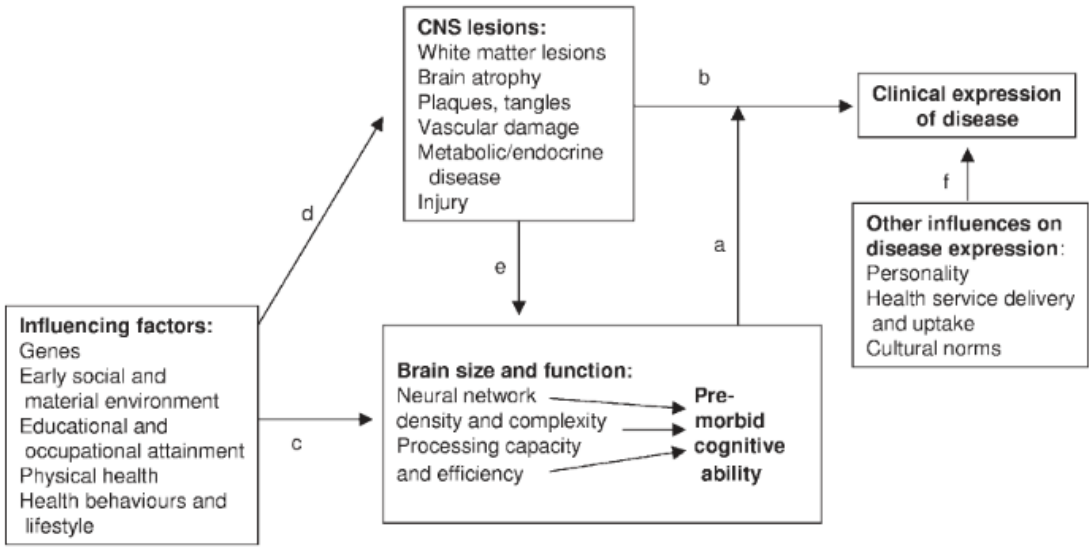
The operational definition of BR requires the inclusion of structural characteristics of the brain and the associated measures of cognition (1). To date, the most widely used indicators of BR are intracranial volume, head circumference, and brain size (265,371). On the other hand, research investigating BM requires measures of age-related brain changes and measures of change in cognition, and therefore BM should be ascertained using longitudinal designs (1).

2.3.5.2 Cognitive reserve, resilience, and maintenance

Early in 2023, Stern and colleagues published a commentary paper on the results of a three-year process on developing consensus definitions for reserve and its associated concepts, as well as research guidelines. The paper reinforced the idea that resilience is a general term that encompasses any concept related to maintaining cognition and function in the face of ageing and disease, and defined CR as "a property of the brain that allows for cognitive performance that is better than expected given the degree of life course related brain changes and brain injury or disease" (1,385). However, in response to this, a revised version of this framework was published by Kremen and colleagues, dividing the concept of reserve into two sub-concepts: CR and resilience, depending on the presence of pathology in the brain. CR was conceptually defined by Kremen as "one's total cognitive resources at a given point in time" (similar to the original definition of reserve proposed by Stern in 2002), while cognitive resilience was defined as the ability to maintain cognitive performance in the face of risk factors for cognitive decline or, in other words, to perform better than expected (similar to the term compensation or neural compensation used by Stern in 2002 and 2009) (379). This reconceptualization responded to what the authors considered are key issues in the previous definition: a logical disconnect between conceptual and operational definitions – whereby operational definitions of CR, such as education, would represent a property of the brain – and the logical dilemma where CR is simultaneously the moderator and moderation effect itself (see operational definition bellow) (379).

Despite the lack of consensus on its conceptual definition, CR is generally thought to reflect the ability of the brain to cope with ageing and pathology. CR is thought to be developed through genetic predisposition and favourable environments beginning in uterine development and through childhood (229,397) and further enhanced during adulthood

through the interplay of various cognitively stimulating activities, including educational attainment and occupational complexity (398). Therefore, it is hypothesised that CR changes over time, originating from the interaction of various markers through the life course, which accumulate over time and could potentially modify the risk of cognitive decline and dementia (383,399–401). In light of this, Richards and Deary proposed a life course model of CR (see Figure 8), which extended Stern's approach to reserve by allowing the reserve model to apply across the life course, recognising that cognitive ability is modifiable at all stages of the life course and that the same factors that influence CR, can influence BR (401).



a. Cognitive reserve is represented by peak pre-morbid cognitive ability.
b. Cognitive reserve modifies the clinical expression of CNS lesions.
c. Cognitive reserve is influenced by many factors across the life course.
d. These same factors influence the accumulation of CNS lesions.
e. CNS lesions in turn damage brain size and function.
f. There are also factors other than CNS lesions that affect disease (especially dementia) expression.

Figure 8 Proposed life course model of cognitive reserve.
Source: Richards & Deary, 2005

CR is theorised to rely on neural reserve – the efficiency, capacity, or flexibility of existing brain networks – and neural compensation – the ability to recruit alternate brain networks and cognitive strategies to maximise cognitive performance in response to increased task demands, deterioration, or damage (231,383,402,403). Hence, in the face of AD pathology, CR's compensation mechanisms impede the onset of cognitive decline. Furthermore, this theory is consistent with the theory of cognitive plasticity, which posits that individual differences in neuronal and cognitive adaptation for normal brain functioning can be influenced by psychosocial characteristics (404,405).

Importantly, despite delaying symptom onset, higher CR has been consistently associated with steeper functional decline after the clinical presentation of dementia (406–414). The theoretical explanation for this counterintuitive observation is that "individuals with the greatest CR will have more advanced pathology at the onset of cognitive decline, less time until they reach the point when pathology overwhelms function, and thus a more rapid rate of decline." (284) (see Figure 9). As a result, CR has been described as a heuristic to help explain individual differences in clinical status relative to ageing and disease and a determinant of progression to AD (384).

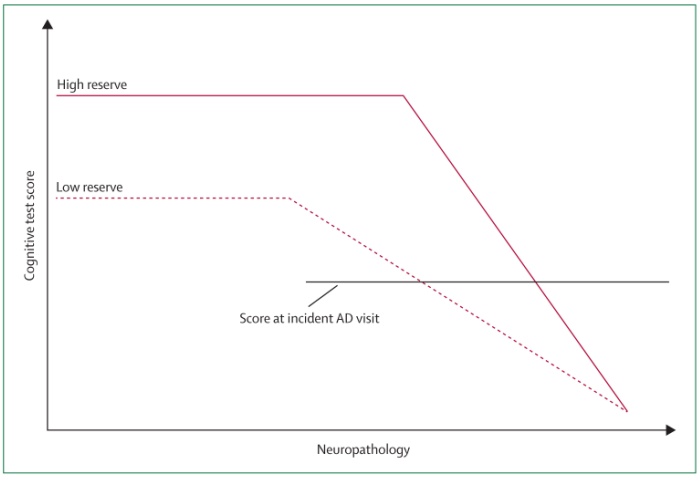


Figure 9 Hypothesised change in memory function over time in individuals with high and low cognitive reserve.
Source: Stern, 2012

A conceptual diagram of the association between fixed and modifiable risk factors, reserve, and cognitive performance appears in Figure 10, which depicts the moderating role of CR on the association between brain changes (age-related atrophy, pathological, or injury-related) and cognitive performance. Evidence to date supports the notion that higher levels of CR are associated with better cognitive performance and a reduced risk of dementia (378). Arguably, the most important aspect of CR is that it appears to be amenable to lifestyle interventions.

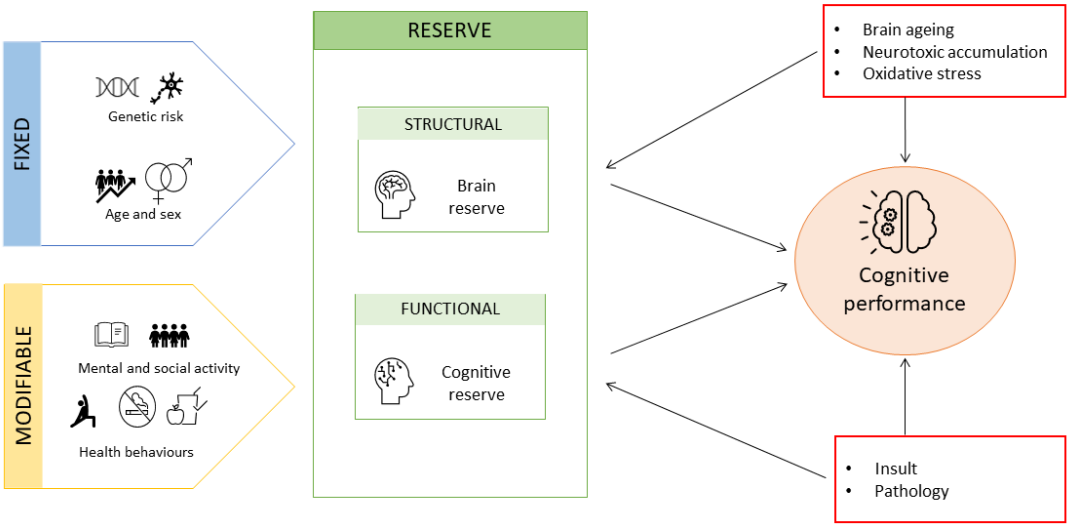


Figure 10 Conceptual diagram of fixed and modifiable risk factors that build into structural and functional resilience and modify the association between brain pathology and cognitive performance.
Informed by Stern and colleagues' framework for concepts of reserve and resilience.

2.3.4.1.2 OPERATIONAL DEFINITION

Stern's 2002 review paper briefly indicated that research investigating cognitive reserve should focus on three components: brain damage, the clinical expression of that damage, and a theoretical mediation of reserve. Furthermore, it suggested that if a research design specified two of the three components, the third could be inferred (265). Later, in 2018, Stern and Habeck published a revised version of this criteria in a report, which presented a formal framework for rigorously deriving and testing CR. The authors listed the following three axioms regarding CR:

1. "Cognitive reserve has well-established proxies like education, intelligence, occupational attainment, leisure activities, and other subject variables that express cognitively stimulating engagement.

2. Cognitive reserve is either an independent factor that influences cognitive performance in addition to brain structure or a moderating factor that influences the relationship between brain structure and cognitive performance; these two manifestations are not exclusive and can conveniently be incorporated in linear regression models that contain (1) brain structure and (2) the putative CR measure and direct effects and (3) an interaction term.
3. Although some of the cognitive reserve proxies might correlate with brain structural measures, cognitive reserve itself is not based on brain structure. […] Such correlations can be conceptualised as brain maintenance. (415)"

In 2020 the Collaboratory emphasised the role of CR as a moderator between pathology and clinical outcome, and thus the operational definition requires the inclusion of the three components detailed in the second axiom. This operational definition conforms with the cognitive benefit criterion, which states that any marker of CR should be associated with higher levels of cognitive performance in the face of brain pathology (379,384,416). The moderation effect is considered the benchmark for CR, whereas the independent effect is considered weaker evidence for a CR effect (211,384,416). Negative moderation effects are considered reflective of CR, suggesting that those with higher CR rely less on brain structure for cognitive function (211,417).

To assess brain structure, cross-sectional studies of CR have relied on brain markers, which refer to measurable aspects of the brain's structure or function that can be used as indicators of cognitive abilities. Brain markers can include structural volumes (e.g., whole brain and hippocampus), white matter integrity and neural activity patterns, as well as Aβ

and tau deposition, which presence has been associated with AD (see Chapter 2, section 2.2.1 'Dementia biomarkers').

Cross-sectional and longitudinal studies incorporating the operational definition of CR have consistently (with few exceptions, i.e., Boyle et al., 2021) suggested that CR modifies the relationship between various brain markers (Aβ – but not tau – cerebral glucose metabolism, cortical thickness, grey matter volume, medial temporal lobe atrophy, vascular pathology) and cognitive function (episodic memory, global cognitive function, and transition from MCI to dementia) (100,418–422). Table A1 in Appendix A summarises some of the CR studies analysing the three components (lifestyle factors, brain markers, and cognition) in controlling or moderation models. Furthermore, a recent systematic review, which included five studies that accounted for brain atrophy, reported that higher CR (assessed through different combinations of composite proxies including education, occupation, intracranial volume, and leisure activities) was associated with a 47% reduced risk of MCI or dementia progression (423).

There are two common operationalisations to assess the factors that may contribute to CR: activity-based, which uses the sociobehavioural proxies and assesses their contribution to cognition through moderation or controlling models, and residual-based, which attempts to measure CR more directly by using residual variance approaches, modelling reserve as cognition not explained by demographic and brain variables (96) (see Figure 11). Both approaches have shown that CR is associated with a reduced risk of dementia after accounting for neuropathology (96,243,256,424–426). A systematic review which assessed the association between CR and dementia while accounting for the level of neuropathology

suggested that both approaches to operationalise reserve have a strong inverse association with MCI and dementia progression, reducing the relative risk of the diagnosis by half (423).

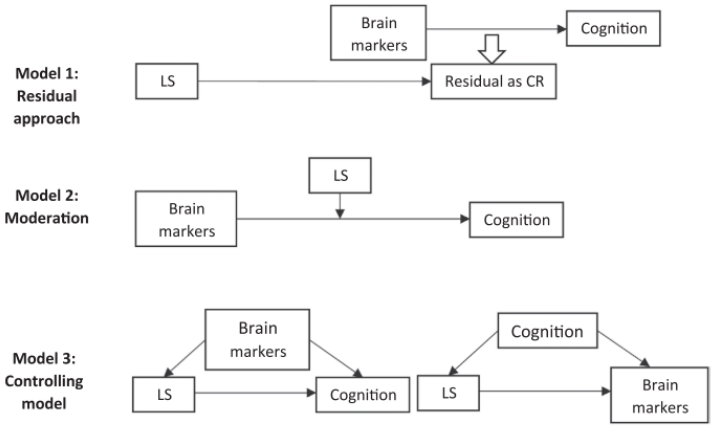


Figure 11 Cognitive reserve mechanisms for the role of life-style factors in the association between brain markers and cognition.
LS: lifestyle-factors; CR: cognitive reserve.
Source: Song et al., 2022

Previous evidence has provided support for the construct validity of activity-based and residual-based measures of reserve (384,427); however, both approaches have also been criticised (428,429). The main criticism of activity-based measures is that they might not accurately represent CR, potentially reflecting another construct (e.g., SEP), and might be related to cognitive performance through other pathways, such as better management of health conditions (423,428). On the other hand, the residual-based approach has been criticised since its adequate measurement depends on the magnitude of the correlation between the measure of pathology (e.g., brain structure) and cognitive function (e.g., memory performance). Moderate or low associations would result in residual scores that would provide little or no predictive value above that provided by the original cognitive score (379). Additionally, residual-based studies might not fully capture CR since the

decomposition approach does not always account for all aspects of neuropathology and usually includes a single cognitive domain (e.g., memory performance) (423).

A recent study comparing residual- and activity-based operationalisations of CR concluded that they might represent complementary approaches serving distinct aims (426). On one hand, residual-based reserve might be informative at the individual level, being useful for clinicians to identify individuals with excessive cognitive deficits and predict an accelerated decline (384,426). On the other hand, activity-based operationalisations are useful for public health and epidemiological research since they provide insight into the potential causes of differences in CR (426,428,429).

2.3.5.3 Sociobehavioural variables influencing reserve

As discussed in the sections above, individual's behaviours and environmental contexts can directly enhance cognitive function. Furthermore, according to CR theory, exposure to a variety of cognitively enriching lifetime experiences can improve the adaptability of cognitive and functional processes, resulting in a greater capacity to cope with brain changes (211,384). Epidemiological research on CR has relied on sociobehavioural variables, also referred to as CR markers or proxies, such as educational attainment, verbal ability, occupation complexity, and leisure activities, which are easily obtained and thus routinely collected as part of most ageing studies (379,384).

2.3.5.3.1 FORMATIVE AND REFLECTIVE MEASURES OF RESERVE

Due to the malleable nature of CR, it is likely that education, occupation, and leisure contribute uniquely to its development, and thus, these variables can be thought of as formative (384,430). Researchers have studied these factors in isolation or grouped them into summary measures (384). Indices representing a combination of these variables are

often preferred over single variables since these factors are related to one another and capture change over time, while single indicators might disregard important components contributing to this complex construct (173,175,211,379,431).

In comparison to CR's formative variables, crystallised cognitive ability, often defined as knowledge acquired over time (see section 2.3.1.1 Crystalised cognitive abilities) (202), has been argued to represent peak cognitive ability in adulthood (401,432), capturing the intellectual ability achieved that does not exclusively depend on access to and quality of formal education (229,230,433). Thus, there is some evidence suggesting that verbal ability might reflect CR, having more robust positive associations with cognitive function independently of brain structure in comparison to other CR markers, including composite markers (211).

2.3.4.3.2 MEASUREMENT OF RESERVE

Both latent variable and composite approaches to measuring CR have appeared in the literature. CR has been previously characterised using methods of dimension reduction such as factor analysis (296,434,435). However, the heterogeneity of the methodology in these investigations has been argued to hinder the comparability of the results across studies and conceals the different influences of the individual proxies by only reporting the shared variance across variables (384,426). Furthermore, methods such as factor analytic and latent variable models have been argued to mis-specify the causal ordering of the variables representing experiences that contribute to the development of CR. In a special series article on the conceptual and measurement challenges in research on CR, Jones and colleagues argue that latent factor measurement is incompatible with CR theory since it

requires that CR be re-conceptualised as a factor antecedent to the variables argued to influence it (404).

Scales creating summary scores of activities, such as education, occupation, and leisure, have also been used in observational studies. Although there is no gold standard questionnaire based on CR proxy indicators (436), two recent systematic reviews found that the Cognitive Reserve Index questionnaire (CRIq) (2) and the Lifetime of Experiences Questionnaire (LEQ) (437) are the most widely used questionnaires to assess factors that contribute to CR (438,439). Both questionnaires are available in English, are appropriate for the general population, and include education, occupation, and leisure activity. An important strength of these indices is that the data to construct them is widely available, making them easily implemented in longitudinal studies of ageing. Furthermore, a recent systematic review aiming to evaluate the measurement properties of cognitive reserve instruments suggested that the CRIq and LEQ have the potential to be used to measure CR in older adults, and that either one seems to be superior to the other (436).

The CRIq was designed to capture the multifactorial nature of reserve and prove a standardized measure of CR acquired during a person's lifetime (2). For the computation of the Cognitive Reserve Index (CRI), each individual component is standardised to make sure they contribute evenly regardless of their scale when the items are added together. The CRIq is available in 11 languages and has been shown to have fair cross-cultural validity, fair content validity, fair to excellent construct validity, and good convergent validity (438). The CRIq is considered a reliable (test-retest) measure of CR (440) and has been previously used to measure CR in Italian, Greek, and English adults (2,441,442). Furthermore, it has been used to measure markers of CR in large observational studies such as ELSA (244).

The LEQ was developed to comprehensively assess complex mental activity over the life course, including education, occupation, and cognitive lifestyle activities, and has been proposed as a useful tool for estimating CR in older individuals (437). The LEQ has shown good content and convergent validity, as well as good test-retest reliability (438). Furthermore, the LEQ has been adapted for secondary data analysis as the Cognitive Lifestyle Score, a simplified proxy for the LEQ, and has been successfully derived in the Cognitive Function and Ageing Study, the Cognitive Function and Ageing Study-Wales, and the Quebec Longitudinal Study of Nutrition and Successful Ageing, significantly predicting cognitive function and dementia, as well as moderating the association between social isolation and cognition (398,443–446).

2.4 Interventions

As presented in section 2.2.2 'Dementia risk factors and prevention', epidemiological research suggests that a decline in the prevalence of dementia is possible if it is driven by changes in access to resources (e.g., education and health care) as well as exposure to suspected developmental, lifestyle, and cardiovascular factors (23). Therefore, future projections of the number of people living with dementia and the age of onset of dementia may be modified by interventions. Projection models have suggested that hypothetical interventions aimed to delay the onset of AD by 2 years can reduce its prevalence by 20%, whereas interventions to delay the onset of AD by 5 years would result in a reduction of 57% of patients with AD, decreasing the societal and economic burden of the disease (447,448). Furthermore, delaying the age of onset of the disease might lead to a compression of cognitive morbidity, deferring the onset of dementia closer to the end of the natural lifespan and reducing the burden of dementia for the ageing population (92,169).

For individuals with AD and their carers, the most important treatment outcomes are improving memory, slowing or stopping disease progression, and treating the ability to participate in daily activities and interests (449). Therefore, finding interventions to reduce the incidence and prevalence of dementia remains a global challenge. The current focus is on two disease-modifying approaches: early targeting of neuropathology through pharmacological interventions and lifestyle interventions (450).

2.4.1 Pharmacological interventions

According to the cholinergic hypothesis, the deterioration of cholinergic neurons and the loss of neurotransmission are the major causes of cognitive decline in AD (451,452). Hence, the enzyme cholinesterase as well as protein, Aβ, and to a lesser extent, tau aggregation (see section 2.2.1 'Dementia biomarkers'), are significant therapeutic targets to prevent, delay, or improve the symptoms of dementia. However, despite their substantial cost, the success rate of drugs targeting AD is disappointingly low (453–455). Over the past 29 years, only five drugs for the symptomatic treatment of AD have reached FDA approval: four cholinesterase inhibitors and memantine (N-methyl-D-aspartate receptor antagonist) (456). Additionally, in 2021, aducanumab (monoclonal antibody targeting Aβ) was the first disease-modifying therapy approved by the US FDA for the treatment of AD, and early in 2023, lecanemab (also a monoclonal antibody targeting Aβ) followed suit by gaining accelerated approval in the US. At higher doses, aducanumab has shown a modest impact on cognitive decline for individuals with MCI or at the early stages of AD, but it does not reverse prior memory loss associated with the disease (457). Similarly, RCT evidence has suggested that at 18 months, lecanemab significantly reduces the presence of Aβ in the brain and influences cognition and function (458). However, due to their modest impact on cognitive function and uncertainties regarding the benefit-risk ratio and cost-effectiveness, the

European Medicines Agency has not approved the use of aducanumab or lecanemab in European countries (457).

A recent umbrella review which included 149 RCT studies investigating the available pharmacological treatments for AD patients, suggested that acetylcholinesterase inhibitors (a neurotransmitter whose hydrolysation is catalysed by cholinesterase enzymes) have modest but significant effects on cognitive and functional decline, while agents targeting Aβ were not effective (459). Supporting this observation, mouse models have shown that Aβ-modifying therapies have a limited effect once neuronal degeneration has begun, suggesting that future AD modifying treatments could be more beneficial if introduced prior to the symptom onset, potentially averting the disease entirely (74,97,460). Currently, studies aiming to treat preclinical dementia are in the planning stages, and research has begun to develop treatments for pathologies that are commonly associated with AD, including other neurodegenerative diseases and cerebrovascular pathologies (460). Furthermore, pharmacological interventions are being used to target some of the best known morbidity risk factors for dementia, such as diabetes, dyslipidaemia, and high blood pressure; however, the results of these efforts have not been translated into a reduced incidence of dementia (461).

2.4.2 Non-pharmacological interventions

In comparison to pharmacological interventions, non-pharmacological interventions are considered more promising and more likely to be more generalisable since they have a lower risk and are not associated with adverse side effects (462). A recent systematic review and meta-analysis examining 28 RCTs suggested that non-pharmacological interventions such as mind-body exercise, dual-task exercise, physical exercise, and cognitive training

significantly improve cognitive function in older individuals with MCI (463). Furthermore, despite the low to moderate evidence, the current World Health Organisation (WHO) guidelines for cognitive decline and dementia risk reduction recommend interventions targeting physical inactivity, tobacco use, poor nutrition, alcohol use disorders, and cognitive function (464).

2.4.2.1 Single domain interventions

A comparative effectiveness review was carried out in 2017 to identify interventions aimed at preventing or delaying the age of onset of cognitive decline, MCI, or AD (465). The review identified 13 types of interventions (cognitive training, physical activity, nutraceuticals, diet, multimodal interventions, hormone therapy, vitamins, antihypertensive treatment, lipid-lowering treatment, nonsteroidal anti-inflammatory drugs, antidementia drugs, diabetes treatment, and "other interventions") of which only two, cognitive training and physical activity, showed promising results, despite their low and medium-strength evidence (465). Furthermore, evidence from a scoping review which included 32 RCTs employing cognitive training or physical exercise, suggested that both intervention approaches are associated with greater improvements in selected cognitive abilities (462).

Cognitive training interventions can be broadly categorised into those that focus on training and practice to improve cognitive function (remediation) and those that focus on maintaining independence and engagement in activities of daily living (compensation) (466,467). Thus, the efficacy of these interventions is usually assessed through the maintenance or improvement of cognitive function and their impact on daily living. Research investigating whether cognitive training improves cognitive function in older adults has suggested that training improves performance in the targeted cognitive domain,

with some studies showing a persistent effect over an extended follow-up (465,468–470), and few interventions showing a transfer to non-trained cognitive domains (471).

There is broad consensus that physical activity interventions can support brain health and reserve. A recent meta-analysis which included 71 trials investigating the effectiveness of physical activity interventions on cognitive function, suggests that all types of exercise (i.e., aerobic exercise, resistance exercise, multicomponent exercise, and mind-body exercise) are effective in maintaining global cognition, and that resistance exercise had the highest potential to slow cognitive decline for individuals with cognitive dysfunction (472). Furthermore, an overview of systematic reviews and meta-analyses found evidence suggesting that multicomponent exercise programmes can improve performance in activities of daily living, ability to walk and balance, and visuospatial function, subsequently benefiting independent living (473).

2.4.2.2 Multidomain interventions

The causes of dementia are multi-factorial, with various observational studies consistently finding an association between vascular and lifestyle risk factors and dementia risk; therefore, multidomain interventions targeting several risk factors represent a promising avenue for preventive effects. Supporting this, a review of multidomain interventions to support healthy cognitive ageing found promising results for the combination of exercise, mental training, diet, and behavioural weight measurement (474). Furthermore, a recent RCT investigating the combined effect of cognitive training and physical exercise suggests that this intervention can synergistically affect later life cognition (475). Furthermore, two recent systematic reviews and meta-analyses comparing multidomain interventions to single-domain interventions reported greater effect sizes in the multidomain group for

cognitive function for individuals with MCI (476), and greater effects for simultaneous intervention compared to sequential ones (477).

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a large 2-year interventional trial, investigated the effect of a multidomain lifestyle intervention in dementia risk among older at-risk individuals. The FINGER intervention arm focuses on diet, exercise, cognitive training, and vascular risk monitoring, while the control arm provides general health advice. The study found a significant group reduction in cognitive decline for the intervention group (478,479). The encouraging findings from this study suggest that multidomain interventions can be implemented for the elderly population at risk of dementia; however, the results have not yet been replicated (450).

The synergistic benefits of pharmacological and non-pharmacological interventions may represent an effective avenue for dementia prevention. A scoping review found that for adults with neurodegenerative diseases, combination therapies significantly improved cognitive test scores compared to medication or non-pharmacological therapy alone (462). However, the results of combination trials have not been conclusive, and the additive or synergistic effects of these treatments need to be studied further.

2.5 Gaps in the literature

Even though cognitive function and dementia risk can be modified throughout life, most studies have exclusively focused on the role of activities during mid- and late-life, with very few studies addressing how multiple life course determinants of cognitive ageing relate to each other and possible interactions between determinants being understudied (215). For instance, despite childhood cognitive ability having been highlighted as a very important

factor influencing cognitive differences in older age (480), a recent systematic review assessing nine studies using data from two UK birth cohorts found inconsistent results for the association between childhood cognition and cognitive decline, suggesting that the relationship might be modified by other factors (198). Therefore, it is not yet clear to what extent other determinants of cognitive ageing modify the association between early-life cognitive ability and older-age cognitive function.

There is growing evidence of various modifiable lifestyle factors which are beneficial to the cognitive function of older adults; however, evidence is needed to understand the potential pathways involved in these associations. One proposed pathway is the direct contribution of these factors to cognitive function, while another might be indirect through their contribution to CR, which in turn modifies the association between brain markers and cognition. Moreover, the sociobehavioural variables commonly associated with CR might not necessarily modify the association between neuropathology and cognition, but might protect against the accumulation of pathology itself, playing a more causal role in dementia and representing a risk factor for cerebrovascular disease and cognitive decline (401). Little is currently known about the potential role of the sociobehavioural factors in brain structure, with existing studies being limited by small sample sizes or suboptimal control for important covariates.

Although CR has received high levels of attention from the research community, there are disparate definitions for the same term in the literature. Thus, research is needed to provide evidence for the latest consensus framework while considering alternative definitions that might better explain these specific concepts. In terms of CR's operational definition, few studies have assessed the association between CR and cognitive function while controlling

for brain markers in cognitively healthy older adults (211,423). There are very few reports on the moderating effects of composite indexes, which include activities undertaken in midlife, such as occupation and leisure activity engagement (481), and even fewer studies analysing a wide range of brain markers. Additionally, research is needed to understand which factors contribute to the establishment, development, and maintenance of CR, particularly in association with cognitive performance and dementia risk.

Despite genetic and biological (e.g., sex and age) variables being important non-modifiable risk factors for cognitive ageing and dementia, very few studies have investigated their moderating role in CR models. To further understand the factors that influence the onset of AD symptoms, data on the relationship of brain markers, genetic risk, sex, age, CR, BR, and cognitive function in asymptomatic older adults are needed (482).

The suggestion that lifestyle factors such as leisure activities can have an influence on cognitive function is very appealing since it implies that individuals might be able to modify their risk of cognitive decline and dementia. Furthermore, understanding the modifiable sources of CR would inform the design of effective and scalable interventions to prevent cognitive ageing and dementia. The 2020 report of the Lancet Commission on dementia prevention recommends “keeping cognitively, physically, and socially active in midlife and later life”(39) yet acknowledges that little evidence exists for any specific activity protecting against dementia. Due to conflicting evidence for the contribution of leisure activity engagement to cognitive function and the possibility of reverse causality, the role of leisure activities in dementia is considered far from settled (211,483,484).

This second chapter covered cognitive ageing and dementia, its risk factors, life-course determinants, and a summary of the interventions available to date; this section revising the gaps in the literature finalises the literature review.

The next chapter, Chapter 3, will cover the aims and objectives of this thesis, while Chapters 4 to 7 will present the individual studies carried out to address some of the gaps in the literature as well as the aims and objectives. Chapter 8 will present a summary of the coordinated approach to deriving a CR marker from the cohort studies included in this work. Finally, Chapter 9 provides a general discussion of the findings, including a section on the key results, future directions, and policy implications.

Chapter 3. Aims and Objectives

This thesis aims to investigate various pathways through which life course factors are associated with cognitive function and dementia.

The project addresses the following objectives:

1. Investigate the moderating role of cognitive reserve (CR), indexed using the Cognitive Reserve Index (CRI) (2) and verbal ability, and APOE e4 in the association between childhood cognitive ability and cognitive function in older age using data from the National Survey of Health and Development (NSHD) (Chapter 4).
2. Investigate the association between the CRI, verbal ability, and brain reserve (BR) using data from the NSHD Insight 46 neuroimaging sub-study and UK Biobank (Chapters 5 and 6).
3. Investigate the moderating role of CR, indexed using the CRI and verbal ability, in the association between brain markers and cognitive function using data from the NSHD Insight 46 neuroimaging sub-study and UK Biobank study (Chapters 5 and 6).
4. Investigate the association between leisure activity engagement and dementia using data from the English Longitudinal Study of Ageing (ELSA) (Chapter 7).

Figure 12 shows the conceptual framework for this PhD which is based on Stern and colleagues' latest CR framework (1) and Richards and Deary's life course model of CR (401). The figure at the top (A) shows the association between the different non-modifiable and modifiable life course variables with cognitive function or dementia, and the interrelation between them. The arrows linking the life course determinants together are illustrative; they indicate the upstream contribution of each variable to the following one in the life course. However, there are multiple ways in which these variables affect each other (e.g.,

cognitive ability contributes to education, verbal ability, and neuropathology independently). The figure at the bottom (B) shows the theorised pathways through which these variables are associated with cognitive function. The studies will focus on path c, which represents the presumed role of the sociobehavioural variables as markers of CR. The study in Chapter 4 investigates the direct association between childhood cognition (path f) and the sociobehavioural variables (path e) and cognitive function. This study also assesses the moderating role of CR markers in the association between childhood cognition and cognitive function (path g). The studies in Chapters 5 and 6 investigate the contribution of the sociobehavioural variables to BR (path d), the association between BR and cognitive function (path b), and the moderating role of CR markers in this association (path a). The study in Chapter 7 focuses on the role of one of the sociobehavioural variables, leisure activity, on the extreme of the spectrum of cognitive dysfunction, dementia diagnosis (path e).

It should be noted that childhood cognition might also directly contribute to adult BR, with the sociobehavioural variables potentially mediating this association. However, although related, this investigation is beyond the scope of this thesis, and therefore, the arrow linking childhood cognition to BR or brain markers is not shown.

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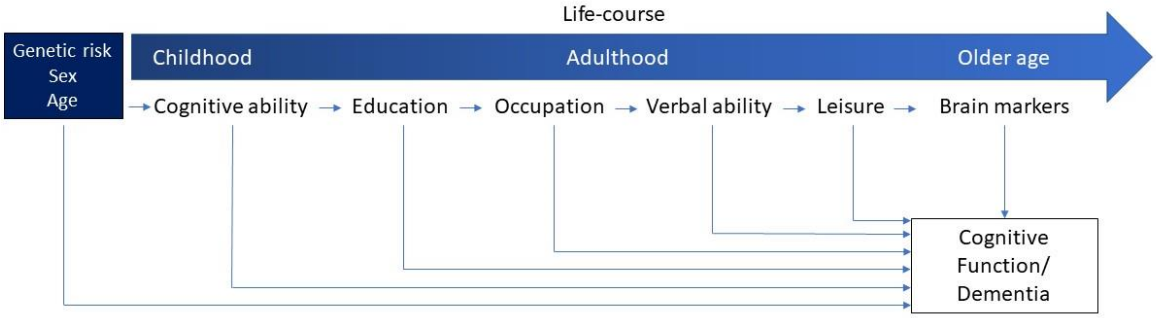

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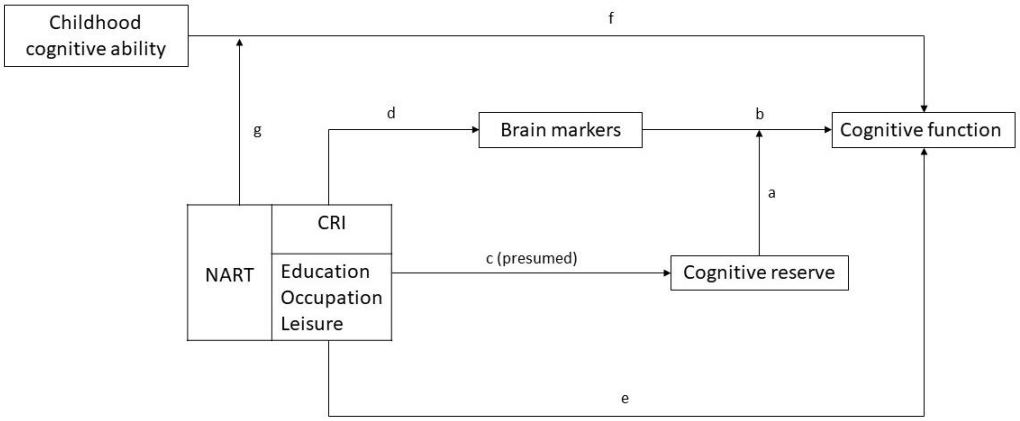


Adapted from Richards and Deary, 2005

A. Summary of the approximate temporal relations of the key life course determinants of cognitive ageing.
B. Theorised pathways of the life course determinants of older-age cognitive function.

Figure 12 PhD conceptual framework

Chapter 4. The moderating role of cognitive reserve markers between childhood cognition and cognitive function in NSHD

The methods and results presented in this chapter have been previously published in *Neurology* (Almeida-Meza, Richards, Cadar, 2022)

4.1 Introduction

As presented in Chapter 2, section 2.3 'Life course determinants of cognitive ageing and dementia' the heterogeneity in cognitive function of older individuals might be related to the exposure and accumulation of risk and protective factors across the life course. Genetic as well as life course factors are considered important determinants of cognitive ageing and dementia (42). Furthermore, it was discussed that according to CR theory the knowledge and experiences individuals accumulate through their lives provide increased resilience against the clinical expression of neuropathology, helping to maintain cognitive function (384,401).

The role of childhood cognition in cognitive ageing has been widely investigated, supporting a consistent association with later-life cognition, and establishing childhood cognition as a reliable early determinant of cognitive ageing (see Chapter 2, section 2.3.1 'Childhood cognitive ability') (198,397,400). Early cognitive ability has been argued to reflect CR since it is least confounded by the negative effect of age or neuropathology, and thus represents an individual's peak cognitive resources, promoting later reserve and resilience (379,396,401). Furthermore, CR is thought to be developed through childhood (229,397) and further enhanced during adulthood through the interplay of various cognitively enhancing activities,

including educational attainment, occupational complexity, and leisure activity engagement (229,285,305,398).

Previous studies have shown that CR's formative variables, such as educational attainment, occupation complexity, and engagement in leisure activities, explain some of the variance in cognitive function during later life, even after accounting for early-life cognitive ability (211,400,480,485). However, it is unclear to what extent these environmental exposures and lifestyle choices modify the association between early-life cognitive ability and cognitive ageing (198,215).

Furthermore, in comparison to CR's formative variables, crystallised cognitive ability, defined as knowledge acquired over time (202), has been argued to reflect CR (401,432), capturing the intellectual ability achieved through experience, and being a better indicator of the quality, benefit, or outcomes of education (211,229,230,433) (see section 2.3.1 "Childhood cognitive ability"). It has been suggested that verbal ability might have more robust positive associations with older age cognitive function, including non-verbal skills, independently of brain structure in comparison to other sociobehavioural markers, including composite markers of CR (211,486,487).

In terms of genetic risk, the APOE e4 has been associated with a faster rate of cognitive decline from midlife and a higher risk of Alzheimer's disease, positioning it as the best-known genetic risk factor for AD (141,142) (see section 2.2.2 "Dementia risk factors and prevention"). Furthermore, previous research has suggested that, despite not being associated with early-life cognitive ability, education, or crystallised cognitive ability, APOE e4 is associated with lower cognitive performance in later life, predicting change in ability from youth (141,229,488) .

4.1.1 Objective

Based on available life course studies investigating sociobehavioural variables and verbal ability as markers of CR (211,244,256,296,397,489) and building on previous path models investigating the life course determinants of cognitive function (229,230), this study aimed to investigate the modifying role of two commonly used markers of CR, the CRI and the National Adult Reading Test (NART), and APOE genotype in the association between childhood cognition and cognitive function at age 69.

4.1.2 Research questions

1) Is there an association between childhood cognitive ability, the CRI, NART, or APOE e4 and cognitive function in older age?
2) Does the CRI, NART or APOE e4 allele modify the association between childhood cognitive ability and cognitive function?

4.1.3 Hypotheses

1) Higher scores of childhood cognition, CRI, and NART would be associated with better cognitive function in older age, and the CRI and NART would each predict higher cognitive function scores for individuals with lower childhood cognition scores.
2) Based on previous evidence, the presence of the APOE e4 would be associated with lower cognitive function. It was hypothesised that APOE e4 would predict lower cognitive scores in later life, especially for individuals with low childhood cognition.

4.2 Methods

4.2.1 Study Population

The data were extracted from the Medical Research Council (MRC) NSHD, also known as the British 1946 birth cohort. NSHD originally comprised a socially stratified sample of 5,362 individuals born within one week of March 1946 through England, Wales, and Scotland. The study has continuously collected data on sociodemographic factors and medical, cognitive, and psychological function from birth through all the relevant developmental stages. The 24th data collection was carried out between 2014 and 2015 when participants were aged 68-69 (490).

For this study, the sample was derived based on the individuals with complete cognitive function data during the nurse interview at age 69. The study was carried out using complete case analysis. See Figure 13 for the flow chart of the analytical sample.

The study protocol received ethical approval from the Great Manchester Local Research Ethics Committee for the five English sites and Scotland Research Ethics Committee for the data collection taking place in Edinburgh. Written informed consent was obtained from the study member at each stage of data collection.

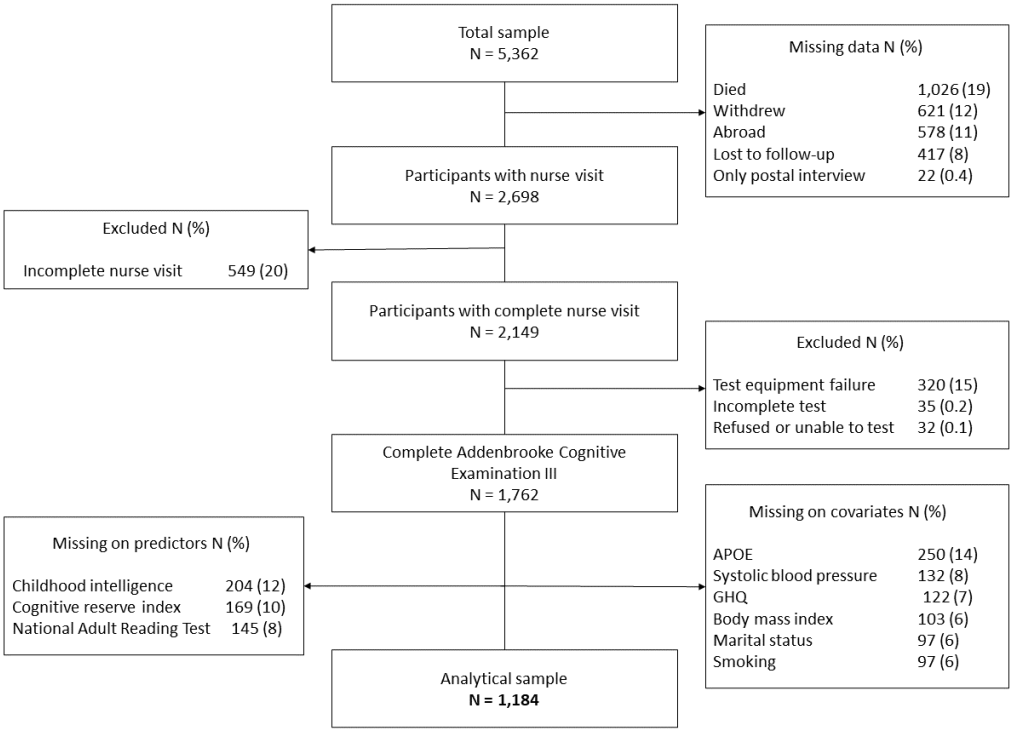


Figure 13 Flowchart of the analytical sample of study members from NSHD.

4.2.2 Measures

4.2.2.1 Childhood cognition

At the age of 8, participants took verbal and nonverbal ability tests devised by the National Foundation for Educational Research (491), which were administered by a teacher and trained personnel. These tests included: (1) Reading Comprehension, (2) Word Reading, (3) Vocabulary, and (4) Picture Intelligence. Scores from these tests were summed to create a total score ranging from 12 to 92, representing overall cognitive ability at this age.

4.2.2.2 The Cognitive Reserve Index questionnaire

The CRIq (2) quantifies various markers of CR, providing a standardised measure (the CRI) of the CR acquired during a person's lifetime. The CRI is a composite measure of educational attainment, occupational class, and leisure activities (see Chapter 2, section 2.3.5 "Reserve" for additional information on the CRI). The data for each component were extracted from

various questionnaires administered to each member during their assessments at ages 26, 43 and 53. The computation of the CRI was carried out in accordance with a previous publication (2): each component was standardised to a mean of 100 and a standard deviation of 15. To calculate the overall CRI, the three corresponding standardised scores were averaged. This average was then re-standardised and transposed to a scale with a mean of 100 and a standard deviation of 15, resulting in the CRI score.

Education. The highest educational attainment by age 26 was classified by the Burnham scale (492). For descriptive purposes and to be consistent with the original calculation of the education component (2), the approximate number of years each qualification represents was calculated as follows: Doctorate (20 years), Masters (17 years), Graduate degree (16 years), GCE 'A' level, Burnham B or Burnham A2 (13 years), Vocational course, sub-GCE or sub-Burnham C, GCE 'O' level or Burnham C (11 years), and none attempted (10 years).

Occupation. Occupational class was assessed through participants' occupation level from age 26 to 43 and their occupation at age 53. The occupation variables were categorised into the following five groups based on the Registrar General classification: professional = 5, intermediate occupations = 4, skilled non-manual = 3, skilled manual or partly skilled = 2, and unskilled = 1. The CRI computation multiples the level of occupation by the number of years spent at each job (2), hence participant's occupation levels from ages 26 to 43 were multiplied by 20 plus their occupation at age 53 times 10, representing 30 years of work and accounting for any changes of work level at midlife.

Leisure activities. Engagement in leisure activities was measured at age 43 through a range of 14 intellectual, social, and physical activities. The selection included activities

related to belonging or running to various organisations, spare time engagement in sports or artistic activities, intellectual activities, and social activities. Participants were included if they had data for at least one leisure activity. A detailed list of the activities selected to create this component can be found in Table 2 and the derivation of these variables and transformation into binary scores is available in Appendix B, section B.2.

Table 2 Activities included in the CRI leisure sub-scale in the NSHD.

1.	Do you help to run/belong to evening classes/ adult education?
2.	Do you help to run/belong to church activities?
3.	Do you help to run/belong to any voluntary services?
4.	Do you help to run/belong to a trade union?
5.	Do you help to run/belong to any sports clubs?
6.	Do you help to run, etc., playgroup, nursery, or school?
7.	Do you help to run the local government?
8.	In your spare time, do you take part in musical, artistic or creative activities?
9.	In your spare time, do you go out to pubs, clubs, or social activities?
10.	Since we last contacted you, have you been on any educational courses or training?
11.	On average, how often would you say you met friends or relatives socially?
12.	Do you regularly do any heavy gardening apart from paid work?
13.	Do you regularly take part in any sports or vigorous leisure activities?
14.	In your spare time do you take part in constructive activities, making things with your hands

The leisure sub-scale score ranged between 0 and 11.

4.2.2.3 National Adult Reading Test

The NART was administered to participants at age 53. This test assesses the ability to pronounce 50 words that violate conventional pronunciation rules and are unlikely to be read correctly unless the reader is familiar with them in written form rather than relying on intelligent guesswork (493). Thus, the NART serves as a measure of crystallised cognitive ability, measuring the knowledge acquired over the life course (432). Previous studies have suggested that the NART might represent an important marker of CR, capturing environmental enrichment afforded by lifelong learning (401,433,494). For the analysis, the

conventional NART scale was reversed, with higher scores showing better performance; the scores range between 1 and 50.

4.2.2.4 Genetic risk

As previously described for this cohort, single nucleotide polymorphism (SNPs) rs429358 and rs7412 (assessed in blood taken at age 53 or 69-71 by a research nurse) were used to determine APOE genotype (229). For this analysis, APOE was categorised as no e4 versus heterozygous e4 or homozygous e4. Due to opposing effects on cognition, participants with e2/e4 were excluded (N=68).

4.2.2.5 The Addenbrooke's Cognitive Examination III

The ACE-III was administered during the nurse visits when participants were 69 years old. The ACE-III is a screen-implemented test of cognitive function and has been validated as a screening tool for cognitive deficits in AD and FTD (495). The ACE-III has a maximum total score of 100 and has a quasinormal distribution. The examination is comprised of five domains: Attention and Orientation (scored 0 to 18), Verbal Fluency (0 to 14), Memory (0 to 26), Language (0 to 26), and Visuospatial Function (0 to 16). A customised version of the ACE-III was administered by iPad using ACEMobile (http://www.acemobile.org). A paper version of the ACE-III was only used when the iPad screening administration was not possible.

4.2.2.6 Model adjustment

The study controlled for various important covariates that are related to cognitive health (see section 2.2.2 Dementia risk factors and prevention) that were measured at age 53. As sociodemographic variables, sex and marital status were included. Marital status was dichotomised between married and not married participants; this last category included

single, separated, divorced, and widowed participants. Physical health was ascertained by body mass index and blood pressure, as well as self-reported diagnosis of a severe illness or disability. Emotional symptoms were self-reported using the General Health Questionnaire 28 (GHQ-28), which is a validated 28 item instrument to detect symptoms of anxiety and depression and psychosocial functioning (496). Smoking behaviour was assessed by asking participants if they currently smoke cigarettes (yes/no).

4.2.3 Statistical analysis

Multivariable regression models were used to test the association between all exposures (i.e., childhood cognition, CRI, NART, and APOE) and the scores in the ACE-III. The association between the exposures and cognitive function was investigated by progressively adjusting for sex and marital status in model 1, further adjusting for physical health in model 2, GHQ-28 in model 3, and cigarette smoking in model 4. Initial investigations were carried out individually for each exposure variable and the ACE-III (see Figure 14). Age was not included since all individuals in the sample have the same age (see section 4.2.1 Study population).

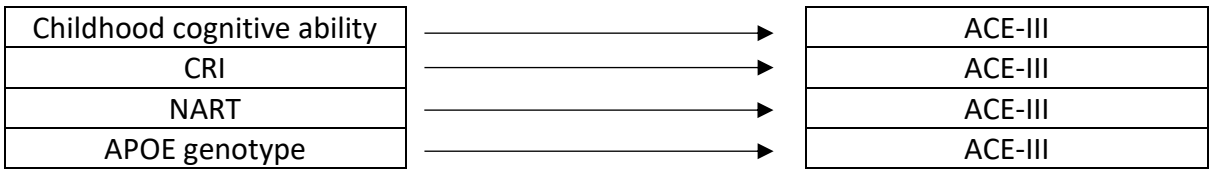


Figure 14 Individual regression models for exposures and ACE-III scores.

Mutually adjusted associations were then investigated for all exposures and cognitive function. The NART is a measure of crystallised cognitive ability that reflects accumulated knowledge (193), and since knowledge is one of the clear benefits of education, the

following models adjusted for both the CRI and NART to test if these were independent predictors of cognitive function (Figure 15).

Figure 15 Mutually adjusted regression models for exposure variables and ACE-III scores.

Additionally, the association between the childhood cognition tests (Reading Comprehension, Word Reading, Vocabulary, and Picture Intelligence) and the ACE-III was investigated while accounting for the CRI, NART, APOE e4, and gradually adjusting for all covariates (Figure 16).

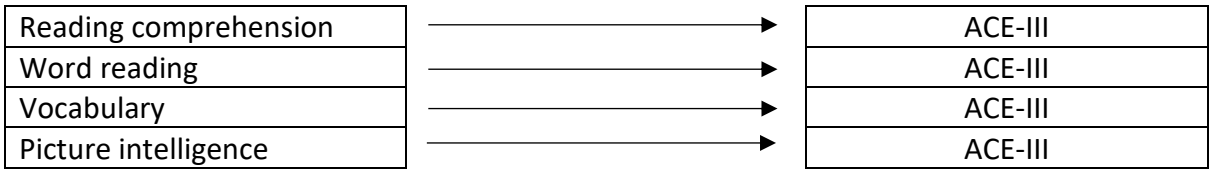


Figure 16 Individual regression models for childhood cognition tests and ACE-III scores.

The association between the individual components of the CRI (education, occupation, and leisure activities) and the ACE-III was also assessed while accounting for childhood cognition, NART, genetic risk and gradually adjusting for all covariates (Figure 17). For the analysis of the components, education and occupation were re-categorised to ensure all levels of the variable were appropriately powered (i.e., based on numbers on each group). Education was grouped into no qualification, ordinary secondary qualifications or below (vocational and 'O' levels or training equivalents), advanced secondary qualifications ('A level' and equivalent), or higher qualifications (degree or equivalent). For occupation, unskilled and partially skilled were merged, skilled manual and skilled non-manual were merged, and intermediate

occupations and professional occupations were merged into a single category. Leisure activity engagement was categorised into tertiles (244).

Figure 17 Mutually adjusted regression models for CRI components and ACE-III scores.

Finally, to assess the independent modifying role of the predictors in the association between childhood cognition and cognitive function in older age, the interactions between childhood cognition and CRI, NART, and APOE were tested. Marginal effect models were carried out to explore and illustrate the interactions between continuous exposure and outcome variables. Additionally, the association between childhood cognition and cognitive function was assessed by stratifying the moderator variables, which were dichotomised above and below the mean (Figure 18).

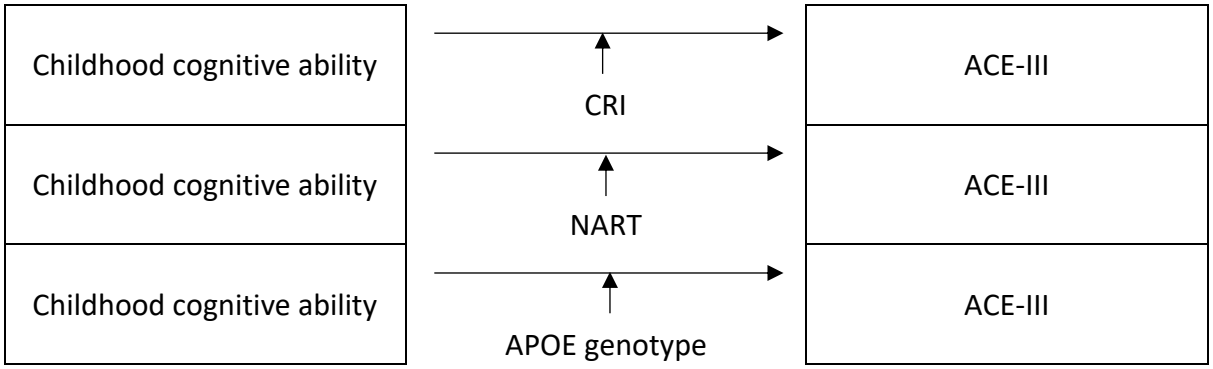


Figure 18 Moderation models for the association between childhood cognition and the ACE-III.

Information on the linear model assumptions and the steps taken to control for any deviations are available in Appendix B. The main analysis was carried out using complete case analysis. To control for false discovery rate due to multiple comparisons, the

Benjamini-Hochberg correction (497) with a q-value of 0.05 was used for all the regression models. The Benjamini-Hochberg was chosen since it considered less conservative and more powerful than the Bonferroni correction (497). Analyses were conducted using Stata MP, Version 16 (Stata Corp).

4.2.4 Sensitivity analysis

The proportion of missing data in the analytical sample ranged from 6% to 14% (see Figure 13). The main analyses were replicated out using imputed data. Missing data on predictors and covariates were estimated using multiple imputations (MI) by chained equations. Additional information on the imputation procedure is available in Appendix B.

4.3 Results

4.3.1 Descriptive statistics

Of the 1,184 participants included in the analysis, 48% were female, and 29% had at least one e4 allele of the APOE gene. At age 26, only 11% of the sample had a graduate degree or higher education (i.e., masters or doctorate), and by age 43, 38% engaged in six or more leisure activities. At age 53, 50% had a professional or intermediate occupation. Furthermore, at the last wave of data collection, the mean score in the ACE-III for the sample was 92 (SD=6), with a minimum score of 53 and a maximum score of 100 (see Figure 13 for the participant flowchart and Tables 3 and 4 for the descriptive characteristics of the sample).

Table 3 Frequency distribution and descriptive characteristics of categorical variables included in the NSHD analyses.

Categorical variables	Categories	N (%)
Education at age 26	No qualification	329 (28)
	GCE 'O' or equivalent	351 (30)
	GCE 'A' or equivalent	362 (31)
	Degree or higher	142 (11)
Leisure activities at age 43	0-4 activities	499 (42)
	5 activities	241 (20)
	6+	444 (38)
Occupation at age 53	Part-skilled and unskilled	150 (13)
	Skilled (manual and non-manual)	439 (37)
	Professional or intermediate	595 (50)
APOE e4	No	836 (71)
	Yes	348 (29)
Sex	Female	563 (48)
	Male	621 (52)
Marital status at age 53	Married	956 (81)
	Not married	228 (19)
Serious illness or disability at age 53	No	1,125 (95)
	Yes	59 (5)
Depressive symptoms at age 53 GHQ-28	0	601 (51)
	1-5	285 (24)
	6-10	178 (15)
	11+	120 (10)
Cigarette smoking at age 53	No	961 (81)
	Yes	223 (19)

Not married: Single, separated, divorced, or widowed.
GHQ-28: General Health Questionnaire.

Table 4 Frequency distribution and descriptive characteristics of continuous variables included in the NSHD analyses.

Continuous variables	Range	Mean (SD)
Childhood cognition at age 8	23-83	53 (9)
CRI	68-152	103 (15)
NART at age 53	1-50	35 (9)
Systolic blood pressure age 53	80-210	135 (19)
Body mass index at age 53	19-49	27 (4)
ACE-III at age 69	53-100	92 (6)

CRI: Cognitive reserve index; NART: National Adult Reading Test; ACE-III: Addenbrooke's Cognitive Examination III.

4.3.2 Research question 1

To assess the independent influence of each exposure on cognitive function, separate models were carried out for childhood cognition, CRI, NART and APOE. In the fully adjusted model, all determinants showed a significant association with cognitive function during older age, except for the APOE genotype (ß=-0.60, -1.36 to 0.17). Furthermore, after adjusting for all covariates, the highest regression coefficient was that of the NART (ß=0.34, 95% CI 0.30-0.38), followed by childhood cognition (ß=0.29, 95% CI 0.26-0.33), and finally, the lowest coefficient was that of the CRI (ß=0.18, 95% CI 0.16-0.20) (see Appendix B, Tables B2 to B5 for gradual adjustment) (see Table 5).

Table 5 Regression coefficients and 95% confidence intervals for the association between childhood cognition, CRI, NART, and APOE on cognitive function (ACE-III) (N=1,184).

Exposures*	**B (95% CI)**	**p-value**
Childhood cognition	0.29 (0.26 to 0.33)	<0.001
CRI	0.18 (0.16 to 0.20)	<0.001
NART	0.34 (0.30 to 0.38)	<0.001
APOE e4: Yes	[Reference]	
No	-0.60 (-1.36 to 0.17)	0.12

*All exposures were analysed in separate models (i.e., not mutually adjusted).
Models fully adjusted for sex, marital status, blood pressure, body mass index, serious illness/disability, GHQ-28, and cigarette smoking.
ACE-III: Addenbrooke's Cognitive Examination III; CRI: Cognitive Reserve Index; NART: National Adult Reading Test.
All statistically significant associations remained significant after the Benjamini-Hochberg correction.

After the initial explorations, all exposures were mutually adjusted by introducing them into the same model. As presented in Table 6, after adjusting for all covariates, it was found that for every unit increase in childhood cognition, the ACE-III score was predicted to increase by 0.10 points on average. Similarly, for every unit increase in the CRI, scores in the ACE-III increase by 0.07, and for every unit increase in the NART, the score in the ACE-III is

predicted to increase by 0.22 points on average. Additionally, once childhood cognition, CRI and NART were included in the model, the presence of the e4 allele significantly predicted lower scores in the ACE-III (ß=-0.71, 95% CI -1.36 to -0.06) (see Appendix B Table B6 for gradual adjustment).

Table 6 Mutually adjusted regression coefficients and 95% confidence intervals for the association between childhood cognition, CRI, NART, and APOE on cognitive function (ACE-III) (N=1, 184).

