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Sex differences in the associations between risk and protective factors with cognition and the brain in cognitively healthy mid-life individuals at risk for late-life dementia

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Declaration

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Summary

Dementia, particularly Alzheimer's disease (AD), is a global epidemic that presents profound challenges to individuals, families, health care systems, and societies throughout the world. As neuropathological changes begin decades before clinical symptoms emerge, mid-life represents a critical window for prevention. Females have a higher incidence of AD than males, even after accounting for longer lifespans, and would therefore particularly benefit from dementia prevention strategies. Building cognitive reserve has become a crucial preventative approach for reducing dementia risk. While education, stimulating activities, and occupational attainment are known reserve contributors, little is understood about how these factors operate differently in females and males during mid-life, whether there are sex differences in brain–cognition relationships, and how these reserve contributors and dementia risks relate to these sex differences at this stage. Addressing these gaps is of vital importance, not only to clarify the mechanisms underlying sex differences in dementia vulnerability but also to inform personalized prevention strategies. To address these questions, I leveraged the PREVENT–Dementia program, a large multi-site study investigating the origins and early diagnosis of dementia in mid-life individuals (N = 700; 40–59 years), who were presently cognitively healthy but at risk for late-life dementia.

Chapter 2 investigated whether reserve contributors enhance cognition in mid-life, and how biological sex and APOE4 status interact to influence the effects of reserve contributors on cognition. A dimensionality reduction technique was used to capture the common cognitive domains underlying a set of sensitive tests for detecting early changes in dementia. Reserve contributors were assessed by years of education and the Lifetime of Experiences Questionnaire. After controlling for the effect of education, I found that individuals with higher engagement in stimulating activities showed better episodic and relational memory, regardless of biological sex and APOE4 status. Furthermore, I found that biological sex and APOE4 interacted in moderating the associations between occupational attainment and episodic and relational memory. APOE4 carrier females with higher occupational attainment showed better cognition.

By contrast, APOE4 carrier males with higher occupational attainment showed worse cognition. These findings suggest that occupational attainment in mid-life boosts cognition against inherited risk of dementia in females, but not males, at risk for late-life dementia.

Chapter 3 explored whether education, another major reserve contributor, would interact with sex to influence the effects of lifestyle activities on cognition and brain structure. First, I found that males with low education showed a significantly positive association between engagement in stimulating activities and multisensory processing. Males with high education showed the opposite effect, a significantly negative association between engagement in stimulating activities and multisensory processing. Females showed no education-dependent effect in this association. Moreover, I found that males with low education showed a significantly positive association between engagement in stimulating activities and global cortical thickness, particularly in those with higher cardiovascular dementia risk [measured by Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) scores]. Females again showed no such effects. These findings suggest that modifiable stimulating activities in mid-life enhance cognition and brain structural health in middle-aged males with low education and high risk for late life dementia.

Chapter 4 focused on the effects of dementia risk factors on cognition and brain structure, and sex differences in brain structure–cognition relationships in mid-life. Dementia risk factors were measured by APOE4 genotype and CAIDE scores. Brain structure was assessed using total grey matter volume, global cortical thickness, and regional thickness measures of several AD signature regions. I found that higher CAIDE scores were associated with poorer cognitive performance and thinner global cortical thickness. By contrast, more engagement in stimulating activities was associated with larger grey matter volume. Importantly, I found significant sex differences in the relationship between brain structure and cognition. Males with greater global cortical thickness showed better episodic and relational memory, whereas females showed no associations between them. Moreover, results suggested that the sex-specific brain–cognition relationship was driven by the precuneus region. These results suggest that cardiovascular risk

of future dementia negatively impact cortical thickness and reveal sex-specific differences in the brain structure–cognition association in cognitively healthy middle-aged individuals.

Following this, **Chapter 5** examined whether there is also sex-specific brain function–cognition relationship in mid-life using connectome-based predictive modelling (CPM) and asked whether reserve contributors and dementia risks relate to the functional connectome underpinning cognition. I found that resting-state functional connectivity significantly predicted episodic and relational memory in mid-life, with distinct predictive networks in females and males: females relied more heavily on default mode network (DMN) connectivity, whereas males did not show this significant relationship. The core regions of DMN have been extensively shown to be vulnerable to the characteristic pathology of Alzheimer's disease even in preclinical stage. Moreover, higher CAIDE scores were associated with weaker, whereas greater engagement in stimulating activities were associated stronger memory-related functional connectivity. These findings reveal sex-specific functional connectome supporting memory and suggest that mid-life lifestyle modification may bolster memory-related brain functional networks that are vulnerable to dementia.

Overall, this thesis highlights that building cognitive reserve is not a one-size-fits-all phenomenon but depends on sex-specific pathways and their interaction with genetic and cardiovascular dementia risks. These findings underscore the importance of tailoring dementia prevention strategies that consider sex, genetic risk, and lifestyle, and promoting equitable access to physically, socially, and intellectually stimulating opportunities as a public health strategy to strengthen cognitive reserve and reduce dementia risk in mid-life, well before the onset of clinical symptoms.

List of Publications and Presentations

This thesis incorporates material already published or currently under review in the following manuscripts:

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The following are presentations arising from this work:

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Other abstract or poster presentation:

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Qi, Q., Deng, F., Dounavi, M., Muniz-Terrera, G., Koychev, I., Malhotra, P., O'Brien, J. T., Ritchie, C. W., Lawlor, B., Naci, L. Sex differences in the associations between education, lifestyle activities, and risk factors on cognition and brain structure in mid-life. Poster presentation at *the Alzheimer's Association International Conference*, Philadelphia, USA, July 2024

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AD	Alzheimer's disease
MCI	Mild cognitive impairment
CSF	Cerebrospinal fluid
NFT	Neurofibrillary tangle
Aβ	beta-amyloid
pTau	Hyperphosphorylated tau
APOE	Apolipoprotein E
CAIDE	Cardiovascular risk factors, Ageing and the Incidence of Dementia
fMRI	functional Magnetic Resonance Imaging
sMRI	structural Magnetic Resonance Imaging
ASL	Arterial spin labeling
PET	Positron emission tomography
WM	White matter
WMH	White matter hyperintensities
TGM	Total grey matter volume
CT	Cortical thickness
TIV	Total intracranial volume
FOV	Field of view
FC	Functional connectivity
CPM	Connectome-based predictive modeling
DMN	Default mode network
FPN	Frontal-parietal network
CON	Cingulo-opercular network
SMN	Sensorimotor network
VSN	Visual network

CBN	Cerebellum network
SN	Salience Network
ROI	Region of interest
FD	Framewise displacement
HRT	Hormone replacement therapy
TBI	Traumatic brain injury
LEQ	Lifetime of Experiences Questionnaire
BMI	Body mass index
PSQI	Pittsburgh Sleep Quality Index
SES	Socio-economic status
VSTMBT	Visual Short-Term Memory Binding task
ANCOVA	Analysis of covariance
CI	Confidence interval
RCT	Randomised-controlled trial

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1. Chapter 1: General Introduction

1.1 The Global Dementia Epidemic and Alzheimer's Disease

Dementia is a global epidemic characterized by memory loss, cognitive decline, and reduced ability to carry out daily tasks (McKhann et al., 2011). According to the World Health Organization (WHO), nearly 57 million individuals worldwide were living with dementia in 2021, and this figure is likely to rise to over 139 million by 2050. In the UK and Ireland, there are currently estimated to be more than one million people living with dementia and this number is expected to rise to 1.5 million by 2040. The condition not only affects those diagnosed who progressively lose functional abilities but also places a significant burden on family members and caregivers (Livingston et al., 2017). As people with dementia require extensive health and social care, the societal impact is profound. The annual global cost of dementia was US$ 1.3 trillion in 2019 and is expected to rise to US$ 2.8 trillion by 2030 (Evans-Lacko et al., 2024). With aging populations, dementia is becoming one of the leading causes of death, imposing profound challenges on individuals, families, health care systems, and societies throughout the world (Prince et al., 2015).

Alzheimer's disease (AD) is the most prevalent cause of dementia, accounting for 60–80% of cases (Blennow et al., 2006). AD is neuropathologically characterized by two abnormal proteins, amyloid plaques and neurofibrillary tangles (NFTs) (Bloom, 2014; Braak et al., 2011; Nelson et al., 2009). Amyloid plaques consist of extracellular aggregation of the beta-amyloid (Aβ) protein (Masters et al., 1985) while NFTs are intraneuronal formation of hyperphosphorylated tau (pTau) protein (Grundke-Iqbal et al., 1986). Although the causes of sporadic AD remain elusive, the Amyloid Cascade Hypothesis posits that Aβ accumulation begins years before

clinical onset and triggers tau hyperphosphorylation and aggregation (Giacobini & Gold, 2013; Hardy & Selkoe, 2002; Hardy & Higgins, 1992). Supporting this hypothesis, human postmortem studies showed that cortical Aβ plaques correlated with subsequent tau tangles in hippocampal and neocortical regions (Braak et al., 2011). Similarly, animal models found that Aβ fibrils and oligomers activated kinases that hyperphosphorylate tau, leading to its misfolding and transneuronal spread along connected circuits (Bloom, 2014; Ittner & Gotz, 2011). However, repeated failures of Aβ-targeted clinical trials have raised questions about the amyloid hypothesis (Giacobini & Gold, 2013). Recent evidence (Arnsten et al., 2021) further challenged this linear relationship by suggesting that tau pathology may, in sporadic AD, arise independently or before Aβ in vulnerable cortical neurons, suggesting a revised view of disease initiation. While tau deposition may occasionally precede Aβ accumulation (Braak & Del Tredici, 2011), most evidence still favors Aβ as a necessary trigger for widespread tau spread beyond the medial temporal lobe and Aβ begins the pathological cascade leading to AD (Ozlen et al., 2022).

The spatial progression of Aβ and tau deposits mirrors the temporal course of AD pathology (Braak et al., 2006; Braak & Braak, 1991; Wang et al., 2016). Aβ deposition follows the Thal phases (Thal et al., 2002), initiating in widely distributed neocortical regions (phase 1), progressing to hippocampus and striatum (phase 2), then spreading to subcortical regions, including putamen, basal forebrain, and thalamus (phase 3), and eventually involving midbrain and cerebellum (phases 4–5). In contrast, tau pathology develops according to the Braak stages (Braak & Braak, 1991; Braak et al., 2011). It starts in the locus coeruleus, moves to the transentorhinal and entorhinal cortex (Braak I–II), then to the hippocampal and neocortical association cortex (Braak III–IV), and eventually throughout the neocortical regions such as frontal, occipital and parietal lobes (Braak V–VI). Moreover, tau accumulation patterns were highly correlated to functional connectivity pattern in AD patients (Franzmeier et al., 2020),

and the presence of Aβ not only accelerated tau spread in AD patients (Franzmeier et al., 2020) but also in normal aging population (Vogel et al., 2020). Together, Aβ and tau exhibit distinct but interrelated spatial deposition patterns (Lee et al., 2022; Pereira et al., 2019), and their interplay ultimately drives the neurodegeneration and cognitive decline characteristic of AD.

Alzheimer's disease has long been managed with symptomatic therapies, such as cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) in mild to moderate stages and the NMDA-receptor antagonist memantine in moderate to severe AD (Birks, 2006; Reisberg et al., 2003; Witt et al., 2004). These drugs slightly delay cognitive decline and functional impairment but do not stop the progression of AD nor ameliorate noticeably the cognitive functions, and are limited by gastrointestinal and central nervous system side effects (Matsunaga et al., 2018; Zuliani et al., 2024). In recent years, focus has shifted to disease-modifying, pathology-targeted therapies that reduce brain Aβ burden in early symptomatic AD populations, with notable progress over the past five years. First, aducanumab received accelerated FDA approval in June 2021 for early symptomatic AD after Phase 3 trials demonstrated dose-dependent plaque clearance and a 22% slowing of clinical decline at 18 months (Budd Haeberlein et al., 2022). Although approved, it was withdrawn from the market in early 2024 amid ongoing controversy over its efficacy and safety. Next, lecanemab gained full approval in January 2023, following the Phase 3 clinical trial, which showed a 27% reduction in clinical decline and greater amyloid removal at 18 months compared with placebo (van Dyck et al., 2023). Finally, donanemab was approved in July 2024, based on the TRAILBLAZER-ALZ 2 Phase 3 trial's finding of a 35% slowing of cognitive decline and 40% smaller loss in activities-of-daily-living scores at 18 months (Sims et al., 2023; Eli Lilly and Company, 2023). European Commission has granted marketing authorization for donanemab for the treatment of early symptomatic AD in September 2025 (Eli Lilly and Company, 2025).

Despite these advances in plaque clearance and clinical benefits, these new drugs are constrained by very high costs, substantial risks of amyloid-related imaging abnormalities (ARIA) (e.g., cerebral edema, microhemorrhages), and limited real-world access (Terao & Kodama, 2024; van Dyck et al., 2023; Zimmer et al., 2025). These challenges highlight an immediate need for more tolerable, cost-effective disease-modifying therapies and earlier risk-burden modification strategies (Livingston et al., 2020; Ritchie et al., 2022).

1.2 Modifiable Lifestyle Risk Factors

Recent evidence suggests that up to 45% of future dementia cases worldwide could be prevented by modifying medical and lifestyle risk factors (Livingston et al., 2024). The Lancet Commission for Dementia periodically reviews high-quality evidence (Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017) and, in its most recent report, developed a 'life-course model' that links 14 modifiable risk factors to specific age periods, along with estimated percentage reduction in dementia incidence if each factor is eliminated (Livingston et al., 2024). In early life (before age 45), lower educational attainment accounts for 5% of the population-attributable risk. In mid-life (45–65 years), ten risk factors collectively represent 30% of dementia risk, with hearing loss (7%) and high LDL cholesterol (7%) as the largest contributors, followed by depression (3%), traumatic brain injury (TBI, 3%), physical inactivity (2%), diabetes (2%), smoking (2%), hypertension (2%), obesity (1%), and excessive alcohol consumption (1%). In later life (over age 65), social isolation (5%), air pollution (3%) and visual loss (2%) are the leading risk factors. Beyond these 14 factors, several other potential risks have been identified but so far lack sufficient evidence for inclusion in the life-course model (Livingston et al., 2024). These include socioeconomic status (SES) and other social determinants of health (Majoka & Schimming, 2021; Wang et al., 2023), sleep disturbances (S.

Wang et al., 2024), diet (Nucci et al., 2024), infections (Sipilä et al., 2021), psychotic disorders (Miniawi et al., 2022), menopause and hormone replacement therapy (Fu et al., 2022), and cardiovascular diseases such as stroke (Kuzma et al., 2018). Although these findings derive from global data, the relative importance of modifiable risk factors varies by region (Mukadam et al., 2019; Santamaria-Garcia et al., 2023). For example, hypertension contributes to a larger share of dementia cases in Latin America (9.3%), China (6.4%), and India (4%) than its global average of 2% (Mukadam et al., 2019). Likewise, low education and obesity account for a higher proportion of dementia risk in those regions (Mukadam et al., 2019).

According to the life-course model, eliminating risk factors in mid-life could reduce dementia incidence by 30%, highlighting this period a critical window for intervention. For example, a meta-analysis of three middle-aged cohorts from the UK found that each unit increase in LDL cholesterol was associated with an 8% higher incidence of all-cause dementia, possibly through increased cerebrovascular risk and Aβ/tau deposition (Wee et al., 2023). Similarly, pooled meta-analysis data on over seven million individuals suggested that having TBI before age 65 was associated with higher risk of dementia (Gardner et al., 2023; Gu et al., 2022). Mid-life depression has also been significantly associated with poorer memory performance in middle-aged individuals (Ritchie et al., 2021). These findings suggest that exposure to many modifiable risk factors begins in mid-life, interventions targeting these factors should implement from the middle-age, if not earlier (Dounavi et al., 2022; Gottesman et al., 2017; Irwin et al., 2018; Lachman et al., 2015; Low et al., 2022a; Ritchie et al., 2024; Ritchie & Ritchie, 2012; Rosicka et al., 2024), prior to the manifestation of substantial brain damage.

1.3 PREVENT–Dementia Program

Motivated by the recognition of mid-life as a critical window for modifying dementia risk, the PREVENT–Dementia program was launched as a multi-site, prospective longitudinal study to investigate the origins and early diagnosis of dementia in mid-life at-risk individuals (Ritchie and Ritchie, 2012; Ritchie et al., 2024). Individuals were aged between 40 and 59 years and were cognitively normal at the time of recruitment, as determined during a thorough clinical examination. Individuals with a diagnosis of MCI, dementia, or known MRI contraindications were excluded. The recruitment target was 50% with, and 50% without parental dementia family history. By profiling mid-life risk factors for late-life neurodegenerative disease and identifying the earliest indices of disease development, PREVENT represents a pioneering epidemiological initiative focused on mid-life as a critical window for intervention. Launched in 2014 as a single-site study in West London, the program has since expanded to additional centres in Edinburgh (2015), Oxford (2017), Cambridge (2017) and Dublin (2018). Detailed protocols of this dataset have been described elsewhere (Ritchie et al., 2024; Ritchie & Ritchie, 2012; Ritchie et al., 2013). Across the five centres, 700 participants have completed extensive phenotyping assessments at Wave 1 (baseline) at the time of this PhD thesis preparation. Wave 2 assessments (2 years after baseline) have also been completed and are pending data release, while Wave 3 of testing (5 to 8 years post baseline) are currently ongoing.

The deep phenotyping assessments encompasses a broad range of measures, including demographic data, biological samples (blood, urine, saliva and optional lumbar puncture for cerebrospinal fluid), genetic data, brain imaging (structural and functional MRI), cognitive testing, and a comprehensive set of self-report questionnaires. These questionnaires assess lifestyle activities (e.g., occupational attainment, leisure activities, diet), physical health (e.g., pregnancy and menstruation, traumatic brain injury, sleep) and mental health (e.g., depression,

stress, anxiety, resilience). In addition to the main PREVENT study, some researchers from institutions across the UK, Ireland and France have recruited small group of PREVENT participants to additional sub-studies, such as retinal imaging, amyloid imaging, tau imaging, oral health research, and studies involving football and rugby cohorts (Ritchie et al., 2024). Overall, the PREVENT cohort provides a unique dataset for investigating mid-life risk factors and early markers of neurodegenerative disease. Data are available open access upon approval of the data access request via the Alzheimer's Disease Data Initiative platform and Dementia Platforms UK platform.

Studies from the PREVENT–Dementia program have provided important early evidence on how key genetic and lifestyle-related risk factors are associated with cognition and the brain in mid-life. In particular, apolipoprotein E4 (APOE4) genotype was associated with better performance in form perception (Ritchie et al., 2017) and episodic and relational memory (Deng et al., 2024), hippocampus atrophy (Dounavi et al., 2020; Dounavi et al., 2022), greater progression of white matter hyperintensities (WMH) (Low et al., 2021), regional hyperperfusion (Dounavi et al., 2021; Dounavi et al., 2023; Mak et al., 2021; McKiernan et al., 2020), and no results in thalamic volumes (Shah et al., 2024) or certain voxel- and texture-based morphometry features (Dounavi et al., 2024a). For the lifestyle-related risk factor, the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) index was used to capture dementia risk related to cardiovascular health in mid-life, higher scores have been associated with poorer performance across multiple cognitive domains (e.g., visual recognition (Ritchie et al., 2017), spatial processing (K. Ritchie et al., 2018), verbal and short-term memory (Deng et al., 2024), decreased cortical thickness (Dounavi et al., 2022), reduced grey matter volume (Liu et al., 2021), higher WMH burden (Low et al., 2022b), more severe small vessel disease and inflammation (Low et al., 2022b), and brain neurochemical changes (Dounavi et al., 2024b). However, none of the existing PREVENT studies have examined sex differences, let alone sex

differences in the associations between lifestyle activities, risk factors, cognition, and brain health in mid-life. Addressing this gap, my PhD research is adding novel evidence on these relationships. The following section introduces in greater detail the effects of APOE4 and CAIDE on cognition and the brain in mid-life.

1.4 Effects of Risk Factors on Cognition and the Brain in Mid-life

1.4.1 APOE4 effect on cognition and the brain

Genetic factors also play a critical role in brain health, and among these, the APOE gene is the most influential in sporadic AD. There are three predominant APOE alleles in humans, the ε2 (APOE2), ε3 (APOE3), and ε4 (APOE4) alleles, which confer different levels of AD risk (Raulin et al., 2022). APOE2 appears to provide some protection against AD (Goldberg et al., 2020; Z. Li et al., 2020), while APOE3, the most common allele, is believed to have a neutral effect on the disease (Wu & Zhao, 2016; Yamazaki et al., 2019). By contrast, APOE4 increases AD risk and is associated with an earlier age of disease onset in general population (Raulin et al., 2022). APOE4 is the strongest and most extensively studied genetic risk factor for dementia, most notably AD, though it has been implicated in other neurodegenerative diseases as well (Fernandez-Calle et al., 2022; Wightman et al., 2021). Its frequency varies by ethnicity, ranging from about 9% in Asian cohorts to 23% in other/mixed populations (Asian 9%, Hispanic 12%, white 14%, African descent 19%, other/mixed 23%) (Jia et al., 2020b). APOE4 heterozygotes (one ε4 allele) face higher risk and earlier onset of AD compared to noncarriers, while homozygotes (two ε4 alleles) have even greater risk and an earlier onset than both heterozygotes and noncarriers, highlighting the dose-dependent effect of ε4 allele (Jia et al., 2020b; Riaz et

al., 2021). By age 85, roughly 50% of APOE4 homozygotes develop AD, compared with only 10% of noncarriers (Genin et al., 2011).

Studies from the PREVENT–Dementia programme and similar middle-aged cohorts have revealed a complex profile of APOE4 effects on cognition in mid-life. APOE4 carriers showed better performance in form perception (Ritchie et al., 2017), immediate recall (Jochemsen et al., 2012), narrative recall (McKiernan et al., 2020), and episodic and relational memory (Deng et al., 2024) compared to non-carriers. Conversely, studies also found that APOE4 was associated with relative impairment in attention (Zimmermann et al., 2019), episodic memory (Eich et al., 2019), and visual memory (Lim et al., 2021) in cognitively healthy middle-aged individuals. How might these early advantages coexist with APOE4's well-established role as a dementia risk factor? One explanation is a compensatory neural response, in the presence of incipient AD-related pathology, APOE4 carriers may leverage additional brain resources to maintain or even enhance cognitive performance (Cacciaglia et al., 2023). Alternatively, these findings align with the hypothesis of antagonistic pleiotropy (Williams, 1957), which proposes that certain genes or alleles may impact fitness differently at different stages in life. Some genes, such as the APOE4, might confer advantages early in life but become detrimental later as the forces of natural selection weaken with age (Byars & Voskarides, 2020; Smith et al., 2019).

APOE4 genotype has also been related to brain structural and functional changes in mid-life. Structural imaging studies consistently report reduced structural integrity in APOE4 carriers versus non-carriers. For example, APOE4 carriers showed volumetric loss in the hippocampal molecular layer (Dounavi et al., 2020; Dounavi et al., 2022), reduced grey matter volume in the right hippocampus, precentral gyrus, and cerebellar cortex (Cacciaglia et al., 2018), decreased cortical thickness in the frontal cortex (Fennema-Notestine et al., 2011), declined white matter integrity (Operto et al., 2019), and greater longitudinal progression of WMH (Low et al., 2021),

relative to non-carriers. But there were no significant differences in the volumes of thalamus or its subregions (Shah et al., 2024), and in the voxel-based or texture-based morphometry (examined features: contrast, entropy, energy, homogeneity) of brain structural alterations (Dounavi et al., 2024a). By contrast, functional changes related to APOE4 genotype have so far been mixed in mid-life, both in task-based and resting-state functional magnetic resonance imaging (fMRI) studies. APOE4 carriers showed hypoactivation in the hippocampal/medial temporal regions during episodic encoding tasks (Trivedi et al., 2006), and hypoconnectivity within these regions (Sheline et al., 2010) and the default mode network (DMN) (Goveas et al., 2013; Patel et al., 2013), compared to non-carriers. However, hyperactivation in the fronto-parietal network (FPN) during a working memory task (Chen et al., 2013) and hyperconnectivity in the DMN (Fleisher et al., 2009) and salience network (SN) (Goveas et al., 2013) have also been reported in middle-aged APOE4 carriers, relative to non-carriers. These functional alterations are complemented by arterial spin-labelling (ASL) studies showing regional hyperperfusion in APOE4 carriers relative to non-carriers (Dounavi et al., 2021; Dounavi et al., 2023; Mak et al., 2021; McKiernan et al., 2020).

1.4.2 CAIDE effect on cognition and the brain

With numerous, interrelated determinants influencing brain health, it is challenging to disentangle their individual and joint contributions to dementia risk. This complexity is compounded by the frequent co-occurrence of multiple risk factors and their potential interactions. Although many modifiable factors, such as physical inactivity, hypertension, obesity, and cholesterol, have been shown to independently elevate dementia risk or influence cognition, a holistic and composite approach is needed to capture their additive impact. A widely used method involves computing a composite multifactor risk score, which quantifies the cumulative burden of several risk factors and helps identify individuals at high risk of

dementia (Anstey et al., 2013; Kivipelto et al., 2006; Vos et al., 2017). Among the existing dementia risk scores that incorporate several risk factors (Barnes et al., 2014; Deckers et al., 2015; Kivipelto et al., 2006), the CAIDE score is tailored specifically for mid-life (Kivipelto et al., 2006) and has been validated in a large US population followed longitudinally over 40 years (Exalto et al., 2014). The CAIDE score captures several modifiable risks related to cardiovascular health, including physical activity level, body mass index, cholesterol, and systolic blood pressure, alongside other risk factors such as age, sex, APOE4 genotype and educational level (Kivipelto et al., 2006).

Studies have also investigated the association of CAIDE scores with cognition and the brain in mid-life. Individuals with higher CAIDE scores had worse performance in visual recognition (Ritchie et al., 2017), spatial processing ability (K. Ritchie et al., 2018), executive function, processing speed and memory (Stephen et al., 2017), and verbal, visuospatial functions, and short-term memory (Deng et al., 2024). Mounting evidence showed that CAIDE score was associated with brain health. For instance, cross-sectionally, higher CAIDE scores were associated with decreased cortical thickness in the precuneus, superior frontal, inferior parietal, and middle temporal cortex (Dounavi et al., 2022; Gourley et al., 2020), lower grey matter volume in the temporal, occipital, and fusiform cortex (Liu et al., 2021), higher WMH burden (Dounavi et al., 2022; Salvadó et al., 2019), more severe cerebral small vessel disease and inflammation (Low et al., 2022b), and brain neurochemical changes (Dounavi et al., 2024b). Moreover, the CAIDE score significantly moderated the relationship of cognition and functional connectivity between locus coeruleus and hippocampus, two key brain regions in AD neuropathology (Deng et al., 2024). Longitudinally, individuals with higher CAIDE scores had greater annual percentage rates of loss in brain volume and enlargement in ventricular volume (T O'Brien et al., 2020), greater grey matter volume loss in the supramarginal gyrus, angular gyrus, precuneus, superior parietal and lateral occipital cortex (Liu et al., 2021), and

greater WMH progression and increased inflammation (Low et al., 2022b) over two years follow-up, compared to those with lower CAIDE scores.

1.5 Cognitive Reserve and Reserve Contributors

Lifestyle also exert a multipronged effect on cognition and brain health. Contrary to the risk factors previously discussed and those captured by the CAIDE score, protective lifestyle activities have been associated with the preservation of cognitive function in older adults (D. Chan et al., 2018) and lower severity of Alzheimer's disease symptoms (Livingston et al., 2024; Livingston et al., 2020). These protective effects are explained through the phenomenon known as cognitive reserve (Stern, 2012; Stern et al., 2020).

The idea of cognitive reserve originated from observations of considerable inter-individual variability in responses to brain aging and AD pathology, whereby some individuals maintain cognitive function despite impaired brain health due to aging or neurodegenerative diseases, while others do not (Arenaza-Urquijo et al., 2024; Stern, 2012). Indeed, approximately 30% of older adults who meet neuropathological criteria for AD at autopsy remain cognitively unimpaired throughout life (Driscoll & Troncoso, 2011; Esiri et al., 2001; Seto et al., 2021). Thus, cognitive reserve has been proposed to account for the disjunction between brain pathology severity and its clinical manifestations (Stern, 2009). Cognitive reserve specifically refers to the adaptability, comprising efficiency, capacity, and flexibility, of cognitive processes, explaining why individuals differ in their susceptibility to cognitive decline in the presence of aging or pathology (Stern et al., 2020). Empirical evidence supports this theory, indicating that individuals with greater cognitive reserve experience slower age-related cognitive decline (D. Chan et al., 2018) and can tolerate higher levels of age-related and dementia-related brain

pathology (Dekhtyar et al., 2019; Livingston et al., 2024; Wang et al., 2017), before functional cognitive impairment becomes evident.

Despite the significant clinical implications of cognitive reserve, directly measuring this construct remains challenging due to its theoretical nature (Stern et al., 2020). Consequently, researchers employed indirect approaches, including sociobehavioral proxies, residual approaches, and neuroimaging techniques, to measure cognitive reserve (Stern et al., 2020). Traditionally, sociobehavioral proxies, such as IQ, educational attainment, occupational complexity, verbal intelligence, leisure activities, and physical engagement, have been widely used given their epidemiological association with lower dementia risk and slower cognitive decline (Boyle et al., 2021; Pappalettera et al., 2024; Stern et al., 2020). In addition to these proxies, the residual-based approach provides another indirect measure by quantifying cognitive reserve as the unexplained variance (residuals) in cognitive function after accounting for the variance explained by brain structure and demographic factors, usually through regression models (Reed et al., 2010; Stern et al., 2020). Neuroimaging approaches, particularly fMRI, offer more direct insights by identifying resting-state or task-related functional activation brain networks that may underlie cognitive reserve (Franzmeier et al., 2017b; Pappalettera et al., 2024; Stern et al., 2020). Nevertheless, there remains no universally accepted gold standard for operationalizing and measuring cognitive reserve across diverse studies.

Higher cognitive reserve is linked to a reduced risk of dementia and, therefore, building cognitive reserve represents a critical strategy for dementia prevention. Cognitive reserve accumulates from exposure to diverse lifetime experiences (Stern et al., 2020). Education, stimulating avocational activities (physical, social and intellectual), and occupational attainment are key contributors to cognitive reserve (Song et al., 2022; Stern, 2012; Stern et al., 2020). Additional epidemiological evidence also showed that bilingualism (Bialystok, 2021;

Calvo et al., 2015), IQ (Barulli & Stern, 2013; Stern, 2002), diet (Gu & Scarmeas, 2011), and socioeconomic status (Barulli & Stern, 2013; Stern, 2002) were associated with reduced dementia risk or less cognitive decline, contributing to greater cognitive reserve. Engaging in cognitively enriching activities, ranging from early-life education and hobbies to employment and social interactions, can help offset brain pathology and genetic predispositions by fostering greater neural connectivity and enhancing information processing capacity (Hu et al., 2013; Valenzuela & Sachdev, 2006; Verghese et al., 2003).

The neural mechanisms underlying cognitive reserve encompass neural reserve, neural compensation, and generic cognitive reserve networks (Steffener & Stern, 2012). Neural reserve refers to the enhanced efficiency or capacity of neural networks enabling individuals to maintain cognitive performance despite age-related brain changes or pathology (Steffener & Stern, 2012). Neural compensation involves recruiting alternative neural networks when primary networks are impaired, facilitating successful cognitive performance in the face of age-related brain changes or pathology (Steffener & Stern, 2012). Moreover, a task-invariant or generic cognitive reserve network, independent of specific task demands, engages broadly across cognitive processes, allowing individuals with greater capability in expressing this network to sustain performance despite aging or pathology (Steffener & Stern, 2012; Stern et al., 2018; van Loenhoud et al., 2020). Together, these processes underpin how lifelong experiences translate into resilient neural architectures, buffering against the effects of aging and neurodegenerative disease.

1.6 Sex Differences in Alzheimer's Disease, Cognition and the Brain

1.6.1 Sex differences in Alzheimer's Disease

Growing evidence showed a disproportionate impact of AD on females (Alzheimer's Association, 2017; Mielke, 2018). Females account for over two-thirds of AD cases and simultaneously shoulder approximately two-thirds of dementia caregiving responsibilities (Alzheimer's Association, 2021). Indeed, apart from age, biological sex is considered one of the greatest risk factors for late-onset AD (Subramaniapillai et al., 2021). Several reasons have been proposed to explain the higher prevalence of AD in females compared to males. One reason is that females are more adversely affected by certain established risk factors for AD. For example, females are more frequently exposed to factors that contribute to AD neuropathology while undertaking caregiving responsibilities, including increased stress (Ma et al., 2018), caregiver burden (Xiong et al., 2020) and mental health problems (Erol et al., 2015). In addition, females carrying the APOE4 genotype are at greater risk for developing AD (Altmann et al., 2014; Farrer et al., 1997) and, once diagnosed, tend to experience faster pathological accumulation and more severe disease progression compared to males with a similar pathological burden (Barnes et al., 2005; Buckley et al., 2018; Edwards et al., 2021).

Another important factor contributing to the higher AD vulnerability in females is the menopausal transition. Menopausal transition is a middle-age phenomenon with knock-on effects on endocrinal (Weber et al., 2014), cardiovascular (Yanes & Reckelhoff, 2011), and metabolic (Rahman et al., 2020) systems that significantly impact brain health (Mosconi et al., 2018; Udeh-Momoh et al., 2021). The rapid decline in estrogen, a key hormonal change during this transition, is thought to heighten AD risk in females (Scheyer et al., 2018; Udeh-Momoh et al., 2021). Studies have shown that premature loss of ovarian function (whether surgical or nonsurgical) was associated with poorer memory in later life (Ryan et al., 2014), that earlier

age at menopause correlated with a higher tau burden (Coughlan et al., 2023), and that reduced lifetime estrogen exposure was linked to increased AD risk (Pike, 2017). Postmenopausal females also tend to exhibit increased levels of amyloid-beta, elevated tau burden, reduced white matter integrity, and glucose hypometabolism (Buckley et al., 2022; Mosconi et al., 2017b; Rahman et al., 2020). These findings have led to the hypothesis that estrogen may be a promising agent for enhancing memory and treating AD (Bonkhoff et al., 2025). Consequently, hormone replacement therapy (HRT) has been considered as a potential intervention to mitigate cognitive decline and lower dementia risk.

However, evidence regarding the efficacy of HRT for dementia prevention remains mixed (Grady et al., 2002; Whitmer et al., 2011). While some smaller-scale studies have reported that HRT use was associated with better cognitive outcomes and reduced dementia risk in females (Saleh et al., 2023; Shao et al., 2012), other studies have found no benefit or even detrimental effects (Coughlan et al., 2025; Resnick et al., 2009; Shumaker et al., 2003; Zhou et al., 2021). Notably, the Women's Health Initiative Memory Study (WHIMS), one of the largest randomized clinical trials launched in 2003, found that HRT initiated after menopause was associated with an increased risk of dementia compared to placebo (Shumaker et al., 2003). These inconsistencies may be attributable to differences in the timing of HRT initiation across studies (Udeh-Momoh et al., 2021). This has led some researchers to propose a 'critical window' hypothesis, suggesting that the potential benefits of HRT may depend on whether it is initiated during the menopausal transition or the early postmenopausal period (Davey, 2013; Manson & Kaunitz, 2016; Sherwin, 2007; Whitmer et al., 2011).

1.6.2 Sex differences in cognition

Beyond prevalence and biological risk profiles, biological sex also significantly influences cognition and cognitive trajectories. Cross-sectionally, females generally show better memory,

notably, verbal and episodic memory, than males (Arenaza-Urquijo et al., 2024; Asperholm et al., 2019; Brunet et al., 2020; Sundermann et al., 2019). Males tend to show better visuospatial skills, but this is a less consistent finding (McCarrey et al., 2016; Murre et al., 2013). The memory advantage in females seems to be stable across the lifespan and still present at very old ages (even over age 75) (Golchert et al., 2019; van Exel et al., 2001). These sex differences have been reported independent of demographics including age, race/ethnicity, education, clinical measurements (i.e., blood pressure), and age-related brain changes (Donohue et al., 2014; Jack et al., 2015), suggesting a robust sex-specific advantage in verbal and episodic memory.

In contrast, longitudinally, evidence on sex differences in rates of cognitive decline in normal aging is mixed. In young and middle adulthood, studies report little to no differences between males and females. For example, Anstey et al. (2021) followed over 7,000 adults of young and middle adulthood (age < 60) over 12 years, and observed no significant differences between males and females in rates of change across cognitive domains including verbal memory, processing speed, verbal ability and working memory. However, a study involving 26,000 middle-aged American participants (mean age = 58) reported that females declined faster than males in global cognition and executive function, yet both sexes showed similar rates of memory decline (Levine et al., 2021). In later life, meta-analyses and cohort studies report no broad sex differences in overall decline (Ferreira et al., 2014; Soldan et al., 2017), though domain-specific sex differences emerge. McCarrey et al. (2016) found that males exhibited steeper losses on perceptuomotor speed/integration, visual memory and visuospatial ability, while females and males had similar declines in verbal learning, language, attention and executive tasks in older adults (mean age = 67). Similarly, Anstey et al. (2021) observed that between ages 68 and 72 females started to experience an accelerated decline in verbal memory compared with males of the same age. Among the oldest-old (> 80 years), these sex differences

in cognitive trajectories appear to diminish. A 13-year follow-up of over 3,000 cognitively healthy elders showed similar episodic memory trajectories in males and females (Golchert et al., 2019). Together, aside from somewhat accelerated verbal memory loss in females and selective visuospatial declines in males in later life, there were inconsistent results in young and middle adulthood and no sex differences at oldest-old ages.

In the context of disease progression, evidence on sex differences in cognitive trajectories is relatively conclusive. Although females typically having verbal and episodic memory advantages over males, they tend to experience more rapid cognitive deterioration once pathological processes begin. In the preclinical stage of AD, cognitively unimpaired females showed more rapid decline than males in composite measures of episodic memory, executive function, and global cognition, even though both sexes had similar cerebrospinal fluid (CSF) amyloid levels (Buckley et al., 2018). Extending this, X. Wang et al. (2024) found that in cognitively unimpaired amyloid-positive individuals, elevated tau burden was associated with poorer cognition only in females not males. Once mild cognitive impairment (MCI) is diagnosed, females continue to demonstrate steeper cognitive declines relative to males (Sohn et al., 2018). Studies focusing on clinical progression consistently reported faster progression from normal cognition to MCI, and subsequently from MCI to AD dementia, in females compared to males (Cieri et al., 2022; Lin et al., 2015; Sundermann et al., 2016a; Sundermann et al., 2016b; Tifratene et al., 2015). For example, Sundermann and colleagues found that female had verbal memory advantage when they were cognitively unimpaired, followed by rapid decline in association with temporal lobe hypometabolism and hippocampal atrophy at the MCI stage (Sundermann et al., 2016a; Sundermann et al., 2016b). This aligns with findings from a recent meta-analysis, which reported greater impairment in several cognitive domains, including semantic and episodic memory, visuospatial, and verbal processing, in females compared to males diagnosed with AD (Irvine et al., 2012). In summary, females generally have

better cognitive performance, particularly in verbal and episodic memory, than males, this advantage diminishes and reverses as neuropathology processes, highlighting a sex-specific cognitive reserve to Alzheimer's disease (Arenaza-Urquijo et al., 2024).

1.6.3 Sex differences in the effects of reserve contributors on cognition

Building and maintaining cognitive reserve is crucial for "successful" aging and prevention of dementia. As mentioned above, several lifestyle activities—including education, occupational attainment, and stimulating activities—have been shown to attenuate age- or disease-related brain damage and lower the risk of developing dementia in older adults (D. Chan et al., 2018; Stern, 2009, 2012; Stern et al., 2020; Valenzuela & Sachdev, 2006). However, it remains unclear whether these reserve contributors can offset dementia risk as early as mid-life, in individuals who are presently healthy but carry the inherited risk (APOE4 genotype) of future dementia.