Exposures	**B (95% CI)**	**p-value**
Childhood cognition	0.10 (0.05 to 0.16)	<0.001
CRI	0.07 (0.05 to 0.09)	<0.001
NART	0.22 (0.15 to 0.28)	<0.001
APOE e4: No Yes	[Reference] -0.71 (-1.36 to -0.06)	0.03
Interactions		
Childhood cognition*CRI	-0.003 (-0.005 to -0.001)	0.002
Childhood cognition*NART	-0.005 (-0.009 to -0.0007)	0.02
Childhood cognition*APOE	0.03 (-0.05 to 0.11)	0.42

Models fully adjusted for sex, marital status, blood pressure, body mass index, serious illness/disability, GHQ-28, and cigarette smoking.
ACE-III: Addenbrooke's Cognitive Examination III; CRI: Cognitive Reserve Index; NART: National Adult Reading Test.
*All exposures were analysed in separate models (i.e., not mutually adjusted).

The investigation of the individual cognitive tests taken at age 8 showed that all four components – Reading Comprehension, Word Reading, Vocabulary, and Picture Intelligence – significantly contributed to the variance of the ACE-III scores (Appendix B, Tables B7 to B10). The fully adjusted effect size for all cognitive tests ranged from 0.05 to 0.08; the lowest one was for Vocabulary while the highest ones were for Reading Comprehension and Picture Intelligence.

Additional investigation of the association of the individual sub-components of the CRI and cognitive function at age 69 showed that after controlling for all covariates, on average,

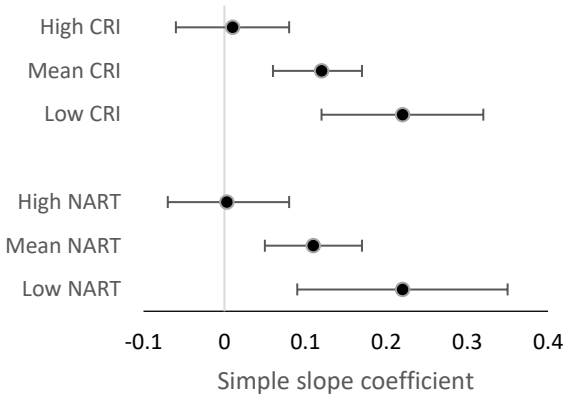
individuals with a degree or higher qualifications scored an additional 1.22 points in the ACE-III in comparison to those with no qualifications. Individuals who engaged in 6 or more leisure activities scored 1.53 additional points in the ACE-III compared to those who engaged in 0 to 4 leisure activities. Finally, individuals with a professional or intermediate occupation scored an additional 1.50 points in the ACE-III in comparison to those with part-skilled or unskilled occupations (see Appendix B, Table B11).

4.3.3 Research question 2

As presented at the bottom of Table 6, significant negative interactions were found between childhood cognition and the CRI, as well as between childhood cognition and the NART, suggesting that the association between childhood cognition on cognitive function in older age is modified by the CRI and by the NART.

Figure 19 presents the simple slopes of childhood cognition at medium (representing the mean) levels of the CRI or NART and above and below two standard deviations of the mean, each representing low and high levels of the CRI or NART. After adjusting for all covariates, it was found that for 30 additional points in the CRI or 20 additional points in the NART, the slope of childhood cognition decreased by approximately 0.10 points. Thus, for individuals with higher CRI or NART scores, the association between childhood cognition and older age cognitive function was weaker. Similarly, stratified regressions showed that, the coefficient of the association between childhood cognition and cognitive function was lower for individuals who scored above the mean in the CRI or NART (CRI: 0.08 versus 0.15; NART: 0.15 versus 0.17) (Table 7).

	B (95% CI)	p-value
CRI		
High*	0.01 (-0.06 to 0.08)	0.77
Medium	0.12 (0.06 to 0.17)	<0.001
Low*	0.22 (0.12 to 0.32)	<0.001
NART		
High*	0.003 (-0.07 to 0.08)	0.94
Medium	0.11 (0.05 to 0.17)	<0.001
Low*	0.22 (0.09 to 0.35)	0.001



CRI: Cognitive Reserve Index; NART: National Adult Reading Test.
*Low and high scores are defined as approximately two standard deviations below and above the mean of the CRI (mean= 103, SD=15) and the NART (mean= 35, SD=10).

Figure 19 Simple slopes of childhood cognition on cognitive function at age 69 years at high, medium, and low scores of the CRI and NART (N=1,184).

Table 7 Stratified regression coefficients and 95% confidence intervals for the association between childhood cognition on cognitive function (ACE-III), at scores above or below the mean of the CRI and NART (N=1,184).

	Stratified cognitive reserve measure			
	CRI <103 N=627		**CRI ≥103** N=557	
	B (95% CI)	p-value	B (95% CI)	p-value
Childhood cognition	0.15 (0.09 to 0.22)	<0.001	0.08 (-0.02 to 0.17)	0.12
NART	0.24 (0.18 to 0.30)	<0.001	0.20 (0.06 to 0.34)	0.006
APOE e4:No Yes	1[Reference] -0.29 (-1.27 to 0.69)	0.56	1[Reference] -1.10 (-1.97 to -0.23)	0.01
	NART <35 N=469		**NART ≥35** N=715	
	B (95% CI)	p-value	B (95% CI)	p-value
Childhood cognition	0.17 (0.07 to 0.26)	0.001	0.15 (0.09 to 0.20)	<0.001
CRI	0.12 (0.07 to 0.17)	<0.001	0.08 (0.06 to 0.11)	<0.001
APOE e4: No Yes	1[Reference] -0.42 (-1.65 to 0.80)	0.50	1[Reference] -0.80 (-1.59 to -0.02)	0.04

Models fully adjusted for sex, marital status, blood pressure, body mass index, serious illness/disability, GHQ-28, and cigarette smoking.
CRI: Cognitive Reserve Index; NART: National Adult Reading Test.

Furthermore, the interaction between childhood cognition and APOE was non-significant (see Table 6), suggesting that the APOE genotype does not modify the association between childhood cognition and cognitive function in older age. However, the stratified analysis in Table 7 showed that for individuals who scored above the mean in the CRI or NART, the APOE e4 allele predicted lower scores in the ACE-III.

4.3.4 Sensitivity analyses

All analyses carried out using imputed data (N=1,762) confirmed the findings from the complete case analyses with similar effect sizes (see Appendix B, Tables B12 and B13).

4.4 Discussion

This study investigated the modifying roles of CR measures and APOE genotype on the association between childhood cognition and cognitive function in older age in the British 1946 birth cohort. Both the formative and reflective measures of CR—here indexed using the CRI and NART, respectively—were found to modify the association between childhood cognitive ability and cognitive function. For individuals with lower childhood cognitive ability, increased scores in either measure resulted in better cognitive performance than what would have been predicted by childhood cognition alone. APOE genotype did not modify the association between childhood cognition and cognitive function.

4.4.1 Cognitive reserve

This study corroborates previous findings highlighting the malleable nature of cognitive function throughout the life course (198,485,498). Furthermore, this study adds to the literature by suggesting that, for individuals with higher CR scores, the association between childhood cognitive ability and older age cognitive function was weaker. Hence, this study provides support to the hypothesis that older age cognition is the result of the interaction of

childhood cognitive ability and CR enhancing factors throughout the life course, which accumulate over time and have the potential to modify the rate of cognitive decline (198,399–401,485).

Evidence from the LBC has suggested that the most significant factor influencing cognitive differences in older age is childhood cognitive ability (480). However, a recent systematic review assessing nine studies using data from LBC and NSHD found inconsistent results for the association between childhood cognition and cognitive decline, suggesting that the relationship might be modified by unknown factors (198). The current findings complement the literature by attributing differences between these two stages to mid-life intellectual enrichment measured using the CRI and NART and suggesting that childhood cognition influences late-life cognitive function only for individuals with low CR during adulthood. Supporting this, a meta-analysis of seven studies found evidence suggesting that for every additional year of education, cognitive ability increased by 1 to 5 points (196). Hence, the results contribute to the understanding of the mechanisms through which early and midlife environmental lifestyle factors affect cognitive ageing and support the relevance of a lifelong investment in the accumulation of CR.

4.4.1.1 Cognitive Reserve Index

In this study, the composite index of CR showed a significant association with cognitive function during older age. These findings are in accordance with previous studies investigating the association between composite sociobehavioural markers of CR and cognitive decline or dementia (244,398,425). A recent study carried out with 1,347 participants from the Beijing Aging Brain Rejuvenation Initiative, investigating the long-lasting effects of education, occupation, and leisure engagement on successful and

pathological cognitive ageing, concluded that all three factors were positively associated with better cognitive function (499). Furthermore, consistent with the findings of previous epidemiological studies investigating the role of education and occupation on cognitive function and dementia (215,230,430), as well as previous analysis carried out in this cohort (229), the sub-component analysis of the CRI showed that higher educational attainment and occupation predicted higher scores in the ACE-III. It has been argued that variables such as education and occupation contribute to the continuity and even improvement of cognitive skills, as well as the development of other important skills such as motivation, social integration, self-efficacy, and self-regulation, all of which predict better cognitive ageing (230,241).

Furthermore, the findings for the leisure activity subscale are in accordance with a previous study in this sample which assessed the longitudinal association between leisure activity engagement and cognition at midlife (305) and with two systematic reviews that found that engagement in cognitive, physical, or other leisure activities was associated with lower risk of cognitive decline (285,300). Cognitive decline in older life can have various causes, including genetic predispositions, physical inactivity, and chronic conditions, such as depression and heart disease, each of these associated with different risk and protective factors which might be modified by a wide variety of lifestyle choices (300–302).

4.4.1.2 National Adult Reading Test

When assessed in adulthood, the NART might provide a reliable marker of CR (401,432) representing environmental enrichment beyond sociodemographic estimates such as years of education (433,500) and capturing mature ability (498). As Cattell argued, the development of crystallised ability is the result of engagement in a variety of activities, the

time and energy devoted to the activities, and the individual's motivation, all of which can take an infinite variety (501). Based on this theory, and building on the findings of a previous path analysis carried out with this cohort (229), the NART was included in the models as an independent marker reflecting CR since the CRI, which can be argued to constitute a formative model, may not always entirely reflect the degree of intellectual ability achieved (502). However, after comparing the role of formative versus reflective measures of CR, the findings suggest that both measures independently modify the association between childhood cognition and cognitive function at age 69 with very similar effect sizes.

4.4.2 APOE genotype

The investigation of the association between APOE genotype on cognitive function showed that, consistent with previous investigations, the APOE e4 allele predicts lower late-life cognition scores, albeit with a small effect size (229,503). Possibly due to the small effect of APOE on the ACE-III, this association was only evident when a larger proportion of the variance was accounted for by childhood cognition, CRI, and NART. However, contrary to the second hypothesis of this study, the interaction analysis suggested that APOE e4 does not modify the association between childhood cognition and cognitive function. Previous investigations have suggested that the influence of APOE e4 depends on the level of cognitive impairment of the sample and the cognitive domain tested (113,151,504), with evidence from this cohort and the LBC suggesting that the adverse effects of APOE e4 tend to manifest in later stages in life, potentially starting in early old age (141,152). Therefore, moderation investigations using data from older individuals are needed to clarify these findings. Furthermore, in contrast to previous moderation investigations that have suggested that the association between APOE e4 and cognition is more noticeable in individuals with lower CR (505,506), the stratified analysis in this study indicated that the

APOE e4 allele significantly predicted lower scores in the ACE-III for individuals with higher CR. This finding might be due to a larger range of ACE-III scores for individuals with the e4 allele when compared to those without (53-100 vs. 64-100) in this sample. Alternatively, the finding might suggest an interaction between APOE and CR. Hence, future work could help elucidate this finding.

4.4.3 Strengths and limitations

This study built upon previous findings of life course determinants of cognitive ageing (229,230) to assess and compare the moderating role of two commonly used measures of CR in the association between childhood cognition and cognitive function. All predictors and the outcome were measured with widely accepted scales and reliable measures across the life course. Furthermore, for a birth cohort with such an extended follow-up period (70 years), this study had a relatively large sample size, which is considered to be representative of the UK population (507). However, despite the lack of pronounced ceiling effects found with some cognitive tests, scores in the ACE-III were negatively skewed, limiting the ability of the CRI and NART to predict improvement for those with high childhood cognition. Despite this, the marked increase in cognitive function scores driven by CR for individuals with low childhood cognition was clearly captured.

The assumption and investigation of the independent effects of the CRI and NART might have resulted in an underestimation of the association between CR markers and cognitive function. Thus, after ascertaining their independence, the subsequent analyses in this thesis where both measures are available will not mutually adjust for the CRI and NART. Additionally, some important limitations of this study are related to selective attrition over time. As previously reported (229), the sample of NSHD participants who were interviewed

at age 69 was comprised of the cohort survivors who are more likely to be healthier, to have a better cognitive function, and to be more socially advantaged than those not followed up, posing the risk of survivor and attrition bias which would affect the external validity of the study. The risk of bias due to missing data was partly addressed by the sensitivity analysis which replicated the main analysis results using multiple imputation. Furthermore, replication in an ethnically diverse sample is necessary to confirm the generalisability of the results.

4.4.4 Conclusion

The study findings suggest that the association between childhood cognitive ability and cognitive function in older age is modified by an intellectually enriching lifestyle, indicating that cognitive ability is subject to environmental influences throughout the life course and that CR can offset the negative impact of low childhood cognition. The present study also underlines the role of the CRI and NART as proposed measures of cognitive reserve since both measures independently modify the association between childhood cognition and cognitive function. Finally, from a policy perspective, the results highlight the importance of CR factors for cognitive maintenance and enhancement through adulthood to prevent old-age cognitive decline, particularly for individuals who might not have benefited from an enriching childhood.

Chapter 5. The moderating role of cognitive reserve between brain markers and cognitive function in NSHD Insight 46

5.1 Introduction

As presented in Chapter 2, section 2.2.1 'Dementia biomarkers', neurodegeneration, Aβ deposition, and cerebrovascular disease constitute some of the neuropathologic key features of dementia, particularly Alzheimer's disease and VaD (94). However, the status of the brain does not fully explain the heterogeneity of cognitive trajectories in ageing (95,96). As presented in Chapter 2, section 2.3.5 'Reserve', sociobehavioural variables such as educational attainment, occupation complexity, and engagement in leisure activities are considered to contribute to CR, which increases the adaptability of cognitive and functional brain processes, and thus is theorised to protect against the clinical manifestation of neuropathology (384).

Consistent with CR theory and its current operational definition (see Chapter 2, section 2.3.5 'Reserve'), various studies have found that sociobehavioural variables can act as CR markers and modify the association between brain markers (e.g., Aβ deposition, neurofibrillary tangles, grey matter volume, hippocampal volume and WMH) and cognitive function (508–513). For instance, a recent study carried out with 351 participants found that education modified the association between Aβ deposition and cognition, whereby individuals with higher education showed a shallower slope in decline in cognition compared to those with lower education (481).

Related to CR theory, BR theory argues that genetic and environmental factors, such as access to good nutrition, health, and education, contribute to the development of the brain's structural integrity proving reserve and promoting maintenance and resilience

against brain pathology, particularly cerebrovascular lesions (379,384,514). Furthermore, it has been argued that sociobehavioural variables such as education or physical activity might not necessarily modify the association between neuropathology and cognition, but contribute to BR by providing protection against the accumulation of pathology or enabling the absorption of age-related brain changes such as cerebrovascular injury, playing a more causal role in dementia and representing a significant risk factor for cerebrovascular disease as well as poorer cognitive functioning (222,304,365,401). A recent systematic review and meta-analysis of 18 studies found support for this idea, suggesting that cognitive and social leisure activities are associated with white matter volume and lesions, as well as regional grey matter volume (391). Hence, sociobehavioural factors might contribute to cognitive function through two resilience mechanisms: CR and BR, by preventing or minimising brain pathology itself. The complex role of sociobehavioural variables as determinants of cognitive ability is captured by Richards and Deary's life course model of CR (401), which proposes two separate pathways for the association between sociobehavioural variables and cognitive function: one path associated with the brain markers directly, and one indirect path through their contribution to CR (see Chapter 2, section 2.3.5 'Reserve').

There is a growing body of epidemiological evidence on protective factors for dementia, yet the mechanisms that underpin these associations remain poorly understood. As presented above, it is still debated whether the sociobehavioural variables related to the risk of dementia are associated with BR or whether they contribute to CR, modifying the association between the brain markers and cognitive function (515). Furthermore, although previous studies have found consistent evidence for the association between CR markers, such as education and crystallised cognitive ability, and cognition (430), there are few studies providing empirical evidence for their effects within models accounting for brain

markers (211), and ever fewer CR studies accounting for childhood cognitive ability. These studies are important because they help address the contribution of early reserve markers, such as childhood cognition, with later life brain and cognitive health (see section 2.3.1 'Childhood cognitive ability').

5.1.1 Objective

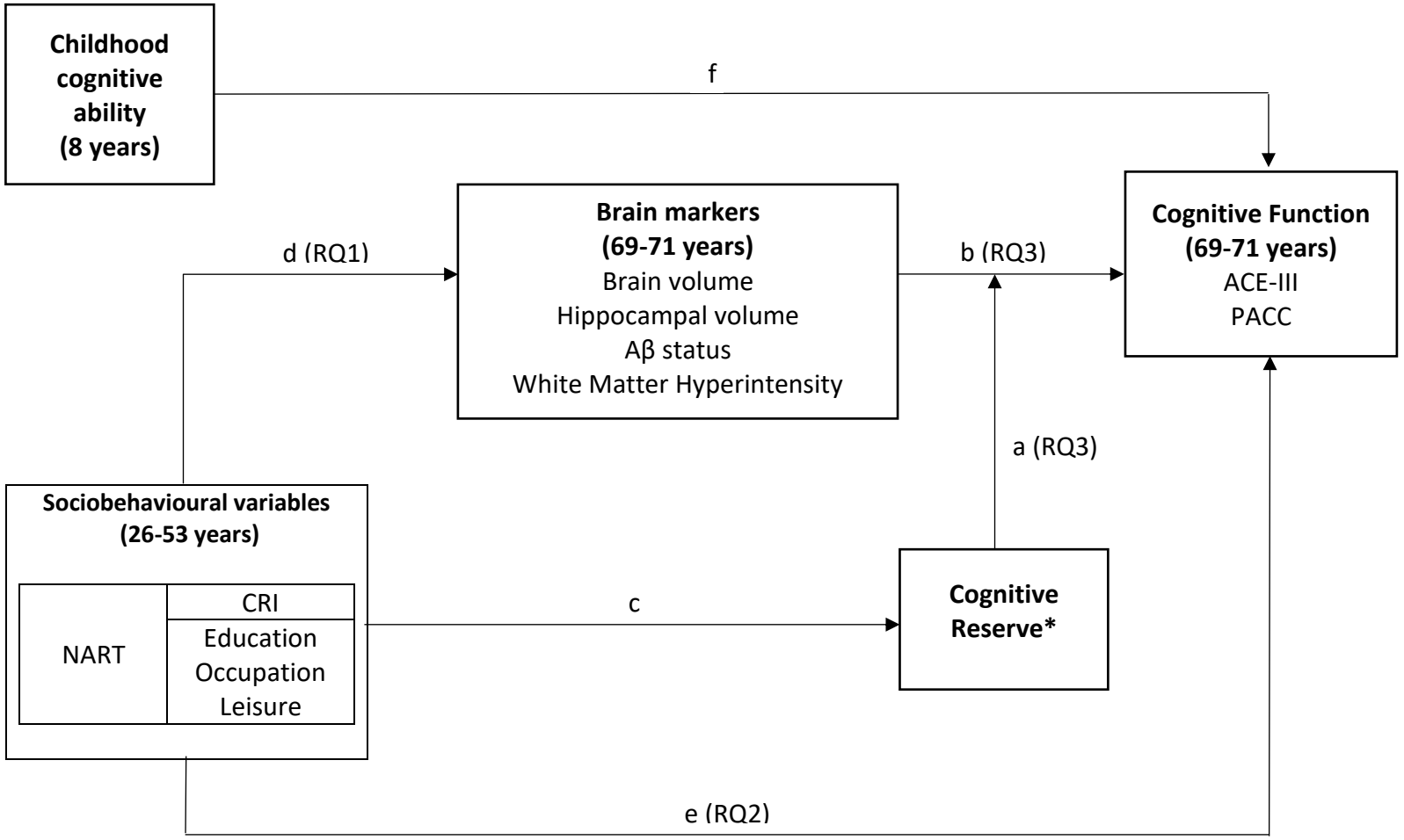
The objective of this study is to describe and understand the conditional nature of the pathways by which life course sociobehavioural variables are associated with cross-sectional brain markers and cognitive function during older age in the Insight 46 sub-study of the NSHD (see Figure 20). The study is informed by Richards and Deary's life course model of CR (401) and builds on the previous work presented in Chapter 6, where it was found the CRI and NART independently modify the association between childhood cognitive ability and cognitive function at age 69, and thus appear to be appropriate markers of CR.

5.1.2 Research questions

1) Is there an association between the CRI or NART and the brain markers (Figure 20, path d)?
2) Do the CRI or NART predict cognitive function (Figure 20, path e)? And are these associations independent of the brain markers?
    a. How does the association between the CRI and cognitive function compare between the NSHD sample and the Insight 46 sub-sample?
3) As CR markers, do the CRI and NART modify the association between the brain markers and cognitive function (Figure 20, paths a and b)?

5.1.3 Hypotheses

1) The CRI and NART will be associated with the brain markers, particularly with vascular brain disease (i.e., WMH).
2) Consistent with the CR hypothesis, higher scores of the CRI or NART will predict higher cognitive function scores, independent of adjustment for the brain markers.
3) The CRI and NART will modify the association between brain markers and cognitive function.



*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 20 Conceptual diagram of proposed pathways for the association between sociobehavioural variables, cognitive reserve, brain markers, and cognitive function

Adapted from Richards and Deary, 2005

5.2 Methods

5.2.1 Study Population

The data was extracted from the MRC NSHD, also known as the British 1946 birth cohort (see Chapter 4 for information on the NSHD sample). At age 69-71, a sub-sample of 502 participants underwent the first neuroimaging examination as part of the Insight 46 sub-study, which included Aβ PET and MRI imaging, as well as detailed clinical and cognitive phenotyping and blood samples (490). Additional information on the criteria for Insight 46 eligibility from the NSHD sample active at 69 years can be found elsewhere (516). Eligibility criteria and an overview of recruitment for Insight 46 are outlined in the study protocol (517).

Due to the reduced sample size (i.e., data from sub-study sample), the analyses were carried out using imputed data (see section 5.2.3 'Statistical Analysis' and Appendix C for additional information). The sample size of each research question varied depending on the availability of the outcome measure. See Figure 21 for participant flowchart.

Ethical approval for Insight 46 sub-study was granted by the National Research Ethics Service Committee London (14/LO/1173).

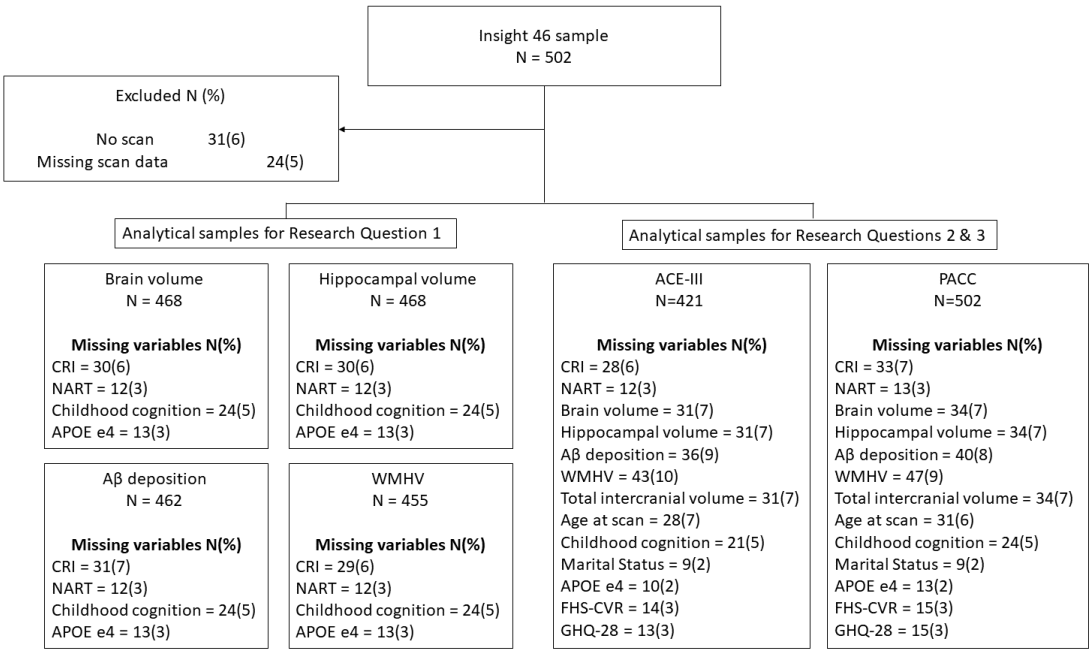


Figure 21 Insight 46 sub-study analytical sample flowchart.

5.2.2 Measures

5.2.2.1 Sociobehavioural variables of CR

As presented in Figure 20, for this analysis, the CRI and NART were used as the sociobehavioural variables predicting BR and cognitive function and as markers of CR, moderating the association between the brain markers and cognitive function. A detailed description of how these measures were collected in NSHD can be found in Chapter 4, section 4.2.2 'Measures'.

5.2.2.2 Brain markers

Imaging was performed at age 69-71 on a single Siemens Biograph mMR 3T PET-MRI scanner (Siemens Healthcare, Erlangen), with simultaneous acquisition of dynamic PET data from 0 to 60 minutes post-injection of 370 MBq ^{18}F-florbetapir (Amyvid) and numerous magnetic resonance sequences including volumetric (1.1mm isotropic) T1 and fluid-

attenuated-inversion-recovery (FLAIR). The full imaging protocol and validation steps have been described previously (517).

Brain and hippocampal volume. Brain volume is considered a gross measure of brain health since smaller brain volumes could indicate neurodegeneration and loss of the number of connections between brain cells, and thus it represents a measure of normal and pathological ageing (518,519). Similarly, hippocampal volume is commonly used in ageing studies, particularly those investigating AD, since smaller volumes have been associated with AD and MCI, as well as with the presence of Aβ and tau deposition (520). Therefore, both total brain and mean hippocampal volume (hereafter referred to simply as brain volume and hippocampal volume) were included as brain markers. Volumetric T1-weighted and FLAIR images underwent visual quality control, before processing using automated pipelines (517): whole-brain segmentation using Multi-Atlas Propagation and Segmentation(521) and hippocampal volume using Similarity and Truth Estimation for Propagated Segmentations (522) with appropriate manual editing.

Aβ status. Aβ deposition was included as a brain marker since it constitutes one of the key biomarkers of AD. The presence and extension of Aβ deposition indicate the severity of the disease (97). In Insight, 46 Aβ deposition was assessed over a 10-minute period, around 50 minutes after injection. Global standardised uptake value ratios were calculated from cortical ROIs, normalised to eroded subcortical white matter. Aβ status (+/-) was determined by taking the 99th percentile of the lower (Aβ-) Gaussian as the cut-point (0.6104), whereby Aβ+ indicates a greater Aβ load.

White matter hyperintensity volume (WMHV). WMHV were included in this study as a brain marker since they are thought to reflect small-vessel cerebrovascular disease. The

most prominent predictors of WMHV severity are age, hypertension, high cholesterol, high blood pressure, atherosclerosis, and heart disease (523–525). Furthermore, increased WMHV have been associated with poorer cognitive performance, representing an important brain marker that is linked to cognitive function in older age (514,523). A validated, unsupervised, automated algorithm, Bayesian Model Selection (526), was used to segment WMH jointly from 3D T1 and FLAIR images, followed by visual quality control, generating a global WMHV including subcortical grey matter but excluding infratentorial regions.

5.2.2.3 Cognitive function

The Addenbrooke's Cognitive Examination III. The ACE-III was administered during the nurse home visits when participants were 69 years old. Additional information on this measure is available in Chapter 4, section 4.2.2 'Measures'.

The Preclinical Alzheimer Cognitive Composite (PACC). For the Insight 46 sample, an adapted version of the PACC was administered at the time of brain imaging when participants were 69 to 71 years old, and therefore it was available for all the participants from the sub-study. The PACC was developed to detect subtle cognitive decline present during the preclinical phase of the disease (527). The PACC is composed of 4 cognitive tests: the Mini-Mental State Examination(MMSE), Logical Memory IIa from the Wechsler Memory Scale-Revised, Digit-Symbol Substitution test from the Wechsler Adult Intelligence Scale-Revised, and the 12-item Face-Name test. The four components were converted into z scores based on the full Insight 46 sample, and then averaged. A higher PACC score indicates better performance. Further description of the calculation of the PACC scores can be found elsewhere (528).

5.2.2.4 Model adjustment

For research question 1, sex, age (at scan), and childhood cognitive ability were included as confounders since they have been associated with the sociobehavioural variables and the brain markers (229,529). Additionally, genetic risk was included as a covariate since it has been associated with brain markers (530). For genetic risk, the APOE was categorised as no e4 (absent) versus heterozygous e4 or homozygous e4 (present) (229) (see Chapter 4, section 4.2.2 "Measures" for description of APOE e4 derivation in NSHD sample). To adjust for the correlation between the brain markers and head size, the models were all adjusted for total intracranial volume (TIV), as calculated using Statistical Parametric Mapping 12 (531), except for the models including Aβ status since its derivation accounts for intracranial volume. Furthermore, as presented in Chapter 2, section 2.3 'Life course determinants of cognitive ageing and dementia', education and occupation have been associated with health outcomes and psychological well-being, which in turn have been associated with brain health (532–534). Therefore, cardiovascular, and psychological health might mediate the association between the CR markers and older age brain markers; thus, these variables were not included in the models for research question 1 since they are likely to lie in the causal pathway.

Sex, childhood cognition, and psychological distress have been associated with educational attainment, occupation, leisure engagement, and cognitive function; therefore, they were included as potential confounders in all models for research question 2 (177,229,535–539). In NSHD, childhood cognition was measured at age 8 and symptoms of psychological distress were measured at age 53 using scores in the GHQ-28. Furthermore, various epidemiological studies have found that the prevalence of cognitive impairment and all-type dementia is lower in married individuals compared to those who are divorced, separated or

widowed (540,541), and some studies have found that compared to single people, married individuals tend to engage in more healthy lifestyles (542). Hence marital status at age 53 was controlled for in all models. Cardiovascular health was measured using the Framingham Heart Study-cardiovascular risk scores (FRS). The FRS provides a sex-specific weighted sum of age, systolic blood pressure, antihypertensive medication usage, history of diabetes, current smoking, and body mass index. For this analysis, the FRS was measured at age 53 since mid- rather than late-life vascular factors are considered major contributors to late-life cognition (130,532,543–545). For genetic risk, the E4 allele of the APOE gene is the best-known genetic risk factor for AD (142); hence APOE e4 status was included.

5.2.3 Statistical Analysis

As presented in section 5.2.1 'Study Population', the data for this analysis came from Insight 46, a sub-sample of the NSHD cohort. Thus, to maximise the sample size, the analyses were carried out using imputed data. For research question 1, the proportion of missing data in the analytical sample ranged from 3% to 7% (see Figure 21). Missing data on predictors and covariates were estimated using multiple imputations by chained equations. Participants were included in research questions 2 and 3 if they had data for at least one of the cognitive function measures; therefore, analyses were carried out with different sample sizes. The proportion of missing data in the analytical sample ranged from 2% to 10% (see Figure 21). Due to the presence of interactions in the models for research question 3, missing data on predictors and covariates were estimated by substantive-model compatible full conditional specification (546). See Appendix C, section C.2 for additional information on the imputation procedure.

For research question 1, separate analyses were performed to investigate associations between the sociobehavioural variables in midlife and each brain marker at age 69-71 (Figure 22). Multiple regression analyses were carried out to test the associations with brain and hippocampal volumes. Logistic regressions were carried out to investigate associations with Aβ status. Due to the non-normal distribution of WMHV, generalized linear models using gamma distribution and log link were used to examine associations with WMHV (532). Additionally, all models gradually adjusted for (Model 1) total intracranial volume, age at scan, sex, (Model 2) childhood cognitive ability, and (Model 3) genetic risk.

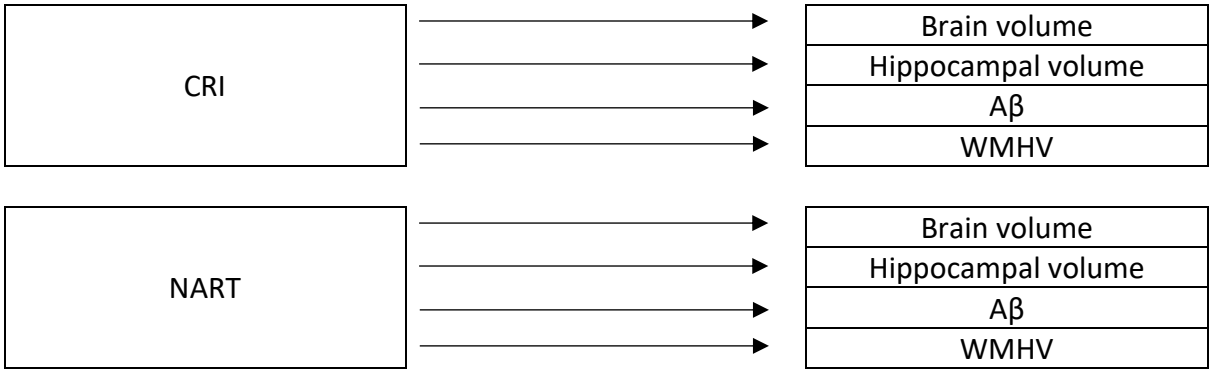


Figure 22 Individual regression models for sociobehavioural variables and brain markers.

For research question 2, the association between CR markers and cognitive function, using the ACE-III as an outcome, was replicated as per the analysis carried out using the NSHD sample in Chapter 4. This association was then tested using the Insight 46 sample, including the ACE-III or PACC as an outcomes and accounting for the different brain markers (Figure 23). The main effects were investigated by progressively adjusting for (Model 1) total intracranial volume (except for Aβ status), age at scan, sex, marital status, and genetic risk, (Model2) childhood cognitive ability, (Model 3) cardiovascular risk factors, and (Model 4) psychological distress.

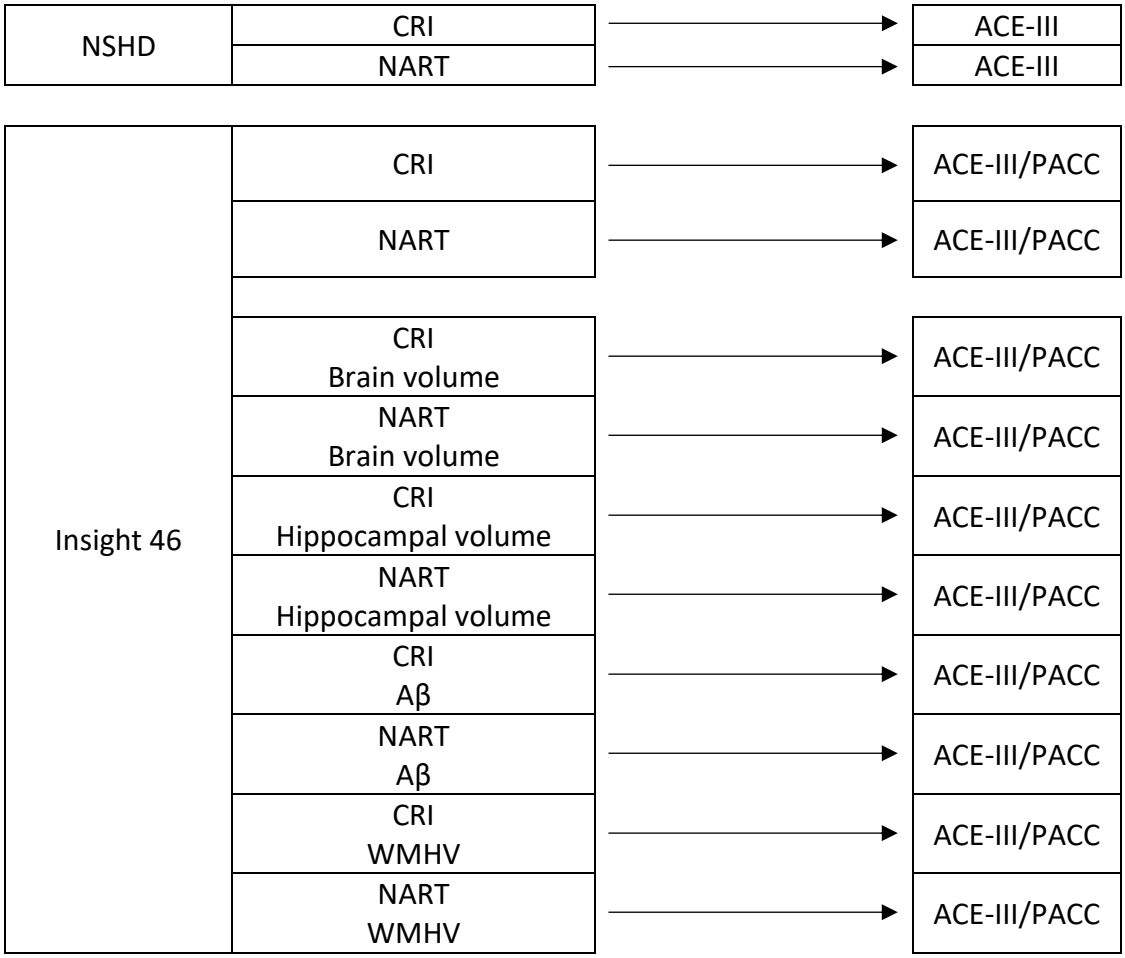


Figure 23 Individual regression models for CRI and NART, unadjusted and adjusted for brain markers, on different cognitive function tests.

For research question 3, the moderating role of the CRI on the association between brain markers and cognitive function was tested (Figure 24). Interactions between the CR measures and the brain markers were assessed, and marginal effect models were carried out to explore the significant interactions. For illustrative purposes and to simplify the comparisons between findings, the scores of the CRI and NART, the continuous brain markers, and the scores of the ACE-III were standardised to calculate the simple slopes of the association between the brain markers and cognitive function at low (two standard

deviations below the mean), medium (at the mean), and high (two standard deviations above the mean) values of CR.

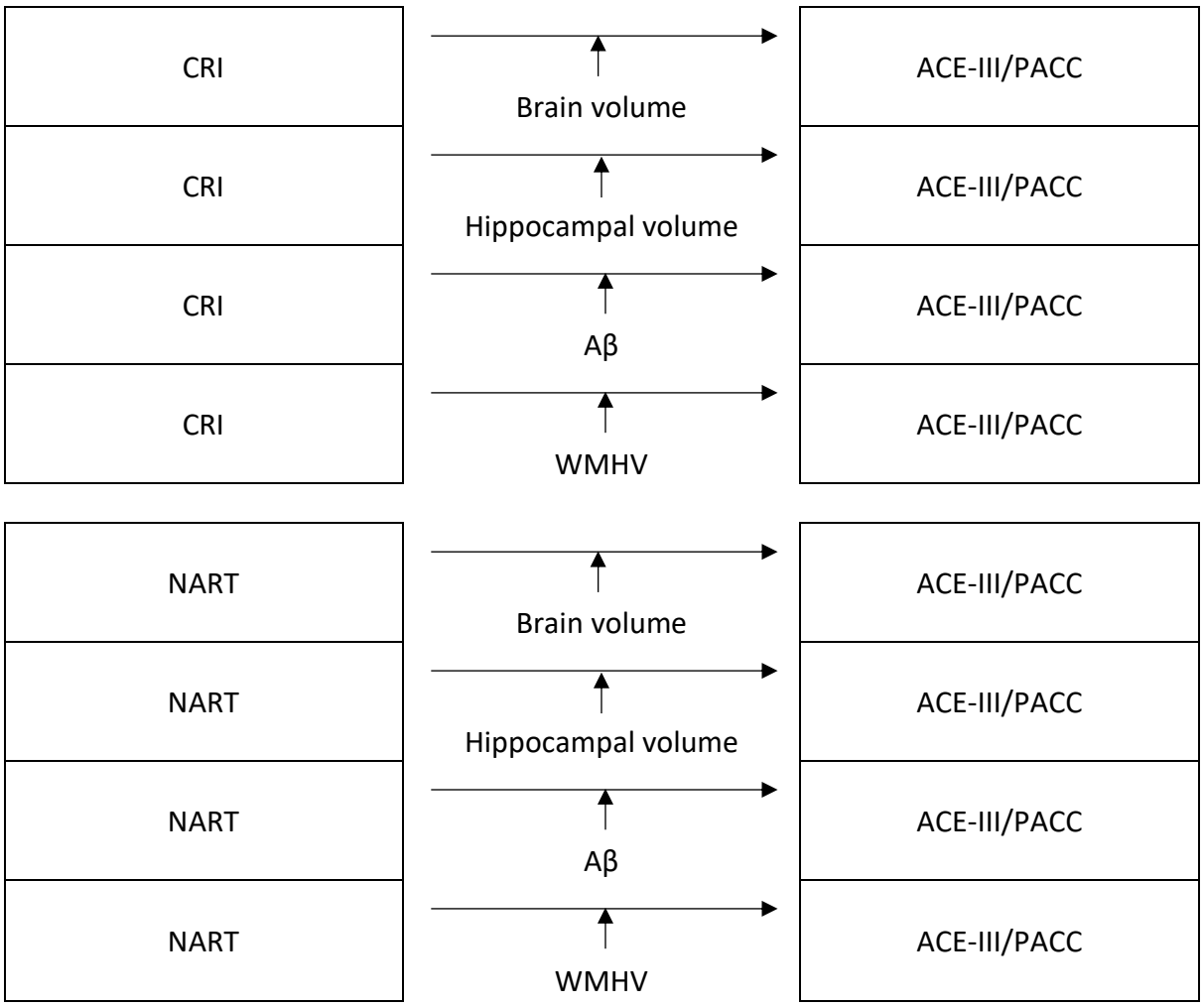


Figure 24 Individual moderation models for brain markers in the association for between the CRI or NART and cognitive function.

Additional analyses were carried out to assess the findings of the main analysis using the individual CRI components: education, occupation, and leisure. For the analysis of the components, education and occupation were re-categorised to ensure all levels of the variable were appropriately powered. The details on this re-categorisation are available in Chapter 4, section 4.2.3 'Statistical analysis'.

Information on the linear model assumptions and the steps taken to control for any deviations are available in Appendix C, section C.1. To control for false discovery rate due to multiple comparisons, the Benjamini-Hochberg correction (497) with a q-value of 0.05 was used for all the regression models. All analyses were conducted using Stata MP, Version 16 (Stata Corp).

5.3 Results

5.3.1 Descriptive statistics

Participant characteristics of the NSHD analytical sample (Chapter 4) and the Insight 46 analytical sub-sample are presented in Tables 8 and 9. For the Insight 46 sub-sample, the distribution of females and males was even; most were married, and the age at the first wave of neuroimaging ranged between 69 to 71. Furthermore, as previously reported (516), when compared with the NSHD analytical sample, the Insight 46 participants appeared to have higher qualifications, hold more complex occupations, and engage in more leisure activities.

Since the CRI is a standardised score which is transposed to a scale with a mean of 100 and a standard deviation of 15, the mean for the NSHD sample and the Insight 46 sample was the same for both. However, the range of values for the NSHD sample was 68 to 152, whereas, for the Insight 46 sample, the CRI scores were slightly higher ranging from 78 to 152. One sample t-test was carried out to compare the NART and cognitive function scores of the NSHD sample and the Insight 46 sub-sample. The NART mean scores in the Insight 46 sub-sample (38) were significantly higher than those in the whole-NSHD sample (36) ($t=7.2$, $p<0.001$). Similarly, the ACE-III mean scores in the Insight 46 sub-sample (93) were significantly higher than those in the whole-NSHD sample (92) ($t=7.4$, $p<0.001$).

Table 8 Frequency distribution of categorical variables included in the NSHD analytical sample and Insight 46 analytical sub-sample.

Categorical variables	Categories	NSHD N (%)	Insight 46 N (%)
Education at age 26	No qualification	329 (28)	78 (16)
	GCE 'O' or equivalent	351 (30)	143 (29)
	GCE 'A' or equivalent	362 (31)	178 (37)
	Degree or equivalent	142 (11)	87 (18)
Leisure activities at age 43	0-4	499 (42)	143 (31)
	5	241 (20)	102 (22)
	6+	444 (38)	224 (47)
Occupation at age 53	Part skilled/unskilled	150 (13)	29 (6)
	Skilled	439 (37)	154 (31)
	Professional	595 (50)	319 (63)
Aβ status at age 69 to 71	Negative	N/A	376 (81)
	Positive		86 (19)
Age at imaging	69	N/A	92 (20)
	70		203 (43)
	71		176 (37)
Sex	Female	621 (52)	246 (49)
	Male	563 (48)	256 (51)
APOE e4	Absent	836 (71)	352 (72)
	Present	348 (29)	137 (28)
Marital status at age 53	Married	956 (81)	413 (84)
	Not married*	228 (19)	80 (16)
GHQ-28 at age 53	0	601 (51)	280 (58)
	1-5	285 (24)	94 (19)
	6+	298 (25)	113 (23)

GHQ-28: General Health Questionnaire.
N/A: Not available.
*Not married: Single, separated, divorced, or widowed.

Table 9 Descriptive characteristics of continuous variables included in NSHD analytical sample and Insight 46 analytical sub-sample.

Continuous variables	**NSHD**			**Insight 46**		
	N	Range	Mean (SD)	N	Range	Mean (SD)
CRI at age 26-53	1,184	68 to 152	103 (15)	469	78 to 152	109 (14)*
NART at age 53	1,184	1 to 50	36 (9)	489	2 to 50	38 (8)*
Brain volume (ml) at age 69 to 71	N/A	-	-	468	819 to 1,494	1100 (100)
WMHV (ml) at age 69 to 71	N/A	-	-	455	0.3 to 34	5 (5)
Hippocampal volume (ml) at age 69 to 71	N/A	-	-	468	2 to 4	3 (0.3)
Total intracranial volume (ml) at age 69 to 71	N/A	-	-	468	1,114 to 1,938	1433 (133)
Childhood cognition at age 8	1,184	23 to 83	53 (9)	478	31 to 83	56 (9)
FRS at age 53	1,184	2 to 61	12 (7)	487	1.5 to 51	11 (7)
ACE-III at age 69	1,184	53 to 100	92 (6)	421	70 to 100	93 (5)*
PACC at age 69-71	N/A	-	-	502	-4 to 2	-0.002 (0.7)

CRI: Cognitive reserve index; NART: National Adult Reading Test; WMHV: White Matter Hyperintensity Volumes; FRS: Framingham cardiovascular risk score; ACE-III: Addenbrooke's Cognitive Examination III; PACC: Preclinical Alzheimer Cognitive Composite.
N/A: Not available.
*$p<0.05$ in one sample t-test comparing NSHD and Insight 46 sample means.

5.3.2 Research question 1

As presented in Table 10, the CRI and NART were generally associated with higher brain and hippocampal volumes, except for the association between the NART and hippocampal volume, where the coefficient was negative. The CRI was weakly associated with lower odds of Aβ positivity, while scores in the NART were not associated with the odds of Aβ positivity. Finally, higher scores in both the CRI and NART were associated with lower WMHV. However, the estimates of these analyses were very small and statistically non-significant (see Appendix C, tables C1 to C8 for gradual adjustment).

Table 10 Estimates and 95% confidence intervals for the associations between CRI or NART on the brain markers.

N	Brain markers	CR marker		p-value
Regression coefficients and 95% confidence intervals				
468	Brain volume	CRI	0.11 (-0.22 to 0.44)	0.50
		NART	0.02 (-0.64 to 0.69)	0.94
468	Hippocampal volume	CRI	0.00 (-0.00 to 0.00)	0.19
		NART	-0.00 (-0.01 to 0.00)	0.06
Odds ratios and 95% confidence intervals				
462	Aβ status	CRI	0.99 (0.97 to 1.01)	0.48
		NART	0.99 (0.96 to 1.04)	0.92
Exponentiated coefficients and 95% confidence intervals				
455	WMHV	CRI	-0.00 (-0.01 to 0.00)	0.28
		NART	-0.00 (-0.02 to 0.01)	0.65

Models adjusted for total intracranial volume, age at scan, sex, childhood cognitive ability, and genetic risk.
CR: Cognitive reserve; CRI: Cognitive reserve index; NART: National Adult Reading Test; WMHV: White matter hyperintensity volumes.
All statistically significant associations remained significant after the Benjamini-Hochberg correction.

Investigation of the CRI sub-components showed that generally, there were no significant associations between education, occupation, or leisure and any of the brain markers. The only exception was the finding that engagement in six or more leisure activities was significantly associated with a larger hippocampal volume (see Appendix C, Table C9).

5.3.3 Research question 2

As presented in Tables 11 and 12, the coefficients of the associations between the CR markers and cognitive function were similar between the NSHD analytical sample and the Insight 46 sub-sample, with those of the NSHD sample being slightly higher. Furthermore, higher scores in the CRI and the NART were significantly associated with higher scores in the ACE-III or PACC, independently of childhood cognitive ability and all brain markers. Across the board, the effect size of the NART was larger than that of the CRI (see Appendix C, Tables C10 to C29, for gradual adjustment).

As previously reported in Chapter 4, childhood cognitive ability was significantly associated with cognitive function. Additionally, it found that the coefficient of the association was larger when the model included the CRI (B=0.16) than when it included the NART (B=0.11). For the associations between the brain markers and cognitive function, larger brain and hippocampal volumes were associated with higher scores of the ACE-III and PACC, whereas higher scores of AB and WMHV were associated with lower scores of cognitive functions. However, only WMHV significantly predicted performance in the ACE-III, whereas all brain markers significantly predicted scores in the PACC (Table 12).

The analysis of the CRI sub-components showed that education, occupation, and leisure engagement were associated with cognitive function, similar to the findings of the NSHD analytical sample. Furthermore, all these associations were still held after adjustment for the different brain markers (see Appendix C, Tables C30 and C31).

Table 11 Regression coefficients and 95% confidence intervals for the association between each CR marker (CRI or NART) and cognitive function (ACE-III) in the NSHD and Insight 46 analytical samples. Individual models unadjusted and adjusted for each brain marker (brain volume, hippocampal volume, Aβ, and WMHV).

Cohort N	Predictors	B (95% CI)	p-value	CR*brain marker Interaction coefficient (p-value)
NSHD 1,184	CRI	0.11 (0.09 to 0.14)	<0.001	-
	NART	0.26 (0.20 to 0.32)	<0.001	
Insight 46 421	CRI	0.10 (0.07 to 0.14)	<0.001	-
	NART	0.20 (0.11 to 0.28)	<0.001	-
	CRI Brain volume	0.10 (0.07 to 0.14) 0.01 (-0.00 to 0.02)	<0.01 0.18	-0.00 (0.01)
	NART Brain volume	0.19 (0.11 to 0.28) 0.01 (-0.00 to 0.02)	<0.001 0.24	-0.00 (0.32)
	CRI Hippocampal volume	0.10 (0.07 to 0.13) 0.57 (-1.04 to 2.18)	<0.001 0.51	-0.19 (0.01)
	NART Hippocampal volume	0.20 (0.11 to 0.29) 1.09 (-0.55 to 2.75)	<0.001 0.19	-0.22 (0.10)
	CRI Aβ status: Negative Positive	0.10 (0.07 to 0.13) [Reference] -0.91 (-2.00 to 0.18)	<0.001 0.10	-0.05 (0.22)
	NART Aβ status: Negative Positive	0.20 (0.11 to 0.28) [Reference] -1.01 (-2.10 to 0.09)	<0.001 0.07	-0.06 (0.52)
	CRI WMHV	0.10 (0.07 to 0.13) -0.08 (-0.15 to -0.01)	<0.001 0.02	0.00 (0.51)
	NART WMHV	0.19 (0.11 to 0.28) -0.08 (-0.15 to -0.01)	<0.001 0.03	0.00 (0.78)

Models adjusted for total intracranial volume (except for Aβ status), age at scan, sex, marital status, APOE genotype, FRS, and GHQ score.
ACE-III: Addenbrooke's Cognitive Examination III; NSHD: National Survey of Health and Development; CRI: Cognitive reserve index; NART: National Adult Reading Test; WMHV: White matter hyperintensity volume.
All statistically significant associations remained significant after the Benjamini-Hochberg correction.

Table 12 Regression coefficients and 95% confidence intervals for the association between each CR marker (CRI or NART) on cognitive function (PACC) in Insight 46 analytical sample. Individual models unadjusted and adjusted for each brain marker (brain volume, hippocampal volume, Aβ, and WMHV).

Predictors	B (95% CI)	p-value	CR*brain marker Interaction coefficient (p-value)
CRI	0.01 (0.01 to 0.02)	<0.001	-
NART	0.03 (0.02 to 0.04)	<0.001	-
CRI Brain volume	0.01 (0.01 to 0.02) 0.00 (0.00 to 0.00)	<0.001 0.02	-0.00 (0.04)
NART Brain volume	0.03 (0.02 to 0.04) 0.00 (0.00 to 0.00)	<0.001 0.01	-0.00(0.18)
CRI Hippocampal volume	0.01 (0.01 to 0.02) 0.20 (-0.04 to 0.44)	<0.001 0.10	-0.02 (<0.001)
NART Hippocampal volume	0.03 (0.02 to 0.04) 0.28 (0.04 to 0.52)	<0.001 0.004	-0.04 (<0.001)
CRI Aβ status: Negative Positive	0.01 (0.01 to 0.02) [Reference] -0.29 (-0.47 to -0.12)	<0.001 0.001	0.00 (0.18)
NART Aβ status: Negative Positive	0.03 (0.02 to 0.04) [Reference] -0.31 (-0.48 to -0.14)	<0.001 <0.001	0.02 (0.03)
CRI WMHV	0.01 (0.01 to 0.02) -0.02 (-0.03 to -0.00)	<0.001 0.008	-0.00 (0.57)
NART WMHV	0.03 (0.02 to 0.04) -0.02 (-0.03 to -0.00)	<0.001 0.005	-0.00 (0.48)

Models adjusted for total intracranial volume (except for Aβ status), age at scan, sex, marital status, APOE genotype, FRS, and GHQ scores.
PACC: Preclinical Alzheimer Cognitive Composite; CRI: Cognitive reserve index; NART: National Adult Reading Test; WMHV: White matter hyperintensity volume.
All statistically significant associations remained significant after Benjamini-Hochberg correction.

5.3.4 Research question 3

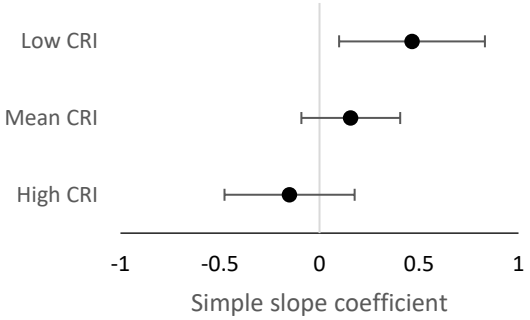
The right side of Tables 11 and 12 shows the coefficients and p-values for the interactions between the CR proxies and the brain markers. Significant negative interactions were found between CRI and brain volume for the ACE-III and PACC, between CRI or NART and hippocampal volume on both outcomes. A significant positive interaction coefficient was found between NART and Aβ status on the PACC.

The interactions are illustrated in Figures 25 and 26. As presented in Figure 25, panels A and C, the association between brain volume and cognitive function was significantly stronger for those with lower scores in the CRI, with the strength of the relationship being attenuated with higher CRI scores. Likewise, as presented in panels B and D, the association between hippocampal volume and cognitive function was stronger for individuals with low CR scores.

Figure 26 illustrates the simple slopes of Aβ positivity on scores of the PACC at different values of the NART. Aβ positivity significantly predicted lower scores in the PACC for individuals with low CR; however, the association weakened as the scores in the CRI increased.

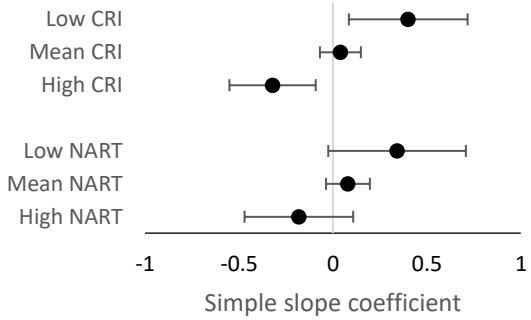
[A] Brain volume on the ACE-III

CRI	B (95% CI)
Low	0.47 (0.10 to 0.83)*
Med.	0.16 (-0.09 to 0.41)
High	-0.15 (-0.48 to 0.18)



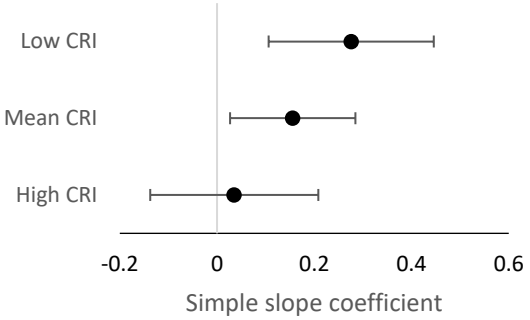
[B] Hippocampal volume on the ACE-III

	B (95% CI)
CRI	
Low	0.40 (0.09 to 0.72)*
Med.	0.04 (-0.07 to 0.15)
High	-0.32 (-0.55 to -0.09)*
NART	
Low	0.34 (-0.03 to 0.71)
Med.	0.08 (-0.04 to 0.20)
High	-0.18 (-0.47 to 0.11)



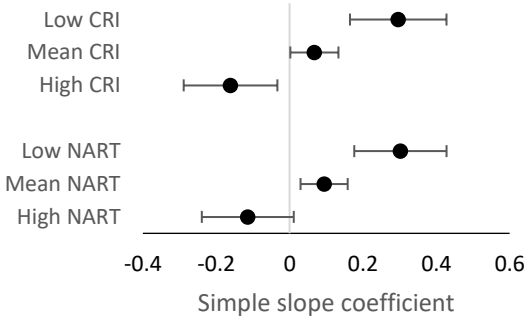
[C] Brain volume on the PACC

CRI	B (95% CI)
Low	0.28 (0.11 to 0.45)*
Med.	0.16 (0.03 to 0.29)*
High	0.04 (-0.14 to 0.21)



[D] Hippocampal volume on the PACC

	B (95% CI)
CRI	
Low	0.30 (0.17 to 0.43)**
Med.	0.07 (0.002 to 0.13)*
High	-0.16 (-0.29 to -0.03)*
NART	
Low	0.30 (0.18 to 0.43)**
Med.	0.09 (0.03 to 0.16)*
High	-0.11 (-0.24 to 0.01)

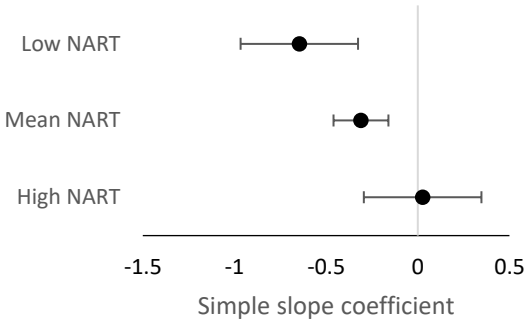


ACE-III: Addenbrooke's Cognitive Examination III; PACC: Preclinical Alzheimer Cognitive Composite; NART: National Adult Reading Test; CRI: Cognitive reserve index; Med: Medium. Low and high scores are defined as two standard deviations below and above the mean.
*p<0.05, **<0.001.

Figure 25 Illustrative plots showing the simple slopes of standardised brain markers on standardised cognitive function at high, medium, and low scores of the standardised cognitive reserve for the associations that showed significant effect modification.

Aβ status on the PACC

NART	B (95% CI)
Low	-0.65 (-0.97 to -0.33)**
Medium	-0.31 (-0.46 to -0.16)**
High	0.03 (-0.29 to -0.33)

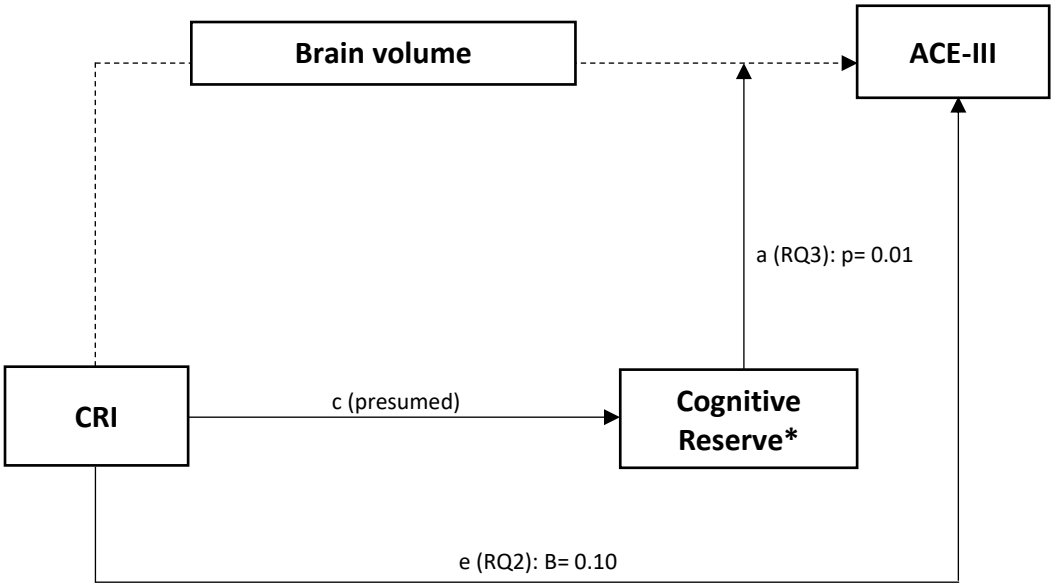


Aβ status: (0 Negative [Reference], 1 Positive].
PACC: Preclinical Alzheimer Cognitive Composite; NART: National Adult Reading Test.
*p<0.05, **<0.001

Figure 26 Plots showing the simple slope of the effect of Aβ status on cognitive function at high, medium, and low scores of cognitive reserve.

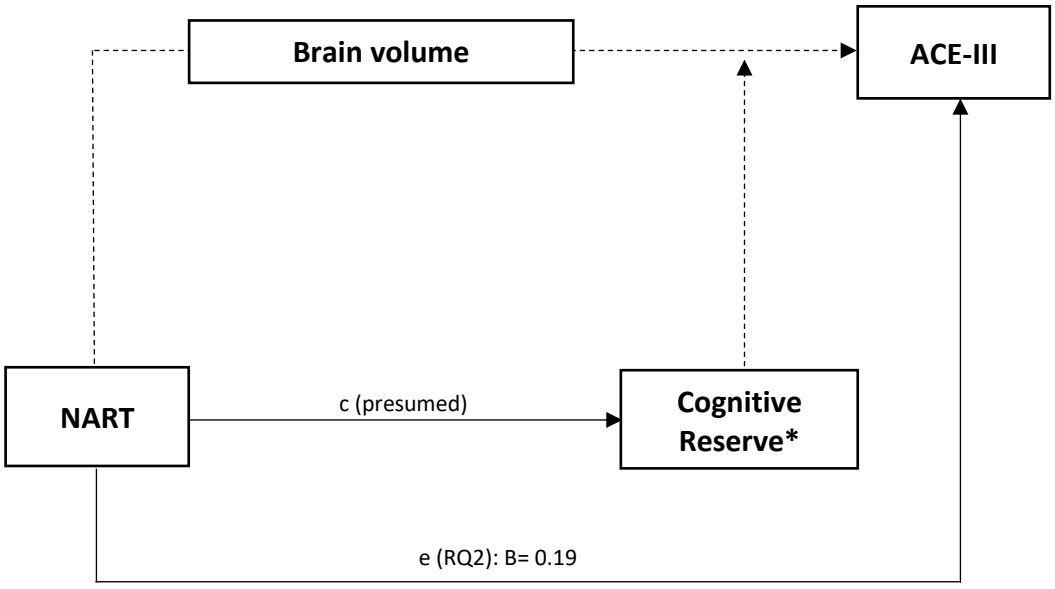
Replication of the moderation found in the main analysis indicated that education and leisure activities interacted with brain volume, while all three subcomponents interacted with hippocampal volume (Appendix C, Tables C30 and C31). The significant interactions are illustrated in Figures C1 through C3 in Appendix C.

Based on the conceptual diagram proposed for this thesis and for this study (Figure 12 and Figure 20), the pathways for the associations between CR and cognitive function for each brain marker are illustrated in Figures 27 and 42.The coefficients for these figures are extracted from Tables 10 to 12. Solid lines show significant associations, whereas dashed lines show non-significant associations.



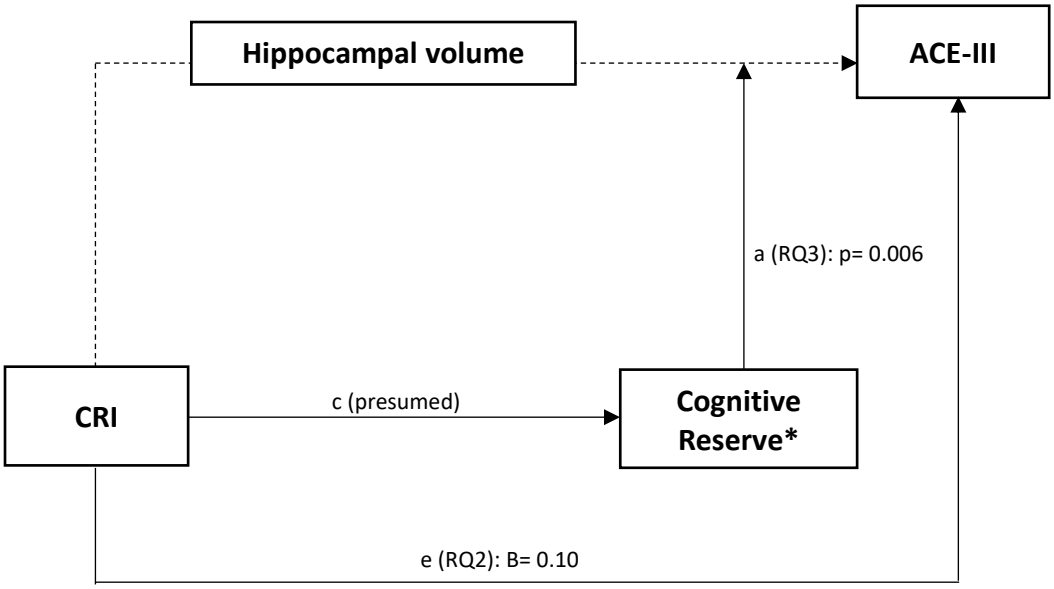
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 27 Pathways for the associations between CRI, brain volume, and ACE-III.



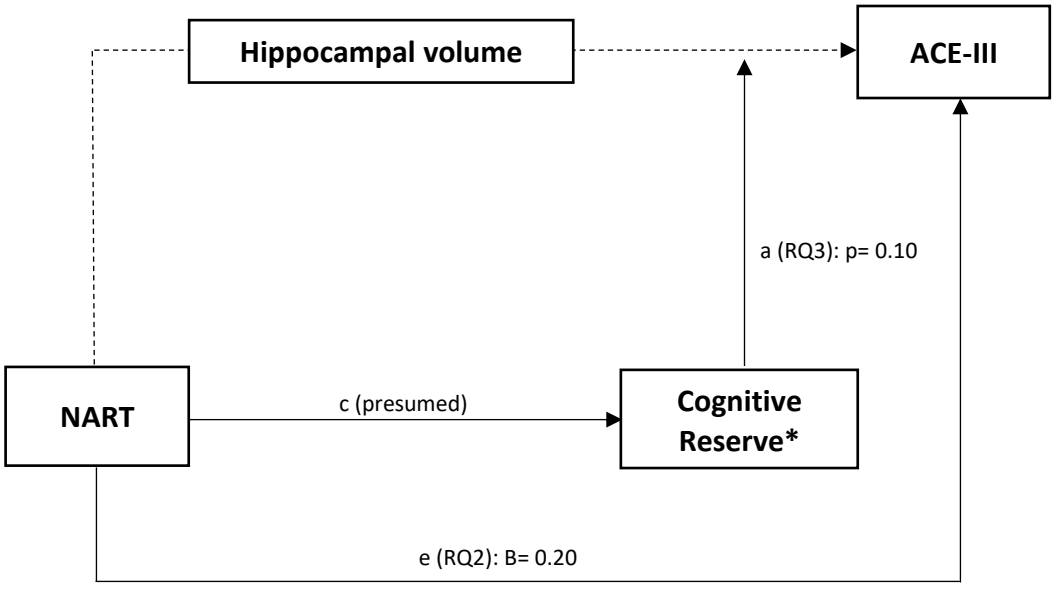
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 28 Pathways for the associations between NART, brain volume, and ACE-III.



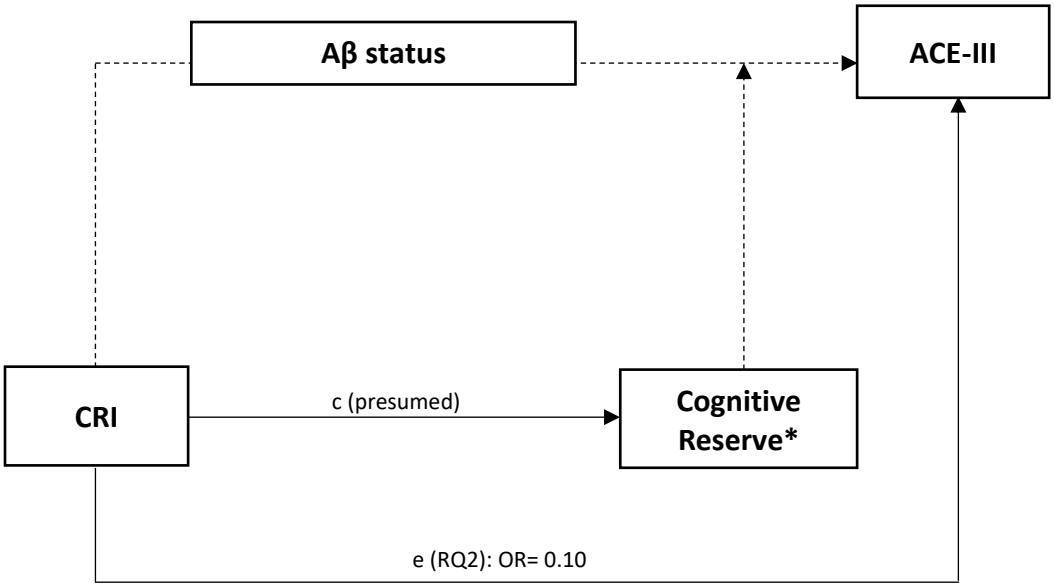
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 29 Pathways for the associations between CRI, brain volume, and ACE-III.



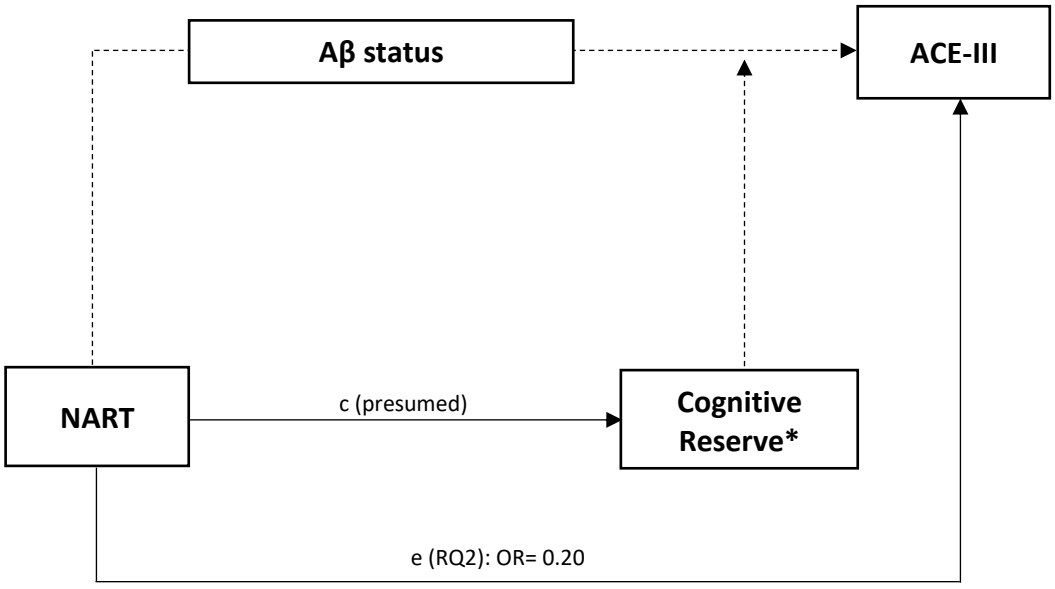
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 30 Pathways for the associations between NART, brain volume, and ACE-III.



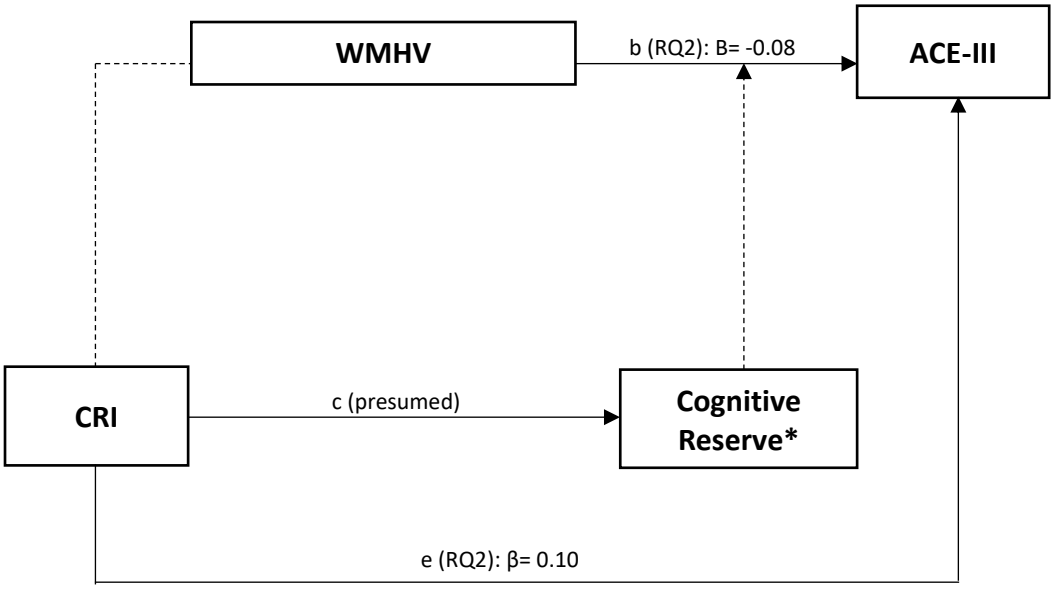
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 31 Pathways for the associations between CRI, brain volume, and ACE-III.



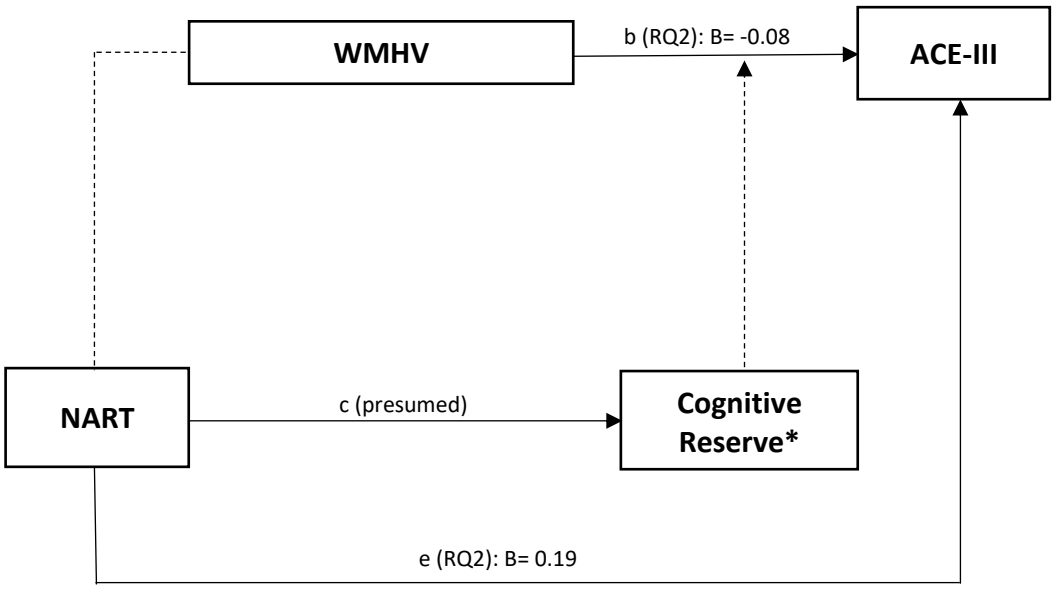
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 32 Pathways for the associations between NART, brain volume, and ACE-III.



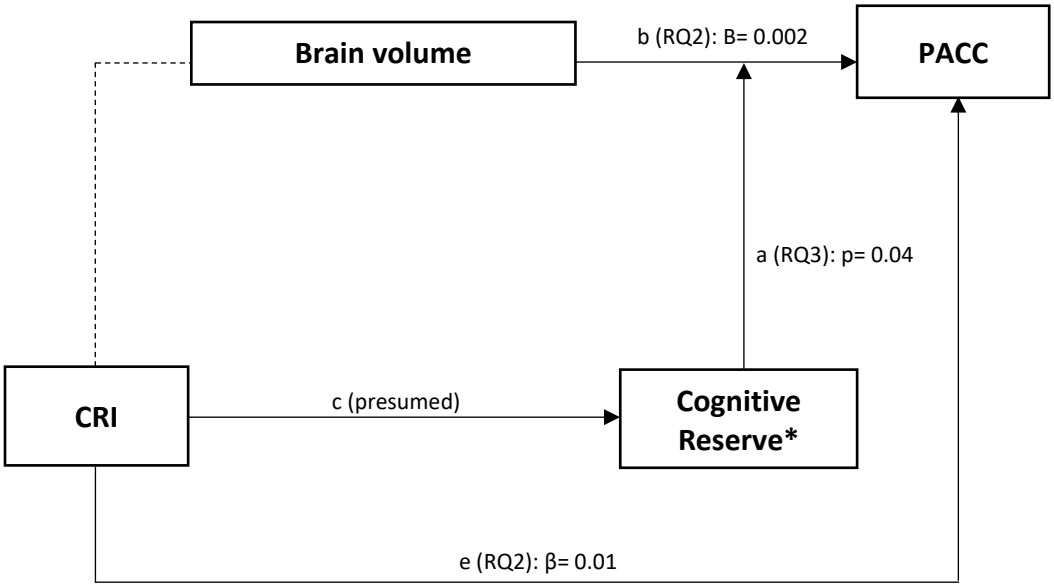
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 33 Pathways for the associations between CRI, brain volume, and ACE-III.



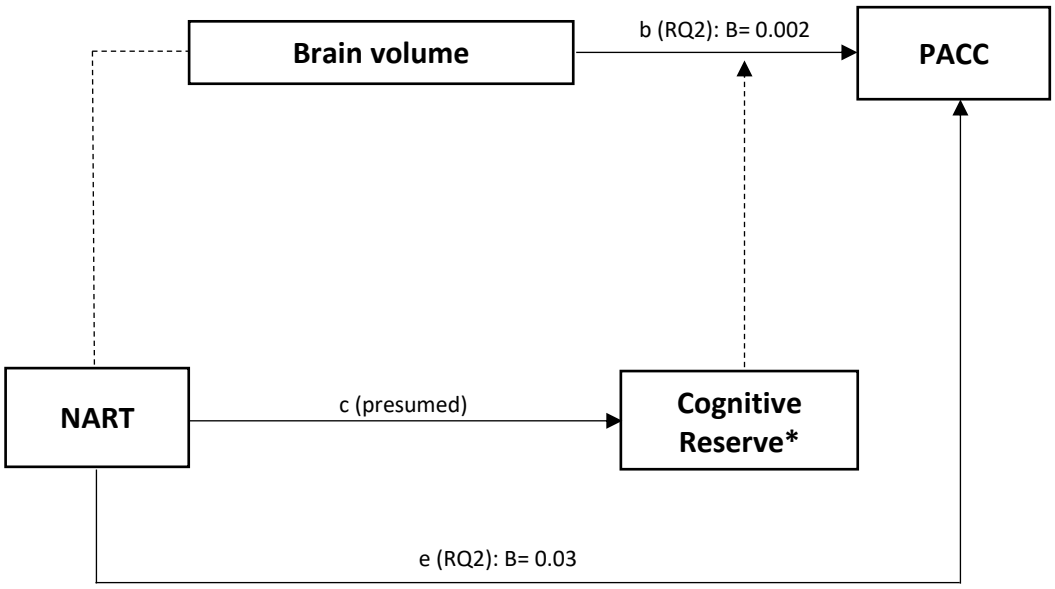
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 34 Pathways for the associations between NART, brain volume, and ACE-III.



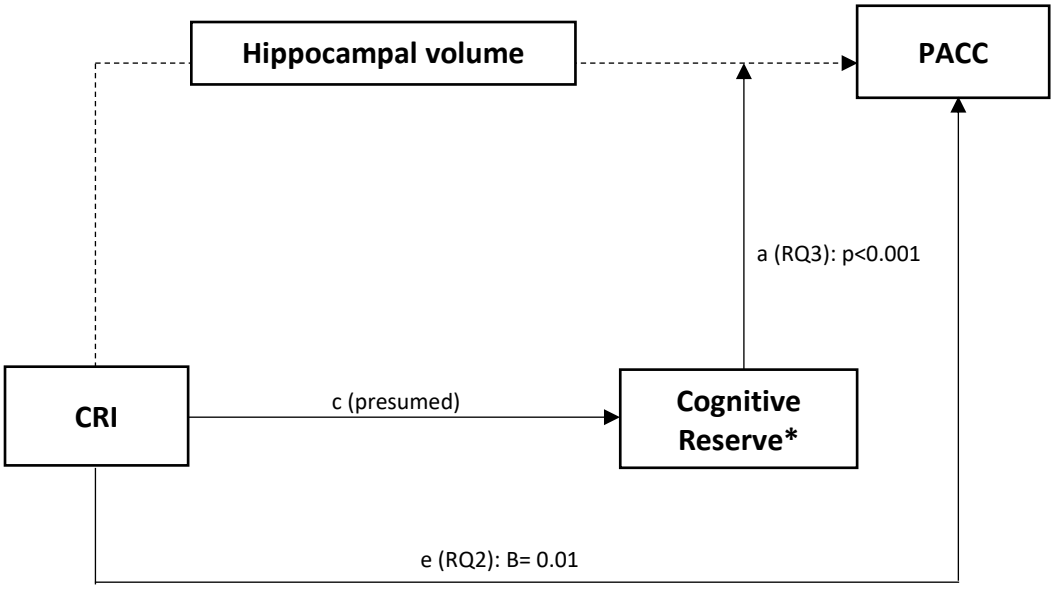
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 35 Pathways for the associations between CRI, brain volume, and PACC.



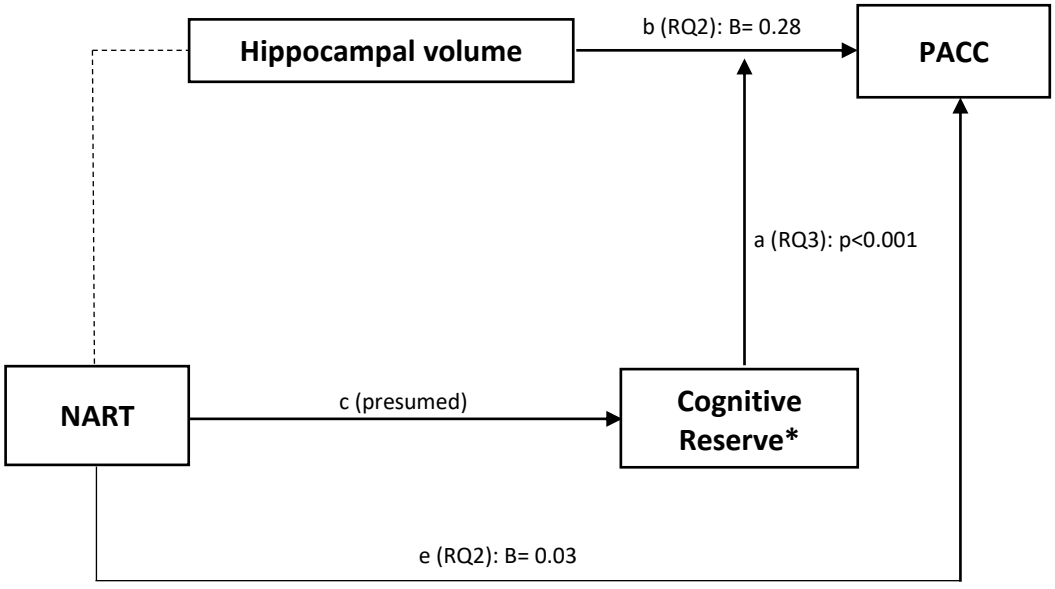
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 36 Pathways for the associations between NART, brain volume, and PACC.



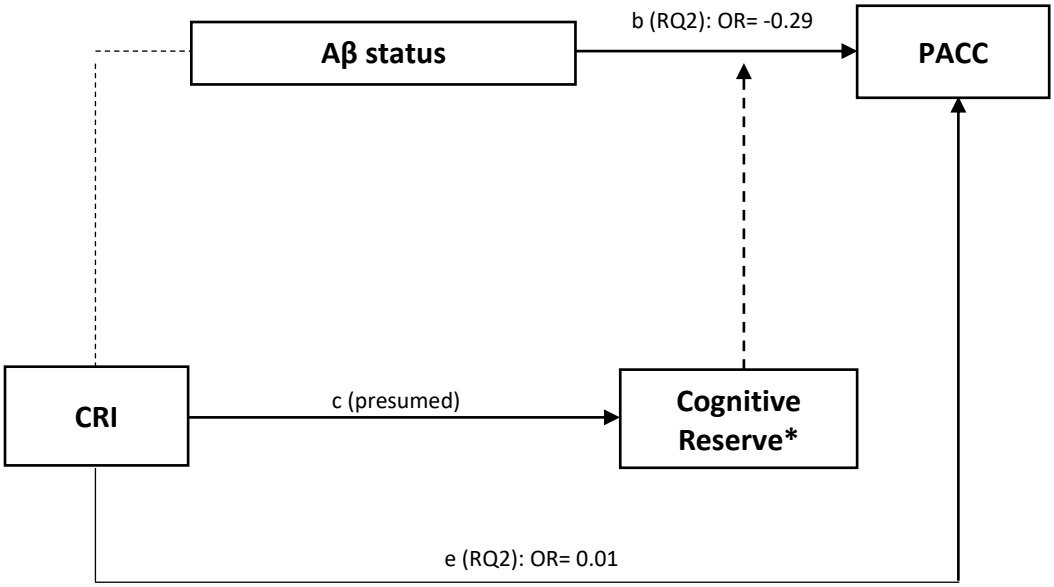
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 37 Pathways for the associations between CRI, brain volume, and PACC.



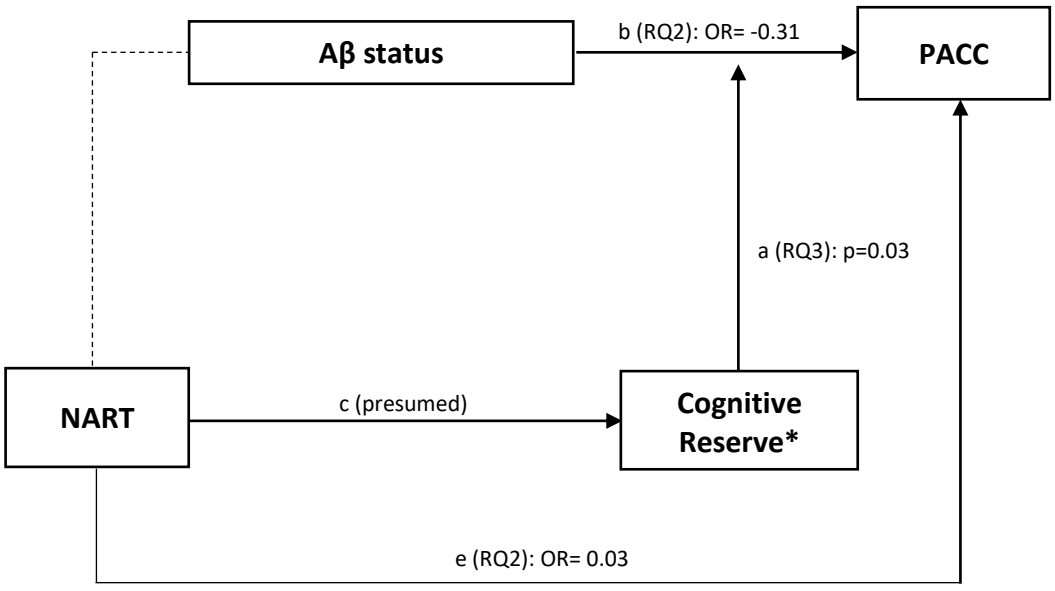
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 38 Pathways for the associations between NART, brain volume, and PACC.



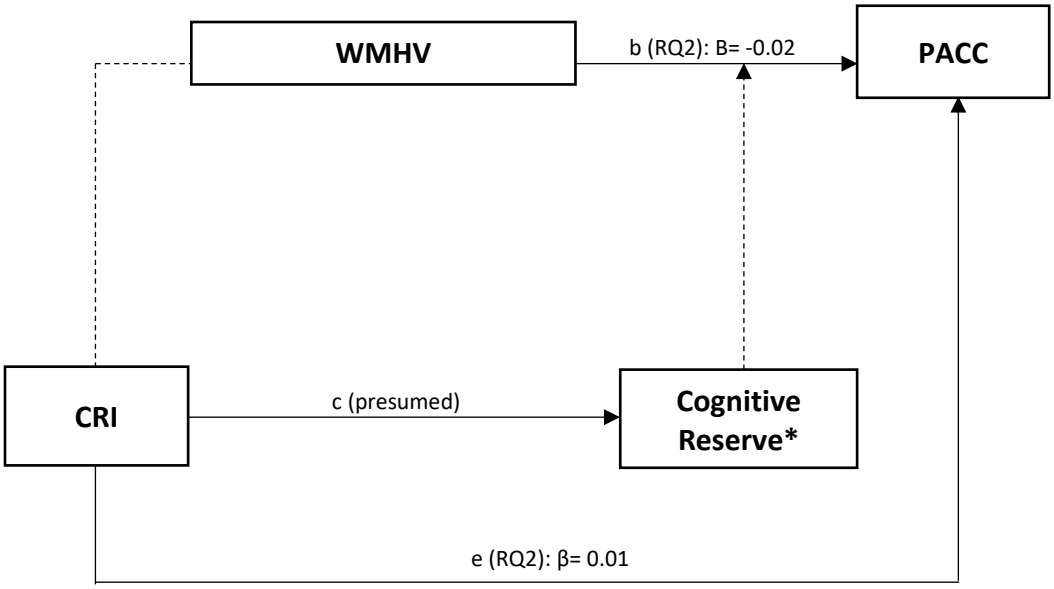
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 39 Pathways for the associations between CRI, brain volume, and PACC.



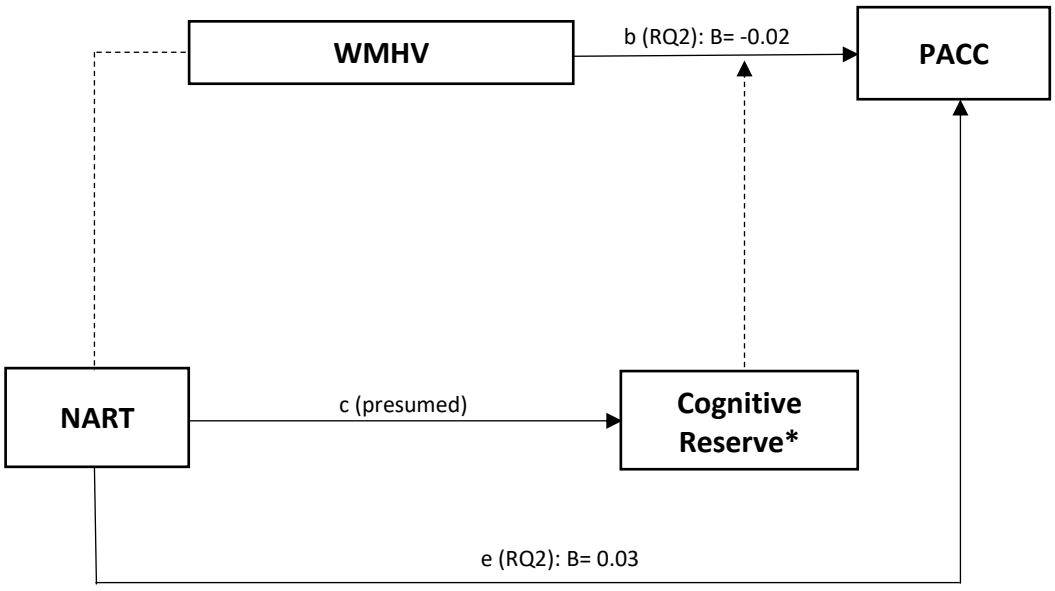
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 40 Pathways for the associations between NART, brain volume, and PACC.



*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 41 Pathways for the associations between CRI, brain volume, and PACC.



*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 42 Pathways for the associations between NART, brain volume, and PACC.

5.4 Discussion

This study investigated the pathways by which sociobehavioural variables are associated with cognitive function during older age using data from Insight 46, the neuroimaging sub-sample of the British 1946 birth cohort. The major findings of this study are: (i) sociobehavioural variables, assessed using the CRI and NART, did not show a statistically significant association with any of the brain markers, suggesting that despite being associated with a better cognitive function, they do not have a significant influence on the brain markers (ii) increased scores of the CRI or NART were associated with higher cognitive function, independently of the brain markers and (iii) moderation analysis suggested that increased scores of CR, measured using the CRI and NART, attenuate the negative effect of brain markers on cognitive function, whereby brain volume, hippocampal volume, and Aβ positivity showed no significant association with cognitive function for individuals with high CR.

5.4.1 Brain reserve

Contrary to the first hypothesis of this study and the findings from previous studies, which have found an association between education, intellectual, and social activities and brain measures (brain structure or Aβ deposition) (391,547–550), the CRI and NART did not predict any of the brain markers. However, these findings are consistent with several studies that have failed to find direct associations between educational attainment, occupational complexity, cognitive and physical activity and brain markers (216,313,510,551–554) and with a large neuroimaging study carried out with 4,422 participants, which found that that education is not associated with brain ageing (555). Therefore, this study provides further evidence for the observation that despite its strong

associations with cognitive function and risk of dementia, experiential and lifestyle factors might not be directly associated with the development of dementia pathology, suggesting that they contribute to the maintenance of function through other mechanisms such as CR (365). Thus, the reduced risk of dementia in highly educated and cognitively active individuals reflects increased CR that provides greater capacity to compensate for disruptions caused by disease pathology, delaying the clinical expression of AD. However, explorations of the CRI subcomponents suggested that engagement in leisure activities was associated with larger hippocampal volume. This finding reflects previous studies that have found higher leisure activity participation to be linked to better brain structure assessed through grey matter volume, prefrontal cortex, hippocampal volume, and white matter lesions (310,391,556,557). A recent study carried out with 431 members of VETSA found that more favourable lifestyles (e.g., social engagement and physical activity) predicted less brain ageing associated with AD and that this association was independent of cognitive ability in early adulthood (396). Similarly, a recent study using data from 368 cognitively healthy older adults from the Swedish National Study of Aging and Care-Kungsholmen found that frequent engagement in social leisure activities was associated with a larger brain volume (304). Hence, this study adds to the literature by providing evidence for an association between engagement in a wide range of intellectual, social, and physical leisure activities and hippocampal volume, thus highlighting these activities as promising avenues for interventions aimed at promoting brain health.

5.4.2 Cognitive reserve

Our findings for the association between the sociobehavioural variables and cognitive function using the Insight 46 sample replicate those from the whole-NSHD sample. These findings suggest that higher scores in the CRI or NART are, again, significantly associated

with higher scores in cognitive function. These findings were also replicated for the analysis using the CRI subcomponents (education, occupation, and leisure). Furthermore, the results showed that these associations are independent of brain volume, hippocampal volume, Aβ status, and WMHV satisfying the independent effect criterion (see Chapter 2, section 2.3.5 'Reserve'), and thus providing further evidence for the role of the CRI and NART as CR proxies (384). These findings are similar to those of a previous study using two neuroimaging datasets, The Irish Longitudinal Study of Ageing (TILDA (n=313) and the Cognitive Reserve/Reference Ability Neural Network Study (CR/RANN) (n=234) (211), which found a positive association for the NART, education, and various composite proxies with cognitive function independent of brain structure (grey matter volume, hippocampal volume, and mean cortical thickness). Consistent with our findings, the study also found that the NART had the largest and most robust effect among all the other CR proxies (211). Hence, taken together, these findings support the argument that, when compared to composite sociobehavioural variables, the NART might better capture life-long learning and intellectual enrichment, particularly for individuals who did not benefit from formal education or an intellectually challenging occupation (209,211,558).

Consistent with the third hypothesis of this study and with previous evidence of significant moderation effects reported for CR proxies in brain-cognition models (482,489,511,559–561), it was found that the CR consistently modified the relationships between brain volume, hippocampal volume, and Aβ status and cognitive function. Both the CRI and NART modified the association between hippocampal volume and function. However, these CR proxies showed different moderating effects on the relationships between brain volume or Aβ status and cognitive function: the CRI significantly interacted with brain volume, while

the NART significantly interacted with Aβ status. Furthermore, contrary to the third hypothesis, neither the CRI nor the NART interacted with WMHV.

The finding that various measures of CR, including scores in the CRI, NART, and the individual sociobehavioural variables: education, occupation, or leisure engagement, modify the association between hippocampal volume and cognition or dementia has been previously reported (213,220,433,512,553,562). Similar to our findings, a recent study using data from TILDA and CR/RANN found that the moderation effects between the NART, education, or various proxy combinations with measures of hippocampal volume were negative, suggesting that individuals with higher CR are less reliant on brain structure to sustain cognitive function (211). However, in contrast to this study, the moderation effects of the Boyle et al. 2021, study did not reach statistical significance; as discussed by the authors, CR moderation effects in the real world are usually small, and therefore, larger sample sizes or more variance in the brain markers are required to detect a significant interaction (211,417). Therefore, the difference in findings could be partly due to the larger statistical power of the present study (38% larger than TILDA and duplicates the sample of CR/RANN).

The moderation effect found for the NART in the association between Aβ positivity and cognitive function is in line with a previous study which found that for higher scores in the NART, increased Aβ deposition was less or not at all associated with neuropsychological performance for cognitively healthy older individuals and for those diagnosed with AD (494). Furthermore, in our study, the significant interaction was only found when cognitive function was measured using the PACC and not the ACE-III. This might be due to the temporality between exposure and outcome when using the ACE-III – the majority of the

participants had their imaging visit two years after completing the cognitive examination, or the PACC's ability to detect subtle variation in performance in cognitively healthy older adults, particularly those with Aβ pathology (563). The elements of the PACC potentially accounting for this sensibility might be the global measure of cognitive state (MMSE) and the Logical Memory IIa from the Wechsler Memory Scale-Revised, which have been individually found to detect subtle cognitive differences associated with Aβ deposition (528). The results from the interactions between CR and WMHV are inconsistent with previous reports showing that CR, proxied using education or principal component measures of intellectual lifestyle (education, occupation, and engagement in cognitive activities), modifies the negative association between WMHV and cognitive function (422,510,564). The differences in findings could be due to the older age range (70 to 90 years old) of the Vemuri et al., 2015 study, and the low frequency of WMHV in this sample (zero-inflated distribution; see Table 9 for descriptive statistics). A moderation effect of CR is more likely in older individuals, who are more prone to accumulating neuropathological changes, such as lesions due to small-vessel vascular disease, than in a relatively younger and cognitively healthy cohort of participants (481,508).

For the CRI sub-components, it was found that education and leisure significantly interacted with brain volume and hippocampal volume, highlighting the role of these two sociobehavioural variables in the moderation effect. However, previous studies have shown inconsistent results regarding education's moderation role in the association between various brain markers (measured through brain infarct or WMHV), and cognition (100,418–420,422,433,481,565–567), supporting the argument that single indicator approaches to measuring CR, such as education, might not be as well established as usually perceived.

5.4.3 Strengths and limitations

This study builds upon previous findings on the role of the CRI or NART as proxies of CR. However, this is the first study to include the CRI and compare it to another well-established proxy of CR, the NART, in a brain-cognition model using data from a birth cohort. The data for this study came from a well-established, representative, community-based cohort study where the CR measures were prospective, thus, avoiding the recall bias common in ageing studies. The Insight 46 sample is also characterised by a very small age range, which solves the issue of the age-effect associated with brain pathologies, neurodegeneration, and decline in cognitive abilities . Furthermore, the study used four different neuroimaging measures associated with the two most common causes of dementia: AD and VaD. The inclusion of childhood cognitive ability in the models also reduces the risk of reverse causality related to higher cognitive ability selecting engagement in healthier or beneficial lifestyles. In terms of the outcome variables, cognitive function was assessed using two widely accepted scales, with the PACC being particularly sensitive to the first signs of cognitive decline in cognitively normal elderly participants.

However, there were some important limitations that need to be considered when interpreting the results. Due to the cross-sectional design of the study, moderation of the relationship between neuropathology and cognitive decline – the gold standard test of CR variables – could not be assessed. Future analyses are necessary to determine whether the effects of these proxies are consistent when assessed in the context of cognitive decline. Another potential methodological issue arose from the use of the ACE-III as an outcome. As presented in Table 8, only 20% of the sample completed the ACE-III at the time of imaging, while the remaining 80% had their imaging visit up to two years after completing the ACE-III. This issue was addressed by including the PACC as an additional outcome. The findings are

generally similar independent of the outcome used, suggesting that the two years difference in data collection between outcome and exposure might not have considerably affected the results. Furthermore, despite including a comprehensive range of brain markers, brain tau, which is considered key for AD diagnosis, was not assessed. Regarding model specification, important issues such as less precise estimates could have arisen due to the lack deprivation variables and the inclusion of the FRS. Deprivation or SEP is often measured in NSHD using occupational class, which for this study was included as a marker of CR (part of the CRI index), thus, the influence of wealth and deprivation, which have been associated with education, leisure engagement, and overall health, was not assessed in the models. Since the derivation of the FRS score accounts for age, it is possible that the models that adjust for both age at scan and the FRS are over adjusted. However, the FRS was kept as a covariate since it captures cardiovascular risk better for a relatively healthy cohort at midlife. Additionally, the limitations associated with survivor and attrition bias described in Chapter 4 also apply to this study, affecting the external validity of the study; therefore, replication in other populations is necessary to confirm the results.

5.4.4 Conclusion

In conclusion, the findings from this study suggest that the association between brain markers and cognitive function in older age is modified by CR. The results reinforce the theory that despite not being associated with the brain markers, certain life experiences contribute to CR, which in turn mitigates the association between brain markers and cognitive function. Hence, this study contributes to the growing body of evidence supporting CR theory and advocates for the feasibility of preserving cognitive function despite the accumulation of brain pathology.

Chapter 6. The moderating role of cognitive reserve between brain markers and cognitive function in the UK Biobank

6.1 Introduction

The current evidence for dementia risk factors is outlined in Chapter 2, section 2.2. "Dementia". The section highlights the importance of age as the most significant risk factor, being a carrier of the e4 allele of the APOE gene, and describes how women appear to be disproportionately affected by dementia in terms of disease prevalence and severity (9,12,33,35,157). It is further described through Chapter 2, section 2.3 "Life course determinates of cognitive ageing and dementia", how biological, genetic, and environmental factors have been associated with the presence of dementia-related neuropathology. For example, studies demonstrate that AD and WMHV increase with age and are linked with the presence of the e4 allele of the APOE gene (568). Furthermore, relative to males, females, particularly APOE e4 carriers, tend to have greater AD pathology and a higher risk for dementia (145–149,157,569–571). Furthermore, as presented in the introduction of Chapter 5, it has been argued that sociobehavioural variables might play a causal role in dementia through their contribution to BR and BM, and thus prevent or minimise brain pathology or cognitive decline (222,365,401).

Although an abundance of studies support the crucial role of biological and genetic factors in the risk of cognitive decline or dementia, there are very few studies investigating the role of genetic, sex, and age-specific effects on models of CR. The scant evidence on the topic has suggested that the association between lifestyle factors and Aβ burden is modified by

sex and APOE e4 gene, and that the moderating role of CR in the association between grey matter atrophy and memory differs across age groups (508,572–574).

In Chapter 5, the relationship between CR, measured using the CRI and NART, brain markers, and cognitive function at age 69-71, was investigated using life course data from 502 participants born in the same week as part of the neuroimaging NSHD sub-study, Insight 46. The findings suggested that both CR markers were not directly associated with any of the brain markers at that age. Instead, increased CR modified the association between brain markers and cognitive function and this association was independent of childhood cognitive ability. However, due to the relatively small sample size and narrow age range of the Insight 46 sample, additional investigations regarding the moderating role of genetics, sex, or age in these associations were not carried out.

UK Biobank is a large prospective cohort study designed to investigate the determinants of health of adults in the UK (575). Over half a million participants completed the baseline assessment for UK Biobank, and over 100,000 participants returned 8 years later for neuroimaging, which was carried out using structural MRI scans and capturing a range of brain markers, including brain volume, hippocampal volume, and WMHV, and enabling one of the largest imaging studies available in the UK. Furthermore, UK Biobank includes the sociobehavioural variables captured by the CRI, enabling comparison of the findings with my previous chapters (e.g., Chapters 4 and 5 using NSHD and Insight 46, respectively). Thus, this represents an ideal opportunity to investigate the associations between CR markers, brain markers, and cognitive function, and assess how these associations differ by genetic risk, sex, and age.

6.1.1 Objective

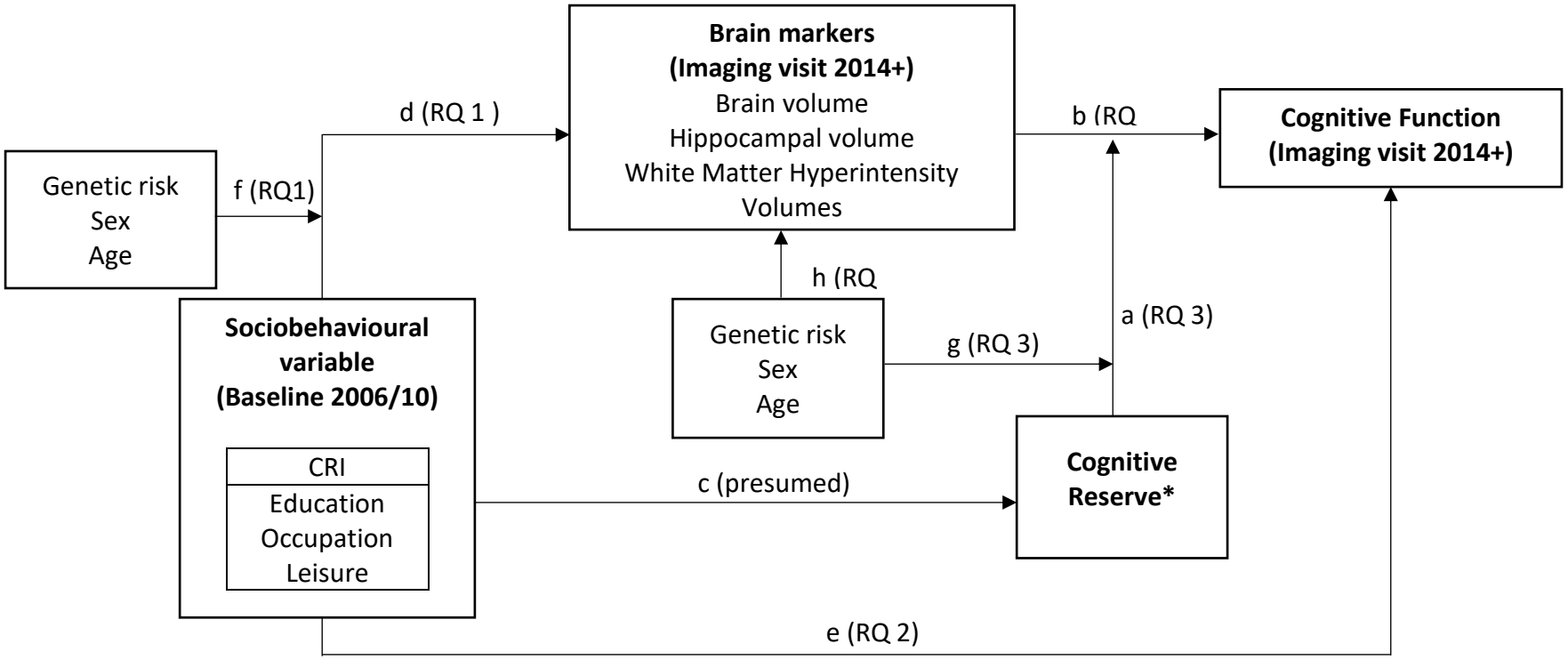
The objective of this study is to investigate the pathways by which sociobehavioural, biological, and genetic factors are associated with cognitive function during older age using cross-sectional brain markers and cognitive function from UK Biobank. The study builds on the studies presented in Chapters 4 and 5, where it was found that CR modifies the association between childhood cognitive ability and cognitive function, as well as the association between brain markers on cognitive function.

6.1.2 Research questions

1) Is there a direct association between the CRI and brain markers (Figure 43, path d)? Does genetic risk, sex, or age modify this association (Figure 43, paths f and h)?
2) Does the CRI predict cognitive function (Figure 43, path e), and is this association independent of brain markers?
3) Does the CRI modify the association between brain markers and cognitive function (Figure 43, paths a and b)? Does genetic risk, sex, or age modify the interaction between the CRI and neuropathology on cognitive function (Figure 43, path g)?

6.1.3 Hypotheses

1) The CRI will be directly associated with brain markers, particularly with vascular brain disease (i.e., WMHV). The association will depend on APOE genotype, sex, and age.
2) Consistent with the CR hypothesis, higher scores of the CRI will predict higher scores of cognitive function, independent of brain markers.
3) The CRI will modify the association between brain markers and cognitive function, and this interaction will depend on APOE genotype, sex, or age.



Mean age at baseline interview: 60 years.
Mean age at imaging visit: 69 years.
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 43 Conceptual diagram of the proposed pathways for the association between sociobehavioural variables, cognitive reserve, brain markers, and cognitive function.

Adapted from Richards and Deary, 2005.

6.2 Methods

6.2.1 Study Population

UK Biobank is a large prospective study designed to investigate the determinants of health of middle-aged and older adults in the UK (575). At baseline assessment (2006 to 2010), over 500,000 adults aged 40 to 70 attended a UK Biobank clinic. Participants provided informed consent and completed touchscreen questionnaires and nurse-led interviews providing information on sociodemographic, lifestyle, and medical history factors, as well as biological samples (blood, urine, and saliva), physical measurements (e.g., height and weight) and consented to their data being linked to their health records. Between 2012 and 2013, a subsample of 20,000 UK Biobank participants underwent repeat testing of all baseline measures. Furthermore, in 2014 UK Biobank conducted the first imaging assessment in which 100,000 participants completed the baseline assessments and underwent brain and body scanning. The study has been described in detail elsewhere (575,576).

This study was carried out using complete case analysis based on individuals with outcome, predictor, and covariate data. Furthermore, since the study aimed to investigate CR and cognitive function in older age, the analytical sample was restricted to individuals over the age of 65 at the first neuroimaging visit (2014). See Figure 44 participant flowchart.

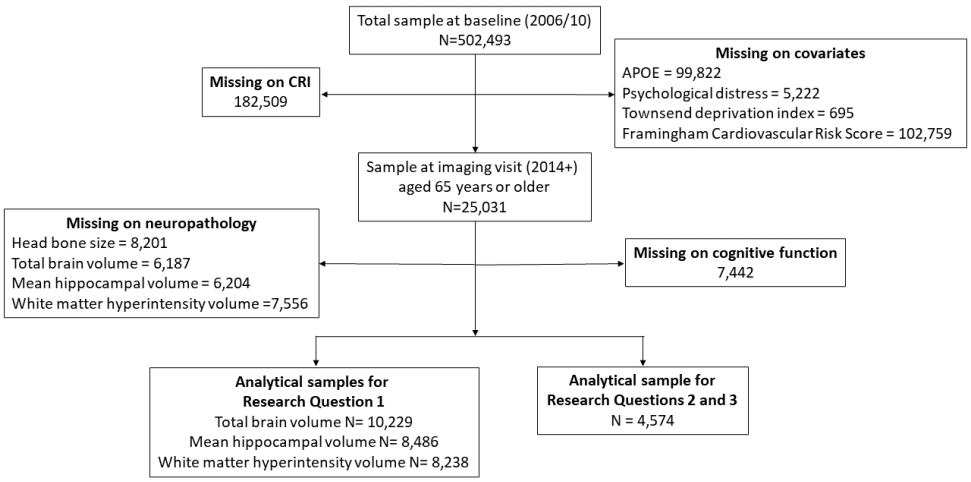


Figure 44 UK Biobank analytical sample flowchart.

6.2.2 Measures

6.2.2.1 Cognitive Reserve Index questionnaire

The CRIq (2) quantifies various markers of CR, providing a standardised measure reflective of the CR (the CRI) acquired during a person's lifetime. The CRI is a composite measure of educational attainment, occupational class, and leisure activities (see Chapter 2, section 2.3.5 "Reserve" for a summary of the evidence relating these components to CR and additional information on the CRI). The data for each component was extracted from the baseline questionnaires (2006 - 2010). Each component was standardised to a mean of 100 and a standard deviation of 15. To calculate the overall CRI, the three corresponding standardised scores (i.e., education, occupation, and leisure activities) were averaged. This average was then re-standardised and transformed to a scale with a mean of 100 and a standard deviation of 15, resulting in the CRI score.

Education. To be consistent with the original calculation of the education component described by Nucci and colleagues(2), the highest educational attainment was recategorised

to represent the approximate number of years each qualification represents: College or university degree (20 years), A level or equivalent (13 years), GCSEs/O level or equivalent (11 years), and no qualification (10 years).

Occupation. Occupational class was also categorised into the classifications specified by Nucci and colleagues (2). Highly responsible or intellectual occupation (managers, senior officials, and professional occupations) = 5, professional occupations (associate professionals) = 4, skilled non-manual work (administrative, secretarial occupations, sales, and customer service occupations) = 3, skilled manual work (skills trades occupation, personal service occupation, process, plant, and machine operatives) =2, and low skilled manual work (elementary occupations) = 1.

Leisure activities. Engagement in leisure activities was assessed through a range of 18 intellectual, social, and physical activities, similar to those collected by Nucci and colleagues in the original CRIq (2). The selection included activities related to the use of technology, social activities, leisure activity engagement, and physical activity. A detailed list of the activities selected to create this component can be found in Table 13. Additional information on how these variables were derived from the original dataset is available in Appendix D.

Table 13 Activities included in CRI leisure sub-scale in UK Biobank.

1.	Driving	Binary (0/1)
2.	Watching television	Binary (0/1)
3.	Computer use	Binary (0/1)
4.	Plays computer games	Binary (0/1)
5.	Mobile phone use	Binary (0/1)
6.	Mobile phone use in last 3 months	Binary (0/1)
7.	Hands-free device/speakerphone use with mobile phone in last 3 months	Binary (0/1)
8.	Friend/family visits	Binary (0/1)
9.	Social activities (sports club or gym, pub or social club, religious group, adult education class, other group activity)	Count (0/5)
10.	Types of physical activity in last 4 weeks (walking for pleasure, other exercises [e.g., swimming, cycling, keeping fit, bowling], strenuous sports, light DIY [e.g., pruning, watering the lawn], heavy DIY [weeding, lawn mowing, carpentry, digging])	Count (0/5)

The leisure sub-scale scores can range between 0 and 15.

6.2.2.2 Brain markers

Postprocessed measures provided by UK Biobank were used in this study and included brain volume (grey and white matter), mean hippocampal volume, and WMHV. The rationale for the inclusion of each of these brain markers and their association with cognitive ageing is provided in Chapter 5, section 5.2.2 “Measures”.

The imaging assessment for UK Biobank participants started in March 2014 and collected data until January 2018. Participants underwent structural MRI scans across four centres in Central, North, South-East and South-West England. A centralised team oversaw training and monitored quality assurance across all four centres, with all staff members having undergone extensive training with an MRI physicist. Harmonisation of data across centres is assured by employing the same scanner models, software, adjustment and tuning techniques, coil types and protocols. In addition, a standardised training programme is provided for radiographers in each centre and standard operating procedures, alongside phantom measurements, servicing, and performance checks that are conducted by a UK

Biobank physicist. Qualitative and quantitative comparisons are performed by external imaging experts to confirm that images are of high quality and suitable for research.

6.2.2.3 Cognitive function

Like the two cognitive assessment tools (i.e., ACE-III and PACC) used in Chapters 4 and 5, which are composed of different tests assessing various cognitive domains, a global measure of cognitive function was created. Compared to individual tests, composite scores are frequently employed to assess cognitive function due to their ability to incorporate data from diverse sources, thus, resulting in a more reliable assessment of performance (417).

During the first neuroimaging data collection (2014), UK Biobank introduced measures assessing cognitive domains known to decline with age (577,578). Due to the size of the UK Biobank sample and the magnitude of data being collected, the cognitive assessment was designed to be brief and to be administered without supervision on a touchscreen computer. A previous study investigating the psychometric properties of the UK Biobank cognitive tests suggested that these tests showed moderate to high concurrent validity and moderate test-retest reliability (577).

The cognitive function measure was built using data from the five tests presented during the imaging study: (1) Trail making tests, part A, which measures speed and accuracy and part B, which measures executive function (reverse coded for the present analysis) (2) symbol digit substitution which measures processing speed and executive function; (3) paired associate learning, which measures verbal episodic memory; (4) towers rearranging test which measures planning ability, a component of executive function; and (5) matrix pattern recognition which measures nonverbal fluid reasoning. To create the overall cognitive function score, only participants with complete data in all five cognitive tests were included.

Of the 45.000 participants who underwent assessment during the neuroimaging visit, 33.386 (74%) had data in all cognitive function domains. The five scores were converted into z scores based on the imaging sample and then averaged (155,304). A higher cognitive function score indicates better performance.