Importantly, females and males do not derive identical benefits from reserve contributors, nor does genetic risk act uniformly across sexes. Education, for example, appears to confer different protection against Alzheimer's pathology in females and males over 60 (Letenneur et al., 2000; Pradier et al., 2014). Occupational attainment also demonstrates sex-specific associations with Alzheimer's risk (Qiu et al., 2003; Santabarbara et al., 2019; Zijlmans et al., 2022), with manual work potentially increasing risk in elderly females but not males (Qiu et al., 2003), while craftsman/shopkeeper roles showed protection in females but increased risk in males (Helmer et al., 2001). Furthermore, IQ appears to confer greater protection against age-related cognitive decline in older males but not in females (Alty et al., 2023). Moreover, sex and APOE4 interact on risk for Alzheimer's disease and related dementias. The APOE4 allele itself is more penetrant in females than males (Payami et al., 1994). Females with an APOE4 allele have increased lifetime risk for dementia (Farrer et al., 1997; Neu et al., 2017), smaller hippocampal volumes (Fleisher et al., 2005; Hobel et al., 2019; Koran et al., 2017), higher CSF amyloid-β and tau

burden (Altmann et al., 2014; Damoiseaux et al., 2012), more postmortem plaques and neurofibrillary tangles (Corder et al., 2004), and worse cognition (Fleisher et al., 2005; Hobel et al., 2019), compared to female noncarriers or male carriers.

To the best of my knowledge, only a few of recent studies have explored how sex and APOE4 jointly relate to cognition and cognitive reserve in older adults. Pa et al. (2022) found that higher physical activity was associated with greater speed reserve in older females but not in males, but this benefit was attenuated in female APOE4 carriers. Alty et al. (2023) found that cognitive reserve, measured through IQ, moderated the rate of age-related cognitive decline in males but not in females. APOE4 genotype did not interact with sex in moderating the associations of IQ and cognitive decline (Alty et al., 2023). However, no research to date has examined how sex and APOE4 interact to influence the associations of mid-life lifestyle factors, specifically occupational complexity and stimulating activities, with cognition. The answer to this question is critical for high precision approaches for Alzheimer's disease prevention and clinical trials. Addressing this gap is the focus of the work described in Chapter 2.

Although education is generally non-modifiable by mid-life, its lifelong influence on brain health is well established (Lam et al., 2024; Lovden et al., 2020). Lower early-life education increases dementia incidence decades later by roughly 5-8% (Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017). Despite extensive literature examining sex and education separately (Bolton et al., 2024; Deckers et al., 2019; Lipnicki et al., 2017; Mezzaca et al., 2022; Palpatzis et al., 2025), relatively few studies have directly investigated their interactions. Early longitudinal studies suggested similar dementia risk reduction across sexes (Letenneur et al., 1999), but larger pooled analyses of over 28,000 participants found that higher education reduced dementia risk only in females but not in males (Launer et al., 1999; Letenneur et al., 2000). In cognitively healthy older adults, highly educated females showed

slower decline in verbal fluency than males with the same educational level (Bloomberg et al., 2021), whereas other evidence points to education-related slowing of cognitive decline only in males (Iwata et al., 2018). In clinical populations, Oliveira et al. (2016) showed that education slowed cognitive decline specifically in females and APOE4 carriers diagnosed with AD, contrasting with Pradier et al. (2014), who found stronger education benefits in male AD patients. Moreover, lower education disproportionately amplified vulnerability to amyloid-β in females with MCI compared to their male counterparts (Koran et al., 2017). These findings highlight a complex, poorly understood interplay between sex and education on cognition and the brain. However, little is known on whether education, another major reserve contributor, would interact with sex to influence the associations of stimulating activities and occupational attainment with cognition and brain health in middle-aged individuals. Addressing this gap is the focus of the work described in Chapter 3.

1.6.4 Sex differences in brain structure

Within the brain, structural differences between males and females have long been established (Cavedo et al., 2018; Gautam et al., 2013; Lee et al., 2018; Sang et al., 2024; Sangha et al., 2021; Seo et al., 2011; Sowell et al., 2007; van Velsen et al., 2013), yet findings remain inconsistent. In cognitively healthy adults, for example, some studies reported thicker frontal and temporal cortices in males (Gautam et al., 2013; Sang et al., 2024), extensive thickness advantages in females across frontal, parietal and occipital regions (Lv et al., 2010; S. J. Ritchie et al., 2018; Sangha et al., 2021), or no significant effect of sex (Cavedo et al., 2018). In MCI and AD populations, cross-sectional studies are similarly mixed. Some have found no baseline sex differences in cortical thickness in AD patients (Seo et al., 2011), while others showed that males with MCI exhibit thinner motor and superior parietal cortices than females with MCI (Sangha et al., 2021). Longitudinally, once Alzheimer's disease is established, females may

experience more rapid thinning in frontotemporal and temporo-parietal association cortices compared to males (Lee et al., 2018).

Volumetric measures reveal a complementary pattern. Males consistently have larger total brain volume than females, however, once controlled for total brain volume, females have a higher percentage of gray matter and males a higher percentage of white matter (Cosgrove et al., 2007). A meta-analysis of 167 neuroimaging studies spanning from infancy to over age 80 reported larger brain volumes and grey matter volume in males (Ruigrok et al., 2014). Building on this, Bethlehem et al. (2022) pooled data from more than 100,000 participants across lifespan and charted normative brain-development trajectories showing that, from birth through age 80, males exceed females in total cerebrum, cortical and subcortical grey matter, white matter volumes and surface area, yet mean cortical thickness remains equivalent. In clinical populations, particularly AD patients, sex differences appear region-specific. Research shows that AD females have greater grey matter volume (Bergamino et al., 2022), smaller hippocampal volumes (Apostolova et al., 2006), less CSF volumetric atrophy in frontal, temporal, and parietal regions (Kidron et al., 1997), whereas males AD patients show increased ventricle-to-brain ratios (Carmichael et al., 2007) and more pronounced cingulate atrophy (Ballmaier et al., 2004; Callen et al., 2004).

By contrast, investigations into whether there are differences in the relationships between brain structure and cognition across sexes remain scarce. To date, only a handful of studies have directly examined sex differences in the association between brain structure and cognitive function, and most have focused on older or clinical populations. For example, Cieri and colleagues (2022) explored how cortical thickness related to verbal memory performance in cognitively healthy older adults, MCI and AD individuals. They found that, in cognitively healthy older adults, females' memory performance was more strongly associated with

thickness in medial temporal and posterior cingulate regions, whereas in males these associations were weaker; in clinical groups, the sex difference in structure–memory coupling diminished with advancing pathology (Cieri et al., 2022). However, mid-life, a key period for brain maturation completion and the emergence of early neuropathological changes, has been largely overlooked with respect to sex-specific structure–cognition associations. We still know little about whether there are sex differences in brain structure–cognition relationship in mid-life, and how late-life dementia risk and reserve contributors relate to brain structure and cognition at this stage. If sex-specific structure–cognition coupling is already evident this early, it could reveal differential vulnerability or resilience pathways that ultimately contribute to females' disproportionate burden of late-life AD. Clarifying these early divergences, and how brain structure is associated with dementia risk and reserve contributors would sharpen our ability to identify at-risk individuals before irreversible neurodegeneration sets in and inform sex-tailored preventive interventions. Filling this gap is the aim of Chapter 4.

1.6.5 Sex differences in brain function

Evidence suggests that changes in brain function may precede even earlier than macroscale structural brain alterations (Fox & Raichle, 2007; Greicius et al., 2004). Functional brain changes have also been observed at an early stage in individuals at risk for dementia (Habib et al., 2017). Resting-state fMRI offers a non-invasive method to investigate spontaneous fluctuations in the blood oxygenation level-dependent (BOLD) signal, reflecting the brain's neuronal baseline activity during a task-free resting state (Biswal & Uddin, 2025; Raimondo et al., 2021). These low-frequency spontaneous oscillations in resting-state fMRI signal reveal an intrinsic spatiotemporal organization within the brain. Regions exhibiting synchronous activity are commonly referred to as intrinsic connectivity networks or canonical networks (Fox et al., 2005; Greicius et al., 2003; Schaefer et al., 2018; Yeo et al., 2011). Intrinsic connectivity

networks serve as potentially sensitive functional marker for identifying at-risk individuals during early stages of AD (Kucikova et al., 2021). Specifically, disrupted connectivity within networks critical for memory function, such as the DMN, salience network, and executive control network, has been observed even in asymptomatic individuals with subjective cognitive decline, a condition considered a precursor of dementia (Viviano & Damoiseaux, 2020).

Furthermore, findings from intrinsic connectivity network studies suggest notable sex differences. Females demonstrated stronger connectivity within the DMN compared to males (Allen et al., 2011; Bluhm et al., 2008; Jamadar et al., 2019; S. J. Ritchie et al., 2018), a feature associated with reduced cognitive decline in some studies (Buckley et al., 2017; Chhatwal et al., 2013). Additionally, females showed a markedly attenuated decline in functional connectivity within the DMN with aging compared to males (Scheinost et al., 2015). Beyond fMRI findings, positron emission tomography (PET) studies have also identified sex differences in metabolic brain function. For example, female brain had younger metabolic brain ages (relative to their chronological age) compared with the male brain throughout the adult lifespan (Goyal et al., 2019), and females showed less extended and less pronounced age-related reduction in brain metabolism relative to males in healthy elderly adults (Malpetti et al., 2017). However, the direct investigation of sex differences in brain functional connectivity in relation to cognitive performance remain limited. To the best of my knowledge, only two recent studies have tackled this question (Ficek-Tani et al., 2023; Ju et al., 2023), one in cognitively healthy older adults and another across a broad adult age span (36–100 years). These gaps highlight the need for approaches that capture distributed, whole-brain connectivity patterns underlying cognition.

Connectome-based predictive modeling (CPM), a data-driven technique, offers a promising approach by linking whole-brain connectivity to specific phenotypes, including cognitive

performance (Shen et al., 2017). CPM has been successfully applied to predict symptom severity, disease states, and cognitive functioning (Prakash et al., 2025; Rohr et al., 2020; Tripathi et al., 2025; Weng et al., 2024; Yip et al., 2019). For example, Ju et al. (2023) applied CPM in healthy adults across a broad age range (36–100 years) and found that females showed enhanced connectivity within posterior DMN regions associated with better memory, whereas males relied more on alternative networks (e.g., visual networks) (Ju et al., 2023). Nevertheless, it remains unknown whether such sex-specific functional connectomes supporting cognition are present in mid-life individuals who are at risk for late-life dementia, and how the functional connectome is associated with dementia risk and reserve contributors. Understanding whether the functional connectome that supports cognition differentially in males and females can provide critical insights into the elevated risk for AD in females and aid the development of early sex-specific biomarkers. This unresolved question is central to Chapter 5, in which I applied CPM to identify large-scale functional networks predictive of cognitive performance in mid-life, specifically aiming to elucidate sex differences.

1.7 Limitations of Previous Studies

Previous research has advanced our understanding of sex differences in cognition, cognitive reserve and brain health in older or clinical populations. However, several key limitations remain unresolved. First, although the interactions of biological sex and genetic risk (e.g., APOE4) on cognition and cognitive reserve have been previously examined in older adults, there is insufficient understanding of how sex and APOE4 together influence the effects of reserve contributors, such as occupational attainment and stimulating activities, on cognition in mid-life. Second, even though education is a well-established protective factor, its interactions with sex on the associations of lifestyle activities with cognition and brain health, as well as

whether their relationships are associated with dementia risk in cognitively healthy middle-aged adults have scarcely been investigated. Additionally, while structural brain differences between females and males are documented, sex differences in the relationships between brain structure and cognition, and how dementia risk factors and reserve contributors relate to brain structure remain understudied during mid-life, a critical period when neuropathological burden begins to accumulate. Finally, despite evidence suggesting sex differences in brain functional networks, it remains unclear whether there is sex-specific functional connectome underlying cognition among mid-life individuals at heightened risk for dementia and how the functional connectome is associated with dementia risk and reserve contributors. Bridging these gaps is essential to uncover the mechanisms underlying sex differences in AD risk and progression, ultimately informing sex-specific precision approaches for early intervention and prevention strategies.

1.8 Overview of the Thesis

Based on the research reviewed in this chapter, there remains a critical need to investigate sex differences in:

(a) the associations between reserve contributors, risk factors, cognition and brain health;

(b) the relationship between brain structure and cognition, and how dementia risk and reserve contributors relate to brain structure and cognition;

(c) the functional connectome underlying cognition, and how this functional connectome is associated with risk factors and reserve contributors in cognitively healthy, middle-aged individuals at risk for late life dementia.

This thesis addresses the three research questions in four empirical chapters, utilizing wave 1 (baseline) data from the PREVENT-Dementia program (N = 700). Accordingly, Chapter 2 and Chapter 3 focus on the first broad question, Chapter 4 on the second, and Chapter 5 on the third.

Chapter 2 investigated whether reserve contributors enhance cognition in mid-life, and how biological sex and APOE4 status interact to influence the effects of reserve contributors on cognition. A dimensionality reduction technique was used to capture the common cognitive domains underlying a set of sensitive tests for detecting early changes in AD. Reserve contributors were assessed by years of education and the Lifetime of Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007). The LEQ is designed to measure a lifespan engagement in a broad range of lifestyle activities across three distinct stages of life: young adulthood (13-29 years), mid-life (30-64 years) and late life (65 years onwards). The LEQ was used to evaluate lifestyle activities specific to mid-life in the PREVENT study, yielding two composite factors, occupational attainment and stimulating activities. The effects of reserve contributors on cognition were first examined. The interactions of sex and APOE4 status on the relationship between reserve contributors and cognition was further tested. My hypotheses were that a) reserve contributors would enhance cognition in mid-life, and b) biological sex and APOE4 would moderate the associations between reserve contributors and cognition, with females deriving greater cognitive benefits compared to males, and APOE4 genotype amplifying sex differences in the associations.

Chapter 3 examined whether education, another major reserve contributor, would interact with sex to influence the effects of lifestyle activities on cognition and brain health, as well as how their relationships are influenced by dementia risk in mid-life. Brain health was measured using two structural measures, total grey matter volume and global cortical thickness. The interactions of sex and education on the associations between stimulating activities, occupational attainment, cognition and brain structural measures were first examined. The effects of risk factors (APOE4 and CAIDE score) on their relationship were further tested. The main hypotheses were that (a) biological sex and education would interact to influence the effects of lifestyle activities on

cognition and brain structure, and (b) risk factors would augment sex differences in these associations.

Chapter 4 focused on the effects of dementia risk and reserve contributors on cognition and brain structure, and sex differences in the relationship between brain structure and cognition in mid-life. Brain structure was assessed using total grey matter volume, global cortical thickness, and regional thickness measures of several AD signature regions. I first investigated the effects of risk factors (APOE4 and CAIDE score) and reserve contributors on cognition and brain structure. Further, I examined whether sex moderated the associations between brain structure and cognition. In cases where a significant interaction of sex and global cortical thickness was detected, follow-up regional analyses were conducted for each of the AD signature regions. I hypothesized that (b) risk factors would be negatively associated with cognition and brain structure, whereas reserve contributors would show positive associations, and (a) biological sex would moderate the relationship between brain structure and cognition.

Chapter 5 applied a data-driven approach, CPM, to identify whole-brain functional connectome underlying cognition in mid-life, with a specific consideration of sex differences. Moreover, this chapter also examined the effects of dementia risk and reserve contributors on the functional connectome supporting cognition in mid-life. I asked three research questions: (a) Do the functional connectome underlying cognition differ between females and males in mid-life? (b) How do dementia risk and reserve contributors influence the functional connectome supporting cognition? (c) Is there a significant interaction between sex and reserve contributors in shaping the functional connectome supporting cognition? My hypotheses were that (a) the functional connectome underlying cognition would differ between females and males in mid-life; (b) dementia risk would negatively, and reserve contributors would positively, relate to the functional connectome associated with cognition; and (c) there would be a

significant interaction between sex and reserve contributors in the cognition-related functional connectome.

2. Chapter 2: Associations between sex and lifestyle activities with cognitive reserve in mid-life adults with genetic risk for Alzheimer's disease

2.1 Introduction

Dementia is a global epidemic that presents profound challenges to individuals, families, health care systems, and societies throughout the world, and there is an urgent need to reduce the rising worldwide prevalence (Livingston et al., 2017). Evidence suggests that up to 45% of future dementia cases can be prevented by modifying medical and lifestyle risk factors (Livingston et al., 2024). As exposure to many modifiable risk factors for dementia begins in mid-life, interventions must be implemented from the middle-age, if not earlier (Dounavi et al., 2022; Gottesman et al., 2017; Irwin et al., 2018; Lachman et al., 2015; Low et al., 2022a; Ritchie et al., 2024; Ritchie & Ritchie, 2012), prior to the manifestation of substantial brain damage.

Higher cognitive reserve is linked to a reduced risk of dementia and, therefore, building cognitive reserve is a crucial preventative approach. Research indicates that individuals with greater cognitive reserve experience slower age-related cognitive decline (D. Chan et al., 2018) and can tolerate higher levels of age-related and dementia-related brain pathology (Dekhtyar et al., 2019; Livingston et al., 2024; Wang et al., 2017), before functional cognitive impairment becomes evident. Education, stimulating avocational activities (physical, social and intellectual), and occupational attainment are key contributors to cognitive reserve (Stern, 2012; Stern et al., 2020). Research indicates that cognitive reserve in older adults is developed through participation in activities that enhance cognitive function. These activities range from early-life

education and hobbies to employment and social interactions. Engaging in such activities can help offset brain pathology and genetic predispositions by fostering greater neural connectivity and enhancing information processing capacity (Hu et al., 2013; Valenzuela & Sachdev, 2006; Verghese et al., 2003).

It remains unknown whether stimulating activities and occupational attainment can offset dementia risk as early as mid-life, in individuals who are presently healthy but carry the inherited risk (APOE4 genotype) of future dementia. Education has garnered a lot of attention, but it's not substantially modifiable in mid-life. Therefore, the additional contribution of stimulating activities and occupational attainment, which are modifiable in mid-life, is of central importance to preventative strategies in this life stage. It is also not clear who benefits the most from these different reserve contributors. For example, evidence suggests that older females and males benefit differently from interventions aimed at reducing dementia risk (Arenaza-Urquijo et al., 2024), e.g., vascular risk factors (Matthews et al., 2016). Females stand to benefit the most from dementia prevention efforts, due to their elevated incidence of all-type dementia, even when accounting for longer lifespan (Gao et al., 1998; Hebert et al., 2013). Furthermore, historically, females have had restricted access to advanced education and opportunities for cognitively stimulating activities, or prolonged employment. These limited opportunities to build cognitive reserve may, in and of themselves, contribute to the higher incidence of dementia in females (Hasselgren et al., 2020). Mounting evidence suggests that sex and APOE4 interact on risk for Alzheimer's disease and related dementias. Compared to males, females exhibit greater penetrance of the APOE4 allele (Payami et al., 1994), an increased risk of dementia if they carry this genetic variant, and faster cognitive decline (Irvine et al., 2012; Yoon et al., 2016). Compared with noncarrier females or APOE4 carrier males, females with an APOE4 allele have increased lifetime risk for AD (Farrer et al., 1997; Neu et al., 2017), smaller adjusted hippocampal volumes (Fleisher et al., 2005; Hobel et al., 2019;

Koran et al., 2017), more pathologic levels of CSF abeta and tau (Altmann et al., 2014; Damoiseaux et al., 2012), more senile plaques and neurofibrillary tangles postmortem (Corder et al., 2004), and poorer cognition (Fleisher et al., 2005; Hobel et al., 2019). Recent studies also indicate that APOE4 carrier females also have greater tau burden based on CSF and tau PET imaging (Buckley et al., 2018; Buckley et al., 2020), and have steeper rates of cognitive decline (Lin et al., 2015) than females without an APOE4 allele.

Only a limited number of recent studies in older adults have investigated the interactions of sex and APOE4 genotype on cognition and cognitive reserve in older adults. Pa et al. (2022) found that higher physical activity was associated with greater cognitive reserve for speed in older females but not in males (mean age = 76.11 ± 6.31 years), but APOE4 carrier status attenuated these associations in females. Alty et al. (2023) found that cognitive reserve, measured through IQ, moderated the rate of age-related cognitive decline in males but not in females. Only males with higher cognitive reserve experienced a slower decline in cognitive functions compared to those with lower cognitive reserve. No interaction between APOE4 genotype and sex on cognitive trajectories was found (Alty et al., 2023). These limited studies highlight the poorly understood, complex interplay between sex, genetic factors, and lifestyle activities in shaping cognitive reserve.

Crucially, whether sex and APOE4 interact to affect the impact of stimulating activities and occupational attainment on cognition in middle-aged individuals remains uncharted territory. To address this gap, this study investigated the impact of biological sex and APOE4 carrier status on the relationship between stimulating activities, occupational attainment, and cognition, in a large cohort of middle-aged and cognitively healthy individuals (N = 700, 40–59 years). This will enable high precision approaches that consider biological sex and APOE4 carrier status to inform strategies for Alzheimer's disease prevention and clinical trials.

2.2 Methods

2.2.1 Participants

700 participants were recruited in the PREVENT–Dementia program, a multi-site, prospective longitudinal study investigating the origins and early diagnosis of dementia in mid-life at-risk individuals (Ritchie et al., 2024). Cognitive, clinical and lifestyle assessments were carried out in the five study sites: Imperial College London, the University of Edinburgh, the University of Cambridge, the University of Oxford and Trinity College Dublin (See Appendix I; SFigure 7.1). Participants were aged between 40 and 59 years and were cognitively normal at the time of recruitment, as determined during a thorough clinical examination. Exclusion criteria for the study were a diagnosis of MCI or dementia and known MRI contraindications. The recruitment target was 50% with, and 50% without parental dementia family history. More details on the study population can be found in (Ritchie & Ritchie, 2012) and (Ritchie et al., 2013). Individuals with incomplete cognitive (N = 31) or clinical (N = 9) data were excluded (See Appendix I; SFigure 7.1 and STable 7.1). The study reports the wave 1 (baseline) testing data, which were completed at the time of manuscript preparation. Wave 2 and 3 of testing are currently ongoing.

2.2.2 Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the London-Camberwell St Giles National Health Service Ethics Committee (REC reference: 12/LO/1023), by the Trinity College Dublin School of Psychology Research Ethics Committee (SPREC022021–010), and the St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee, all of which operate according to the Helsinki Declaration of 1975 (and as revised in 1983). All participants provided written informed consent.

2.2.3 APOE Genotyping

In brief, genomic DNA was isolated from blood samples and APOE genotyping was performed. All members of the research and clinical teams were blind to the result of APOE genotyping. In this study, APOE4 risk was determined by ≥1 APOE4 allele. 264/700 carried ≥1 APOE4 allele (See Table 1). For further details, see (Ritchie et al., 2017).

2.2.4 Biological Sex

While the dichotomies of sex and gender are no longer considered to be sharply discrete, in this study 'sex' was defined as an individual's natal or biological sex, and was self-reported in the Brain Injury Screening Questionnaire.

2.2.5 Menopausal Status

Self-reported menopausal status was determined from the pregnancy and menstruation survey administered during the clinical assessments, particularly the answer to the question: "Are you postmenopausal?". 'Yes' were categorized as postmenopausal, 'No' as premenopausal. Of the 433 female participants, 149 (34.41%) were postmenopausal, 233 were premenopausal. 51 participants who answered 'don't know' were excluded from further analyses. As this prospective longitudinal study commenced in 2014, it was not designed to include detailed assessments of menopausal status.

2.2.6 Clinical and Lifestyle-bases Assessments

Blood pressure was measured after five minutes of supine rest. Blood samples were collected from overnight fasted participants and immediately analysed for standard biochemistry and haematology measures at local laboratories. Hypertension and hyperlipidemia were analyzed as binary variables. Hypertension was defined as an average diastolic blood pressure ≥ 90

mmHg, systolic blood pressure ≥ 140 mmHg, or a positive history of hypertension as reported during the medical history interview. Hyperlipidemia was defined as total cholesterol > 6.5 mmol/L or a positive history of hyperlipidemia reported in the medical history interview. Body mass index (BMI) was analyzed as a continuous variable, calculated by dividing weight (kg) by height (m^2).

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI score ranges from 0 to 21, whereby higher scores indicate poorer sleep quality. 'Poor' sleep was binarized at a cut-off of PSQI score > 5 (Buysse et al., 1989). Smoking status and alcohol intake were assessed through a lifestyle interview. Participants were first asked if they were nonsmokers/nondrinkers, ex-smokers/ex-drinkers, or current smokers/drinkers. Smoking status was binarized if they were current smokers. Ex-drinkers and current drinkers were asked to estimate the number of glasses of wine, beer, and stronger alcohol consumed per week, and the total number of units per day/week was calculated. 'High' alcohol intake was defined as consuming more than 21 units per week.

2.2.7 Cognitive Reserve Contributors

Lifetime education was measured by the total number of years each participant had engaged in formal schooling, with reported values ranging from 0 – 38 years. The Lifetime of Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007) was used to measure engagement in a broad range of lifestyle activities across three distinct stages of life: young adulthood (13–29 years), mid-life (30–64 years), and late life (65 years onwards), and only the mid-life activities were examined. For each life-stage, the LEQ provides two sub-scores that capture (a) "specific" activities – the primary activity undertaken in that stage, i.e., in mid-life this constitutes occupational attainment – and, (b) "non-specific" activities – engagement in physical, social and intellectual activities, in each stage. The LEQ comprises a standardized scoring approach,

as follows. The mid-life stimulating activities (i.e., 'non-specific score') were assessed by the frequency of engagement in 7 physically, socially and intellectually stimulating activities, scored on a 6-point Likert scale of frequency (never, less than monthly, monthly, fortnightly, weekly, daily). Scores range from 0 – 35, with higher scores reflecting more frequent engagement in such activities. The items included in the scale are socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in physical activity that is mildly, moderately, or vigorously energetic, reading, practicing a second language and travel. The travel item asks participants if they have visited any of a list of continents between the ages of 30–54. Responses were scored on a 6-point scale as follows: none, 1-2 regions, 3-4 regions, 5 regions, 6 regions, 7 regions.

The mid-life occupational attainment (i.e., 'specific score') is comprised of two sub-scores that measure (a) occupational complexity and (b) managerial responsibility. For the first, participants were asked to record their primary occupation in each 5-year interval from age 30 to age at assessment. Each reported occupation was scored on a scale of 0-9, according to the International Standard Classification of Occupations (ISCO 08) guidelines (https://www.ilo.org/public/english/bureau/stat/isco/isco08/) and relating to the skill level associated with occupations, where managers score 1, professionals 2, technicians and associate professionals score 3, and so on. Participant scores were inverted and summed. The second sub-score measured the managerial responsibility associated with reported occupations. The managerial complexity score was based on participants' responses to the LEQ question: "Did any of your jobs require you to be in charge of or responsible for other people? If yes, indicate job title, number of years in position, and an estimate of the number of people you were in charge of." Participants were instructed to provide information on up to four occupations where they had managerial responsibilities. If participants indicated that they were employed in a managerial capacity, the number of people that they oversaw in four of their reported

occupations was documented. Managerial responsibility was scored as follows: 0 people = 8, 1-5 people = 16, 5-10 people = 24 and 10+ people = 32. The highest score across occupations was recorded as the managerial responsibility sub-score, thus capturing the maximum level of leadership responsibility achieved during the participant's mid-life career. Occupational attainment was derived by summing the occupational complexity and managerial sub-scores and multiplying them by a normalization factor of 0.25, to ensure that mid-life specific and non-specific scores have comparable mean values (Valenzuela & Sachdev, 2007).

2.2.8 Cognitive Assessments

Cognitive function was assessed with the Cognito neuropsychological battery (Ritchie et al., 2014), and the Visual Short-Term Memory Binding task (VSTMBT) (Parra et al., 2010), yielding 13 summary variables. The Cognito battery examines information processing across a wide range of cognitive functions in adults of all ages and is not restricted to those functions usually implicated in dementia detection in the elderly. It tests several aspects of cognition, including attention (task: visual attention), memory (tasks: narrative recall, description recall, implicit memory, name-face association, working memory), language (tasks: phoneme comprehension, verbal fluency) and visuospatial abilities (task: geometric figure recognition) (K. Ritchie et al., 2018; Ritchie et al., 2014). 11 summary variables from the Cognito battery capturing the above functions (K. Ritchie et al., 2018; Ritchie et al., 2014) were used [see Appendix I, Supplementary Methods]. The VSTMBT (Parra et al., 2010) is a computer-based task that assesses visual short-term memory binding of single features, e.g., complex shape or colour combinations, or feature conjunctions, e.g., shape and colour combinations. The two summary variables used from the VSTMBT were the percentage of correctly recognized items from the two conditions (see Appendix I).

2.2.9 Cognitive Analyses

Based on our previously published method (Deng et al., 2024), rotated principal component analysis clustered the above-mentioned multiple cognitive measures (13 summary variables) into related cognitive domains (see Appendix I). Parallel analysis and plotted scree plots determined the number of components that best represented the original 13 cognitive measures. The eigenvalues of the first three components were larger than 95th percentile of the randomly generated eigenvalues (See Appendix I; SFigure 7.2A), thus showing that the three components (C) solution best represented the data. The three components were then rotated to be uncorrelated with each other and could cumulatively explain a total of 40% percentage of the variance (C1 = 16%, C2 = 12%, C3 = 11%) (SFigure 7.2B).

2.2.10 Statistical Approach

The statistical analyses were conducted with the Statistical Package for Social Sciences (SPSS V.27) and R software (https://www.R-project.org/). Outlier assessment was summarized in the Appendix I (SFigure 7.3). The normality of the data was assessed by combining the visualization of a quantile-quantile plot and the Shapiro–Wilk test. Demographic and clinical information of the study cohort were analysed across sexes using chi-square (χ^2 tests) for categorical variables (Race, hypertension, hyperlipidemia, poor sleep, current smoker, high alcohol intake, APOE4), and Mann-Whitney U tests or independent samples t-tests for continuous variables (*Mann-Whitney U test*: age, BMI, years of education, stimulating activities, occupational attainment, and short-term memory binding; *independent samples t-test*: episodic and relational memory, and multisensory processing), depending on whether they met the assumption of normality in this cohort. Multicollinearity assessment for the three reserve contributors showed no significant collinearity (Appendix I, STable 7.4).

Independent hierarchical regression models investigated the effects of reserve contributors (education, stimulating activities, and occupational attainment) on each cognitive domain and the moderating role of sex and APOE4. First the models examined the main effects of reserve contributors and sex on cognitive domains, then the 2-way interaction term of contributor × sex was added to examine the moderation effect of sex, with age and the other two contributors included as covariates. For any observed significant 2-way interactions, the moderating role of APOE4 was tested with 3-way interactions of APOE4 × sex × reserve contributor on cognition, with age and the other two contributors included as covariates. The effect of lifetime education was controlled for when considering the impact of stimulating activities and occupational attainment on cognition. The number of participants in each cell of the sex × APOE4 factorial design is reported in Appendix I, STable 7.5. Further analyses controlling, in addition to age, for other potential confounds (i.e., BMI, race, hypertension, hyperlipidemia, sleep, alcohol, smoking status) corroborated the results (see Appendix I; STables 7.6-7.8). Simple slope analyses tested the significance of the slopes of the regression lines for any significant interactions. The Bonferroni correction was used to correct for multiple comparisons in the analyses of main effects of reserve contributors and sex on cognition. We followed up significant main effects that were in line with previous literature by performing one three-way interaction model, between sex × occupational attainment × APOE4, that directly investigated the study question.

2.3 Results

2.3.1 Demographics

Demographic variables, cognition, and reserve contributors scores of the cohort are summarized in Table 2.1. Females and males did not differ significantly in APOE4 carrier status, years of education, stimulating activities, and 2/3 cognitive domains. Females were slightly younger than males (on average by 1 year), and had significantly lower occupational attainment, and significantly higher episodic and relational memory. Females and males also differed significantly in BMI, hypertension and alcohol intake.

Table 2.1 Participant characteristics

Participant characteristics	All	Females	Males	*p* value	Effect size
N	660	408	252	–	–
Age (y)	52.0 (9.0)	52.0 (8.0)	53.0 (10.0)	0.03	0.08
Race (% Caucasian)	95.9%	95.8%	96.0%	0.99	<0.001
BMI	27.0 (6.5) (n=659)	26.3 (7.2) (n=407)	27.8 (4.7) (n=252)	<0.001	0.15
Hypertension (%)	17.1%	11.3%	26.6%	<0.001	0.19
Hyperlipidemia (%)	23.4% (n=644)	21.3% (n=395)	26.9% (n=249)	0.12	0.06
Poor sleep (%)	51.8% (n=657)	52.6% (n=407)	50.4% (n=250)	0.64	0.02
Current smoker (%)	5.8% (n=657)	4.7% (n=405)	7.5% (n=252)	0.18	0.05
High alcohol intake (%)	17.4% (n=655)	12.1% (n=405)	26.0% (n=250)	<0.001	0.17
APOE4 (% Carriers)	38.2%	38.0%	38.5%	0.96	0.002
Years of education	17.0 (5.0)	17.0 (5.0)	17.0 (3.0)	0.18	0.05
Stimulating activities	18.0 (5.0)	18.0 (5.0)	18.0 (4.0)	0.19	0.05
Occupational attainment	13.8 (6.3)	12.6 (7.1)	15.0 (6.3)	<0.001	0.21
Episodic and relational memory	0.001 (1.0)	0.17 (1.0)	-0.28 (1.0)	<0.001	0.47
Multisensory processing	-4e-5 (1.0)	0.01 (1.0)	-0.02 (1.1)	0.70	0.03
Short-term memory binding	0.12 (1.1)	0.09 (1.1)	0.15 (1.0)	0.39	0.03

NOTE: median (interquartile range, IQR) was reported for non-normal distributed continuous variables. Mean (SD) was reported for normal distributed continuous variables. Effect size was determined using *r* for Mann-Whitney U test, Cohen's *d* for independent samples t-test and φ for the Chi-Square test. Abbreviations: APOE4, Apolipoprotein E4 genotype; BMI, body mass index.

2.3.2 Cognitive Performance

A unique set of cognitive measures from the initial 13 (with high coefficients; criterion threshold > 0.4) was closely related to each cognitive component (C1–C3). The mapping of cognitive functions invoked by the highest loading measures (Figure 2.1), determined the cognitive functions in each domain. The four measures that loaded strongly on C1 reflected memory recall with a strong episodic element (3/4: descriptive recall, narrative recall, name-face association [recall of relations]) in different modalities (i.e., verbal, visuo- spatial); thus, this domain was labelled 'episodic and relational memory.' The four measures that loaded strongly on C2 reflected processing of visual, auditory/linguistic and multisensory integration of audio-visual information; thus, this domain was labelled 'multisensory processing.' The two measures that loaded strongly on C3 reflected the visual short term memory binding task (VSTMBT), which involved recalling of single features (shape) or feature binding (shape and colour); thus, this domain was labelled 'short-term memory binding' (Figure 2.1). The cognitive loading of the first component, labelled the episodic and relational memory domain, replicated a previous finding (with an independent pilot sub-group, N = 210) of the PREVENT–Dementia cohort (Deng et al., 2024), demonstrating that the analysis is robust in capturing the most varying cognitive functions for this mid-life cohort.

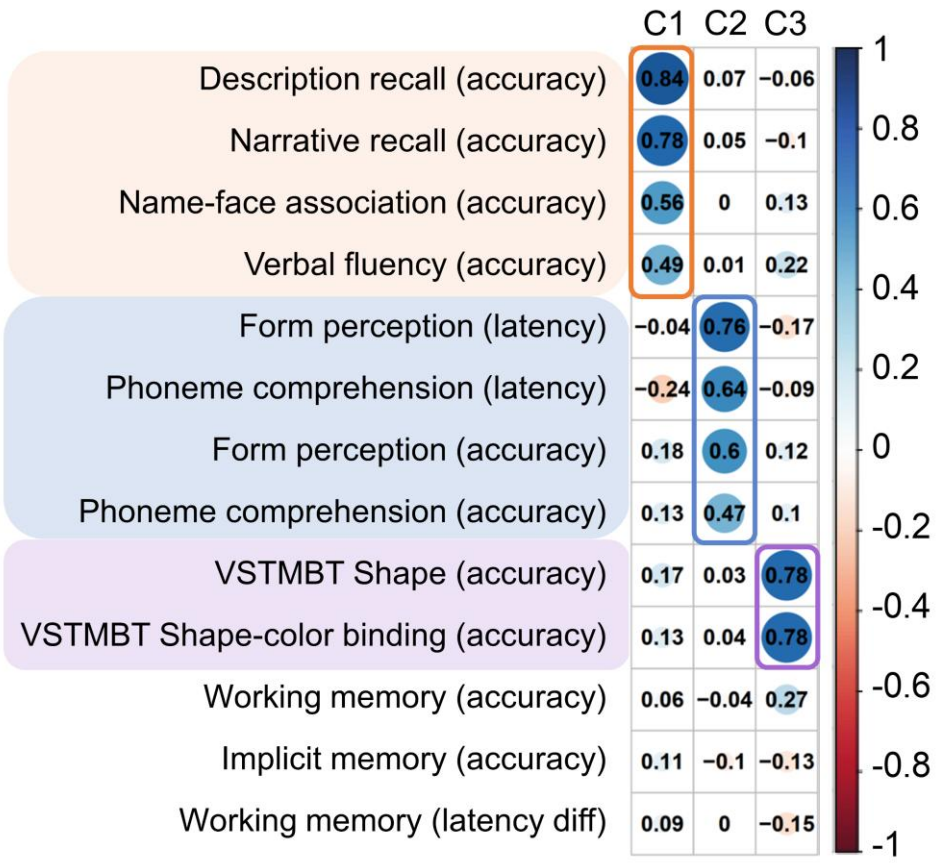

Figure 2.1 Cognitive data reduction. *The figure shows the loadings of each cognitive measure (in rows) on each cognitive component (in columns). A larger absolute coefficient (darker colors and larger solid circles) represents a closer relationship between the cognitive measure and the corresponding component. Cognitive measures with a coefficient > 0.4 on each component were used to interpret the cognitive functions contributing to each component. Cool/warm colors represent the positive/negative relationships between cognitive measures and components, as shown in the color-bar scale. The color-bar indicates loading values, and higher loading values indicate stronger contribution to corresponding components. Abbreviations: C, component; VSTMBT, visual short-term memory binding task; diff, difference. C1: Episodic and relational memory; C2: Multisensory processing; C3: Short-term memory binding.*

2.3.3 Sex Differences in Cognition and Reserve Contributors

Females had better episodic and relational memory compared to males ($p = 8.82\times10^{-9}$, Cohen's $d = 0.47$) (Figure 2.2A). Females had significantly lower occupational attainment than males ($p = 1.33\times10^{-7}$, Cohen's $r = 0.21$) (Figure 2.2B).