6.2.2.4 Model adjustment

All covariates were assessed at baseline (2006-2010). For research question 1, sex and age were included as a confounders since they have been associated with the sociobehavioural variables and brain markers (89,569). Additionally, genetic risk was included as covariate since it has been associated with brain markers (530). APOE genotype was determined using SNPs rs429358 and rs7412 using the same approach described for NSHD (see Chapter 4, section 4.2.2 "Measures"). APOE was categorised as no e4 versus heterozygous e4 or homozygous e4. Due to opposing effects on cognition, participants with e2/e4 were excluded (N=9,987). To adjust for correlations between brain markers and head size, the models adjusted for skull area, except for brain volume since its derivation accounted for head size. As discussed in Chapter 5, section 5.2.3 'Statistical Analysis' other variables, such as cardiovascular health and psychological distress, were not included in the models for research question 1 since they are likely to contribute to the causal pathway.

For research question 2, age, sex, and material deprivation were included as sociodemographic confounders (537,538). The Townsend deprivation index (TDI) was used as a measure of material deprivation. The TDI was derived from national census data about car ownership, household overcrowding, occupation, and unemployment aggregated for postcodes of residence (579,580). Higher TDI scores indicate higher social deprivation. Genetic risk was assessed using APOE genotype, categorised as no e4 versus heterozygous

e4 or homozygous e4. Since psychological distress has been associated with the sociobehavioural variables and with cognitive function, it was included in the models (536,539). Psychological distress was assessed via self-reported visits to a general practitioner or psychiatrist for nerves, anxiety, tension, or depression; it was coded dichotomously (yes/no). Cardiovascular health was measured using the FRS (581). The FRS is a sex-specific weighted sum of age, systolic blood pressure, antihypertensive medication usage, history of diabetes, current smoking, and body mass index. Furthermore, other important health variables were captured via the presence of longstanding illness, disability, or infirmity; this was coded dichotomously (yes/no).

Marital status information was not explicitly available, and therefore, these analyses did not control for marital status.

6.2.3 Statistical analyses

Due to the large sample size of the UK Biobank cohort, the analyses were carried out using complete data. All analyses were restricted to participants with complete data in the CRI, each of the brain markers, cognitive function, and covariates. The missing data on the predictors, outcomes, and covariates are presented in Figure 44.

For research question 1, the sample sizes vary depending on the data available for each brain marker (Figure 44 for the participant flowchart). Multiple regression analyses were carried out to test the associations with CRI and brain volume and hippocampal volume (Figure 45). Due to the non-normal distribution of WMHV, generalized linear models using gamma distribution and log link were used to investigate associations with CRI and WMHV. Before testing for interactions, the initial explorations of the association between CRI and brain markers were carried out and adjusted for sex, age, and APOE genotype. Afterwards,

two-way, and three-way interactions were assessed for all potential moderators (sex, age, and APOE genotype).

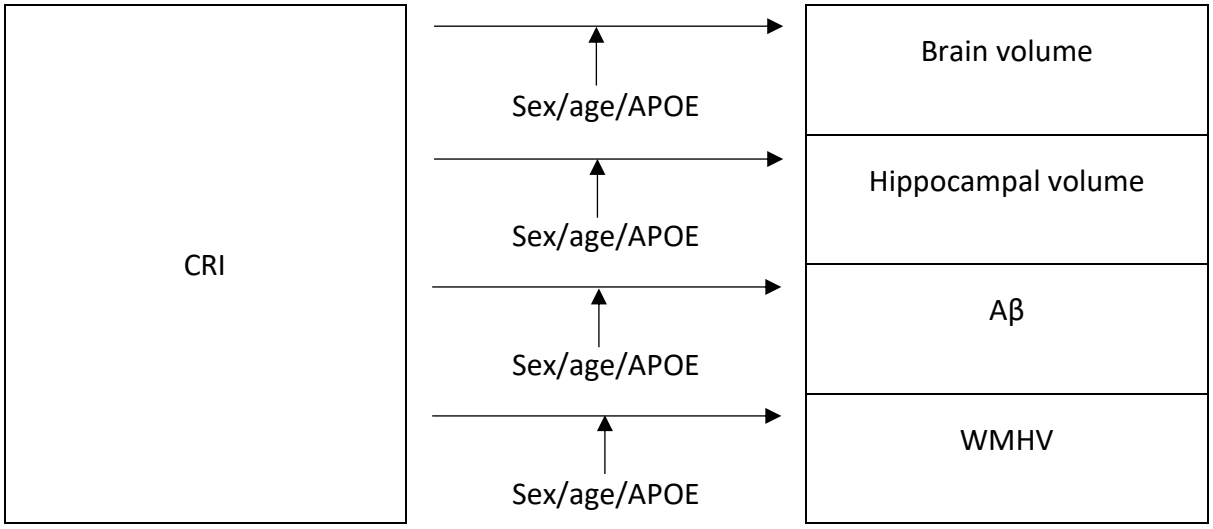


Figure 45 Individual regression models for CRI and brain markers, including moderation analysis by sex, age, or APOE.

For research question 2, the association between the CRI and cognitive function was first tested without adjustment for brain markers and then tested while accounting for them (Figure 46). Models were gradually adjusted for covariates: (Model 1) total intracranial volume (except brain volume), age, sex, and APOE genotype; (Model 2) TDI; (Model 3) FRS, longstanding illness, or disability; and (Model 4) psychological distress.

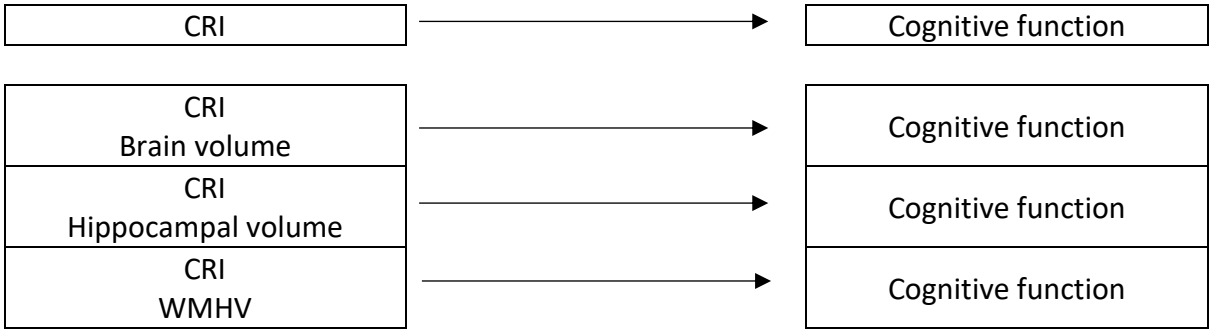


Figure 46 Individual regression models for CRI, unadjusted and adjusted for brain markers, on cognitive function.

For research question 3, the moderating role of the CRI in the association between brain markers and cognitive function was tested by investigating interaction effects between the CRI and the different brain markers (Figure 47). Additionally, two-way, and three-way interactions were assessed for other potential moderators (i.e., sex, age, and APOE genotype). Furthermore, to illustrate the significant interactions and aid comparisons, the continuous variables (i.e., CRI and neuropathology measures) were standardised to calculate simple slopes of the association between brain markers and cognitive function at low (two standard deviations below the mean), medium (at the mean), and high (two standard deviations above the mean) values of the CRI. Furthermore, to illustrate the significant interactions with age, age was categorised into three levels: younger (two standard deviations below the mean [53 years]), medium (at the mean [60 years]), and older (two standard deviations above the mean [68 years]) age groups. APOE genotype and sex were used as binary variables, and hence, any significant interactions were illustrated by stratifying the sample.

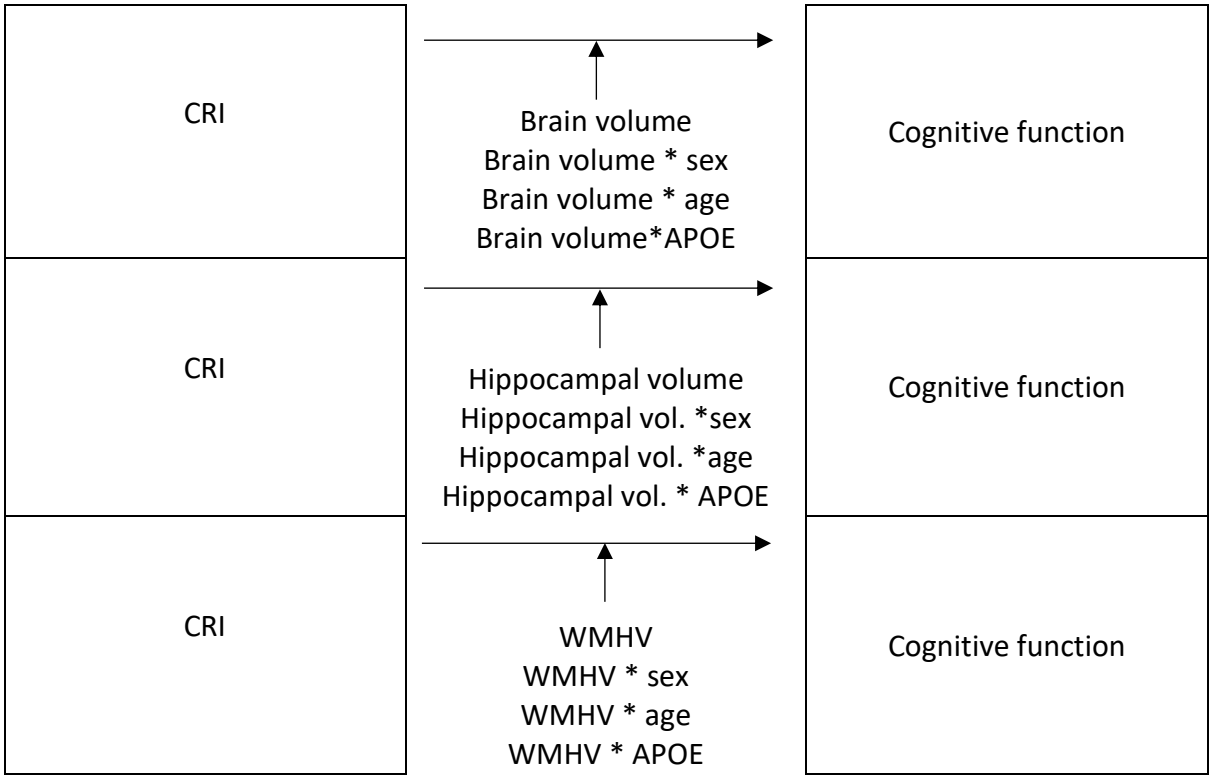


Figure 47 Individual moderation models for brain markers in the association between the CRI and cognitive function.

Additional analyses were carried out to assess the findings of the main analyses using the individual CRI components: education, occupation, and leisure. For the analysis of the components, education and occupation were re-categorised to ensure all levels of the variable were appropriately powered. Education was grouped into no qualifications, O level or equivalent; A levels, NVQ or equivalent; other professional qualifications; and college or university degree. Occupation was grouped as low-skilled manual work or skilled manual work; skilled non-manual work; professional occupation; and highly responsible or intellectual occupations. Leisure activity engagement was categorised into tertiles (244). For research question 1, the association between the CRI sub-components and the different brain markers were tested. Furthermore, any significant interactions in the main analysis

(i.e., using the CRI) were replicated with the sub-components. For research questions 2, the association between the CRI sub-components and cognitive function was assessed with and without the adjustment for brain markers. Finally, for research question 3, the modifying role of the CRI-components was evaluated in the association between brain markers and cognitive function.

Information on the linear model assumptions and the steps taken to control for any deviations are available in Appendix D, section D.1. To control for false discovery rate due to multiple comparisons, the Benjamini-Hochberg correction (497) with a q-value of 0.05 was used for all the regression models. The Benjamini-Hochberg was chosen since it considered less conservative and more powerful than the Bonferroni correction. All analyses were conducted using Stata MP, Version 16 (Stata Corp).

6.2.3.1 Sensitivity analysis

Due to the variation in sample sizes between research questions, a sensitivity analysis was carried out for research question 1 using the same analytical sample used for research questions 2 and 3.

6.3 Results

6.3.1 Descriptive statistics

Tables 14 and 15 present the descriptive characteristics of the participants with complete data on the outcomes, CRI, and relevant covariates for the three research questions. At baseline, the mean age of the sample was 60 years, and the proportion of females and males was similar. The mean age at the first neuroimaging visit was 69, which was like that of the Insight 46 sample (70 years), but with a much broader range in UK Biobank (65 to 82) than in Insight 46 (69 to 71).

Across all outcomes, the distribution of the sample characteristics was similar. Compared to the NSHD (CRI range: 68 to 152) and Insight 46 samples (CRI range: 78 to 152), the range of the scores of the CRI was lower, with a minimum of 56 and a maximum score of 138. Most participants had college or university education, highly responsible or intellectual occupations, and reported engaging in 7 to 8 leisure activities.

Despite the Insight 46 and UK Biobank samples having similar mean ages at imaging, UK Biobank participants had larger brain volumes (Insight 46=1100.17 cm^3 vs UK Biobank=1461.12 cm^3; t=578.67, p<0.001) hippocampal volumes (Insight 46=3.13 cm^3 vs UK Biobank=3.77 cm^3; t=133.32, p<0.001), and WMHV (Insight 46=5.11 cm^3 vs UK Biobank=6.61 cm^3; t=18.07, p<0.001). These results did not differ depending on the size of the analytical sample from the UK Biobank.

Table 14 Descriptive characteristics of the categorical variables included in the UK Biobank analyses by research question and outcome.

Categorical variables	Categories	RQ1			RQ2&3
		Brain volume (10,229)	Hippocampal volume (8,486)	WMHV (8,238)	Cognitive function (4,574)
		N (%)			
Education	No qualification	830 (8)	692 (8)	674 (8)	301 (7)
	O level/GCSE	1,244 (12)	1,041 (12)	1,012 (12)	557 (12)
	A level or equivalent	503 (5)	410 (5)	393 (5)	220 (5)
	NVQ or equivalent	1,076 (11)	930 (11)	899 (11)	491 (11)
	Other professional qualification	1,691 (17)	1,448 (17)	1,414 (17)	782 (17)
	College or university degree	4,885 (48)	3,965 (47)	3,846 (47)	2,223 (48)
Occupation	Low skilled manual work	251 (3)	209 (3)	205 (3)	102 (2)
	Skilled manual work	1,235 (12)	1,045 (12)	1,014 (12)	557 (12)
	Skilled non-manual work	1,656 (16)	1,400 (17)	1,355 (17)	686 (15)
	Professional occupation	1,763 (17)	1,462 (17)	1,410 (17)	782 (17)
	Intellectual occupation	5,324 (52)	4,370 (52)	4,254 (52)	2,447 (54)
Leisure	0-6 activities	3,347 (33)	2,723 (32)	2,633 (32)	1,439 (32)
	7 to 8 activities	3,731 (37)	3,106 (37)	3,029 (37)	1,705 (37)
	9+ activities	3,151 (31)	2,657 (31)	2,576 (31)	1,430 (31)
Sex	Female	4,801 (47)	3,974 (47)	3,876 (47)	2,091 (46)
	Male	5,428 (53)	4,512 (53)	4,362 (53)	2,483 (54)
APOE-e4 carrier	No	7,674 (76)	6,360 (75)	6,184 (75)	3,476 (76)
	Yes	2,555 (24)	2,126 (25)	2,054 (25)	1,098 (24)
Illness, disability, or infirmity	No	-	-	-	3,516 (77)
	Yes				1,058 (23)
Psychological distress	No	-	-	-	3,220 (70)
	Yes				1,354 (30)

RQ: Research question; WMHV: White matter hyperintensity volume.

Note: The sample size differs between research questions due to data availability.

Table 15 Descriptive characteristics of continuous variables included in the UK Biobank analyses by research question and outcome.

Continuous variables	RQ1						RQ2&3	
	Brain volume (10,229)		Hippocampal volume (8,486)		WMHV (8,238)		Cognitive function (4,574)	
	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)
CRI	56 to 138	104 (13)	56 to 128	104 (13)	56 to 138	104 (13)	59 to 138	105 (13)
Cognitive function	-	-	-	-	-	-	-4 to 2	-0.11 (0.60)
Brain volume (cm^3)	1,144 to 1,706	1,461 (63)	-	-	-	-	1,209 to 1,683	1,461 (62)
Hippocampal volume (cm^3)	-	-	1.63 to 6.56	3.77 (0.44)	-	-	2 to 7	4 (0.44)
WMHV (cm^3)	-	-	-	-	0.05 to 90.45	6.61 (7.52)	0.05 to 90.5	6.9 (7.7)
Head bone size (cm^3)	-	-	0.17 to 0.29	0.22 (0.02)	0.17 to 0.29	0.22 (0.02)	0.18 to 0.29	0.22 (0.02)
Age at baseline	52 to 70	60 (4)	53 to 70	60 (4)	53 to 79	60 (4)	53 to 70	60 (4)
Age at imaging	65 to 82	69.35 (3.41)	65 to 81	69.19 (3.27)	65 to 81	69.20 (3.27)	65 to 81	69.33 (3.33)
TDI	-	-	-	-	-	-	-6 to 9	-2 (3)
FRS	-	-	-	-	-	-	2 to 85	17 (10)

RQ: Research question; CRI: Cognitive reserve index; WMHV: White matter hyperintensity volumes; TDI: Townsend deprivation index; FRS: Framingham Heart Study Cardiovascular Risk Scores.

Note: The sample size differs between research questions due to data availability.

6.3.2 Research question 1

Higher CRI was significantly associated with lower brain volume, where for every unit increase in CRI, the score of brain volume decreased by 0.11 cm^3 (Table 16). This association was modified by sex and age in a three-way interaction. For females, the CRI appeared to predict lower brain volumes for younger individuals, whereas for males, the CRI seemed to predict larger brain volumes for younger individuals (Figure 48). There was no evidence of an APOE-e4 interaction.

The CRI was significantly associated with higher hippocampal volumes. For every unit increase in the CRI, the hippocampal volume increased by 0.001 cm^3 on average (Table 16). Higher CRI was also associated with lower WMHV, but not significantly. There was no evidence of sex, age or APOE-e4 interactions for the association of the CRI with hippocampal volume or WMHV.

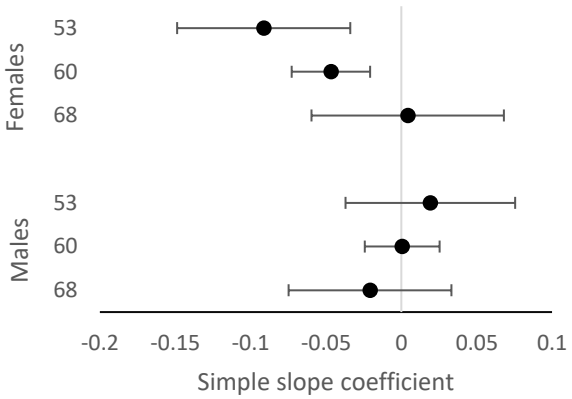
Due to the variation in sample sizes between research questions, analyses were re-run using the smaller analytical sample used for research questions 2 and 3 which additionally required complete cognitive data (n=4,574) (see Appendix D, Table D2). The results show that the effect size and direction of the associations were the same as per the main analysis. However, the association between the CRI and brain volume was non-significant, while the association between the CRI and hippocampal volume remained significant.

Table 16 Regression coefficients and 95% confidence intervals for the associations between CRI, age, sex, genetic risk, and different brain markers.

Brain marker (N)	Predictors	B (95% CI)	p-value	Interaction coefficient (p-value)	
Regression coefficients and 95% confidence intervals					
Brain volume (10,229)				CRI*sex CRI*age CRI*APOE CRI*sex*age CRI*sex*APOE CRI*age*APOE	0.21 (0.02) 0.01 (0.35) -0.17 (0.11) -0.04 (0.07) 0.21 (0.31) -0.02 (0.59)
	CRI	-0.11 (-0.20 to -0.02)	0.01		
	Age	-4.93 (-5.25 to -4.61)	<0.001		
	APOE-e4 carrier: No Yes	[Reference] 0.97 (-1.73 to 3.66)	0.48		
	Sex: Female Male	[Reference] -10.24 (-12.61 to -7.88)	<0.001		
Hippocampal volume (8,486)				CRI*sex CRI*age CRI*APOE CRI*sex*age CRI*sex*APOE CRI*age*APOE	0.00 (0.38) -0.00 (0.59) 0.00 (0.47) -0.00 (0.77) 0.00 (0.69) -0.00 (0.42)
	CRI	0.01 (0.00 to 0.01)	<0.001		
	Age	-0.02 (-0.03 to -0.02)	<0.001		
	APOE-e4 carrier: No Yes	[Reference] -0.03 (-0.05 to -0.009)	0.005		
	Sex: Female Male	[Reference] 0.09 (0.07 to 0.12)	<0.001		
Exponentiated coefficients and 95% confidence intervals					
WMHV (8,238)				CRI*sex CRI*age CRI*APOE CRI*sex*age CRI*sex*APOE CRI*age*APOE	-0.00 (0.40) 0.00 (0.17) -0.00 (0.32) -0.00 (0.56) -0.00 (0.61) 0.00 (0.36)
	CRI	-0.01 (-0.01 to 0.01)	0.18		
	Age	0.06 (0.05 to 0.07)	<0.001		
	APOE-e4 carrier: No Yes	[Reference] 0.06 (0.01 to 0.12)	0.03		
	Sex: Female Male	[Reference] 0.06 (0.01 to 0.12)	0.03		

Models adjusted for head bone size (except brain volume), age, sex, and genetic risk.
CRI: Cognitive reserve index; WMHV: White matter hyperintensity volumes.
All statistically significant associations remained significant after Benjamini-Hochberg correction.

N	Age	B (95% CI)	p-value
		Females	
4,801	53	-0.09 (-0.15 to -0.03)	0.002
	60	-0.05 (-0.07 to -0.02)	<0.001
	68	0.004 (-0.06 to 0.07)	0.90
		Males	
5,428	53	0.02 (-0.04 to 0.08)	0.50
	60	0.001(-0.02 to 0.03)	0.96
	68	-0.02 (-0.08 to 0.03)	0.45



Age groups are classified into mean and two standard deviations above and below the mean.
*p≤0.01, **≤0.001.

Figure 48 Illustrative plots showing the sex-stratified simple slopes of the CRI on standardised brain volume at the medium (age 60), low (-2 std, age 53) and high (+2 std age 68) baseline age.

Table D3 in Appendix D demonstrates the additional analyses of the CRI sub-components on the brain markers. For brain volume, there were opposing effects of education, occupation, and leisure: higher education and occupation were associated with lower brain volumes, while increased leisure activity engagement was associated with higher brain volumes.

The sex-and-age interaction for the CRI and brain volume was further explored by decomposing the CRI into its sub-components and illustrating these three-way interactions. In women, higher education was associated with lower brain volume to a similar extent across ages (Figure D1a). In males, higher education was associated with lower brain volume, particularly for older individuals (Figure D1b).

In women, higher occupation was associated with lower brain volume, and this association seems to be slightly stronger with increasing age (Figure D2a). In men, higher occupation was associated with lower brain volume, particularly for older individuals (Figure D2b).

In women aged 63 and over, intermediate engagement in leisure activities was associated with higher brain volumes (Figure D3a). In men, intermediate and high leisure activities were generally associated with higher brain volume, particularly for younger participants. (Figure D3b).

Education and leisure activity were each associated with larger hippocampal volumes, particularly for a higher level of leisure, which was the sub-component most associated with hippocampal volume (Table D3 and Figures D4 and D5). Higher occupation seemed to be the sub-component mostly associated with reduced WMHV (Table D3 and Figure D6).

6.3.3 Research question 2

Higher CRI, brain volume, hippocampal volume, and lower WMHV were positively associated with cognitive function. The strength of the association between CRI and cognition remained unchanged after adjustment for the different neuropathology measures (see Table 17 and Appendix D, Tables D4 to D7 for gradual adjustment of covariates).

Table 17 Regression coefficients and 95% confidence intervals for the association between the CRI and cognitive function. Individual models unadjusted and adjusted for each brain marker (brain volume, hippocampal volume, and WMHV) (N=4,574).

Predictors	B (95% CI)	p-value	Interaction coefficient (p-value)	
CRI	0.01 (0.01 to 0.01)	<0.001	-	-
CRI Brain volume	0.01 (0.01 to 0.01) 0.00 (0.00 to 0.00)	<0.001 0.007	CRI*Brain volume	0.00 (0.08)
			CRI*Brain volume*sex	0.00 (0.53)
			CRI*Brain volume*age	-0.00 (0.72)
			CRI*Brain volume*APOE	-0.00 (0.42)
CRI Hippocampal volume	0.01 (0.01 to 0.01) 0.10 (0.06 to 0.14)	<0.001 <0.001	CRI*Hip. volume	-0.00 (0.88)
			CRI*Hip. volume*sex	-0.00 (0.67)
			CRI*Hip. volume*age	-0.00 (0.61)
			CRI*Hip. volume*APOE	0.00 (0.88)
CRI WMHV	0.01 (0.01 to 0.01) -0.00 (-0.00 to -0.00)	<0.001 <0.001	CRI*WMHV	0.00 (0.39)
			CRI*WMHV*sex	-0.00 (0.46)
			CRI*WMHV*age	-0.00 (0.13)
			CRI*WMHV*APOE	-0.00 (0.01)

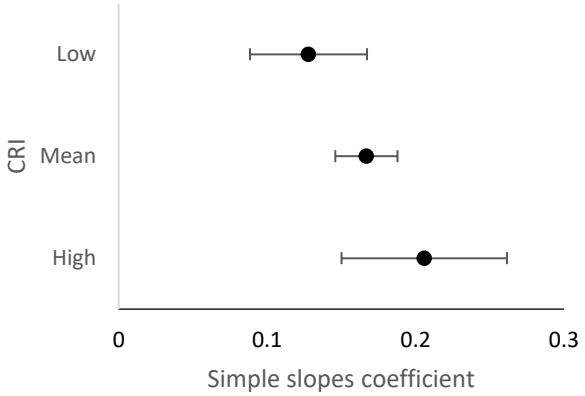
Models adjusted for total intracranial volume (except brain volume), sex, age, genetic risk, TDI, FRS, illness, and psychological distress.
CRI: Cognitive reserve index; WMHV: White matter hyperintensity volume.
All statistically significant associations remained significant after Benjamini-Hochberg correction.

6.3.4 Research question 3

Moderation analysis indicated that the association between brain volume and cognitive function was modified by the CRI (Table 17). The right side of Figure 49 illustrates this interaction, where the strength of the association between brain volume and cognitive function increased as scores in the CRI increased.

The interaction analysis also indicated that the association between WMHV and cognitive function was modified by CRI and APOE genotype (Table 17). For APOE-e4 carriers, the association between WMHV and cognitive function was stronger in those with higher CRI. On the other hand, for APOE-e4 non-carriers, the association between WMHV and cognitive function was stronger for those with lower CRI (Figure 50). There was no evidence of a moderation effect of CRI on the relationship between hippocampal volume and cognitive function (Table 17).

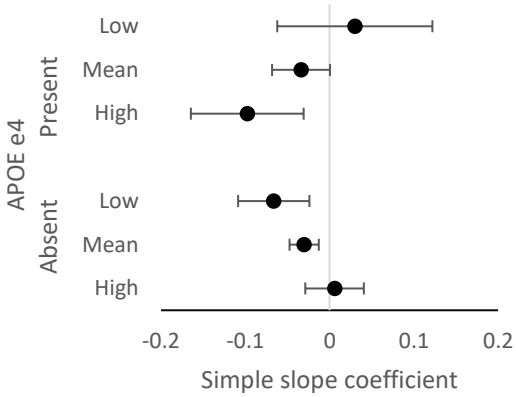
CRI	B (95% CI)	p-value
Low	0.13 (0.09 to 0.17)	<0.001
Medium	0.17 (0.15 to 0.19)	<0.001
High	0.21 (0.15 to 0.26)	<0.001



CRI: Cognitive reserve index

Figure 49 Illustrative plots and visual representation showing the simple slopes of standardised brain volume on cognitive function at low, medium, and high standardised scores of the CRI.

N	CRI	B (95% CI)	p-value
1,098		**APOE e4 present**	
	Low	0.03 (-0.06 to 0.12)	0.52
	Med.	-0.03 (-0.07 to 0.0005)	0.05
	High	-0.10 (-0.17 to -0.03)	0.004
3,476		**APOE e4 absent**	
	Low	-0.07 (-0.11 to -0.02)	0.002
	Med.	-0.03 (-0.05 to -0.01)	0.001
	High	0.006 (-0.03 to 0.04)	0.74

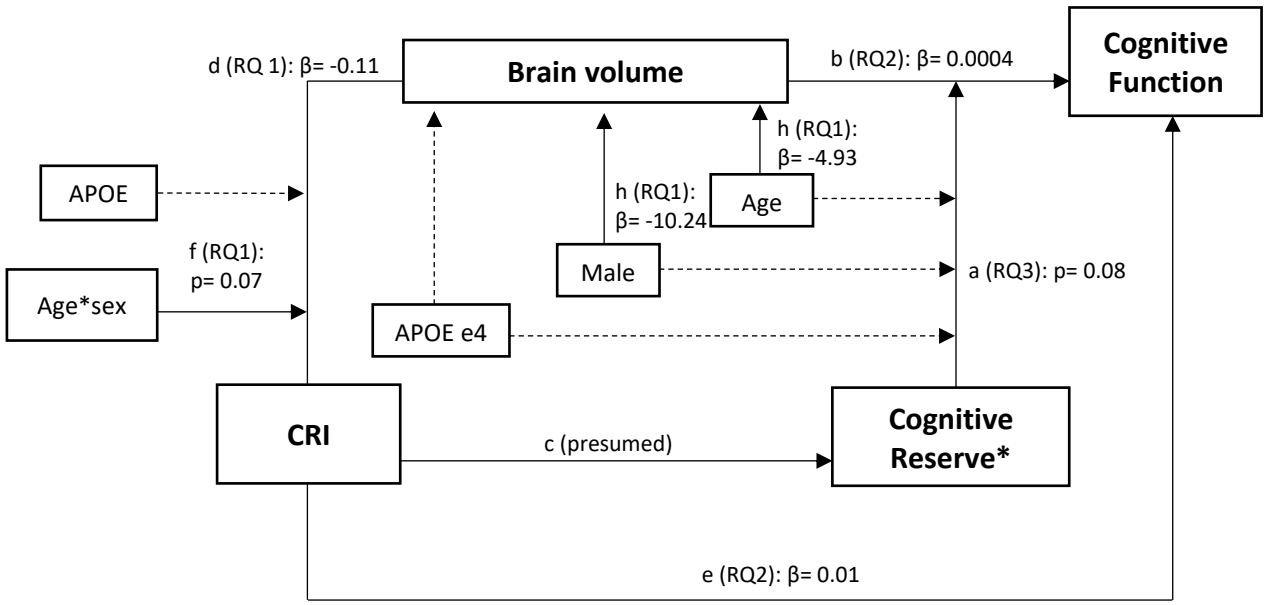


CRI: Cognitive reserve index; Med: Medium.
*p<0.01, **<0.001

Figure 50 Illustrative plots showing the APOE stratified simple slopes of standardised white matter hyperintensity volumes on standardised total cognitive function at low, medium, and high scores of the CRI.

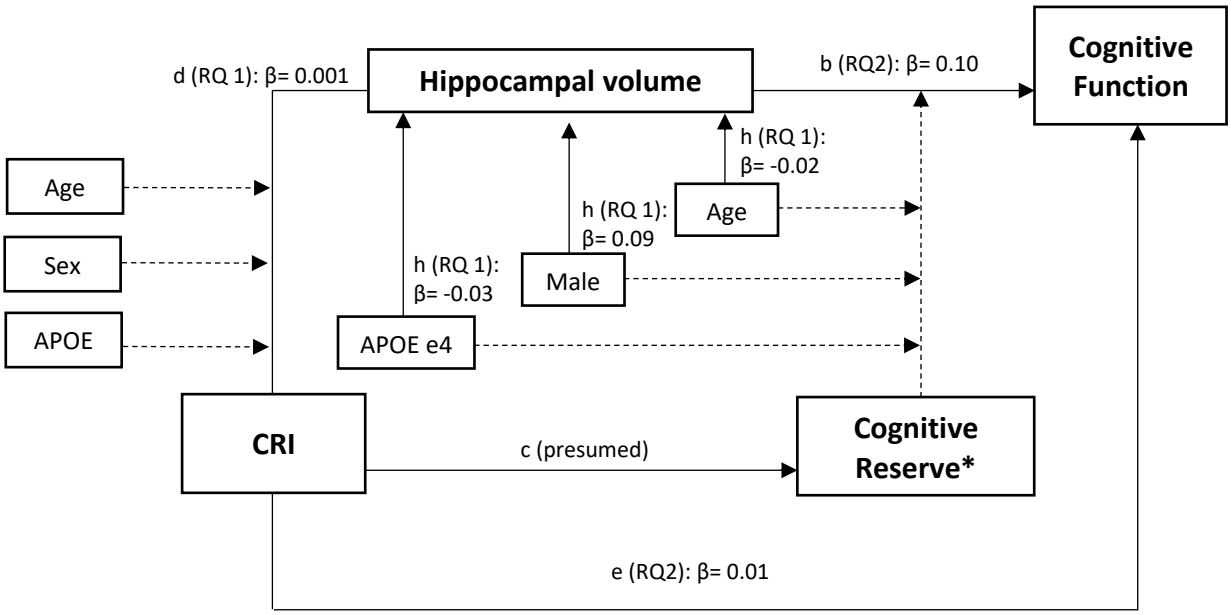
Table D8 in Appendix D demonstrates the additional analyses of the moderating effect of CRI sub-components in the associations between the neuropathology measures and cognitive function. Leisure activity significantly modified the association between brain volume and cognitive function, where intermediate engagement in leisure activities were associated with higher brain volume (Figure D7). Education, occupation, and leisure did not significantly modify the association between hippocampal volume and cognitive function. Finally, education modified the association between WMHV and cognitive function. Increased WMHV was associated with worse cognitive function for individuals with lower qualifications (Figure D8).

Based on the conceptual diagrams proposed for this thesis and for this study (Figures 12 and 43), the pathways for the associations between CR and cognitive function for each brain marker are illustrated in Figures 51 and 53. The coefficients for these figures are extracted from Tables 16 and 17. Solid lines show significant associations, whereas dashed lines show non-significant associations.



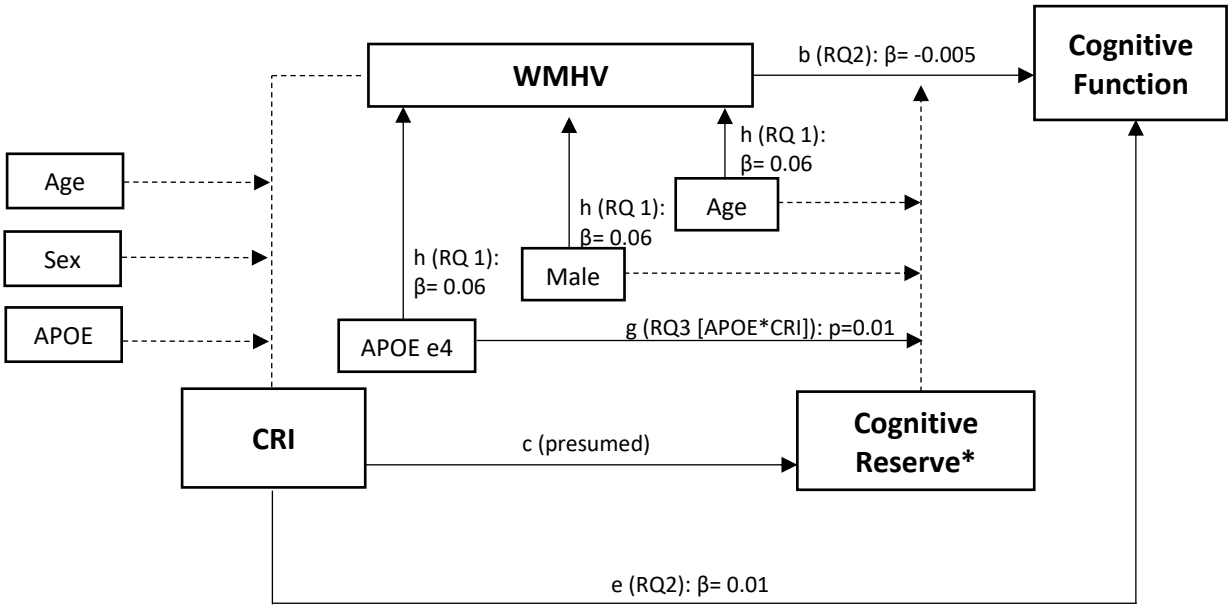
*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 51 Pathways for the associations between CRI, brain volume, and cognitive function



*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 52 Pathways for the associations between CRI, hippocampal volume, and cognitive function



*Since cognitive reserve cannot be measured directly, it was proxied using sociobehavioural variables.

Figure 53 Pathways for the associations between CRI, hippocampal volume, and cognitive function

6.4 Discussion

This study investigated the associations between CRI, brain markers, and cognitive function and assessed how these associations differ by genetic risk, sex, and age. The major findings are: (i) sociobehavioural variables, assessed using the CRI, showed a statistically significant negative association with brain volume and a positive association with hippocampal volume, but no significant association with WMHV. Moderation analysis suggested that sex and age modified the association between the CRI and brain volume but not hippocampal volume; (ii) the CRI predicted higher cognitive function, even after accounting for neuropathology; (iii) moderation analysis suggested that the association between brain volume and cognitive function is modified by the CRI, and the association between WMHV and cognitive function is modified by both the CRI and APOE genotype. The association between hippocampal volume and cognitive function was not modified by the CRI.

Consistent with the findings using data from NSHD and Insight 46 (Chapters 4 and 5), the results from this study showed that higher CRI, brain volume, hippocampal volume, and lower WMHV were positively associated with cognitive function. The strength of the association between CRI and cognition remained unchanged after adjustment for the different neuropathology measures satisfying the independent effect criterion (see Chapter 2, section 2.3.5 'Reserve') and providing further evidence for the role of the CRI as a proxy for CR (384). The findings were also replicated for the analysis using the CRI subcomponents (education, occupation, and leisure).

6.4.1 Brain volume

Figure 51 summarises the findings for the associations between neuropathology, cognitive function, and brain volume. The CRI had a direct negative association with brain volume,

with the strength of this effect being stronger for younger females. Furthermore, the CRI had a direct association with cognitive function, which was independent of brain volume. The CRI also modified the association between brain volume and cognitive function, whereby the association was stronger for individuals with higher CR. These findings suggest that the sociobehavioural variables have a multifaceted role in older age cognitive function, contributing to it through various direct and indirect pathways, including CR.

Despite some studies showing no direct association between CR markers and neurodegenerative (e.g., Aβ) or vascular (e.g., WMHV) pathologies (554) – including the findings from Chapter 5 using Insight 46 data – the findings in the literature are mixed, with some studies suggesting that more years of education are associated with greater brain weight or volume (216,309). For example, previous evidence from UK Biobank studies has found evidence for a cross-sectional association between education and regional cortical volumes (n=1,289) and between frequent social engagement and grey matter volume in the occipital lobe (n=7,152) (310,555). These studies provide some evidence for the BR theory (see Chapter 2, section 2.3.5 'Reserve'), which proposes that cognitively stimulating experiences entail changes in brain structure and organization (e.g., enhanced synaptodendritic development, more complex axonal projections, and enhanced myelination and neurogenesis) (216), leading to greater brain weight. Thus, the hypothesis for research question 1 was that the CRI would be associated with higher brain volume. However, the findings from the present analysis suggest that the CRI was associated with lower brain volume, and that this association was modified by sex and age in a three-way interaction whereby the negative association seemed stronger, particularly for younger women. Additional investigation into the CRI-subcomponents suggested that education and occupation may drive the effect of CRI on smaller brain volumes, but the effects did not

remain robust in the sensitivity analysis using a smaller sample. On one hand, the unexpected finding for the association between the CRI and brain volume could reflect idiosyncratic characteristics of the UK Biobank cohort (i.e., that the analytical sample is comprised of highly educated females who had smaller brains). On the other hand, the results could be explained by the large sample size, which increases the sensitivity to real effects and to artefactual associations due to confounding effects (582).

Consistent with the second hypothesis for this study and with the findings from Insight 46, the CRI modified the effect of brain volume and cognitive function. However, in contrast to Insight 46 findings, where the slope of the association between brain volume and cognitive function was stronger for individuals with lower CRI, in the UK Biobank, the slope of the association was stronger for individuals with higher scores in the CRI. Further investigation of the CRI sub-components revealed that leisure engagement appeared to drive the effect. This finding is consistent with various studies showing that high CR in cognitively healthy elders is associated with better cognitive function, as well as better brain marker measurements than those with low CR (304,583–585). Since CR's ability to predict cognitive function depends on the degree of neuropathology (586), it is possible that the findings reflect the effect of CR on cognitive function on larger and, thus, potentially healthier brains where its effect is only additive since there is no damage or loss to compensate for. It is possible that these findings reflect the lifelong stability of cognitive function in people with larger brains, which might also be associated with an increased engagement in leisure activities (304). In Insight 46, the compensatory effect of CR might be at play given the smaller brain volumes which might result from age- or pathology-related atrophy. Despite the two cohorts having similar ages at the time of imaging, the difference between cohorts

on brain volumes could be explained by UK Biobank's "healthier volunteer" selection bias (587).

6.4.2 Hippocampal volume

The CRI had a direct positive association with hippocampal volume, and age, sex, and genetic risk did not modify this association. Furthermore, the CRI had a direct association with cognitive function which was independent of hippocampal volume. However, the CRI did not modify the cognitive expression of lower hippocampal volume. Thus, the findings suggest that the CRI was associated with cognitive function through two different pathways, but not through CR (Figure 52).

In accordance with the first hypothesis for this study, the findings consistently showed that the CRI was significantly associated with higher hippocampal volumes and that education and leisure might be driving this effect. This finding replicates those of a previous study using UK Biobank data (n= 19,793) which also found that there was a small significant positive effect of level of education on average hippocampal volume (520). The findings are also in line with previous studies that have found an association between CR markers such as educational attainment and hippocampal volume (588,589). The potential neuroprotection of lifestyle factors on the hippocampus is of particular interest to cognitive ageing research, given that hippocampal atrophy is considered a sensitive biomarker for AD (590–593). The biological mechanisms that might underlie the neuroprotective effects of lifestyle on the brain have been theorised to work at a molecular level (e.g., synaptic plasticity and BDNF) and at a cellular scale (e.g., neurogenesis, synaptogenesis, and angiogenesis), with some evidence suggesting that these mechanisms might be specific to hippocampal integrity (589,594). Furthermore, the sub-component results provide

additional evidence for the association between leisure activity engagement and hippocampal volume, consistent with that found and discussed in Chapter 5 – once again highlighting the theory that lifelong participation in diverse and stimulating activities promotes normal cognitive function and brain health through hippocampal protection.

In contrast to the findings from Chapter 5 using Insight 46 data, the CRI did not modify the association between hippocampal volume and cognitive function. The conclusions of this study are also at odds with previous studies that consistently found that CR proxies modify the association between hippocampal volume and cognition or dementia (213,220,433,512,553,562), and with a recent study using UK Biobank data (N=15,585) which found that the moderating effect of CR proxies become more pronounced for the hippocampus for older individuals (417). As the findings for the interaction between brain volume and CR discussed above, the hippocampal volumes of UK Biobank were significantly higher than those in Insight 46 and thus it is possible that when pathology is low, the compensatory effect of CR is not yet measurable for this sample. It is also likely that the sample size was not large enough to detect the interaction effect. Previous evidence has supported this idea, suggesting that CR's ability to predict cognitive function becomes stronger as the sample size and evidence of neuropathology increases (417,586).

6.4.3 WMHV

As expected, the CRI showed a negative, although not significant, association with WMHV, and this association was not modified by genetic risk, sex, or age. However, the CRI was directly and independently associated with cognitive function. Furthermore, a three-way interaction between the CRI, WMHV, and APOE e4 on cognitive function suggested that the strength of the association between WMHV and cognitive function was dependent on the

level of CRI and the presence of APOE e4. These findings indicate that, despite not being directly associated with the WMHV, the CRI is associated with cognitive function directly and independently, as well as indirectly through CR – although the direction and size of the effect of this last pathway depend on genetic risk (Figure 53).

As expected, the CRI was negatively associated with WMHV even if the association did not reach statistical significance. This finding is at odds with the results from one study that found that higher education significantly predicted lower WMHV (595), but is in accordance with another study using UK Biobank which found no association between frequency of leisure activity engagement and WMHV (n=7,152) (310). The finding is also in accordance with those from Chapter 5 using Insight 46 data, and with other studies which have failed to find a statistically significant association between CR proxies and vascular brain pathologies (216,510,570). Despite the contradictory evidence in the literature, the findings from this study are in line with CR theory and provide evidence for the observation that CR proxies do not directly protect the brain against the development of WMHV up to age 70.

While previous findings have found that CR modifies the risk of cognitive decline or dementia, little is known about how APOE alters the effect of CR on the risk of developing cognitive impairment. The very few studies investigating these main and interaction effects have found evidence for independent effects of APOE e4 and CR on cognitive decline and dementia (596,597), with various studies suggesting that the CR is equally protective in both e4 carriers and non-carriers (596–599). The results of this study show that CRI and APOE genotype modify the effect of WMHV on cognitive function with opposite effects of the CRI depending on the presence or absence of the APOE e4 genotype: the negative association between WMHV and cognitive function was stronger for APOE e4 carriers with high CRI and

for APOE e4 non-carriers with low CRI. Consistent with previous evidence (510,600), the analysis of the CRI subcomponents suggested that the interaction was carried out by education. The moderation findings from this study were unexpected yet somewhat consistent with previous studies suggesting that for individuals at higher risk of dementia, higher CR might exacerbate the negative cognitive effects of brain pathology (510) suggesting a "compression of morbidity" for a longer period followed by a steeper decline (see Chapter 2, section 2.3.5 'Reserve'). Furthermore, as described in Chapter 2, Section 2.2.1 "Dementia biomarkers", APOE e4 carriers have been found to be at increased risk of developing cerebrovascular abnormalities associated with WMHV (145–150). Thus, it could be that for individuals at higher risk of WMHV due to the presence of the APOE e4 genotype, by age 70, the CRI buffering effect is depleted and thus, the cognitive decline associated with WMHV is more pronounced. The findings might also reflect the effect of the CRI and APOE e4 pulling cognitive function in opposite directions. However, due to UK Biobank's overall "healthier volunteer" bias, these findings should be interpreted with care and warrant additional investigation.

6.4.4 Strengths and limitations

A major strength of the study is its large sample of participants with data for the CR components, validated cognitive tests (601) assessing domains known to decline with age, and structural brain MRI scans. The size of the sample also allowed for the sub-group analysis of three-way interactions. Some of the limitations of this study are related to limited data, namely verbal ability tests, AD pathology neuroimaging (i.e., Aβ and tau), and marital status data. Regarding verbal ability, UK Biobank collects data on crystallised cognitive ability using an adapted version of the National Institute of Health Toolbox Picture Vocabulary. However, at the time of this analysis, the data was not yet made available.

Another important limitation is the cross-sectional nature of the associations between cognitive function and brain markers and thus, the inability to test for cognitive decline. However, the health outcomes of all UKB participants are being followed long-term, and future analysis will be able to include a measure of verbal ability as a CR proxy and prospective studies of the moderating role of CR in the association between neuropathology and cognitive decline. As discussed in the previous chapter, section 5.4.3 'Strengths and limitations', since the derivation of the FRS score accounts for age, it is possible that the models that adjust for both age at scan and the FRS are over adjusted. However, the FRS was kept as a covariate since it captures cardiovascular risk better for a relatively healthy cohort at midlife. Additionally, the cognitive function tests in UK Biobank have been previously criticised due to their non-standardised and brief nature, ultimately questioning the validity of the tests (577). Furthermore, participants were only included if they had complete data in all cognitive tests, which could increase the risk of selection bias. As previously mentioned, it is important to acknowledge that the UK Biobank had a low response rate (602) which resulted in selection bias.

One of the primary focus areas of Chapters 4 to 6 was to investigate the CR hypothesis in older, cognitively healthy individuals. However, given the highly educated and healthy status of the participants, this precluded the observation of a wide variance in the brain markers and cognitive function scores. Additionally, most population-based studies investigating lifestyle factors and cognitive function have been conducted among highly educated urban populations. Thus, future studies using data from participants in the pre-clinical stages of dementia could focus on populations including individuals from more deprived backgrounds or with limited education where a wider variance for the brain markers and cognitive function measures might be available.

6.4.5 Conclusion

In conclusion, the findings from this study suggest an association between the CRI and brain markers, showing a negative association with brain volume, which was modified by age and sex, and a positive association with hippocampal volume. Furthermore, the study found a significant association between the CRI and cognitive function, independent of brain markers. However, the moderating role of the CRI in the association between brain markers and cognitive function was less clear. The findings from this study encourage further analysis using the UK Biobank dataset to disentangle the association between sociobehavioural variables and brain volume, and the role of CR markers in the association between neuropathology and cognitive function once brain age- or pathology-related volumetric changes have accumulated for this sample.

Chapter 7. The association between cognitive and social leisure activity engagement and dementia in ELSA

The methods and results presented in this chapter have been previously published in the *Journal of Alzheimer's Disease* (Almeida-Meza, Steptoe, Cadar, 2021).

7.1 Introduction

Lifestyle-related factors have been found to play a crucial role in modifying the risk of dementia, particularly for those activities that improve the brain's resilience. Hence, improving brain and CR capacity through healthy lifestyle choices represents a promising preventive avenue against dementia development (284). As individuals reach middle and older age, activities such as education and occupation might not always be feasible modifiable risk factors. However, leisure engagement might represent a relevant avenue since they are more amenable to intervention (187).

Leisure time activities, described as activities that are independent of work and the purpose of which is enjoyment or well-being (283), appear to have an essential role in maintaining brain health and contributing to CR capacity (287). Chapter 2, section 2.3.4 "Leisure" summarises the evidence for the association between engagement in intellectual, social, and physical leisure activity and cognitive function and dementia risk, as well as the potential pathways through which these activities contribute to BR and cognitive function.

Consistent with BR theory, evidence from Chapters 4 to 6 supports the association between leisure engagement and hippocampal volume. Furthermore, the results of the studies carried out with NSHD and UK Biobank data suggest that the association between leisure activity engagement and cognitive function is independent of brain markers, and that

leisure engagement modifies the association between brain and hippocampal volume, supporting CR theory. Thus, compared to education and occupation, leisure activity engagement appears to be the most robust brain and CR marker.

Previous studies have shown that engaging in a wide variety of hobbies has protective effects against dementia onset, with a study finding a 14% decreased risk of dementia for those who report engaging in a higher number of activities (603). The risk of dementia has also been found to differ depending on sociodemographic factors such as sex and marital status. Evidence from 461 participants from the Louisiana Brain Study suggested sex differences in cognition, depression, and vascular risk, with men having higher vascular risk with lower cognitive performance compared to women, and women being more likely to have depression (42). Furthermore, engagement in healthy lifestyle behaviours has been associated with being married and a reduced risk of dementia when compared to those who are single or widowed (604). Additionally, the effect of marital status on dementia appears to be particularly important for men, for whom being married represents a protective factor (605). Furthermore, as discussed in Chapter 2, section 2.3.4 'Leisure', people engage in different types of leisure depending on age, gender, and marital status, with intellectual and social activities appearing to be suitable for dementia prevention in ageing populations.

Most research examining the relationship between engagement in intellectual and social leisure activities and dementia has been carried out cross-sectionally or longitudinally with relatively shorter follow-up periods, raising the question of reverse causality (187,606). Moreover, it is still unclear which specific activities affect cognition to a greater degree and whether the favourable effects of a healthy lifestyle on the brain are independent of sex, marital status, and the risk of death (310). Thus, this study sought to investigate intellectual

and social leisure activity by grouping these activities into two distinct domains and exploring their longitudinal association with dementia incidence.

7.1.1 Objective

The study was carried out with data from ELSA, a population-based cohort of older adults living in England. The study aimed to investigate the association between two distinctive domains of intellectual and social activities and dementia risk, while accounting for the risk of death over a follow-up period of up to 15 years. The modifying roles of sex and marital status in the relationship between leisure activities and dementia incidence were also examined. Additionally, the role of each social and intellectual leisure activity on dementia risk was investigated.

7.1.2 Research questions

1) Are the intellectual and social leisure domains associated with dementia incidence? If so, do sex and marital status modify these associations?
2) Which of the individual intellectual and social activities are associated with dementia risk? For the activities that show an association, do sex and marital status modify the association?

7.1.3 Hypotheses

1) Engagement in intellectual and social engagement will be associated with lower dementia incidence.
2) The association between intellectual and social engagement and dementia will be stronger for females and married individuals.

7.2 Methods

7.2.1 Study population

The data were extracted from the ELSA, a longitudinal observational study of a representative sample of people living in England, aged fifty years and older (607). Data collection has been carried out every two years since 2002, using computer-assisted personal interviewing. The study sample is refreshed periodically with new participants to maintain the age structure of 50 and older. The baseline for the present analysis was either wave 1 (2002-2003) for those core members who started the study at this initial stage or waves 3 (2006-2007) or 4 (2008-2009) for those who joined the study as refreshment samples. At the time of this analysis, the latest available data were from wave 8 (2016-2017), ensuring a follow-up period of up to 15 years for those who joined at wave 1 (n=7,733), up to 11 years for those who joined as refreshment sample at wave 3 (n=92); and up to 9 years for those who joined as refreshment sample at wave 4 (n=205).

The study was carried out using complete case analysis based on individuals with data in the outcome, predictors, and covariates. Participants with dementia at their baseline assessments were excluded. See Figure 54 for the flow chart of the analytical sample.

Ethical approval for data collection in ELSA was granted by the National Research Ethics Service (London Multicentre Research Ethics Committee) in accordance with the Declaration of Helsinki. All participants provided informed consent.

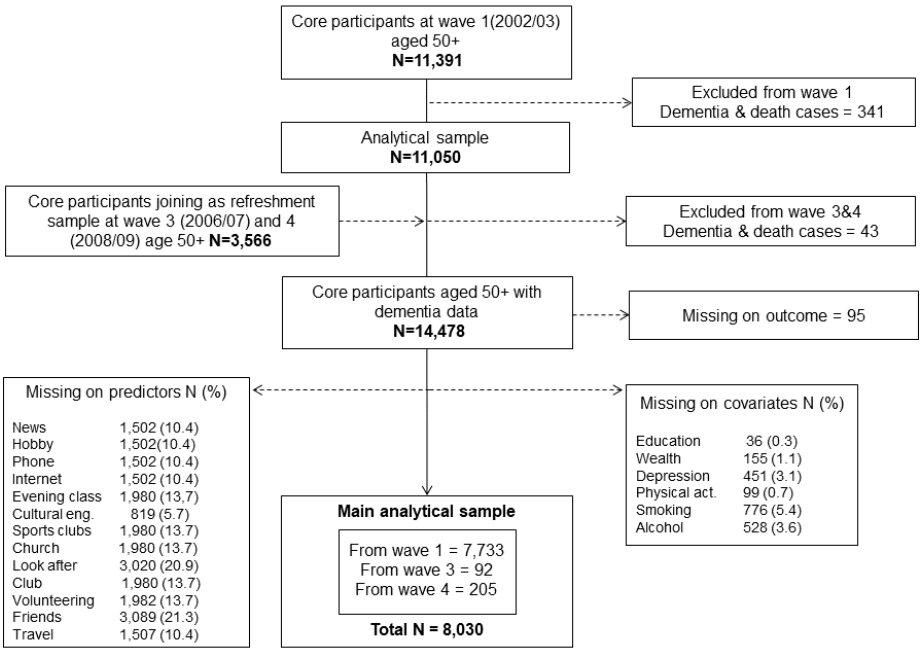


Figure 54 Flowchart of participants selected for the current analyses from ELSA.
*Numbers of excluded participants are non-mutually exclusive

7.2.2 Measures

7.2.2.1 Leisure activities

The 13 individual leisure activities were extracted at baseline from various questionnaires enquiring about cultural engagement, community engagement, and participation in various recreational activities. The questions had different answer categories, including binary measures or frequency of participation. Therefore, all answers were re-grouped into binary responses, so one point was allocated for each individual activity. Activities that captured similar measures, such as 'participation in social activities' and 'meeting with friends', were clustered into a single variable (see Appendix E, Table E1 for the derivation of leisure variables). The activities were then classified as intellectually stimulating or socially stimulating leisure activities, resulting in two aggregate scores reflecting the total number of activities participants engaged in. Using the same approach as previous studies investigating

different domains of leisure engagement (365,608), activities were classified as cognitive if they included information processing as a central feature, and social or physical demands were secondary or minimal. See Table 18 for the leisure activity classification. The domains indicate broad measures of intellectual and social leisure, reducing the measurement error specific to each individual leisure activity.

Table 18 Individual leisure activities categorised into intellectual or social domains in ELSA.

	Intellectual	**Social**
1.	Reading newspapers	Membership to sports clubs
2.	Having a hobby or pastime	Church groups
3.	Using a mobile phone	Looking after others (e.g., grandchildren)
4.	Using the internet or email	Belonging to an organization (e.g., political or union group)
5.	Attending art or music groups	Charitable associations and/or volunteering
6.	Cultural engagement	Belong to a social club and/or meeting with friends
7.	-	Taking holidays in the UK, abroad, and/or day trips

7.2.2.2 Dementia

Dementia was determined at each wave using an algorithm based on a combination of a positive self-reported or informant-reported physician diagnosis of dementia or a score above the threshold of 3.38 (commonly used cut-off point with specificity=0.84 and sensitivity=0.82) (609,610) on the 16-question Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (611). When individuals were not able to participate personally in the interview, the IQCODE questionnaire was administered to a family member or caregiver, who evaluated the changes in everyday cognitive function (e.g., remembering names of family members) compared to 2 years ago. Each IQCODE item is scored from 1

(much improved) to 5 (much worse). In the present study, 133 (32%) of 412 cases of dementia were classified with dementia via higher scores on the IQCODE scale.

7.2.2.3 Mortality

For participants who consented to data linkage (96.5% of sample) (612), mortality data records up to December 2018, were obtained from the National Health Service Central Register.

7.2.2.4 Model adjustment

Self-reported sex and marital status (categorized as married, single/divorced, and widowed) were identified as confounders as well as possible moderators. Socioeconomic covariates were captured through education and wealth quintiles. Education was captured in five categories: higher education or degree; A levels or O-levels; NVQ1, or CSE; foreign qualifications, or other qualifications; and no qualifications. The wealth variable reflects the accumulation of assets over the life course, it includes financial wealth, the value of properties, business assets and physical wealth minus any debt. The baseline median wealth for the overall sample included in this analysis was £15,100 (613). Health conditions were assessed through physician diagnoses of coronary heart disease, stroke, hypertension, and diabetes. Depressive symptoms were ascertained with the 8-item Centre for Epidemiologic Studies Depression Scale (CES-D), which is designed to measure depressive symptomatology in the general population (614). Finally, lifestyle behaviours (physical activity, smoking, and alcohol intake) were also considered.

7.2.3 Statistical analysis

Descriptive statistics for those who remained dementia-free and those who developed dementia during the study period were carried out by level of engagement in intellectual

and social leisure activities and covariates, using independent sample t-tests for continuous measures (leisure activity domains and CES-D) and Pearson chi-square test for categorical variables.

Death has been identified as a competing risk for dementia and is related to some lifestyle factors. Treating death as non-informative censoring of an outcome in longitudinal studies may result in biased estimates (615). Therefore, to investigate the relationship between the leisure activity categories and dementia incidence, while considering the competing risk of death, Fine and Gray proportional subdistribution hazard models were carried out (616). Survival age was used as the underlying time variable. Survival age was derived using survival time, which was calculated using the participants' baseline age until the age they reported dementia diagnosis or the end of the study period (i.e., last wave before dropout or wave 8).

Two separate analyses were carried out for the intellectual and social leisure activity domains; each domain was defined as the number of activities performed (i.e., count variables).

Additional individual analyses were carried out for each of the 13 individual leisure activities. The frequency of participation was used when available, such as cultural engagement (i.e., never, less than once a year, once or twice a year, every few months), volunteering (i.e., never, less than once a year or up to twice a year, every few months) and meeting with friends (i.e., never, once, or twice a month, once or twice a week, three or more times a week). All other leisure activities were grouped into participation versus no participation (binary). Sub-hazard ratios (SHR) and their respective 95% confidence intervals were calculated using 4 models: Model 1 adjusted for sex and marital status; model 2 also

included education and wealth; model 3 further adjusted for health conditions, including depressive symptoms; and model 4 further adjusted for lifestyle behaviours. Additionally, the interactions with sex and marital status with all predictor variables were explored.

Information on the proportional hazard assumptions is available in Appendix E. Due to the large sample size, the analyses were carried out using complete data. All analyses were weighted using the baseline cross-sectional weights derived in ELSA to ensure the sample is representative of the English population. All analyses were conducted in Stata MP, Version 16 (Stata Corp).

7.2.3.1 Sensitivity analysis

Several sensitivity analyses were carried out to assess the dementia diagnosis procedure, the varying study entries, and data missingness. The first sensitivity analysis addressed the different classifications of dementia diagnosis (i.e., doctor diagnosis and IQCODE scores) by excluding participants that were classified as having dementia through the IQCODE score. The second sensitivity analysis addressed the varying baseline assessments by excluding participants who joined the study as refreshment samples at waves 3 or 4. The final sensitivity analyses were conducted to assess the impact of missing data by performing multiple imputations using chained equations and repeating the analyses for the leisure domains.

7.3 Results

7.3.1 Descriptive statistics

The analytical sample was comprised of 8,030 participants (81, 726.92 person-years) with an average baseline age of 63.8 (SD=9.60) years. The sample consisted of 3,568 (44%) males

and 4,462 (56%) females (Table 19). At the time of the event or last wave of follow-up, the mean age for all participants was 74 (SD=9.31) years, ranging from 52 to 102.

From the overall sample, 412 participants were diagnosed with dementia, accounting for 5.13% cumulative incidence during the 15-year follow-up period. The group of individuals with dementia included 180 (44%) males and 232 (56%) females with a median age of 81 (SD=8.22) years at the time of dementia diagnosis. Furthermore, 2,192 (27%) participants died within the study period, with a mean age at death of 81 (SD=9.53) years. From this group, 274 died after receiving a dementia diagnosis.

Initial statistical investigation showed that participants who developed dementia were older, had less education, were more likely to be widowed, and were diagnosed with comorbidities at baseline (see Table 19). The group of participants who developed dementia generally engaged in less intellectual and social leisure activities than those who did not develop dementia. The percentages of the baseline sample engaging in each leisure activity are also presented in Table 20.

Table 19 Baseline characteristics of participants in ELSA with and without dementia at follow-up.

Characteristics	**No dementia (n=7,618)**	**Dementia (n=412)**	**p-value**
Age: 50-59	3,224 (42%)	37 (9%)	<0.001
60-69	2,382 (31%)	114 (28%)	
70-79	1,501 (20%)	156 (38%)	
≥80	511 (7%)	105 (25%)	
Sex: Male	3,388 (44%)	180 (44%)	0.755
Female	4,230 (56%)	232 (56%)	
Marital status: Married or remarried	5,258 (69%)	243 (59%)	<0.001
Single/Divorced or legally separated	1,249 (16%)	48 (12%)	
Widowed	1,111 (15%)	121 (29%)	
Education: Higher education	2,014 (26%)	70 (17%)	<0.001
A-levels	1,887 (25%)	78 (19%)	
<A-levels	345 (5%)	22 (5%)	
Foreign/other	673 (9%)	39 (10%)	
No qualification	2,699 (35%)	203 (49%)	
Wealth: 5 (highest)	1,118 (15%)	98 (24%)	<0.001
4	1,411 (19%)	77 (19%)	
3	1,558 (20%)	93 (22%)	
2	1,705 (22%)	70 (17%)	
1 (lowest)	1,826 (24%)	74 (18%)	
Physical Activity: Sedentary	1,084 (14%)	110 (27%)	<0.001
1	1,114 (15%)	81 (20%)	
2	2,296 (30%)	119 (29%)	
3	1,590 (21%)	63 (15%)	
Active	1,534 (20%)	39 (9%)	
CHD: No	6,904 (91%)	333 (81%)	<0.001
Yes	714 (9%)	79 (19%)	
Stroke: No	7,392 (97%)	382 (93%)	<0.001
Yes	226 (3%)	30 (7%)	
Hypertension: No	4,900 (64%)	228 (55%)	<0.001
Yes	2,718 (36%)	184 (45%)	
Diabetes: No	7,145 (94%)	375 (91%)	0.025
Yes	473 (6%)	37 (9%)	
Smoke: No	6,325 (83%)	355 (86%)	0.097
Yes	1,293 (17%)	57 (14%)	
Alcohol: 1-2 month/never	2,851 (37%)	194 (47%)	<0.001
1-2 week/daily	4,767 (63%)	218 (53%)	
Depressive symptoms (CES-D) *	1.40(1.85)	1.91 (1.99)	<0.001

Data displayed as n (%) or *means ± SD

CHD: Coronary heart disease. CES-D: Centre for Epidemiologic Studies Depression Scale.

Table 20 Distribution of baseline leisure activity engagement for participants with and without dementia at follow-up.

Characteristics	**No dementia (n=7,618)**	**Dementia (n=412)**	**p-value**
Newspaper: No	2,308 (30%)	133 (32%)	0.394
Yes	5,310 (70%)	279 (68%)	
Hobby: No	1,340 (18%)	106 (26%)	<0.001
Yes	6,278 (82%)	306 (74%)	
Phone: No	2,792 (37%)	237 (57%)	<0.001
Yes	4,826 (63%)	175 (43%)	
Internet: No	4,855 (64%)	342 (83%)	<0.001
Yes	2,763 (36%)	70 (17%)	
Art or music groups: No	6,476 (85%)	358 (87%)	0.295
Yes	1,142 (15%)	54 (13%)	
Sports clubs: No	5,977 (78%)	363 (88%)	<0.001
Yes	1,641 (22%)	49 (12%)	
Church: No	5,940 (78%)	294 (71%)	0.002
Yes	1,678 (22%)	118 (29%)	
Look after others: No	5,951 (78%)	349 (85%)	0.002
Yes	1,667 (22%)	63 (15%)	
Club or organization: No	4,134 (54%)	239 (58%)	0.137
Yes	3,484 (46%)	173 (42%)	
Travel: No	809 (11%)	77 (19%)	<0.001
Yes	6,809 (89%)	335 (81%)	
Social club: No	5,958 (78%)	324 (79%)	0.836
Yes	1,660 (22%)	88 (21%)	
Volunteering: Never	5,202 (68%)	309 (75%)	0.004
Once to twice a year or less	457 (6%)	12 (3%)	
Every few months or more	1,959 (26%)	91 (22%)	
Cultural engagement: Never	4,704 (62%)	311 (75%)	<0.001
Less than once a year	1,430 (19%)	52 (13%)	
Once or twice a year	1,074 (14%)	30 (7%)	
Every few months	410 (5%)	19 (5%)	
Meeting friends: Every few months or never	1,182 (15%)	72 (17%)	0.390
Once or twice a month	1,879 (25%)	99 (24%)	
Once or twice a week	3,288 (43%)	164 (40%)	
Three or more times a week	1,269 (17%)	77 (19%)	
Intellectual leisure activities domain*	3.08 (1.39)	2.46 (1.31)	<0.001
Social leisure activities domain*	3.20 (1.37)	2.94 (1.38)	<0.001

Data displayed as n (%) or *means ± SD

7.3.2 Research question 1

7.3.2.1 Intellectual leisure activities

At baseline, most participants (70%) engaged in 2 to 4 intellectual activities, with only 3% reporting no engagement in any intellectual leisure activities and 4% participating in 6 activities (see Appendix E, Figure E1).

The competing risk regression showed a significant association between intellectual leisure activities and dementia after controlling for all covariates (SHR: 0.91, 95% CI 0.83-0.99, p=0.003). This model also showed a positive association between increased depressive symptomatology (SHR: 1.08, 95% CI 1.02-1.23, p=0.004) and dementia incidence, and a significant negative association with increased physical activity (SHR 0.61, 95% CI 0.41-0.92, p=0.02) and dementia incidence.

Additional exploration for effect modification by marital status showed a significant interaction (p=0.05). As presented in Table 21, after stratification for marital status, it was found that in the fully adjusted model, an increased engagement in intellectual leisure activities was associated with a decreased incidence of dementia for married individuals (n=5,501; SHR: 0.85, 95% CI 0.76 to 0.96, p=0.007) (see Figure 55); although this was only the case when intellectual engagement was entered as a continuous variable and not as categorical (Table 22).The association between intellectual leisure activities and dementia was non-significant for the single/divorced (n= 1,297; SHR: 1.11, 95% CI 0.85 to 1.45, p=0.46) and widowed (n=1,232; SHR: 0.98, 95% CI 0.83 to 1.17, p=0.86) stratum (see Appendix E, Table E2 for gradual adjustment). The interaction between the intellectual leisure activities domain and sex was non-significant (p=0.79).

Table 21 Sub-hazard ratios and 95% confidence intervals of the competing risk models indicating the incidence of dementia for engagement in leisure activities.

Domains	N	Model 4	p-value
Intellectual leisure activities			
Married	5,501	0.85 (0.76 to 0.96)	0.007
Single or divorced	1,297	1.11 (0.85 to 1.45)	0.46
Widowed	1,232	0.98 (0.83 to 1.17)	0.86
Social leisure activities	8,030	0.98 (0.90 to 1.06)	0.20

Intellectual leisure activities are stratified by marital status.
Model 1: Sex and marital status. Model 2: Model 1 + education and wealth. Model 3: Model 2 + physical health covariates and depression. Model 4: Model 3 + lifestyle factors.

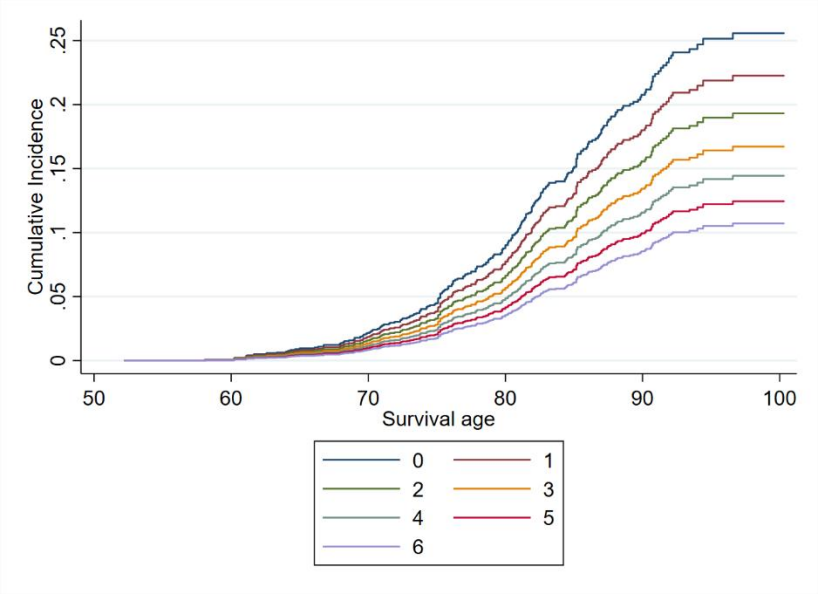


Figure 55 Competing risk regressions by the number of intellectual activities performed by married individuals aged 50+ in ELSA.

Table 22 Sub-hazard rations and 95% confidence intervals of the competing risk models indicating the incidence of dementia by the number of intellectual activities performed.

Number of intellectual leisure activities	Model 4
0	Reference
1	1.35 (0.64 to 2.87)
2	0.97 (0.46 to 2.03)
3	0.84 (0.39 to 1.82)
4	0.70 (0.31 to 1.56)
5	0.66 (0.26 to 1.67)
6	0.50 (0.15 to 1.82)

Model 1: Sex and marital status. Model 2: Model 1 + education and wealth. Model 3: Model 2 + physical health covariates and depression. Model 4: Model 3 + lifestyle factors.

7.3.2.2 Social leisure activities

As in the case of intellectual activities, 72% of participants reported 2 to 4 social leisure activities, while 1% did not engage in any social activity. Only 0.64% of the participants engaged in 7 social activities (see Appendix E, Figure E1).

The association between the social domain of leisure activities and dementia incidence is presented in Table 21. The minimally adjusted model showed a significant association between engagement in social leisure activities and dementia incidence (SHR 0.92, 95% CI 0.86 to 0.99, p=0.03). However, in Model 2, the association between social leisure and dementia was explained after adjusting for educational attainment and wealth (SHR: 0.95, 95% CI 0.88 to 1.03, p=0.20) (see Appendix E, Table E2 for gradual adjustment). The interactions between the social leisure domain and sex (p=0.70) or marital status (single/divorced p=0.09; widowed p=0.12) were non-significant.

In terms of covariates, it was found that increased depressive symptomatology (SHR: 1.08, 95% CI 1.03-1.13, p=0.003) and physical activity (SHR: 0.59, 95% CI 0.39 to 0.88, p=0.01) were significantly associated with a reduced dementia incidence.

7.3.4 Research question 2

Table 23 summarizes the competing risk regressions indicating the incidence of dementia for individual leisure activities. Model 1 showed a significant association between individual activities and dementia incidence for reading the newspapers (SHR 0.77, 95% CI 0.63 to 0.95, p=0.02), having a hobby (SHR 0.72, 95% CI 0.58 to 0.91, p=0.005), using the mobile phone (SHR 0.74, 95% CI 0.60 to 0.91, p=0.004), using the internet (SHR 0.74, 95% CI 0.56 to 0.97, p=0.03), cultural engagement for those who do it once or twice a year (SHR 0.66, 95% CI 0.45 to 0.97, p=0.03), sports clubs (SHR 0.67, 95% CI 0.50 to 0.91, p=0.01), and volunteering for those who engage in the activity every few months (SHR 0.78, 95% CI 0.62 to 0.99, p=0.05) (see Appendix E, Tables E3 and E4 for gradual adjustment). However, after adjustment for all covariates, it was found that only two activities: reading the newspaper (SHR 0.79, 95% CI 0.64 to 0.98, p=0.03) and using a mobile phone (SHR 0.80, 95% CI 0.65 to 0.99, p=0.04) maintained a significant and independent association with dementia incidence.

Table 23 Sub-hazard ratios and 95% confidence intervals of the competing risk models indicating the incidence of dementia for individual leisure activities.

Domains	SHR (95% CI)
Intellectual leisure activities	
Reading newspapers: No	[Reference]
Yes	0.79 (0.64to0.98)*
Having a hobby or pastime: No	[Reference]
Yes	0.85 (0.66 to 1.08)
Using a mobile phone: No	[Reference]
Yes	0.80 (0.65 to 0.99)*
Using the internet: No	[Reference]
Yes	0.82 (0.61 to 1.09)
Art or music groups: No	[Reference]
Yes	1.14 (0.84 to 1.56)
Cultural engagement: Never	[Reference]
Less than once a year	1.01 (0.74 to 1.38)
Once or twice a year	0.83 (0.55 to 1.24)
Every few months	1.63 (0.99 to 2.68)
Social leisure activities	
Sports clubs: No	[Reference]
Yes	0.83 (0.60 to 1.14)
Church groups: No	[Reference]
Yes	1.16 (0.93 to 1.46)
Look after others: No	[Reference]
Yes	0.79 (0.60 to 1.04)
Organization membership: No	[Reference]
Yes	1.01 (0.81 to 1.26)
Volunteering: Never	[Reference]
Less than once a year or up to twice a year	0.75 (0.42 to 1.33)
Every few months	0.91 (0.70 to 1.17)
Meeting with friends: Never	[Reference]
Once or twice a month	1.08 (0.80 to 1.48)
Once or twice a week	0.87 (0.66 to 1.16)
Three or more times a week	0.96 (0.69 to 1.34)
Holiday: No	[Reference]
Yes	0.97 (0.74 to 1.27)

Model adjusted for sex and marital status, education, wealth, physical health covariates, depression, and lifestyle factors. *p<0.05, **p≤0.001.

Additional interaction analyses were carried out for each leisure activity. As presented in Table 24, there was a significant interaction between sex and reading the news (p=0.06) and between sex and phone use (p=0.06). There was also a significant interaction between marital status and having a hobby (p=0.04). After stratification, it was found that reading the newspapers was significantly associated with a decreased incidence of dementia in females

(SHR 0.65 95% CI 0.49 to 0.84, p=0.001), mobile phone usage in males (SHR 0.61, 95% CI 0.45 to 0.84, p=0.002) and having hobbies in married individuals (SHR 0.70, 95% CI 0.51 to 0.95, p=0.02), independent of all covariates (see Appendix E, Table E5 for gradual adjustment).

Table 24 Sub-hazard ratios and 95% confidence intervals of the competing risk models indicating the incidence of dementia for individual activities with significant interactions for sex and marital status.

Individual leisure activities	**SHR (95% CI)**
Reading newspapers*sex (p=0.061)	
Males: No	[Reference]
Yes	1.04 (0.73 to 1.50)
Females: No	[Reference]
Yes	0.65 (0.49 to 0.84)**
Phone use*sex (p=0.056)	
Males: No	[Reference]
Yes	0.61 (0.45 to 0.84)*
Females: No	[Reference]
Yes	1.05 (0.78 to 1.40)
Hobby*marital status (p=0.044)	
Married or remarried: No	[Reference]
Yes	0.70 (0.51 to 0.95)*
Single or divorced: No	[Reference]
Yes	1.43 (0.67 to 3.07)
Widowed: No	[Reference]
Yes	1.01 (0.64 to 1.60)

Sex, marital status, education, wealth, physical health covariates, depression, and lifestyle factors.
*p<0.05, **p≤0.001

7.3.5 Sensitivity analyses

All sensitivity analyses confirmed the results found in the primary analyses. Appendix E, Tables E6 to E7 present the results for the first two sensitivity analyses using complete data. Sensitivity analysis 3 showed that after performing multiple imputation, the results for the intellectual leisure activity domain were similar for married individuals (SHR 0.90, 95% CI 0.81 to 0.99, p=0.04). Furthermore, comparably to the analysis performed using complete

data, the results for the social activity domain were non-significant (SHR 0.96, 95% CI 0.90 to 1.03, p=0.27).

7.4 Discussion

This study investigated the association between leisure engagement, categorized into two distinctive domains of intellectual and social activities, in relation to dementia incidence in a representative sample of the English population aged 50 years and older. The major findings from this study are: (i) increased engagement in intellectual leisure activities was negatively and independently associated with dementia incidence in married individuals, but not in those who were single, divorced, or widowed; (ii) there was no association between social leisure engagement and dementia risk; and (iii) the individual investigation of leisure activities suggested that reading the newspaper for females, mobile phones use for males, and engaging in hobbies for married individuals are associated with a reduced risk of dementia. All analyses accounted for the competing risk of death, and the findings were independent of important risk factors such as education, wealth, vascular health, diabetes, depressive symptoms, physical activity, smoking, and alcohol intake.

7.4.1 Intellectual and social leisure domains

The findings from the intellectual domain exploration contribute to the growing body of evidence from observational studies suggesting that an intellectually engaged lifestyle is associated with a reduced risk of dementia (617). A meta-analysis comprising 19 studies found significant evidence for the association between participation in mentally stimulating activities and a reduced risk of cognitive impairment or dementia in later life (316). It is theorized that leisure time activities that are cognitively stimulating, such as reading, solving puzzles, and learning experiences, may protect the brain by improving and maintaining the

brain's flexibility and adaptability, directly contributing to CR (372,618). Furthermore, intellectual activities involving cultural engagement have also shown an association with reduced dementia risk, possibly due to the activities providing individuals with novel experiences and opportunities to engage socially, contributing positive affect and CR simultaneously (619). Regarding the significant interaction with marital status found in this study, previous studies have suggested that marital status has a moderating role in the association between leisure activities and cognitive ageing, with a systematic review highlighting that being married is associated with healthier lifestyle behaviours, and consequently, to a reduced risk of dementia (604).

The findings for the social leisure domain and dementia incidence are in accordance with previous studies with extended follow-up periods (two decades) that have found non-significant associations between engagement in social activities and dementia (320,620). However, these findings are in contrast with more recent investigations supporting this association. A systematic review and meta-analysis, comprising 19 longitudinal cohorts with 2 to 15 years of follow-up, exploring the impact of participating in various social activities, found an increased risk of dementia for individuals who reported less social engagement (329). Despite these conflicting results, studies investigating the interplay between social relations and leisure engagement have shown that these activities are not independent players, but are interrelated and interdependent (621). Therefore, a socially active lifestyle might still have implications for dementia prevention, given its association with other risk factors such as increased leisure engagement and reduced loneliness (622) (see Chapter 2, section 2.3.4 'Leisure'). It is also possible that unmeasured confounding or loss of power after stratification for marital status (1,297 participants were single or divorced, 1,232 were

widowed, vs 5,501 participants who were married) might account for the finding that social leisure is not significantly associated with dementia incidence.

7.4.3.1 Physical activity and depression

The present analyses on both leisure activity domains highlighted the influence of engagement in physical activities and the importance of depressive symptoms in the incidence of dementia. The findings are consistent with other studies that have suggested that physical activity reduces the risk of cognitive impairment and dementia of any type (305,347,623). Physical leisure activities might positively affect stress reduction and improved neurotransmission, thereby enhancing CR, BR, and BM (348) (see Chapter 2, section 2.3.4 “Leisure”). Additionally, depression has been widely recognized as an important risk factor for dementia (624). Depressive symptoms might reduce engagement in leisure activities and indirectly for CR enhancement due to its debilitating impact on behaviour and social engagement (625).

7.4.2 Individual leisure activities

The investigation of the modifying effects of sex and marital status on individual leisure activities and dementia highlighted some differences in dementia incidence, with a reduced risk for females who read newspapers, males who use a mobile phone, and married individuals who participate in hobbies. Reading has shown a robust contribution to health through various studies, supporting that solitary non-strenuous activities contribute to CR and healthy cognitive ageing (626,627). Furthermore, a recent study found that general device usage (i.e., smartphone, computer, and tablet) was associated with fewer subjective cognitive concerns in individuals over the age of 65 (628). Similarly, an earlier longitudinal study investigating mobile phone use and cognition in older people found that frequent

long-term use of a mobile phone was associated with better cognitive function (629). This research by Ng and colleagues (629) found that mobile phone users were more likely to be males who work and are socially active, both activities being predictors of healthy cognitive ageing.

The findings from this study differ from those of a previous ELSA analysis, which found a significant association between internet use during midlife and incident dementia. In their study, d'Orsi et al. (630) used data from 8,238 participants with a 10-year follow-up from baseline at wave 1 (2002-2003) to wave 6 (2006-2013) and controlled for similar covariates to the ones in this study. Despite using a similar approach to investigate this association, the difference in findings might suggest a reduction in the protective effect of internet use over time. A previous study examining leisure activity participation found a significant association with dementia incidence when ascertained for a short period of time after baseline (1 - 5 years) but not when ascertained for more extended periods of time (6 – 10 and 11 – 15 years) (631). Hence, these findings support the idea that different leisure activities might have short-term or long-term effects on the risk of dementia development. Alternatively, it is also possible that there is an age-associated change in the quality of internet use over time (e.g., less intellectual challenge) or that older participants who started using the internet in their older age had an above-average level of cognitive functioning and therefore compensated for the potential neurological damage occurring and delaying the time to dementia diagnosis.

Despite some leisure activities showing an association with dementia incidence, the association of each leisure activity with dementia was generally ambiguous. This might reflect the idea that engagement in a wide variety of intellectual activities, and not

necessarily engagement in specific leisure activities, may be protective against dementia (49,244).

7.4.3 Strengths and limitations

Dementia may develop insidiously for years before the onset of the clinical symptoms, often making it difficult to establish a temporal sequence between risk factors and dementia diagnosis. Hence, longitudinal studies, such as this one, are required to better understand protective lifestyle factors for dementia. With a 15-year follow-up, this study was able to ascertain a lower dementia incidence for married individuals who engage in intellectual leisure activities, minimising the issue of reverse causality while accounting for the competing risk of death. Furthermore, the study benefitted from a large population sample in comparison to previous studies that might have extended follow-up periods but had reduced power. The study also controlled for covariates that have been identified as confounders in the association between dementia and a comprehensive set of leisure activities, including wealth. To preserve the analytical sample, the models did not introduce additional covariates, such as APOE e4, since biomarker data was only collected from a sub-sample of ELSA. The association between CRI and dementia controlling for genetic risk has been researched before in this dataset (244).

However, an important methodological issue that needs to be considered is the classification of leisure activities into either intellectual or social domains. Some activities considered in this study involve both intellectual and social engagement; hence their type might be somewhat arbitrary due to the overlap between the two domains. Another methodological issue is related to the self-reported dementia diagnosis, which could underestimate the number of participants with dementia in the study due to the

misclassification of cases. However, the sensitivity analysis that excluded individuals classified with dementia via high IQCODE scores found similar results to those of the main analysis. Last, there is a potential attrition bias due to the longitudinal nature of the study, although this was reduced by using the sample weights.

Research investigating leisure engagement as a predictor would benefit from a standardised definition and categorization of leisure activity and its categorization into cognitive, social, and physical activities, or a latent trait approach to identifying the key factors driving the association between leisure engagement and dementia risk. Furthermore, future work investigating the role of leisure activities on cognitive decline trajectories related to subsequent dementia risk could further elucidate the mechanisms involved in these associations during the prodromal stages of the disease. More research is needed to understand the association between individual leisure activities as markers of CR and dementia risk. Future work could consider the role of different follow-up periods and the onset and time of exposure to a particular activity. Longitudinal investigations researching leisure engagement trajectories from early to older age, focusing on habit formation, the stability of these habits, and how they relate to cognitive function, could inform future policies and interventions for dementia prevention starting early in life. Since participation in leisure activities tends to decline in the preclinical phases of dementia (299), studies with extended follow-up periods are also desirable. Finally, due to the relevance of leisure engagement as an intervention for dementia prevention, future research should pay particular attention to determining causality. RCTs investigating optimal activities to maintain or improve cognitive function in older age would inform interventions.

7.4.4 Conclusion

In conclusion, this study provides evidence for the contribution of intellectual leisure activities to CR and the subsequent reduced risk of dementia incidence. The findings highlight the importance of assessing the role of sex and marital status on the association between leisure activities and dementia risk.

Chapter 8. Comparison of CRI measures and derivation across cohorts

For this thesis, the CRIq was used to derive a CR marker, the CRI, across three cohorts: NSHD, Insight 46, and UK Biobank. Furthermore, although the study carried out in Chapter 7 did not include a derivation of the CRI, an investigation of the association between the CRI and dementia incidence across 15 years of follow-up using ELSA data was conducted by the author as part of their master's degree (244). Thus, this chapter will focus on the harmonisation of the CRI across different studies, ensuring they are comparable and providing an opportunity to use a coordinated analysis approach to investigate the robustness, replicability, and generalisability of the association between the CRI and cognitive function or dementia (632,633). Taken together, the evidence from the previous chapters and the comparisons from this chapter demonstrate the replicability of the procedures carried out for this thesis, as well as the feasibility of using the CRI to investigate CR in population-based studies of ageing.

8.1 Education

In NSHD, educational attainment was reported when participants were aged 26, whereas in UK Biobank and ELSA, educational attainment was reported at the baseline examination when participants were 60 and 64 years old on average, respectively. As described in the 'Methods' section of Chapters 4 and 6, to be consistent with the CRI calculation, educational attainment was transformed into years of education by approximating the number of years it takes to complete each qualification. However, there was a slight variation in these approximations since they were based on the granularity of the data available and in the classification used in each dataset for previous research. A summary table with the

distribution of participants in the educational attainment categories for each analytical sample (i.e., individuals with data for cognitive function outcome) is available in Table 25.

As discussed in Chapter 5, section 5.3 'Results', when compared with the whole-NSHD analytical sample, the Insight 46 participants had higher qualifications (516). Furthermore, in comparison to NSHD, Insight 46, and ELSA samples, UK Biobank participants were more educated, with over half of the sample having professional qualifications or above; this reflects the selective nature of the UK Biobank sample.

The association between educational attainment and cognitive function across the three cohorts is summarised in Table 26. Differences in the significance of the findings across the individual investigations might respond to differences in sample size and covariate adjustment (e.g., availability of data on childhood cognition, marital status, SEP). Thus, to help comparisons while maintaining the power of each sample, in this and the subsequent sections of Chapter 8, a coordinated analysis was carried out by standardising the scores of the ACE-III, and adjusting the models for similar covariates (632,633). The results show that across the board, education was significantly associated with cognitive function, with the highest educational category predicting better cognitive scores.

Table 27 summarises the investigation of the incidence of dementia by different levels of educational attainment in ELSA. Cox proportional hazard regression models were used for this analysis; however, the proportional hazard assumption was not met, and separate models were carried out before and after the age of 80 (244). The investigation found that having a university degree or higher was associated with a lower risk of dementia for the younger age group, but not for the older age group.

Table 25 Frequency distribution of educational attainment categories and approximate years of education for the analytical samples across cohorts.

CRI classification	**NSHD** (N=1,184)		**Insight 46** (N=486)		**UK Biobank** (N=4,574)		**ELSA** (N=12,280)	
Years	Degree	N (%)	Degree	N (%)	Degree	N (%)	Degree	N (%)
20	Doctorate	6 (0.5)	Doctorate	3 (0.6)	College or university	2,223 (49)	-	-
19	-	-	-	-	Other professional qualification	782 (17)	-	-
17	Masters	8 (0.7)	Masters	4 (0.8)	-	-	-	-
16	Graduate degree	128 (11)	Graduate degree	80 (17)	-	-	-	-
15	-	-	-	-	NVQ/HND/HNC or equivalent	491 (11)	University degree or higher	3,204 (26)
13	A level or equivalent	362 (31)	A level or equivalent	178 (37)	A level or equivalent	220 (5)	-	-
12	-	-	-	-	-	-	A level or equivalent	2,953 (24)
11	GCSEs/O level or equivalent	351 (30)	GCSEs/O level or equivalent	143 (29)	-	-	-	-
10	No qualification	329 (28)	No qualification	78 (16)	GCSEs/O level/CSEs or equivalent	557 (12)	-	-
8	-	-	-	-	-	-	Completed education or school certificate	1,479 (12)
7	-	-	-	-	No qualification	301 (7)	-	-
4	-	-	-	-	-	-	Lacking formal qualification	4,644 (38)

Table 26 Association between educational attainment and cognitive function across different cohorts.

	NSHD	**Insight 46**		**UK Biobank**	
	ACE-III* (N=1,184)	ACE-III* (N=421)	PACC (N=502)	Cognitive function score (N=4,574)	
Education categories	B (95% CI)			Education categories	B (95% CI)
No qualification	[Reference]	[Reference]	[Reference]	None, O level, or equivalent	[Reference]
GCE 'O' or equivalent	0.63 (0.48 to 0.78)	0.52 (0.25 to 0.80)	0.31 (0.12 to 0.49)	A level, NVQ, or equivalent	0.15 (0.09 to 0.21)
GCE 'A' or equivalent	0.90 (0.76 to 1.05)	0.99 (0.72 to 1.27)	0.60 (0.42 to 0.78)	Other professional qualification	0.17 (0.12 to 0.23)
Degree or equivalent	1.20 (1.04 to 1.35)	1.22 (0.90 to 1.53)	0.86 (0.65 to 1.06)	College or university degree	0.34 (0.29 to 0.39)

*ACE-III standardised scores.

All models adjusted for sex, age, APOE genotype, cardiovascular risk, and psychological distress.

Table 27 Association between education attainment and dementia incidence

	ELSA	
	Dementia (N=12,280)	
	Age 50 to 79 years (N=9,155)	Age ≥ 80 years (N=3,125)
Education categories	Hazard ratio (95% CI)	
Lacking formal qualification	[Reference]	[Reference]
Completed education or school certificate	1.04 (0.70 to 1.53)	0.96 (0.70 to 1.33)
A level or equivalent	0.99 (0.70 to 1.40)	0.98 (0.71 to 1.37)
University degree or higher	0.56 (0.36 to 0.88)	1.27 (0.93 to 1.74)

Model adjusted for sex, marital status, wealth, smoking, cardiovascular risk factors, and depressive symptoms.

8.2 Occupation

The original CRI questionnaire enquires about the occupations individuals have held over their lifetime, as well as the number of years they have held each job. Thus, given the availability of the data, in NSHD, the occupational class was based participants' main occupation from age 26 to 43 and at age 53 (see Chapter 4, section 4.2 'Methods' for additional information). In UK Biobank and ELSA, the occupational class was identified at baseline, when participants had an average age of 60 and 64 years, respectively.

The descriptive tables in Chapters 4 and 5 for NSHD and Insight 46 samples provide the distribution of participants in occupation at age 53 since this age potentially captures the highest occupational class individuals acquired up to that age and was used for the CRI sub-component analysis. Table 28 below provides the distribution of the participants in the occupational categories from ages 26 to 42 and those at age 53. Overall, in NSHD and Insight 46 samples, the distribution of participants in the occupational classes is similar across the age groups, with most participants holding intermediate occupations (e.g., associate professionals) in both samples. In comparison, most ELSA participants held skilled non-manual or professional occupations. The UK Biobank sample appeared to hold higher occupations, with most participants holding what Nucci et al. 2012 categorised as highly responsible or intellectual occupations (e.g., managers, senior officials, and professional occupations.

The associations between occupation and cognitive function across cohorts are summarised in Table 29. The results show that in all cohorts, occupation was significantly associated with cognitive function. Furthermore, Table 30 summarises the Cox proportional hazard regression model investigating the association between occupational attainment

categorised into low, medium, and high levels and dementia incidence (244). The analysis suggested that higher occupational class predicted a lower risk of dementia.

Table 28 Frequency distribution of occupational class for the analytical samples across cohorts

CRI		**NSHD** (N=1,184)			**Insight 46** (N=416)			**UK Biobank** (N=4,574)		**ELSA** (N=12,280)	
Score	Occupation classification	26 to 43 years		53 years	26 to 43 years		53 years	60 years		64 years	
5	Highly responsible/ intellectual	Professional	91 (8)	101 (9)	Professional	47 (11)	49 (12)	Highly responsible / intellectual	2,447 (54)	Highly responsible/ intellectual	738 (6)
4	Professional	Intermediate	497 (42)	494 (42)	Intermediate	220 (53)	220 (53)	Professional	782 (17)	Professional	3,423 (28)
3	Skilled non-manual	Skilled non-manual	289 (24)	286 (24)	Skilled non-manual	88 (21)	87 (21)	Skilled non-manual	686 (15)	Skilled non-manual	2,931 (24)
2	Skilled manual	Skilled manual or partly skilled	284 (24)	268 (23)	Skilled manual or partly skilled	59 (14)	56 (14)	Skilled manual	557 (12)	Skilled manual	2,135 (17)
1	Low skilled manual	Unskilled	23 (2)	35 (3)	Unskilled	2 (0.5)	4 (1)	Low skilled manual	102 (2)	Low skilled manual	3,053 (25)

Table 29 Association between occupation and cognitive function across different cohorts

	NSHD	**Insight 46**		**UK Biobank**	
	ACE-III* (N=1,184)	ACE-III* (N=421)	PACC (N=502)	Cognitive function score (N=4,574)	
Occupation categories	B (95% CI)			Occupation categories	B (95% CI)
Part skilled & unskilled	[Reference]	[Reference]	[Reference]	Low-skilled or skilled manual	[Reference]
Skilled	0.51 (0.29 to 0.74)	0.21 (-0.22 to 0.64)	0.14 (-0.13 to 0.42)	Skilled non-manual	0.20 (0.14 to 0.27)
Professional	0.96 (0.74 to 1.18)	0.73 (0.31 to 1.14)	0.55 (0.29 to 0.82)	Professional	0.21 (0.15 to 0.28)
				Highly responsible or intellectual	0.33 (0.28 to 0.38)

*ACE-III standardised scores.
All models adjusted for sex, age, APOE genotype, cardiovascular risk, and psychological distress.

Table 30 Association between occupation and dementia incidence

	ELSA
	Dementia (N=12,280)
Occupation tertiles	Hazard ratio (95% CI)
Low	[Reference]
Medium	0.70 (0.57 to 0.85)
High	0.72 (0.56 to 0.91)

Model adjusted for sex, marital status, wealth, smoking, cardiovascular risk factors, and depressive symptoms.

8.3 Leisure

The leisure activities included for the CRI computation varied in each cohort depending on the data available. Since the exact activities were not always available, activities similar or associated with the ones in the CRI questionnaire were selected. Furthermore, various dimensions of the variable (e.g., engagement and frequency) were included and recategorised into binary variables (see Appendix B Table B1 and Appendix D Table D1) to ensure the information on leisure engagement was captured for most participants.

As presented at the bottom of Table 31, on average, NSHD and Insight 46 participants engaged in five leisure activities, UK Biobank participants engaged in eight activities, while ELSA participants engaged in 11. Despite the UK Biobank and ELSA samples being older (60- and 64-years vs 43 years) when these data were collected, UK Biobank and ELSA participants appeared to engage in more leisure activities. This might be explained by the presence of relatively healthy individuals in UK Biobank as well as the availability of more leisure activities data in the ELSA dataset . The leisure activities ranged between 0 to 11 in NSHD and Insight 46 samples, 0 to 15 in UK Biobank, and 0 to 25 in ELSA.

To ensure an even distribution of participants across the leisure categories, the variable was divided into tertiles. The association between leisure engagement and cognitive function across the three cohorts is summarised in Table 32. Engagement in more leisure activities was significantly associated with better cognitive performance across all cohorts.

Cox proportional hazard regression models were used to investigate the association between leisure and dementia incidence in ELSA (Table 33). However, the proportional hazard assumption was not met and separate models were carried out before and after the age of 85 (244). The investigation found that for individuals in the 50 to 84 years age group,

higher level of leisure activity was associated with lower dementia incidence. However, for those over the age of 85 leisure activities showed no significant association with dementia.

Table 31 Frequency distribution of leisure activities for the analytical samples across cohorts

CRI	NSHD				UK Biobank			ELSA		
			NSHD	Insight 46						
Leisure activities	Activity	Score	N (%)	N (%)	Activity	Score	N (%)	Activity	Score	N (%)
Reading newspapers and magazines	-	-	-	-	-	-	-	Respondent reads daily newspaper	0 1	3,905 (33) 7,801 (67)
Domestic chores	-	-	-	-	-	-	-	How respondent finds getting to the supermarket	0 1	790 (7) 10,848 (93)
								Prepare a hot meal	0 1	11,821 (96) 471 (4)
								Shopping for groceries	0 1	11,260 (92) 1,032 (8)
Driving	-	-	-	-	Time spent driving	0 1	607 (21) 2,341 (79)	Respondent drives a car or van	0 1	2,029 (21) 7,740 (79)
Leisure activities	Do you take part in sports or vigorous leisure activities	0 1	551 (47) 629 (53)	184 (38) 300 (62)	Types of physical activity in last 4 weeks	0 1 2 3 4 5	138 (3) 723 (16) 1,342 (29) 1,515 (33) 701 (15) 155 (4)	Respondent has a hobby or pastime	0 1	2,632 (23) 9,074 (77)
					Time spent watching television	0 1	981 (23) 3,252 (77)	Does mild sports or activities	0 1	1,797 (15) 10,495 (85)
								Does vigorous sports or activities	0 1	8,728 (71) 3,564 (29)
								Does moderate sports or activities	0 1	3,097 (25) 9,195 (75)
Using new technologies	-		-	-	Time spent user computer	0 1	2,228 (65) 1,208 (35)	Respondent owns a mobile phone	0 1	4,212 (36) 7,494 (64)
					Plays computer games	0 1	3,769 (82) 805 (18)	Respondent uses the internet or email	0 1	7,249 (62) 4,457 (38)
					Length of mobile phone use	0 1	726 (16) 3,822 (84)	Ability to use new gadgets	0 1	83 (57) 63 (43)

					Weekly usage of mobile phone use in last 3 months	0 1	2,459 (63) 1,448 (37)			
					Hands-free device use in last 3 months	0 1	3,155 (80) 768 (20)			
Social activities	How often would you say you met friends or relatives socially?	0 1	9 (1) 1,172 (99)	2 (1) 482 (99)	Frequency of friend/family visits	0 1	356 (8) 4,204 (92)	Political party, trade union, or environmental groups	0 1	9,739 (85) 1,752 (15)
	Do you go out to pubs, clubs, or social activities?	0 1	331 (28) 853 (72)	132 (27) 352 (73)	Leisure/social activities	0 1 2 3 4 5	1,211 (27) 1,978 (43) 1,098 (24) 256 (6) 30 (0.7) 1 (0.02)	Sports clubs, gyms, exercise classes	0 1	9,145 (80) 2,346 (20)
	Do you run/belong to a trade union?	0 1	1,068 (90) 115 (10)	437 (90) 48 (10)	-	-	-	Tenant groups, resident groups, neighbourhood watch	0 1	9,466 (82) 2,025 (18)
	Do you run/belong to any sports clubs?	0 1	860 (73) 322 (27)	326 (67) 158 (33)	-	-	-	Church or other religious groups	0 1	9,155 (80) 2,336 (20)
	Do you run playgroup, nursery, or school?	0 1	1,051 (89) 130 (11)	420 (87) 64 (13)	-	-	-	Social club	0 1	9,186 (80) 2,305 (20)
	Do you help run the local government?	0 1	1,163 (99) 17 (1)	478 (99) 6 (1)	-	-	-	Any other organisations, club, or societies	0 1	8,783 (76) 2,708 (24)
	Do you run/belong to church activities?	0 1	973 (83) 205 (17)	377 (78) 107 (22)	-	-	-	Respondent has any friends	0 1	641 (6) 10,997 (95)
								Meets up with friends	0 1	3,708 (33) 7,401 (66)
Cinema, theatre	-	-	-	-	-	-	-	Respondent goes to the cinema	0 1	9,753 (82) 2,160 (18)
								Respondent goes to the theatre, concert, or opera	0 1	9,047 (76) 2,883 (24)

DIY (e.g., gardening)	Do you do any heavy gardening apart from paid work?	0 1	690 (59) 483 (41)	247 (52) 230 (48)	-	-	-	Doing work around the house or garden	0 1	10,504 (85) 1,788 (15)
Looking after grandchildren/ nephews /nieces or elderly parents	-	-	-	-	-	-	-	Respondent looked after anyone in the past week	0 1	7,945 (79) 2,138 (21)
	In your spare time do you take part in constructive activities, making things with your hands	0 1	572 (48) 610 (52)	237 (49) 247 (51)	-	-	-	-	-	-
Voluntary work	Do you run/belong to any voluntary services?	0 1	1,055 (90) 122 (10)	416 (86) 66 (14)	-	-	-	Does voluntary work	0 1	9,485 (77) 2,796 (23)
								Charitable associations	0 1	9,409 (82) 2,082 (18)
Artistic activities	In your spare time, do you take part in musical, artistic or creative activities?	0 1	765 (65) 417 (35)	301 (62) 184 (38)	-	-	-	Education, art, or music groups or evening classes	0 1	9,971 (87) 1,520 (13)
Exhibitions, concerts, conferences	Do you run/belong to evening classes/ adult education?	0 1	983 (83) 195 (17)	389 (81) 94 (20)	-	-	-	Respondent goes to art gallery or museum	0 1	9,864 (83) 2,035 (17)
	Have you been on any educational courses or training?	0 1	592 (51) 591 (49)	198 (41) 286 (59)	-	-	-			
Journeys lasting several days	-	-	-	-	-	-	-	Respondent has taken a holiday in the UK in the last 12 months	0 1	4,829 (41) 6,877 (59)
								Respondent has taken a holiday abroad in the last 12 months	0 1	5,975 (51) 5,731 (49)

Children	-	-	-	-	-	-	-	Respondent has any children	0 1	1,542 (13) 10,126 (87)
Pet care	-	-	-	-	-	-	-	Do you keep any pets inside your house/flat	0 1	5,642 (67) 2,761 (33)
Managing one's current account	-	-	-	-	-	-	-	Ability to handle financial maters	0 1	86 (50) 85 (50)
								Managing money	0 1	12,047 (98) 245 (2)
Total range	0 to 11 activities				0 to 15 activities			0 to 25 activities		
Mean (SD)			5 (2)	5 (2)		8 (2)			11 (4)	
Total tertiles	0-4 5 6+		499 (42) 241 (20) 444 (38)	143 (31) 102 (22) 224 (47)	0-6 7 to 8 9+	0-4 5-12 13-25		663 (5) 6,379 (52) 5,251 (43)	3,719 (30) 4,168 (34) 4,393 (36)	

Table 32 Association between leisure engagement and cognitive function across different cohorts

	NSHD	**Insight 46**		**UK Biobank**	
	ACE-III* (N=1,184)	ACE-III* (N=421)	PACC (N=502)	Cognitive function score (N=4,574)	
Leisure activities	B (95% CI)			Leisure activities	B (95% CI)
0-4	[Reference]	[Reference]	[Reference]	0-6	[Reference]
5	0.38 (0.23 to 0.53)	0.40 (0.13 to 0.68)	0.29 (0.11 to 0.47)	7-8	0.05 (0.005 to 0.09)
6+	0.60 (0.48 to 0.73)	0.61 (0.38 to 0.83)	0.27 (0.12 to 0.42)	9+	0.11 (0.07 to 0.15)

*ACE-III standardised scores.

All models adjusted for sex, age, APOE genotype, cardiovascular risk, and psychological distress.

Table 33 Association between leisure and dementia incidence

	ELSA	
	Dementia (N=12,280)	
	Age 50 to 84 years (N=10,692)	Age ≥ 85 years (N=1,588)
Leisure tertiles	Hazard ratio (95% CI)	
Low	[Reference]	[Reference]
Medium	0.92 (0.72 to 1.18)	0.83 (0.59 to 1.17)
High	0.74 (0.56 to 0.99)	0.79 (0.53 to 1.17)

Model adjusted for sex, marital status, wealth, smoking, cardiovascular risk factors, and depressive symptoms.

8.4 CRI

Since the CRI is standardised to a mean of 100 with a standard deviation of 15, the scores were equal across all samples. However, due to the differences in the availability of data and the way in which the individual sub-components were measured in each dataset, the range of the CRI scores varied. In NSHD, the CRI scores ranged from 68 to 152, followed by UK Biobank (56 to 138) and ELSA (63 to 140), while Insight 46 had the smallest range of scores (78 to 152).

Table 34 summarises the unstandardised coefficients with their associated 95% confidence intervals, as well as the standardised coefficients for the association between the CRI and cognitive function across the three cohorts used in this thesis. Across all cohorts, higher scores of the CRI predict higher cognitive function, with a standardised coefficient ranging from 0.24 in UK Biobank to 0.45 in NSHD. The results also highlight a relatively smaller sample size, like that of Insight 46, is enough to detect an association between the CRI and cognitive function.

As summarised in Table 35, higher scores of the CRI were significantly associated with a lower dementia incidence. These findings suggest that the CRI is a reliable instrument to investigate the association between multiple sociobehavioural variables and cognitive function or dementia.

Table 34 Comparison of CRI unstandardised (B) and standardised (β) coefficients across different cohorts

NSHD		**Insight 46**				**UK Biobank**	
ACE-III* (N=1,184)		ACE-III* (N=421)		PACC (N=502)		Cognitive function score (N=4,574)	
B (95% CI)	β	B (95% CI)	β	B (95% CI)	β	B (95% CI)	β
0.03 (0.02 to 0.03)	0.45	0.03 (0.02 to 0.03)	0.42	0.02 (0.02 to 0.03)	0.39	0.01 (0.009 to 0.01)	0.24

*ACE-III standardised scores.
All models adjusted for sex, age, APOE genotype, cardiovascular risk, and psychological distress.

Table 35 Association between the CRI and dementia incidence

	ELSA
	Dementia (N=12,280)
CRI tertiles	Hazard ratio (95% CI)
Low	[Reference]
Medium	0.73 (0.59 to 0.92)
High	0.65 (0.48 to 0.89)

Model adjusted for sex, marital status, wealth, smoking, cardiovascular risk factors, and depressive symptoms.

Chapter 9. General discussion

9.1 Summary

This thesis assessed the different pathways, including those contributing to BR and CR, through which various sociobehavioural variables contribute to cognitive function in older age. The evidence for these pathways is summarised in Figure 56. The studies focused on the roles of the CRI and NART as markers of CR (pathway c). The studies also investigated the role of sex, age, genetic risk, and marital status in these associations. This work addressed the relative contribution of the different components of the CRI, as well as an investigation of the intellectual and social components of leisure activity engagement and their association with dementia incidence. The findings of each study were discussed in relation to the pre-specified hypotheses and in the context of the existing literature in each individual chapter.

Based on the aims and objectives, the findings of the thesis are summarized below:

i) The investigation of the moderating role of CR and APOE e4 in the association between childhood cognitive ability and cognitive function in older age (Objective 1, Chapter 4) suggested that an early and strong determinant of old age, cognitive ability, can be modified by CR. For individuals with initially lower childhood cognitive ability, CR, as indexed by the CRI and NART, predicted higher later life cognitive performance. APOE genotype did not modify the association between childhood cognition and cognitive function.

ii) Evidence suggests that sociobehavioural variables are associated with cognitive function, but their direct association with BR is less clear (Objective 2). In the

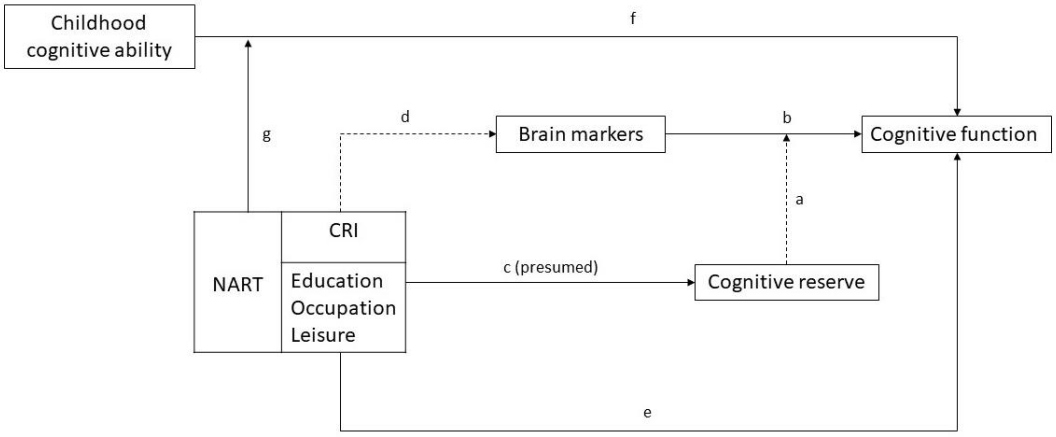
present investigations, the NART showed no association with brain markers (Chapter 5), but findings using the CRI were inconsistent across studies (Chapters 5 and 6): there was no association between the CRI and any of the brain markers in Insight 46, but in UK Biobank, there was a negative association with brain volume, with age and sex appearing to play an important modifying role.

iii) Previous evidence has provided support for the association between brain markers and cognitive function, with reserve theory proposing that CR modifies this association (Objective 3). The CR investigations in Chapters 5 and 6 supported the role of the CRI and NART as markers of CR. Evidence suggested that the association between brain markers and cognitive function depended on CR, but these findings were inconsistent across studies. For instance, in Insight 46, the CRI and NART modified the association between hippocampal volume and cognitive function, but there was no evidence of an interaction between CR and hippocampal volume in UK Biobank. APOE e4 genotype appeared to play an important modifying role in these associations.

   a. It was also found that CR as indexed by the CRI or NART, was consistently associated with cognitive function, independently of childhood cognitive (Chapters 4 and 5) ability and brain markers (Chapters 5 and 6).
   b. And, compared to the CRI sub-components (i.e., education, occupation, and leisure), the role of CR was better indicated by the CRI or NART, with the NART showing the largest coefficient (Chapter 5).

iv) From the three CRI sub-components, leisure appeared to be the most relevant (followed by education), showing a consistent association with cognitive function and brain markers, as well as showing a modifying role in the association

between brain markers and cognitive function. The more detailed investigation of the association between two distinct domains of leisure engagement (cognitive and social) and dementia (Objective 4, Chapter 7) showed that intellectual leisure engagement was inversely and independently associated with dementia incidence in married individuals. Engagement in social leisure was not associated with dementia risk.



Solid lines show paths with evidence of association.
Dashed lines show paths with inconsistent evidence of association.

Figure 56 Theorised pathways of the life course determinants of older age cognitive function.

9.2 Interpretation of key results

9.2.1 Life course approach to cognitive function

The studies in Chapters 4 and 5 in this thesis employed a life course approach to investigate the consistency and predictability of cognitive function over time (cognitive stability) and the extent to which cognitive function can be changed or improved through experience (cognitive modifiability). The studies focused on the influence of various key genetic and

socio-behavioural factors on late-life cognitive function across different stages of life, including childhood, young adulthood, mid-life, and older age. Consistent with previous evidence, the results underscored the stability of cognitive ability, and thus its role as an early factor influencing old age cognitive function. Furthermore, an important contribution of this thesis is the evidence highlighting the modifying role of sociobehavioural factors across the life course in the association between childhood cognitive ability and older age cognitive function (see Figure 56, paths f and g).

Based on the findings from this thesis, both cognitive stability and modifiability play important roles in cognitive function and cognitive ageing. Specifically, when looking at research from NSHD, the evidence seems to point to the idea that the relationships between cognitive ability and sociobehavioural factors flow in both directions, with the magnitude of the association between sociobehavioural factors and cognitive function being larger for individuals with low childhood cognition (229,230). Thus, in terms of cognitive function, the evidence seems to support the proposition that how individuals start in life does not wholly determine their future.

9.2.2 Pathways to cognitive function

The studies in Chapters 5 and 6 highlighted that the life course determinants were associated with cognitive function through two pathways, each assuming different mechanisms. Childhood cognitive ability, the CRI (including its sub-components), and the NART were consistently associated with cognitive function through what could be called a direct sociobehavioural pathway (Figure 56, paths e and f). Furthermore, there was some evidence supporting the association between the CRI and NART with cognitive function indirectly through a neuropsychological pathway because of their theorised contribution to

CR (Figure 56, path a). However, it was unclear if the sociobehavioural variables are associated with brain markers, and thus, contribute to a BR pathway (Figure 56, path d).

9.2.2.1 Sociobehavioural pathway

The association of the exposure variables to cognitive function through a sociobehavioural pathway is in accordance with the cognitive-enrichment hypothesis, which suggests that different dimensions of an active lifestyle promote healthy cognitive ageing (634). Furthermore, life course epidemiology cannot be discussed without addressing social inequalities of health. Education, work environment, social networks, and leisure pursuits are also indicators of SEP, and therefore, the sociobehavioural pathway highlights the influence of cumulative advantage (176). Exposures such as cognitive ability, education, and occupation might be inter-related, with one factor increasing the chance of subsequent exposure to the other. For example, children from more affluent backgrounds are more likely to be exposed to positive health behaviours, access medical care, and have more educational opportunities, which can turn to more job openings, safe and stimulating work environments, and a wide diversity of choices for recreation during adulthood (400). The relevance of SEP as the underlying factor driving the cumulative exposure to lifelong CR-enhancing factors has been supported by studies that have found indirect associations between early life SEP and adult cognitive function through the former's contribution to later measures of SEP (229,242,635,636).

9.2.2.2 Brain reserve pathway

The findings showed some support for the current definition of BR. The latest framework for concepts of reserve and resilience defines BR as reflecting "the neurobiological status of the brain (number of neurons, synapses, etc.) at any point in time", which is associated with

cognitive function (1). The reserve literature has also suggested that genetic and environmental factors might influence the structural characteristics of the brain, and thus, influence BR.

The work carried out in this thesis generally supported the association between brain markers and cognitive function but found conflicting or no evidence for an association between the CRI or NART and the brain markers. However, the studies provided support for the association between leisure engagement and larger hippocampal volumes. The hippocampus is the brain structure critical for the acquisition of knowledge and the formation and consolidation of memories, exhibiting the ability to adapt and reorganise its structure or function (plasticity) in response to environmental and behavioural factors such as stimulation and exercise (637). The neuroplasticity that characterises this brain structure is theorised to make it vulnerable to ageing and neurodegeneration as well as responsive to behavioural interventions aimed at improving its plasticity (638). Various short-term (induction of BDNF) and medium-term (neurogenesis, synaptogenesis, and formation of more complex dendritic branching patterns) neuroprotective mechanisms have been identified as potentially underlying the association between leisure engagement and integrity of the hippocampus (594,639). Thus, the findings are consistent with the idea that hippocampal neurogenesis is regulatable in cognitively healthy adults.

9.2.2.3 Cognitive reserve pathway

Stern and colleagues recently defined CR conceptually as "a property of the brain that allows for cognitive performance that is better than expected given the degree of life course related brain changes and brain injury or disease" (1). However, although the results do not conflict with the definition, they are better framed under Stern's original conceptualisation,

which subdivided CR into neural reserve and neural compensation (373) (see Chapter 2, Table 1). According to Stern, neural reserve represents the inter-individual variability in brain networks or cognitive paradigms that underlie task performance in a healthy brain (373). This aspect of CR matches Kremen and colleagues' updated definition, where CR represents "an individual's total or overall cognitive resources" or peak cognitive ability (379) – it's worth noting that in their life course model of CR, Richards and Deary also conceptualise CR as premorbid cognitive ability. Furthermore, as proposed by Richards and Deary, the results from this thesis support the idea that cognitive ability is modifiable across the life course and that some of the variance in older age cognitive function can be explained due to the contribution of environmental and lifestyle factors to both, CR and BR (401).

The other aspect of Stern's proposed neural implementation of reserve is neural compensation, which was described as inter-individual variability in the ability to compensate for brain pathology's disruption of standard processing networks by using brain structures or networks (373). This aspect is captured by Stern's latest conceptual definition of CR – "performance that is better than expected" (1). Kremen and colleagues referred to this ability to maintain cognitive performance simply as 'resilience' (379). The results from this thesis found a consistent and significant association between the CRI or NART and cognitive function. This association was independent of all brain markers, supporting the notion that the CRI and NART explain inter-person variation in the cognitive response to the brain markers, and satisfy the independent effect criteria of CR. However, the fulfilment of the moderation effect criteria was less consistent across cohorts. Therefore, using Stern's original definition and Kremen's CR definition update, the studies found evidence for the

contribution of sociobehavioural variables to CR (or the neural reserve aspect of CR), but the evidence was less consistent for resilience (or the neural compensation aspect of CR).

The primary focus of the CR studies was on cognitively healthy individuals in the preclinical phase of dementia. However, by definition, resilience can only be measured in the face of pathology or injury, and therefore, it is possible that given the healthy status of the participants, the moderating effect of CR cannot yet be appropriately measured due to a lack of substantial variation in brain markers. Compared to the general population, the Insight 46 and UK Biobank cohorts are comprised of healthy individuals who are more likely to have a better cognitive function, and to be more socially advantaged (229,490,516,602). Thus, despite the advanced age of the participants, individuals with sufficient dementia pathology may be underrepresented in these analyses.