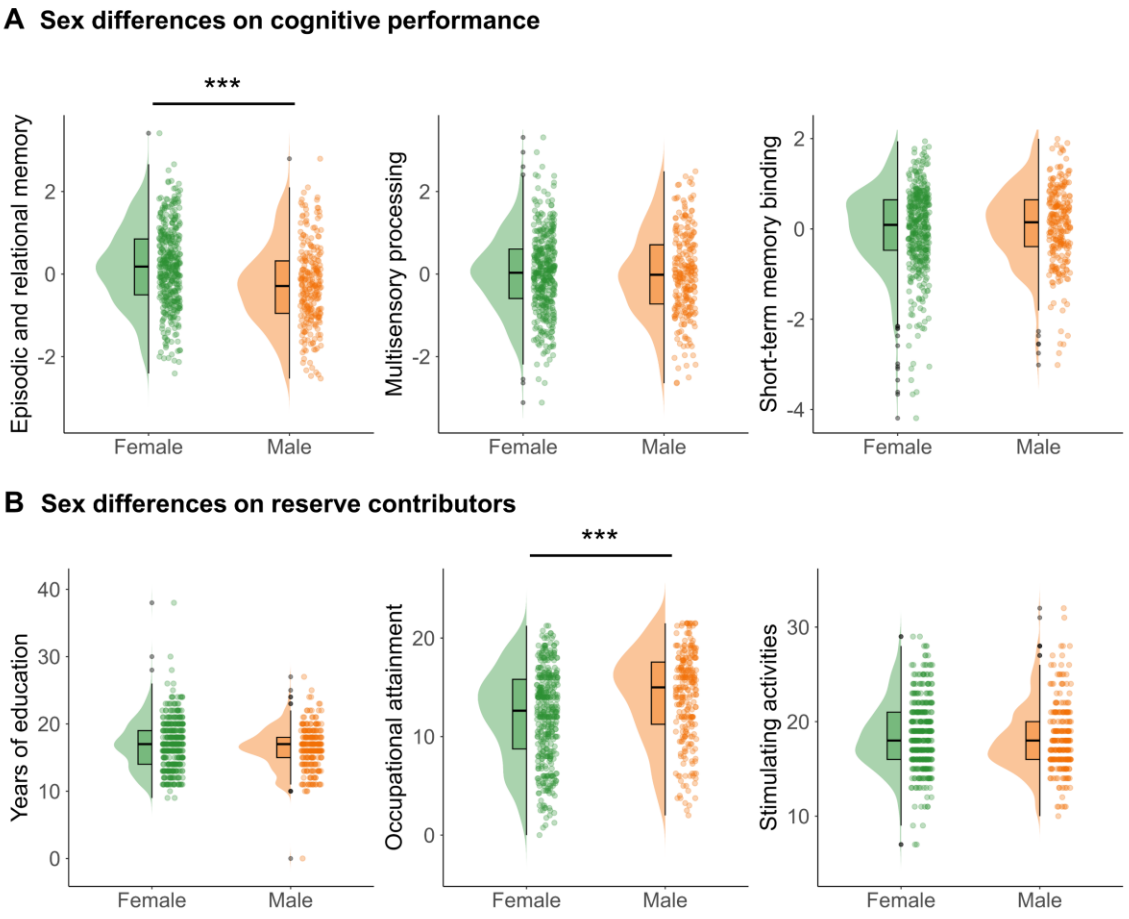

Figure 2.2 Sex differences on cognition and reserve contributors. *(A) Sex differences on cognitive domains. (B) Sex differences on reserve contributors. Females had significantly better episodic and relational memory than males. Females have significantly lower occupational attainment than males. The violin plots show the data distribution. The line that divides the box into two parts represents the median value. The ends of the box represent the upper (Q3) and lower (Q1) quartiles of the data. The extreme lines of the boxplot show Q3 + 1.5 × interquartile*

*to Q1 – 1.5 × interquartile range. The black dots beyond the extreme lines show potential outliers. *** = $p < 0.0005$.*

2.3.4 Reserve Contributors and Cognition in Mid-life

Education was significantly positively associated with episodic and relational memory (β (SE) = 0.05 (0.01), 95% Confidence Interval [CI] 0.03–0.07, $p = 5.64\times10^{-5}$; corrected for multiple comparisons), independently of stimulating activities, occupational attainment, sex, and age (Table 2.2). No sex × education interaction was observed. No association with education was observed for the other two cognitive domains.

Stimulating activities were significantly positively associated with episodic and relational memory (β (SE) = 0.05 (0.01), CI 0.03–0.07, $p = 4.68\times10^{-6}$; corrected for multiple comparisons) (Table 2.2, Figure 2.3A), independently of education, occupational attainment, sex, and age (Table 2.2). No sex × stimulating activities interaction was observed. No association with stimulating activities was observed for the other two cognitive domains (Figure 2.3A).

Occupational attainment was not significantly associated with cognition for the whole cohort (Figure 2.3B) in any of the three cognitive domains.

Table 2.2 Regression coefficients for the main effects of reserve contributors on episodic and relational memory

	Model summary	R^2	F	*p* value
		0.14	20.53	<0.001

DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Episodic and relational memory	Years of education	0.05 (0.01)	[0.03, 0.07]	<0.001
	Stimulating activities	0.05 (0.01)	[0.03, 0.07]	<0.001
	Occupational attainment	0.003 (0.01)	[-0.01, 0.02]	0.71
	Sex	0.41 (0.08)	[0.26, 0.56]	<0.001
	Age	-0.02 (0.01)	[-0.03, -0.01]	0.008

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals.

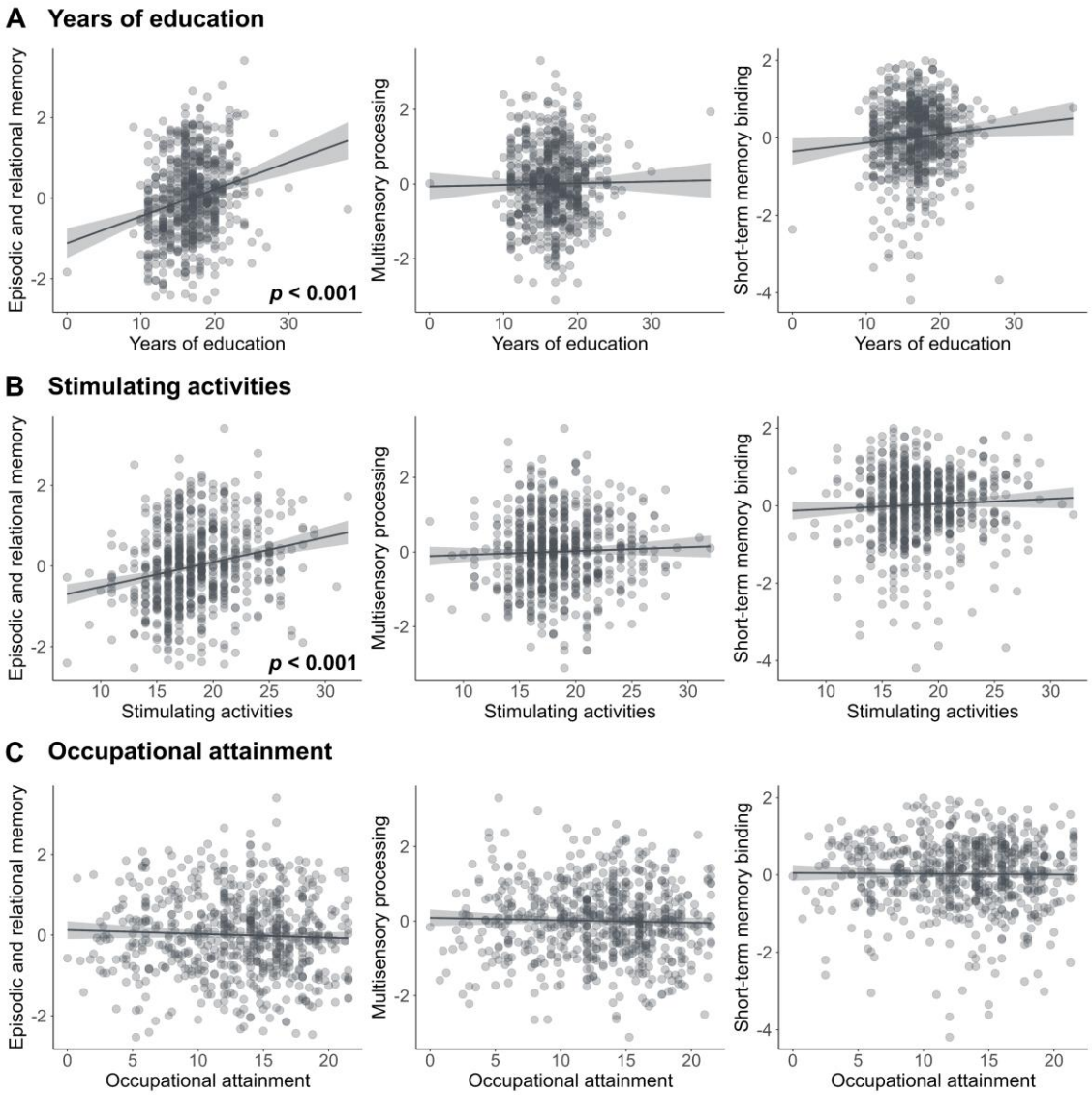

Figure 2.3 Association of reserve contributors with cognition. *(A) The effects of education, (B) stimulating activities, and (C) occupational attainment on each of the three cognitive domains are shown. Higher education was significantly associated with better episodic and relational memory. Higher engagement in stimulating activities was significantly associated with better episodic and relational memory. The effect of each reserve contributor was estimated after controlling confounding variables, as well as the other two contributors. On the x axis, higher scores represent greater education/stimulating activities/occupational attainment, and on the y axis, higher scores represent better cognition.*

2.3.5 Sex Differences in the Association Between Occupational Attainment and Cognition in APOE4 Carriers

Based on significant differences observed between females and males in episodic and relational memory (Table 2.2, Figure 2.2A), and in occupational attainment (Figure 2.2B), the impact of sex on the association between this cognitive ability and occupational attainment was investigated. A trend interaction sex × occupational attainment was found (β (SE) = 0.14 (0.08), CI -0.007–0.29, p = 0.06) (Table 2.3 – Model A, Figure 2.4A). There was a significant three-way interaction APOE4 × sex × occupational attainment (β (SE) = 0.33 (0.16), CI 0.02–0.64, p = 0.037; Table 2.3 – Model B), which can be explained by the presence of a significant interaction sex × occupational attainment only for APOE4 carriers (β (SE) = 0.38 (0.13), CI 0.12–0.63, p = 0.003; Figure 2.4B–C). Simple slope analyses for APOE4 carrier showed a trend positive relationship for females (β (SE) = 0.16 (0.08), CI -0.002–0.32, p = 0.053), and a significantly negative association (β (SE) = -0.20 (0.10), CI -0.40–-0.001, p = 0.049) for males (Figure 2.4B), between occupational attainment and episodic and relational memory. As the cohort's age group covers the menopause transition, a post-hoc analysis was conducted to investigate whether menopause impacted the association between occupational attainment and cognition in females. No effect of menopause was found (See Appendix I; STable 7.3).

Table 2.3 Regression coefficients for models including 2-way or 3-way interactions of IVs on episodic and relational memory

Model A: 2-way interaction

Model summary	R^2	F	*p* value
	0.14	17.76	<0.001

DV	IV	β (SE)	95% CI	*p* value
Episodic and relational memory	Occupational attainment	-0.08 (0.06)	[-0.20, 0.05]	0.23
	Sex	0.40 (0.08)	[0.25, 0.55]	<0.001
	Years of education	0.05 (0.01)	[0.03, 0.07]	<0.001
	Stimulating activities	0.05 (0.01)	[0.03, 0.07]	<0.001
	Age	-0.02 (0.01)	[-0.03, -0.004]	0.01
	Sex*Occupational attainment	0.14 (0.08)	[-0.007, 0.29]	0.06

Model B: 3-way interaction

Model summary	R^2	F	*p* value
	0.15	11.75	<0.001

DV	IV	β (SE)	95% CI	*p* value
Episodic and relational memory	APOE4	0.03 (0.12)	[-0.22, 0.27]	0.83
	Sex	0.31 (0.10)	[0.12, 0.51]	0.001
	Occupational attainment	-0.01 (0.08)	[-0.17, 0.14]	0.87
	APOE4*Sex	0.22 (0.16)	[-0.08, 0.53]	0.16
	APOE4*Occupational attainment	-0.19 (0.12)	[-0.43, 0.06]	0.13
	Sex*Occupational attainment	0.03 (0.09)	[-0.16, 0.21]	0.78
	APOE4*Sex*Occupational attainment	0.33 (0.16)	[0.02, 0.64]	0.037
	Years of education	0.05 (0.01)	[0.02, 0.07]	<0.001
	Stimulating activities	0.05 (0.01)	[0.03, 0.07]	<0.001
	Age	-0.02 (0.01)	[-0.03, -0.002]	0.03

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals.

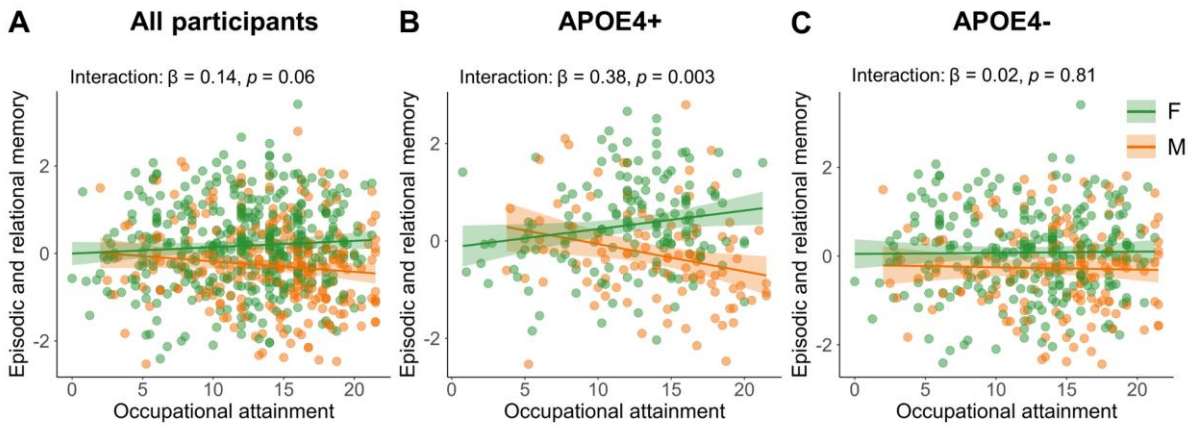

Figure 2.4 Sex differences in the associations between occupational attainment, cognition and APOE4 genotype in mid-life. *(A) A trend effect interaction is shown between sex and occupational attainment on episodic and relational memory. (B) A significant interaction is shown between sex and occupational attainment on episodic and relational memory in APOE4 carriers. (C) APOE4 non-carriers showed no significant interactions between sex and occupational attainment. On the x axis, higher scores represent greater occupational attainment, and on the y axis, higher scores represent better episodic and relational memory.*

2.4 Discussion

This study investigated the impact of sex and APOE4 carrier status on the relationship between mid-life stimulating activities, occupational attainment, and cognition, in a cohort of individuals (N = 700), who were presently cognitively healthy, but carried genetic risk for late-life AD. We leveraged the PREVENT–Dementia program (Ritchie & Ritchie, 2012), one of the world's largest studies investigating the origins and early diagnosis of dementia in mid-life at-risk individuals. After controlling for the effect of education, we found that individuals with higher engagement in physically, socially and intellectually stimulating activities showed better episodic and relational memory, regardless of biological sex and APOE4 status. Significant sex differences in APOE4 carriers were found in the association between occupational attainment and cognition. APOE4 carrier females with higher occupational attainment showed better cognition, whereas APOE4 carrier males with higher occupational attainment showed worse cognition. These findings suggest that cognitive reserve contributors that are modifiable in mid-life boost cognition in middle-age, with sex and APOE4 status significantly affecting this relationship. They highlight the urgent need for high precision approaches that consider biological sex and APOE4 carrier status to inform Alzheimer's disease prevention strategies and clinical trials.

Higher engagement in physically, socially and intellectually stimulating activities in mid-life was associated with stronger cognition in a composite domain capturing episodic and relational memory, independently of sex, age, years of education and occupational attainment. This result replicates a previous finding (Heneghan et al., 2023) with a pilot sub-group (N = 210) of the PREVENT–Dementia cohort. These activities comprised socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in energetic physical activities, reading, practicing a second language and travel, suggesting that cognition in mid-

life can benefit from the combination of a wide variety of stimulating activities. Effects were seen only in the domain of episodic and relational memory, two of the earliest cognitive functions that show changes in pre-symptomatic AD (Grober et al., 2008; Laukka et al., 2012; Small et al., 2003). Impairment of episodic memory is the hallmark of AD in the majority of cases (Welsh et al., 1992), and studies have found it to be strongly associated with conversion from MCI to AD (Albert et al., 2018), in older adults. Similarly, relational memory tasks, especially with a semantic memory aspect, have been used to differentiate between MCI and healthy aging (Ahmed et al., 2008), again in older adults. To the best of our knowledge, effects of stimulating activities on episodic and relational memory (or multisensory processing and short-term memory as tested here) have not previously been reported in mid-life individuals. We caution that the interpretability of the effect of lifestyle activities on each individual cognitive function is limited by their composite assessment in this study and requires individuation in future studies. Furthermore, the stimulating activities reported here are a composite score of seven discrete items. Conversely, the aggregate consideration of cognitive domains and avocational lifestyle activities may increase the power to detect early and subtle cognitive changes due to lifestyle in at-risk mid-life individuals, an estimated 23 years from dementia onset (Dounavi et al., 2022). Importantly, our results extend previous literature in older adults and suggest that, well before a potential dementia diagnosis, modifiable avocational activities can strengthen cognitive functions that are vulnerable to early dementia neuropathology, and, thus, are promising cost-effective interventions for building cognitive reserve from mid-life.

The key question in this study, however, was to investigate the impact of sex and APOE4 carrier status on the association between reserve contributors and cognition in mid-life. To the best of our knowledge this is the first study to report a sex-specific effect of occupational attainment on cognitive ability, in individuals who are presently cognitively healthy but carry the genetic

risk (APOE4) for late-life AD. Why do APOE4 carrier females with higher occupational attainment in mid-life show stronger cognitive ability? While the precise mechanism is unclear, multidimensional vulnerability influences to AD in middle-aged APOE4 carrier females likely render them more responsive to protective lifestyle activities. First, in mid-life, multi-system vulnerabilities set in motion by the menopausal transition (Udeh-Momoh et al., 2021), can lead to metabolic deficiencies and ultimately cognitive decline (Brinton et al., 2015), thus exposing middle-aged females to higher risk for AD. Second, historically, females have accrued higher vulnerability to neurodegeneration, relative to males, through barriers to key reserve contributors, such as educational and occupational opportunities, leading to lower cognitive reserve (Russ et al., 2013). Third, these female-specific vulnerabilities may be further exacerbated (Barha & Liu-Ambrose, 2018) by interactions with genetic risk for late-onset AD (Corder et al., 1993). A recent review study in older adults [age > 65 years] found that females benefited from reserve contributors more than males (Subramaniapillai et al., 2021). Our finding advances the state-of-the-art understanding by suggesting that occupational attainment may offset the impact of APOE4 genetic risk in females from mid-life, by boosting cognitive abilities that are both vulnerable to AD risk and early AD neuropathology (Grober et al., 2008; Irish et al., 2011; Laukka et al., 2012).

APOE4 carrier males showed a negative association between occupational attainment and episodic and relational memory. Previous studies in older adults have found that high job strain was associated with worse cognition (Sabbath et al., 2016) and cognitive decline (Pan et al., 2019) in males, but not in females. One potential explanation for these findings may be the substantial sex differences in both the magnitude and the duration of stress response, shaped by male (e.g., testosterone) and female (e.g., estradiol) sex hormones (Herman et al., 2016). In light of the observed males' significantly higher occupational attainment, our results further suggest that APOE4 carriership in males may be associated with a domain-general cognitive

resource limitation, leading to a dose effect on the relationship between occupational attainment and episodic and relational memory. The significantly weaker episodic and relational memory relative to females, observed in the male cohort, suggests a cognitive vulnerability in this domain, which may explain why episodic and relational memory decreases with stronger engagement of domain-general cognitive resources in high strain occupational duties.

The above interpretations relating to biological (sex hormones, menopausal transition, AD biomarkers) variables are plausible but as-of-yet untested, given that these data were not directly measured in this study. Thus, future studies are needed to understand the underlying mechanisms associated with divergent effects of lifestyle factors in middle-aged females versus males with inherited dementia risk.

Methodological Considerations

The lifestyle activity scores were obtained from self-report answers to the LEQ (Valenzuela & Sachdev, 2007), which is an internationally validated and widely used instrument, but may, nevertheless, include some level of recall bias in reporting. The scoring of occupational complexity is affected by length of work history. This limitation was mitigated by controlling for age in statistical analyses. The data presented is from PREVENT–Dementia, an ongoing longitudinal program commenced in 2014, that did not include detailed assessment of menopause status. Detailed and objective measurements, including hormonal assays are necessary to investigate in future studies the interactions between menopause status and dementia risk factors in middle-aged females. The possibility that higher education may determine high avocational activities, occupational attainment, and cognition has been considered but is not likely. We found that the effect of lifestyle activities on cognitive ability was independent of the total years of education, which shows that education does not directly

drive this effect. Furthermore, mid-life occupational attainment was associated with improved cognitive performance only in APOE4 carrier females, who were not more educated than APOE4 non-carrier females, or males. We caution that the interpretability of the effect of lifestyle activities on each individual cognitive function is limited by their composite assessment in this study and requires individuation in future studies. The study population are mainly (95%) of white Caucasian ethnicity, not dissimilar to the historic ethnic mix of older people in the UK and Ireland, which limits generalizability of findings beyond individuals of European ancestry. Finally, the observational cross-sectional data (from the baseline visit) presented in this study limit conclusions on causality. Future studies from the ongoing testing waves two and three (2 and 8 years post baseline respectively) of this multi-site study will determine the longitudinal impact of modifiable lifestyle activities in middle-aged individuals at risk for late life dementia.

2.5 Conclusion

The majority of previous studies have focused on the effect of reserve contributors on cognition or AD pathology in late life (Clare et al., 2017; Xu et al., 2019; Zijlmans et al., 2022). One recent study, including individuals aged from 50–80 years, showed sex-specific effects of IQ, as a proxy of cognitive reserve, on age-related cognitive decline (Alty et al., 2023). The current study makes a novel contribution by showing interactions between sex, APOE4 and reserve contributors on cognition in mid-life. We show a positive effect of stimulating activities on cognition in middle-aged individuals regardless of sex and inherited risk, and of occupational attainment in individuals with inherited risk for late-life AD, while controlling for educational differences. Our findings demonstrate that occupational attainment in mid-life contributes to cognitive reserve against inherited risk of dementia in females, but not males, at risk for late-

life AD. They suggest that sex and APOE4 carrier status are important variables to consider for building high precision dementia prevention strategies and clinical trials.

3. Chapter 3: Sex differences in the associations between education and lifestyle activities on cognition and brain structure in mid-life

3.1 Introduction

In Chapter 2, I demonstrated that more engagement in physically, socially, and intellectually stimulating activities was positively associated with better cognition in mid-life. Additionally, occupational attainment appeared protective against inherited dementia risk, but notably, this benefit was observed exclusively in females. These sex-specific effects, aligning with recent studies on older adults (Alty et al., 2023; Pa et al., 2022), highlight that reserve-building factors might operate differently in males and females in mid-life. Importantly, these studies commonly adjusted for educational attainment, yet little is known about how education might itself affect these sex-specific effects of lifestyle on cognition and brain health.

Education is widely recognized as a critical contributor to cognitive reserve (Stern, 2012; Stern et al., 2020), which has previously been shown to protect against both age-related and dementia-related cognitive decline (Chapko et al., 2018; Zeki Al Hazzouri et al., 2011), independent of neuropathological burden (Bennett et al., 2003; Brayne et al., 2010; Suemoto et al., 2022). Although education is generally non-modifiable by mid-life, its impact on cognition begins in early childhood and persist throughout the lifespan (Lam et al., 2024; Lovden et al., 2020). Lower educational attainment at early life confers substantially greater dementia risk decades later, increasing incidence by approximately 5-8% (Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017). Beyond direct cognitive and dementia risk implications, education strongly predicts individuals' future occupational opportunities and income levels (Lahelma et al., 2004; Torssander & Erikson, 2010), so education frequently serves as a proxy

for socioeconomic status (SES) (Darin-Mattsson et al., 2017; Rodriguez Roca et al., 2023), another domain consistently linked to dementia risk (Fratiglioni et al., 2020; Livingston et al., 2017; Moceri et al., 2001; Yaffe et al., 2013) and cognitive reserve (Fotenos et al., 2008; Jefferson et al., 2011; Krueger et al., 2025; Nunes & Silva Nunes, 2021; Stern, 2009).

Despite extensive literature investigating sex and education independently (Bolton et al., 2024; Deckers et al., 2019; Lipnicki et al., 2017; Mezzaca et al., 2022; Palpatzis et al., 2025), relatively few studies have directly assessed their interactions on dementia risk, cognitive decline, and neuropathological burden. Early longitudinal studies reported that education equally reduced dementia risk in males and females (Letenneur et al., 1999). However, pooled analyses of over 28,000 participants across European cohorts revealed that higher education reduced dementia risk in females but not in males (Launer et al., 1999; Letenneur et al., 2000). In cognitively healthy older adults, Bloomberg et al. (2021) found no sex differences in memory decline across educational levels, but observed that highly educated females experienced a slower verbal fluency decline than equally educated males, a pattern absent among those with lower educational levels. Conversely, Iwata et al. (2018) showed that highly educated males exhibited significantly slower cognitive decline compared to less educated males, while this protective effect of education was not observed in females. In MCI and AD patients, Oliveira et al. (2016) found that education slowed cognitive decline specifically among females and APOE4 carriers diagnosed with AD. This contrasts with Pradier et al. (2014), who found that education provided greater cognitive benefits in males than in females with AD. Moreover, lower educational attainment disproportionately increased vulnerability to amyloid-β in females compared to males, specifically impairing executive function in MCI group (Koran et al., 2017). These studies highlight the poorly understood, complex interplay between sex and education on cognition and the brain. To date, however, whether sex and education interact with cognitive

reserve contributors to affect cognition and brain structure in middle-aged individuals remains unexplored.

Given the importance of early intervention, studies in preclinical AD populations have used risk stratification approaches to investigate early changes in cognition and the brain, including APOE4 genotype (Donix et al., 2012; Lambert et al., 2013). Among dementia risk scores that incorporate lifestyle risk factors (Barnes et al., 2014; Deckers et al., 2015; Kivipelto et al., 2006), the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) score which was developed based on middle-aged individuals is tailored specifically for mid-life (Kivipelto et al., 2006) and has been validated in a large US population followed longitudinally over 40 years (Exalto et al., 2014). Studies of PREVENT and other similar cohorts have revealed the two risk factors – APOE4 genotype and CAIDE score – significantly impact cognition (Deng et al., 2024; K. Ritchie et al., 2018; Ritchie et al., 2017) and brain structure (Dounavi et al., 2022; Gourley et al., 2020) in mid-life. For example, APOE4 carriers showed poorer attention (Zimmermann et al., 2019), episodic memory (Eich et al., 2019), and visual memory performances (Lim et al., 2021) in mid-life. Higher CAIDE scores in mid-life have been associated with worse verbal, visuospatial, and short-term memory functions (Deng et al., 2024) and spatial abilities (K. Ritchie et al., 2018) in cognitively healthy mid-life participants. Elevated CAIDE scores were related to greater brain atrophy (O'Brien et al., 2020), widespread cortical thinning (Dounavi et al., 2022), higher white matter hyperintensity burden (Low et al., 2022b), and greater severity of small vessel disease (Low et al., 2022a). It remains unknown however whether these risk factors would influence the associations between sex, education and lifestyle activities on cognition and brain structure from as early as mid-life.

To address this gap, this chapter investigated 1) the interactions of biological sex and educational level on the relationship between stimulating activities, occupational attainment,

cognition, and brain structure, 2) the effects of risk factors on these associations in a large cohort of middle-aged and cognitively healthy individuals (N = 700, 40–59 years). Understanding these interactions holds substantial promise for informing sex-specific, educationally tailored strategies aimed at enhancing cognitive reserve and mitigating dementia risk.

3.2 Methods

3.2.1 Participants

The same mid-life cohort investigated in the previous chapters was included in this study (N = 700). For a detailed description of the cohort, please refer to Chapter 2, Section 2.2.1. In total, 700 participants (267 male; 433 female) took part in cognitive and clinical assessments. For the regression analyses on cognition, individuals with incomplete cognitive data (N = 31) and missing data in educational level (N = 3) were excluded, resulting in a final cognitive analysis cohort of 666 participants. For the regression analyses on the brain, out of the initial 700 participants, 663 completed MRI scanning. Exclusions due to incidental findings (N = 18), incomplete demographics (N = 8) reduced the MRI analysis cohort to 637 participants (See Appendix II; SFigure 8.1). The study reports the wave 1 (baseline) testing data, which were completed at the time of thesis preparation. Wave 2 and 3 of testing are currently ongoing.

3.2.2 Biological sex

While the dichotomies of sex and gender are no longer considered to be sharply discrete, in this study 'sex' was defined as an individual's natal or biological sex and was self-reported in the Brain Injury Screening Questionnaire.

3.2.3 Educational level

Educational level was measured based on the self-reported highest levels of education completed by the participant. Given that participants in the PREVENT cohort are generally well-educated, nearly all had completed high school/secondary education, except for one individual who reported no education. Each participant's educational level was recoded into three categories: low (no education, primary school, high school, or trade/technical/non-university education), medium (college or university) and high (postgraduate education).

3.2.4 Risk factors

APOE Genotyping

In brief, genomic DNA was isolated from blood samples and APOE genotyping was performed. All members of the research and clinical teams were blind to the result of APOE genotyping. In this study, APOE4 risk was determined by ≥1 APOE4 allele. 264/700 carried ≥1 APOE4 allele. For further details, see Ritchie et al. (2017).

Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score

CAIDE score is a composite measure designed to estimate future dementia risk using mid-life cardiovascular factors (Fayosse et al., 2020; Sindi et al., 2015). This score incorporates age, sex, years of education, APOE4 genotype, physical activity level, BMI, cholesterol, and systolic blood pressure (Kivipelto et al., 2006). Participants self-reported their age, sex, and years of education via questionnaires. Genomic DNA was isolated from blood samples and APOE genotyping was performed. Physical activity was evaluated through the self-reported Lifetime Experience Questionnaire (Valenzuela & Sachdev, 2007), capturing both frequency and intensity of physical activity. BMI was calculated from the height and weight of the participants, cholesterol levels were analyzed from blood samples, and systolic blood pressure was recorded in a supine position as the mean of three separate measurements. Each variable was assigned a specific number of points based on its contribution to dementia risk, resulting in an overall CAIDE score ranging from 0 to 18, with higher scores indicating greater dementia risk.

3.2.5 Measurement of Lifestyle Activities

Details of the measurements for lifestyle activities (LEQ instrument) can be found in Chapter 2 (Section 2.2.7).

3.2.6 Cognitive Assessments

Full descriptions of the cognitive assessments used in this study can be found in Chapter 2 (Sections 2.2.8 & 2.3.2). Briefly, rotated principal component analysis clustered 13 cognitive measures into three related cognitive components (C): C1, episodic and relational memory; C2, multisensory processing; and C3, short-term memory binding (see Chapter 2, Figure 2.1).

3.2.7 MRI Data Acquisition and Processing

As part of the PREVENT-Dementia MRI protocol, all study sites used 3T Siemens (Siemens Healthcare, Erlangen, Germany) scanners with models varying depending on the scanning site (Verio, PRISMA, Prisma Fit, Skyra). A 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) (repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, 160 slices, field of view (FOV) = 240 × 256 mm^2, flip angle = 9°, voxel size = 1 mm^3 isotropic) scan were acquired. In an independent study by the PREVENT research team (Dounavi et al., 2022), all scans were corrected for field inhomogeneities using the Advanced Normalisation Toolbox (ANTs) N4 algorithm (Tustison et al., 2010).

Freesurfer version 7.1.0 (https://surfer.nmr.mgh.harvard.edu/) was used for data processing (Fischl, 2012). The recon-all pipeline was run with default settings for each participant. After recon-all, the brain masks and surfaces were inspected, and manual corrections were applied (a) in the form of erosion of non-brain voxels from the brain mask or non-WM voxels from the WM mask, (b) in the form of filling of areas where the brain was not correctly identified, or (c) with the addition of control points in cases where white matter was not successfully identified. Finally, the cortical thickness in 68 regions was quantified based on the Desikan-Killiany atlas (Desikan et al., 2006). The total grey matter volume (TGM) was derived for each participant. Furthermore, the global cortical thickness (CT) was obtained by averaging the values from the bilateral hemispheres for each participant. The ComBat harmonization (Fortin et al., 2018;

Fortin et al., 2017), an empirical Bayesian method, was applied to remove the study site effect, but preserved essential variables, which were age, sex, years of education, family history of dementia, and APOE status. All data were harmonized in a single step after data acquisition was completed. Site-level characteristics were examined to assess whether key assumptions for harmonization were reasonably satisfied (Jodoin et al., 2025) (Appendix II, Supplementary Results).

3.2.8 Statistical Approach

The statistical analyses were conducted with the SPSS V.27 and R software (https://www.R-project.org/). The normality of the data was assessed by combining the visualization of a quantile-quantile plot and the Shapiro–Wilk test. Demographic and clinical information of the study cohort were analysed across sexes using chi-square (χ^2 tests) for categorical variables (educational level, APOE4), and Mann-Whitney U tests or independent samples t-tests for continuous variables (*Mann-Whitney U test*: age, CAIDE, stimulating activities, occupational attainment, and short-term memory binding; *independent samples t-test*: episodic and relational memory, multisensory processing, total grey matter volume, and global cortical thickness), depending on whether they met the assumption of normality in this cohort.

Analysis of covariance (ANCOVA) was used separately to test for education group differences in three cognitive domains, and lifestyle factors (stimulating activities and occupational attainment) while controlling for age and sex. ANCOVA was also used to test for education group differences in two brain structural measures (TGM and global CT) while controlling for age, sex and total intracranial volume (TIV). Bonferroni correction for multiple comparisons was performed in post-hoc tests. Independent multiple regression models investigated the 3-way interaction between education (reference group = low education), lifestyle, and sex on three cognitive domains and two brain structural measures, with age, the other lifestyle factor and

TIV (for brain structural models only) included as covariates. For any observed significant 3-way interactions, subsequent regression models were conducted separately in the male- or female-only group that contributed to the interaction, to examine whether risk factors (APOE4 and CAIDE) further moderated these effects. Each of these models included a 3-way interaction term of education × lifestyle × risk factor and the corresponding covariates. Simple slope analyses tested the significance of the slopes of the regression lines for any significant interactions. The number of participants in each cell of factorial analyses are reported in Appendix II, STable 8.9–8.10.

It should be noted that some assumptions underlying ComBat harmonization may not have been fully met in the present study (Appendix II, Supplementary Results). In particular, variability in sample size across sites, including one site with a relatively small sample (N = 17) (Appendix II, STable 8.11), may have contributed to less stable estimation of covariate effects. This was reflected in the visual inspection of site-specific age and sex effects on structural measures, where the Dublin site (Trinity) showed some deviation from the overall pattern observed in the larger sites (Appendix II, SFigure 8.2). However, as most sites demonstrated consistent age-/sex- related trends, this deviation is more likely to reflect sampling variability rather than a systematic violation of ComBat assumptions. Age distributions showed substantial overlap across sites within the targeted mid-life range (40–60 years), despite minor differences in distribution shape (Appendix II, SFigure 8.3). To assess the robustness of the findings, primary analyses were repeated using non-harmonized data. The main results remained largely consistent, with key associations between sex, stimulating activities, education on global cortical thickness remaining statistically significant (Appendix II, STable 8.12). This supports the robustness of the findings and suggests they are unlikely to be driven solely by the harmonization procedure.

3.3 Results

3.3.1 Demographics

Demographic variables, lifestyle activities, cognitive performance, and brain structural measures of the cohort are summarized in Table 3.1. Females and males did not differ significantly in APOE4 carrier status, stimulating activities, 2/3 cognitive domains, and global cortical thickness. Females were slightly younger than males (on average by 1 year), and had significantly lower CAIDE scores and occupational attainment, and showed significantly higher episodic and relational memory. Females also had significantly lower total grey matter volume and total intracranial volume compared to males, which is consistent with previous findings (Barnes et al., 2010; Long et al., 2024).

Table 3.1 Participant characteristics

Participant characteristics	All	Females	Males	*p* value	Effect size
N	666	414	252	–	–
Age (y)	52.0 (9.0)	52.0 (8.0)	53.0 (10.0)	0.03	0.09
Educational level (%)					
Low	24.3%	24.2%	24.6%		
Medium	44.9%	43.0%	48.0%	0.30	0.06
High	30.8%	32.9%	27.4%		
APOE4 (% Carriers)	37.9% (n=660)	37.8% (n=410)	38.0% (n=250)	0.96	0.002
CAIDE	6.0 (4.0) (n=658)	6.0 (3.0) (n=408)	7.0 (4.0) (n=250)	<0.001	0.24
Stimulating activities	18.0 (5.0)	18.0 (5.0)	18.0 (4.0)	0.26	0.04
Occupational attainment	13.8 (6.3)	12.6 (7.2)	15.0 (6.4)	<0.001	0.20
Episodic and relational memory	0.002 (1.0)	0.17 (1.0)	-0.27 (1.0)	<0.001	0.45
Multisensory processing	0.002 (1.0)	0.01 (1.0)	-0.01(1.1)	0.81	0.02
Short-term memory binding	0.12 (1.1)	0.08 (1.1)	0.16 (1.0)	0.35	0.05
Total grey matter volume (cm^3)	645.6 (55.4) (n=637)	618.9 (40.8) (n=395)	689.2 (47.9) (n=242)	<0.001	1.61
Global cortical thickness (mm)	2.43 (0.06) (n=637)	2.43 (0.06) (n=395)	2.43 (0.07) (n=242)	0.89	0.01
Total intracranial volume (cm^3)	1485.4 (158.2) (n=637)	1417.3 (131.2) (n=395)	1596.6 (133.9) (n=242)	<0.001	1.36

NOTE: median (interquartile range, IQR) was reported for non-normal distributed continuous variables. Mean (SD) was reported for normal distributed continuous variables. Effect size was determined using *r* for Mann-Whitney U test, Cohen's *d* for independent samples t-test and φ for the Chi-Square test. Abbreviations: APOE4, Apolipoprotein E4 genotype; CAIDE, Cardiovascular Risk Factors, Aging and Dementia.

3.3.2 Sex Differences in the Associations Between Education, Stimulating Activities, Risk Factors and Cognition

One-way ANCOVAs were conducted separately for each of the three cognitive domains across low-, medium-, and high-education groups, with age and sex as covariates. There was a significant main effect of education on episodic and relational memory ($F(2, 661) = 14.89$, $p < 0.001$, partial eta squared = 0.04). Post-hoc comparisons using Bonferroni test indicated that both medium-education ($p < 0.001$) and high-education groups ($p < 0.001$) had better episodic and relational memory compared to low-education group (Figure 3.1A). No significant differences in multisensory processing or short-term memory binding were found among three education groups (Figure 3.1B–C).

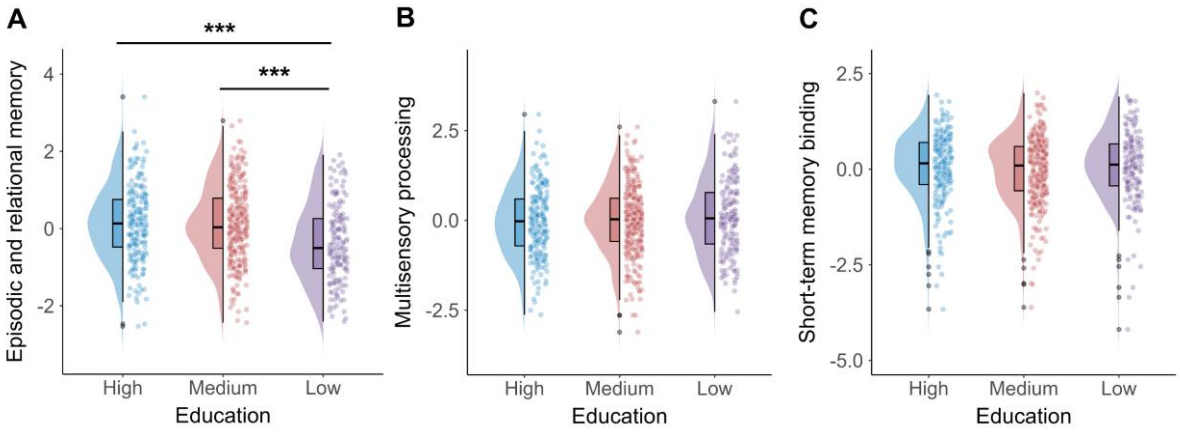

Figure 3.1 Group differences in cognitive performances across education levels. *(A) Episodic and relational memory; (B) multisensory processing; (C) short-term memory binding. The high- and medium-education groups had significantly better episodic and relational memory compared to low-education group. The violin plots show the data distribution. The line that divides the box into two parts represents the median value. The ends of the box represent the upper (Q3) and lower (Q1) quartiles of the data. The extreme lines of the boxplot show Q3 + 1.5 × interquartile to Q1–1.5 × interquartile range. The black dots beyond the extreme lines show potential outliers. *** = $p < 0.0005$*

One-way ANCOVAs were conducted separately for stimulating activities and occupational attainment among three educational groups after controlling for age and sex. There was a significant difference in stimulating activities among three education groups ($F(2, 661) = 16.82$, $p < 0.001$, partial eta squared = 0.05). Post-hoc comparisons using Bonferroni test showed that individuals with high ($p < 0.001$) and medium education ($p < 0.001$) had more engagement in stimulating activities compared to those with low education (Figure 3.2A). Additionally, there was a significant difference in occupational attainment among three education groups ($F(2, 661) = 9.56$, $p < 0.001$, partial eta squared = 0.03). Post-hoc comparisons using Bonferroni test showed high-education group had higher occupational attainment compared to medium-education ($p = 0.009$) and low-education groups ($p < 0.001$) (Figure 3.2B).

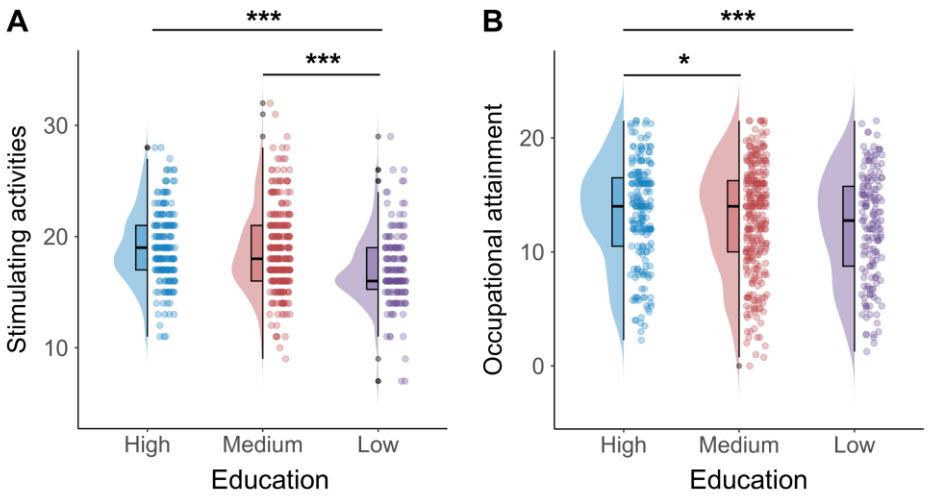

Figure 3.2 Group differences in lifestyle activities across education levels. *(A) Stimulating activities; (B) occupational attainment. The high- and medium-education groups had significantly more engagement in stimulating activities compared to low-education group. The high-education group also had significantly greater occupational attainment compared to medium and low-education groups. The violin plots show the data distribution. The line that divides the box into two parts represents the median value. The ends of the box represent the upper (Q3) and lower (Q1) quartiles of the data. The extreme lines of the boxplot show Q3 + 1.5 × interquartile to Q1 – 1.5 × interquartile range. The black dots beyond the extreme lines show potential outliers. * = $p < 0.05$; *** = $p < 0.0005$*

A significant 3-way interaction between education, stimulating activities, and sex was observed for multisensory processing [Education (high vs. low) × stimulating activities × sex: β (SE) = 0.27 (0.07), CI 0.12–0.41, $p_{\text{-corrected}} < 0.001$] (Table 3.2), which can be explained by the presence of a significant interaction education × stimulating activities only for males (all $p < 0.010$), but not for females (all $p > 0.70$) (Figure 3.3A–B). Simple slope analyses further revealed that, among males, higher engagement in stimulating activities was associated with better multisensory processing for low education group (β (SE) = 0.15 (0.05), CI 0.06–0.25, $p = 0.001$), but with poorer multisensory processing for high education group (β (SE) = -0.13 (0.04), CI -0.20 – -0.05, $p = 0.001$), and the effect was not significant for medium education group (Figure 3.3B). No education × stimulating activities × sex interaction was found for the other two cognitive domains (episodic and relational memory, and short-term memory binding) (Appendix II, STable 8.1–8.2). No education × occupational attainment × sex interaction was found for any of the three cognitive domains (Appendix II, STable 8.3–8.5). The results for 3-way interaction were corrected for multiple comparisons using Bonferroni method.

Based on the presence of a significant interaction education × stimulating activities on multisensory processing was observed only for males (Figure 3.3), the effects of risk factors on the associations were investigated in males. No effects of APOE4 or CAIDE on the associations of education, stimulating activities and multisensory processing were found in males.

Table 3.2 Regression coefficients for the model including 3-way interaction of sex × education × stimulating activities on multisensory processing

Model summary		R^2	F	*p* value
		0.05	2.51	0.002
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Multisensory processing	Education (Medium) (reference = low education)	-0.48 (0.17)	[-0.81, -0.14]	0.01
	Education (High) (reference = low education)	-0.38 (0.19)	[-0.75, -0.01]	0.05
	Stimulating activities	0.15 (0.05)	[0.06, 0.25]	0.001
	Sex	-0.31 (0.18)	[-0.66, 0.04]	0.08
	Occupational attainment	-0.002 (0.01)	[-0.02, 0.02]	0.79
	Age	-0.01 (0.01)	[-0.03, 0.001]	0.07
	Education (Medium vs. Low)*stimulating activities	-0.14 (0.05)	[-0.25, -0.04]	0.01
	Education (High vs. Low)*stimulating activities	-0.28 (0.06)	[-0.40, -0.16]	<0.001
	Education (Medium vs. Low)*sex	0.41 (0.21)	[-0.01, 0.83]	0.06
	Education (High vs. Low)*sex	0.19 (0.23)	[-0.27, 0.64]	0.41
	Stimulating activities*sex	-0.12 (0.05)	[-0.23, -0.01]	0.03
	Education (Medium vs. Low)*stimulating activities*sex	0.15 (0.06)	[0.02, 0.27]	0.019
	Education (High vs. Low)*stimulating activities*sex	0.27 (0.07)	[0.12, 0.41]	<0.001

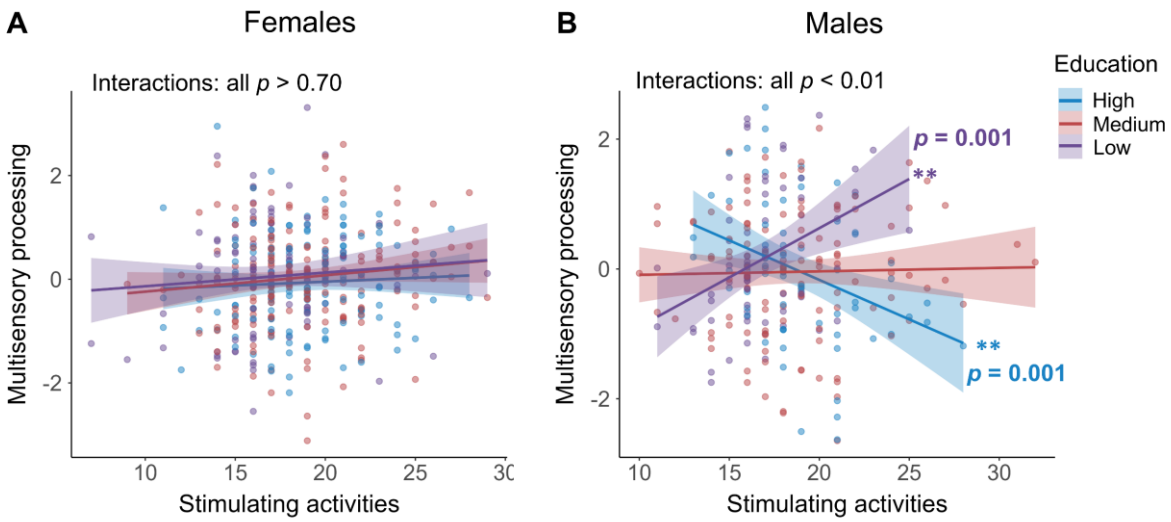

Figure 3.3 Associations of sex, education, stimulating activities and multisensory processing. *(A) Females showed no significant interaction between educational level and stimulating activities on multisensory processing. (B) A significant interaction is shown between educational level and stimulating activities on multisensory processing in males. On the x axis, higher scores represent more engagement in stimulating activities, and on the y axis, higher scores represent better multisensory processing. ** = $p < 0.005$*

3.3.3 Sex Differences in the Associations Between Education, Stimulating Activities, Risk Factors and Brain Structure

One-way ANCOVAs were conducted separately for each of the two brain structural measures among three education groups after controlling for age, sex and TIV. No significant differences in TGM or global CT were found among three education groups (Figure 3.4A–B).

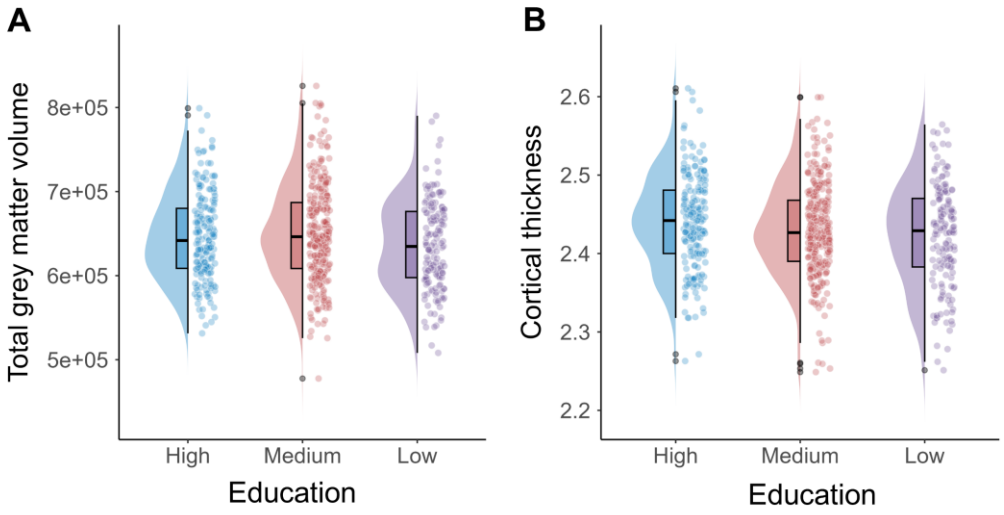

Figure 3.4 Group differences in brain structural measures across education levels. *(A) total grey matter volume; (B) global cortical thickness. No significant differences across education groups in total grey matter volume or global cortical thickness. The violin plots show the data distribution. The line that divides the box into two parts represents the median value. The ends of the box represent the upper (Q3) and lower (Q1) quartiles of the data. The extreme lines of the boxplot show Q3 + 1.5 × interquartile to Q1 – 1.5 × interquartile range. The black dots beyond the extreme lines show potential outliers.*

A significant 3-way interaction between education, stimulating activities, and sex was observed for global CT [Education (medium vs. low) × stimulating activities × sex: β (SE) = 0.01 (0.004), CI 0.002–0.017, $p_{\text{-corrected}} = 0.024$; education (high vs. low) × stimulating activities × sex: β (SE) = 0.01 (0.004), CI 0.002–0.019, $p_{\text{-corrected}} = 0.032$] (Table 3.3), which can be explained by the presence of a significant interaction education × stimulating activities only for males (all $p < 0.020$), not for females (all $p > 0.30$) (Figure 3.5A–B). Simple slope analyses for males showed a significantly positive relationship for low education group (β (SE) = 0.007 (0.003), CI 0.002–0.013, $p = 0.009$) (Figure 3.5B), and no significant relationship for medium and low education groups (all $p > 0.66$), between stimulating activities and global CT. No education × stimulating activities × sex interaction was observed on TGM (Appendix II, STable 8.6). No education × occupational attainment × sex interaction was found in any of the two brain structural measures (Appendix II, STable 8.7–8.8). The results for 3-way interaction were corrected for multiple comparisons using Bonferroni method.

Table 3.3 Regression coefficients for the model including 3-way interaction of sex × education × stimulating activities on global cortical thickness

Model summary	R^2	F	*p* value
	0.08	3.92	<0.001

DV	IV	β (SE)	95% CI	*p* value
Global cortical thickness	Education (Medium) (reference = low education)	0.01 (0.01)	[-0.01, 0.03]	0.33
	Education (High) (reference = low education)	0.01 (0.01)	[-0.01, 0.04]	0.28
	Stimulating activities	0.007 (0.003)	[0.002, 0.01]	0.009
	Sex	0.005 (0.01)	[-0.02, 0.03]	0.62
	Occupational attainment	-0.001 (0.001)	[-0.002, 0.0003]	0.13
	Age	-0.002 (<0.001)	[-0.003, -0.001]	<0.001
	TIV	<0.001 (<0.001)	[3e-09, 7e-08]	0.03
	Education (Medium vs. Low)*stimulating activities	-0.008 (0.003)	[-0.01, -0.002]	0.01
	Education (High vs. Low)*stimulating activities	-0.01 (0.004)	[-0.02, -0.001]	0.02
	Education (Medium vs. Low)*sex	-0.003 (0.01)	[-0.04, 0.01]	0.31
	Education (High vs. Low)*sex	-0.01 (0.01)	[-0.03, 0.03]	0.84
	Stimulating activities*sex	-0.01 (0.003)	[-0.02, -0.003]	0.01
	Education (Medium vs. Low)*stimulating activities*sex	0.01 (0.004)	[0.002, 0.017]	0.012
	Education (High vs. Low)*stimulating activities*sex	0.01 (0.004)	[0.002, 0.019]	0.016

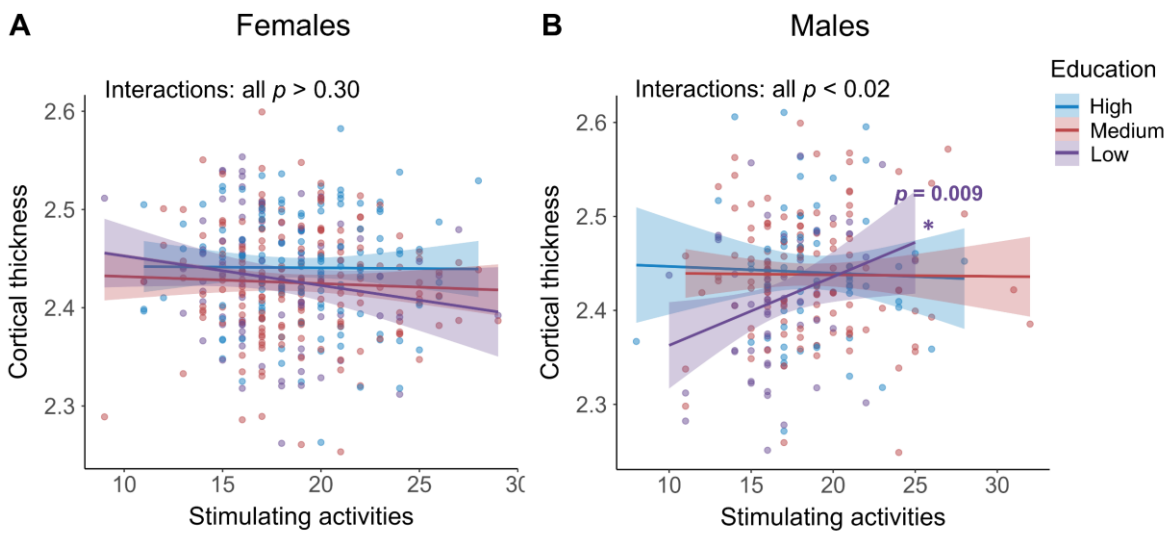

Figure 3.5 Associations of sex, education, stimulating activities and global cortical thickness. *(A) Females showed no significant interaction between educational level and stimulating activities on global cortical thickness. (B) A significant interaction is shown between educational level and stimulating activities on global cortical thickness in males. On the x axis, higher scores represent more engagement in stimulating activities, and on the y axis, higher scores represent thicker global cortical thickness.* ***** *= p < 0.05*

Based on the presence of a significant interaction education × stimulating activities on global CT was observed only for males (Figure 3.5), the effects of risk factors on the associations were investigated in males. A significant 3-way interaction education × stimulating activities × CAIDE on global CT was also found in males [Education (medium vs. low) × stimulating activities × CAIDE: β (SE) = -0.002 (0.001), CI -0.004–-0.0005, $p_{\text{-corrected}}$ = 0.030] (Table 3.4, Figure 3.6). Simple slope analyses showed a significantly positive relationship between stimulating activities and global CT for low education males with medium CAIDE values (β (SE) = 0.007 (0.003), CI 0.001–0.013, p = 0.026) and high CAIDE scores (β (SE) = 0.012 (0.003), CI 0.005–0.019, p = 0.001). No effect of APOE4 on the associations was observed in males. The results for 3-way interaction were corrected for multiple comparisons using Bonferroni method.

Table 3.4 Regression coefficients for the model including 3-way interaction of CAIDE × education × stimulating activities on global cortical thickness in males

Model summary	R^2	F	*p* value
	0.16	3.29	<0.001

DV	IV	β (SE)	95% CI	*p* value
Global cortical thickness	Education (Medium) (reference = low education)	-0.11 (0.14)	[-0.38, 0.16]	0.42
	Education (High) (reference = low education)	0.10 (0.18)	[-0.26, 0.46]	0.58
	Stimulating activities	-0.004 (0.01)	[-0.02, 0.008]	0.50
	CAIDE	-0.03 (0.01)	[-0.06, -0.005]	0.02
	Occupational attainment	-0.003 (0.001)	[-0.005, -0.001]	0.002
	TIV	<0.001 (<0.001)	[-1e-08, 1e-07]	0.10
	Education (Medium vs. Low)*stimulating activities	0.008 (0.01)	[-0.007, 0.02]	0.29
	Education (High vs. Low)*stimulating activities	-0.003 (0.01)	[-0.02, 0.02]	0.75
	Education (Medium vs. Low)*CAIDE	0.04 (0.02)	[0.01, 0.07]	0.02
	Education (High vs. Low)*CAIDE	0.01 (0.03)	[-0.04, 0.06]	0.75
	Stimulating activities*CAIDE	0.002 (0.001)	[<0.001, 0.003]	0.02
	Education (Medium vs. Low)*stimulating activities*CAIDE	-0.002 (0.001)	[-0.004, -5e-04]	0.015
	Education (High vs. Low)*stimulating activities*CAIDE	-0.001 (0.001)	[-0.003, 0.002]	0.64

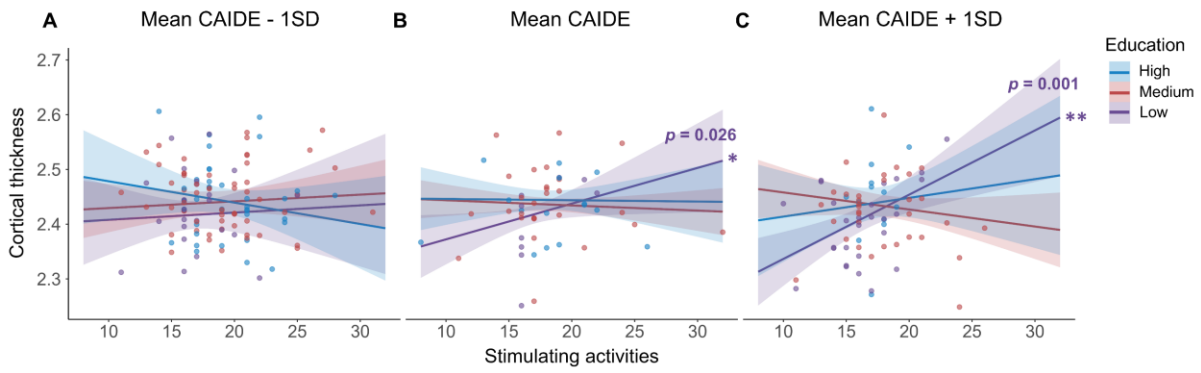

Figure 3.6 Associations of CAIDE, education, stimulating activities and global cortical thickness in males. *(A) Mean CAIDE - 1SD group; (B) Mean CAIDE group; (C) Mean CAIDE + 1SD group. More engagement in stimulating activities was associated with thicker global cortical thickness in low educated males with medium and high CAIDE scores. On the x axis, higher scores represent more engagement in stimulating activities, and on the y axis, higher scores represent thicker global cortical thickness. * = p < 0.05; ** = p < 0.005*

3.4 Discussion

This chapter investigated the effects of sex and education on the relationship between mid-life stimulating activities, occupational attainment, cognition, and brain structure in a cohort of individuals (N = 700), who were presently cognitively healthy, but at risk for late-life dementia. Participants with high educational level had significantly better episodic and relational memory, greater occupational attainment, and more engagement in stimulating activities in mid-life than those with low education. After controlling for the effect of occupational attainment, I found significant sex differences in the associations between educational level, stimulating activities and cognition. Low-educated males with higher engagement in physically, socially and intellectually stimulating activities showed better multisensory processing, whereas high-educated males showed the opposite effect, however, no significant differences among three education groups were observed in these associations in females. Moreover, I found that low-educated males with more engagement in stimulating activities showed thicker global cortical thickness, and females again showed no education-dependent effects in the associations between stimulating activities and global cortical thickness. The positive associations in low-educated males were more pronounced in those with high CAIDE scores. These findings suggest that lifestyle activities that are modifiable in mid-life can enhance cognition and brain structural health in a sex-specific way in middle-aged population, despite low education levels in early life. They highlight the need for high precision prevention strategies that account for both biological sex and educational background in Alzheimer's disease clinical trials.

Individuals with high education had better cognition and greater occupational attainment, and engaged more frequently in stimulating activities than those with low education, independently of sex and age. This finding is consistent with evidence that education was associated with better cognition (Lam et al., 2024; Lovden et al., 2020; Tari et al., 2023) and lower dementia

risk (Baumgart et al., 2015; Beydoun et al., 2014), and strongly predicts subsequent occupational opportunities and income levels (Lahelma et al., 2004; Torssander & Erikson, 2010). Lower education often translates into reduced occupational attainment and earnings, perpetuating socioeconomic disadvantage and limiting access to enriching activities, such as socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in energetic physical activities, reading, practicing a second language and travel, that contribute to cognitive reserve. Moreover, lower levels of education may coincide with a lack of knowledge on healthy behaviours and their benefits, leading to poorer management of lifestyle factors associated with cognitive decline (Jia et al., 2020a; Jin et al., 2023; Koch et al., 2019; Lipnicki et al., 2019; Panagiotakos et al., 2004).

The key question in this study, however, was to investigate the impact of sex and education on the associations between lifestyle activities, cognition and brain structure in mid-life. To the best of my knowledge, this is the first study to report a sex-specific association between education and stimulating activities on cognitive ability and brain structure, in middle-aged individuals who are presently cognitively healthy but at risk for late-life dementia. I found that males with low education and high education showed different association between stimulating activities and multisensory processing, however, no significant differences among education groups were observed in these associations in females. One potential explanation for these findings may be that males and females accrue cognitive reserve via distinct life-course exposures (Arenaza-Urquijo et al., 2024). In Chapter 2, occupational attainment was associated with better episodic and relational memory only in females (Qi et al., 2024), whereas here stimulating activities was associated with better multisensory processing exclusively in males, especially those with lower education. These sex-specific pathways mirrors findings in older adults showing that males and females benefit differently from reserve contributors, with higher IQ associated with slower age-related cognitive decline in older males but not in females (Alty

et al., 2023) and higher physical activity associated with greater speed reserve in older females but not in males (Pa et al., 2022). Additionally, the mid-life sample spans the menopausal transition, a period marked by declining estrogen levels that significantly impact brain health (Mosconi et al., 2017b; Udeh-Momoh et al., 2021). Postmenopause has been associated with increased levels of amyloid-β, elevated tau burden, reduced white matter integrity, and glucose hypometabolism (Buckley et al., 2022; Mosconi et al., 2017a; Rahman et al., 2020). The absence of detailed hormonal assays or menopausal staging in PREVENT precluded analysis of whether endocrine shifts attenuate the cognitive and structural benefits of stimulating activities in females. Future studies should incorporate objective and rigorous measurements of hormone and menopause to determine how estrogen changes interact with lifestyle activities in shaping female brain health.

Furthermore, effects were seen only in the domain of multisensory processing, where the form perception task assessing visuospatial ability had the strongest loading. Impaired visuospatial function is one of the earliest cognitive deficits observed in AD (Laukka et al., 2012; Mandal et al., 2012; Williams et al., 2020) and has previously been linked to elevated dementia risk in this cohort (Deng et al., 2024; K. Ritchie et al., 2018; Ritchie et al., 2017). Previous studies in older adults have showed that an active lifestyle was associated with better visuospatial function (Muiños & Ballesteros, 2018; Tsai et al., 2016; Wang & Tsai, 2016). Findings from this study advance the literature, by showing that engagement in stimulating lifestyle activities may boost cognitive functions that are very vulnerable to dementia risk and early neuropathology from as early as mid-life (Laukka et al., 2012; Mandal et al., 2012; Williams et al., 2020).

Why males with low versus high education showed distinct associations between stimulating activities and cognition? Although the precise mechanisms underlying this divergence remain unclear, one potential explanation is that individuals with low education accumulate greater

vulnerability to dementia-related neuropathology and cognitive decline (Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017). Lower education was associated with barriers to other key reserve contributors, such as reduced occupational complexity, and fewer opportunities to cognitively stimulating activities, and subsequently lower cognitive reserve (Oreopoulos & Salvanes, 2011; Schudde & Bernell, 2019; Vuolo et al., 2016). Consequently, these accumulated vulnerability influences to dementia in low-educated males likely render them more responsive to protective lifestyle activities. In contrast, males with higher education showed a counterintuitive negative association between engagement in stimulating activities and cognition. One possible reason could be due to occupational factors. Higher education typically leads to higher occupational attainment (Oreopoulos & Salvanes, 2011; Schudde & Bernell, 2019; Vuolo et al., 2016) which are often associated with increased stress levels and adversely affecting brain health (Agbenyikey et al., 2015; Dong et al., 2018). Moreover, my earlier findings in Chapter 2 showed that higher occupational attainment was negatively associated with cognitive performance only in males. Previous studies in older adults have also found that high job strain was associated with worse cognition (Sabbath et al., 2016) and cognitive decline (Pan et al., 2019) in males. Although occupational attainment was statistically controlled for in the model, unmeasured dimensions of job strain, such as excessive workloads, prolonged working hours, low job control, and emotional labor, may counteract or even reverse the cognitive benefits derived from stimulating activities among highly educated males.

Another key question here was whether risk factors impact the interactions between education and stimulating activities on cognition and brain structure in males. I found that CAIDE score moderated the associations between education, stimulating activities, and global cortical thickness in males. Specifically, low-educated males with medium or high CAIDE scores showed positive relationships between stimulating activities and global cortical thickness, whereas this association was not observed among males with low CAIDE scores. Higher mid-

life CAIDE scores have previously been related to increased severity of white matter hyperintensity and medial temporal lobe atrophy two to three decades later in older population (Vuorinen et al., 2015). Within a substudy of the PREVENT cohort, Dounavi et al. (2022) have found that higher CAIDE scores were associated with widespread cortical thinning (affecting 20 out of total 34 cortical regions examined) already in mid-life. Consequently, males with lower education and elevated CAIDE scores may exhibit greater vulnerability in brain structure, rendering their cortical thickness particularly responsive to protective lifestyle activities. APOE4 genotype did not moderate these interactions in males. In other words, when considering genetic risk factors independently, no differences emerged between high- and low-risk groups in the relationship between education, stimulating activities and global cortical thickness in males. It was only when a risk score (CAIDE) incorporating genetic risk alongside cardiovascular factors and age, that such interactions in males were unravelled. Together, these results provide evidence that beneficial effects from stimulating activities on male brain structure may be driven by cardiovascular risk factors included in CAIDE score (i.e., blood pressure, cholesterol, body mass index). However, I caution that the interpretability of the effect of CAIDE on the associations in males is limited by the relatively small sample size in each subgroup in this study (e.g., in high CAIDE group, high education: n = 13; Medium education: n = 33; Low education: n = 27) and requires further replication and validation in larger samples in future studies.

Methodological considerations

Participants in the PREVENT cohort are generally well-educated, nearly all had completed secondary education, and only one individual reported no formal schooling. The findings may not generalize to low- and middle-income populations or to individuals with minimal educational attainment. Education was measured solely by highest level completed, without

accounting for the quality or context of schooling. Variations in curricular rigor, institutional resources, or early-life learning environments may contribute additional variance in the findings that the measurement used here could not capture. The present analyses are based on observational cross-sectional data. Future studies from the ongoing testing waves two and three of this multi-site study are essential to establish temporal and potentially causal links between sex, education, lifestyle activities, cognition and brain structure in middle-aged individuals at risk for late life dementia. Finally, I caution that the interpretability of the effect of lifestyle activities on each individual function is limited by their composite cognitive assessment in this study and requires individuation in future studies.

3.5 Conclusion

In summary, the findings of the current study suggest that engagement in the variety of activities can enhance cognition and maintain brain structure in mid-life, and mitigate the negative impact of low educational level from early childhood in males, but not females, with elevated CAIDE scores. Given that lifestyle factors serve both as risks and protections against dementia , adopting healthy lifestyle may currently represent the most effective defense against sporadic late-onset Alzheimer's disease. Because the activities highlighted here are both modifiable and cost-effective, they present attractive targets for early-life prevention and intervention. Moreover, such non-pharmacological approaches could be particularly impactful in low- and middle-income countries, where educational barriers are more pronounced than in high-income regions and many people have low formal education (Livingston et al., 2020). They also highlight the need for high precision prevention strategies that account for both biological sex and educational background in Alzheimer's disease clinical trials.

4. Chapter 4: Sex differences in the relationship between cognition and brain structure in mid-life individuals at risk for future dementia

4.1 Introduction

In Chapters 2 and 3, I have shown sex-specific association between reserve contributors, cognition, and brain structure independently. The aim of this empirical study of my thesis is to investigate whether the brain structure–cognition relationships differ between females and males in mid-life.

Growing evidence has shown a disproportionate impact of AD on females (Alzheimer's Association, 2017; (Mielke, 2018). Females comprise over two-thirds of AD cases and simultaneously shoulder approximately two-thirds of dementia caregiving responsibilities (Alzheimer's Association, 2021). Consequently, females are exposed to more adverse factors that may contribute to AD neuropathology, including increased stress (Ma et al., 2018) and caregiver burden (Xiong et al., 2020). In addition, females carrying the APOE4 genotype are at greater risk for developing AD (Altmann et al., 2014; Farrer et al., 1997) and, once diagnosed, tend to experience faster pathological accumulation and more severe disease progression compared to men with comparable pathologic burden (Barnes et al., 2005; Buckley et al., 2018; Edwards et al., 2021). Mid-life is a critical period for females, as the menopausal transition triggers cascading effects on endocrinal (Weber et al., 2014), cardiovascular (Yanes & Reckelhoff, 2011), and metabolic (Rahman et al., 2020) systems that significantly impact brain health (Mosconi et al., 2018; Udeh-Momoh et al., 2021). The rapid decline in estrogen, the

primary female sex hormone, in the years leading up to menopause and after menopause increases vulnerability to AD in females (Scheyer et al., 2018; Udeh-Momoh et al., 2021). A recently published review considering the relationship between estrogen and modifiable risks for late life dementia found that estrogen depletion during menopause exacerbated the effects of mid-life risks in females, including LDL cholesterol, smoking and depression (Gregory et al., 2025).

Biological sex also shapes cognitive trajectories in aging (Buckley et al., 2018) and AD progression (Cieri et al., 2022). Although females typically have verbal and episodic memory advantages over males (Arenaza-Urquijo et al., 2024; Asperholm et al., 2019; Brunet et al., 2020; Sundermann et al., 2019), they experience a more rapid memory decline than males over time among clinically normal older adults (Buckley et al., 2018), and even with the same level of AD pathological burden, during the transition from MCI to AD (Cieri et al., 2022).

Neuroimaging studies, including my own work, have also showed sex differences in brain structural measures. Sex differences in cortical thickness have been reported across both cognitively healthy (Cavedo et al., 2018; Gautam et al., 2013; Sang et al., 2024; Sowell et al., 2007; van Velsen et al., 2013) and clinical populations (Lee et al., 2018; Sangha et al., 2021; Seo et al., 2011). However, the results are mixed. In cognitively healthy adults, for example, some studies reported thicker cortex in frontal and temporal regions in males (Gautam et al., 2013; Sang et al., 2024), whereas other studies found thicker cortex in females across frontal, parietal and occipital lobes (Lv et al., 2010; S. J. Ritchie et al., 2018; Sangha et al., 2021). Still others have observed no significant effect of sex (Cavedo et al., 2018). In MCI and AD populations, cross-sectional studies are likewise inconclusive. Some have found no baseline sex differences in cortical thickness among AD patients (Seo et al., 2011), whereas others report that males with MCI continue to exhibit thinner cortex, most notably in primary motor and

superior parietal regions, compared to females with MCI (Sangha et al., 2021). Longitudinal data reveal that, once Alzheimer's disease is established, females experience more rapid cortical thinning than males across frontotemporal and temporo-parietal association cortices (Lee et al., 2018).

Turning to brain volume measures, males typically show larger brain volume than females (Barnes et al., 2010; Bethlehem et al., 2022), however, once controlled for total brain volume, females have a higher percentage of gray matter and males a higher percentage of white matter (Cosgrove et al., 2007). In chapter 3, I also found that males had larger total grey matter volume and total intracranial volume compared to females in the PREVENT cohort. A meta-analysis of 167 neuroimaging studies also reported that from newborns to older adults over 80 years old, males exhibit larger brain volumes and grey matter volume than females (Ruigrok et al., 2014). Extending this work, Bethlehem et al. (2022) pooled data from 101,457 participants across lifespan to chart normative brain-development trajectories and showed that, from birth through more than age 80, males have larger total cerebrum, cortical and subcortical grey matter, white matter volumes and surface area, but not mean cortical thickness than females. In clinical cohorts, particularly AD patients, sex differences appear region-specific. Research shows that AD females have larger grey matter volume (Bergamino et al., 2022), smaller hippocampal volumes (Apostolova et al., 2006), less CSF volumetric atrophy in frontal, temporal, and parietal regions compared to AD males (Kidron et al., 1997) whereas males with AD show a higher ventricle-to-brain ratio (Carmichael et al., 2007), and more pronounced anterior and posterior cingulate atrophy than female AD patients (Ballmaier et al., 2004; Callen et al., 2004). Together, the accumulating evidence indicates that there are sex differences in cognition and brain structure among cognitively healthy and cognitively impaired adults. However, little is known on the sex differences in the relationship between cognition and brain structure in the middle-aged population.

Moreover, studies from the pilot data of PREVENT cohort (N = 210) have revealed that two mid-life risk factors, APOE4 genotype and CAIDE score, significantly impact the cognition (Deng et al., 2024; K. Ritchie et al., 2018; Ritchie et al., 2017) and brain structure (Low et al., 2022b; O'Brien et al., 2020) of middle-aged individuals (For more details see Chapter 1, section 1.3). However, it remains unknown whether these two risk factors also relate to cognition and brain structure in the full PREVENT cohort (N = 700). Conversely, higher cognitive reserve is linked to a reduced risk of dementia and, therefore, building cognitive reserve is a crucial preventative approach. Education, stimulating activities (physical, social and intellectual), and occupational attainment are key contributors to cognitive reserve (Stern, 2012; Stern et al., 2020). Engaging in such activities may help offset brain pathology and genetic predispositions by enhancing neural efficiency and connectivity (Hu et al., 2013; Valenzuela & Sachdev, 2006). However, it remains unknown whether reserve contributors may buffer against dementia risk effects on brain health in mid-life.

To this end, this chapter aimed to address three key questions in a large cohort of cognitively healthy middle-aged individuals. First, I investigated the effects of dementia risk factors and reserve contributors on cognition and brain structure in mid-life. Second, I examined the moderating role of sex on the association between brain structure and cognition. Third, I sought to determine whether sex and risk factors would interact to influence the relationship between brain structure and cognition. My hypotheses were that a) risk factors for late life dementia would be significantly associated with cognition and brain structure in mid-life, and reserve contributors would offset the effects of dementia risks on brain health; b) sex would moderate the association between brain structure and cognition; and c) sex and risk factors would interact to influence the brain structure–cognition relationship in this middle-aged cohort. Unraveling these associations has implications for devising targeted sex-specific intervention for dementia prevention.

4.2 Methods

4.2.1 Participants

The same mid-life cohort investigated in the previous chapters was included in this study (N = 700). For a detailed description of the cohort, please refer to Chapter 2 (Section 2.2.1). In total, 700 participants (267 male; 433 female) took part in cognitive and clinical assessments. From the recruited participants, 663 participants finished MRI scans. Participants who had incidental findings on MRI scans (N = 18), had incomplete cognitive data (N = 29) and clinical data (N = 1) were excluded, resulting in N = 615 for the regression analyses (See Appendix III; SFigure 9.1). The study reports the wave 1 (baseline) testing data, which were completed at the time of this thesis preparation. Wave 2 and 3 of testing are currently ongoing.

4.2.2 Biological Sex

While the dichotomies of sex and gender are no longer considered to be sharply discrete, in this study 'sex' was defined as an individual's natal or biological sex and was self-reported in the Brain Injury Screening Questionnaire.

4.2.3 Risk Factors

Details of risk factors (APOE4 and CAIDE score) investigated in this study can be found in Chapter 3 (Section 3.2.4).

4.2.4 Cognitive Reserve Contributors

Details of the measurements for cognitive reserve contributors can be found in Chapter 2 (Section 2.2.7).

4.2.5 Cognitive Assessments

Full descriptions of the cognitive assessments used in this study can be found in Chapter 2 (Section 2.2.8 & 2.3.2). Briefly, rotated principal component analysis clustered 13 cognitive measures into three related cognitive components (C): C1, episodic and relational memory; C2, multisensory processing; and C3, short-term memory binding (see Chapter 2, Figure 2.1).

4.2.6 MRI Acquisition and Processing

Details on MRI acquisition parameters are described in Chapter 3 (Section 3.2.7). Freesurfer version 7.1.0 (https://surfer.nmr.mgh.harvard.edu/) was used for data processing (Fischl, 2012). The recon-all pipeline was run with default settings for each participant. After recon-all, the brain masks and surfaces were inspected, and manual corrections were applied (a) in the form of erosion of non-brain voxels from the brain mask or non-WM voxels from the WM mask, (b) in the form of filling of areas where the brain was not correctly identified, or (c) with the addition of control points in cases where white matter was not successfully identified. Finally, the cortical thickness in 68 regions was quantified based on the Desikan-Killiany atlas (Desikan et al., 2006). Absolute total grey matter volume (TGM) was obtained for each participant, and relative TGM was calculated by dividing absolute TGM by total intracranial volume (TIV) to adjust for individual differences in head size. Global cortical thickness (CT) was obtained by averaging the values from the bilateral hemispheres for each participant. Based on previous literature (Dickerson et al., 2009; McEvoy et al., 2009; Schwarz et al., 2016), we chose nine regions of interest (ROIs) as AD signature regions: entorhinal, fusiform, parahippocampal, temporal pole, precuneus, isthmus cingulate, inferior temporal, middle temporal, superior temporal. The mean cortical thickness within each ROI was calculated by averaging the values from the bilateral hemispheres.

4.2.7 Statistical Approach

The statistical analyses were conducted with the SPSS V.27 and R software (https://www.R-project.org/). The normality of the data was assessed by combining the visualization of a quantile-quantile plot and the Shapiro–Wilk test. Demographic and clinical information of the study cohort were analyzed across sexes using chi-square (χ^2 tests) for categorical variable (APOE4), and Mann-Whitney U tests or independent samples t-tests for continuous variables (*Mann-Whitney U test*: age, years of education, CAIDE, multisensory processing, short-term memory binding, absolute TGM, relative TGM, and seven regional cortical thickness [precuneus, middle temporal, inferior temporal, superior temporal, entorhinal, isthmus cingulate, and temporal pole]; *independent samples t-test*: episodic and relational memory, global cortical thickness, and two regional cortical thickness [fusiform and parahippocampal]), depending on whether they met the assumption of normality in this cohort. Relative TGM was used exclusively for comparing sex differences in demographic and clinical information. All subsequent regression models employed absolute TGM. Accordingly, throughout the rest of this thesis, "TGM" refers to absolute total grey matter volume unless otherwise specified.

I conducted a multicollinearity assessment using Tolerance and Variance Inflation Factor (VIF) metrics (Studenmund, 2014; Montgomery et al., 2001) before regression analyses. Multicollinearity assessment for TGM and total intracranial volume (TIV) showed no significant collinearity (Appendix III, STable 9.2; all VIFs < 5). Independent multiple regression models investigated the main effects of risk factors (APOE4 and CAIDE) on cognitive domains and brain structural measures (TGM and global CT). Age, sex and years of education were included as covariates in all models, except those including the CAIDE score, as CAIDE already accounts for these demographics. In models involving brain structural measures, TIV and scan sites (regarded as a dummy variable) were added as additional covariates.