However, when looking at the findings from the individual studies, the healthy status of the participants makes the Insight 46 resilience results particularly noteworthy. The findings suggested that CR modified the association between brain volume, hippocampal volume, or Aβ deposition and cognitive function. Of these brain markers, reduced hippocampal volume and Aβ accumulation often occur during the early preclinical phases of dementia and represent some of the best established pathological hallmarks of the disease, particularly AD (590–593,640). Thus, the findings suggest that hippocampal volume and Aβ status might represent suitable brain markers to investigate resilience at the early stages of the dementia process. Moreover, both the CRI and NART interacted with hippocampal volume; still, they showed different interaction effects with Aβ status and brain volume, further suggesting that these measures represent related yet separate aspects of resilience. The results also point to the idea that buffering of the clinical manifestations of the health status of one

brain structure does not necessarily mean buffering of another and thus, suggest that resilience models should consider different brain markers.

The inconsistency of findings between Insight 46 and UK Biobank could be explained by the highly selective nature of UK Biobank, the differences in the brain markers between cohorts – where UK Biobank participants had larger brain and hippocampal volumes, and the adjustment of childhood cognitive ability, which reduced the unexplained residual variance in cognitive function scores in Insight 46, thus increasing the ability to detect the small moderating effect.

9.2.3 The CRI and NART as markers of cognitive reserve

Across all studies, the CRI and NART were consistently and independently associated with cognitive function, even after adjustment for various brain markers. Thus, these two measures represent appropriate markers of CR in population-based studies. Furthermore, the CRI and NART appear to be related yet independent measures of CR, each representing different aspects of the construct: the CRI represents a formative measure capturing those experiences that contribute to its development, while the NART represents a more direct measure of cognitive reserve, being reflective of knowledge acquired over time (crystalised cognitive ability) and being highly correlated with other cognitive abilities.

In terms of the sensitivity of the CR measures, the results from Chapter 4 suggested that the CRI and NART modify the association between childhood cognitive ability and older age cognitive function with similar effect sizes. However, when accounting for brain markers, the analyses carried out in Chapters 5 and 6 suggested that when compared to the individual measures of education, occupation, or leisure, CR was better indicated by the CRI or by the NART, with the NART showing the largest coefficient for the association with

cognitive function. This observation is consistent with previous evidence (211) and the developing definitions of CR (379). As specified by Stern and colleagues, sociobehavioural variables represent lifelong CR-enhancing factors, and thus, a relatively more distal proxy of CR (384). Thus, compared to the CRI, the NART represents a more direct measure of CR's definition as "one's total cognitive resources" or "peak cognitive ability" (230,379). The inclusion of the CRI or NART as markers of CR in population-based studies should consider these differences and choose the appropriate measure depending on their availability and the aim of the investigation.

9.2.4 The relevance of leisure engagement

The studies in this thesis found consistent evidence for the association between leisure engagement and cognitive function and dementia, as well as their contribution to BR and CR. This thesis also contributed to the idea that not all activities contribute to the risk of cognitive impairment equally, highlighting the role of intellectual leisure activities in reducing dementia incidence. Overall, the findings show that an increased number of leisure activities is associated with brain and cognitive health and contributed to the literature by providing evidence of the longitudinal association of leisure engagement and reduced dementia risk. Importantly, the contribution of leisure activities to older-age cognition appears to operate through the sociobehavioural, CR, and BR pathways, underscoring their relevance for dementia prevention policies and intervention.

9.2.5 The roles of sex, age, marital status, and genetics

Epidemiological research on cognitive ageing and its determinants has suggested that differences in findings depend on sex, age, marital status, and genetic risk, with a large proportion of variance in cognitive function being explained by interactions between

modifiable and non-modifiable factors (39,400). The findings from this thesis suggested that sex, age, and APOE e4 play important roles in moderating the brain and CR pathways to cognitive function. Regarding genetic risk and age, data from NSHD and LBC have suggested that the magnitude of the association between APOE e4 and genetic risk might augment as individuals age, and that at relatively younger ages, the magnitude might be underestimated due to negative confounding by childhood cognitive ability and CR (141,641). The study carried out with UK Biobank suggested that both, CR and APOE e4, modify the association between WMHV and cognitive function. Additionally, the study carried out using ELSA highlighted the association between being married and engagement in healthier lifestyle behaviours, suggesting that engagement in intellectual leisure was associated with a lower incidence of dementia for married individuals. Taken together, these findings suggest that the cognitive benefits of the sociobehavioural variables might vary depending on sex, age, marital status, and genetic risk.

9.3 Methodological strengths and limitations

This thesis has several strengths, most of which have been summarised in each chapter. Nevertheless, a major strength to highlight is the use of publicly available datasets of panel studies. These datasets are large, which is important for moderation analysis, and contained important variables for the derivation of the CRI, as well as neuroimaging, genetic, and cognitive data. Furthermore, both ELSA and NSHD are considered nationally representative of the English population, which is critical for making inferences about the population, and UK Biobank is an ethnically diverse large-scale study allowing for group comparisons without loss of power.

Another important strength is the coordinated analysis used to investigate CR. The heterogeneity in the measures and research methods employed in CR studies has impeded the ability to compare findings across various studies. The lack of consistency in the analytical approaches make it difficult to understand the reasons behind the variations in results. Therefore, the derivation of the CRI across cohorts and the use of a similar and relatively simple study design to test the CR hypothesis optimised the comparison of the results and allowed the studies to estimate the existence and size of the relationship, and the conditions under which the association is strongest (633).

The results of this thesis should be interpreted in the context of their limitations and thus, the shortcomings of each study are detailed in the discussion section of the relevant chapters. However, this section will also address the most important overarching issues that might represent potential sources of bias and limit the generalisability of the results.

In multipurpose cohort studies like NSHD, UK Biobank, and ELSA, the measures for exposures, outcomes, and covariates may not be comprehensive. For example, the information on years of education had to be inferred, and the available variables for occupation do not provide information on complexity, job control, mental workload, novelty, and intellectual demands. Leisure activity engagement may also lack information regarding the type, frequency, intensity, and duration of the activity. Furthermore, biomedical measures may be broad as the studies were not designed specifically for investigating cognitive function or dementia. For instance, data on tau deposition was absent, while amyloid status was limited. Finally, in terms of the outcome measures used, the cognitive tests do not assess all cognitive domains, and the diagnosis of dementia in ELSA does not include hospital episode statistics.

It is also important to note limitations related to the study samples. The disproportionate burden of cognitive impairment and dementia among individuals from black and minority ethnic groups has been well documented, and research is needed to better understand the variety of risk factors across different ethnic groups (642–644). However, NSHD and ELSA are ethnically homogenous cohorts comprised of White British individuals of European descent. Additionally, although relatively more representative of ethnic minorities, UK Biobank does not cover the entire socioeconomic spectrum, representing highly educated, wealthy, and healthy individuals. Thus, the lack of diversity in research limits the generalisability of the findings to the UK population.

9.4 Future directions

The results have implications for future observational and intervention research studies investigating the determinants of cognitive ageing and dementia, and thus, suggestions regarding the findings from each study are provided in each chapter. The main overarching themes are: (i) the modification effect of CR in the relationship between neuropathology and cognitive decline, especially in studies with longitudinal cognitive assessments with long intervals; (ii) including a comprehensive range of brain markers, particularly those containing brain tau and functional measures; (iii) and considering the role of sex, age, marital status, and genetic risk in lifestyle and cognitive function research.

The framework of social determinants of health suggests that social contexts lead to unequal exposure, vulnerability, and consequences of health-damaging conditions, with the worst exposure and consequences found in the most impoverished groups (645). However, most research on this subject, including cognitive ageing and dementia research, has focused on Western, educated, industrialised, rich, and democratic populations. Since the

data for this thesis came from relatively affluent people of white European ancestry, the studies presented here fall into this category.

There is evidence suggesting that in the UK, ethnicity and areal-level deprivation are independently associated with an increased risk of dementia and younger age at dementia diagnosis (613,646). There might be multiple factors contributing to this increase in dementia risk: exposure to adverse events throughout the life course and differences in reserve, which might be reflected in differences in access to reserve-enhancing factors such as education, occupation, and leisure engagement (647). However, there is scant evidence to support this and research to understand the life course determinants of cognitive ageing and dementia in diverse populations is urgently needed (646,647).

The underrepresentation of diverse populations in dementia prevention research has been highlighted as a concern for public health. Due to the lack of diversity, studies fail to capture important differences in the disease process across different ethnicities and socioeconomic backgrounds. Therefore, it is important for dementia prevention research to include a diverse range of participants, including those from different ethnicities, socioeconomic backgrounds, and geographic regions. This will help ensure that research findings are applicable to a wider range of individuals and can inform effective public health strategies to prevent and treat dementia.

9.5 Policy implications

As outlined in Chapter 1, as the population ages, the number of people living with dementia is expected to increase dramatically, representing significant pressures on the individual, their families, society, and the health care system. Therefore, dementia prevention has been established as a public health priority. Epidemiological evidence identifying factors

influencing cognitive ageing represents an important prerequisite for implementing national and clinical level primary prevention policies. This thesis provides evidence for a relationship between lifestyle factors and older age cognitive function and dementia which has important implications for current and future policies targeted at modifying individual behaviour to prevent or reduce the risk of dementia.

The evidence from this thesis supports the WHO's global action plan on the public health response to dementia reduction on the importance of modifiable risk factors such as educational attainment and learning, cognitively stimulating activities, physical activity, and social engagement (648). However, despite England being one of the first nations to produce a national dementia policy (649), according to the *All Our Health* guide by the UK Office for Health Improvement & Disparities, only 34% of UK adults believe dementia risk is modifiable (650). Thus, health care professionals, community leaders, and public figures can promote advice regarding lifestyle behaviours to encourage people of all ages to lead brain-healthy lifestyles and reduce the risk of cognitive decline or dementia in older age.

More specifically, the life course approach of this thesis sheds light on the idea that all stages of life play an important role in influencing cognitive function, and importantly, that cognitive ability can be modified through the life course. However, the rising cost of living and associated increasing social inequality in the UK is expected to affect children from lower-income families by impacting their access to healthcare, nutrition, safe housing, education, and social support (651). Disadvantaged circumstances in childhood leading to a lower cognitive ability may be overcome to some extent by policies and governmental support addressing social inequalities such as the Sure Start Children's Centres, Pupil Premium grants, Free School Meals, National Living Wage and Minimum Wage, Social

Housing Programs, and increases to welfare benefit such as Universal Credit. Furthermore, governmental efforts to reduce cognitive decline and dementia should start early in life, especially for individuals from deprived populations with investment in key public services such as healthcare and education and provision of safe and affordable housing (647).

A final implication for policy is the availability of spaces and opportunities to increase physical activity, complex mental activity, cultural engagement and reduce loneliness by promoting social engagement. As recommended by the WHO's guide for age friendly cities (652), environmental adaptations to outdoor spaces and buildings, access and affordability of age-friendly transportation, access and range of opportunities, and awareness of events, could promote leisure activity participation. In line with this, the UK government included a social prescribing model as part of the 'A Connected Society' strategy, which works in partnership with local communities to address social loneliness (653). To date, the progress of this strategy has been related to laying its foundations, and a measurement of its impact is not yet available (654). If successful, the strategy could be used to promote other leisure activities as non-pharmacological preventive interventions for cognitive decline and dementia.

Access to safe community recreation facilities and parks, leisure centres, community activities (e.g., volunteering, art activities, group learning, reading clubs, gardening, cooking classes) and cultural events might represent important avenues to increase leisure engagement from early to older age. However, individuals from less advantaged backgrounds, who often lack financial resources, transportation, equipment, and time, might be excluded or unable to access these activities. Therefore, governmental, and not-for-profit organisations in liaison with community members can provide access to recreation

opportunities targeted at less advantaged populations through subsidized programs, free and low-cost programming, and access to recreational facilities, equipment, and supplies. Outreach, social capital, freedom to choose, and leisure education have been previously identified as key pillars supporting recreation and leisure participation for individuals from less advantaged backgrounds (655). Furthermore, these programmes have been found to be particularly successful for families with low income, when the individuals feel valued and supported and when the services are paired with transportation and child care (656). Interventions delivered via community-based organisations, private sector organisations, and government agencies offer an opportunity for targeting and supporting those at particularly higher risk. Furthermore, health care professionals can help increase the use of these spaces and awareness of their availability through social prescribing while considering appropriate activities given the resources, physical state, and level of physical activity of the individual.

9.6 Conclusions

The results of this thesis add to growing evidence for the multiple pathways through which various sociobehavioural variables are associated with older-age cognitive function and dementia risk. The studies found strong and consistent evidence for the association between childhood cognitive ability, the CRI (including its sub-components: education, occupation, and leisure), verbal ability and cognitive function, highlighting the role of CR for individuals with initially lower cognitive ability. The studies found some evidence for BR and CR, highlighting the malleability of the hippocampus and the buffering role of CR in the association between hippocampal volume and cognitive function. Furthermore, the findings suggested that maintaining an intellectually engaged lifestyle reduces the risk of dementia,

particularly for married individuals. These findings have relevance for interventions and public policies aimed at reducing dementia risk in older life.

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Appendix A. Studies investigating cognitive reserve using controlling or moderation models

Table A1. CR studies analyzing its three essential components (lifestyle factors, brain markers [AD-related structural pathology and biomarkers and/or cerebrovascular disease biomarkers], and cognition) in controlling or moderation models.

Study	Sample	Study design	Brain marker	CR marker	Outcome	Results
Jin et al., 2023 (417)	Cognitively normal older adults. N=4,731 and N=15,585	Cross-sectional.	Global brain volume, total cortical surface area, mean cortical thickness, hippocampal volume, mean cortical thickness of temporal lobe-medial aspect, temporal lobe-lateral aspect, frontal lobe, parietal lobe, and occipital lobe.	Educational attainment, fluid intelligence at baseline, physical activity, leisure activity, social interactions, and composite CR score (26 possible combinations).	Cognitive function.	Negative moderating effect of CR proxies in the association between brain measures and cognitive function. The degree of moderation varies depending on the specific CR proxy, brain marker, cognitive domain, and age group. Age influenced CR proxies' moderating effects in hippocampal regions.
Li et al., 2023 (657)	Cognitively normal older adults. N=179	Cross-sectional.	Lacunes and volumes of hippocampus, ventricles, gray matter, white matter, and WMHV.	Composite score (education and social support).	Cognitive function.	Stronger positive association between CR and cognition in women. Negative association between CR and MCI. Higher hippocampal and total white matter volume were associated with better cognition only in people with low CR.
Ko et al., 2022 (481)	Cognitively normal and cognitively impaired middle-aged and older adults. N=351	Cross-sectional.	Aβ deposition, AD-signature region cerebral glucose metabolism (AD-CM), AD-signature region cortical thickness (AD-CT).	Years of formal education, premorbid intelligence quotient, occupational complexity, and lifetime cognitive activity.	Cognitive function.	Education modified Aβ deposition and cognition. Education, premorbid intelligence, and lifetime cognitive activity modified AD-CM and cognition. Occupational complexity modified cortical atrophy AD-CT and cognition. The moderation effects were similarly observed in cognitively impaired individuals, but not in cognitively unimpaired individuals.

Boyle et al., 2021 (211)	Independent samples of cognitively normal middle-aged and older adults. N=313 and 234	Cross-sectional.	Grey matter volume, hippocampal volume, and mean cortical thickness.	Education, occupational complexity, verbal intelligence, leisure activities, and exercise.	Verbal fluency, processing speed, executive function, episodic memory, and global cognitive function.	No moderation effects were observed. Robust positive and independent (brain structure) associations with cognitive function for verbal intelligence, education, and 16 possible combinations of proxies.
Durrani et al., 2021 (658)	Cognitively normal young and middle-aged adults. N=10,916	Cross-sectional.	Vascular brain injury (non-lacunar brain infracts or WMHV)	Composite score (education, involvement in social activities, marital status, height, and leisure physical activity).	Cognitive function.	CR was associated with higher cognition. Vascular brain injury was associated with lower cognition, but this association was not modified by CR.
Li et al., 2021 (659)	Cognitively normal older adults. N=1,697	Longitudinal.	Global AD pathology burden (Aβ and tau), chronic infracts, cerebral vascular disease, Lewy bodies, and hippocampal sclerosis.	Composite score (education, early-, mid-, and late-life cognitive activities and late-life social activity).	Cognitive function.	High CR is associated with slower decline in cognition. This association remained significant in the presence of high AD pathology or gross infracts.
Casaletto et al., 2020 (660)	Independent samples of cognitively normal older adults. N=344 and 485	Cross-sectional.	Total gray matter volume, WMHV, and global fractional anisotropy.	Physical leisure and cognitive leisure activities.	Cognitive function.	In one cohort, only physical activity was associated with gray matter volume while in the other cohort only cognitive activity was associated with WMHV. In both cohorts, greater cognitive leisure, but not physical leisure, related to better cognition, independent of age and brain structure.
Kwak et al., 2020 (508)	Cognitively normal older adults. N=110	Cross-sectional.	Grey matter volume.	Composite score (education and vocabulary subtest score).	Episodic memory (immediate recall, short-delay recall, long-delay recall, and recognition subtests).	The moderating effect of CR on Immediate Recall, Short-delay Recall, and Recognition scores differed across age groups. The buffering effect of CR on cognitive decline due to brain atrophy is more evident in old-old elderly people.
Snitz et al., 2020 (661)	Cognitively normal older adults. N=100	Longitudinal.	Aβ deposition.	Baseline cognitive ability, lifestyle variables, occupational measures,	Cognitive function.	Premorbid cognitive ability predicts cognitive status and maintenance of unimpaired cognition in the presence of Aβ.

				physical and cognitive activities.		
Xu et al., 2019 (553)	Cognitively normal older adults. N=1,602	Longitudinal.	Global AD pathology burden, B-amyloid plaques, and tangles, chronic infracts and microinfarcts, cerebral vascular disease, Lewy bodies, and hippocampal sclerosis.	CR latent composite score (education; early-, mid-, and late-life cognitive activities, and social activities in late life).	Dementia diagnosis.	CR was not associated with most brain pathologies. Independent and significant association of CR with dementia. High CR was associated with dementia risk, even among individuals with high AD and gross infracts.
Udeh-Momoh et al., 2019 (533)	Cognitively normal older adults. N=91	Longitudinal.	Cerebrospinal fluid cortisol and Aβ.	CR latent composite score (standarised intracranial volume and lifetime experience).	Transition from MCI to AD.	High cortisol and Aβ associated with risk of transition. Moderating effect of reserve on cortisol/Aβ and clinical transition: high reserve reduces AD progression risk in high-risk individuals.
Buchman et al., 2019 (562)	Cognitively normal older adults. N=450	Longitudinal.	AD and other brain pathologies.	Physical activity.	Cognitive function.	Active lifestyle was associated with better cognition and reduced odds of dementia, independent of AD and other age-related brain pathologies. No interaction between physical activity and AD pathology.
Groot et al., 2018 (387)	Older adults with biomarker evidence of AD. N=663	Cross-sectional	Total grey matter volume.	Education.	Memory, attention, executive functioning, language, and visuospatial ability.	The association of CR on attention and executive functioning were greater in predementia than in dementia participants. Better cognitive performance in all domains for individuals with high CR and BR (adjusted for neuropathology).
Chan et al., 2018 (511)	Cognitively normal older adults. N=205	Cross-sectional.	Total grey matter volume.	Lifetime of Experiences Questionnaire (LEQ) (mid-life).	Cognitive function.	LEQ was independently associated with late-life cognitive ability. The LEQ moderated the relationship between brain markers and cognitive ability: people with higher LEQ were less dependent on brain structure.

Resende et al., 2018 (512)	Cognitively normal and cognitively impaired older adults. N=183	Cross-sectional.	Hippocampal volume.	Years of education.	Episodic memory.	Interaction of education with left hippocampus significantly predicted variation on memory scores.
Soldan et al., 2017 (411)	Middle aged cognitively normal adults. N=303	Longitudinal.	AD biomarkers composite score (amyloid, phosphorylated tau, and neurodegeneration)	Composite score (years of education, reading, and vocabulary).	Rate of change in cognition.	High CR is associated with better cognitive performance but does not modify rate of change in cognition. CR is associated with faster cognitive decline after symptom onset of MCI.
Pettigrew et al., 2017 (489)	Middle aged cognitively normal adults. N=232	Longitudinal.	Cortical thickness.	Composite score (years of education, reading, and vocabulary).	Progression from normal to onset of MCI symptoms.	CR and cortical thickness independently associated with symptom onset. Interaction between CR and cortical thickness for risk of progression: people with high CR compensate for cortical thinning at early phase of AD.
Soldan et al., 2015 (482)	Middle aged cognitively normal adults. N=245	Longitudinal.	Hippocampus, amygdala, and entorhinal cortex volumes.	Composite score (years of education, reading ability, and cognitive function).	Onset of clinical symptoms associated with MCI.	Medial temporal atrophy, CR, and APOE e4 independently predict time to symptom onset. Interaction between left entorhinal cortex and CR: smaller volumes predicted symptom onset only for individuals with low CR.
Vemuri et al., 2015 (422)	Cognitively normal older adults. N=393	Longitudinal.	Vascular disease (WMHV and brain infracts) and amyloid pathology.	Principal components: early life non-leisure activity and mid/late-life cognitive activity.	Cognitive decline.	The vascular and amyloid pathology processes are independent, and both drive cognitive decline. CR offsets the deleterious effect of both pathologies on cognitive trajectories.
Steffener et al., 2014 (559)	Cognitively normal young and older adults. N=84	Cross-sectional.	Cortical thickness and subcortical volumes.	Composite score (education and verbal ability)	Cognitive function.	Support for the role of lifetime exposures as CR proxies and not brain maintenance. Differences in gray matter volume and thickness on cognition are moderated by CR.

Vuoksimaa et al., 2013 (560)	Cognitively normal middle-aged men. N=494	Cross-sectional.	Hippocampal volume.	Cognitive ability at age 20.	Episodic memory.	No significant direct association between hippocampal volume and episodic memory. Significant interaction: positive association between hippocampal volume and episodic memory only for people with lower cognitive ability at age 20.
Soldan et al., 2013 (561)	Cognitively normal middle age and older adults. N=239	Longitudinal.	Aβ, tau, and cerebrospinal fluid.	Composite score (reading ability, vocabulary, and years of education).	Progression from normal cognition to AD symptom onset.	Lower CR, lower Aβ, and higher tau were associated with progression. No interaction between CR and Aβ. Significant interaction between CR and tau: higher CR protective at lower levels of tau.
Vemuri et al., 2011 (433)	Cognitively normal and cognitively impaired older adults. N=399	Cross-sectional.	Structural abnormality index (neurodegeneration, cerebrospinal tau and Aβ, WMHV).	Reading ability.	Cognitive function.	Cognitively normal participants: variability in cognition was partly explained by CR, and not by AD biomarkers. Cognitively impaired participants: CR, and AD biomarkers, independently explain variability cognitive performance. Additive association between AD biomarkers and CR on cognition.
Yaffe et al., 2011 (100)	Cognitively normal older adults. N=997	Longitudinal.	Plasma Aβ.	Years of education, and literacy.	Cognitive function.	Aβ was associated with cognitive decline. CR modified this association: for high CR, Aβ was less associated with cognitive decline.
Rentz et al., 2010 (494)	Cognitively normal and cognitively impaired older adults N=83	Cross-sectional.	Aβ deposition.	Education and reading ability.	Neuropsychological performance.	Aβ deposition is associated with lower cognitive performance in all participants. CR modified this association: higher levels of CR, Aβ deposition was less associated with poor neuropsychological performance.
Perneczky et al., 2009 (420)	Cognitively impaired older adults.	Cross-sectional.	Medial temporal lobe atrophy.	Education.	Cognitive function.	Significant inverse association between medial temporal atrophy and cognition.

	N=270					Education modifies this association: at any level of pathology, cognition was higher for better educated participants.
Bennett et al., 2006 (662)	Cognitively normal older adults. N=89	Longitudinal.	AD pathology global measure.	Social network.	Cognitive function.	AD pathology associated with worse cognitive function. Even at severe levels of global AD, cognitive function remained higher for those with larger network sizes. This was also true for tau pathology, not Aβ.
Bennett et al., 2005 (419)	Cognitively normal and cognitively impaired older adults. N=156	Cross-sectional.	Aβ and tau.	Years of education.	Cognitive function.	Aβ and tau were associated with level of cognition. Education modified the association of amyloid with cognition but not the association of tau with cognition.
Dufouil et al., 2003 (564)	Cognitively normal older adults. N=845	Longitudinal.	WMHV.	Education level.	Cognitive function.	Education modifies the consequences of WMHV on cognition. Higher education was associated with less cognitive deterioration related to WMHV.
Bennett et al., 2003 (418)	Cognitively normal older adults. N=130	Cross-sectional.	Aβ and tau.	Years of education.	Cognitive function.	Aβ and tau were associated with cognitive function. Education modified the relation of Aβ and cognition, but not tau and cognition.

Appendix B. The moderating role of cognitive reserve markers between childhood cognition and cognitive function in NSHD

B.1 Model assumptions

The linearity assumption was confirmed using a scatterplot, while multicollinearity was ruled out by assessing the Variance Inflation Factor (VIF). All VIF values were small (<1.97), with a mean of 1.54. A histogram of the standardised residuals revealed a slight negative skew. However, since the sample size for this study is large, violations of the normality assumption are not expected to impact the results (663). Furthermore, a spread-level plot suggested a mild pattern of heteroskedasticity; hence, a heteroskedasticity-consistent standard error estimator of the parameter estimates was employed in all models (664). To control for false discovery rate due to multiple comparisons, the Benjamini-Hochberg correction (497) with a q-value of 0.05 was used for all the regression models.

B.2 Data imputation

The analytical sample was set at the number of individuals with outcome data (ACE-III). From the 2,698 participants who were invited at age 69 to receive a nurse visit, 2,149 (80%) had the interview, and 2,082 (97% of individuals with home visit) agreed or provided data for the ACE-III. However, only 1,762 (82% of individuals with home visit) had usable data due to equipment failures in 320 (18%) of cases (229).

As presented in Chapter 4, Figure 13, the variables with the largest amount of missingness in the outcome were APOE genotype (14%), childhood cognitive ability (12%), and the CRI (10%). All other variables had a missingness equal or under 8%. Sex was the only variable with complete data.

Exploration of missingness patterns revealed that 67% of the dataset had a pattern of no missing values in any of the variables. The two most common missing patterns were those of complete data for all variables except for APOE genotype (7%), and complete data for all variables except childhood cognitive ability (7%). Finally, a comparison of missing and non-missing groups on scores on the outcome (cognitive function) were explored using t-tests. The analysis suggested that individuals with missing data on the NART scored significantly lower in the ACE-III than those with complete data (ACE-III mean for individuals with NART data = 92; ACE-III mean for individuals without NART data = 89; $t=5.76$, $p<0.001$). There were no significant differences in cognitive function scores across the missing and non-missing categories of the other variables.

To impute all missing variables simultaneously, multiple imputation using chained equations was performed. All the variables used in the analytical model (including the outcome and interaction terms) were included in the imputation model to ensure comparability. In total, 50 imputations were added, and a random seed was used to ensure reproducibility. The methods used for the imputation were: regression (CRI, NART, childhood cognition, interactions between childhood cognition and CRI [childhood cognition*CRI], and childhood cognition and NART [childhood cognition*NART], blood pressure, and BMI), ordinal logistic regression (GHQ), and logistic regressions (marital status, smoking, illness, and APOE genotype). Data on the ACE-III and sex were registered and included in the imputation process as regular variables since they did not have missing data. The stability of the parameter estimates across seeds was tested using Monte Carlo error estimates.

B.2 Leisure activities

Table B1. Derivation of leisure activity variables for CRI leisure sub-component.

Variable label (variable name)	Original variable coding	Coding for study
Do you help to run/belong to any voluntary services? (volsr89)	Don't belong Belong to	0 1
Do you help to run/belong to a trade union? (trur89)	Don't belong Belong to	0 1
Do you help to run/belong to any sports clubs? (sptr89)	Don't belong Belong to	0 1
Do you help to run, etc., playgroup, nursery, or school? (schr89)	Don't belong Belong to	0 1
Do you help to run the local government? (lgr89)	Don't belong Belong to	0 1
In your spare time, do you take part in musical, artistic or creative activities? (musr89)	No Yes	0 1
In your spare time, do you go out to pubs, clubs, or social activities? (pubr89)	No Yes	0 1
Since we last contacted you, have you been on any educational courses or training? (train89)	No Yes	0 1
Do you regularly do any heavy gardening apart from paid work? (gdn89)	No Yes	0 1
In your spare time do you take part in constructive activities, making things with your hands (maker89)	No Yes	0 1
Do you regularly take part in any sports or vigorous leisure activities (exer89)	No Yes	0 1
Do you help to run/belong to evening classes/ adult education? (adecr89)	Don't belong Help to run Belong	Don't belong = 0 Help to run/belong=1
Do you help to run/belong to church activities? (chchr89)	Don't belong Help to run Belong	Don't belong=0 Help to run/belong=1
On average, how often would you say you met friends or relatives socially? (frnd89)	Never 1-2 times a month 3-5 times a month 6-10 times a month 11-15 times a month More than 15 times	Never=0 1 to 15+ times=1

Variable coding: 0=no engagement; 1=engagement.

B.3 Tables and figures

Table B2. Regression coefficients and 95% confidence intervals of the effect of childhood cognition, gradually adjusting for covariates, on cognitive function at age 69 (N=1,184)

Variable	Model 1	Model 2	Model 3	Model 4
Childhood cognition	0.30 (0.27 to 0.34)**	0.30 (0.26 to 0.33)**	0.30 (0.26 to 0.33)**	0.29 (0.26 to 0.33)**
Sex: Male Female	[Reference] -0.12 (-0.72 to 0.49)	[Reference] -0.10 (-0.73 to 0.53)	[Reference] -0.11 (-0.73 to 0.52)	[Reference] -0.12 (-0.75 to 0.50)
Marital status: Married Not married	[Reference] -0.53 (-1.36 to 0.30)	[Reference] -0.61 (-1.44 to 0.22)	[Reference] -0.61 (-1.44 to 0.22)	[Reference] -0.45 (-1.31 to 0.41)
Blood pressure		0.003 (-0.02 to 0.02)	0.002 (-0.02 to 0.02)	0.003 (-0.02 to 0.02)
Body mass index		-0.11 (-0.19 to -0.03)*	-0.11 (-0.19 to -0.03)*	-0.12 (-0.20 to -0.04)*
Serious illness/disability: No Yes		[Reference] -1.39 (-3.18 to 0.40)	[Reference] -1.39 (-3.22 to 0.44)	[Reference] -1.33 (-3.16 to 0.50)
GHQ-28: 0 1-5 6-10 11+			[Reference] 0.27 (-0.45 to 0.98) -0.005 (-0.96 to 0.95) 0.03 (-1.05 to 1.11)	[Reference] 0.31 (-0.40 to 1.03) 0.003 (-0.96 to 0.97) 0.04 (-1.04 to 1.11)
Cigarette smoking: No Yes				[Reference] -1.11 (-1.94 to -0.29)*

GHQ-28: General Health Questionnaire.
*p<0.05, **p≤0.001.

Table B3. Regression coefficients and 95% confidence intervals of the effect of the Cognitive Reserve Index (CRI), gradually adjusting for covariates, on cognitive function at age 69 (N=1,184)

Variable	Model 1	Model 2	Model 3	Model 4
CRI	0.18 (0.16 to 0.20)**	0.18 (0.16 to 0.20)**	0.18 (0.16 to 0.20)**	0.18 (0.16 to 0.20)**
Sex: Male Female	[Reference] 0.77 (0.15 to 1.38)*	[Reference] 0.81 (0.17 to 1.46)*	[Reference] 0.84 (0.19 to 1.49)*	[Reference] 0.82 (0.16 to 1.47)*
Marital status: Married Not married	[Reference] -0.35 (-1.18 to 0.47)	[Reference] -0.43 (-1.26 to 0.39)	[Reference] -0.43 (-1.26 to 0.40)	[Reference] -0.37 (-1.22 to 0.48)
Blood pressure		0.01 (-0.01 to 0.03)	0.009 (-0.01 to 0.03)	0.009 (-0.01 to 0.03)
Body mass index		-0.10 (-0.19 to -0.02)*	-0.10 (-0.19 to -0.02)*	-0.11 (-0.19 to -0.02)*
Serious illness/disability: No Yes		[Reference] -1.58 (-3.43 to 0.27)	[Reference] -1.46 (-3.34 to 0.42)	[Reference] -1.44 (-3.33 to 0.44)
GHQ-28: 0 1-5 6-10 11+			[Reference] 0.17 (-0.56 to 0.89) -0.07 (-1.04 to 0.90) -0.42 (-1.54 to 0.71)	[Reference] 0.19 (-0.54 to 0.91) -0.06 (-1.04 to 0.91) -0.41 (-1.53 to 0.71)
Cigarette smoking: No Yes				[Reference] -0.45 (-1.34 to 0.44)

GHQ-28: General Health Questionnaire.
*p<0.05, **p≤0.001.

Table B4. Regression coefficients and 95% confidence intervals of the effect of the National Adult Reading Test (NART), gradually adjusting for covariates, on cognitive function at age 69 (N=1,184)

Variable	Model 1	Model 2	Model 3	Model 4
NART	0.35 (0.31 to 0.39)**	0.34 (0.30 to 0.38)**	0.34 (0.30 to 0.38)**	0.34 (0.30 to 0.38)**
Sex: Male Female	[Reference] 0.07 (-0.51 to 0.65)	[Reference] 0.10 (-0.51 to 0.70)	[Reference] 0.11 (-0.50 to 0.71)	[Reference] 0.10 (-0.51 to 0.70)
Marital status: Married Not married	[Reference] -0.62 (-1.38 to 0.14)	[Reference] -0.68 (-1.44 to 0.08)	[Reference] -0.68 (-1.44 to 0.09)	[Reference] -0.58 (-1.37 to 0.20)
Blood pressure		0.003 (-0.02 to 0.02)	0.002 (-0.02 to 0.02)	0.002 (-0.02 to 0.02)
Body mass index		-0.07 (-0.15 to 0.01)	-0.07 (-0.15 to 0.01)	-0.07 (-0.15 to 0.007)
Serious illness/disability: No Yes		[Reference] -1.63 (-3.48 to 0.22)	[Reference] -1.58 (-3.47 to 0.32)	[Reference] -1.54 (-3.43 to 0.36)
GHQ-28: 0 1-5 6-10 11+			[Reference] 0.14 (-0.55 to 0.82) -0.12 (-1.05 to 0.80) -0.17 (-1.19 to 0.85)	[Reference] 0.16 (-0.52 to 0.84) -0.12 (-1.04 to 0.82) -0.16 (-1.18 to 0.86)
Cigarette smoking: No Yes				[Reference] -0.66 (-1.47 to 0.15)

GHQ-28: General Health Questionnaire.

*p<0.05, **p≤0.001.

Table B5. Regression coefficients and 95% confidence intervals of the effect of *APOE* genotype, gradually adjusting for covariates, on cognitive function at age 69 (N=1,184).

Variable	Model 1	Model 2	Model 3	Model 4
***APOE* e4:** Yes	[Reference]	[Reference]	[Reference]	[Reference]
No	-0.53 (-1.31 to 0.24)	-0.57 (-1.34 to 0.20)	-0.56 (-1.33 to 0.20)	-0.60 (-1.36 to 0.17)
Sex: Male	[Reference]	[Reference]	[Reference]	[Reference]
Female	-0.24 (-0.92 to 0.44)	-0.24 (-0.94 to 0.46)	-0.25 (-0.95 to 0.46)	-0.27 (-0.98 to 0.43)
Marital status: Married	[Reference]	[Reference]	[Reference]	[Reference]
Not married	-0.56 (-1.49 to 0.36)	-0.69 (-1.61 to 0.23)	-0.69 (-1.61 to 0.23)	-0.42 (-1.37 to 0.53)
Blood pressure		-0.001 (-0.02 to 0.02)	-0.002 (-0.02 to 0.02)	-0.0007 (-0.02 to 0.02)
Body mass index		-0.15 (-0.24 to -0.06)**	-0.15 (-0.25 to -0.06)**	-0.17 (-0.26 to -0.07)**
Serious illness/disability: No		[Reference]	[Reference]	[Reference]
Yes		-1.96 (-4.07 to 0.15)	-1.92 (-4.05 to 0.21)	-1.81 (-3.94 to 0.32)
GHQ-28: 0			[Reference]	[Reference]
1-5			0.23 (-0.58 to 1.04)	0.30 (-0.50 to 1.10)
6-10			0.26 (-0.80 to 1.31)	0.26 (-0.80 to 1.32)
11+			-0.17 (-1.51 to 1.17)	-0.15 (-1.47 to 1.16)
Cigarette smoking: No				[Reference]
Yes				-1.85 (-2.80 to -0.90)**

GHQ-28: General Health Questionnaire.

*p<0.05, **p≤0.001.

Table B6. Regression coefficients and 95% confidence intervals of the effect of childhood cognition at age 8, Cognitive Reserve Index (CRI) from age 26 to 53, and the National Adult Reading Test (NART) at age 53, progressively adjusting for covariates, on cognitive function at age 69 (N=1,184).

Variable	Model 1	Model 2	Model 3	Model 4
Childhood cognition	0.11 (0.05 to 0.16)**	0.10 (0.05 to 0.16)**	0.10 (0.05 to 0.16)**	0.10 (0.05 to 0.16)**
CRI	0.07 (0.05 to 0.10)**	0.07 (0.05 to 0.10)**	0.07 (0.05 to 0.10)**	0.07 (0.05 to 0.09)**
NART	0.22 (0.16 to 0.28)**	0.22 (0.15 to 0.28)**	0.22 (0.15 to 0.28)**	0.22 (0.15 to 0.28)**
APOE e4: No Yes	[Reference] -0.71 (-1.36 to -0.06)*	[Reference] -0.71 (-1.36 to -0.07)*	[Reference] -0.70 (-1.35 to -0.06)*	[Reference] -0.71 (-1.36 to -0.06)*
Sex: Male Female	[Reference] 0.35 (-0.23 to 0.94)	[Reference] 0.39 (-0.22 to 1.00)	[Reference] 0.41 (-0.20 to 1.02)	[Reference] 0.40 (-0.22 to 1.01)
Marital status: Married Not married	[Reference] -0.51 (-1.26 to 0.24)	[Reference] -0.56 (-1.31 to 1.19)	[Reference] -0.56 (-1.31 to 0.19)	[Reference] -0.52 (-1.29 to 0.26)
Blood pressure		0.006 (-0.01 to 0.02)	0.006 (-0.01 to 0.02)	0.006 (-0.01 to 0.02)
Body mass index		-0.07 (-0.14 to 0.01)	-0.06 (-0.14 to 0.01)	-0.07 (-0.14 to 0.01)
Serious illness/disability: No Yes		[Reference] -1.42 (-3.16 to 0.31)	[Reference] -1.35 (-3.13 to 0.43)	[Reference] -1.34 (-3.12 to 0.45)
GHQ-28: 0 1-5 6-10 11+			[Reference] 0.10 (-0.56 to 0.76) -0.18 (-1.07 to 0.71) -0.21 (-1.18 to 0.76)	[Reference] 0.11 (-0.54 to 0.77) -0.18 (-1.07 to 0.72) -0.21 (-1.18 to 0.76)
Cigarette smoking: No Yes				[Reference] -0.30 (-1.11 to 0.51)
Interactions				
Childhood cognition*CRI Childhood cognition*NART Childhood cognition*APOE				-0.003 (-0.005 to -0.001)* -0.005 (-0.009 to -0.0007)* 0.03 (-0.05 to 0.11)

GHQ-28: General Health Questionnaire.
*p<0.05, **p≤0.001.

Table B7. Regression coefficients and 95% confidence intervals of the effect of reading comprehension at age 8, gradually adjusting for covariates, on cognitive function at age 69 (N=1,184).

Variable	Model 1	Model 2	Model 3	Model 4
Reading Comprehension	0.08 (0.03 to 0.12)*	0.08 (0.03 to 0.13)**	0.08 (0.03 to 0.13)*	0.08 (0.03 to 0.13)*
CRI	0.08 (0.06 to 0.10)**	0.08 (0.05 to 0.10)**	0.08 (0.05 to 0.10)**	0.08 (0.05 to 0.10)**
NART	0.23 (0.17 to 0.29)**	0.23 (0.17 to 0.29)**	0.23 (0.17 to 0.29)**	0.23 (0.17 to 0.29)**
***APOE* e4:** No Yes	[Reference] -0.70 (-1.35 to -0.04)*	[Reference] -0.71 (-1.36 to -0.05)*	[Reference] -0.70 (-1.35 to -0.05)*	[Reference] -0.70 (-1.35 to -0.05)*
Sex: Male Female	[Reference] 0.35 (-0.24 to 0.94)	[Reference] 0.38 (-0.23 to 1.00)	[Reference] 0.40 (-0.21 to 1.02)	[Reference] 0.39 (-0.23 to 1.01)
Marital status: Married Not married	[Reference] -0.53 (-1.28 to 0.22)	[Reference] -0.59 (-1.34 to 0.17)	[Reference] -0.59 (-1.34 to 0.17)	[Reference] -0.55 (-1.32 to 0.23)
Blood pressure		0.006 (-0.01 to 0.03)	0.005 (-0.01 to 0.02)	0.005 (-0.01 to 0.02)
Body mass index		-0.07 (-0.14 to 0.009)	-0.07 (-0.14 to 0.01)	-0.07 (-0.15 to 0.008)
Serious illness/disability: No Yes		[Reference] -1.57 (-3.33 to 0.19)	[Reference] -1.49 (-3.29 to 0.31)	[Reference] -1.48 (-3.29 to 0.33)
2GHQ-28: 0 1-5 6-10 11+			[Reference] 0.09 (-0.56 to 0.75) -0.20 (-1.09 to 0.70) -0.24 (-1.22 to 0.74)	[Reference] 0.11 (-0.55 to 0.77) -0.19 (-1.09 to 0.71) -0.24 (-1.22 to 0.75)
Cigarette smoking: No Yes				[Reference] -0.29 (-1.10 to 0.53)

GHQ-28: General Health Questionnaire.
*p<0.05, **p≤0.001.

Table B8. Regression coefficients and 95% confidence intervals of the effect of word reading at age 8, gradually adjusting for covariates, on cognitive function at age 69 (N=1,184).

Variable	Model 1	Model 2	Model 3	Model 4
Word Reading	0.07 (0.02 to 0.12)*	0.07 (0.02 to 0.12)*	0.07 (0.02 to 0.12)*	0.07 (0.02 to 0.12)*
CRI	0.08 (0.06 to 0.11)**	0.08 (0.06 to 0.11)**	0.08 (0.06 to 0.11)**	0.08 (0.06 to 0.10)**
NART	0.23 (0.17 to 0.29)**	0.23 (0.17 to 0.29)**	0.23 (0.17 to 0.29)**	0.23 (0.16 to 0.29)**
***APOE* e4:** No Yes	[Reference] -0.69 (-1.35 to -0.04)*	[Reference] -0.70 (-1.36 to -0.05)*	[Reference] -0.69 (-1.35 to -0.04)*	[Reference] -0.70 (-1.35 to -0.05)*
Sex: Male Female	[Reference] 0.37 (-0.21 to 0.96)	[Reference] 0.41 (-0.21 to 1.02)	[Reference] 0.43 (-0.18 to 1.05)	[Reference] 0.42 (-0.20 to 1.04)
Marital status: Married Not married	[Reference] -0.53 (-1.28 to 0.22)	[Reference] -0.59 (-1.34 to 0.17)	[Reference] -0.58 (-1.34 to 0.17)	[Reference] -0.54 (-1.32 to 0.23)
Blood pressure		0.005 (-0.01 to 0.02)	0.005 (-0.01 to 0.02)	0.005 (-0.01 to 0.02)
Body mass index		-0.06 (-0.14 to 0.01)	-0.06 (-0.14 to 0.01)	-0.07 (-0.14 to 0.01)
Serious illness/disability: No Yes		[Reference] -1.55 (-3.32 to 0.23)	[Reference] -1.46 (-3.27 to 0.36)	[Reference] -1.44 (-3.26 to 0.38)
GHQ-28: 0 1-5 6-10 11+			[Reference] 0.08 (-0.58 to 0.74) -0.20 (-1.10 to 0.70) -0.30 (-1.29 to 0.69)	[Reference] 0.10 (-0.56 to 0.75) -0.20 (-1.10 to 0.70) -0.29 (-1.28 to 0.70)
Cigarette smoking: No Yes				[Reference] -0.30 (-1.11 to 0.52)

GHQ-28: General Health Questionnaire.
*p<0.05, **p≤0.001.

Table B9. Regression coefficients and 95% confidence intervals of the effect of vocabulary at age 8, gradually adjusting for covariates, on cognitive function at age 69 (N=1,184).

Variable	Model 1	Model 2	Model 3	Model 4
Vocabulary	0.06 (0.02 to 0.10)*	0.05 (0.01 to 0.09)*	0.05 (0.01 to 0.09)*	0.05 (0.01 to 0.09)*
CRI	0.08 (0.06 to 0.10)**	0.08 (0.06 to 0.10)**	0.08 (0.06 to 0.10)**	0.08 (0.05 to 0.10)**
NART	0.25 (0.20 to 0.30)**	0.25 (0.19 to 0.30)**	0.25 (0.20 to 0.30)**	0.25 (0.19 to 0.30)**
***APOE* e4:** No Yes	[Reference] -0.64 (-1.30 to 0.02)	[Reference] -0.65 (-1.31 to 0.009)	[Reference] -0.64 (-1.29 to 0.02)	[Reference] -0.64 (-1.30 to 0.01)
Sex: Male Female	[Reference] 0.45 (-0.13 to 1.03)	[Reference] 0.49 (-0.11 to 1.09)	[Reference] 0.51 (-0.09 to 1.12)	[Reference] 0.50 (-0.10 to 1.11)
Marital status: Married Not married	[Reference] -0.50 (-1.25 to 0.25)	[Reference] -0.55 (-1.30 to 0.20)	[Reference] -0.55 (-1.30 to 0.21)	[Reference] -0.51 (-1.29 to 0.27)
Blood pressure		0.007 (-0.01 to 0.03)	0.006 (-0.01 to 0.03)	0.006 (-0.01 to 0.03)
Body mass index		-0.06 (-0.14 to 0.02)	-0.06 (-0.14 to 0.02)	-0.06 (-0.14 to 0.02)
Serious illness/disability: No Yes		[Reference] -1.40 (-3.16 to 0.36)	[Reference] -1.32 (-3.12 to 0.49)	[Reference] -1.31 (-3.11 to 0.50)
2GHQ-28: 0 1-5 6-10 11+			[Reference] 0.10 (-0.57 to 0.76) -0.17 (-1.07 to 0.74) -0.26 (-1.24 to 0.72)	[Reference] 0.11 (-0.56 to 0.77) -0.16 (-1.07 to 0.74) -0.26 (-1.24 to 0.72)
Cigarette smoking: No Yes				[Reference] -0.27 (-1.08 to 0.55)

GHQ-28: General Health Questionnaire.
*p<0.05, **p≤0.001.

Table B10. Regression coefficients and 95% confidence intervals of the effect of picture intelligence at age 8, gradually adjusting for covariates, on cognitive function at age 69 (N=1,184).

Variable	Model 1	Model 2	Model 3	Model 4
Picture Intelligence	0.08 (0.04 to 0.12)**	0.08 (0.04 to 0.12)**	0.08 (0.04 to 0.12)**	0.08 (0.04 to 0.12)**
CRI	0.08 (0.05 to 0.10)**	0.08 (0.05 to 0.10)**	0.08 (0.05 to 0.10)**	0.08 (0.05 to 0.10)**
NART	0.25 (0.20 to 0.30)**	0.25 (0.20 to 0.30)**	0.25 (0.20 to 0.30)**	0.25 (0.19 to 0.30)**
***APOE* e4:** No Yes	[Reference] -0.67 (-1.32 to -0.01)	[Reference] -0.67 (-1.33 to -0.02)	[Reference] -0.66 (-1.32 to -0.01)	[Reference] -0.67 (-1.32 to -0.02)*
Sex: Male Female	[Reference] 0.40 (-0.18 to 0.98)	[Reference] 0.44 (-0.17 to 1.04)	[Reference] 0.46 (-0.15 to 1.06)	[Reference] 0.44 (-0.16 to 1.05)
Marital status: Married Not married	[Reference] -0.49 (-1.23 to 0.26)	[Reference] -0.54 (-1.29 to 0.21)	[Reference] -0.54 (-1.29 to 0.21)	[Reference] -0.51 (-1.28 to 0.27)
Blood pressure		0.006 (-0.01 to 0.03)	0.006 (-0.01 to 0.03)	0.006 (-0.01 to 0.03)
Body mass index		-0.07 (-0.14 to 0.009)	-0.07 (-0.14 to 0.01)	-0.07 (-0.14 to 0.008)
Serious illness/disability: No Yes		[Reference] -1.39 (-3.14 to 0.37)	[Reference] -1.32 (-3.12 to 0.47)	[Reference] -1.31 (-3.11 to 0.49)
2GHQ-28: 0 1-5 6-10 11+			[Reference] 0.08 (-0.58 to 0.75) -0.15 (-1.03 to 0.74) -0.20 (-1.17 to 0.77)	[Reference] 0.09 (-0.57 to 0.76) -0.15 (-1.03 to 0.75) -0.20 (-1.17 to 0.77)
Cigarette smoking: No Yes				[Reference] -0.24 (-1.05 to 0.57)

GHQ-28: General Health Questionnaire.
*p<0.05, **p≤0.001.

Table B11. Regression coefficients and 95% confidence intervals of the effect of education, occupation, and leisure activities, gradually adjusting for covariates, on cognitive function at age 69 (N=1,184).

Variable	Model 1	Model 2	Model 3	Model 4
Childhood cognition	0.10 (0.05 to 0.16)**	0.10 (0.05 to 0.16)**	0.10 (0.05 to 0.16)	0.10 (0.05 to 0.16)
Education: No qualification	[Reference]	[Reference]	[Reference]	[Reference]
GCE 'O' or equivalent	1.29 (0.42 to 2.17)*	1.24 (0.36 to 2.12)*	1.26 (0.38 to 2.14)*	1.25 (0.37 to 2.14)*
GCE 'A' or equivalent	1.32 (0.37 to 2.26)*	1.27 (0.32 to 2.22)*	1.27 (0.32 to 2.22)*	1.25 (0.30 to 2.20)*
Degree or equivalent	1.30 (0.18 to 2.43)*	1.23 (0.09 to 2.37)*	1.25 (0.11 to 2.39)*	1.22 (0.07 to 2.37)*
Leisure activities: 0-4	[Reference]	[Reference]	[Reference]	[Reference]
5	1.16 (0.35 to 1.96)*	1.15 (0.34 to 1.96)*	1.16 (0.36 to 1.96)*	1.14 (0.34 to 1.94)*
6+	1.52 (0.84 to 2.21)**	1.55 (0.86 to 2.24)**	1.55 (0.86 to 2.24)**	1.53 (0.83 to 2.22)**
Occupation: Part skilled & unskilled	[Reference]	[Reference]	[Reference]	[Reference]
Skilled	1.11 (-0.06 to 2.28)	1.15 (-0.03 to 2.32)	1.14 (-0.04 to 2.32)	1.13 (-0.06 to 2.32)
Professional	1.52 (0.31 to 2.73)*	1.52 (0.30 to 2.73)*	1.51 (0.29 to 2.74)*	1.50 (0.27 to 2.73)*
NART	0.21 (0.15 to 0.28)**	0.21 (0.15 to 0.28)**	0.21 (0.15 to 0.28)**	0.21 (0.14 to 0.28)**
***APOE* e4:** No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	-0.67 (-1.32 to -0.01)	-0.67 (-1.32 to -0.03)*	-0.66 (-1.31 to -0.02)	-0.67 (-1.32 to -0.02)*
Sex: Male	[Reference]	[Reference]	[Reference]	[Reference]
Female	0.24 (-0.37 to 0.84)	0.26 (-0.37 to 0.90)	0.28 (-0.35 to 0.91)	0.27 (-0.36 to 0.91)
Marital status: Married	[Reference]	[Reference]	[Reference]	[Reference]
Not married	-0.55 (-1.30 to 0.21)	-0.60 (-1.35 to 0.15)	-0.60 (-1.35 to 0.16)	-0.56 (-1.34 to 0.22)
Blood pressure		0.005 (-0.01 to 0.02)	0.005 (-0.01 to 0.02)	0.005 (-0.01 to 0.02)
Body mass index		-0.07 (-0.14 to 0.009)	-0.07 (-0.14 to 0.01)	-0.07 (-0.14 to 0.009)
Serious illness/disability: No		[Reference]	[Reference]	[Reference]
Yes		-1.38 (-3.18 to 0.42)	-1.32 (-3.17 to 0.53)	-1.30 (-3.16 to 0.55)
GHQ-28: 0			[Reference]	[Reference]
1-5			0.09 (-0.56 to 0.75)	0.11 (-0.55 to 0.76)
6-10			-0.23 (-1.12 to 0.66)	-0.23 (-1.12 to 0.67)
11+			-0.18 (-1.16 to 0.80)	-0.17 (-1.15 to 0.80)
Cigarette smoking: No				[Reference]
Yes				-0.28 (-1.08 to 0.52)

GHQ-28: General Health Questionnaire.
*p<0.05, **p≤0.001.

Table B12. Regression coefficients and 95% confidence intervals of the effect of childhood cognition at age 8, cognitive reserve index (CRI) from age 26 to 53, and the National Adult Reading Test (NART) at age 53 on cognitive function at age 69 using imputed data (N=1,762).

Variable	Model 1	Model 2	Model 3	Model 4
Childhood cognition	0.12 (0.08 to 0.16)**	0.12 (0.08 to 0.16)**	0.12 (0.08 to 0.16)**	0.12 (0.08 to 0.17)**
CRI	0.08 (0.06 to 0.10)**	0.08 (0.06 to 0.10)**	0.08 (0.06 to 0.10)**	0.07 (0.05 to 0.09)**
NART	0.22 (0.17 to 0.27)**	0.22 (0.17 to 0.26)**	0.22 (0.17 to 0.26)**	0.22 (0.17 to 0.26)**
***APOE* e4:** No Yes	[Reference] -0.62 (-1.19 to -0.06)*	[Reference] -0.62 (-1.19 to -0.05)*	[Reference] -0.62 (-1.19 to -0.06)*	[Reference] -0.63 (-1.20 to -0.07)*
Sex: Male Female	[Reference] 0.62 (0.14 to 1.09)*	[Reference] 0.60 (0.10 to 1.10)*	[Reference] 0.64 (0.14 to 1.14)*	[Reference] 0.62 (0.12 to 1.12)*
Marital status: Married Not married	[References] -0.08 (-0.68 to 0.53)	[Reference] -0.09 (-0.69 to 0.51)	[Reference] -0.09 (-0.70 to 0.51)	[Reference] -0.03 (-0.65 to 0.59)
Blood pressure		-0.004 (-0.02 to 0.01)	-0.004 (-0.02 to 0.01)	-0.004 (-0.02 to 0.01)
Body mass index		-0.02 (-0.08 to 0.04)	-0.02 (-0.08 to 0.04)	-0.02 (-0.08 to 0.04)
Serious illness/disability: No Yes		[Reference] -0.74 (-2.00 to 0.52)	[Reference] -0.66 (-1.94 to 0.63)	[References] -0.65 (-1.94 to 0.64)
GHQ-28: 0 1-5 6-10 11+			[Reference] -0.14 (-0.72 to 0.44) -0.57 (-1.28 to 0.14) -0.26 (-1.07 to 0.55)	[Reference] -0.12 (-0.70 to 0.46) -0.56 (-1.27 to 0.16) -0.24 (-1.05 to 0.57)
Cigarette smoking: No Yes				[References] -0.48 (-1.16 to 0.20)
Interactions				
Childhood cognition*CRI Childhood cognition*NART Childhood cognition*APOE				-0.004 (-0.005 to -0.002)** -0.006 (-0.01 to -0.003)** -0.002 (-0.03 to 0.22)

GHQ-28: General Health Questionnaire.
*p<0.05, **p≤0.001.

Table B13. Stratified estimates of the effect of childhood cognition at age 8 on cognitive function at 69 at scores above or below the mean of the National Adult Reading Test (NART) or the Cognitive Reserve Index (CRI) using imputed data (N=1,762).

Variable	**Cognitive reserve stratified**	
	CRI <103 N=945	**CRI ≥103** N=785
	B (95% CI)	B (95% CI)
Childhood cognition	0.18 (0.13 to 0.23)**	0.10 (0.03 to 0.16)*
NART	0.25 (0.20 to 0.30)**	0.20 (0.10 to 0.30)**
APOE e4: No Yes	[Reference] -0.23 (-1.10 to 0.63)	[Reference] -1.00 (-1.76 to -0.25)
	NART <35 N=702	**NART ≥35** N=1,039
	B (95% CI)	B (95% CI)
Childhood cognition	0.21 (0.14 to 0.28)**	0.14 (0.10 to 0.18)**
CRI	0.12 (0.08 to 0.17)**	0.09 (0.06 to 0.11)**
APOE e4: No Yes	[Reference] -0.60 (-1.67 to 0.48)	[Reference] -0.57 (-1.24 to 0.10)

Fully adjusted models. Estimation sample varies across imputations (sample sizes vary between 702 and 723 NART <35 stratum, between 1039 and 1060 for NART ≥35 stratum, between 945 and 977 for the CRI <103 stratum, and between 785 and 817 for the CRI ≥103 stratum.
*p<0.05, **p≤0.001.

Appendix C. The moderating role of cognitive reserve between brain markers and cognitive function in NSHD Insight 46

C.1 Model assumptions

For all relevant models, linearity assumption was assessed by a scatterplot, while multicollinearity was ruled out by assessing the Variance Inflation Factor (VIF). For research question 1 all mean VIF values were small (<2.63) and spread-level plots suggested no evidence of heteroskedasticity for any of the linear regression models. For research questions 2 and 3 all mean VIF values were also small (<2.16). For the ACE-III a histogram of the standardised residuals revealed a slight negative skew, but minor violations of the normality assumption are not expected to impact the results (663). However, a spread-level plot suggested a mild pattern of heteroskedasticity; hence, and thus, a heteroskedasticity-consistent standard error estimator of the parameter estimates was employed in all regression models where the ACE-III was the outcome (664). For the PACC, the histogram of the standardised residuals was consistent with a normal distribution, and the spread-level plot did not suggest heteroskedasticity. The level of statistical significance was set at $p<0.05$ except for interactions where it was set at $p<0.10$. To control for false discovery rate due to multiple comparisons, the Benjamini-Hochberg correction (497) with a q-value of 0.05 was used for all the regression models.

C.2 Data imputation

C.2.1 Research question 1

For research question 1, the analytical sample was set at the number of individuals with outcome data (brain markers). From the 841 NSHD participants who were invited to the neuroimaging study, 502 (60%) attended the research centre, from which 471 (93%) completed the MRI scan (528). From this group, 468 participants had usable data on brain and hippocampal volumes, 462 had data on Aβ, and 455 had data on WMHV.

As presented in Chapter 5, Figure 21, the variable with the largest amount of missingness on the brain markers was the CRI (6%). Sex, total intracranial volume, and age at scan had complete data on all brain marker outcomes.

Exploration of missingness patterns for brain volume and hippocampal volume revealed that 85% of the dataset had a pattern of no missing values in any of the variables. The most common missing pattern was that of complete data for all variables except for the CRI (6%). Similarly, the exploration of missingness patterns for Aβ and WMHV revealed that 84% of the sample had complete data for all variables, and that 6% had complete data for all variables except the CRIq. A comparison of missing and non-missing groups across the brain markers was explored using t-tests or chi-square tests. The analyses suggested that individuals with missing data did not differ significantly in their brain marker scores to those with complete data.

Separate datasets were created to impute the data for each brain marker (except brain volume and hippocampal volume that had the same number of observations). To impute missing variables simultaneously, multiple imputations using chained equations were performed. All the variables used in the analytical model (including the outcome and interaction terms) were included in the imputation model to ensure comparability. In total, 50 imputations were added, and a random seed was used to ensure reproducibility. The

methods used for the imputation were: regression (CRI, NART, and childhood cognition), and logistic regression (APOE genotype). Data on the brain markers, sex, total intracranial volume, and age at scan were registered and included in the imputation process as regular variables since they did not have missing data. The stability of the parameter estimates across seeds was tested using Monte Carlo error estimates.

C.2.2 Research questions 2 and 3

The analytical samples were set at the number of individuals with data in each of the two cognitive function tests (ACE-III and PACC). From the Insight 46 sample, the entire sample had data for the PACC, while 421 participants had data for the ACE-III (84%).

For both samples, the variables with the largest amount of missingness on cognitive function were Aβ and WMHV (from 10 to 8%). Sex had complete data on all brain marker outcomes.

Exploration of missingness patterns for the ACE-III revealed that 72% of the dataset had a pattern of no missing values in any of the variables. The most common missing pattern was that of incomplete data for age at scan, brain volume, hippocampal volume, total intracranial volume, Aβ, and WMHV, accounting for 6%. Furthermore, 5% of the dataset had data for all variables except the CRI, and 4% had data for all variables except childhood cognitive ability. A comparison of missing and non-missing groups on scores on the ACE-III were explored using t-tests. The analysis suggested that individuals with missing data on the NART scored significantly lower in the ACE-III than those with complete data (ACE-III mean for individuals with NART data = 94; ACE-III mean for individuals without NART data = 90; $t=2.86$, $p<0.05$). There were no significant differences in cognitive function scores across the missing and non-missing categories of the other variables.

Exploration of missingness patterns for the PACC revealed that 73% of the dataset had no missing values in any of the variables. The most common pattern of missingness was missing on age at scan, brain volume, hippocampal volume, total intracranial volume, Aβ, and WMHV, accounting for 6%. Furthermore, 5% of the dataset had data for all variables except the CRI, and 4% had data for all variables except childhood cognitive ability. A comparison of missing and non-missing groups on scores on the ACE-III were explored using t-tests. The analysis suggested that individuals with missing data on the NART scored significantly lower in the PACC than those with complete data (PACC mean for individuals with NART data = 0.01; PACC mean for individuals without NART data = -0.62; $t=3.10$, $p<0.05$). Furthermore, individuals with missing data on marital status scores significantly lower in the PACC than those with complete data (PACC mean for individuals with marital data = 0.007; PACC mean for individuals without marital data = -0.50; $t=2.05$, $p<0.05$). There were no significant differences in cognitive function scores across the missing and non-missing categories of the other variables.

Separate datasets were created to impute the data for each cognitive function test and for each brain marker. Multiple imputation of covariates by substantive model compatible fully conditional specification were carried out. This approach was chosen over multiple imputation using chained equations (as previous chapter) because it accommodates models which contain interaction effects (665). The substantive model was specified by regressing the outcome on to the predictors and covariates, including the interaction terms. In total, 50 imputations were added, and a random seed was used to ensure reproducibility. The methods used for the imputation were: regression (CRI, NART, childhood cognition, FRS, total intracranial volume, brain volume, hippocampal volume, and WMHV), ordinal logistic regression (age at scan and GHQ), and logistic regression (Aβ, marital status and APOE

genotype). The stability of the parameter estimates across seeds was tested using Monte Carlo error estimates.

C.2 Tables and Figures

Table C1. Regression coefficients and 95% confidence intervals for the association between CRI and brain volume (N=468).

	Model 1	Model 2	Model 3
CRI	0.06 (-0.24 to 0.36)	0.11 (-0.22 to 0.44)	0.11 (-0.22 to 0.44)
TIV	0.72 (0.68 to 0.76)**	0.72 (0.68 to 0.76)**	0.72 (0.68 to 0.76)**
Age at scan	-9.81 (-15.34 to -4.28)**	-9.77 (-15.31 to -4.23)**	-9.58 (-15.10 to -4.05)**
Sex: Female Male	[Reference] -22.71 (-33.53 to -11.88)**	[Reference] -23.31 (-34.26 to -12.36)**	[Reference] -23.48 (-34.41 to -12.56)**
Childhood cognition		-0.20 (-0.73 to 0.33)	-0.20 (-0.73 to 0.33)
APOE-e4 carrier: No Yes			[Reference] 8.61 (-0.61 to 17.83)

CRI: Cognitive Reserve Index; TIV: Total intracranial volume.
** p<0.001, * p<0.05.

Table C2. Regression coefficients and 95% confidence intervals for the association between the NART and brain volume (N=468).

	Model 1	Model 2	Model 3
NART	-0.06 (-0.59 to 0.47)	0.04 (-0.62 to 0.71)	0.02 (-0.64 to 0.69)
TIV	0.72 (0.68 to 0.77)**	0.72 (0.68 to 0.77)**	0.72 (0.68 to 0.77)**
Age at scan	-9.80 (-15.34 to -4.27)**	-9.72 (-15.27 to -4.17)**	-9.53 (-15.07 to -3.99)**
Sex: Female Male	[Reference] -22.78 (-33.65 to -11.91)**	[Reference] -23.02 (-33.95 to -12.10)**	[Reference] -23.19 (-34.09 to -12.29)**
Childhood cognition		-0.15 (-0.77 to 0.46)	-0.15 (-0.76 to 0.47)
APOE-e4 carrier: No Yes			[Reference] 8.56 (-0.66 to 17.78)

NART: National Adult Reading Test; TIV: Total intracranial volume.
** p<0.001, * p<0.05.

Table C3. Regression coefficients and 95% confidence intervals for the association between the CRI and hippocampal volume (N=468).

	Model 1	Model 2	Model 3
CRI	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
TIV	0.00 (0.00 to 0.00)**	0.00 (0.00 to 0.00)**	0.00 (0.00 - 0.00)**
Age at scan	-0.03 (-0.06 to 0.01)	-0.03 (-0.06 to 0.01)	-0.03 (-0.06 to 0.01)
Sex: Female Male	[Reference] 0.05 (-0.02 to 0.12)	[Reference] 0.05 (-0.02 to 0.12)	[Reference] 0.05 (-0.02 to 0.12)
Childhood cognition		0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
APOE-e4 carrier: No Yes			[Reference] -0.01 (-0.07 to 0.05)

CRI: Cognitive Reserve Index; TIV: Total intracranial volume.
** p<0.001, * p<0.05.

Table C4. Regression coefficients and 95% confidence intervals for the association between NART and hippocampal volume (N=468).

	Model 1	Model 2	Model 3
NART	-0.00 (-0.00 to 0.00)	-0.00 (-0.01 to 0.00)	-0.00 (-0.01 to 0.00)
TIV	0.00 (0.00 to 0.00)**	0.00 (0.00 to 0.00)**	0.00 (0.00 - 0.00)**
Age at scan	-0.03 (-0.06 to 0.01)	-0.03 (-0.06 to 0.01)	-0.03 (-0.06 to 0.01)
Sex: Female Male	[Reference] 0.05 (-0.02 to 0.12)	[Reference] 0.05 (-0.02 to 0.12)	[Reference] 0.05 (-0.02 to 0.12)
Childhood cognition		0.00 (0.00 to 0.01)*	0.00 (0.00 to 0.01)*
APOE-e4 carrier: No Yes			[Reference] -0.01 (-0.07 to 0.05)

NART: National Adult Reading Test; TIV: Total intracranial volume.
** p<0.001, * p<0.05.

Table C5. Regression coefficients and 95% confidence intervals for the association between CRI and amyloid status (N=462).

	Model 1	Model 2	Model 3
CRI	0.99 (0.98 to 1.01)	0.99 (0.97 to 1.01)	0.99 (0.97 to 1.01)
Age at scan	0.89 (0.65 to 1.23)	0.89 (0.65 to 1.23)	0.91 (0.65 to 1.27)
Sex: Female Male	[Reference] 1.24 (0.77 to 2.01)	[Reference] 1.27 (0.78 to 2.07)	[Reference] 1.21 (0.73 to 2.01)
Childhood cognition		1.01 (0.98 to 1.04)	1.01 (0.98 to 1.05)
APOE-e4 carrier: No Yes			[Reference] 4.53 (2.73 to 7.50)**

CRI: Cognitive Reserve Index; TIV: Total intracranial volume.
** p<0.001, * p<0.05.

Table C6. Regression coefficients and 95% confidence intervals for the association between NART and amyloid status (N=462).

	Model 1	Model 2	Model 3
NART	1.01 (0.98 to 1.04)	1.00 (0.97 to 1.04)	0.99 (0.96 to 1.04)
Age at scan	0.89 (0.65 to 1.23)	0.89 (0.65 to 1.22)	0.90 (0.64 to 1.26)
Sex: Female Male	[Reference] 1.21 (0.75 to 1.93)	[Reference] 1.21 (0.76 to 1.95)	[Reference] 1.15 (0.70 to .89)
Childhood cognition		1.01 (0.97 to 1.04)	1.01 (0.97 to 1.05)
APOE-e4 carrier: No Yes			[Reference] 4.53 (2.73 to 7.50)**

NART: National Adult Reading Test; TIV: Total intracranial volume.
** p<0.001, * p<0.05.

Table C7. Regression coefficients and 95% confidence intervals for the association between CRI and WMHV (N=455).

	Model 1	Model 2	Model 3
CRI	-0.00 (-0.01 to 0.00)	-0.00 (-0.01 to 0.00)	-0.00 (-0.01 to 0.00)
TIV	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
Age at scan	0.09 (-0.05 to 0.22)	0.09 (-0.05 to 0.22)	0.09 (-0.04 to 0.22)
Sex: Female Male	[Reference] -0.29 (-0.55 to -0.03)*	[Reference] -0.28 (-0.55 to -0.02)*	[Reference] -0.29 (-0.55 to -0.02)*
Childhood cognition		0.01 (-0.01 to 0.02)	0.00 (-0.01 to 0.02)
APOE-e4 carrier: No Yes			[Reference] 0.07 (-0.16 to 0.30)

CRI: Cognitive Reserve Index; TIV: Total intracranial volume; WMHV: White matter hyperintensity volume.
** p<0.001, * p<0.05.

Table C8. Regression coefficients and 95% confidence intervals for the association between NART and WMHV (N=455).

	Model 1	Model 2	Model 3
NART	-0.00 (-0.01 to 0.01)	-0.00 (-0.02 to 0.01)	-0.00 (-0.02 to 0.01)
TIV	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
Age at scan	0.09 (-0.05 to 0.22)	0.08 (-0.05 to 0.22)	0.09 (-0.05 to 0.22)
Sex: Female Male	[Reference] -0.29 (-0.56 to -0.03)*	[Reference] -0.29 (-0.55 to -0.03)*	[Reference] -0.29 (-0.56 to -0.03)*
Childhood cognition		0.01 (-0.01 to 0.02)	0.01 (-0.01 to 0.02)
APOE-e4 carrier: No Yes			[Reference] 0.08 (-0.16 to 0.31)

NART: National Adult Reading Test; TIV: Total intracranial volume; WMHV: White matter hyperintensity volume.
** p<0.001, * p<0.05.

Table C9. Regression coefficients and 95% confidence intervals for the associations between education, occupation, and leisure and brain markers.

N	Brain marker	Predictor	β (95% CI)
Regression coefficients and 95% confidence intervals			
468	Brain volume	Education: No qualification	[Reference]
		GCE 'O' or equivalent	-9.37 (-22.26 to 3.52)
		GCE 'A' or equivalent	-4.36 (-17.52 to 8.79)
		Degree or equivalent	2.80 (-13.56 to 19.16)
		Leisure: 0-4	[Reference]
		5	8.22 (-3.48 to 19.93)
		6+	4.10 (-5.51 to 13.71)
		Occupation: Part skilled/unskilled	[Reference]
		Skilled	8.08 (-10.17 to 26.33)
		Professional	6.78 (-11.15 to 24.73)
468	Hippocampal volume	Education: No qualification	[Reference]
		GCE 'O' or equivalent	0.01 (-0.08 to 0.10)
		GCE 'A' or equivalent	-0.02 (-0.10 to 0.07)
		Degree or equivalent	0.01 (-0.10 to 0.12)
		Leisure: 0-4	[Reference]
		5	0.04 (-0.04 to 0.12)
		6+	0.07 (0.007 to 0.13)*
		Occupation: Part skilled/unskilled	[Reference]
		Skilled	-0.04 (-0.16 to 0.08)
		Professional	-0.003 (-0.12 to 0.12)
Odds ratios and 95% confidence intervals			
462	Aβ status	Education: No qualification	[Reference]
		GCE 'O' or equivalent	0.93 (0.43 to 2.00)
		GCE 'A' or equivalent	0.88 (0.40 to 1.91)
		Degree or equivalent	0.85 (0.33 to 2.21)
		Leisure: 0-4	[Reference]
		5	1.17 (0.59 to 2.33)
		6+	0.88 (0.49 to 1.58)
		Occupation: Part skilled/unskilled	[Reference]
		Skilled	0.85 (0.26 to 2.83)
		Professional	1.04 (0.32 to 3.35)
Exponentiated coefficients and 95% confidence intervals			
455	WMHV	Education: No qualification	[Reference]
		GCE 'O' or equivalent	0.09 (-0.22 to 0.40)
		GCE 'A' or equivalent	0.09 (-0.22 to 0.39)
		Degree or equivalent	-0.20 (-0.57 to 0.17)
		Leisure: 0-4	[Reference]
		5	-0.15 (-0.43 to 0.14)
		6+	-0.001 (-0.23 to 0.23)
		Occupation: Part skilled/unskilled	[Reference]
		Skilled	0.06 (-0.38 to 0.51)
		Professional	0.06 (-0.38 to 0.49)

Models adjusted for total intracranial volume, age at scan, sex, childhood cognitive ability, and genetic risk.

All statistically significant associations remained significant after Benjamini-Hochberg correction.

*p<0.05, **p≤0.001.

Table C10. Regression coefficients and 95% confidence intervals for the association between CRI and cognitive function (ACE-III) (N=421).

	Model 1	Model 2	Model 3	Model 4
CRI	0.14 (0.11 to 0.17)**	0.10 (0.07 to 0.13)**	0.10 (0.07 to 0.13)**	0.10 (0.07 to 0.14)**
Sex: Female Male	[Reference] -1.05 (-1.85 to -0.25)*	[Reference] -0.82 (-1.60 to -0.05)*	[Reference] -0.87 (-1.93 to 0.18)	[Reference] -0.89 (-1.96 to 0.18)
Marital status: Married Not-married	[Reference] -1.37 (-2.64 to -0.10)*	[Reference] -1.53 (-2.77 to -0.28)*	[Reference] -1.53 (-2.78 to -0.28)*	[Reference] -1.54 (-2.81 to -0.28)*
APOE-e4 carrier: No Yes	[Reference] 0.04 (-0.88 to 0.95)	[Reference] 0.08 (-0.77 to 0.93)	[Reference] 0.08 (-0.77 to 0.93)	[Reference] 0.08 (-0.78 to 0.93)
Childhood cognition		0.16 (0.11 to 0.21)**	0.16 (0.11 to 0.21)**	0.16 (0.11 to 0.21)**
FRS			0.01 (-0.07 to 0.08)	0.01 (-0.07 to 0.08)
GHQ-28: 0 1 to 5 6+				[Reference] 0.22 (-0.87 to 1.31) -0.09 (-1.02 to 0.83)

CRI: Cognitive Reserve Index; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III

** p<0.001, * p<0.05

Table C11. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (ACE-III) (N=421).

	Model 1	Model 2	Model 3	Model 4
NART	0.27 (0.20 to 0.33)**	0.20 (0.11 to 0.28)**	0.19 (0.11 to 0.28)**	0.19 (0.11 to 0.28)**
Sex: Female Male	[Reference] -0.28 (-1.08 to 0.51)	[Reference] -0.26 (-1.04 to 0.52)	[Reference] -0.05 (-1.10 to 0.99)	-[Reference] 0.06 (-1.11 to 0.99)
Marital status: Married Not-married	[Reference] -1.40 (-2.57 to -0.23)*	[Reference] -1.49 (-2.68 to -0.31)*	[Reference] -1.48 (-2.68 to -0.29)*	[Reference] -1.49 (-2.70 to -0.28)*
APOE-e4 carrier: No Yes	[Reference] -0.00 (-0.87 to 0.86)	[Reference] 0.04 (-0.81 to 0.88)	[Reference] 0.03 (-0.81 to 0.88)	[Reference] 0.03 (-0.82 to 0.88)
Childhood cognition		0.11 (0.05 to 0.18)*	0.11 (0.05 to 0.18)*	0.11 (0.04 to 0.18)*
FRS			-0.02 (-0.10 to 0.05)	-0.02 (-0.10 to 0.05)
GHQ-28: 0 1 to 5 6+				[Reference] 0.09 (-1.04 to 1.21) 0.00 (-0.92 to 0.92)

NART: National Adult Reading Test; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III.

** p<0.001, * p<0.05.

Table C12. Regression and 95% confidence intervals for the association between the CRI and cognitive function (PACC) (N=502).

	Model 1	Model 2	Model 3	Model 4
CRI	0.02 (0.02 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**
Sex: Female Male	[Reference] -0.46 (-0.58 to -0.34)**	[Reference] -0.41 (-0.52 to -0.29)**	[Reference] -0.44 (-0.59 to -0.28)**	[Reference] -0.43 (-0.59 to -0.28)**
Marital status: Married Not-married	[Reference] -0.06 (-0.22 to 0.10)	[Reference] -0.07 (-0.22 to 0.08)	[Reference] -0.07 (-0.23 to 0.08)	[Reference] -0.07 (-0.23 to 0.08)
APOE-e4 carrier: No Yes	[Reference] 0.02 (-0.11 to 0.15)	[Reference] 0.02 (-0.10 to 0.15)	[Reference] 0.02 (-0.10 to 0.15)	[Reference] 0.02 (-0.10 to 0.15)
Childhood cognition		0.03 (0.02 to 0.03)**	0.03 (0.02 to 0.03)**	0.03 (0.02 to 0.03)**
FRS			0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.01)
GHQ-28: 0 1 to 5 6+				[Reference] 0.01 (-0.14 to 0.16) 0.04 (-0.10 to 0.18)

CRI: Cognitive Reserve Index; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; PACC: Preclinical Alzheimer Cognitive Composite.
** p<0.001, * p<0.05.

Table C13. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (PACC) (N=502).

	Model 1	Model 2	Model 3	Model 4
NART	0.04 (0.03 to 0.05)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**
Sex: Female Male	[Reference] -0.36 (-0.47 to -0.24)**	[Reference] -0.34 (-0.45 to -0.23)**	[Reference] -0.34 (-0.49 to to0.20)**	[Reference] -0.34 (-0.48 to -0.19)**
Marital status: Married Not-married	[Reference] -0.05 (-0.21 to 0.10)	[Reference] -0.06 (-0.21 to 0.09)	[Reference] -0.06 (-0.21 to 0.09)	[Reference] -0.06 (-0.21 to 0.09)
APOE-e4 carrier: No Yes	[Reference] 0.01 (-0.12 to 0.13)	[Reference] 0.01 (-0.11 to 0.14)	[Reference] 0.01 (-0.11 to 0.14)	[Reference] 0.01 (-0.11 to 0.14)
Childhood cognition		0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**
FRS			0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.01)
GHQ-28: 0 1 to 5 6+				[Reference] -0.02 (-0.16 to 0.13) 0.04 (-0.10 to 0.18)

NART: National Adult Reading Test; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; PACC: Preclinical Alzheimer Cognitive Composite.
** p<0.001, * p<0.05.

Table C14. Regression coefficients and 95% confidence intervals for the association between CRI and cognitive function (ACE-III) adjusting for brain volume (N=421).

	Model 1	Model 2	Model 3	Model 4
CRI	0.14 (0.10 to 0.17)**	0.10 (0.07 to 0.13)**	0.10 (0.07 to 0.13)**	0.10 (0.07 to 0.13)**
Brain volume	0.01 (-0.01 to 0.02)	0.01 (-0.00 to 0.02)	0.01 (-0.00 to 0.02)	0.01 (-0.00 to 0.02)
TIV	-0.00 (-0.01 to 0.01)	-0.00 (-0.01 to 0.00)	-0.00 (-0.01 to 0.00)	-0.00 (-0.01 to 0.00)
Age at scan	0.12 (-0.44 to 0.68)	0.08 (-0.45 to 0.60)	0.08 (-0.45 to 0.62)	0.09 (-0.45 to 0.62)
Sex: Female Male	[Reference] -1.34 (-2.41 to -0.27)*	[Reference] -0.84 (-1.88 to 0.20)	[Reference] -0.95 (-2.18 to 0.27)	[Reference] -0.98 (-2.21 to 0.25)
Marital status: Married Not-married	[Reference] -1.37 (-2.63 to -0.10)*	[Reference] -1.50 (-2.74 to -0.27)*	[Reference] -1.51 (-2.75 to -0.27)*	[Reference] -1.52 (-2.77 to -0.26)*
APOE-e4 carrier: No Yes	[Reference] -0.03 (-0.94 to 0.89)	[Reference] 0.00 (-0.85 to 0.86)	[Reference] 0.01 (-0.85 to 0.86)	[Reference] 0.01 (-0.85 to 0.86)
Childhood cognition		0.16 (0.11 to 0.21)**	0.16 (0.11 to 0.21)**	0.16 (0.11 to 0.21)**
FRS			0.01 (-0.06 to 0.09)	0.01 (-0.06 to 0.09)
GHQ-28: 0 1 to 5 6+				[Reference] 0.14 (-0.96 to 1.24) -0.20 (-1.15 to 0.75)

CRI: Cognitive Reserve Index; TIV: Total intracranial volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III.
** p<0.001, * p<0.05.

Table C15. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (ACE-III) adjusting for brain volume (N=421).

	Model 1	Model 2	Model 3	Model 4
NART	0.26 (0.19 to 0.33)**	0.19 (0.11 to 0.28)**	0.19 (0.11 to 0.28)**	0.19 (0.11 to 0.28)**
Brain volume	0.01 (-0.01 to 0.02)	0.01 (-0.00 to 0.02)	0.01 (-0.00 to 0.02)	0.01 (-0.00 to 0.02)
TIV	-0.00 (-0.01 to 0.01)	-0.00 (-0.01 to 0.01)	-0.00 (-0.01 to 0.01)	-0.00 (-0.01 to 0.01)
Age at scan	0.21 (-0.34 to 0.76)	0.16 (-0.37 to 0.70)	0.16 (-0.39 to 0.70)	0.16 (-0.39 to 0.70)
Sex: Female Male	[Reference] -0.62 (-1.67 to 0.43)	[Reference] -0.45 (-1.50 to 0.59)	[Reference] -0.31 (-1.51 to 0.88)	[Reference] -0.32 (-1.52 to 0.87)
Marital status: Married Not-married	[Reference] -1.40 (-2.58 to -0.23)*	[Reference] -1.48 (-2.67 to -0.29)*	[Reference] -1.48 (-2.67 to -0.28)*	[Reference] -1.48 (-2.68 to -0.27)*
APOE-e4 carrier: No Yes	[Reference] -0.06 (-0.93 to 0.81)	[Reference] -0.03 (-0.88 to 0.82)	[Reference] -0.03 (-0.88 to 0.82)	[Reference] -0.03 (-0.89 to 0.82)
Childhood cognition		0.11 (0.05 to 0.18)**	0.11 (0.05 to 0.18)**	0.11 (0.04 to 0.18)*
FRS			-0.02 (-0.09 to 0.06)	-0.02 (-0.09 to 0.06)
GHQ-28: 0 1 to 5 6+				[Reference] 0.03 (-1.10 to 1.16) -0.09 (-1.04 to 0.86)

NART: National Adult Reading Test; TIV: Total intracranial volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III.
** p<0.001, * p<0.05.

Table C16. Regression coefficients and 95% confidence intervals from the association between CRI and cognitive function (ACE-III) adjusting for hippocampal volume (N=421).

	Model 1	Model 2	Model 3	Model 4
CRI	0.14 (0.10 to 0.17)**	0.10 (0.07 to 0.13)**	0.10 (0.07 to 0.13)**	0.10 (0.07 to 0.13)**
Hippocampal volume	0.57 (-1.11 to 2.25)	0.53 (-1.06 to 2.12)	0.54 (-1.06 to 2.13)	0.57 (-1.04 to 2.18)
TIV	0.00 (-0.00 to 0.01)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
Age at scan	0.06 (-0.48 to 0.60)	0.00 (-0.50 to 0.50)	0.00 (-0.50 to 0.51)	0.01 (-0.50 to 0.52)
Sex: Female Male	[Reference] -1.48 (-2.52 to -0.44)*	[Reference] -1.01 (-2.01 to -0.00)*	[Reference] -1.05 (-2.28 to 0.18)	[Reference] -1.07 (-2.31 to 0.16)
Marital status: Married Not-married	[Reference] -1.40 (-2.69 to -0.12)*	[Reference] -1.54 (-2.80 to -0.28)*	[Reference] -1.54 (-2.81 to -0.28)*	[Reference] -1.56 (-2.83 to -0.28)*
APOE-e4 carrier: No Yes	[Reference] 0.03 (-0.89 to 0.95)	[Reference] 0.07 (-0.78 to 0.93)	[Reference] 0.08 (-0.79 to 0.94)	[Reference] 0.07 (-0.79 to 0.94)
Childhood cognition		0.16 (0.11 to 0.21)**	0.16 (0.11 to 0.21)**	0.16 (0.11 to 0.21)**
FRS			0.01 (-0.07 to 0.08)	0.01 (-0.07 to 0.08)
GHQ-28: 0 1 to 5 6+				[Reference] 0.24 (-0.86 to 1.34) -0.10 (-1.04 to 0.84)

CRI: Cognitive Reserve Index; TIV: Total intracranial volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III.
** p<0.001, * p<0.05.

Table C17. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (ACE-III) adjusting for hippocampal volume (N=421).

	Model 1	Model 2	Model 3	Model 4
NART	0.27 (0.19 - 0.34)**	0.20 (0.11 - 0.29)**	0.20 (0.11 - 0.29)**	0.20 (0.11 - 0.29)**
Hippocampal volume	1.30 (-0.36 - 2.96)	1.11 (-0.52 - 2.74)	1.08 (-0.55 - 2.72)	1.10 (-0.55 - 2.75)
TIV	0.00 (-0.00 - 0.01)	0.00 (-0.00 - 0.00)	0.00 (-0.00 - 0.00)	0.00 (-0.00 - 0.00)
Age at scan	0.18 (-0.35 - 0.71)	0.12 (-0.40 - 0.64)	0.11 (-0.41 - 0.63)	0.11 (-0.41 - 0.64)
Sex: Female Male	[Reference] -0.78 (-1.77 - 0.22)	[Reference] -0.63 (-1.62 - 0.36)	[Reference] -0.46 (-1.64 - 0.72)	[Reference] -0.47 (-1.64 - 0.71)
Marital status: Married Not-married	[Reference] -1.44 (-2.62 - -0.26)*	[Reference] -1.52 (-2.71 - -0.32)*	[Reference] -1.51 (-2.71 - -0.31)*	[Reference] -1.52 (-2.74 - -0.30)*
APOE-e4 carrier: No Yes	[Reference] 0.00 (-0.87 - 0.87)	[Reference] 0.04 (-0.81 - 0.89)	[Reference] 0.04 (-0.82 - 0.89)	[Reference] 0.03 (-0.83 - 0.89)
Childhood cognition		0.10 (0.04 - 0.17)*	0.11 (0.04 - 0.17)*	0.11 (0.04 - 0.17)*
FRS			-0.02 (-0.09 - 0.05)	-0.02 (-0.09 - 0.06)
GHQ-28: 0 1 to 5 6+				[Reference] 0.15 (-0.98 - 1.28) 0.01 (-0.91 - 0.93)

NART: National Adult Reading Test; TIV: Total intracranial volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III.
** p<0.001, * p<0.05.

Table C18. Regression coefficients and 95% confidence intervals from the association between CRI and cognitive function (ACE-III) adjusting for amyloid status (N=421).

	Model 1	Model 2	Model 3	Model 4
CRI	0.14 (0.11 to 0.17)**	0.10 (0.07 to 0.13)**	0.10 (0.07 to 0.13)**	0.10 (0.07 to 0.13)**
Aβ status: Negative Positive	[Reference] -0.72 (-1.88 to 0.44)	[Reference] -0.88 (-1.95 to 0.19)	[Reference] -0.88 (-1.96 to 0.20)	[Reference] -0.91 (-1.99 to 0.18)
Age at scan	0.05 (-0.48 to 0.58)	-0.02 (-0.52 to 0.47)	-0.02 (-0.53 to 0.48)	-0.02 (-0.53 to 0.49)
Sex: Female Male	[Reference] -1.05 (-1.86 to -0.25)*	[Reference] -0.81 (-1.59 to -0.04)*	[Reference] -0.82 (-1.88 to 0.24)	[Reference] -0.84 (-1.91 to 0.24)
Marital status: Married Not-married	[Reference] -1.41 (-2.68 to -0.13)*	[Reference] -1.57 (-2.82 to -0.32)*	[Reference] -1.57 (-2.82 to -0.31)*	[Reference] -1.58 (-2.85 to -0.32)*
APOE-e4 carrier: No Yes	[Reference] 0.21 (-0.77 to 1.19)	[Reference] 0.30 (-0.60 to 1.20)	[Reference] 0.30 (-0.60 to 1.20)	[Reference] 0.30 (-0.60 to 1.21)
Childhood cognition		0.16 (0.11 to 0.22)**	0.16 (0.11 to 0.22)**	0.16 (0.11 to 0.22)**
FRS			0.00 (-0.08 to 0.08)	0.00 (-0.07 to 0.08)
GHQ-28: 0 1 to 5 6+				[Reference] 0.24 (-0.84 to 1.32) -0.14 (-1.07 to 0.80)

CRI: Cognitive Reserve Index; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III.
** p<0.001, * p<0.05.

Table C19. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (ACE-III) adjusting for amyloid status (N=421).

	Model 1	Model 2	Model 3	Model 4
NART	0.27 (0.20 to 0.34)**	0.20 (0.11 to 0.28)**	0.20 (0.11 to 0.28)**	0.20 (0.11 to 0.28)**
Aβ status: Negative Positive	[Reference] -0.92 (-2.05 to 0.20)	[Reference] -0.99 (-2.08 to 0.10)	[Reference] -1.00 (-2.09 to 0.10)	[Reference] -1.01 (-2.10 to 0.09)
Age at scan	0.13 (-0.40 to 0.66)	0.06 (-0.45 to 0.58)	0.05 (-0.47 to 0.57)	0.05 (-0.47 to 0.58)
Sex: Female Male	[Reference] -0.28 (-1.07 to 0.52)	[Reference] -0.25 (-1.03 to 0.53)	[Reference] -0.01 (-1.06 to 1.03)	-[Reference] 0.02 (-1.08 to 1.04)
Marital status: Married Not-married	[Reference] -1.45 (-2.62 to -0.29)*	[Reference] -1.54 (-2.73 to -0.36)*	[Reference] -1.53 (-2.72 to -0.34)*	[Reference] -1.54 (-2.74 to -0.33)*
APOE-e4 carrier: No Yes	[Reference] 0.24 (-0.68 to 1.16)	[Reference] 0.30 (-0.59 to 1.19)	[Reference] 0.30 (-0.60 to 1.19)	[Reference] 0.30 (-0.60 to 1.20)
Childhood cognition		0.11 (0.05 to 0.18)**	0.11 (0.05 to 0.18)*	0.11 (0.05 to 0.18)*
FRS			-0.03 (-0.10 to 0.05)	-0.03 (-0.10 to 0.05)
GHQ-28: 0 1 to 5 6+				[Reference] 0.11 (-1.00 to 1.23) -0.04 (-0.96 to 0.88)

NART: National Adult Reading Test; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III.
** p<0.001, * p<0.05.

Table C20. Regression coefficients and 95% confidence intervals for the association between CRI and cognitive function (ACE-III) adjusting for WMHV (N=421).

	Model 1	Model 2	Model 3	Model 4
CRI	0.14 (0.10 - 0.17)**	0.10 (0.07 - 0.13)**	0.10 (0.07 - 0.13)**	0.10 (0.07 - 0.13)**
WMHV	-0.06 (-0.13 - 0.00)	-0.08 (-0.15 - -0.01)*	-0.08 (-0.15 - -0.01)*	-0.08 (-0.15 - -0.01)*
TIV	0.00 (-0.00 - 0.01)	0.00 (-0.00 - 0.01)	0.00 (-0.00 - 0.01)	0.00 (-0.00 - 0.01)
Age at scan	0.08 (-0.45 - 0.61)	0.03 (-0.47 - 0.53)	0.04 (-0.46 - 0.54)	0.04 (-0.46 - 0.55)
Sex: Female Male	[Reference] -1.54 (-2.56 - -0.51)*	[Reference] -1.06 (-2.06 - -0.07)*	[Reference] -1.21 (-2.42 - 0.00)	[Reference] -1.22 (-2.43 - -0.00)*
Marital status: Married Not-married	[Reference] -1.40 (-2.69 - -0.11)*	[Reference] -1.55(-2.80 - -0.29)*	[Reference] -1.55 (-2.81 - -0.30)*	[Reference] -1.56 (-2.83 - -0.30)*
APOE-e4 carrier: No Yes	[Reference] 0.08 (-0.83 - 1.00)	[Reference] 0.12 (-0.72 - 0.97)	[Reference] 0.13 (-0.72 - 0.98)	[Reference] 0.13 (-0.73 - 0.98)
Childhood cognition		0.16 (0.11 - 0.22)**	0.16 (0.11 - 0.22)**	0.16 (0.11 - 0.22)**
FRS			0.02 (-0.06 - 0.09)	0.02 (-0.06 - 0.09)
GHQ-28: 0 1 to 5 6+				[Reference] 0.17 (-0.92 - 1.27) -0.07 (-1.00 - 0.87)

CRI: Cognitive Reserve Index; WMHV: White matter hyperintensity volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III.
** p<0.001, * p<0.05.

Table C21. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (ACE-III) adjusting for WMHV (N=421).

	Model 1	Model 2	Model 3	Model 4
NART	0.26 (0.19 to 0.33)**	0.19 (0.11 to 0.28)**	0.19 (0.11 to 0.28)**	0.19 (0.11 to 0.28)**
WMHV	-0.07 (-0.14 to -0.00)*	-0.08 (-0.15 to -0.01)*	-0.08 (-0.15 to -0.01)*	-0.08 (-0.15 to -0.01)*
TIV	0.00 (-0.00 to 0.01)	0.00 (-0.00 to 0.01)	0.00 (-0.00 to 0.01)	0.00 (-0.00 to 0.01)
Age at scan	0.17 (-0.36 to 0.70)	0.12 (-0.40 to 0.63)	0.11 (-0.41 to 0.63)	0.11 (-0.41 to 0.63)
Sex: Female Male	[Reference] -0.82 (-1.81 to 0.17)	[Reference] -0.68 (-1.66 to 0.31)	[Reference] -0.57 (-1.74 to 0.60)	[Reference] -0.57 (-1.74 to 0.60)
Marital status: Married Not-married	[Reference] -1.43 (-2.61 to -0.25)*	[Reference] -1.52 (-2.71 to -0.32)*	[Reference] -1.51 (-2.71 to -0.31)*	[Reference] -1.52 (-2.73 to -0.31)*
APOE-e4 carrier: No Yes	[Reference] 0.05 (-0.82 to 0.91)	[Reference] 0.09 (-0.76 to 0.93)	[Reference] 0.08 (-0.76 to 0.93)	[Reference] 0.08 (-0.77 to 0.93)
Childhood cognition		0.11 (0.05 to 0.18)**	0.11 (0.05 to 0.18)**	0.11 (0.05 to 0.18)**
FRS			-0.01 (-0.08 to 0.06)	-0.01 (-0.08 to 0.06)
GHQ-28: 0 1 to 5 6+				[Reference] 0.05 (-1.08 to 1.17) 0.04 (-0.89 to 0.96)

NART: National Adult Reading Test; WMHV: White matter hyperintensity volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; ACE-III: Addenbrooke's Cognitive Examination III.
** p<0.001, * p<0.05.

Table C22. Regression coefficients and 95% confidence intervals for associations between CRI and cognitive function (PACC) adjusting for brain volume (N=502).

	Model 1	Model 2	Model 3	Model 4
CRI	0.02 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**
Brain volume	0.00 (-0.00 to 0.00)	0.00 (0.00 to 0.00)*	0.00 (0.00 to 0.00)*	0.00 (0.00 to 0.00)*
TIV	-0.00 (-0.00 to 0.00)	-0.00 (-0.00 to 0.00)	-0.00 (-0.00 to 0.00)	-0.00 (-0.00 to 0.00)
Age at scan	-0.04 (-0.12 to 0.04)	-0.05 (-0.12 to 0.03)	-0.04 (-0.12 to 0.03)	-0.04 (-0.12 to 0.03)
Sex: Female Male	[Reference] -0.52 (-0.68 to -0.37)**	[Reference] -0.44 (-0.59 to -0.29)**	[Reference] -0.48 (-0.67 to -0.30)**	[Reference] -0.48 (-0.67 to -0.30)**
Marital status: Married Not-married	[Reference] -0.07 (-0.24 to 0.09)	[Reference] -0.08 (-0.24 to 0.09)	[Reference] -0.08 (-0.24 to 0.08)	[Reference] -0.08 (-0.25 to 0.09)
APOE-e4 carrier: No Yes	[Reference] 0.01 (-0.14 to 0.15)	[Reference] 0.00 (-0.13 to 0.14)	[Reference] 0.00 (-0.13 to 0.14)	[Reference] 0.00 (-0.13 to 0.14)
Childhood cognition		0.03 (0.02 to 0.03)**	0.03 (0.02 to 0.03)**	0.03 (0.02 to 0.03)**
FRS			0.00 (-0.01 to 0.02)	0.00 (-0.01 to 0.02)
GHQ-28: 0 1 to 5 6+				[Reference] -0.00 (-0.16 to 0.15) 0.03 (-0.10 to 0.16)

CRI: Cognitive Reserve Index; TIV; Total intracranial volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; PACC: Preclinical Alzheimer Cognitive Composite.
** p<0.001, * p<0.05.

Table C23. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (PACC) adjusting for brain volume (N=502).

	Model 1	Model 2	Model 3	Model 4
NART	0.04 (0.03 to 0.05)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**
Brain volume	0.00 (0.00 to 0.00)*	0.00 (0.00 to 0.00)*	0.00 (0.00 to 0.00)*	0.00 (0.00 to 0.00)*
TIV	-0.00 (-0.00 to 0.00)	-0.00 (-0.00 to 0.00)	-0.00 (-0.00 to 0.00)	-0.00 (-0.00 to 0.00)
Age at scan	-0.02 (-0.09 to 0.06)	-0.03 (-0.10 to 0.05)	-0.03 (-0.10 to 0.05)	-0.03 (-0.10 to 0.05)
Sex: Female Male	[Reference] -0.42 (-0.57 to -0.28)**	[Reference] -0.39 (-0.54 to -0.25)**	[Reference] -0.41 (-0.60 to -0.23)**	[Reference] -0.41 (-0.59 to -0.22)**
Marital status: Married Not-married	[Reference] -0.06 (-0.22 to 0.10)	[Reference] -0.07 (-0.23 to 0.09)	[Reference] -0.07 (-0.23 to 0.09)	[Reference] -0.07 (-0.23 to 0.09)
APOE-e4 carrier: No Yes	[Reference] -0.01 (-0.14 to 0.13)	[Reference] -0.01 (-0.14 to 0.13)	[Reference] -0.01 (-0.14 to 0.13)	[Reference] -0.00 (-0.14 to 0.13)
Childhood cognition		0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**
FRS			0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.01)
GHQ-28: 0 1 to 5 6+				[Reference] -0.03 (-0.18 to 0.13) 0.03 (-0.10 to 0.16)

NART: National Adult Reading Test; TIV: Total Intracranial Volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; PACC: Preclinical Alzheimer Cognitive Composite.
** p<0.001, * p<0.05.

Table C24. Regression coefficients and 95% confidence intervals for the association between CRI and cognitive function (PACC) adjusting for hippocampal volume (N=502).

	Model 1	Model 2	Model 3	Model 4
CRI	0.02 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**
Hippocampal volume	0.22 (-0.04 to 0.47)	0.19 (-0.05 to 0.44)	0.20 (-0.04 to 0.44)	0.20 (-0.04 to 0.44)
TIV	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
Age at scan	-0.05 (-0.13 to 0.03)	-0.05 (-0.13 to 0.02)	-0.05 (-0.13 to 0.02)	-0.05 (-0.13 to 0.02)
Sex: Female Male	[Reference] -0.57 (-0.72 to -0.42)**	[Reference] -0.50* (-0.64 to -0.35)*	[Reference] -0.53 (-0.71 to -0.35)**	[Reference] -0.53 (-0.71 to -0.35)**
Marital status: Married Not-married	[Reference] -0.08 (-0.24 to 0.09)	[Reference] -0.08 (-0.25 to 0.08)	[Reference] -0.09 (-0.25 to 0.08)	[Reference] -0.09 (-0.26 to 0.08)
APOE-e4 carrier: No Yes	[Reference] 0.02 (-0.12 to 0.16)	[Reference] 0.01 (-0.12 to 0.15)	[Reference] 0.01 (-0.12 to 0.15)	[Reference] 0.01 (-0.12 to 0.15)
Childhood cognition		0.03 (0.02 to 0.03)**	0.02 (0.02 to 0.03)**	0.02 (0.02 to 0.03)**
FRS			0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.02)
GHQ-28: 0 1 to 5 6+				[Reference] 0.02 (-0.13 to 0.18) 0.05 (-0.08 to 0.18)

CRI: Cognitive Reserve Index; TIV; Total intracranial volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; PACC: Preclinical Alzheimer Cognitive Composite.
** p<0.001, * p<0.05.

Table C25. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (PACC) adjusting for hippocampal volume (N=502).

	Model 1	Model 2	Model 3	Model 4
NART	0.04 (0.03 to 0.05)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**
Hippocampal volume	0.32 (0.07 to 0.56)*	0.28 (0.04 to 0.52)*	0.28 (0.04 to 0.52)*	0.28 (0.04 to 0.52)*
TIV	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
Age at scan	-0.02 (-0.10 to 0.06)	-0.03 (-0.11 to 0.04)	-0.03 (-0.11 to 0.04)	-0.03 (-0.11 to 0.04)
Sex: Female Male	[Reference] -0.48 (-0.62 to -0.34)**	[Reference] -0.45 (-0.59 to -0.31)**	[Reference] -0.46 (-0.64 to -0.29)**	[Reference] -0.46 (-0.64 to -0.28)**
Marital status: Married Not-married	[Reference] -0.08 (-0.23 to 0.08)	[Reference] -0.08 (-0.24 to 0.08)	[Reference] -0.08 (-0.24 to 0.08)	[Reference] -0.08 (-0.24 to 0.08)
APOE-e4 carrier: No Yes	[Reference] 0.00 (-0.13 to 0.14)	[Reference] 0.00 (-0.13 to 0.14)	[Reference] 0.00 (-0.13 to 0.14)	[Reference] 0.01 (-0.13 to 0.14)
Childhood cognition		0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**
FRS			0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.01)
GHQ-28: 0 1 to 5 6+				[Reference] 0.01 (-0.15 to 0.16) 0.06 (-0.07 to 0.19)

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Table C26. Regression coefficients and 95% confidence intervals for the association between CRI and cognitive function (PACC) adjusting for amyloid status (N=502).

	Model 1	Model 2	Model 3	Model 4
CRI	0.02 (0.02 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**
Aβ status: Negative Positive	[Reference] -0.27 (-0.46 to -0.09)*	[Reference] -0.29 (-0.47 to -0.12)*	[Reference] -0.29 (-0.47 to -0.12)*	[Reference] -0.29 (-0.47 to -0.12)*
Age at scan	-0.06 (-0.14 to 0.02)	-0.07 (-0.14 to 0.01)	-0.07 (-0.14 to 0.01)	-0.07 (-0.14 to 0.01)
Sex: Female Male	[Reference] -0.45 (-0.57 to -0.34)**	[Reference] -0.40 (-0.51 to -0.28)**	[Reference] -0.41 (-0.58 to -0.24)**	[Reference] -0.41 (-0.58 to -0.24)**
Marital status: Married Not-married	[Reference] -0.07 (-0.23 to 0.09)	[Reference] -0.08 (-0.24 to 0.08)	[Reference] -0.08 (-0.24 to 0.08)	[Reference] -0.08 (-0.25 to 0.08)
APOE-e4 carrier: No Yes	[Reference] 0.08 (-0.06 to 0.22)	[Reference] 0.09 (-0.04 to 0.22)	[Reference] 0.09 (-0.05 to 0.22)	[Reference] 0.09 (-0.05 to 0.22)
Childhood cognition		0.03 (0.02 to 0.03)**	0.03 (0.02 to 0.03)**	0.03 (0.02 to 0.03)**
FRS			0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.01)
GHQ-28: 0 1 to 5 6+				[Reference] 0.02 (-0.13 to 0.17) 0.03 (-0.10 to 0.16)

CRI: Cognitive Reserve Index; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; PACC: Preclinical Alzheimer Cognitive Composite.
** p<0.001, * p<0.05.

Table C27. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (PACC) adjusting for amyloid status (N=502).

	Model 1	Model 2	Model 3	Model 4
NART	0.04 (0.03 to 0.05)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**
Aβ status: Negative Positive	[Reference] -0.31 (-0.48 to -0.13)**	[Reference] -0.31 (-0.48 to -0.14)**	[Reference] -0.31 (-0.49 to -0.14)**	[Reference] -0.31 (-0.48 to -0.14)**
Age at scan	-0.03 (-0.11 to 0.04)	-0.05 (-0.12 to 0.03)	-0.05 (-0.12 to 0.03)	-0.05 (-0.12 to 0.03)
Sex: Female Male	[Reference] -0.35 (-0.46 to -0.24)**	[Reference] -0.33 (-0.44 to -0.22)**	[Reference] -0.32 (-0.49 to -0.15)**	[Reference] -0.32 (-0.49 to -0.15)**
Marital status: Married Not-married	[Reference] -0.06 (-0.22 to 0.09)	[Reference] -0.07 (-0.23 to 0.08)	[Reference] -0.07 (-0.23 to 0.08)	[Reference] -0.07 (-0.23 to 0.09)
APOE-e4 carrier: No Yes	[Reference] 0.08 (-0.06 to 0.21)	[Reference] 0.08 (-0.05 to 0.21)	[Reference] 0.08 (-0.05 to 0.21)	[Reference] 0.08 (-0.05 to 0.21)
Childhood cognition		0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**
FRS			-0.00 (-0.01 to 0.01)	-0.00 (-0.01 to 0.01)
GHQ-28: 0 1 to 5 6+				[Reference] -0.01 (-0.16 to 0.15) 0.03 (-0.10 to 0.16)

NART: National Adult Reading Test; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; PACC: Preclinical Alzheimer Cognitive Composite.
** p<0.001, * p<0.05.

Table C28. Regression coefficients and 95% confidence intervals for the association between CRI and cognitive function (PACC) adjusting for WMHV (N=502).

	Model 1	Model 2	Model 3	Model 4
CRI	0.02 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**	0.01 (0.01 to 0.02)**
WMHV	-0.01 (-0.03 to -0.00)*	-0.01 (-0.03 to -0.00)*	-0.01 (-0.03 to -0.00)*	-0.01 (-0.03 to -0.00)*
TIV	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
Age at scan	-0.05 (-0.13 to 0.03)	-0.06 (-0.13 to 0.02)	-0.05 (-0.13 to 0.02)	-0.05 (-0.13 to 0.02)
Sex: Female Male	[Reference] -0.58 (-0.72 to -0.43)**	[Reference] -0.50 (-0.64 to -0.36)**	[Reference] -0.54 (-0.72 to -0.36)**	[Reference] -0.54 (-0.71 to -0.36)**
Marital status: Married Not-married	[Reference] -0.08 (-0.25 to 0.08)	[Reference] -0.09 (-0.26 to 0.07)	[Reference] -0.10 (-0.26 to 0.07)	[Reference] -0.10 (-0.27 to 0.07)
APOE-e4 carrier: No Yes	[Reference] 0.02 (-0.12 to 0.16)	[Reference] 0.02 (-0.12 to 0.15)	[Reference] 0.02 (-0.12 to 0.15)	[Reference] 0.02 (-0.12 to 0.15)
Childhood cognition		0.03 (0.02 to 0.03)**	0.03 (0.02 to 0.03)**	0.03 (0.02 to 0.03)**
FRS			0.00 (-0.01 to 0.02)	0.00 (-0.01 to 0.02)
GHQ-28: 0 1 to 5 6+				[Reference] -0.00 (-0.16 to 0.15) 0.05 (-0.08 to 0.18)

CRI: Cognitive Reserve Index; WMHV: White matter hyperintensity volume; TIV; Total intracranial volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; PACC: Preclinical Alzheimer Cognitive Composite.
** p<0.001, * p<0.05.

Table C29. Regression coefficients and 95% confidence intervals for the association between NART and cognitive function (PACC) adjusting for WMHV (N=502).

	Model 1	Model 2	Model 3	Model 4
NART	0.04 (0.03 to 0.05)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**	0.03 (0.02 to 0.04)**
WMHV	-0.01 (-0.03 to -0.00)*	-0.01 (-0.03 to -0.00)*	-0.02 (-0.03 to -0.00)*	-0.02 (-0.03 to -0.00)*
TIV	0.00 (0.00 to 0.00)*	0.00 (-0.00 to 0.00)	0.00 (0.00 to 0.00)*	0.00 (0.00 to 0.00)*
Age at scan	-0.02 (-0.10 to 0.05)	-0.04 (-0.11 to 0.04)	-0.04 (-0.11 to 0.04)	-0.04 (-0.11 to 0.04)
Sex: Female Male	[Reference] -0.48 (-0.62 to -0.35)**	[Reference] -0.46 (-0.59 to -0.32)**	[Reference] -0.47 (-0.65 to -0.30)**	[Reference] -0.47 (-0.64 to -0.29)**
Marital status: Married Not-married	[Reference] -0.08 (-0.24 to 0.08)	[Reference] -0.09 (-0.25 to 0.07)	[Reference] -0.09 (-0.25 to 0.07)	[Reference] -0.09 (-0.25 to 0.08)
APOE-e4 carrier: No Yes	[Reference] 0.00 (-0.13 to 0.14)	[Reference] 0.01 (-0.12 to 0.14)	[Reference] 0.01 (-0.12 to 0.14)	[Reference] 0.01 (-0.12 to 0.14)
Childhood cognition		0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**	0.02 (0.01 to 0.03)**
FRS			0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.01)
GHQ-28: 0 1 to 5 6+				[Reference] -0.02 (-0.18 to 0.13) 0.06 (-0.07 to 0.18)

NART: National Adult Reading Test; WMHV: White matter hyperintensity volume; TIV; Total intracranial volume; FRS: Framingham cardiovascular risk score; GHQ-28: General Health Questionnaire; PACC: Preclinical Alzheimer Cognitive Composite.
** p<0.001, * p<0.05.

Table C30. Regression coefficients and 95% confidence intervals for the associations between education, occupation, and leisure, and cognitive function (ACE-III) in NSHD analytical sample and Insight 46 analytical sub-sample.

N		Predictor	**B (95% CI)**	**Interaction p-value CRI component and brain marker**
	ACE-III			
1,184 NSHD		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 2.49 (1.68 to 3.29)** 3.33 (2.48 to 4.18)** 3.74 (2.55 to 4.93)**	-
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 1.86 (0.89 to 2.83)** 3.28 (2.28 to 4.28)**	-
		Leisure: 0-4 5 6+	[Reference] 1.78 (0.98 to 2.58)** 2.33 (1.65 to 3.02)**	-
421 Insight 46				
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 1.62 (0.37 to 2.88)* 3.11 (1.80 to 4.42)** 3.52 (1.93 to 5.11)**	-
		Occupation: Part skilled/unskilled Skilled Professional	1[Reference] 0.37 (-1.47 to 2.21) 2.09 (0.28 to 3.90)*	-
		Leisure: 0-4 5 6+	[Reference] 1.77 (0.61 to 2.93)* 2.32 (1.35 to 3.29)**	-
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 1.66 (0.40 to 2.92)* 3.13 (1.82 to 4.45)** 3.44 (1.82 to 5.06)**	0.05
		Brain volume	0.007 (-0.002 to 0.02)	
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 0.35 (-1.48 to 2.18) 2.09 (0.29 to 3.90)*	0.70
		Brain volume	0.008 (-0.001 to 0.02)	
		Leisure: 0-4 5 6+	[Reference] 1.72 (0.57 to 2.88)** 2.28 (1.31 to 3.25)**	<0.001
		Brain volume	0.006 (-0.003 to 0.02)	
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 1.60 (0.34 to 2.86)* 3.15 (1.84 to 4.46)** 3.49 (1.88 to 5.11)**	0.004
		Hippocampal volume	0.87 (-0.53 to 2.28)	
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 0.41 (-1.43 to 2.25) 2.09 (0.29 to 3.90)*	0.004

		Hippocampal volume	0.64 (-0.79 to 2.08)	
		Leisure: 0-4 5 6+	[Reference] 1.70 (0.54 to 2.85)**= 2.28 (1.30 to 3.26)**	<0.001
		Hippocampal volume	0.36 (-1.08 to 1.79)	
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 1.58 (0.32 to 2.85) 3.06 (1.74 to 4.37)** 3.41 (1.79 to 5.03)**	0.35
		Aβ status	-0.93 (-1.99 to 0.14)	
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 0.40 (-1.42 to 2.23) 2.10 (0.30 to 3.90)*	0.31
		Aβ status	-1.15 (-2.25 to -0.05)*	
		Leisure: 0-4 5 6+	[Reference] 1.76 (0.60 to 2.92)* 2.31 (1.33 to 3.29)**	0.10
		Aβ status	-0.99 (-2.07 to 0.08)	
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 1.62 (0.36 to 2.89)* 3.16 (1.86 to 4.47)** 3.34 (1.73 to 4.95)**	0.72
		WMHV	-0.08 (-0.15 to -0.002)	
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 0.36 (-1.48 to 2.18) 2.04 (0.24 to 3.84)*	0.60
		WMHV	-0.08 (-0.16 to -0.007)*	
		Leisure: 0-4 5 6+	[Reference] 1.73 (0.57 to 2.88)* 2.37 (1.39 to 3.35)**	0.20
		WMHV	-0.08 (-0.16 to -0.01)*	

CRI: Cognitive reserve index; ACE-III: Addenbrooke's Cognitive Examination III; PACC: Preclinical Alzheimer Cognitive Composite; WMHV: White matter hyperintensity volume. Models adjusted for total intracranial volume (except for Aβ *status), age at scan, sex, marital status, childhood cognitive ability, APOE genotype, FRS, and GHQ scores.*

All statistically significant associations remained significant after Benjamini-Hochberg correction.

*p<0.05, **p≤0.001.

Table C31. Associations between education, occupation, and leisure, and cognitive function (PACC) in the Insight 46 analytical sub-sample.

N		Predictor	**B (95% CI)**	**Interaction p-value CRI component and brain marker**
502 Insight 46	**PACC**			
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 0.18 (0.002 to 0.37) 0.38 (0.20 to 0.57)** 0.52 (0.29 to 0.74)**	-
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 0.06 (-0.20 to 0.32) 0.34 (0.09 to 0.60)*	-
		Leisure: 0-4 5 6+	[Reference] 0.25 (0.08 to 0.41)* 0.18 (0.04 to 0.32)*	-
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 0.19 (0.007 to 0.37)* 0.39 (0.21 to 0.58)** 0.49 (0.25 to 0.72)**	0.08
		Brain volume	0.002 (0.0003 to 0.003)*	
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 0.03 (-0.23 to 0.29) 0.31 (0.06 to 0.56)*	0.18
		Brain volume	0.002 (0.0003 to 0.003)*	
		Leisure: 0-4 5 6+	[Reference] 0.24 (0.07 to 0.40)* 0.17 (0.03 to 0.31)*	0.008
		Brain volume	0.002 (0.0003 to 0.003)*	
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 0.17 (-0.01 to 0.35) 0.39 (0.20 to 0.57)** 0.48 (0.25 to 0.71)**	<0.001
		Hippocampal volume	0.24 (0.05 to 0.44)*	
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 0.05 (-0.20 to 0.31) 0.32 (0.07 to 0.57)**	0.19
		Hippocampal volume	0.21 (0.01 to 0.41)*	
		Leisure: 0-4 5 6+	[Reference] 0.23 (0.07 to 0.40)* 0.16 (0.02 to 0.30)*	0.002
		Hippocampal volume	0.21 (0.008 to 0.41)*	
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 0.17 (-0.01 to 0.34) 0.37 (0.19 to 0.55)** 0.47 (0.24 to 0.70)**	0.03

		Aβ status	-0.32 (-0.47 to -0.16)**	
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 0.04 (-0.22 to 0.29) 0.32 (0.07 to 0.57)*	0.30
		Aβ status	-0.34 (-0.50 to -0.19)**	
		Leisure: 0-4 5 6+	[Reference] 0.24 (0.08 to 0.41)* 0.16 (0.03 to 0.30)*	0.64
		Aβ status	-0.33 (-0.49 to -0.18)**	
		Education: No qualification GCE 'O' or equivalent GCE 'A' or equivalent Degree or equivalent	[Reference] 0.18 (-0.007 to 0.37) 0.38 (0.19 to 0.58)** 0.47 (0.23 to 0.72)**	0.29
		WMHV	-0.01 (-0.03 to -0.003)*	
		Occupation: Part skilled/unskilled Skilled Professional	[Reference] 0.03 (-0.24 to 0.31) 0.31 (0.04 to 0.58)*	0.30
		WMHV	-0.02 (-0.03 to -0.003)*	
		Leisure: 0-4 5 6+	[Reference] 1.76 (0.56 to 2.97)** 2.33 (1.34 to 3.33)**	0.30
		WMHV	-0.08 (-0.15 to -0.0007)	

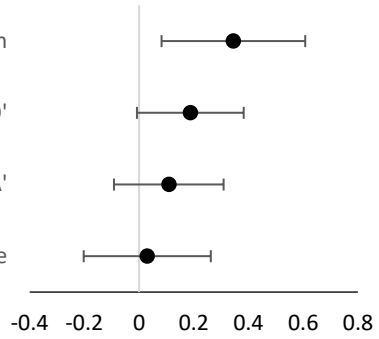
CRI: Cognitive reserve index; ACE-III: Addenbrooke's Cognitive Examination III; PACC: Preclinical Alzheimer Cognitive Composite; WMHV: White matter hyperintensity volume. Models adjusted for total intracranial volume (except for Aβ *status), age at scan, sex, marital status, childhood cognitive ability, APOE genotype, FRS, and GHQ scores.*

All statistically significant associations remained significant after Benjamini-Hochberg correction.

*p<0.05, **p≤0.001.