Independent multiple regression models investigated the 2-way interaction of sex × brain structure (TGM and global CT) on each of three cognitive domains, with age, years of education, TIV and scan sites (dummy variable) included as covariates. If a significant 2-way interaction of sex × global CT emerged, follow-up analyses were conducted separately on each of the nine AD signature regions. Each model included a 2-way sex × regional CT interaction term alongside the same covariates. For any observed significant 2-way interactions above, the moderating role of risk factors (APOE4 and CAIDE) were tested with 3-way interactions of risk factor × sex × brain structure on cognition, with the aforementioned covariates. Simple slope analyses tested the significance of the slopes of the regression lines for any significant interactions. Correction for multiple comparisons was implemented using the Bonferroni method to control type I error.

4.3 Results

4.3.1 Demographics

Demographic variables, cognition, and brain structural measures of the cohort are summarized in Table 4.1. Females and males did not differ significantly in age, years of education, APOE4 carrier status, two of the three cognitive domains, global cortical thickness and 8/9 regional cortical thickness measures. Females had significantly lower CAIDE scores, significantly higher episodic and relational memory, and significantly greater cortical thickness in the parahippocampal cortex. Females also had significantly smaller absolute total grey matter volume, but the sex difference disappeared in relative TGM after adjusting for individual differences in head size (Table 4.1; Figure 4.1–4.2).

Table 4.1 Participant characteristics

Participant characteristics	All	Females	Males	*p* value	Effect size
N	615	382	233	–	–
Age (y)	52.0 (8.0)	52.0 (8.0)	53.0 (10.0)	0.07	0.07
Years of education	17.0 (5.0)	17.0 (5.0)	17.0 (3.0)	0.11	0.07
APOE4 (% Carriers)	38.4%	38.9% (n=378)	37.7% (n=231)	0.76	0.009
CAIDE	6.0 (4.0)	6.0 (3.0) (n=377)	7.0 (5.0) (n=231)	<0.001	0.21
Episodic and relational memory	0.03 (1.0)	0.19 (1.0)	-0.23 (1.0)	<0.001	0.43
Multisensory processing	0.03 (1.3)	0.04 (1.2)	0.01(1.4)	0.68	0.02
Short-term memory binding	0.12 (1.1)	0.09 (1.2)	0.16 (1.1)	0.26	0.05
Total grey matter volume absolute (cm^3)	644.12 (79.92)	618.33 (59.22)	688.67 (63.75)	<0.001	0.61
Total grey matter volume relative ¶	0.43 (0.03)	0.43 (0.03)	0.43 (0.03)	0.18	0.05
Global cortical thickness	2.43 (0.07)	2.43 (0.06)	2.43 (0.07)	0.12	0.13
Regional cortical thickness	–	–	–	–	–
Precuneus	2.39 (0.11)	2.39 (0.11)	2.37 (0.11)	0.06	0.08
Middle temporal	2.75 (0.15)	2.75 (0.12)	2.76 (0.19)	0.50	0.03
Inferior temporal	2.69 (0.15)	2.70 (0.15)	2.69 (0.16)	0.20	0.05
Superior temporal	2.75 (0.15)	2.75 (0.14)	2.74 (0.16)	0.17	0.06
Entorhinal	3.15 (0.29)	3.15 (0.28)	3.15 (0.31)	0.86	0.01
Fusiform	2.68 (0.09)	2.68 (0.09)	2.67 (0.09)	0.21	0.10
Parahippocampal	2.65 (0.19)	2.67 (0.19)	2.62 (0.18)	<0.001	0.30
Isthmus cingulate	2.21 (0.17)	2.21 (0.16)	2.21 (0.16)	0.48	0.03
Temporal pole	3.51 (0.34)	3.51 (0.35)	3.51 (0.31)	0.52	0.03

NOTE: median (interquartile range, IQR) was reported for non-normal distributed continuous variables. Mean (SD) was reported for normal distributed continuous variables. Effect size was determined using *r* for Mann-Whitney U test, Cohen's *d* for independent samples t-test and φ for the Chi-Square test. ¶ Relative total grey matter volume (TGM) is calculated as absolute

TGM divided by total intracranial volume. Abbreviations: APOE4, Apolipoprotein E4 genotype; CAIDE, Cardiovascular Risk Factors, Aging and Dementia.

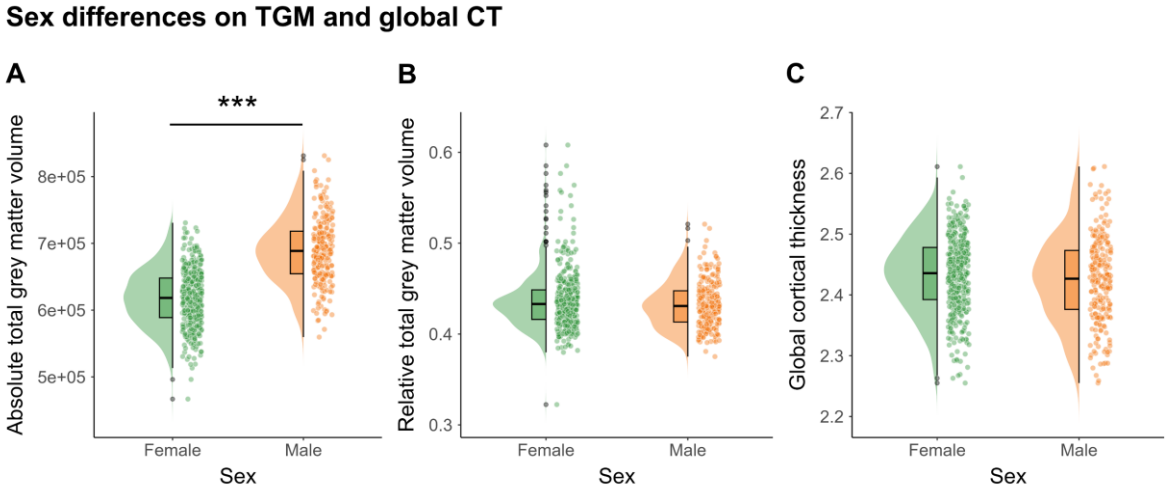

Figure 4.1 Sex differences on TGM and global CT. *Sex differences on (A) absolute total grey matter volume; (B) relative absolute total grey matter volume; (C) global cortical thickness. Females had significantly smaller absolute total grey matter volume than males. The violin plots show the data distribution. The line that divides the box into two parts represents the median value. The ends of the box represent the upper (Q3) and lower (Q1) quartiles of the data. The extreme lines of the boxplot show Q3 + 1.5 × interquartile to Q1 – 1.5 × interquartile range. The black dots beyond the extreme lines show potential outliers. *** = $p < 0.0005$.*

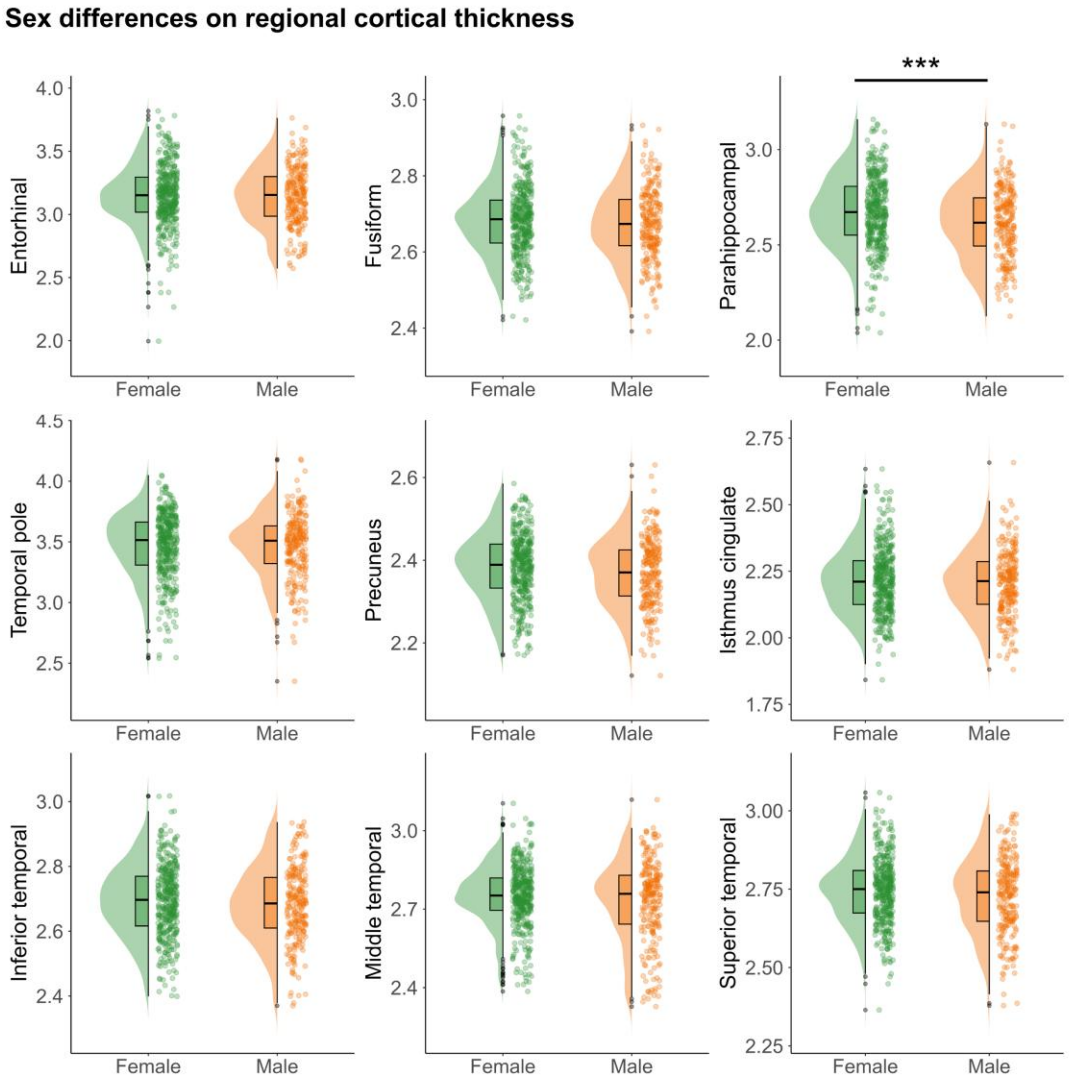

Figure 4.2 Sex differences on cortical thickness among nine regions. *Females had significantly thicker cortical thickness in the parahippocampal cortex than males. The violin plots show the data distribution. The line that divides the box into two parts represents the median value. The ends of the box represent the upper (Q3) and lower (Q1) quartiles of the data. The extreme lines of the boxplot show Q3 + 1.5 × interquartile to Q1 – 1.5 × interquartile range. The black dots beyond the extreme lines show potential outliers. *** = $p < 0.0005$.*

4.3.2 Effects of Risk Factors on Cognition and Brain Structure

CAIDE score was significantly negatively associated with episodic and relational memory (β (SE) = -0.04 (0.01), CI -0.07 – -0.01, $p_{\text{-corrected}}$ = 0.020) (Figure 4.3A, Table 4.2) and short-term memory binding (β (SE) = -0.04 (0.01), CI -0.07– -0.02, $p_{\text{-corrected}}$ = 0.003) (Figure 4.3A, Table 4.2). No association with CAIDE was observed for multisensory processing. No association with APOE4 was observed for the three cognitive domains (Table 4.2).

CAIDE score was significantly negatively associated with global cortical thickness (β (SE) = -0.003 (0.001), CI -0.005– -0.002, $p_{\text{-corrected}} < 0.001$) (Figure 4.3B, Table 4.2), after controlling for TIV and scan sites. No association with CAIDE was observed for TGM. No association with APOE4 was observed for TGM and global cortical thickness (Table 4.2).

Table 4.2 Regression coefficients for the effects of risk factors on cognition and brain structure

Risk factor	Episodic and relational memory			Multisensory processing			Short-term memory binding §			Total grey matter volume			Global cortical thickness		
	β (SE)	***t***	***p***	***β (SE)***	***t***	***p***	***β (SE)***	***t***	***p***	***β (SE)***	***t***	***p***	***β (SE)***	***t***	***p***
APOE4	0.12 (0.08)	1.59	0.11	-0.07 (0.08)	-0.87	0.39	0.03 (0.08)	0.33	0.74	298.8 (240.3)	0.12	0.90	0.005 (0.005)	0.89	0.37
CAIDE	**-0.04 (0.01)**	**-2.73**	**0.007**	0.001 (0.01)	0.08	0.93	**-0.04 (0.01)**	**-3.19**	**0.001**	-925.2 (448.7)	-2.06	0.04	**-0.003 (0.001)**	**-3.78**	**<0.001**

Note: unstandardized coefficients β and standard error (SE) were reported. All models controlled for corresponding covariates. Highlights and bold values indicate significant results after Bonferroni correction. § Removed two outliers in short-term memory binding. DV, dependent variable; IV, independent variable; CI, confidence intervals; APOE4, Apolipoprotein E4 genotype; CAIDE, Cardiovascular Risk Factors, Aging and Dementia.

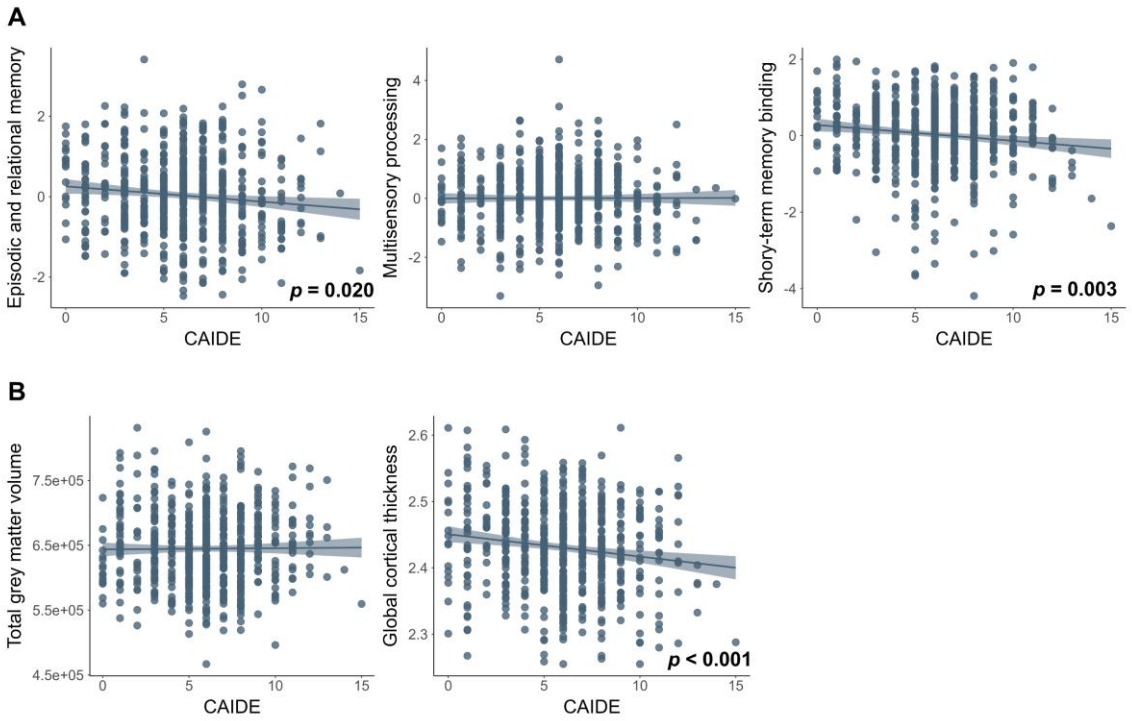

Figure 4.3 Associations of CAIDE with cognition and brain structure. *The effects of CAIDE on (A) cognitive domains, and (B) brain structural measures. Higher CAIDE score was significantly associated with worse episodic and relational memory and short-term memory binding. Higher CAIDE score was significantly associated thinner global cortical thickness. On the x axis, higher scores represent higher cardiovascular dementia risk, and on the y axis, higher scores represent better cognition/larger total grey matter volume/thicker cortical thickness. P values were corrected for multiple comparisons.*

4.3.3 Effects of Reserve Contributors on Brain Structure

Stimulating activities were significantly positively associated with TGM (β (SE) = 927.7 (340.4), CI 259.1–1596.2, $p_{\text{-corrected}}$ = 0.013) (Figure 4.4A, Table 4.3), independently of education, occupational attainment, sex, age, TIV and scan sites. No associations with education or occupation were observed for TGM (Table 4.3).

No association with any of the reserve contributors was observed for global cortical thickness (Figure 4.4B, Table 4.3).

Table 4.3 Regression coefficients for the effects of reserve contributors on brain structure

Brain structural measures	Reserve contributors	β (SE)	95% CI	t	*p* value
Total grey matter volume	Years of education	638.9 (357.4)	[-63.0, 1340.8]	1.79	0.074
	Stimulating activities	**927.7 (340.4)**	**[259.1, 1596.2]**	**2.73**	**0.007**
	Occupational attainment	-169.4 (280.5)	[-720.3, 381.5]	-0.60	0.546
	Age	-1076.6 (235.8)	[-1539.7, -613.5]	-4.57	<0.001
	Sex	-29971.9 (2916.0)	[-35698.6, -24245.1]	-10.3	<0.001
	TIV	0.24 (0.01)	[0.22, 0.26]	27.3	<0.001
Global cortical thickness	Years of education	0.001 (0.001)	[-0.0001, 0.003]	1.82	0.070
	Stimulating activities	-0.001 (0.001)	[-0.002, 0.001]	-0.69	0.488
	Occupational attainment	-0.001 (0.001)	[-0.002, 0.0002]	-1.55	0.121
	Age	-0.002 (0.001)	[-0.003, -0.001]	-3.74	<0.001
	Sex	0.004 (0.006)	[-0.009, 0.016]	0.59	0.558
	TIV	4.2e-8 (1.9e-8)	[5.3e-9, 7.8e-8]	2.25	0.025

Note: unstandardized coefficients β and standard error (SE) were reported. All models controlled for scan sites as a dummy variable. Highlights and bold values indicate significant results after Bonferroni correction. CI, confidence intervals.

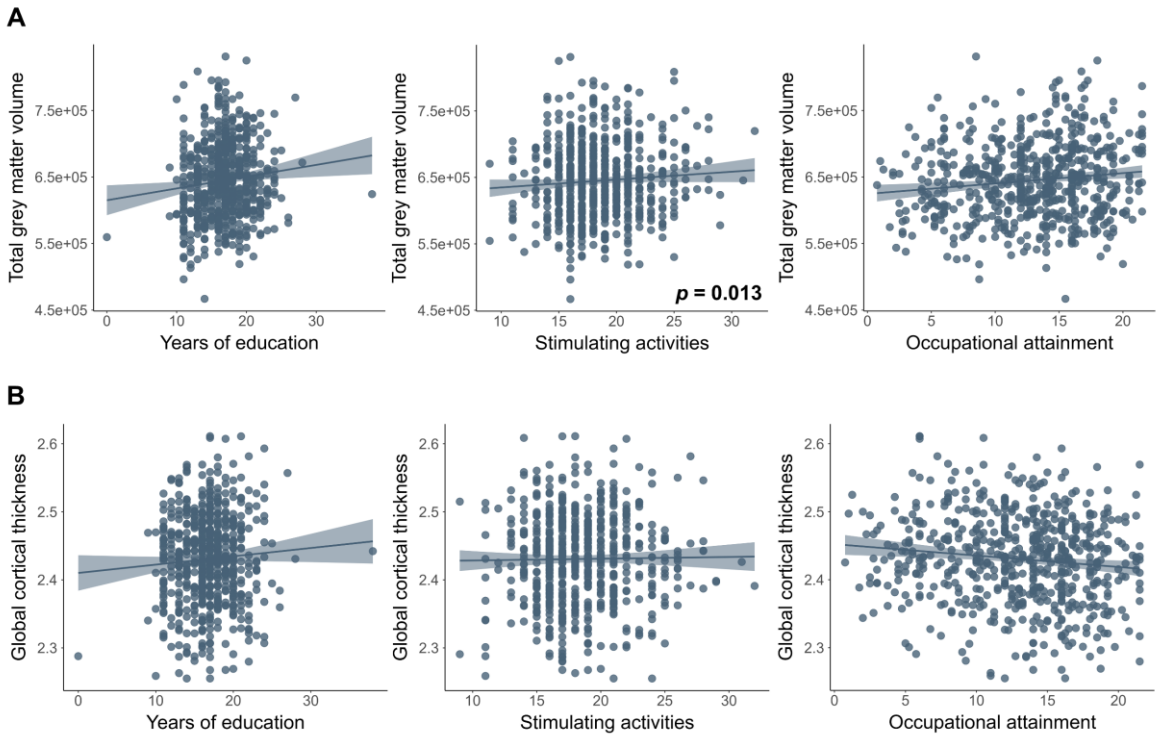

Figure 4.4 Associations of reserve contributors with brain structure. *The effects of reserve contributors on (A) total grey matter volume, and (B) global cortical thickness. More engagement in stimulating activities was associated with higher total grey matter volume. On the x axis, higher scores represent greater education/stimulating activities/occupational attainment, and on the y axis, higher scores represent better larger total grey matter volume/thicker cortical thickness. P values were corrected for multiple comparisons.*

4.3.4 Sex Differences in the Association Between Global Cortical Thickness and Cognition

There was a significant interaction sex × global cortical thickness on episodic and relational memory among all participants after Bonferroni correction (β (SE) = -0.20 (0.07), CI -0.34 – -0.05, $p_{\text{-corrected}}$ = 0.027) (Table 4.4, Figure 4.5B), independently of age, education, TIV and scan sites. Simple slope analysis showed a significantly positive association between global cortical thickness and episodic and relational memory for males (β (SE) = 1.78 (0.88), CI 0.04–3.52, p = 0.045), but not for females (β (SE) = -1.35 (0.77), CI -2.87–0.17, p = 0.082). There were no significant interactions between sex and global cortical thickness on the other two cognitive domains (multisensory processing and short-term memory binding; Table 4.4). No sex × TGM interaction was observed for the whole cohort in any of the three cognitive domains (Table 4.4).

Table 4.4 Regression coefficients for the model including 2-way interaction of sex × brain structural measures (TGM/global CT) on cognition

Cognitive domain	Interaction term	β (SE)	95% CI	t	*p* value
Episodic and relational memory	Sex*TGM	0.11 (0.09)	[-0.08, 0.29]	1.13	0.260
	Sex*Global CT	**-0.20 (0.07)**	**[-0.34, -0.05]**	**-2.62**	**0.009**
Multisensory processing	Sex*TGM	-0.08 (0.10)	[-0.28, 0.11]	-0.84	0.403
	Sex*Global CT	-0.09 (0.08)	[-0.25, 0.07]	-1.14	0.254
Short-term memory binding	Sex*TGM	0.09 (0.10)	[-0.11, 0.29]	0.85	0.394
	Sex*Global CT	-0.003 (0.08)	[-0.16, 0.16]	-0.04	0.966

Note: unstandardized coefficients β and standard error (SE) were reported. All models controlled for age, sex, education, TIV, and scan sites. Highlights and bold values indicate significant results after Bonferroni correction. CI, confidence intervals; TGM, total grey matter volume; CT, cortical thickness.

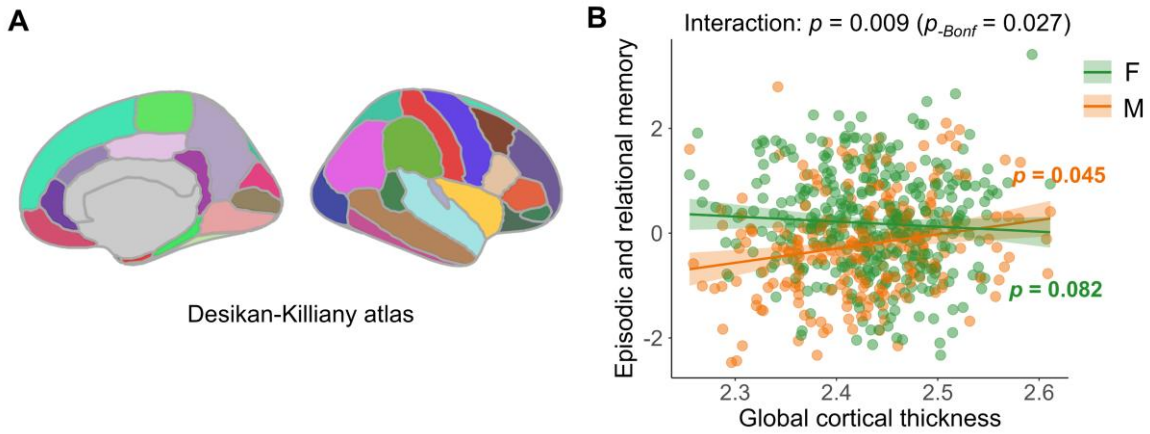

Figure 4.5 Associations of sex, global cortical thickness, and episodic and relational memory. *(A) Regions based on the Desikan-Killiany atlas are shown for the medial (left) and lateral (right) views. (B) Interactions of sex and global cortical thickness on episodic and relational memory. On the x axis, higher scores represent greater global cortical thickness, and on the y axis, higher scores represent better episodic and relational memory. Abbreviations: F, female; M, male.*

4.3.5 Sex Differences in the Association Between Regional Cortical Thickness and Cognition

I found that males showed a positive association between global cortical thickness and episodic and relational memory, while females did not show this association. In the subsequent analysis, I investigated whether this relationship was driven by specific AD signature regions and whether risk factors affected the association between regional cortical thickness and cognition.

Among the nine AD signature regions (Figure 4.6A), I only found a significant interaction sex × regional cortical thickness on episodic and relational memory in precuneus after Bonferroni correction (β (SE) = -0.24 (0.08), CI -0.39 – -0.09, $p_{\text{-corrected}}$ = 0.009) (Table 4.5, Figure 4.6B), independently of age, education, TIV and scan sites. Specifically, there was a significant relationship between precuneus cortical thickness and cognition for males (β (SE) = 1.81 (0.75), CI 0.34–3.27, p = 0.016), but not for females (β (SE) = -1.11 (0.59), CI -2.28–0.05, p = 0.062). There were no significant interactions between sex and regional cortical thickness on episodic and relational memory in the other eight regions after Bonferroni corrections (Table 4.5, Figure 4.6B).

Table 4.5 Associations of sex × regional cortical thickness interaction term with episodic and relational memory

Cognitive domain	Interaction term	β (SE)	95% CI	t	*p* value
Episodic and relational memory	Sex*Precuneus CT	**-0.24 (0.08)**	**[-0.39, -0.09]**	**-3.19**	**0.001**
	Sex*Middle temporal CT	-0.19 (0.07)	[-0.33, -0.04]	-2.48	0.013
	Sex*Inferior temporal CT	-0.13 (0.08)	[-0.03, 0.02]	-1.72	0.086
	Sex*Superior temporal CT	-0.07 (0.08)	[-0.22, 0.08]	-0.92	0.359
	Sex*Entorhinal CT	0.04 (0.08)	[-0.11, 0.20]	0.55	0.586
	Sex*Fusiform CT	-0.04 (0.08)	[-0.19, 0.11]	-0.51	0.609
	Sex*Parahippocampal CT	0.04 (0.08)	[-0.11, 0.20]	0.54	0.587
	Sex*Isthmus cingulate CT	-0.10 (0.08)	[-0.25, 0.06]	-1.24	0.214
	Sex*Temporal pole CT	-0.04 (0.08)	[-0.19, 0.11]	-0.52	0.601

Note: Unstandardized coefficients β and standard error (SE) were reported. Each row denotes a separate model. All models controlled for age, sex, education, TIV, and scan sites. Highlights and bolded values indicate significant results after Bonferroni correction. CI, confidence intervals; CT, cortical thickness.

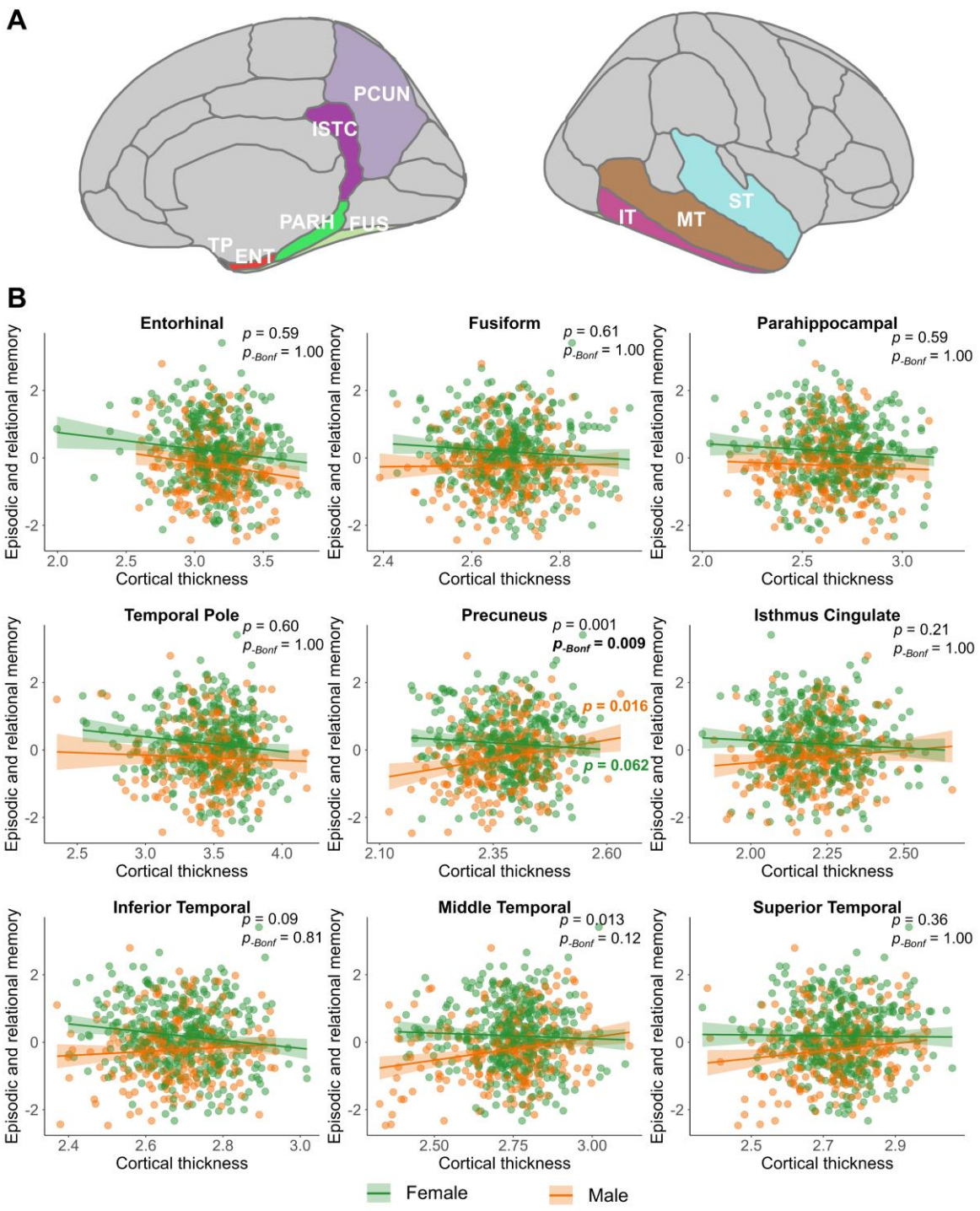

Figure 4.6 Associations of sex, regional cortical thickness, and episodic and relational memory. *(A) Nine AD signature regions based on the Desikan-Killiany atlas are shown for the medial (left) and lateral (right) views. (B) Interactions of sex and nine regional thickness on episodic and relational memory. On the x axis, higher scores represent greater cortical thickness, and on the y axis, higher scores represent better episodic and relational memory. P values were corrected for multiple comparisons across nine regions of interest. Abbreviations:*

TP, temporal pole; ENT, entorhinal; PARH, parahippocampal; FUS, fusiform; ISTC, isthmus cingulate; PCUN, precuneus; IT, inferior temporal; MT, middle temporal; ST, superior temporal.

4.3.6 Associations Between Risk Factors, Sex, Cortical Thickness and Cognition

Based on significant 2-way interactions of sex × global cortical thickness on episodic and relational memory, the impact of risk factors on this association was investigated. There were no significant 3-way interactions of APOE4/CAIDE × sex × global cortical thickness on episodic and relational memory (see Appendix III, STable 9.1).

Follow-up analyses on significant 2-way interactions of sex × precuneus cortical thickness on episodic and relational memory, the impact of risk factors on this association was also investigated. However, no significant 3-way interactions of APOE4/CAIDE × sex × precuneus cortical thickness were observed on episodic and relational memory (see Appendix III, STable 9.1).

4.4 Discussion

This study investigated the effects of risk factors on cognition and brain structure, and the effects of sex and risk factors on the relationship between brain structure and cognition, in the PREVENT cohort (N = 700). I found that higher CAIDE scores were associated with poorer performance in two cognitive domains, episodic and relational memory, and short-term memory binding. Higher CAIDE scores were also associated with lower global cortical thickness. By contrast, I found that more engagement in stimulating activities was associated with larger grey matter volume. Importantly, I found significant sex differences in the relationship between brain structure and cognition. Males with greater global cortical thickness showed better episodic and relational memory, whereas females showed no associations. Moreover, the sex-specific brain–cognition relationship was driven by the precuneus region. Males with greater precuneus cortical thickness showed better episodic and relational memory, and females again showed no associations. However, risk factors, APOE4 or CAIDE, did not interact with sex to affect the relationship between brain structure and cognition. These results shed light on some of the earliest cognitive and brain structural alterations due to cardiovascular risk of future dementia and sex-specific brain–cognition relationship in cognitively healthy middle-aged individuals.

Higher CAIDE scores were significantly associated with poorer episodic and relational memory and short-term memory binding in mid-life. This finding resonates with previous studies in a pilot (N = 210) sample of this cohort, which related higher CAIDE scores to worse performance in memory, processing speed, executive function (Stephen et al., 2017), and verbal, visuospatial functions and short-term memory (Deng et al., 2024). Furthermore, I also observed a negative association between CAIDE scores and global cortical thickness. This aligns with previous studies, both within PREVENT and in other middle-aged cohorts, of CAIDE-related brain structural changes such as widespread cortical thinning, greater brain volume atrophy,

ventricular enlargement, and more pronounced white matter lesions (Dounavi et al., 2022; Gourley et al., 2020; O'Brien et al., 2020; Stephen et al., 2017). However, I did not observe any effects of APOE4 on cognition and brain structure. The null results of APOE4 on cognition and brain structure may relate to inconsistent findings in the literature. While some studies have found that APOE4 was associated with poorer cognition or brain structure (Eich et al., 2019; Mak et al., 2024), others have observed null (Dounavi et al., 2022; Heneghan et al., 2023) or even beneficial effects of APOE4 (Deng et al., 2024; Ritchie et al., 2017; Zokaei et al., 2020), which have been interpreted in the context of antagonistic pleiotropy (Williams, 1957). Together, by replicating these CAIDE effects in the full PREVENT cohort, the present study provided strong evidence that cardiovascular dementia risk, as captured by the CAIDE score, was associated with early alterations of brain structure and cognition as early as mid-life.

In contrast to associations with the CAIDE score, I found that higher engagement in physically, socially and intellectually stimulating activities was associated with larger total grey matter volume. This finding makes an important contribution by extending previous work that has predominantly examined older adults to a cognitively healthy mid-life population. Most prior studies have focused on late life (Burzynska et al., 2014; Erickson et al., 2011; Raffin et al., 2021), with only a limited number including middle-aged to older cohorts (Raichlen et al., 2020). Studies in older adults have found that engagement in lifestyle activities was associated with less age-related reductions in hippocampal volume (Erickson et al., 2011; Suo et al., 2012; Valenzuela et al., 2008), cortical thickness (Raffin et al., 2021; Rektorova et al., 2020), and white matter integrity (Burzynska et al., 2014; Kleemeyer et al., 2016; Palta et al., 2021). The stimulating activities in current study comprised socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in energetic physical activities, reading, practicing a second language and travel. These suggests that diverse stimulating activities may help maintain or even boost brain structural health from mid-life. Moreover, these

opposing associations of dementia risk and reserve factors may reflect potentially different mechanisms, with vascular and metabolic pathways contributing to risk-related brain atrophy (Qiu & Fratiglioni, 2015), and neuroplasticity and neural efficiency supporting reserve-related brain maintenance (Hu et al., 2013; Stern et al., 2020; Valenzuela & Sachdev, 2006).

The key question in this study was to examine the effect of sex on the relationship between brain structure and cognition. To the best of my knowledge, this is the first study to show sex differences in the association between global (or precuneus) cortical thickness and cognition in mid-life. Males showed a positive association between global (or precuneus) cortical thickness and episodic and relational memory, while females showed no relationship between them. Previous research has suggested that cognition can be relatively preserved despite age- or disease-related changes in brain structure, a phenomenon often described as a dissociation between cognition and brain structure (D. Chan et al., 2018; Cieri et al., 2021; Lee et al., 2018). This dissociation has been interpreted within the framework of cognitive reserve (Stern, 2012; Stern et al., 2020), whereby some individuals maintain cognitive function despite impaired brain health due to aging or neurodegenerative diseases, while others do not (Arenaza-Urquijo et al., 2024; Stern, 2012). For example, Chan et al. (2018) found that cognitive performance in older adults with higher engagement in stimulating activities was less dependent on brain structure, whereas cognition in those with lower engagement was more strongly related to current structural brain health, a pattern consistent with the concept of cognitive reserve. Within this framework, sex differences in cognitive reserve have been proposed, with females potentially exhibiting greater reserve capacity than males (Cieri et al., 2021; Lee et al., 2018). Such reserve may allow females to maintain cognitive performance even in the presence of structural brain changes in the current study. In line with this interpretation, the absence of a significant association between cortical thickness and memory performance in females in the current study may reflect greater cognitive reserve, whereas the positive structure–cognition

relationship observed in males may indicate that their cognitive performance is more closely dependent on structural brain integrity.

Consistent with this framework, prior studies across the lifespan have shown that females often maintain comparable or superior cognitive performance despite reduced or equivalent brain integrity. For instance, females with MCI outperformed males in verbal memory despite equal levels of moderate hippocampal atrophy (Sundermann et al., 2016a), equivalent hypometabolism (Sundermann et al., 2016b) and similar neuropathological burdens (Sundermann et al., 2017). In cognitively healthy older adults, females exhibited better verbal memory performance despite poorer brain functional architecture compared to males (Cieri et al., 2021). Similar results were also observed in younger cohorts, where young females showed more efficient "small-world" brain network topology than males, indicative of enhanced neural processing efficiency (Sun et al., 2015). Furthermore, (Colom et al., 2013) observed that despite females having smaller hippocampal volume compared to males, their cognitive performance was comparable, and hippocampal volume–cognition associations were primarily positive in males but weak or negative in females. Importantly, this interpretation does not preclude the presence of sex differences in brain structure per se. In the current study, females showed significantly greater parahippocampal cortical thickness than males, which may contribute to their advantage in episodic and relational memory. However, despite this structural advantage, no sex differences were observed in the associations between parahippocampal cortical thickness and episodic and relational memory, and neither females nor males showed significant relationships between parahippocampal cortical thickness and memory performance (Figure 6B). Instead, sex differences emerged in the structure–cognition associations of the precuneus, a region that did not show a significant sex difference in cortical thickness.

Why might this reserve be especially pronounced in the precuneus? The precuneus is among the earliest and most vulnerable regions for tau tangles (Jones et al., 2017)and amyloid-β depositions (Aghakhanyan et al., 2018; Palmqvist et al., 2017), even before clinical symptoms emerge. As a core hub of the DMN, a network implicated in Alzheimer's vulnerability (Elman et al., 2016; Palmqvist et al., 2017), the precuneus may play a key role in compensatory processes (e.g., enhanced connectivity or metabolic efficiency) that preserve episodic and relational memory in females. Supporting this, previous research found stronger DMN connectivity in females (Allen et al., 2011; Bluhm et al., 2008; Jamadar et al., 2019; S. J. Ritchie et al., 2018), associated with lower cognitive decline (Buckley et al., 2017) and impairment (Chhatwal et al., 2013). However, evidence suggests that female's cognitive reserve may diminish as pathology progresses. For example, females initially maintain cognitive performance despite hippocampal atrophy better than men, but this advantage declines significantly following the transition to more advanced cognitive impairment (Koran et al., 2017). The current findings further support the hypothesis that females harness greater initial reserve in critical regions like the precuneus, at least in mid-life, although such reserve may weaken with increasing neuropathological burden. Future longitudinal studies will be essential to determine the role of sex-specific associations in the transition from normal to pathological aging.

Another key question asked in this study was whether risk factors would interact with sex to influence the relationship between brain structure and cognition. Contrary to my hypothesis, neither APOE4 genotype nor CAIDE score interacted with sex to affect this brain–cognition relationship. Several factors may underlie this null finding. Multiple studies suggest the existence of an inflection point of APOE4 effects around age 60, when APOE4 is more closely associated with Alzheimer's disease neuropathology (Saddiki et al., 2020). For instance, a recent diffusion MRI study revealed that cortical microstructural (orientation dispersion index)

trajectories in temporal regions split between APOE4 carriers and non-carriers at roughly age 60 (Mak et al., 2024). Similarly, researchers also showed that amyloid accumulation increased exponentially at age 60 in APOE4 carriers (Koychev et al., 2020), roughly a decade before the onset of greater cognitive decline in APOE4 carriers (Christensen et al., 2008; Rawle et al., 2018). Because the PREVENT participants had a mean age of only 52 years, the APOE4 effects on the sex-specific brain–cognition relationships are likely to become more pronounced in later life stages (i.e. around age 60). Furthermore, although CAIDE scores exceeding 8 confer substantial probabilities of future dementia, ranging from approximately 4% to as high as 29% within 40 years among middle-aged adults (Exalto et al., 2014; Kivipelto et al., 2006), relatively few of PREVENT participants exceed this threshold. Detecting interaction effects, especially three-way interactions, typically requires greater statistical power than main effects (Brysbaert, 2019; Sommet et al., 2023). The relatively small subgroup of high CAIDE (> 8) individuals in the mid-life cohort therefore limits the ability to detect subtle CAIDE × sex × brain structure interactions on cognition. Future longitudinal follow-up into participants' sixth and seventh decades, with larger high-risk samples, will be essential to determine whether APOE4 and CAIDE ultimately amplify sex differences in brain–cognition relationships.

Methodological Considerations

The PREVENT–Dementia program, initiated in 2014, prioritizes mid-life risk profiling and longitudinal follow-up, but lacks well-established preclinical biomarkers (e.g., amyloid or tau PET, CSF measures). This limits our ability to disentangle whether the observed sex-specific brain–cognition relationship reflects underlying Alzheimer's pathology. Future work incorporating fluid biomarkers or PET imaging will be essential to elucidate the pathological processes driving any sex differences. I caution that the interpretability of the effect of risk on

each individual cognitive function is limited by their composite assessment in this study and requires individuation in future studies. Finally, the observational cross-sectional nature of the present study precludes causal inference. Ongoing longitudinal waves two and three and beyond of this multi-site study will be critical for establishing the temporal dynamics of sex-specific brain–cognition relationships and for testing whether dementia risk factors ultimately amplify these sex differences over time.

4.5 Conclusion

In summary, this current study showed that higher cardiovascular dementia risk, indicated by the CAIDE score, was associated with worse cognition and reduced cortical thickness in cognitively healthy middle-aged individuals. By contrast, more engagement in stimulating activities was associated with larger grey matter volume. These findings suggest that cardiovascular dementia risk and reserve factors may influence brain structure through different neurobiological mechanisms. The current study makes a novel contribution by showing sex-specific brain structure–cognition relationship. Males showed a positive association between global (or precuneus) cortical thickness and cognition, whereas this association was absent in females, suggesting female's advantage of cognitive reserve in mid-life. These findings shed light on some of the earliest cognitive and brain structural alterations due to cardiovascular risk of future dementia and suggest that biological sex is an important variable to consider in cognitive reserve and resilience field.

5. Chapter 5: Connectome-based predictions of cognition and sex differences in mid-life individuals at risk for future dementia

5.1 Introduction

Having identified sex-specific differences in the relationship between brain structure and cognition in mid-life in the previous chapter, this chapter extends the inquiry to brain function, asking whether the functional connectome supporting cognition also shows sex-specific organisation, and whether dementia risks and reserve contributors relate to these functional networks in mid-life.

Episodic and relational memory are among the earliest cognitive functions to show changes in pre-symptomatic AD (Grober et al., 2008; Laukka et al., 2012; Small et al., 2003). Indeed, impairment of episodic memory is the hallmark of AD in the majority of cases (Welsh et al., 1992). Relational memory tasks, especially with a semantic memory aspect, have been used to differentiate between MCI and healthy aging (Ahmed et al., 2008). Although females experience higher AD incidence (Alzheimer's Association, 2021; Mielke, 2018) and exhibit faster progression once clinical pathology accelerates (Lin et al., 2015; Tifratene et al., 2015; van Loenhoud et al., 2019), they consistently outperform males in episodic memory tasks across the lifespan (Arenaza-Urquijo et al., 2024; Asperholm et al., 2019; Golchert et al., 2019), a pattern also observed in PREVENT cohort (Chapter 2; Qi et al., 2024). Understanding whether sex differences in functional connectome patterns underlie these behavioural differences may provide insight into why females show initial cognitive advantages yet greater vulnerability once pathological processes accelerate.

Episodic and relational memory is subserved by distributed brain networks involving the default mode, salience and frontoparietal networks (Alm et al., 2022; Kim, 2016; Palacio & Cardenas, 2019; Ray et al., 2020; Ritchey et al., 2015). Disrupted functional connectivity within these networks have been found in MCI and AD patients (Bai et al., 2009; Greicius et al., 2004; Sorg et al., 2007), and even in asymptomatic older adults (age > 60 years) with amyloid burden (Nakamura et al., 2017; Song et al., 2015; Sperling et al., 2009). Despite mounting studies on network dysfunction in aging and disease, only a few studies have investigated how sex differences in these networks underpin sex differences in memory performance. For example, Ju et al. (2023) and Ficek-Tani et al. (2023) provided preliminary evidence that, in healthy adults, females exhibited stronger connectivity within key DMN nodes, especially in posterior regions, which was associated with better memory performance, whereas males displayed alternative network profiles (e.g., more reliance on visual networks). These findings underscore the need for approaches that capture distributed, whole-brain connectivity patterns underlying cognition.

Connectome-based predictive modeling (CPM) provides a powerful, data-driven approach for addressing these gaps by linking whole-brain connectivity patterns to individual differences in cognitive performance (Shen et al., 2017). CPM has been successfully used to predict cognitive functioning, symptom severity, and disease states across a rang of populations (Prakash et al., 2025; Rohr et al., 2020; Tripathi et al., 2025; Weng et al., 2024; Yip et al., 2019). To date, however, only one CPM study has examined sex differences in brain-based predictors of memory performance, and this work was conducted in a broad healthy aging cohort spanning early adulthood to late life (36–100 years; Ju et al., 2023). It therefore remains unclear whether sex-specific functional connectomes supporting episodic and relational memory are detectable in mid-life individuals who are currently cognitively healthy but at risk for late-life dementia.

Dementia risk and reserve contributors may further influence the memory-related functional connectome. APOE4 and mid-life CAIDE score are well-established dementia risks associated with cognitive (Deng et al., 2024; K. Ritchie et al., 2018; Ritchie et al., 2017) and brain structural changes in mid-life (Dounavi et al., 2022; Low et al., 2022b; O'Brien et al., 2020). However, the effects of these risk factors on brain functional connectivity during this stage, especially on brain connectivity that underlies memory performance, have not been investigated. Conversely, modifiable reserve contributors, such as engagement in stimulating activities and occupational attainment, may confer cognitive reserve by promoting neural efficiency and connectivity (Hu et al., 2013; Stern et al., 2020; Valenzuela & Sachdev, 2006). In our previous work, engagement in stimulating activities was positively associated with episodic and relational memory in mid-life independent of education (Heneghan et al., 2023; Qi et al., 2024), while occupational attainment showed a sex-specific positive association with episodic and relational memory in at-risk mid-life individuals (Qi et al., 2024). It is currently unknown whether either stimulating activities, or occupational attainment also relate to memory-related functional connectome and whether they offset dementia risk effects in mid-life, 20-30 years prior to typical symptom onset.

Chapter 2 identified a three-way interaction between biological sex, APOE4, and occupation on episodic and relational memory (Qi et al., 2024), but the brain functional mechanisms underlying this interaction remain unclear. In particular, it is unknown whether there are sex-specific functional patterns that enable females, especially APOE4 carrier females, to benefit from occupational attainment on their cognition.

To address these gaps, this chapter had three aims: 1) to identify whole-brain functional connectome associated with episodic and relational memory using the CPM approach, with a specific consideration of sex differences; 2) to investigate whether dementia risk (APOE4,

CAIDE) and mid-life reserve contributors (stimulating activities, occupational attainment) are related to the functional connectome underlying memory performance; 3) to test whether the interaction of biological sex, APOE4 and occupational attainment observed in episodic and relational memory is reflected in this functional connectome.

5.2 Methods

5.2.1 Participants

The same mid-life cohort investigated in the previous chapters was included in this study (N = 700). For a detailed description of the cohort, please refer to Chapter 2, Section 2.2.1. Of the initial 700 participants, 647 had MRI scans available for analysis. Participants were then excluded due to poor image quality (n = 9), incidental findings (n = 17), inadequate field of view (n = 29) and missing demographic information (n = 7), resulting in 585 participants for fMRI data preprocessing. Subsequently, individuals with incomplete cognitive data (n = 20) or excessive head motion (n = 72) were removed (for details, see Section 2.6 MRI data acquisition and pre-processing), leaving 488 participants (316 Females/172 Males) for the CPM analyses. A detailed breakdown of participant exclusions is available in the Appendix IV and SFigure 10.1. The study reports the wave 1 (baseline) testing data, which were completed at the time of this thesis preparation. Wave 2 and 3 of testing are currently ongoing.

5.2.2 Biological Sex

While the dichotomies of sex and gender are no longer considered to be sharply discrete, in this study ‘sex’ was defined as an individual’s natal or biological sex, and was self-reported in the Brain Injury Screening Questionnaire.

5.2.3 Risk Factors

Full description of risk factors investigated in this study can be found in Chapter 4 (Section 4.2.3).

5.2.4 Cognitive Reserve Contributors

Reserve contributors (stimulating activities, occupational attainment) were assessed using the Lifetime of Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007). See Chapter 2 (Section 2.2.7) for a full description of the LEQ assessment used in this study.

5.2.5 Cognitive Assessments

Full descriptions of the cognitive assessments used in this study can be found in Chapter 2 (Section 2.2.8 & 2.3.2). Briefly, rotated principal component analysis clustered 13 cognitive measures into three related cognitive components (C): C1, episodic and relational memory; C2, multisensory processing; and C3, short-term memory binding. In this study, I focused on the first components, episodic and relational memory, as these functions are among the earliest to show changes in pre-symptomatic AD (Grober et al., 2008; Laukka et al., 2012; Small et al., 2003; Welsh et al., 1992). The cognitive loadings of the first component were replicated in two independent pilot sub-groups of the PREVENT–Dementia cohort (Deng et al., 2024; Qi et al., 2024), demonstrating that the analysis is robust in capturing the most varying cognitive functions for this mid-life cohort. Additionally, consistent evidence from the literature demonstrates that females outperform males in episodic memory across the lifespan (Arenaza-Urquijo et al., 2024; Asperholm et al., 2019; Golchert et al., 2019). This sex difference was also evident in the PREVENT cohort, where females exhibited significantly better performance in episodic and relational memory compared to males (Qi et al., 2024).

5.2.6 MRI Data Acquisition and Pre-processing

As part of the PREVENT-Dementia MRI protocol, all study sites used 3T Siemens (Siemens Healthcare, Erlangen, Germany) scanners with models varying depending on the scanning site (Verio, PRISMA, Prisma Fit, Skyra). The resting-state fMRI was obtained using a gradient-

echo EPI sequence with the following parameters: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle = 90°, FOV = 192 × 192 mm^2, voxel size = 3 mm^3 isotropic, 33 interleaved slices covering the whole brain, and in total 330 volumes acquired in about 11 min. In addition, high-resolution brain structural images were acquired for each participant using a 3D T1-weighted magnetization prepared rapid gradient-echo (MPRAGE) sequence (TR = 2,300 ms, TE = 2.98 ms, slice thickness = 1 mm, FOV = 240 × 256 mm^2, flip angle = 9°, voxel size = 1 mm^3 isotropic, and 160 slices).

The resting-state fMRI data were preprocessed using the Automatic Analysis (AA) software package (Cusack et al., 2014) based on the Statistical Parametric Mapping (SPM) software (https://www.fil.ion.ucl.ac.uk/spm/). I first performed the slice timing and motion correction. Then, I co-registered functional images to the individual structural images and normalized them in the Montreal Neurological Institute (MNI) standard space. The functional images were then smoothed with a Gaussian smoothing kernel of 6 mm full width at half maximum (FWHM) and were temporally band-pass filtered (0.01-0.08 Hz). In addition, I applied a general linear model (GLM) including 24 head motion parameters and white matter (WM) and cerebrospinal fluid (CSF) signals to reduce residual effects of head motion and other noise confounders. The 24 parameters included six original rigid-body motion parameters, the first-order temporal derivatives of these six parameters, and 12 quadratic terms of the original motion parameters and their derivatives (Satterthwaite et al., 2013).

Head motion can significantly inflate functional connectivity estimates (Frew et al., 2022; Power et al., 2014; Yan et al., 2013). To mitigate this, I carefully measured and controlled for head motion using a “scrubbing” procedure (Power et al., 2012). Specifically, I calculated framewise displacement (FD) as an index of data quality (see Appendix for details), which quantifies head movement between consecutive frames. Frames exceeding an FD threshold of

0.3 mm were flagged as motion-contaminated and removed prior to functional connectivity calculation (Power et al., 2012). To ensure sufficient data remained after scrubbing, I applied a participant inclusion criterion requiring at least 150 frames (~5 min) of usable data, based on wide agreement that ~5 min of fMRI data is adequate for resting-state functional connectivity analyses (Van Dijk et al., 2010). After scrubbing, the included participants retained 84.3 % ± 13.2 % of frames, with a mean FD of 0.16 ± 0.03 mm. The mean FD across retained frames was further regressed in the CPM analysis to account for residual head motion effects (Power et al., 2014). Importantly, there was no significant association of mean FD with episodic and relational memory (r = -0.01, p = 0.89). This suggests that head movement did not significantly influence the results.

5.2.7 Functional Connectivity Network Construction

The Dosenbach 160 atlas (Dosenbach et al., 2010) was used to extract the mean time series, constructing a functional connectivity (FC) matrix for each participant. Due to constraints in scanning, some participants' functional imaging did not have an adequate FOV, missing either top or bottom slices. Structural T1-weighted images were complete and unaffected by these constraints. To address this limitation, I removed 25 brain nodes and retained 585 participants whose data all shared the same 135 nodes. The detailed procedure is documented in Cao et al. (2025). The 135 regions based on the Dosenbach atlas comprising 6 networks, including the default mode network (DMN, 32 ROIs), frontoparietal network (FPN, 20 ROIs), cingulo-opercular network (CON, 31 ROIs), sensorimotor network (SMN, 22 ROIs), visual network (VSN, 22 ROIs), and cerebellum network (CBN, 8 ROIs). Pearson's correlation coefficients were computed between the mean time series of each pair of nodes, and a Fisher's r-to-z transformation was then applied to normalize the correlation coefficients. Finally, I further applied the ComBat harmonization (Fortin et al., 2017), an empirical Bayesian method, to

remove any scanning site effect. The harmonized 135×135 FC matrix for each participant was used in the subsequent CPM analysis. All data were harmonized in a single step after data acquisition was completed. Site-level characteristics were examined to assess whether key assumptions for harmonization were reasonably satisfied (Jodoin et al., 2025) (Appendix IV, Supplementary Results).

5.2.8 Connectome-based Predictive Modeling (CPM)

CPM is a data-driven approach that identifies pairwise connections between brain regions that are most strongly correlated with a given phenotype (Shen et al., 2017). Using the FC matrix, I applied CPM to identify brain connections associated with episodic and relational memory across all participants, as well as separately for female-only and male-only groups (three separate models). Within each model, I implemented a repeated 10-fold cross-validation (CV) procedure, randomly dividing participants into ten groups. Nine groups were used as the training set, while the remaining group as the testing set. To account for the random splits, this 10-fold CV process was repeated 100 times and the average predictive performance across iterations was reported. As illustrated in Figure 5.1, CPM consists of the following steps: (1) In the training set, I performed partial regression to identify connections in the FC matrix significantly associated with a behavioural phenotype (here, episodic and relational memory) while controlling for age, years of education and mean FD. (2) Feature selection. A significance threshold of $p = 0.05$ was applied to select relevant connections. Connections positively or negatively correlated with memory performance were categorized into positive and negative networks, respectively. (3) Network strength calculation. For each participant in the training set, I calculated network strength by summing the selected connections from the FC matrix separately for positive and negative networks. I also estimated the combined network strength by subtracting the strength of the negative network from the strength of the positive network.

(4) Model building. Then predictive linear models were built between the positive/negative/combined network strength (independent variable) and episodic and relational memory (dependent variable) in the training set, with age, years of education, and mean FD included as covariates. (5) Model application. For each participant in the testing set, I computed the network strengths and input them into the trained linear models, along with the aforementioned covariates, to generate predictions for episodic and relational memory performance. (6) Model assessment. The predictive performance was evaluated by correlating the observed and predicted episodic and relational memory.

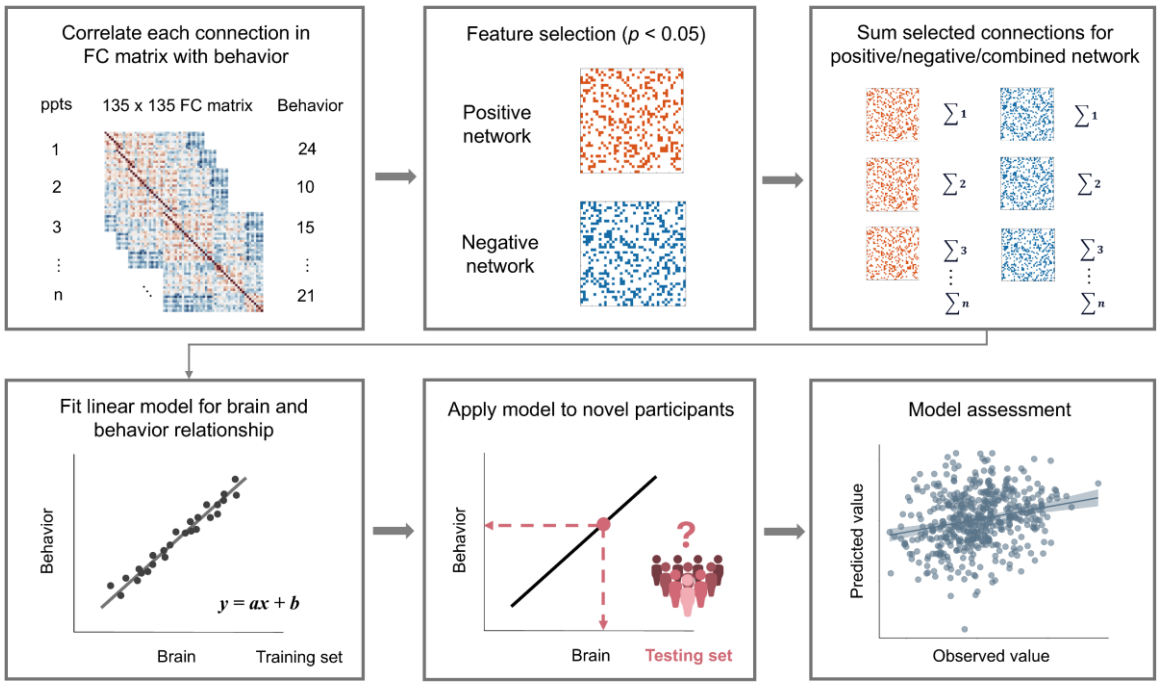

Figure 5.1. Schematic overview of CPM. *(Step 1) In the training set, each connection in the functional connectivity matrix is correlated with the behavioral phenotype, controlling for covariates. (Step 2) A threshold of p = 0.05 is applied to select significant connections. Connections positively or negatively correlated with the behavioral phenotype were categorized into positive and negative networks, respectively. (Step 3) Network strengths are computed by summing the selected positive and negative connections, respectively. Combined network*

strength was also estimated by subtracting the strength of the negative from the strength of the positive network. (Step 4) Predictive linear models were built between the positive/negative/combined network strength and the behavioral phenotype in the training set. (Step 5) For each participant in the testing set, the network strength is calculated and input into the trained linear models along with the covariates, to generate predictions for the behavioral phenotype. (Step 6) Model performance is evaluated by correlating the observed and predicted values.

5.2.9 Sensitivity Analyses

I performed several supplementary analyses to assess the influence of potential confounding factors on the main results. First, I used different CV schemes to examine the robustness of the CPM results: 5-fold and 20-fold. Next, to account for the influence of head motion on the predictive performance, I conducted CPM analyses with different exclusion criteria for head motion (mean FD < 0.3, 0.4 and 0.5 mm). Finally, I explored the sensitivity of the predictive performance to different thresholds for feature selection (p < 0.005, 0.01, and 0.1).

5.2.10 External Validation: Cam-CAN dataset

Participants

I used an open dataset of participants from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) project (available at http://www.mrc-cbu.cam.ac.uk/datasets/camcan/) as the external validation dataset. Cam-CAN is a large-scale, collaborative research project aimed at elucidating the neurocognitive mechanisms underlying healthy cognitive ageing. The detailed protocol for this project has been described previously (Shafto et al., 2014; Taylor et al., 2017). The Cam-CAN cohort comprises healthy volunteers aged 18-88 years. From a total of 708

participants, I selected 206 middle-aged individuals (40–59 years old) who had complete demographic data (e.g., age, sex, years of education) and episodic memory tests (assessed by the Wechsler Logical Memory task). This selection aligns with the age group of the PREVENT dataset.

MRI acquisition and pre-processing

The MRI data were collected at the Medical Research Council Cognition and Brain Science Unit (MRI-CBSU) using a 3T Siemens TIM Trio scanner with a 32-channel head coil. Full descriptions of the MRI protocols have been described elsewhere (Taylor et al., 2017). Resting-state fMRI data were acquired using a T2*-weighted EPI sequence with participants resting with their eyes closed. 261 volumes were acquired, and each volume contained 32 axial slices (in descending order) with a slice thickness of 3.7 mm and an interslice gap of 20% (TR = 1970 ms, TE = 30 ms, FA = 78°, FOV = 192 × 192 mm^2, voxel size = 3 mm × 3 mm × 4.44 mm). The structural MRI data were acquired using a T1-weighted MPRAGE sequence (TR = 2250 ms, TE = 2.99 ms, FA = 9°, FOV = 256 mm × 240 mm × 192 mm, voxel size = 1 mm^3 isotropic).

Resting-state fMRI data were preprocessed by the Cam-CAN group using a standard preprocessing pipeline with SPM and AA software (Cusack et al., 2014). Details of the pipeline are described in (Taylor et al., 2017). Briefly, raw functional data were unwarped using field map images for distortion correction due to magnetic field inhomogeneities, realigned for motion correction, and corrected for slice timing. Functional images were then coregistered with T1 structural images and normalised to MNI standard space.

Additional preprocessing steps were applied to the functional data before computing the FC matrices. Functional images were then smoothed with a Gaussian smoothing kernel of 6 mm FWHM and were temporally band-pass filtered (0.01-0.08 Hz). I next applied a GLM including 24 head motion parameters and WM and CSF signals to reduce residual effects of head motion

and other noise confounders. Participants with excessive head motion were removed using the same "scrubbing" procedure adopted for the PREVENT dataset, resulting in the exclusion of 45 individuals and leaving N = 161 participants (83 Females/78 Males) for further analysis. After scrubbing, the included participants retained 88.3 % ± 12.4 % of frames, with a mean FD of 0.14 ± 0.03 mm. The mean FD across retained frames was also regressed out in the CPM analysis to mitigate any remaining head motion effects (Power et al., 2014). Importantly, mean FD was not significantly associated with episodic memory ($r = -0.11$, $p = 0.18$), indicating that head motion was not a substantial potential confound of the external validation results.

Functional connectivity network construction

All procedures of constructing 135×135 FC matrices were the same as those described in Methods Section *Functional Connectivity Network Construction*.

External generalizability of CPM validation

To examine the generalizability of the predictive models from the PREVENT-Dementia cohort, I applied the identified CPM models to the middle-aged participants in the Cam-CAN dataset. I fitted the positive/negative network strength of the Cam-CAN dataset to the trained linear models and generated the predicted scores for episodic memory, with age, years of education, and mean FD included as covariates. Furthermore, I estimated the predictive performances of the identified CPM models by calculating the correlation between the predicted episodic memory scores and episodic memory scores in the Cam-CAN dataset.

5.2.11 Statistical Approach

For each model in the CPM analysis, I conducted a permutation test to assess the significance of the predictive performance, defined as the correlation between the observed and predicted values. To generate a null distribution of these correlation values, I randomly shuffled the

correspondence of the behavioral data and the FC matrix of the participants, and reran the CPM pipeline 5000 times using the shuffled data. Based on this null distribution, I set statistical significance at $p < 0.05$ (95% confidence level) for the predictive performance of all participants' model and generalization in Cam-CAN. The Bonferroni correction method was used for all participants, female-only and male-only models. The CPM analyses were conducted with MATLAB R2022a (MathWorks, Natick, MA) using the CPM package (https://github.com/rorytboyle/flexible_cpm).

The following statistical analyses were conducted with R software (https://www.R-project.org/). The normality of the data was assessed by combining the visualization of a quantile-quantile plot and the Shapiro–Wilk test. Demographic and clinical information of the study cohort were analysed across sexes using chi-square (χ^2 tests) for categorical variables (APOE4), and Mann-Whitney U tests or independent samples t-tests for continuous variables (*Mann-Whitney U test*: age, years of education, CAIDE score, stimulating activities, occupational attainment, short-term memory binding, and mean FD; *independent samples t-test*: episodic and relational memory, and multisensory processing), depending on whether they met the assumption of normality in this cohort.

Independent linear regression models investigated the main effects of dementia risks and reserve contributors on the functional connectome associated with episodic and relational memory. In the subsequent analyses, I focused on the strengths of the positive and negative networks, as the combined network model did not significantly predict episodic and relational memory. Specifically, first the models examined the main effects of risk factors (CAIDE and APOE4) on positive and negative network strength separately, with mean FD included as covariate. Then the models examined the main effects of reserve contributors (stimulating activities and occupational attainment) on positive and negative network strength separately,

with age, sex, years of education, and mean FD included as covariates. Building on Chapter 2's findings, which found a trend interaction of sex × occupation and a significant three-way interaction APOE4 × sex × occupation on episodic and relational memory, I further investigated the two-way interaction of sex × occupation and three-way interaction of APOE4 × sex × occupation on positive and negative network strength separately. In these analyses, stimulating activities, years of education, age, sex, and mean FD were included as covariates. The Bonferroni correction was used to correct for multiple comparisons.

It should be noted that some assumptions underlying ComBat harmonization may not have been fully met in the present study (Appendix IV, Supplementary Results). In particular, variability in sample size across sites, including one site with a relatively small sample (N = 13) (Appendix IV, STable 10.16), may have led to less stable estimation of covariate effects. This was reflected in the visual inspection of site-specific age effects, where smaller sites showed deviations from the overall pattern observed in larger sites (Appendix IV, SFigure 10.2). However, as the majority of sites demonstrated consistent age-related trends, these deviations are more likely to reflect sampling variability rather than a systematic violation of ComBat assumptions. Age distributions showed substantial overlap across sites within the targeted mid-life range (40–60 years), despite minor differences in distribution shape (Appendix IV, SFigure 10.3). Importantly, primary CPM analyses were repeated using non-harmonized data, and the main findings remained consistent, with functional connectivity predicting memory performance in all participants and in females, but not in males (Appendix IV, STable 10.17). This supports the robustness of the results and suggests that they are unlikely to be driven solely by the harmonization procedure.

5.3 Results

5.3.1 Demographics

Demographic variables, cognition, and lifestyle activities scores of the PREVENT cohort are summarized in Table 5.1. Females and males did not differ significantly in age, years of education, APOE4 carrier status, stimulating activities, 2 of the 3 cognitive domains, and head motion. Females had significantly lower CAIDE scores, significantly lower occupational attainment, and significantly higher episodic and relational memory.

Table 5.1 Participant characteristics

Participant characteristics	All	Females	Males	*p* value	Effect size
PREVENT-Dementia cohort					
N	488	316	172	–	–
Age (y)	52.0 (8.0)	52.0 (8.0)	52.0 (10.0)	0.33	0.04
Years of education	17.0 (4.0)	17.0 (5.0)	17.0 (3.0)	0.35	0.04
APOE4 (% Carriers)	38.3%	37.3%	40.1%	0.55	0.03
CAIDE	6.0 (4.0)	5.0 (4.0)	6.0 (5.0)	<0.001	0.20
Episodic and relational memory	0.02 (1.0)	0.18 (1.0)	-0.29 (0.9)	<0.001	0.49
Multisensory processing	-0.01 (1.0)	0.02 (1.0)	-0.07 (1.1)	0.35	0.09
Short-term memory binding	0.14 (1.1)	0.11 (1.2)	0.17 (1.1)	0.21	0.06
Occupational attainment	13.3 (6.3)	12.5 (6.8)	14.8 (6.9)	<0.001	0.20
Stimulating activities	18.0 (5.0)	18.0 (5.0)	18.0 (4.3)	0.18	0.06
Mean FD	0.16 (0.04)	0.16 (0.04)	0.17 (0.05)	0.19	0.06

NOTE: median (interquartile range, IQR) was reported for non-normal distributed continuous variables. Mean (SD) was reported for normal distributed continuous variables. Effect size was determined using *r* for Mann-Whitney U test, Cohen's *d* for independent samples t-test and φ for the Chi-Square test. Abbreviations: APOE4, Apolipoprotein E4 genotype; CAIDE, Cardiovascular Risk Factors, Aging and Dementia; FD, framewise displacement.

5.3.2 Prediction of Episodic and Relational Memory

Using resting-state functional connectivity data from the training set, the connectome-based predictive models were able to predict episodic and relational memory performance in novel participants (i.e., those in the testing set of the 10-fold cross-validation) across the entire cohort. Both positive and negative network models significantly predicted episodic and relational memory performance (positive: r = 0.161, $p < 0.001$; negative: r = 0.108, $p = 0.013$), whereas the combined network model did not reach significance after Bonferroni correction (r = 0.104, $p > 0.05$ after correction) (Figure 5.2A).

In the female-only group, the positive network model significantly predicted memory performance (r = 0.184, $p = 0.001$), but the negative and combined network models (negative: r = 0.112, combined: r = 0.140, both $p > 0.05$ after Bonferroni correction) did not (Figure 5.2B). In contrast, none of the models, positive, negative or combined network models, significantly predicted episodic and relational memory in the male-only group (positive: r = 0.01, negative: r = 0.164, combined: r = 0.142, all $p > 0.05$ after Bonferroni correction) (Figure 5.2C). In addition, Steiger's Z value was used to test the difference in model performances between female-only and male-only models. Female-only group significantly outperformed male-only group in positive network model (Z = 1.845, $p = 0.033$).

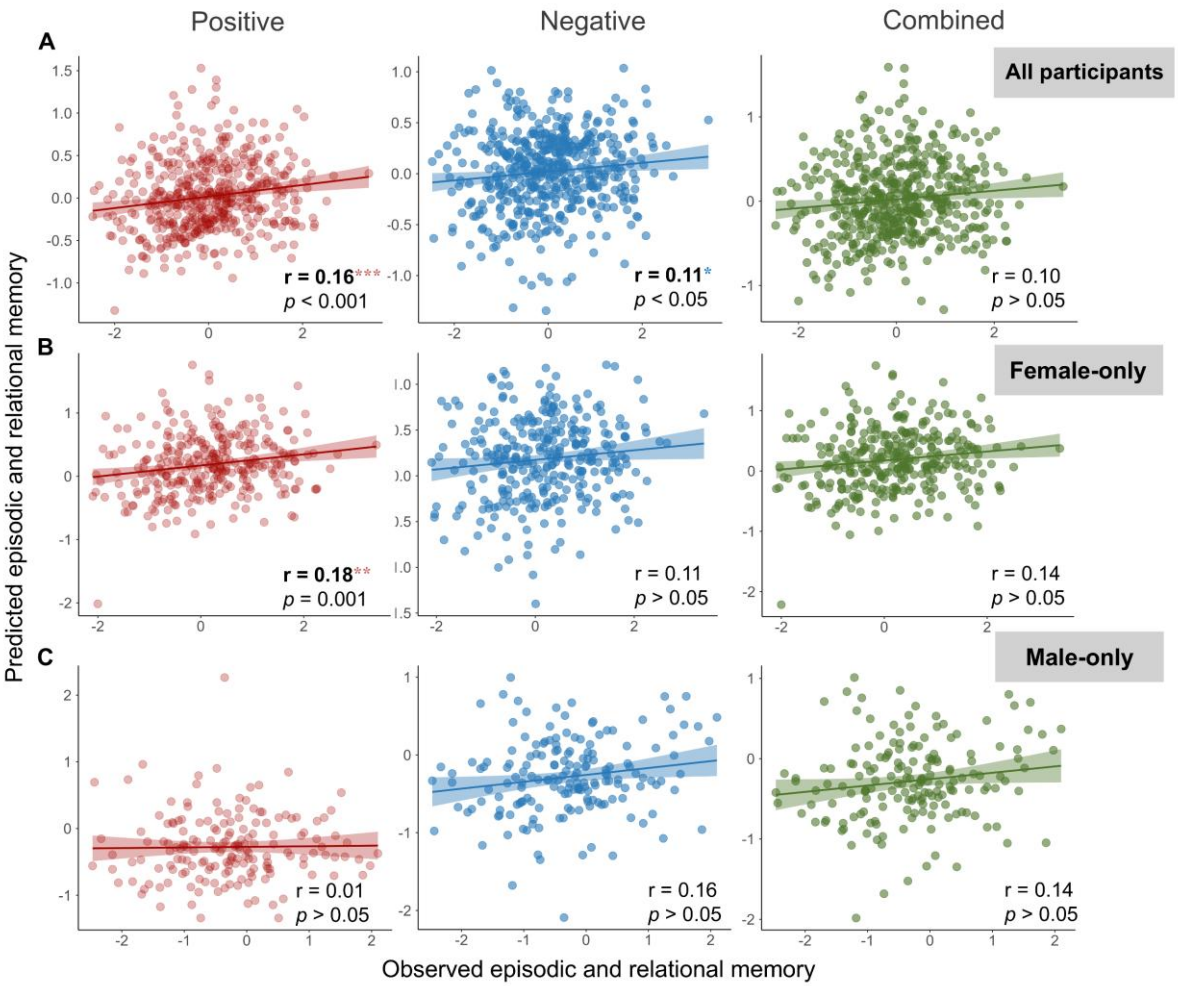

Figure 5.2 CPM predictive performances of episodic and relational memory. *Correlation between observed and predicted episodic and relational memory of positive, negative and combined network for (A) all participants, (B) female-only group, and (C) male-only group. *** = $p < 0.0005$; ** = $p < 0.005$; * = $p < 0.05$.*

5.3.3 Functional Connectomes of Episodic and Relational Memory

I divided the 135 nodes into six macroscale regions and applied the parcellation to the positive and negative networks to obtain the number of connections between regions involved in the

prediction. Within the entire cohort, for the positive prediction network contained 353 edges (3.90 % of the total 9045 edges) that positively correlated with episodic and relational memory. The negative prediction network contained 86 edges (0.95 % of the total 9045 edges) that negatively correlated with episodic and relational memory. The connectome patterns of positive and negative predictive networks are shown in Figure 5.3A. The matrix plots in Figure 5.3A shows the important networks that significantly predicted episodic and relational memory among all participants. In relation to canonical functional networks (Noble et al., 2017), in the positive network connectome, the DMN contributed the most to the within-network connections (44 edges). The connection between DMN and CON contributed the most to the between-network connections (50 edges). The other network pairs (DMN-SMN: 35 edges; within CON: 32 edges) were also important predictors of episodic and relational memory. The negative network connectome was characterised by the within-network connections of CON (20 edges), and the between-network connections between DMN and FPN (22 edges), as well as connections between SMN and CON (15 edges). In relation to the nodal level, detailed information on the top 20 nodes from the positive and negative networks for all the participants group is provided in Appendix IV, STable 10.2–10.3.

Similarly, in the female-only group, the positive prediction network contained 338 edges (3.73 % of the total 9045 edges) that positively correlated with episodic and relational memory. The negative prediction network contained 70 edges (0.77 % of the total 9045 edges) that negatively correlated with episodic and relational memory (Figure 5.3B). In the positive network connectome, the DMN contributed the most to the within-network connections (40 edges). The connection between DMN and CON contributed the most to the between-network connections (43 edges). The negative network connectome was characterised by the between-network connections between DMN and FPN (16 edges); however, the negative network model did not predict memory performance after correction. Detailed information on the top 20 nodes from

the positive and negative networks for the female-only group is provided in Appendix IV, STable 10.4–10.5.

In the male-only group, for the positive prediction network contained 140 edges (1.55 % of the total 9045 edges) that positively correlated with episodic and relational memory. The negative prediction network contained 503 edges (5.56 % of the total 9045 edges) that negatively correlated with episodic and relational memory (Figure 5.3C). The connectomes in the male-only models were different from those in all participants and female-only models. Specifically, the positive network connectome was characterized by within-network connections of FPN and DMN, and the negative network connectome was characterized by between- and within-networks connection of CON, DMN and VSN. Detailed information on the top 20 nodes from the positive and negative networks for the male-only group is provided in Appendix IV, STable 10.6–10.7.

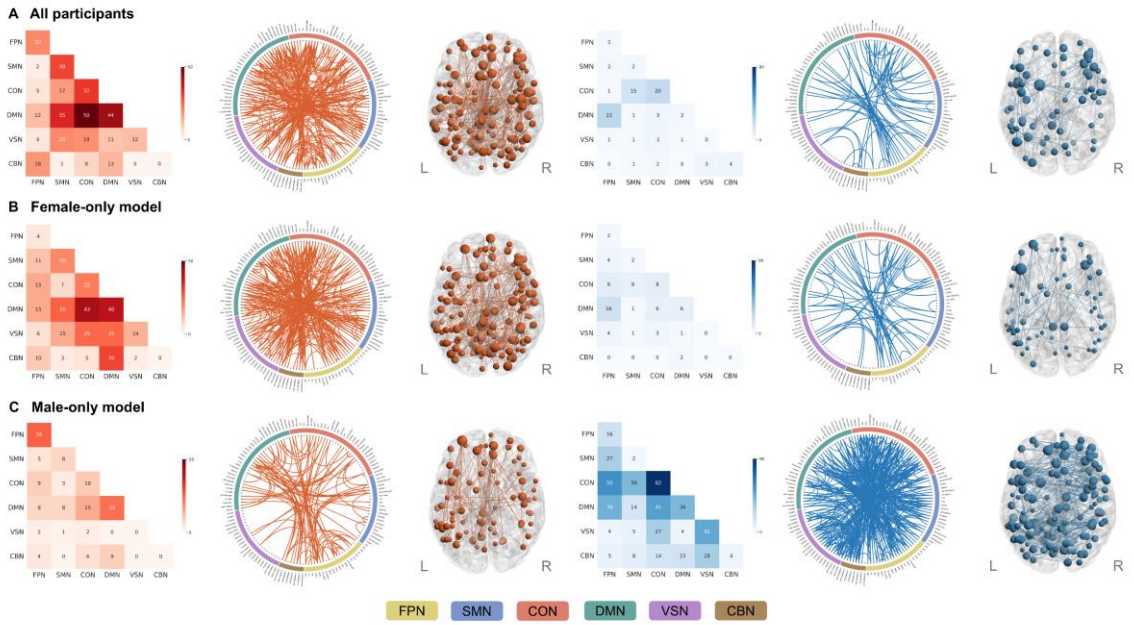

Figure 5.3 Connectome of positive and negative networks of episodic and relational memory. *Connectivity matrices, circular plots and glass brains of positive and negative networks for (A) all participants, (B) female-only group, and (C) male-only group. Red and blue matrices/spheres/nodes represent positive and negative networks respectively. Abbreviation: FPN, frontoparietal network; SMN, sensorimotor network; CON, cingulo-opercular network; DMN, default mode network; VSN, visual network; CBN, cerebellum network; R/L, right/left hemisphere.*

5.3.4 Sensitivity Analyses of CPM

Several additional analyses confirmed that the CPM model consistently predicted episodic and relational memory using functional connectivity across the cohort and for females, but not for males. First, a different cross-validation scheme ($k = 5$) did not affect predictive performance, with significant predictions observed for positive ($r = 0.161$, $p < 0.001$) and negative ($r = 0.108$,

p = 0.010), but not for combined networks (p > 0.05 after correction) across all participants. The positive network model significantly predicted memory performance (r = 0.184, p = 0.001), but the negative and combined network models (both p > 0.05 after Bonferroni correction) were not able to predict memory performance in the female-only group. None of the models, positive, negative or combined network models, significantly predicted episodic and relational memory in the male-only group (all p > 0.05 after Bonferroni correction) (Table 5.2). Second, the model remained robust when varying the feature selection threshold (p = 0.005 or 0.01), producing similar results for all participants, female-only and male-only groups (Table 5.3). Finally, using different head motion exclusion criteria (mean FD < 0.4 or 0.5 mm) also did not alter the results (Table 5.4).