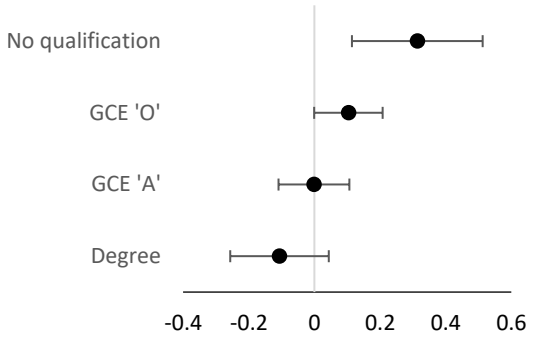
[A] Brain volume on the ACE-III

Education	B (95% CI)
No qualification	0.35 (0.08 to 0.60)*
GCE 'O'	0.19 (-0.01 to 0.38)
GCE 'A'	0.11 (-0.09 to 0.31)
Degree	0.03 (-0.20 to 0.26)



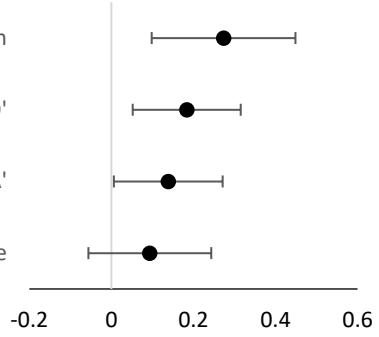
[B] Hippocampal volume on the ACE-III

Education	B (95% CI)
No qualification	0.31 (0.11 to 0.51)*
GCE 'O'	0.10 (-0.01 to 0.21)
GCE 'A'	-0.001 (-0.11 to 0.11)
Degree	-0.11 (-0.26 to 0.04)



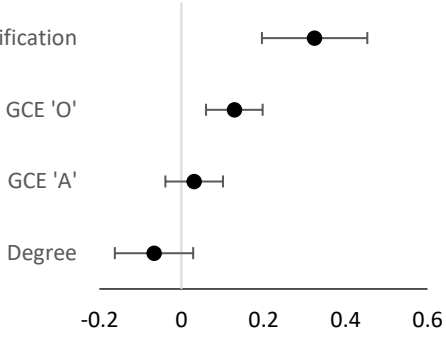
[C] Brain volume on the PACC

Education	B (95% CI)
No qualification	0.27 (0.10 to 0.45)*
GCE 'O'	0.18 (0.05 to 0.32)*
GCE 'A'	0.14 (0.01 to 0.27)
Degree	0.09 (-0.06 to 0.24)



[D] Hippocampal volume on the PACC

Education	B (95% CI)
No qualification	0.33 (0.20 to 0.45)*
GCE 'O'	0.13 (0.06 to 0.20)*
GCE 'A'	0.03 (-0.04 to 0.10)
Degree	-0.07 (-0.16 to 0.03)

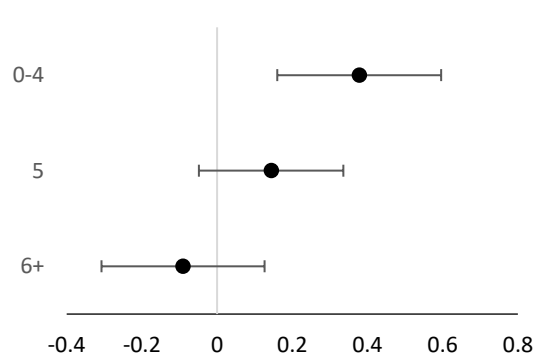


ACE-III: Addenbrooke's Cognitive Examination III; PACC: Preclinical Alzheimer Cognitive Composite.
*p<0.05, **<0.001.

Figure C1. Illustrative plots showing the simple slopes of standardised brain markers on cognitive function at different levels of education for the associations that showed significant effect modification.

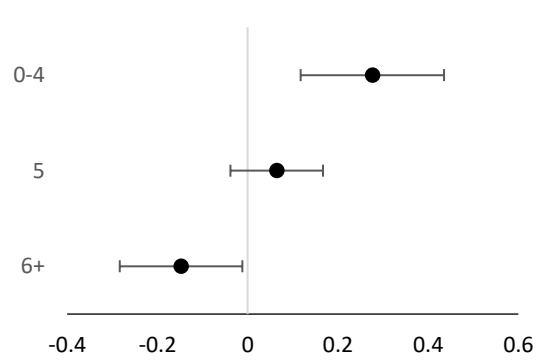
[A] Brain volume on the ACE-III

Leisure	B (95% CI)
0-4	0.38 (0.16 to 0.60)*
5	0.14 (-0.05 to 0.34)
6+	-0.09 (-0.31 to 0.13)



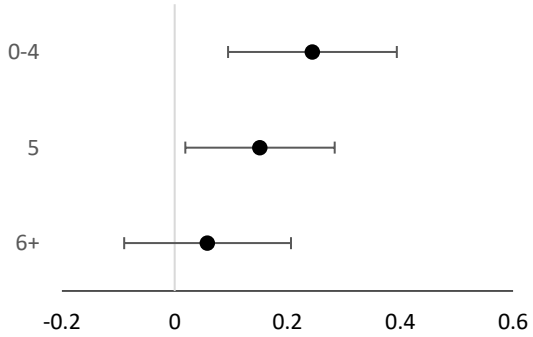
[B] Hippocampal volume on the ACE-III

Leisure	B (95% CI)
0-4	0.28 (0.12 to 0.44)*
5	0.07 (-0.04 to 0.17)
6+	-0.15 (-0.28 to -0.01)



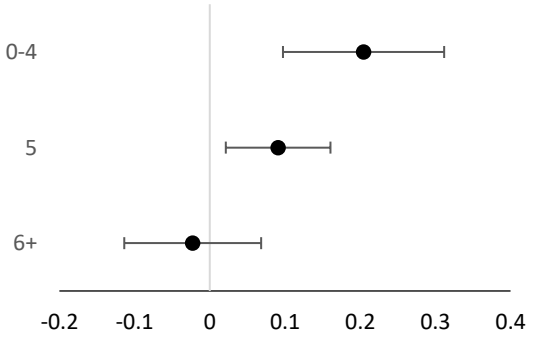
[C] Brain volume on the PACC

Leisure	B (95% CI)
0-4	0.24 (0.10 to 0.39)*
5	0.15 (0.02 to 0.28)*
6+	0.06 (-0.09 to 0.21)



[D] Hippocampal volume on the PACC

Leisure	B (95% CI)
0-4	0.21 (0.10 to 0.31)*
5	0.09 (0.02 to 0.16)*
6+	-0.02 (-0.11 to 0.07)

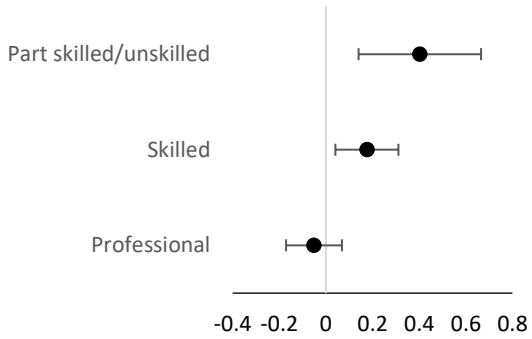


ACE-III: Addenbrooke's Cognitive Examination III; PACC: Preclinical Alzheimer Cognitive Composite.
*p<0.05, **<0.001.

Figure C2. Illustrative plots showing the simple slopes of standardised brain markers on cognitive function at different levels of leisure for the associations that showed significant effect modification.

Hippocampal volume on the ACE-III

	B (95% CI)
Occupation	
Part skilled/unskilled	0.40 (0.14 to 0.67)*
Skilled	0.18 (0.04 to 0.31)*
Professional	-0.05 (-0.17 to 0.07)



ACE-III: Addenbrooke's Cognitive Examination III; PACC: Preclinical Alzheimer Cognitive Composite.
*p<0.05, **<0.001.

Figure C3. Illustrative plots showing the simple slopes of standardised hippocampal volume on cognitive function at different levels of occupation for the associations that showed significant effect modification.

Appendix D. The moderating role of cognitive reserve between brain markers and cognitive function in UK Biobank

D.1 Model assumptions

For all relevant models the linearity assumption was assessed by scatterplot, while multicollinearity was ruled out by assessing the Variance Inflation Factor (VIF). For research question 1 all VIF values were small (<1.31) with a mean of 1.17 and spread level plots suggested no evidence of heteroskedasticity for any of the linear regression models (brain volume and hippocampal volume). For research questions 2 and 3, all VIF value were also small (<2.25) with a mean of 1.36. However, a histogram of the distribution of cognitive function, as well as one of the standardised residuals revealed a slight negative skew. However, due to the large sample size of this study, minor violations of the normality assumption were not expected to impact the results (663). Furthermore, a spread-level plot suggested a mild pattern of heteroskedasticity; hence, a heteroskedasticity-consistent standard error estimator of the parameter estimates was employed in all models(664). The level of statistical significance was set at $p<0.05$ except for interactions where it was set at $p<0.10$. To control for false discovery rate due to multiple comparisons, the Benjamini-Hochberg correction (497) with a q-value of 0.05 was used for all the regression models

D.2 Leisure activities

Table D1. Derivation of leisure activity variables for CRI leisure sub-component.

Variable label (variable name)	Original variable coding	Coding for study
Time spent driving (n_1090_0_0)	0 to 24 hours	0 to 1h = 0 2 to 24h = 1
Time spent watching television (n_1070_0_0)	0 to 24 hours	0 to 1h = 0 2 to 24h = 1
Time spent user computer (n_1080_0_0)	0 to 24 hours	0 to 1h = 0 2 to 24h = 1
Plays computer games (n_2237_0_0)	Never/rarely Sometimes Often	Never/rarely=0 Sometimes/often=1
Length of mobile phone use (n_1110_0_0)	Never used a mobile phone <=1 year 2 to 4 years 5 to 8 years >8 years	Never/>1 year = 0 2 to 8+ years = 1
Weekly usage of mobile phone use in last 3 months (n_1120_0_0)	Less than 5 minutes 5 to 29 minutes 30 to 59 minutes 1 to 3 hours 4 to 6 hours >6 hours	<5 to 29 minutes=0 30 minutes to >6 hours=1
Hands-free device/speakerphone use with mobile phone in last 3 months (n_1130_0_0)	Never Less than half the time About half the time More than half the time Always	Never=0 Less than half the time to always=1
Frequency of friend/family visits (n_1031_0_0)	No friends/family Never Once every few months About once a month About once a week 2 to 4 times a week Daily	No friends to once every few months=0 About once a month to daily=1
Social activities (n_6160_0_0)	Sports club or gym Pub or social club Religious group Adult education class Other group activity	1 point for each activity (count variable [0 to 5])
Types of physical activity in last 4 weeks (n_6164_0_0)	Walking for pleasure Other exercises Strenuous sports Light DIY Heavy DIY	1 point for each activity (count variable [0 to 5])

Variable coding: 0=no engagement; 1=engagement.

D.3 Tables and Figures

Table D2. Regression coefficients and 95% confidence intervals of the associations between CRI and brain markers (N=4,574).

Brain marker	CRI	Interaction p-value	
Regression coefficients and 95% confidence intervals			
Brain volume	-0.10 (-0.23 to 0.03)	CRI*sex	0.39
		CRI*age	0.63
		CRI*APOE	0.22
		CRI*sex*age	0.17
		CRI*sex*APOE	0.71
		CRI*age*APOE	0.20
Hippocampal volume	0.001 (0.0003 to 0.002)*	CRI*sex	0.97
		CRI*age	0.33
		CRI*APOE	0.36
		CRI*sex*age	0.94
		CRI*sex*APOE	0.79
		CRI*age*APOE	**0.02**
Exponentiated coefficients and 95% confidence intervals			
WMHV	-0.002 (-0.004 to 0.0009)	CRI*sex	0.96
		CRI*age	0.19
		CRI*APOE	0.77
		CRI*sex*age	0.94
		CRI*sex*APOE	0.58
		CRI*age*APOE	0.33

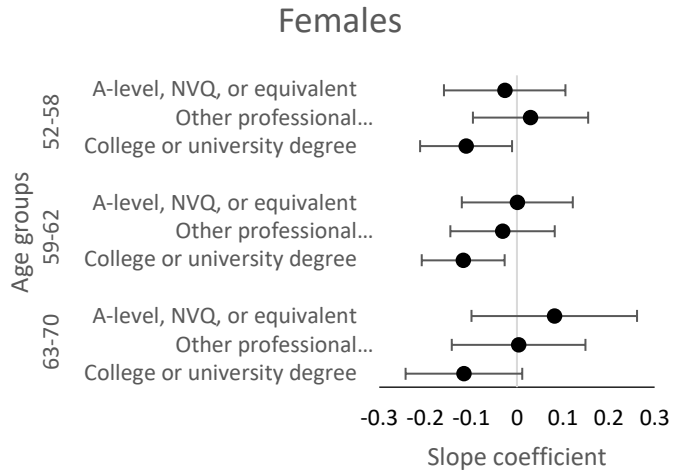
CRI: Cognitive reserve index; WMHV: White matter hyperintensity volumes Models adjusted for head bone size (except brain volume), age, sex, and genetic risk
All statistically significant associations remained significant after Benjamini-Hochberg correction.
*p<0.05, **p≤0.001.

Table D3. Regression coefficients and 95% confidence intervals of the associations between education, occupation, and leisure and brain markers.

Brain marker (N)	CR marker	B (95% CI)
	Regression coefficients and 95% confidence intervals	
Brain volume (10,229)	Education: None, O level, or equivalent A level, NVQ or equivalent Other professional qualification College or university degree	[Reference] -1.64 (-5.58 to 2.31) 0.56 (-3.29 to 4.42) -8.30 (-11.40 to -5.20)**
	Occupation: Low skilled or skilled manual Skilled non-manual Professional Highly responsible or intellectual	[Reference] -3.83 (-8.17 to 0.50) -5.75 (-9.93 to -1.57)* -5.52 (-8.98 to -2.06)*
	Leisure: 0-6 7-8 9+	[Reference] 3.50 (0.69 to 6.30)* 2.98 (0.04 to 5.93)
Hippocampal volume (8,486)	Education: None, O level, or equivalent A level, NVQ or equivalent Other professional qualification College or university degree	[Reference] 0.003 (-0.03 to 0.03) 0.02 (-0.01 to 0.05) 0.02 (0.0009 to 0.05)*
	Occupation: Low skilled or skilled manual Skilled non-manual Professional Highly responsible or intellectual	[Reference] 0.004 (-0.03 to 0.04) -0.009 (-0.04 to 0.02) 0.02 (-0.005 to 0.05)
	Leisure: 0-6 7-8 9+	[Reference] 0.02 (0.002 to 0.04)* 0.03 (0.003 to 0.05)*
	Exponentiated coefficients and 95% confidence intervals	
WMHV (8,238)	Education: None, O level, or equivalent A level, NVQ or equivalent Other professional qualification College or university degree	[Reference] 0.003 (-0.08 to 0.08) 0.0009 (-0.08 to 0.08) -0.009 (-0.07 to 0.06)
	Occupation: Low skilled or skilled manual Skilled non-manual Professional Highly responsible or intellectual	[Reference] -0.08 (-0.16 to 0.01) -0.06 (-0.14 to 0.03) -0.07 (-0.14 to -0.002)
	Leisure: 0-6 7-8 9+	[Reference] -0.009 (-0.07 to 0.05) -0.03 (-0.09 to 0.03)

Models adjusted for head bone size (except brain volume),sex, age, and APOE status
All statistically significant associations remained significant after Benjamini-Hochberg correction.
*p<0.05, **p≤0.001.

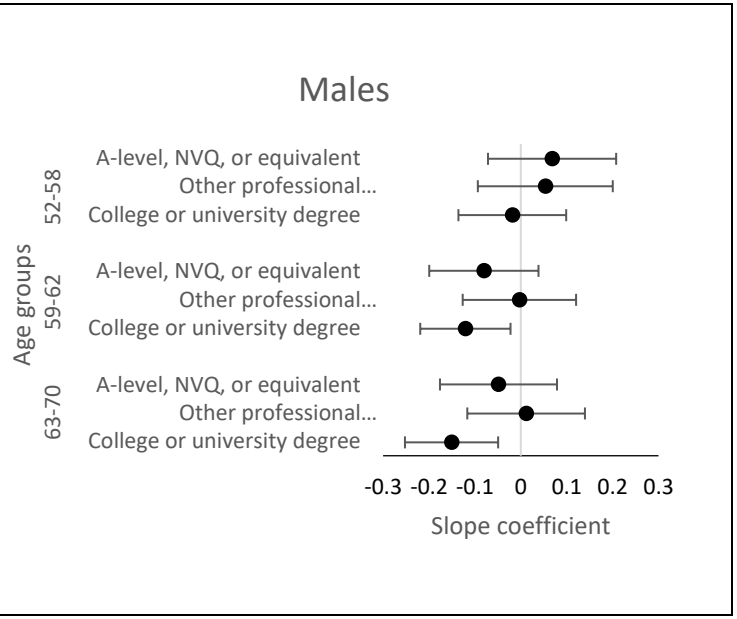
Age (N)	Education	B (95% CI)	p-value
	Females		
52 to 58 (1,832)	None, O level, or equivalent	[Reference]	
	A level, NVQ or equivalent	-0.03 (-0.16 to 0.11)	0.69
	Other professional qualification	0.03 (-0.10 to 0.16)	0.64
	College or university degree	-0.11 (-0.21 to -0.01)	0.03
59 to 62 (1,901)	None, O level, or equivalent	[Reference]	
	A level, NVQ or equivalent	0.0008 (-0.12 to 0.12)	0.99
	Other professional qualification	-0.03 (-0.15 to 0.08)	0.59
	College or university degree	-0.12 (-0.21 to -0.03)	0.01
63 to 70 (1,068)	None, O level, or equivalent	[Reference]	
	A level, NVQ or equivalent	0.08 (-0.10 to 0.26)	0.38
	Other professional qualification	0.004 (-0.14 to 0.15)	0.96
	College or university degree	-0.12 (-0.24 to 0.01)	0.08



Age groups classified into mean and two standard deviations above and below the mean.
*p≤0.01, **<0.001.

Figure D1a. Illustrative plots showing the slope coefficients for **females** of education on standardised brain volume at mean, low (-2 std) and high (+2 std) values of baseline age.

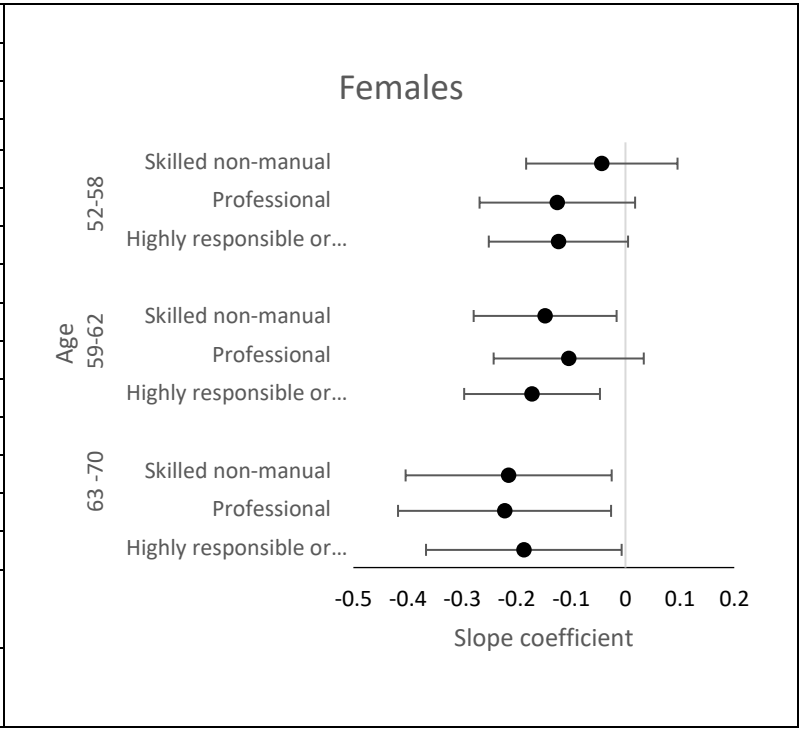
Age (N)	Education	B (95% CI)	p-value
	Males		
52 to 58 (1,680)	None, O level, or equivalent	[Reference]	
	A level, NVQ or equivalent	0.07 (-0.07 to 0.21)	0.34
	Other professional qualification	0.05 (-0.09 to 0.20)	0.48
	College or university degree	-0.02 (-0.14 to 0.10)	0.76
59 to 62 (2,150)	None, O level, or equivalent	[Reference]	
	A level, NVQ or equivalent	-0.08 (-0.19 to 0.04)	0.19
	Other professional qualification	-0.003 (-0.13 to 0.12)	0.96
	College or university degree	-0.12 (-0.22 to -0.02)	0.02
63 to 70 (1,598)	None, O level, or equivalent	[Reference]	
	A level, NVQ or equivalent	-0.05 (-0.18 to 0.08)	0.46
	Other professional qualification	0.01 (-0.12 to 0.14)	0.86
	College or university degree	-0.15 (-0.25 to -0.05)	0.004



Age groups classified into mean and two standard deviations above and below the mean.
*p≤0.01, **<0.001.

Figure D1b. Illustrative plots showing the slope coefficients for **males** of education on standardised brain volume at mean, low (-2 std) and high (+2 std) values of baseline age.

Age (N)	Occupation	B (95% CI)	p-value
	Females		
52 to 58 (1,832)	Low skilled or skilled manual	[Reference]	
	Skilled non-manual	-0.04 (-0.18 to 0.10)	0.54
	Professional	-0.13 (0.27 to 0.02)	0.09
	Highly responsible or intellectual	-0.12 (-0.25 to 0.005)	0.06
59 to 62 (1,901)	Low skilled or skilled manual	[Reference]	
	Skilled non-manual	-0.15 (-0.28 to -0.02)	0.03
	Professional	-0.10 (-0.24 to 0.03)	0.14
	Highly responsible or intellectual	-0.17 (-0.30 to -0.05)	0.007
63 to 70 (1,068)			
	Low skilled or skilled manual	[Reference]	
	Skilled non-manual	-0.22 (-0.40 to -0.03)	0.03
	Professional	-0.22 (-0.42 to -0.03)	0.03
	Highly responsible or intellectual	-0.19 (-0.37 to -0.007)	0.04



Age classified into tertiles for even distribution of the sample.

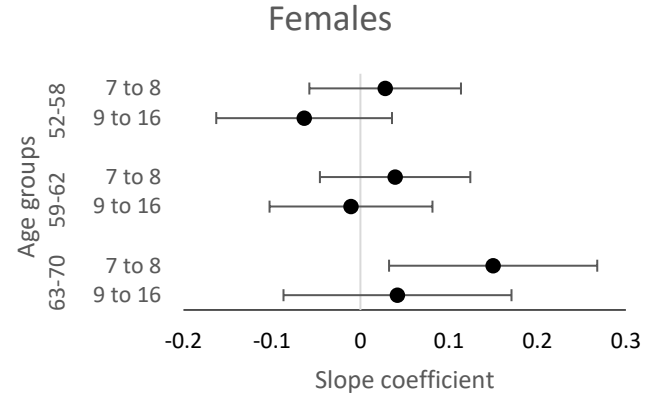
Figure D2a. Illustrative plots showing the slope coefficients for **females** of occupation on standardised brain volume at mean, low (-2 std) and high (+2 std) values of baseline age.

Age (N)	Occupation	B (95% CI)	p-value
	Males		
52 to 58 (1,680)	Low skilled or skilled manual	[Reference]	
	Skilled non-manual	-0.06 (-0.23 to 0.11)	0.51
	Professional	-0.004 (-0.14 to 0.13)	0.95
	Highly responsible or intellectual	-0.008 (-0.11 to 0.10)	0.88
59 to 62 (2,150)	Low skilled or skilled manual	[Reference]	
	Skilled non-manual	0.07 (-0.08 to 0.22)	0.37
	Professional	-0.04 (-0.17 to 0.08)	0.50
	Highly responsible or intellectual	0.001 (-0.09 to 0.09)	0.98
63 to 70 (1,598)	Low skilled or skilled manual	[Reference]	
	Skilled non-manual	0.0007 (-0.17 to 0.17)	0.99
	Professional	-0.13 (-27 to 0.004)	0.06
	Highly responsible or intellectual	-0.09 (-0.19 to 0.02)	0.11

Age classified into tertiles for even distribution of the sample.

Figure D2b. Illustrative plots showing the slope coefficients for **males** of occupation on standardised brain volume at mean, low (-2 std) and high (+2 std) values of baseline age.

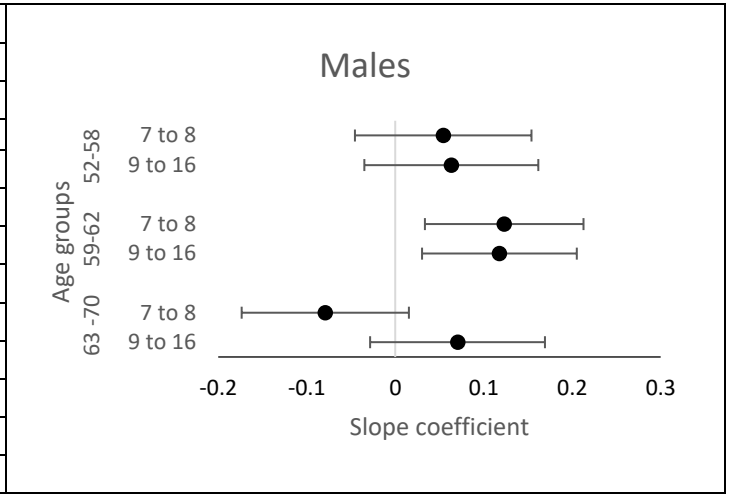
Age (N)	Leisure	B (95% CI)	p-value
	Females		
52 to 58 (1,832)	0-6	[Reference]	
	7-8	0.03 (-0.06 to 0.11)	0.52
	9-16	-0.06 (-0.16 to 0.04)	0.21
59 to 62 (1,901)	0-6	[Reference]	
	7-8	0.04 (-0.05 to 0.12)	0.37
	9-16	-0.01 (-0.10 to 0.08)	0.82
63 to 70 (1,068)	0-6	[Reference]	
	7-8	0.15 (0.03 to 0.27)	0.01
	9-16	0.04 (-0.09 to 0.17)	0.52



Age classified into tertiles for even distribution of the sample.

Figure D3a. Illustrative plots showing the slope coefficients for **females** of leisure on standardised brain volume at mean, low (-2 std) and high (+2 std) values of baseline age.

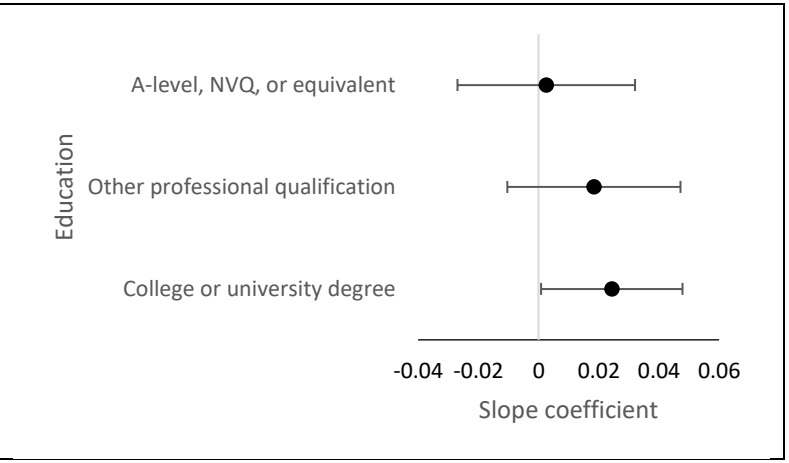
Age (N)	Leisure	B (95% CI)	p-value
	Males		
52 to 58 (1,680)	0-6	[Reference]	
	7-8	0.05 (-0.05 to 0.15)	0.29
	9-16	0.06 (-0.04 to 0.16)	0.21
59 to 62 (2,150)	0-6	[Reference]	
	7-8	0.12 (0.03 to 0.21)	0.007
	9-16	0.12 (0.03 to 0.21)	0.008
63 to 70 (1,598)	0-6	[Reference]	
	7-8	-0.08 (-0.17 to 0.02)	0.10
	9-16	0.07 (-0.03 to 0.17)	0.16



Age classified into tertiles for even distribution of the sample.

Figure D3b. Illustrative plots showing the slope coefficients for **males** of leisure on standardised brain volume at mean, low (-2 std) and high (+2 std) values of baseline age.

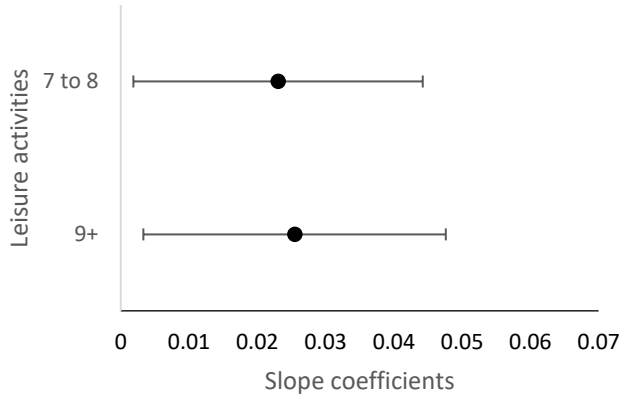
Education	B (95% CI)	p-value
None, O level, or equivalent	[Reference]	
A level, NVQ or equivalent	0.003 (-0.03 to 0.03)	0.87
Other professional qualification	0.02 (-0.01 to 0.05)	0.21
College or university degree	0.02 (0.001 to 0.05)	0.04



Age groups classified into mean and two standard deviations above and below the mean.
*p≤0.01, **<0.001

Figure D4. Illustrative plots showing the slope coefficients of education on hippocampal volume.

Leisure	B (95% CI)	p-value
0 to 6	[Reference]	
7 to 8	0.02 (0.002 to 0.04)	0.03
9+	0.03 (0.003 to 0.05)	0.02



Age groups classified into mean and two standard deviations above and below the mean.
*p≤0.01, **<0.001

Figure D5. Illustrative plots showing the slope coefficients of leisure activities on hippocampal volume.

Occupation	B (95% CI)	p-value
Low skilled or skilled manual	[Reference]	
Skilled non-manual	-0.08 (-0.16 to 0.01)	0.09
Professional	-0.06 (-0.14 to 0.03)	0.18
Highly responsible or intellectual	-0.07 (-0.14 to -0.002)	0.05

Age groups classified into mean and two standard deviations above and below the mean.
*p≤0.01, **<0.001

Figure D6. Illustrative plots showing the slope coefficients of occupation on white matter hyperintensity volumes.

Table D4. Regression coefficients and 95% confidence intervals for the association between the CRI and cognitive function (N=4,574).

Variables	Model 1	Model 2	Model 3	Model 4
CRI	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**
Sex: Female Male	[Reference] -0.03 (-0.07 to -0.00)	[Reference] -0.04 (-0.07 to -0.00)	[Reference] 0.03 (-0.02 to 0.07)	[Reference] 0.03 (-0.02 to 0.07)
Age	-0.04 (-0.04 to -0.03)**	-0.04 (-0.04 to -0.03)**	-0.03 (-0.04 to -0.03)**	-0.03 (-0.04 to -0.03)**
APOE-e4 carrier: No Yes	[Reference] -0.09 (-0.13 to -0.05)**	[Reference] -0.09 (-0.13 to -0.05)**	[Reference] -0.09 (-0.13 to -0.05)**	[Reference] -0.09 (-0.13 to -0.05)**
TDI		-0.01 (-0.02 to -0.01)**	-0.01 (-0.02 to -0.00)**	-0.01 (-0.02 to -0.01)**
FRS			-0.00 (-0.01 to -0.00)**	-0.00 (-0.01 to -0.00)**
Illness: No Yes			[Reference] -0.01 (-0.05 to 0.03)	[Reference] -0.01 (-0.05 to 0.03)
Psychological distress: No Yes				[Reference] 0.01 (-0.03 to 0.04)

TDI: Townsend Deprivation Index; FRS: Framingham cardiovascular risk score.
*p≤0.01, **<0.001.

Table D5. Regression coefficients and 95% confidence intervals for the association between CR and cognitive function adjusted for brain volume (N=4,575).

Variables	Model 1	Model 2	Model 3	Model 4
CRI	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**
Sex: Female Males	[Reference] -0.03 (-0.06 to 0.00)	[Reference] -0.03 (-0.06 to 0.00)	[Reference] 0.03 (-0.02 to 0.07)	[Reference] 0.03 (-0.02 to 0.07)
Age	-0.04 (-0.04 to -0.03)**	-0.04 (-0.04 to -0.03)**	-0.03 (-0.04 to -0.03)**	-0.03 (-0.04 to -0.03)**
APOE-e4 carrier: No Yes	[Reference] -0.09 (-0.13 to -0.06)**	[Reference] -0.09 (-0.13 to -0.06)**	[Reference] -0.09 (-0.13 to -0.06)**	[Reference] -0.09 (-0.13 to -0.06)**
Brain volume	0.00 (0.00 to 0.00)*	0.00 (0.00 to 0.00)*	0.00 (0.00 to 0.00)*	0.00 (0.00 to 0.00)*
TDI		-0.01 (-0.02 to -0.01)**	-0.01 (-0.02 to -0.01)**	-0.01 (-0.02 to -0.01)**
FRS			-0.00 (-0.01 to -0.00)**	-0.00 (-0.01 to -0.00)**
Illness: No Yes			[Reference] -0.01 (-0.05 to 0.03)	[Reference] -0.01 (-0.05 to 0.03)
Psychological distress: No Yes				[Reference] 0.01 (-0.03 to 0.04)

TDI: Townsend Deprivation Index; FRS: Framingham cardiovascular risk score.
*p≤0.01, **<0.001.

Table D6. Regression coefficients and 95% confidence intervals for the association between CR and cognitive function adjusting for hippocampal volume (N=4,574).

Variables	Model 1	Model 2	Model 3	Model 4
CRI	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**
Sex: Female Male	[Reference] -0.09 (-0.13 to -0.06)**	[Reference] -0.09 (-0.13 to -0.06)**	[Reference] -0.04 (-0.09 to 0.01)	[Reference] -0.04 (-0.09 to 0.01)
Age	-0.04 (-0.04 to -0.03)**	-0.04 (-0.04 to -0.03)**	-0.03 (-0.04 to -0.03)**	-0.03 (-0.04 to -0.03)**
APOE e4 carrier: No Yes	[Reference] -0.09 (-0.13 to -0.05)**	[Reference] -0.09 (-0.13 to -0.05)**	[Reference] -0.09 (-0.13 to -0.05)**	[Reference] -0.09 (-0.13 to -0.05)**
Hippocampal volume	0.10 (0.06 to 0.14)**	0.10 (0.06 to 0.14)**	0.10 (0.06 to 0.14)**	0.10 (0.06 to 0.14)**
TIV	2.54 (1.42 to 3.65)**	2.53 (1.41 to 3.65)**	2.35 (1.23 to 3.47)**	2.35 (1.23 to 3.47)**
TDI		-0.01 (-0.02 to -0.00)**	-0.01 (-0.02 to -0.00)**	-0.01 (-0.02 to -0.00)**
FRS			-0.00 (-0.01 to -0.00)**	-0.00 (-0.01 to -0.00)**
Illness: No Yes			[Reference] -0.00 (-0.04 to 0.03)	[Reference] -0.00 (-0.04 to 0.03)
Psychological distress: No Yes				[Reference] 0.01 (-0.03 to 0.04)

TDI: Townsend Deprivation Index; FRS: Framingham cardiovascular risk score.
*p≤0.01, **<0.001.

Table D7. Regression coefficients and 95% confidence intervals for the association between CR and cognitive function adjusting for white matter hyperintensity volumes (N=4,574).

Variables	Model 1	Model 2	Model 3	Model 4
CRI	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**	0.01 (0.01 to 0.01)**
Sex: Female Male	[Reference] -0.08 (-0.12 to -0.04)**	[Reference] -0.08 (-0.12 to -0.04)**	[Reference] -0.03 (-0.08 to 0.01)	[Reference] -0.03 (-0.08 to 0.01)
Age	-0.04 (-0.04 to -0.03)**	-0.04 (-0.04 to -0.03)**	-0.03 (-0.04 to -0.03)**	-0.03 (-0.04 to -0.03)**
APOE e4 carrier: No Yes	[Reference] -0.09 (-0.13 to -0.05)**	[Reference] -0.09 (-0.13 to -0.05)**	[Reference] -0.09 (-0.13 to -0.05)**	[Reference] -0.09 (-0.13 to -0.05)**
WMHV	-0.01 (-0.01 to -0.00)**	-0.01 (-0.01 to -0.00)**	-0.00 (-0.01 to -0.00)**	-0.00 (-0.01 to -0.00)**
TIV	3.14 (2.04 to 4.24)**	3.12 (2.02 to 4.22)**	2.95 (1.84 to 4.05)**	2.95 (1.84 to 4.05)**
TDI		-0.01 (-0.02 to -0.01)**	-0.01 (-0.02 to -0.01)**	-0.01 (-0.02 to -0.01)**
FRS			-0.00 (-0.01 to -0.00)*	-0.00 (-0.01 to -0.00)*
Illness: No Yes			[Reference] -0.00 (-0.04 to 0.04)	[Reference] -0.00 (-0.04 to 0.04)
Psychological distress: No Yes				[Reference] 0.01 (-0.03 to 0.04)

TDI: Townsend Deprivation Index; FRS: Framingham cardiovascular risk score.
*p≤0.01, **<0.001.

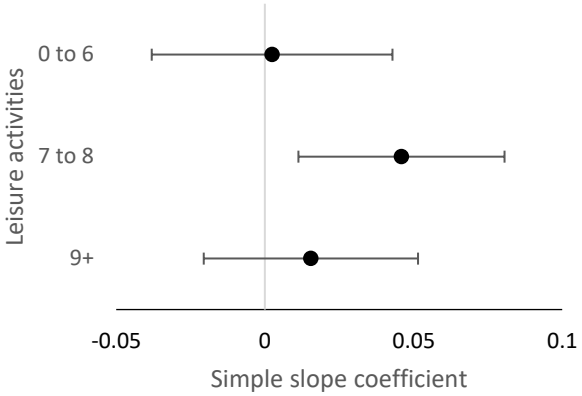
Table D8. Regression coefficients and 95% confidence intervals for the associations between education, occupation, and leisure, and cognitive function adjusting for neuropathology (N=4,574).

Predictor	B (95% CI)	Interaction p-value	
Education: None, O level, or equivalent	[Reference]	-	
A level, NVQ or equivalent	0.15 (0.09 to 0.20)**		
Other professional qualification	0.17 (0.11 to 0.22)**		
College or university degree	0.34 (0.29 to 0.39)**		
Occupation: Low skilled or skilled manual	[Reference]	-	
Skilled non-manual	0.20 (0.13 to 0.26)**		
Professional	0.21 (0.15 to 0.28)**		
Highly responsible or intellectual	0.32 (0.27 to 0.38)**		
Leisure: 0-6	[Reference]	-	
7-8	0.03 (-0.002 to 0.08)		
9+	0.10 (0.05 to 0.14)**		
Brain volume			
Education: None, O level, or equivalent	[Reference]	Education*Brain volume	>0.10
A level, NVQ or equivalent	0.15 (0.09 to 0.20)**		
Other professional qualification	0.17 (0.11 to 0.22)**		
College or university degree	0.34 (0.30 to 0.39)**		
Brain volume	0.0005 (0.0002 to 0.0008)*		
Occupation: Low skilled or skilled manual	[Reference]	Work*Brain volume	>0.10
Skilled non-manual	0.20 (0.14 to 0.27)**		
Professional	0.22 (0.15 to 0.28)**		
Highly responsible or intellectual	0.33 (0.27 to 0.38)**		
Brain volume	0.0004 (0.00009 to 0.0007)*		
Leisure: 0-6	[Reference]	Leisure*Brain volume	**<0.10**
7-8	0.02 (-0.003 to 0.08)		
9+	0.10 (0.05 to 0.14)**		
Brain volume	0.0003 (0.00001 to 0.0006)*		
Hippocampal volume			
Education: None, O level, or equivalent	[Reference]	Education*Hippocampal volume	>0.10
A level, NVQ or equivalent	0.14 (0.08 to 0.20)**		
Other professional qualification	0.16 (0.10 to 0.22)**		
College or university degree	0.33 (0-.28 to 0.38)**		
Hippocampal volume	0.10 (0.06 to 0.14)**		
Occupation: Low skilled or skilled manual	[Reference]	Leisure* Hippocampal volume	>0.10
Skilled non-manual	0.19 (0.13 to 0.26)**		
Professional	0.21 (0.14 to 0.27)**		
Highly responsible or intellectual	0.31 (0.26 to 0.37)**		
Hippocampal volume	0.10 (0.06 to 0.14)**		
Leisure: 0-6	[Reference]	Leisure* Hippocampal volume	>0.10
7-8	0.04 (-0.004 to 0.08)		
9+	0.09 (0.05 to 0.14)**		
Hippocampal volume	0.10 (0.06 to 0.15)**		
White matter hyperintensity volumes			
Education: None, O level, or equivalent	[Reference]	Education*WMHV	**<0.10**
A level, NVQ or equivalent	0.15 (0.09 to 0.20)**		
Other professional qualification	0.16 (0.11 to 0.22)**		
College or university degree	0.33 (0.28 to 0.38)**		
WMHV	-0.005 (-0.007 to -0.002)**		
Occupation: Low skilled or skilled manual	[Reference]	Work*WMHV	>0.10
Skilled non-manual	0.19 (0.13 to 0.26)**		
Professional	0.20 (0.14 to 0.27)**		
Highly responsible or intellectual	0.31 (0.26 to 0.37)**		
WMHV	-0.004 (-0.007 to -0.002)**		
Leisure: 0-6	[Reference]	Leisure*WMHV	>0.10
7-8	0.04 (-0.003 to 0.08)		
9+	0.09 (0.05 to 0.14)**		
WMHV	-0.005 (-0.007 to -0.002)*		

WMHV: White matter hyperintensity volume. Models adjusted for head bone size (except brain volume), sex, age, APOE genotype, TDI, FRS, psychological distress.

*All statistically significant associations remained significant after Benjamini-Hochberg correction.**p≤0.01, **<0.001.

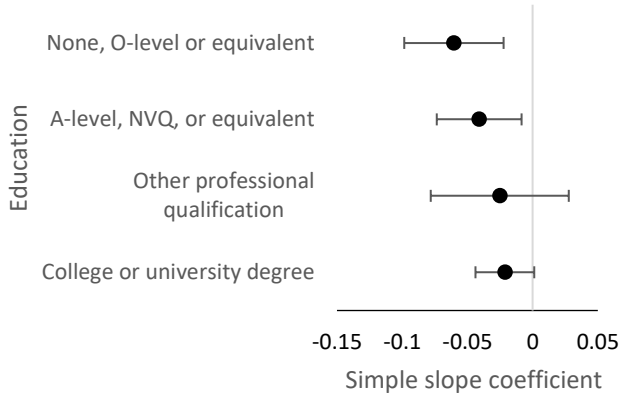
Leisure activities	B (95% CI)	p-value
0 to 6	0.002 (-0.04 to 0.04)	0.91
7 to 8	0.05 (0.01 to 0.08)	0.01
9+	0.02 (-0.02 to 0.05)	0.40



CRI: Cognitive reserve index.
*p<0.01, **<0.001.

Figure D7. Illustrative plots and visual representation showing the simple slopes of standardised brain volume on cognitive function at different levels of leisure activity engagement.

Education	B (95% CI)	p-value
None, O level, or equivalent	-0.06 (-0.10 to -0.02)	0.002
A level, NVQ or equivalent	-0.04 (-0.07 to -0.009)	0.01
Other professional qualification	-0.03 (-0.08 to 0.03)	0.34
College or university degree	-0.02 (-0.04 to 0.001)	0.06



CRI: Cognitive reserve index.
*p<0.01, **<0.001.

Figure D8. Illustrative plots and visual representation showing the simple slopes of standardised white matter hyperintensity volumes on cognitive function at different levels of educational attainment.

Appendix E. The association between cognitive and social leisure activity engagement and dementia in ELSA

E.1 Model assumptions

The variance inflation factor for all variables included in these analyses was < 1.39, suggesting no multicollinearity since values greater than 2.5 are considered high. The highest correlation was a moderate-low association between cognitive leisure activities and education ($r=0.43$, $p<0.001$). Using the Schoenfeld residuals it was found that the cognitive leisure and social leisure domains met the proportional hazard assumption. Statistical significance was at or below the 0.05 level.

E.2 Data imputation

The analytical sample was set to the number of individuals with outcome data (dementia diagnosis or death). As presented in Chapter 7, Figure 54, the covariate with the largest amount of missing data was smoking status (5.4%). Sex, coronary heart disease, stroke, hypertension, and diabetes diagnosis had complete data.

Exploration of missingness patterns revealed that 59% of the dataset had a pattern of no missing values in any of the variables. The most common pattern was that of complete data for all variables except for 'looking after others' (14%).

To impute all missing values simultaneously, multiple imputations using chained equations was performed. All the variables used in the analytical model (including the outcome and interaction terms) were included in the imputation model to ensure comparability. In total, 50 imputations were added, and a random seed was used to ensure reproducibility. The

methods used for the imputation were: logistic regression (reading newspapers, having a hobby or pastime, using a mobile phone, attending art or music groups, membership to sports clubs, church groups, looking after others, belonging to an organisation, belong to a social club, taking holidays in the UK or abroad, smoker status, alcohol consumption), ordinal logistic regression (cultural engagement, charitable associations or volunteering, meeting with friends, education, wealth, physical activity), multinomial logistic regression (marital status), and poission regression (depressive symptoms). Data on the outcome, coronary heart disease, stroke, hypertension, and diabetes were registered and included in the imputation process as regular variables since they did not have missing data. The cognitive and social domains were created after the imputation procedure, as passive variables. The stability of the parameter estimates across seeds was tested using Monte Carlo error estimates.

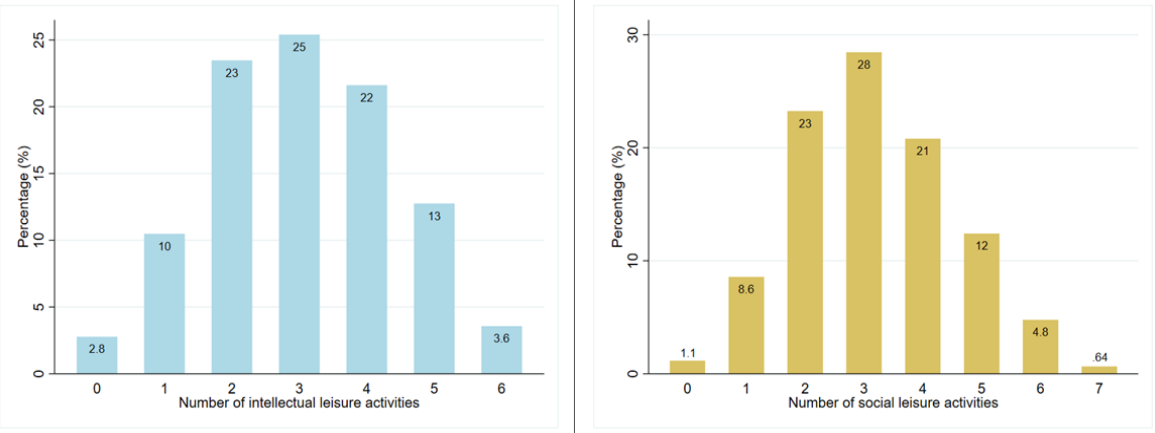
E.2 Leisure activities

Table E1. Derivation of leisure variables.

Variable label (variable name)		Original variable coding	Coding for study
Intellectual			
Reading newspapers (scptpa2)		Yes = 1 No = 0	Yes = 1 No = 0
Having a hobby or pastime (scptpa3)		Yes = 1 No = 0	Yes = 1 No = 0
Using a mobile phone (scptpa8)		Yes = 1 No = 0	Yes = 1 No = 0
Using the internet or email (scptpa7)		Yes = 1 No = 0	Yes = 1 No = 0
Attending art or music groups (scorg5)		Yes = 1 No = 0	Yes = 1 No = 0
Cultural engagement	How often goes to cinema (spcin)	Twice a month or more About once a month Every few months Once or twice a year Less than once a year Never	Every few months to twice a month or more = 1 Once or twice a year to never = 0
	How often do you go to the theatre, concert, or opera (sptea)	Twice a month or more About once a month Every few months Once or twice a year Less than once a year Never	Every few months to twice a month or more = 1 Once or twice a year to never = 0
	How often do you visit an art gallery or museum (spmus)	Twice a month or more About once a month Every few months Once or twice a year Less than once a year Never	Every few months to twice a month or more = 1 Once or twice a year to never = 0
Social			
Sports club, gym, exercise classes (scorg7)		Yes = 1 No = 0	Yes = 1 No = 0
Church groups (scorg3)		Yes = 1 No = 0	Yes = 1 No = 0
Looking after others (spcaa)		Yes = 1 No = 0	Yes = 1 No = 0
Belonging to organisation	Political party, trade union, or environmental groups (scorg1)	Yes = 1 No = 0	Yes = 1 No = 0
	Any other organisations, clubs, or societies (scorg8)	Yes = 1 No = 0	Yes = 1 No = 0
	Tenant groups, resident groups, neighbourhood watch (scorga2)	Yes = 1 No = 0	Yes = 1 No = 0
	Charitable associations (scorg4)	Yes = 1 No = 0	Yes = 1 No = 0

Charitable associations or volunteering	How often do you do voluntary work? (wpvw)	Twice a month or more About once a month Every few months About once or twice a month Less than once a year Never	Twice a month or more to every few months = 1 About once or twice a month to Never = 0
Belong to social club or meet with friends	Respondent is a member of social clubs (scorg6)	Yes = 1 No = 0	Yes = 1 No = 0
	On average how often do you meet up with friends (scfrdg)	Three or more times a week Once or twice a week Once or twice a moth Every few months Once or twice a year	Three or more times a week to once or twice a month = 1 Every few months to once or twice a year = 0
Taking holidays in the UK or abroad	I have taken a holiday in the UK in the last 12 months (scptpa4)	Yes = 1 No = 0	Yes = 1 No = 0
	I have taken a holiday abroad in the last 12 months (scptpa5)	Yes = 1 No = 0	Yes = 1 No = 0
	I have gone on a daytrip or outing in the last 12 months (scptpa6)	Yes = 1 No = 0	Yes = 1 No = 0

E.3 Tables and Figures



Number of intellectual leisure activities

Number of social leisure activities

Figure E1. Engagement in cognitive and social leisure activities in the sample.

Table E2. Sub-hazard ratios and 95% confidence intervals of the competing risk models indicating the incidence of dementia for engagement in leisure activities.

Domains	N	Model 1	Model 2	Model 3	Model 4
Intellectual leisure activities					
Married	5,501	0.80 (0.73-0.89)**	0.83 (0.74-0.92)**	0.84 (0.76-0.94)*	0.85 (0.76-0.96)*
Single or divorced	1,297	0.99 (0.79-1.24)	0.99 (0.77-1.27)	1.07 (0.84-1.36)	1.11 (0.85-1.45)
Widowed	1,232	0.96 (0.82-1.11)	0.96 (0.82-1.13)	0.97 (0.83-1.14)	0.98 (0.83-1.17)
Social leisure activities	8,030	0.92 (0.86-0.99)*	0.95 (0.88-1.03)	0.97 (0.89-1.04)	0.98 (0.90-1.06)

Intellectual leisure activities are stratified by marital status.
Model 1: Sex and marital status. Model 2: Model 1 + education and wealth. Model 3: Model 2 + physical health covariates and depression. Model 4: Model 3 + lifestyle factors.
*p<0.05, **p≤0.001.

Table E3. Sub-hazard ratios and 95% confidence intervals of the competing risk models indicating the incidence of dementia for intellectual leisure activities.

Domains	Model 1	Model 2	Model 3	Model 4
Intellectual leisure activities				
Reading newspapers: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.77 (0.63-0.95)*	0.78 (0.63-0.97)*	0.79 (0.64-0.98)	0.79 (0.64-0.98)*
Having a hobby or pastime: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.72 (0.58-0.91)*	0.77 (0.61-0.97)*	0.81 (0.64-1.03)	0.85 (0.66-1.08)
Using a mobile phone: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.74 (0.60-0.91)*	0.78 (0.63-0.97)	0.79 (0.64-0.98)	0.80 (0.65-0.99)*
Using the internet: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.74 (0.56-0.97)*	0.79 (0.59-1.05)	0.81 (0.61-1.08)	0.82 (0.61-1.09)
Art or music groups: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.96 (0.71-1.28)	1.09 (0.80-1.48)	1.11 (0.82-1.51)	1.14 (0.84-1.56)
Cultural engagement: Never	[Reference]	[Reference]	[Reference]	[Reference]
Less than once a year	0.84 (0.62-1.13)	0.93 (0.68-1.28)	0.97 (0.71-1.33)	1.01 (0.74-1.38)
Once or twice a year	0.66 (0.45-0.97)*	0.75 (0.50-1.12)	0.79 (0.53-1.18)	0.83 (0.55-1.24)
Every few months	1.25 (0.78-2.01)	1.49 (0.91-2.44)	1.55 (0.95-2.54)	1.63 (0.99-2.68)

Model 1: Sex and marital status. Model 2: Model 1 + education and wealth. Model 3: Model 2 + physical health covariates and depression. Model 4: Model 3 + lifestyle factors.
*p<0.05, **p≤0.001.

Table E4. Sub-hazard ratios and 95% confidence intervals of the competing risk models indicating the incidence of dementia for social leisure activities.

	Model 1	Model 2	Model 3	Model 4
Social leisure activities				
Sports clubs: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.67 (0.50-0.91)*	0.72 (0.53-0.98)*	0.74 (0.54-1.00)	0.83 (0.60-1.14)
Church groups: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	1.10 (0.89-1.37)	1.18 (0.94-1.47)	1.18 (0.94-1.48)	1.16 (0.93-1.46)
Look after others: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.81 (0.61-1.06)	0.78 (0.59-1.03)	0.78 (0.59-1.02)	0.79 (0.60-1.04)
Organization membership: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.90 (0.73-1.09)	0.98 (0.79-1.21)	0.99 (0.80-1.23)	1.01 (0.81-1.26)
Volunteering: Never	[Reference]	[Reference]	[Reference]	[Reference]
Less than once a year/up to twice a year	0.67 (0.37-1.19)	0.71 (0.40-1.27)	0.73 (0.41-1.30)	0.75 (0.42-1.33)
Every few months	0.78 (0.62-0.99)*	0.84 (0.66-1.08)	0.88 (0.69-1.14)	0.91 (0.70-1.17)
Meeting with friends: Never	[Reference]	[Reference]	[Reference]	[Reference]
Once or twice a month	1.01 (0.74-1.37)	1.05 (0.77-1.42)	1.07 (0.79-1.46)	1.08 (0.80-1.48)
Once or twice a week	0.80 (0.61-1.07)	0.82 (0.62-1.08)	0.84 (0.63-1.11)	0.87 (0.66-1.16)
Three or more times a week	0.92 (0.66-1.29)	0.90 (0.64-1.25)	0.92 (0.66-1.28)	0.96 (0.69-1.34)
Holiday: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.82 (0.63-1.06)	0.87 (0.67-1.14)	0.94 (0.71-1.23)	0.97 (0.74-1.27)

Model 1: Sex and marital status. Model 2: Model 1 + education and wealth. Model 3: Model 2 + physical health covariates and depression. Model 4: Model 3 + lifestyle factors.
*p<0.05, **p≤0.001.

Table E5. Sub-hazard ratios and 95% confidence intervals of the competing risk models indicating the incidence of dementia for individual activities with significant interactions for sex and marital status.

Individual leisure activities	Model 1	Model 2	Model 3	Model 4
Reading newspapers*sex (p=0.06)				
Males: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	1.03 (0.73-1.46)	1.02 (0.72-1.46)	1.02 (0.72-1.47)	1.04 (0.73-1.50)
Females: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.64 (0.49-0.84)**	0.65 (0.50-0.85)*	0.65 (0.50-0.86)*	0.65 (0.49-0.84)**
Phone use*sex (p=0.06)				
Males: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.58 (0.42-0.79)**	0.62 (0.45-0.84)*	0.62 (0.45-0.85)*	0.61 (0.45-0.84)*
Females: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.95 (0.73-1.24)	0.98 (0.74-1.31)	0.99 (0.75-1.33)	1.05 (0.78-1.40)
Hobby*marital status (p=0.04)				
Single or divorced: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.58 (0.43-0.77)**	0.62 (0.46-0.85)*	0.66 (0.49-0.89)*	0.70 (0.51-0.95)*
Married or remarried: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	1.14 (0.57-2.26)	1.09 (0.54-2.20)	1.42 (0.67-3.01)	1.43 (0.67-3.07)
Widowed: No	[Reference]	[Reference]	[Reference]	[Reference]
Yes	0.91 (0.60-1.41)	0.93 (0.60-1.44)	0.98 (0.63-1.52)	1.01 (0.64-1.60)

Model 1: Sex and marital status. Model 2: Model 1 + education and wealth. Model 3: Model 2 + physical health covariates and depression. Model 4: Model 3 + lifestyle factors.
*p<0.05, **p≤0.001.

Table E6. Subhazard ratios and 95% confidence intervals of the competing risk models for individuals with a doctor diagnosis of dementia, N= 7,897 participants (279 observations).

Domains	N	Model 1	Model 2	Model 3	Model 4
Intellectual activities					
Married	5,423	0.83 (0.74-0.93)**	0.84 (0.73-0.95)*	0.86 (0.75-0.97)*	0.86 (0.75-0.98)*
Single or divorced	1,282	1.03 (0.78-1.38)	1.06 (0.78-1.44)	1.14 (0.86-1.53)	1.17 (0.85-1.62)
Widowed	1,192	1.00 (0.83-1.21)	0.96 (0.78-1.19)	0.96 (0.78-1.19)	0.97 (0.78-1.20)
Social leisure activities	7,897	0.95 (0.87-1.03)	0.96 (0.87-1.05)	0.97 (0.89-1.07)	0.98 (0.89-1.08)

Model 1: Sex and marital status. Model 2: Model 1 + education and wealth. Model 3: Model 2 + physical health covariates and depression. Model 4: Model 3 + lifestyle factors.
*p<0.05, **p≤0.001.

Table E7. Sub-hazard ratios and 95% confidence intervals of the competing risk models for participants joining at wave 1 only, N=7,733 participants (410 dementia cases).

Domains	N	Model 1	Model 2	Model 3	Model 4
Intellectual leisure activities					
Married	5,285	0.80 (0.73-0.89)**	0.82 (0.74-0.92)**	0.84 (0.75-0.94)*	0.85 (0.76-0.96)*
Single or divorced	1,230	0.99 (0.79-1.23)	0.99 (0.78-1.27)	1.07 (0.84-1.36)	1.11 (0.85-1.45)
Widowed	1,218	0.96 (0.82-1.11)	0.96 (0.82-1.13)	0.97 (0.83-1.14)	0.99 (0.83-1.17)
Social leisure activities	7,733	0.93 (0.86-0.99)*	095 (0.88-1.03)	0.97 (0.89-1.05)	0.98 (0.91-1.07)

Model 1: Sex and marital status. Model 2: Model 1 + education and wealth. Model 3: Model 2 + physical health covariates and depression. Model 4: Model 3 + lifestyle factors.
*p<0.05, **p≤0.001.