Table 5.2 Influence of cross-validation schemes on the CPM performance

k-fold CV schemes	Groups	Positive network		Negative network		Combined network	
		r	*p*	r	*p*	r	*p*
10-fold (Main results)	All participants	0.161	**<0.001**	0.108	**0.013**	0.104	0.035
	Female-only	0.184	**0.001**	0.112	0.025	0.140	0.023
	Male-only	0.010	0.418	0.164	0.024	0.142	0.084
5-fold	All participants	0.158	**0.002**	0.111	**0.010**	0.100	0.047
	Female-only	0.180	**0.002**	0.108	0.030	0.133	0.026
	Male-only	0.022	0.362	0.158	0.029	0.128	0.096

Note: CV, cross-validation. Bold font indicates p value survived after Bonferroni correction.

Table 5.3. Influence of feature selection thresholds on the CPM performance

Feature selection thresholds	Groups	Positive network		Negative network		Combined network	
		r	*p*	r	*p*	r	*p*
$p < 0.005$	All participants	0.144	**0.005**	0.144	**0.003**	0.112	0.039
	Female-only	0.185	**0.002**	0.161	**0.011**	0.157	0.020
	Male-only	0.064	0.271	0.182	0.030	0.170	0.056
$p < 0.01$	All participants	0.160	**0.001**	0.114	0.023	0.119	0.028
	Female-only	0.174	**0.004**	0.135	0.018	0.143	0.027
	Male-only	0.054	0.267	0.183	0.025	0.170	0.053

Note: Bold font indicates *p* value survived after Bonferroni correction.

Table 5.4. Influence of head motion exclusion criteria on the CPM performance

Head motion exclusion criteria	Groups	Positive network		Negative network		Combined network	
		r	*p*	r	*p*	r	*p*
Mean FD < 0.4	All participants	0.128	**0.004**	0.143	**<0.001**	0.048	0.256
	Female-only	0.130	**0.008**	0.136	**0.011**	0.034	0.347
	Male-only	0.013	0.404	0.134	0.031	0.053	0.295
Mean FD < 0.5	All participants	0.130	**0.004**	0.129	**0.003**	0.056	0.198
	Female-only	0.131	**0.012**	0.134	**0.008**	0.046	0.291
	Male-only	0.039	0.295	0.111	0.081	0.043	0.336

Note: FD, framewise displacement. Bold font indicates *p* value survived after Bonferroni correction.

5.3.5 Generalizability: External Validation in Cam-CAN

The demographic information of the Cam-CAN cohort is shown in Appendix IV, STable 10.1. The positive, negative and combined networks identified from all participants of PREVENT dataset could not predict episodic memory in mid-life adults in the Cam-CAN dataset (r = 0.06, r = 0.06, and r = 0.08, respectively, all $p > 0.05$). The positive, negative and combined networks identified from female-only and male-only groups of the PREVENT dataset also could not predict episodic memory in female or male participants in the Cam-CAN dataset (female-only: r = 0.02, r = -0.002, and r = 0.02, respectively, all $p > 0.05$; male-only: r = 0.03, r = -0.04, and r = -0.05, respectively, all $p > 0.05$).

5.3.6 Sex Differences in Network Strength

Females had significantly higher positive network strength compared to males ($p < 0.001$) (Figure 5.4A). Females and males did not have significant difference in the negative network strength (Figure 5.4B).

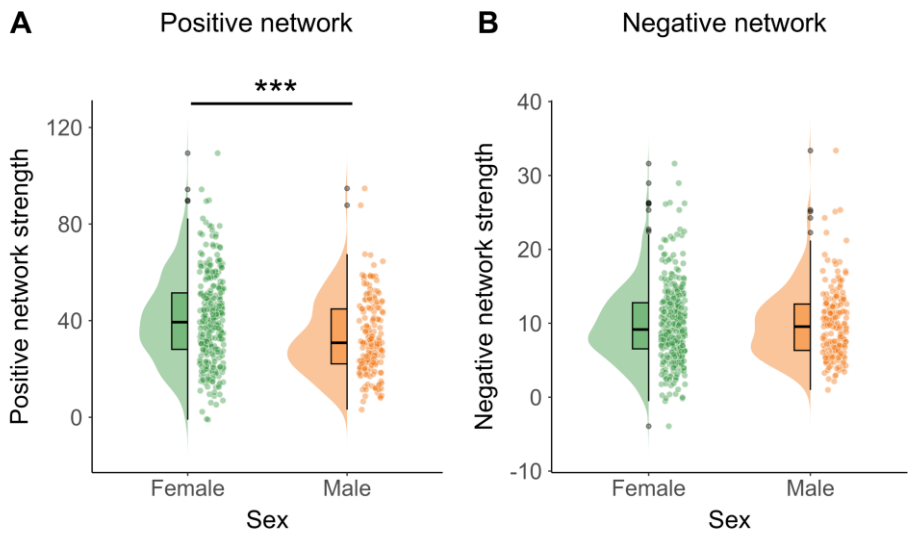

Figure 5.4 Sex differences in network strength. *The effect of biological sex on (A) positive network strength, and (B) negative network strength. Females have higher positive network strength than males. The violin plots show the data distribution. The line that divides the box into two parts represents the median value. The ends of the box represent the upper (Q3) and lower (Q1) quartiles of the data. The extreme lines of the boxplot show Q3 + 1.5 × interquartile to Q1–1.5 × interquartile range. The black dots beyond the extreme lines show potential outliers.* *** *= $p < 0.0005$*

5.3.7 Association Between Risk Factors and Network Strength in Mid-life

CAIDE score was significantly negatively associated with positive network strength (β (SE) = -0.83 (0.29), 95% Confidence Interval [CI] -1.39– -0.27, $p_{\text{-corrected}}$ = 0.007; corrected for multiple comparisons), independently of mean FD (Table 5.5, Figure 5.5A). No association with CAIDE was observed for negative network strength after multiple comparisons correction (Figure 5B) (See Appendix IV, STable 10.8).

No association with APOE4 was observed for positive or negative network strength (Appendix IV, STable 10.9–10.10).

Table 5.5 Regression coefficients for the effects of CAIDE on positive network strength

Model summary		R^2	F	*p* value
		0.04	11.20	<0.001
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Positive network strength	CAIDE	-0.83 (0.29)	[-1.39, -0.27]	0.004
	Mean FD	39.33 (9.89)	[19.90, 58.76]	<0.001

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals.

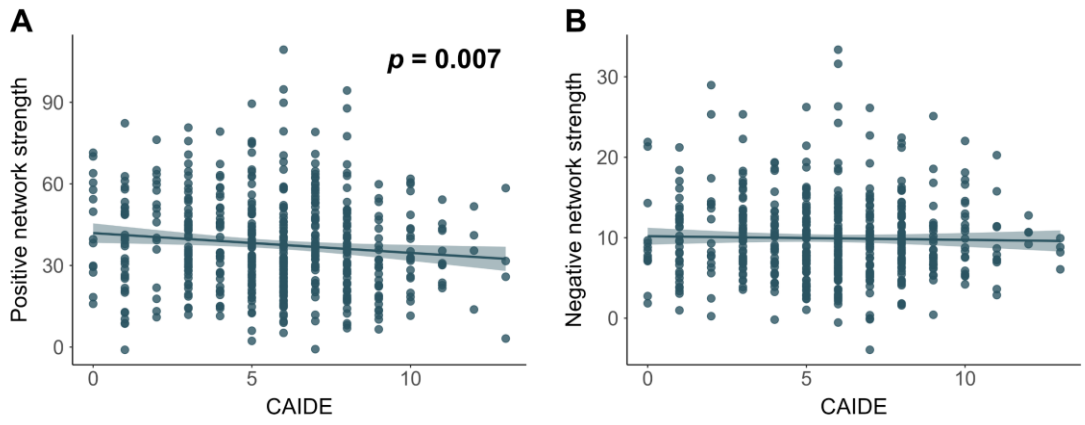

Figure 5.5 Association between CAIDE score and network strength. *The effect of CAIDE on (A) positive network strength, and (B) negative network strength. Higher CAIDE score was significantly associated with reduced positive network strength. On the x axis, higher scores represent higher cardiovascular dementia risk, and on the y axis, higher scores represent higher network strength.*

5.3.8 Association Between Lifestyle Activities and Network Strength in Mid-life

Stimulating activities were significantly positively associated with positive network strength (β (SE) = 0.85 (0.22), CI 0.41–1.29, $p_{\text{-corrected}} < 0.001$; corrected for multiple comparisons) (Table 5.6, Figure 5.6A), independently of occupational attainment, education, sex, age, and mean FD. No association with stimulating activities was observed for negative network strength (Figure 5.6B) (See Appendix IV, STable 10.11).

Occupational attainment was significantly positively associated with positive network strength (β (SE) = 0.85 (0.22), CI 0.41–1.29, $p_{\text{-noncorrected}} < 0.04$) (Table 5.6, Figure 5.6C), but this effect did not survive after multiple comparisons correction. No association with occupational attainment was observed for negative network strength (Figure 5.6D) (See Appendix IV, STable 10.11).

Table 5.6 Regression coefficients for the effects of lifestyle activities on positive network strength

Model summary		R^2	F	*p* value
		0.11	10.41	<0.001
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Positive network strength	Stimulating activities	0.85 (0.22)	[0.41, 1.29]	<0.001
	Occupational attainment	0.38 (0.18)	[0.02, 0.74]	0.040†
	Years of education	-0.35 (0.24)	[-0.82, 0.12]	0.144
	Sex	7.74 (1.63)	[4.53, 10.95]	<0.001
	Age	-0.55 (0.15)	[-0.85, -0.25]	<0.001
	Mean FD	40.27 (9.67)	[21.27, 59.27]	<0.001

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals. †, this effect of occupational attainment did not survive after Bonferroni correction.

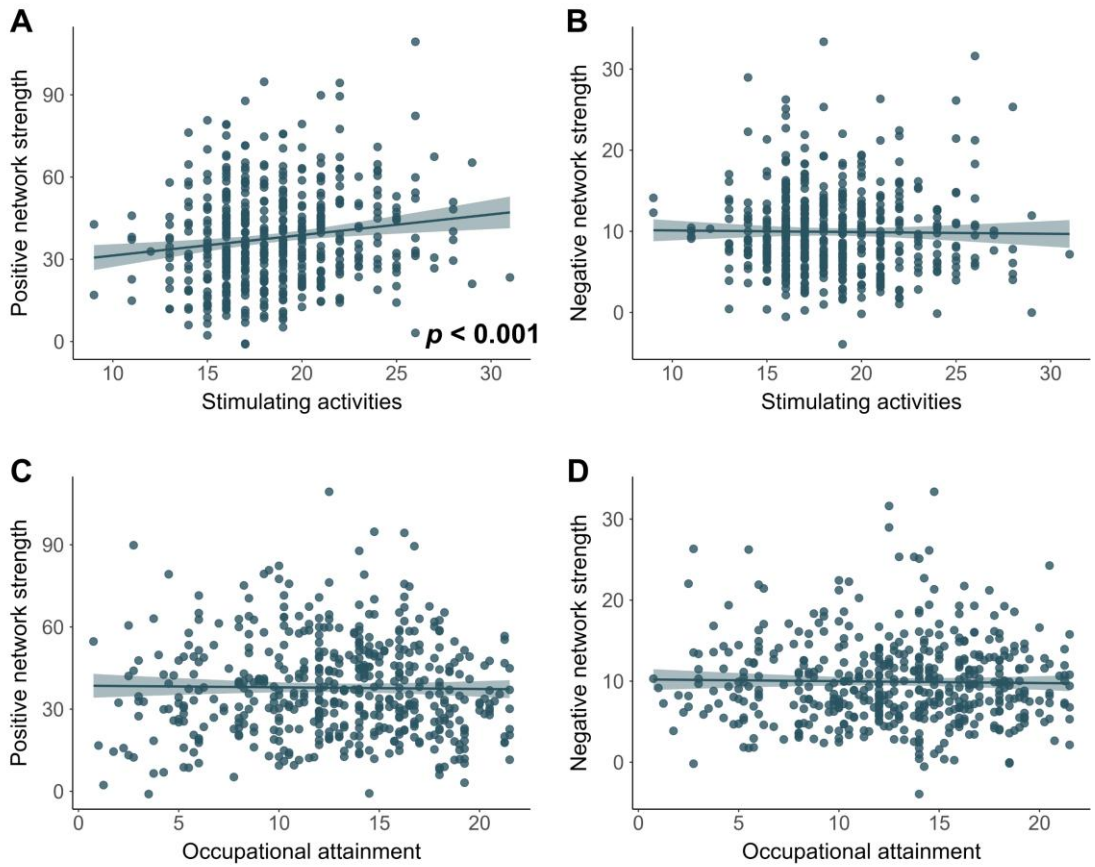

Figure 5.6 Associations between lifestyle activities and network strength. *The effect of stimulating activities on (A) positive network strength, and (B) negative network strength. The effect of occupational attainment on (C) positive network strength, and (D) negative network strength. Higher engagement in stimulating activities was significantly associated with higher positive network strength, regardless of occupational attainment, years of education, sex, age and head motion. On the x axis, higher scores represent greater stimulating activities/occupational attainment, and on the y axis, higher scores represent higher network strength.*

5.3.9 Association Between Lifestyle Activities, Sex and APOE4 on Network Strength

No significant sex × occupation interaction or significant three-way interaction APOE4 × sex × occupation was observed for positive or negative network strength (See Appendix IV, STable 10.12–10.15).

5.4 Discussion

This study identified the whole-brain functional connectome associated with episodic and relational memory using an advanced connectome-based approach. Additionally, it identified significant associations of dementia risks and reserve contributors with this functional connectome, in a cohort of middle-aged individuals (N = 700), who were presently cognitively healthy but at risk for late-life dementia. This chapter's findings indicated that, by using the CPM method, the resting-state functional connectivity could significantly predict episodic and relational memory in mid-life adults, with sex differences in model accuracies. Moreover, I found that higher CAIDE score was associated with weaker memory-related connectivity. More engagement in physically, socially and intellectually stimulating activities was associated with stronger memory-related connectivity, regardless of age, sex, years of education, and head motion. Models identified from the PREVENT cohort could not predict episodic memory of mid-life participants in an external independent dataset.

CPM analyses showed that the resting-state functional connectivity significantly predicted episodic and relational memory in the PREVENT cohort of mid-life individuals. The positive network connectome was characterized by within-DMN connections and connections between the DMN and CON (which largely overlapped with salience network). This suggested that stronger connectivity of these networks was associated with better episodic and relational memory. This finding is consistent with previous findings showing that episodic and relational memory is subserved by a distributed network, including the default mode network and salience network (Alm et al., 2022; Kim, 2016; Palacio & Cardenas, 2019; Ritchey et al., 2015). The negative network was dominated by connections between the DMN and FPN, suggesting that stronger DMN-FPN connectivity was associated with worse episodic and relational memory. This negative relationship is supported by previous studies showing that higher connectivity

between the DMN and FPN was associated with poorer cognition (Bagarinao et al., 2019), especially worse episodic memory (Zhukovsky et al., 2023). Moreover, in preclinical older individuals with established amyloid-β deposition, the increased connectivity of DMN–FPN mediates the negative effect of amyloid-β burden on episodic memory. It has been suggested that Amyloid-β accumulation may promote its own spread via enhanced DMN–FPN connectivity, eventually leading to worse episodic memory (Zhukovsky et al., 2023). This suggests that adverse network connectivity pattern may already be present prior to significant amyloid-β accumulation or clinical symptoms onset in mid-life.

Although the combined network is often assumed to provide stronger predictive performance in CPM by integrating information from both positive and negative connections, this pattern was not observed in the present study. While the combined network was significant at the uncorrected level ($p = 0.035$), it did not survive correction for multiple comparisons, indicating a weaker and less robust effect than the positive and negative networks considered separately. One possible explanation is that the positive and negative networks identified here may reflect partially distinct, rather than directly opposing, aspects of memory-related functional organisation. Under such circumstances, combining them into a single summary measure may reduce the specificity of each signal and attenuate the overall predictive effect. This interpretation appears more plausible than a simple difference in network size, given that the negative network contained fewer edges than the positive network (negative: 86 edges; positive: 353 edges).

In females, predictive edges derived from both between- and within-network connections of the DMN, specifically those identified in the positive network, contributed significantly to episodic and relational memory performance, whereas negative network connections were sparse and nonpredictive. In contrast, males exhibited a higher proportion of edges from the negative

network (notably involving the CON), but the overall model was a trend effect rather statistically significant. The key novelty of these findings is that CPM identified sex differences in functional connectome underlying memory performance specifically in mid-life adults who are presently cognitively healthy but carried risks for late life dementia (e.g., approximately 50% with a family history of dementia and 38% APOE4 carriers). This mid-life, at-risk focus extends prior work that has primarily examined broader healthy aging cohorts spanning early adulthood to late life (Ju et al., 2023; aged 36 to 100). The observed reliance on DMN connectivity in females converges with recent CPM evidence in broader healthy aging samples, where the DMN contributed more strongly to predicted memory in females (Ju et al., 2023), as well as with studies of higher within-DMN connectivity in females, which was associated with better memory performance (Ficek-Tani et al., 2023). However, the findings in males also diverge from Ju et al. (2023), rather than a male-only model driven by the visual network, males in the current study showed a predominance of the CON (or salience network) alongside reduced model significance. Differences in sample characteristics and age range may partly account for these divergent findings in males. Finally, the observation that memory prediction in females is preferentially anchored in DMN connectivity may be relevant for understanding sex-specific vulnerability to AD, given that increased posterior DMN connectivity has been associated with an elevated risk of Alzheimer's disease (Mormino et al., 2011; Schultz et al., 2017). Taken together, these results suggests that sex differences in functional connectome underlying episodic and relational memory are present already in mid-life, and may represent an early network-level signature that potentially contributes to females' elevated risk of AD.

For the female-only group, positive network model, but not negative or combined network models, predicted episodic and relational memory. In contrast, for the male-only group, none of the models was able to significantly predict episodic and relational memory. One possible reason for this discrepancy is the relatively smaller sample size available for males. As

demonstrated by (Marek et al., 2022), brain-wide association studies typically require thousands of subjects to reliably capture subtle brain–behaviour associations. Thus, an insufficient male sample may have limited the ability to detect the true connectivity–memory relationship in males.

Regarding the model generalisation, the models performed robustly across different cross-validation schemes, feature selection thresholds and motion exclusion criteria within the internal PREVENT dataset. However, when the model trained on PREVENT was applied to mid-life participants from the Cam-CAN cohort, the predictions for episodic memory failed to generalize. Several factors may account for this failure in external validation. First, differences in sample characteristics may to have played a role. The PREVENT cohort had a slightly higher mean age (52 vs. 48 years) and a higher proportion of females (64.8% vs. 51.6%) than the Cam-CAN cohort. As noted by previous studies, predictive models are highly sensitive to demographic differences, and deviations from the training sample's "stereotypical" profile can lead to substantial performance declines due to dataset shift (Greene et al., 2022; Rosenblatt et al., 2024). Second, different episodic memory assessments between cohorts likely introduced measurement noise that attenuated the brain–behaviour prediction accuracy (Gell et al., 2024). Due to the poor generalisability, I remain cautious in interpreting these findings but consider it a target for further investigation. Future research should try to address these issues by matching demographic profiles and standardising cognitive assessments across cohorts to improve model generalisability.

A key question in this chapter was whether dementia risk factors relate to the functional connectome underlying episodic and relational memory. To the best of my knowledge, this is the first study to show that higher CAIDE scores were significantly associated with weaker network connectivity supporting episodic and relational memory, in a cohort of presently

cognitively healthy mid-life individuals. This finding extends existing work by linking cardiovascular dementia risk not simply to global functional connectivity, but specifically to the functional networks most relevant for memory performance during mid-life. To date, only two studies have investigated associations between CAIDE scores and functional connectivity. (Farkas et al., 2025) found reduced connectivity in the default mode, salience, and central attention networks in older adults with high CAIDE compared to those with low CAIDE scores. (Cao et al., 2023) showed that connectivity within and between the cingulo-opercular and sensorimotor networks significantly predicted CAIDE scores in a mid-life cohort. However, they did not examine whether CAIDE is associated with the functional networks specifically supporting episodic and relational memory. In this context, the present findings suggest that elevated dementia risk may already be associated with functional networks well before the onset of overt cognitive impairment. In addition, APOE4 genotype did not influence this memory-related functional connectome. In other words, when the genetic risk alone was considered, no significant effect was found. It was only when a risk score (CAIDE) incorporating genetic risk in combination with lifestyle factors, sex and age were considered, that such effect was unravelled. These results provide strong evidence that brain–behaviour alterations in individuals with higher CAIDE scores may be driven by modifiable lifestyle risk factors included in this cardiovascular dementia risk score (i.e., blood pressure, cholesterol, physical activity, body mass index). Previous studies have linked exposure to cardiovascular risk factors during mid-life to cognitive decline and increased dementia risk in later life (Debette et al., 2009; Lamar et al., 2020). Specifically, CAIDE scores exceeding 8 confer substantial probabilities of future dementia, ranging from approximately 4% to as high as 29% within 40 years among middle-aged adults (Exalto et al., 2014; Kivipelto et al., 2006). Given these established relationships, a portion of participants in the PREVENT cohort with elevated CAIDE scores (>8) may eventually develop dementia. Consistent with previous findings, our

group's recent work demonstrated that higher CAIDE scores were negatively associated with episodic and relational memory in mid-life (Qi et al., 2023). The present study further extends these behavioural findings by providing evidence suggesting that the negative relationship between cardiovascular dementia risk and cognitive performance may be mainly mediated by disruptions in these connectivity.

Notably, the positive connectome predominantly comprised within- and between-network connections involving the DMN. The DMN has been extensively shown to be vulnerable to AD pathology. In preclinical AD, amyloid-beta deposition preferentially accumulates within DMN regions (Elman et al., 2016; Palmqvist et al., 2017) and is negatively associated with its functional connectivity, even among cognitively healthy older adults (Mormino et al., 2011; Palmqvist et al., 2017; Sheline et al., 2010). Furthermore, disrupted DMN connectivity was commonly observed in individuals with MCI (Gili et al., 2011) and clinically diagnosed AD (Gour et al., 2014; Grieder et al., 2018), and its connectivity changes was closely related to disease progression and conversion from MCI to AD (Damoiseaux et al., 2012; Petrella et al., 2011). These findings suggest that the memory-related functional connectome, particularly involving the DMN, is vulnerable to the negative effects of cardiovascular dementia risk in mid-life.

Another key question in this study was whether reserve contributors were associated with the memory-related functional connectome. To the best of my knowledge, this is the first study to show that higher engagement in physically, socially and intellectually stimulating activities in mid-life was associated with stronger connectivity of memory-related networks, particularly involving connections of DMN, independently of sex, age, and years of education. The stimulating activities comprised socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in energetic physical activities, reading,

practicing a second language and travel. Although we observed a similar trend for occupational attainment, this effect did not survive after multiple comparisons correction and should therefore be interpreted with caution. Importantly, the activities highlighted here are modifiable, cost-effective, and can be promoted at the population level. Thus, they present feasible targets for preventative strategies from early-life. Moreover, such non-pharmacological approaches could be particularly impactful in low- and middle-income countries, where barriers to greater educational and occupational attainments are more pronounced than in high-income regions. These findings align with a recent intervention study, in which Lee et al. (2024) reported increased DMN connectivity and better working memory after a 6-month cognitive activity intervention among older adults (mean age: 66.3 ± 4.3 years) with subjective cognitive decline, compared to the control group. Observing similar associations in the middle-aged cohort emphasizes the potential preventive benefits of engaging in stimulating activities earlier in life (Arenaza-Urquijo & Vemuri, 2018; Kivipelto et al., 2018). Additionally, in previous chapters I have demonstrated that greater engagement in stimulating activities was positively associated with episodic and relational memory in mid-life (Heneghan et al., 2023; Qi et al., 2024). DMN connectivity may underlie cognitive reserve (Ersoezlue et al., 2023; Franzmeier et al., 2017a; Vockert et al., 2024), for example, stronger connectivity of the DMN has been associated with reduced cognitive decline despite amyloid burden (Buckley et al., 2017). Taken together, these findings lend support to the cognitive reserve hypothesis (Stern, 2012), indicating that an enriched lifestyle during mid-life may help maintain or even enhance the functional connectivity of memory-related networks, thereby potentially delaying future cognitive decline.

Finally, I did not observe a significant three-way interaction of biological sex, occupational attainment, APOE4 on the memory-related functional connectome. Several possible reasons may account for this null finding. The cognitive measures of episodic and relational memory might be more sensitive to the influences of biological sex, APOE4 status, and occupational

attainment than the functional imaging metrics used to define the brain organization. fMRI-based measures can be inherently noisy and have lower test–retest reliability (Elliott et al., 2020; Noble et al., 2019; Poldrack et al., 2017; Zuo & Xing, 2014). Thus, even when a behavioral effect is present, the corresponding neural mechanism may be too weak or masked by noise to be detected reliably. Moreover, although advanced machine learning techniques were employed to capture the complex brain–behavior relationship, the identified functional connectome explained only 2.6% of the variance in episodic and relational memory, after accounting for age and year of education. Consistent with prior reports (Woo et al., 2017), this suggests that even state-of-the-art neuroimaging models capture only a modest fraction of the variability in cognitive outcomes. With over 95% of the variance remaining unexplained, it is likely that additional, unmeasured factors contribute to cognitive variability. These findings underscore the need for larger sample sizes and the integration of multimodal imaging data in future studies to better disentangle the contributions of sex-specific neural patterns, genetic risk factors, and life course experiences such as occupational attainment.

Methodological considerations

Despite these promising findings, several limitations warrant consideration. The resting-state fMRI data presents incomplete brain coverage that affects the analysis of large-scale brain network connectivity or organisation. Future research using fMRI data with complete brain coverage are needed to validate these findings. Lifestyle activity scores were relied on self-reported questionnaires, which are prone to recall bias and measurement errors. The study population are mainly of white Caucasian ethnicity, not dissimilar to the historic ethnic mix of older people in the UK and Ireland, which limits generalizability of findings beyond individuals of European ancestry. Finally, this study is cross-sectional; thus, causal inferences regarding the

relationship between network connectivity and future cognitive decline cannot be made. Future studies from the ongoing testing waves two and three (2 and 8 years post baseline respectively) of this study will determine whether the identified connectivity patterns predict subsequent memory deterioration.

5.5 Conclusion

The unique contribution of this study is to provide evidence that resting-state functional connectivity predicts episodic and relational memory among cognitively healthy middle-aged individuals at risk for late life dementia, with sex differences in the predictive performance of brain-behaviour models. These findings revealed that higher cardiovascular dementia risk, indicated by increased CAIDE scores, was associated with weaker memory-related connectivity, predominantly involving the DMN. Conversely, higher engagement in stimulating activities during mid-life enhanced the functional connectivity underlying episodic and relational memory, supporting the cognitive reserve hypothesis. These findings not only advance our understanding of the neural mechanisms underlying sex differences in memory performance, but also have important implications for early intervention and prevention strategies in Alzheimer's disease.

6. Chapter 6: General Discussion

It is increasingly recognised that dementia neuropathology starts decades before clinical symptoms emerge, and that mid-life represents a critical window for prevention. Yet, despite accumulating evidence that lifestyle activities contribute to resilience against dementia, little is known about how these influences operate differently in females and males during mid-life, and how they relate to brain–cognition relationships at this stage. Addressing these gaps is of vital importance, not only to clarify the mechanisms underlying sex differences in dementia vulnerability but also to inform personalised prevention. This thesis addressed four research questions, progressing from behavioural associations to the underlying neural mechanisms. Chapter 2 established the behavioural associations by asking whether reserve contributors, specifically occupational attainment and stimulating activities, enhance cognition in mid-life and whether these effects are moderated by biological sex and APOE4 status. Given that education is also a key reserve contributor but was treated as a covariate in Chapter 2, Chapter 3 then examined education explicitly: does education interact with sex to moderate the associations between reserve contributors and cognition or brain structure, and are these associations influenced by dementia risk factors? Having identified sex-specific associations between reserve contributors and cognition/brain, Chapter 4 focused on how dementia risk factors and reserve contributors relate to brain structure, and whether brain structure–cognition relationships differ between females and males—insights that may help elucidate mechanisms contributing to sex disparities in Alzheimer's disease risk and inform sex-specific biomarkers. Finally, Chapter 5 extended the inquiry to brain function, asking whether whole-brain functional networks supporting memory show sex-specific organisation and whether dementia risk and reserve contributors are related to these functional architectures. The following sections

summarise the main and novel findings of each empirical chapter, then consider the implications and limitations of the research presented here, and finally, suggest future research directions.

6.1 Summary of Findings

The first empirical study in this thesis (Chapter 2) addressed whether reserve contributors enhance cognition in mid-life, and how biological sex and APOE4 status interact to influence the effects of reserve contributors on cognition. This chapter first investigated the effects of reserve contributors on cognition in mid-life, and then the interactions of sex and APOE4 status on the relationship between reserve contributors and cognition, in a cohort of individual who were presently cognitively healthy, but carried genetic risk for late-life dementia. After controlling for the effect of education, I found that individuals with higher engagement in physically, socially and intellectually stimulating activities showed better episodic and relational memory, regardless of biological sex and APOE4 status. Furthermore, I found that biological sex and APOE4 interacted in moderating the associations between occupational attainment and cognition. APOE4 carrier females with higher occupational attainment showed better cognition. By contrast, APOE4 carrier males with higher occupational attainment showed worse cognition. Taken together, this study makes a novel contribution by showing interactions between sex, APOE4 and occupational attainment on cognition in mid-life. I show a positive effect of stimulating activities on cognition in middle-aged individuals regardless of biological sex and inherited risk for late-life dementia, while controlling for educational differences. The current findings demonstrate that occupational attainment in mid-life boosts cognition against inherited risk of dementia in females, but not males, at risk for late-life dementia. They suggest

that sex and APOE4 status are important variables to consider for building high precision dementia prevention strategies and clinical trials.

Building on these findings, Chapter 3 explored whether education, another major reserve contributor, would interact with sex to influence the associations of lifestyle activities with cognition and brain structure. This line of inquiry emerged because education was statistically controlled for in Chapter 2, yet its potential moderating role remained unexplored. Chapter 3 examined the interaction of sex and education on the relationship between mid-life stimulating activities, occupational attainment, cognition, and brain structure, and also investigated whether these relationships are influenced by dementia risk factors. First, I found significant sex differences in the associations between education, stimulating activities and cognition. Males with low education showed a significantly positive association between engagement in physically, socially and intellectually stimulating activities and multisensory processing. In other words, higher engagement in stimulating activities was associated with better multisensory processing. Males with high education showed the opposite effect, or a significantly negative association between engagement in stimulating activities and multisensory processing. Females showed no education-dependent effect in the association between stimulating activities and cognition. Moreover, I found that males with low education, showed a significantly positive association between engagement in stimulating activities and global cortical thickness. In other words, higher engagement is stimulating activities was associated with higher global cortical thickness in males with low education. The positive associations in low-educated males were more pronounced in those with high CAIDE scores. Specifically, males with low education, and high CAIDE scores, who engaged more in stimulating activities had thicker global cortical thickness. Females showed no education-dependent effects in the association between stimulating activities and global cortical thickness. These findings suggest that modifiable stimulating activities in mid-life enhance cognition and

brain structural health in middle-aged males with low education and high risk for late life dementia. These effects were sex specific, for males only.

Having identified sex-specific behavioural and structural effects of reserve contributors (i.e., education, occupational attainment, stimulating activities), the next step was to examine how dementia risk and reserve contributors affect brain structure, and whether brain structure–cognition relationships differ between females and males. Investigating brain structure–cognition relationships during mid-life is crucial because neuropathological changes in dementia begin decades before clinical symptoms manifest (Jack Jr et al., 2013; Ritchie et al., 2015), and structural MRI markers can point to neurodegenerative changes long before measurable cognitive decline (Mak et al., 2017). Accordingly, the third empirical study (Chapter 4) focused on the effects of dementia risk and reserve contributors on cognition and brain structure, and sex differences in the relationship between brain structure and cognition in mid-life. I found that higher CAIDE scores were associated with poorer performance in two cognitive domains, episodic and relational memory, and short-term memory binding. Higher CAIDE scores were also associated with thinner global cortical thickness. By contrast, I found that more engagement in stimulating activities was associated with larger grey matter volume. Importantly, I found significant sex differences in the relationship between brain structure and cognition. Males with greater global cortical thickness showed better episodic and relational memory, whereas females showed no associations between global cortical thickness and episodic and relational memory. Moreover, out of 9 regions tested, results suggested that the sex-specific brain–cognition relationship was driven by the precuneus region. Males with greater precuneus cortical thickness showed better episodic and relational memory. However, risk factors, APOE4 or CAIDE, did not interact with sex to moderate the relationship between brain structure and cognition. These results suggest that cardiovascular risk of future dementia

negatively impact cortical thickness, and reveal sex-specific differences in the brain structure–cognition association in cognitively healthy middle-aged individuals.

Previous studies suggest that functional alterations in the brain may precede macroscale structural brain changes (Fox & Raichle, 2007; Greicius et al., 2004). For example, functional disruptions have been observed in preclinical dementia (Habib et al., 2017). Therefore, building upon the structural findings from Chapter 4, Chapter 5 examined whether there is also sex-specific brain function–cognition relationship in mid-life, and asked whether reserve contributors and dementia risk relate to the functional connectome underpin cognition. Chapter 5 identified whole-brain functional networks associated with episodic and relational memory by using a CPM approach and sex-specific predictive networks supporting memory, and examined the effects of risk factors and reserve contributors on the memory-related functional connectome in mid-life. The first novel finding of this chapter was that resting-state functional connectivity (FC) significantly predicted episodic and relational memory in mid-life, with distinct predictive networks in females and males: females relied more heavily on DMN connectivity, whereas males did not show this significant relationship. The core regions of DMN have been extensively shown to be vulnerable to the characteristic pathology of Alzheimer's disease even in preclinical stage (Elman et al., 2016; Palmqvist et al., 2017). The second novel finding was that CAIDE scores and reserve contributors exerted opposing impacts on the memory-related networks. Higher CAIDE scores were associated with weaker, whereas greater engagement in stimulating activities were associated with stronger memory-related functional connectivity. These findings reveal sex-specific functional mechanisms that support memory and suggest that mid-life lifestyle modification may bolster memory-related brain functional networks that are vulnerable to AD.

6.2 Interpretation and Implications

6.2.1 Associations of risk factors with cognition and the brain in mid-life

The novel finding related to risk factors in this thesis was that APOE4 allele, the main genetic risk factor for late-onset sporadic AD, interacted with sex in affecting the associations between occupational attainment and episodic and relational memory (Chapter 2). Apart from its interaction with biological sex, I did not observe any effects of APOE4 on cognition or the brain (Chapter 4 and Chapter 5).

Several factors likely contribute to these null findings. First, results regarding APOE4 effects across studies are inconsistent. Although extensive work shows that APOE4 is a major genetic risk factor for AD and can impair cognition in old age (Eich et al., 2019; Raulin et al., 2022; Zimmermann et al., 2019), other research in the healthy population suggests opposite effects, i.e., positive associations with APOE4 in young or mid-life adults. For example, PREVENT sub-studies with smaller samples (N = 210) have found that APOE4 was associated with better cognitive performance and greater functional segregation (Deng et al., 2024; Deng et al., 2023). These effects are consistent with the hypothesis of antagonistic pleiotropy (Williams, 1957), which proposes that deleterious genes, such as the APOE4 gene allele, have survived through evolution because they might confer an advantage early in life, when humans are reproductively fit (Byars & Voskarides, 2020). Second, the deleterious impact of APOE4 appears to intensify after age 60, when APOE4 is more closely associated with AD neuropathology (Saddiki et al., 2020), as shown by studies indicating an inflection in cortical microstructure and amyloid deposition around that age (Koychev et al., 2020; Mak et al., 2024). For instance, a diffusion MRI study showed that cortical microstructural trajectories in temporal regions diverged between APOE4 carriers and non-carriers at roughly age 60 (Mak et al., 2024). Similarly, amyloid accumulation was found to increase exponentially at age 60 in APOE4 carriers

(Koychev et al., 2020), roughly a decade before the onset of greater cognitive decline in APOE4 carriers (Christensen et al., 2008; Rawle et al., 2018). With a mean age of 52, The PREVENT cohort is likely too young to manifest overt APOE4-related decline, and such effects are likely to become more pronounced as participants approach 60 and beyond.

The other risk factor that I focused on in the thesis, the CAIDE score, was found to be highly related to cognition and the brain in cognitively healthy, middle-aged individuals. In Chapter 4 and Chapter 5, I found that higher CAIDE scores were significantly associated with worse cognition in the domains of episodic and relational memory, and short-term memory binding, and lower global cortical thickness. Cognition and brain structure have previously been found to be vulnerable to CAIDE risk in mid-life (Deng et al., 2024; Dounavi et al., 2022; Liu et al., 2021; Ritchie et al., 2017). For example, higher CAIDE score was associated with poorer verbal, visuospatial functions, and short-term memory (Deng et al., 2024), poorer visual recognition (Ritchie et al., 2017), increased brain atrophy (Liu et al., 2021), and widespread cortical thinning (Dounavi et al., 2022). However, the novel contribution of this thesis with respect to CAIDE, is the finding that CAIDE was not only significantly associated with cognition and brain structure, but also it was significantly associated with brain function, particularly in functional networks supporting episodic and relational memory, in mid-life. This finding further extends the behavioural findings by providing evidence suggesting that the negative relationship between CAIDE scores and cognitive performance may be mediated by disruptions in functional networks.

Together, the results indicate that genetic risk alone (APOE4) may not exert a measurable impact in cognition or brain structure/function in mid-life. It was only when a risk score (CAIDE) incorporating genetic risk in combination with lifestyle factors, sex and age was considered, that such effect was unravelled. The CAIDE score captures several modifiable risks

related to cardiovascular health, including systolic blood pressure, cholesterol, body mass index, and physical activity, alongside other risks, such as age, sex, APOE4 genotype and educational level. Therefore, the results of this thesis provide strong evidence that early cognitive and brain changes associated with dementia are likely primarily driven by mid-life cardiovascular risk factors. The findings suggest that early interventions targeting these modifiable factors in mid-life can help maintain cognitive and brain health. Randomised-controlled trials (RCTs) are needed to establish causality in future studies.

6.2.2 Associations of reserve contributors with cognition and the brain in mid-life

Risk and protective factors often co-occur throughout the lifespan and contribute to ageing and dementia-related cognitive decline trajectories. In contrast to the cardiovascular risk composite captured by the CAIDE score, several reserve contributors, such as education, occupational attainment, and stimulating activities are associated with the preservation of cognitive function (D. Chan et al., 2018) and reduced dementia symptom severity (Dekhtyar et al., 2019; Livingston et al., 2020; Livingston et al., 2017; Wang et al., 2017) in older adults. It remains an open research question, however, whether building up cognitive reserve in mid-life can offset the risk of late life dementia.

In Chapter 2, I found that greater years of education was associated with better episodic and relational memory, aligning with previous evidence strongly suggests that education contributes to cognitive reserve in later life (D. Chan et al., 2018; Richards & Deary, 2005). The novel finding regarding reserve contributors in this chapter was that, independently of education, more frequent engagement in physically, socially and intellectually stimulating activities was associated with better episodic and relational memory. This effect was independent of age, sex, years of education, and occupational attainment in mid-life. This result replicates a previous finding (Heneghan et al., 2023) with a sub-group (N = 210) of the PREVENT cohort. Episodic

and relational memory functions are two of the earliest cognitive functions that show changes in pre-symptomatic AD (Grober et al., 2008; Laukka et al., 2012; Small et al., 2003). Impairment of episodic memory is the hallmark of AD in the majority of cases (Welsh et al., 1992), and studies have found it to be strongly associated with conversion from MCI to AD (Albert et al., 2018), in older adults. Similarly, relational memory tasks, especially with a semantic memory aspect, have been used to differentiate between MCI and healthy aging (Ahmed et al., 2008), again in older adults. Furthermore, in Chapter 4, I found that the episodic and relational memory declined with increasing dementia risk as measured by the CAIDE score in mid-life.

Apart from the effects of lifestyle activities on cognition, its association with brain health was also found in this thesis. I found that higher engagement in physically, socially and intellectually stimulating activities was associated with larger total grey matter volume (Chapter 4). Moreover, I found that higher engagement in stimulating activities, as well as greater occupational attainment (did not survive after multiple comparisons corrections) in mid-life, was associated with stronger functional connectivity supporting episodic and relational memory, predominantly involving connections of DMN, independently of sex, age, and years of education (Chapter 5). The core regions of DMN have been extensively shown to be vulnerable to the characteristic pathology of Alzheimer's disease even in preclinical stage (Elman et al., 2016; Palmqvist et al., 2017). Furthermore, disrupted DMN connectivity was commonly observed in individuals with MCI (Gili et al., 2011) and clinically diagnosed AD (Gour et al., 2014; Grieder et al., 2018), and its connectivity changes was closely related to disease progression and conversion from MCI to AD (Damoiseaux et al., 2012; Petrella et al., 2011). These findings make an important contribution by extending previous literature in older adults to the mid-life population. Studies in older adults have found that lifestyle activities mitigated age-related reductions in hippocampal volume (Erickson et al., 2011; Suo et al., 2012), cortical

thickness (Raffin et al., 2021; Rektorova et al., 2020), white matter integrity (Burzynska et al., 2014; Kleemeyer et al., 2016; Palta et al., 2021), and functional connectivity (Domingos et al., 2021; Soldan et al., 2021). The stimulating activities in the current study comprised socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in energetic physical activities, reading, practicing a second language and travel. The results of this thesis therefore suggest that diverse stimulating activities may help maintain or even enhance brain structure and memory-related functional networks as early as mid-life, particularly through supporting the connectivity of the DMN, which is among the earliest networks affected by neuropathology even in preclinical stage of dementia (Elman et al., 2016; Palmqvist et al., 2017).

Taken together, these findings lend support to the cognitive reserve hypothesis (Stern, 2012), indicating that, well before a potential dementia diagnosis, an enriched lifestyle may help maintain or even enhance brain structure and memory-related networks as early as mid-life, thereby potentially delaying future cognitive decline.

6.2.3 Sex-specific associations of reserve contributors with cognition and the brain in mid-life

Investigating whether lifestyle activities boost cognition in mid-life is not enough—we also need to know for whom. There is a growing appeal for personalised intervention strategies that can target high-risk individuals (Altomare et al., 2021; Coley et al., 2022; Frisoni et al., 2023; Livingston et al., 2024). Multidomain lifestyle interventions hold the greatest promise in dementia prevention (Baker et al., 2025; Coley et al., 2022; Hafdi et al., 2021), yet multidomain should not imply a one-size-fits-all recommendations. Growing evidence shows that females have a disproportionately higher incidence of Alzheimer's disease, accounting for over two-thirds of cases (Alzheimer's Association, 2021; Mielke, 2018). Moreover, females are more

adversely affected by several risk factors, including increased stress (Ma et al., 2018), caregiver burden (Xiong et al., 2020), and the APOE4 genotype (Altmann et al., 2014), which accelerates pathological progression compared to males (Buckley et al., 2018; Edwards et al., 2021). The menopausal transition further marks a critical period of heightened vulnerability, as hormonal changes can disrupt endocrinal, cardiovascular, and metabolic systems (Rahman et al., 2020; Weber et al., 2014; Yanes & Reckelhoff, 2011) and lead to greater amyloid and tau accumulation, reduced white matter integrity, and glucose hypometabolism in postmenopausal females (Buckley et al., 2022; Mosconi et al., 2017b; Rahman et al., 2020). Therefore, both researchers and policymakers need to consider which group, females or males, could benefit the most from specific reserve-building factors. Chapter 2 and 3 address this question.

In Chapter 2, I found that females and males derived distinct benefits from occupational attainment on their episodic and relational memory, the earliest cognitive functions that show changes in pre-symptomatic AD (Grober et al., 2008; Laukka et al., 2012). The presence of APOE4 allele amplified sex differences in this relationship; APOE4 carrier females with higher occupational attainment showed better cognition, whereas APOE4 carrier males showed the opposite effect. These results suggest that modifiable lifestyle activities, particularly occupational attainment, may offset cognitive decrements in APOE4 carrier females. Occupational attainment is a key reserve contributor (Stern, 2012; Stern et al., 2020) and has been positively associated with late-life cognition and decreased dementia symptoms (Huang et al., 2020; Smart et al., 2014), but to date this relationshiop was not investigated in a mid-life cohort. Historically, females have encountered barriers to key reserve contributors, such as educational and occupational opportunities, leading to lower cognitive reserve and higher vulnerability to neurodegeneration (Hasselgren et al., 2020). Our finding advances understanding by showing that occupational attainment specific to mid-life contributes to cognitive reserve against inherited risk of dementia, or even incipient dementia neuropathology,

in mid-life females who are presently cognitively healthy but carry the APOE4 allele. Females leave full-time occupation in mid-life (New York Times, 2014) disproportionally in higher numbers than any other life stage due to increased caregiving duties. Therefore, the results of this thesis suggest that the retention of females in workplace may be important for protecting brain health in this high-risk population, and, thus, needs to be supported with appropriate policy development. These female-specific associations of occupational attainment and cognition in mid-life are not only novel, but highlight an urgent need for high precision preventative interventions informed by sex and APOE4 status, as well as for policy changes that help retain middle-aged females in the workplace. Given that males are less likely to leave full-time employment and hold more senior leadership positions across nearly all industries than females (Global Gender Gap Report, 2023), and did not show the same cognitive benefits from higher occupational attainment in this thesis, such interventions and policy changes may need to be sex-specific, addressing barriers that uniquely affect females.

Chapter 3 discusses, more sex-specific effects on cognition and brain health in another prominent reserve factor, that of stimulating activities. I showed that engagement in physically, socially and intellectually stimulating activities was associated with better multisensory processing and thicker global cortical thickness, exclusively in males with lower education, and furthermore, particularly for those with higher CAIDE scores. No significant education-dependent effects in these associations were observed in females. Lower education has been associated with barriers to other key reserve contributors, such as reduced occupational complexity, and fewer opportunities to stimulating avocational activities, leading to lower cognitive reserve (Oreopoulos & Salvanes, 2011; Schudde & Bernell, 2019; Vuolo et al., 2016). Moreover, previous studies have found poorer cardiovascular health in males relative to females in mid-life (Y. Li et al., 2020; Sabia et al., 2012). Researchers from PREVENT programme have also shown that male participants carried a higher cardiovascular risk burden than females in

this cohort, with higher rates of hypertension, being overweight, current smoking, excessive alcohol consumption (> 21 units per week) and diabetes (Ritchie et al., 2024). These disparities likely contribute to a higher cardiovascular disease load in middle-aged males, including cerebral small vessel disease, which is associated with white matter damage (Gottesman et al., 2014; Topiwala et al., 2017). Males also had higher CAIDE scores than females in our cohort (see Table 1 in Chapter 3). These accumulated vulnerability influences to dementia in low-educated males with higher CAIDE scores likely render them more responsive to protective lifestyle activities. These activities represent a diverse set, including socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engaging in physical activities, reading, practicing a second language, and travelling. Because the activities highlighted here are diverse, modifiable, and cost-effective, they present feasible targets for early-life preventative preventions. Moreover, such non-pharmacological approaches could be particularly impactful in low- and middle-income countries, where educational barriers are more pronounced than in high-income regions and many people have lower levels of formal education (Livingston et al., 2020).

As seen above, the results of this thesis suggest that the brain health of males and females benefits from different cognitive reserve factors. One potential explanation for these sex-specific findings is that males and females may accrue cognitive reserve via distinct life-course exposures (Arenaza-Urquijo et al., 2024). This aligns with evidence in older adults showing that males and females benefit differently from reserve contributors. For example, higher IQ, which is linked to education (Hegelund et al., 2020; Ritchie & Tucker-Drob, 2018), is associated with slower age-related cognitive decline in older males but not in females (Alty et al., 2023), whereas higher physical activity is associated with greater reserve in older females but not in older males (Pa et al., 2022). Another potential explanation could relate to differences in mid-life risk factor profiles between females and males. For example, in the PREVENT mid-life

cohort males reported higher rates of hearing loss, hypertension, overweight, current smoking, TBI, alcohol use, and diabetes, whereas females reported higher rates of poor sleep and physical inactivity (Ritchie et al., 2024). Given the complex interactions of dementia risk and reserve factors, cognition and brain health (Low et al., 2022a; Rosicka et al., 2024), these different profiles may contribute to the sex-specific associations observed. Future studies integrating multimodal neuroimaging, genetic, and hormonal markers are needed to fully elucidate the neurobiological basis of these sex differences, which will be crucial for developing high-precision, personalised prevention and intervention strategies for individuals at risk of dementia.

Taken together, the findings from Chapter 2 and 3 suggest that applying personalized sex-specific strategies lead to more successful dementia prevention. Based on converging evidence from Chapter 2 and Chapter 3, greater occupational attainment is better for females, especially for female APOE4 carriers, whereas more engagement in stimulating activities is more beneficial for males, particularly for males with lower education and higher CAIDE scores. Future intervention strategies need to consider several factors together, including biological sex, APOE4 status, and educational background in Alzheimer's disease clinical trials.

6.2.4 Sex-specific brain–cognition relationships in mid-life

In the preceding sections, I discussed sex-specific associations of distinct reserve contributors, such as occupational attainment and stimulating activities, with both cognitive performance and brain measures in mid-life. This section shifts focus to sex-specific brain–cognition relationships in mid-life. Chapter 4 presents the relationships between brain structure and cognition, and Chapter 5 shows the relationships between brain function and cognition. Investigating these brain–cognition relationships during mid-life is crucial because neuropathological changes in dementia begin decades before clinical symptoms manifest (Jack Jr et al., 2013; Ritchie et al., 2015), and both structural and functional MRI markers may provide

early biomarker of neurodegenerative changes long before measurable cognitive decline (Habib et al., 2017; Mak et al., 2017). Since cognitive abilities depend on the intricate interplay of brain structure and function, elucidating how these relationships differ by sex may illuminate the mechanisms underlying the elevated risk and faster progression to dementia observed in females (Arenaza-Urquijo et al., 2024; Irvine et al., 2012; Nebel et al., 2018), ultimately guiding the development of sex-specific biomarkers and targeted early-intervention strategies.

Chapter 4 presents the novel finding of sex-specific differences in the association between global (and locally, in the precuneus region) cortical thickness and cognition in mid-life. Males showed a positive association between global (and precuneus) cortical thickness and episodic and relational memory, while females did not show this relationship between them. The current findings may be explained by a sex-specific cognitive reserve (Cieri et al., 2021; Lee et al., 2018), which is characterized by a dissociation between cognition and brain structure, meaning that structural deterioration does not necessarily lead to cognitive decline (Bialystok, 2021). Specifically, the cognitive advantage observed in females may reflect this reserve, allowing them to maintain cognitive performance despite changes in brain structure (Arenaza-Urquijo et al., 2024; Bialystok, 2021). This hypothesis is supported by multiple lines of research. For instance, females with MCI outperformed males in verbal memory despite equal levels of moderate hippocampal atrophy (Sundermann et al., 2016a), equivalent hypometabolism (Sundermann et al., 2016b) and similar AD pathology burdens (Sundermann et al., 2017). Similar results were also observed in cognitively healthy older adults. Females exhibited better verbal memory performance despite poorer brain functional architecture compared to males (Cieri et al., 2021). The present findings extend this literature by showing that sex-specific differences in the relationship between brain structure and cognition are already present in mid-life, and may underlie the different cognitive ageing and neuropathology trajectories of males and females.

Chapter 5 presents a novel finding of sex-specific differences in the predictive performance of connectome predictive modelling (CPM) of episodic and relational memory based on functional connectivity (FC). FC could only significantly predict episodic and relational memory in females, but not in males. The functional connectome associated with episodic and relational memory was primarily driven by the DMN-dominated positive network in females. This finding suggested that episodic and relational memory in females is reliant on the FC of the DMN, but this was not the case for males. Supporting this interpretation, several studies have reported that healthy older females exhibited higher DMN connectivity relative to older males (Ficek-Tani et al., 2023). Ju et al. (2023) found that brain-based predictors of memory performance also differed by sex, with DMN activity contributing more to predicted memory scores in females, whereas the visual network activity contributing more to predicted memory scores in males. Moreover, females showed more segregation of the DMN while males showed more segregation of visual networks (Ju et al., 2023).

In light of many behavioural studies demonstrating a premorbid episodic memory advantage in females relative to males (Arenaza-Urquijo et al., 2024; Asperholm et al., 2019; Golchert et al., 2019), our finding that resting-state DMN connectivity predicted episodic and relational memory in middle-aged females, but not males, suggests a crucial mechanistic link. Some researchers have suggested that females' early memory superiority is a "memory reserve" that delays clinical decline despite accumulating amyloid pathology (Sundermann et al., 2016b). The present CPM results suggests that this reserve may be attributed to the increased functional connectivity of the DMN. Specifically, the female-driven positive network emerging from our analyses suggests that heightened DMN connectivity may underlie a female advantage in memory.

Moreover, this sex-specific coupling between DMN connectivity and memory performance may offer a perspective on why females not only bear a higher incidence of AD (Alzheimer's Association, 2021; Mielke, 2018) but also exhibit more rapid progression once clinical pathology accelerates (Lin et al., 2015; Tifratene et al., 2015; van Loenhoud et al., 2019). Female's initial advantage in episodic memory has been proposed as a form of "memory reserve" that may delay the impact of disease (Sundermann et al., 2016b). Supporting this view, amyloid accumulation has been linked to poorer memory and hippocampal atrophy in cognitively normal males but not females (Caldwell et al., 2017). However, these sex differences appear to diminish at MCI stage, when females, despite their premorbid advantage, show a more rapid decline in relation to temporal lobe FDG-PET hypometabolism and hippocampal atrophy—particularly within DMN core regions—compared to males (Caldwell et al., 2017; Sundermann et al., 2016a; Sundermann et al., 2016b). If females rely more heavily on DMN integrity to maintain memory function in mid-life, early disruption of this network by dementia pathology could precipitate a sharper loss of compensatory capacity, thereby accelerating cognitive deterioration in females. By shedding light on the functional network substrate of female memory reserve, our results yield critical insight into sex-specific vulnerabilities and may guide the development of targeted interventions aimed at bolstering DMN connectivity before clinical onset.

6.3 Limitations

Several limitations of the present thesis should be acknowledged. First, the study population consisted mainly of White, well-educated individuals, with limited representation from other ethnic groups, lower educational backgrounds, or low- and middle-income countries (LMICs). Recent evidence indicates that dementia incidence rates differ across ethnic groups: age-

adjusted rates were highest among Black and Hispanic individuals, followed by American Indian or Alaska Native, Asian, and White individuals across most US regions (Kornblith et al., 2022). Moreover, high-income countries have been the focus of most dementia research, and LMICs remain underrepresented, with limited evidence on dementia risk prevalence, prediction, prevention, and risk reduction (Alshahrani et al., 2024). Given these disparities, the study population restricts the generalizability of the findings to more diverse and globally representative cohorts.

Second, the thesis focused exclusively on cognitively healthy individuals and did not include clinical populations such as those with MCI or AD dementia. As a result, it was not possible to examine whether the observed associations would be comparable, stronger, or weaker in populations at different stages along the disease continuum. In addition, no biomarker data were available for amyloid or tau, which limits the ability to determine whether the findings are influenced by preclinical Alzheimer's disease pathology. The absence of such data reduces the capacity to distinguish between changes related to normal ageing and those that may be driven by pathological processes. Incorporating biomarkers and clinical populations in future work will therefore be essential for clarifying disease-specific versus normal ageing mechanisms.

Third, CAIDE scores and stimulating activities were measured using composite indices that aggregated several items. While such indices are useful for summarising risk or lifestyle in a simplified way and may increase statistical power to detect subtle effects, they inevitably obscure the unique contributions of specific items. For instance, particular cardiovascular risk factors (e.g., BMI, cholesterol, systolic blood pressure) or types of stimulating activities (e.g., physical activity, socializing, reading) may differ in their strength of association with cognition and brain outcomes. The inability to disentangle these contributions limits the precision of interpretation. Future analyses using more fine-grained measures would help to determine

which specific lifestyle and risk factors are most influential in mid-life cognitive and brain health.

Fourth, socio-economic status (SES) is one of the most significant predictors of cognition and brain health. For example, previous studies have shown that lower SES was strongly associated with poorer brain health (M. Y. Chan et al., 2018; Krueger et al., 2025). SES is commonly indicated by several factors, such as individual's education, social class, occupation, and income (Darin-Mattsson et al., 2017; Kraft & Kraft, 2021). However, SES was not comprehensively assessed in the current PREVENT dataset (lack of information on social class and income), which precluded the investigation of how SES may influence the associations between sex, reserve contributors, risk factors, cognition, and brain measures. Given the well-established role of SES in shaping cognitive and brain health across the lifespan (M. Y. Chan et al., 2018; Hackman et al., 2010; Krueger et al., 2025), the lack of SES measures is an important limitation.

Fifth, female-specific reproductive and hormonal factors, such as menopausal status, age at menopause, hormone levels, and the type of ovarian function loss (surgical vs. nonsurgical), were not available in the current dataset. These factors have been shown to influence female's brain and cognitive outcomes (Barth et al., 2025; Coughlan et al., 2023; Guo et al., 2025; Phung et al., 2010; Wood Alexander et al., 2025), but could not be examined in the present analyses. The PREVENT steering group is revising the protocol to include detailed menopause and hormonal measures from wave 3 onwards, which will allow more refined investigations in the future.

An additional limitation is that PREVENT data were collected across both pre- and post-Covid periods, with a small proportion of participants, particularly at the Dublin site, assessed after the onset of the pandemic. Although the present thesis did not directly investigate the effects of Covid-19, pandemic-related factors, such as poorer mental health, increased stress, reduced

social interaction, and changes in everyday or stimulating activities, may have influenced lifestyle measures as well as cognitive performance. As a result, some associations reported here may have been affected, to an unknown extent, by broader contextual changes related to the pandemic rather than only by the factors of primary interest. While this is unlikely to fully account for the present findings, it should be acknowledged as a potential source of variability. Future studies should aim to assess and control for pandemic-related influences more explicitly where relevant.

Finally, although I performed several validation analyses to test the robustness of the CPM results, the fMRI scans in the PREVENT cohort exhibited incomplete brain coverage. The study was originally designed with a particular focus on medial temporal lobe function, where NFT pathology accumulates (Ritchie & Ritchie, 2012), which led to limited whole-brain coverage. Despite considerable efforts in our lab to select a parcellation that balanced participant retention with node inclusion, several regions in the parietal lobe and cerebellum had to be excluded. The absence of these nodes may therefore have reduced the reliability of the findings and led to an underestimation of brain–cognition associations or obscured important network-level contributions. Future studies employing fMRI protocols with full brain coverage will be crucial to validate and extend the current results.

Taken together, these limitations highlight the need for future studies to incorporate more diverse and representative samples, include biomarker and hormonal data, collect comprehensive SES information, and ensure full brain coverage in neuroimaging. Addressing these issues will improve the interpretability and generalizability of findings on the relationships between sex, reserve contributors, risk factors with cognition and brain health in mid-life.

6.4 Future Directions

6.4.1 Mechanisms underlying sex differences in the associations between reserve contributors and cognition

This thesis provided evidence for sex-specific associations between reserve contributors and cognition in cognitively healthy middle-aged individuals. However, the mechanisms through which females and males differentially benefit from reserve contributors in mid-life remain unclear. Neurobiological mechanisms warrant particular investigation, given the established role of sex hormones in cognitive function and brain health (Barth et al., 2023; Hara et al., 2015). Future studies could examine how fluctuations in hormonal levels interact with reserve contributors to influence cognitive outcomes differently in males and females. Specifically, research could investigate whether the neuroprotective effects of education, occupational attainment, and stimulating activities are moderated by hormonal levels, particularly in relation to the menopause transition in females.

Neuroinflammatory processes and vascular health, both of which exhibit sex-dependent patterns (Gebhard et al., 2020; Muller et al., 2025), are additional candidates that may contribute to the observed differences. For example, microglial activation—the hallmark of neuroinflammation—has been shown to differ by sex (Villa et al., 2018; Wu et al., 2024), with females exhibiting stronger immune responses that may increase vulnerability to neurodegeneration in mid-life and beyond (Franceschi et al., 2018; Muller et al., 2025). Similarly, vascular risk factors such as hypertension and diabetes have been associated with differential cognitive outcomes in males and females, with females appearing more vulnerable to the cognitive consequences of cerebrovascular pathology (Kaur et al., 2024; Verhagen et al., 2022). Additionally, advanced neuroimaging techniques, including diffusion tensor imaging and independent component analysis in fMRI, could elucidate sex-specific patterns of structural

and functional brain networks that moderate the relationship between reserve contributors and cognitive performance. Integrating these neurobiological, neuroinflammatory, vascular factors and neuroimaging techniques will be crucial for clarifying the mechanisms underlying sex differences in reserve-related benefits.

6.4.2 Longitudinal predictions and advanced predictive modeling

The results presented in this thesis were based on cross-sectional PREVENT data, which limits the ability to investigate long-term predictions and causal relationships. Future research could build on the predictors identified here to examine longitudinal trajectories and predictive validity across multiple domains. Short-term longitudinal predictions represent an immediate priority. The memory-related functional networks identified in Chapter 5 provide promising candidates for predicting episodic memory performance in PREVENT wave 2/3. Future analyses could examine whether baseline network connectivity patterns predict not only memory performance at follow-up, but also rates of memory decline or stability. Importantly, these predictions should be examined separately for males and females, given the sex differences identified in the current work. Moreover, the PREVENT study is collecting amyloid and tau data. Although sample size is still limited, expanding the current CPM analyses on resting-state fMRI to amyloid and tau measures would provide valuable insight into whether the accumulation of these pathologies predicts subsequent cognitive outcomes.

Extended follow-up will become increasingly valuable as participants are tracked over longer time windows. This will allow researchers to test the predictive value of current findings for the development of MCI and progression to clinical dementia diagnosis. Rather than focusing solely on endpoint predictions, future research could also model individual trajectories of cognitive change and examine how reserve contributors influence these trajectories. For example, one recent study modelled individual's age-related cognitive trajectories and found

that IQ, a key reserve contributor, moderated the rate of age-related cognitive decline in older males but not in older females (Alty et al., 2023). Approaches such as latent growth curve modeling or generalized additive mixed-effects regression (Alty et al., 2023) could help identify whether certain reserve contributors predict slower rates of decline or stability over time in mid-life.

Finally, the relationship between brain activity and cognition may not be strictly linear. While CPM assumes linear associations between functional connectivity and behaviour (Shen et al., 2017), this may not fully capture more complex patterns. Advanced machine learning approaches such as NBS-Predict (Serin et al., 2021) and XGBoost (Chen & Guestrin, 2016) offer promising alternatives. NBS-Predict has been shown to perform as well as, or better than, traditional algorithms (e.g., LASSO, Elastic Net) and CPM in feature selection and prediction accuracy (Serin et al., 2021). XGBoost can better accommodate nonlinear relationships between functional connectivity and cognition. Incorporating such methods in future studies could improve the precision and robustness of brain–behaviour prediction.

6.4.3 Replicability and generalisability

Future studies should prioritise assessing the replicability and generalisability of the current findings in other middle-aged cohorts. Replication across independent samples is essential to establish the robustness of sex-specific associations between reserve contributors, cognition, and brain function. Large-scale longitudinal cohorts such as the ALFA project (Molinuevo et al., 2016) and the Wisconsin Registry for Alzheimer's Prevention (WRAP) (Sager et al., 2005) offer particularly valuable opportunities for this work. These cohorts share the aim of identifying early pathophysiological changes and developing prevention programmes, but they differ from PREVENT in terms of recruitment strategies, participant demographics, and cultural contexts.

Testing whether the observed associations hold across these diverse populations will strengthen confidence in their reliability and allow researchers to explore whether findings are specific to particular cultural, socioeconomic, or educational contexts. Importantly, PREVENT participants are predominantly White and highly educated, which limits generalisability. By drawing on cohorts with more varied ethnic and educational backgrounds, future research could assess whether reserve contributors confer similar benefits across groups, or whether their influence is shaped by broader social determinants of health. Such cross-cohort comparisons could also address questions of measurement harmonisation, helping to identify core reserve-related markers that are robust across studies and populations. This work will be critical for translating research findings into public health strategies that are globally applicable.

6.4.4 Investigation of the effects of menopause and hormones on female brain health

The new PREVENT data collection protocol will provide an important opportunity to examine how menopausal transition and associated hormonal changes shape females' cognition and brain health in mid-life. Evidence suggests that perimenopause is a period of heightened vulnerability to cognitive decline and brain alterations (Ding et al., 2013; Jacobs et al., 2016; Stefanowski et al., 2023), with several neuroimaging studies linking menopausal transition to brain glucose hypometabolism (Ding et al., 2013), reduced grey matter volume (Goto et al., 2011; Mosconi et al., 2021; Mosconi et al., 2018), white matter lesions (Wen et al., 2009), and increased amyloid burden (Mosconi et al., 2018). Building on this, future research could test whether reserve contributors, such as education, occupational attainment, and stimulating activities, buffer against menopause-related changes in brain networks and memory performance. A promising approach would be to examine interactions between reserve contributors and sex hormones in predicting neuroimaging outcomes. For example, longitudinal neuroimaging could be used to determine whether females with higher occupational attainment

show greater resilience to menopause-associated reductions in DMN connectivity, a pathway disrupted in Alzheimer's disease (Gili et al., 2011; Gour et al., 2014; Grieder et al., 2018). Similarly, repeated cognitive assessments across the peri- to postmenopausal years would allow the characterisation of individual trajectories and the identification of females who maintain stable function despite hormonal decline. Such work would extend existing literature by situating menopause not only as a biological transition but also as a context in which reserve contributors may exert differential protective effects. Ultimately, this line of research could inform sex-specific intervention strategies to mitigate cognitive decline and reduce later dementia risk in females.

6.4.5 Validation in randomised controlled trials

The associations reported in this thesis highlight modifiable lifestyle and occupational factors that may serve as protective contributors to cognition and brain health in mid-life. A critical next step is to test whether these observational findings translate into intervention efficacy within RCTs. The recently published US POINTER trial provides encouraging evidence that structured, multidomain lifestyle interventions can improve global cognition in older adults at risk of dementia (Baker et al., 2025). In this large, 2-year RCT (n = 2,111; mean age = 68 years), participants who received a structured, higher-intensity lifestyle program (including physical, cognitive, dietary, and social components) showed significantly greater improvements in global cognition compared with those in a self-guided intervention arm. Notably, benefits were consistent across APOE4 carriers and noncarriers, and exploratory subgroup analyses suggested no sex differences. The trial demonstrated that a relatively low-cost, multidomain, nonpharmacological intervention can yield measurable cognitive benefits in a large and diverse at-risk population.

Although POINTER focused on older adults (60–79 years), mid-life represents a critical period for dementia prevention. Future RCTs could adapt similar multidomain intervention frameworks to target middle-aged individuals, when lifestyle factors may exert the strongest influence on cognitive reserve and long-term trajectories of decline (Livingston et al., 2024; Livingston et al., 2020). In particular, testing whether structured interventions differentially benefit males and females would be important, given the sex-specific associations identified in the present thesis and the heightened Alzheimer's risk in females. Thus, embedding midlife-focused, sex-sensitive RCTs within ongoing large-scale prevention efforts would provide a rigorous test of whether reserve contributors can be leveraged to reduce dementia risk in mid-life.

6.5 Conclusion

In summary, this thesis aimed to investigate sex differences in the associations between reserve contributors, risk factors, cognition and brain health, as well as sex differences in brain–cognition relationships across structural and functional aspects, and how these are influenced by risk factors and reserve contributors in cognitively healthy middle-aged individuals, from 40 to 59, at risk of later life dementia. Greater occupational attainment was associated with better episodic and relational memory only in females, especially among female APOE4 carriers. In contrast, more engagement in stimulating activities was associated with better multisensory processing and thicker global cortical thickness exclusively in males with lower education, particularly for those with higher CAIDE scores. These findings indicate that females and males may accrue cognitive reserve through distinct pathways. I also identified sex-specific brain–cognition relationships in mid-life. Males showed a positive association between global (or precuneus) cortical thickness and episodic and relational memory, while no

such relationship was observed in females. In stead, females' episodic and relational memory relied more heavily on DMN connectivity, whereas for males there was no significant relationship between resting-state functional connectivity and episodic and relational memory. These results provide support for the hypothesis of female-specific cognitive reserve in episodic memory. Furthermore, CAIDE was not only significantly associated with cognition and brain structure, but also it was significantly associated with memory-related networks in mid-life. Importantly, an enriched lifestyle, including greater engagement in physically, socially and intellectually stimulating activities, appeared to help preserve or even enhance brain structure and memory-related networks at this stage, thereby potentially delaying cognitive decline.

Collectively, these findings highlight that building cognitive reserve is not a one-size-fits-all phenomenon but is shaped by sex-specific pathways and their interaction with genetic and cardiovascular risk factors. These findings carry important clinical and policy implications, underscoring the need for tailored intervention strategies that consider sex, genetic risk, and lifestyle, and for policies that promote equitable access to physically, socially, and intellectually stimulating opportunities as a public health strategy to strengthen cognitive reserve and reduce dementia risk in mid-life, well before the onset of clinical symptoms.

7. Appendix I: Supplementary information for Chapter 2

7.1 Supplementary Methods

7.1.1 Cognitive variables

The eleven cognitive summary variables from the COGNITO battery were:

1. *Working memory*. The ‘double task’ requires the subject to simultaneously locate specific shapes (visual stimuli) and count presented sounds (auditory stimuli). The outcome variable is the total number of correct responses for shape recognition.
2. *Working memory*. This task consists of two parts - the ‘double task’ described above and a visual task. The visual task requires the subject to locate specific shapes (visual stimuli) without the presentation of auditory stimuli. The outcome variable is the mean time difference in milliseconds between the 'double task' and the visual task.
3. *Narrative recall*. The task requires the subject to recall a series of elements which have a logical sequence (a short story). The outcome variable is the total number of correct elements on immediate recall of a story with a temporal progression requiring attention to macrostructure.
4. *Description recall*. The task requires the subject to recall a series of elements that have a visual sequence (e.g., describing the layout of a house). The outcome variable is the total number of correct elements recalled of a description without thematic progression requiring attention to microstructure and recall of spatial location. The narrative and description recall tasks are similar in terms of word frequency in the language and syntactic structure.
5. *Implicit memory*. The task requires the subject to recognise as soon as possible a name that is constructed progressively on the screen in 15 steps. The outcome variable is the

difference in the number of steps required for recognition between names never seen and names previously learned.

6. *Name-face association*. Participants are presented with a set of faces and names, and the goal is to remember and correctly associate each face with its corresponding name. During the learning phase, participants are required to learn the associations between the faces and names, which they are then required to recall after a delay. During the recall phase participants are shown a series of faces, some of which have been shown previously and associated with names. Participants decide whether the face has appeared before. If participants say they have seen the face before, they are asked for the name. The outcome variable is the number of names correctly recalled.
7. *Form perception*. The task requires the subject to discriminate form and line orientation by matching a sample complex figure to one of six presented figures. The outcome variable is the number of correct responses.
8. *Form perception speed*. The task is the same as above. The outcome variable is the mean time of correct responses in milliseconds.
9. *Phoneme comprehension*. The task requires the subject to select one of six presented objects that illustrates a word. The six objects include shape, phonetic and semantic distractors. The outcome is the number of correct responses.
10. *Phoneme comprehension speed*. The task is the same as above. The outcome variable is the mean time of correct responses in milliseconds.
11. *Verbal fluency*. The task requires the subject to name as many objects as they can think of, given a semantic and a phonemic cue. The outcome variable is the total sum of the number of words generated in 60s using both a semantic (vegetables) and a phonemic (letter P) cue.

The two summary variables from the Visual Short-term Memory Binding task were:

12. *Visual short-term memory binding test (shape only condition)*. The task requires the subject to identify whether the shape of the test stimuli (three random 6-sided polygons) matches the studied stimuli. The outcome variable is the percentage of correctly recognised shapes after a short retention period.
13. *Visual short-term memory binding test (shape-colour binding condition)*. The task requires the subject to identify whether both the shape and colour of the test stimuli match the studied stimuli. The outcome variable is the percentage of correct recognition of combinations of shape and colour of the test stimuli after a short retention period.

7.1.2 Behavioural data reduction

Sharp breaks in the “scree" plot of the successive eigenvalues suggest the appropriate number of components to extract. We also conducted a parallel analysis that compares the scree of components of the actual data with that of a random data matrix of the same size as the original (Horn, 1965). The detailed steps are: 1) We simulated a random normal data matrix of the same number of original cognitive variables (n = 13) and the same number of participants (n = 669). 2) We extracted eigenvalues from the simulated data matrix. We repeated these two steps 500 times to create a set of 500 parallel eigenvalues. 3) We took the mean and 95th percentile of all eigenvalues generated by principal components analysis of random data sets. The results were a vector of mean (and 95th percentile) eigenvalues equal in size to the original number of cognitive variables (n = 13). 4) We compared the eigenvalues of the actual data to that of parallel random data sets. Specifically, we plotted eigenvalues from the actual and random data sets and kept only those components whose eigenvalues are greater than 95th percentile of eigenvalues from the random data sets. Supplementary Figure 7.2A shows the scree plots of eigenvalues based on the actual data matrix (in blue line) and simulated data matrices at baseline (left panel) and follow-up (right panel) The mean eigenvalues are in dashed grey line, and the 95th percentile of eigenvalues are in red line. The shaded areas indicate that the eigenvalues of

components based on the actual data were larger than the mean and 95th percentile of eigenvalues from the random data sets. Supplementary Figure 7.2B shows the proportion of variance that each component explained, and the cumulative variance of the three components.

7.1.3 Outliers Assessment

To assess the distribution of the latency measures for cognitive tasks, we generated histogram and density plots, as shown in SFigure 7.3. Potential outliers in the three latency measures were identified using the Mean ± 3 × SD method for normally distributed data (working memory latency difference) and the [Q1 − 3 × IQR, Q3 + 3 × IQR] method for skewed data (form perception and phoneme comprehension latencies). Despite identifying one potential outlier in both the working memory and phoneme comprehension measures, we chose to retain the two potential outliers as there was no evidence to suggest they were due to measurement error; rather, they likely reflected genuine variability in cognitive performance.

7.1.4 Multicollinearity Assessment

To assess potential multicollinearity among the reserve contributors included as independent variables in our regression models, we conducted a multicollinearity assessment using Tolerance and Variance Inflation Factor (VIF) metrics (Studenmund, 2014; Montgomery et al., 2001). Tolerance values close to 1 indicate low multicollinearity, while VIF values below the commonly accepted threshold of 5 suggest that multicollinearity is not a significant concern (Studenmund, 2014; Montgomery et al., 2001).

7.2 Supplementary Results

7.2.1 Cognitive components

The components can be interpreted by mapping out the cognitive functions that the highest loading measures tapped into (Figure 2.1 in the main text). For the first component (C1), given that the highest loading measures were assessing response accuracy, and were positively loaded on C1, higher value means better performance. The cognitive functions that the highest three loading measures tapped into were verbal (narrative recall), spatial (description recall) and relational memory (name-face association). Accordingly, C1 was labelled as 'episodic and relational memory'. For the second component (C2), the highest loading measures were assessing response latency, and were positively loaded on C2. Therefore, higher value means poorer performance. For clarity of graphical display and comparison to the other two components, we reversed the signs of the values to make larger values represent better performance. Based on the cognitive functions that the highest loading measures tapped into, C2 was labelled as 'multisensory processing'. For the third component (C3), the highest loading measures were assessing response accuracy, and were positively loaded on C3, higher value means better performance. Based on cognitive functions that the highest loading measures tapped into, C3 was labelled as 'short-term memory binding'.

7.2.2 Multicollinearity of reserve contributors

We examined the multicollinearity of reserve contributors in our regression models by calculating Tolerance and VIF metrics (STable 7.4). The Tolerance values for all independent variables were close to 1, with the lowest being 0.787, and the VIF values were all around 1, with the highest being 1.271. These results indicate that multicollinearity is not a significant issue in our model.

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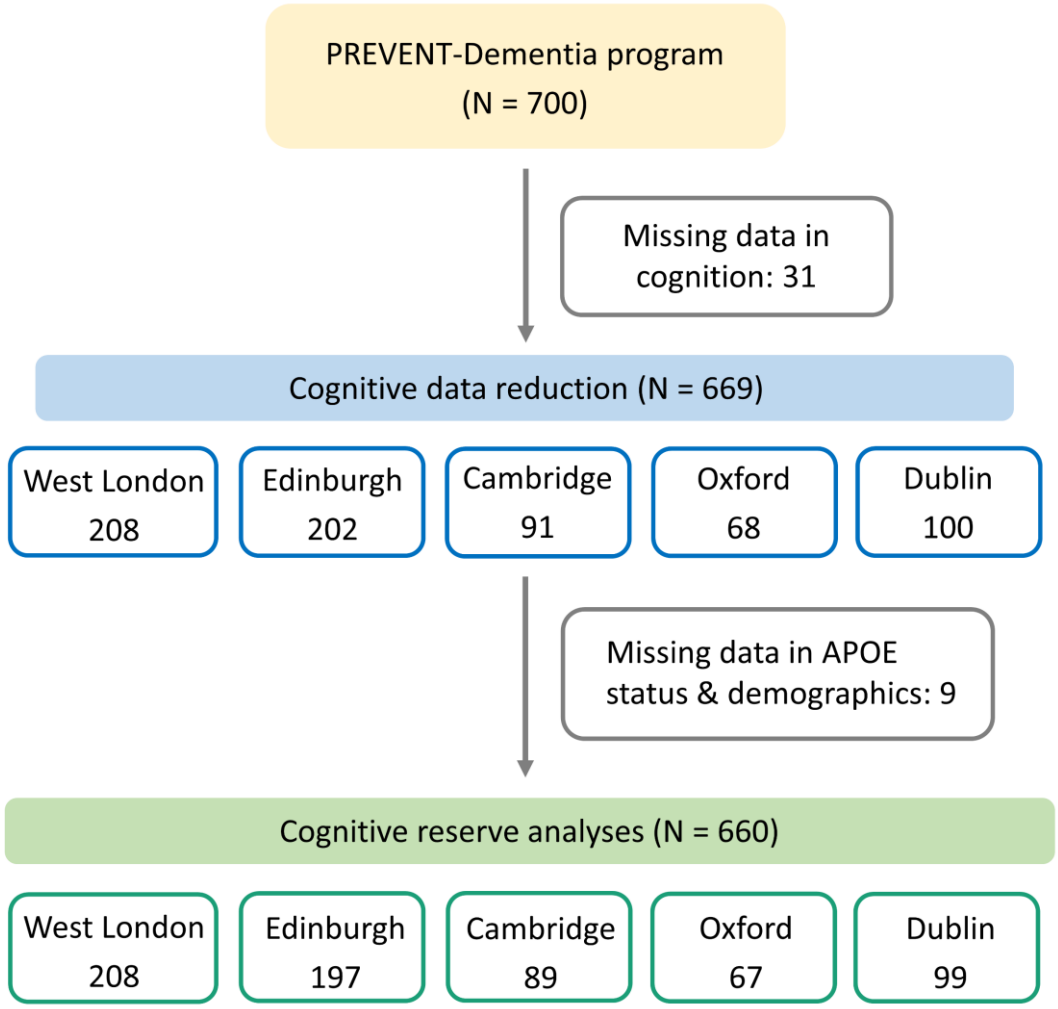
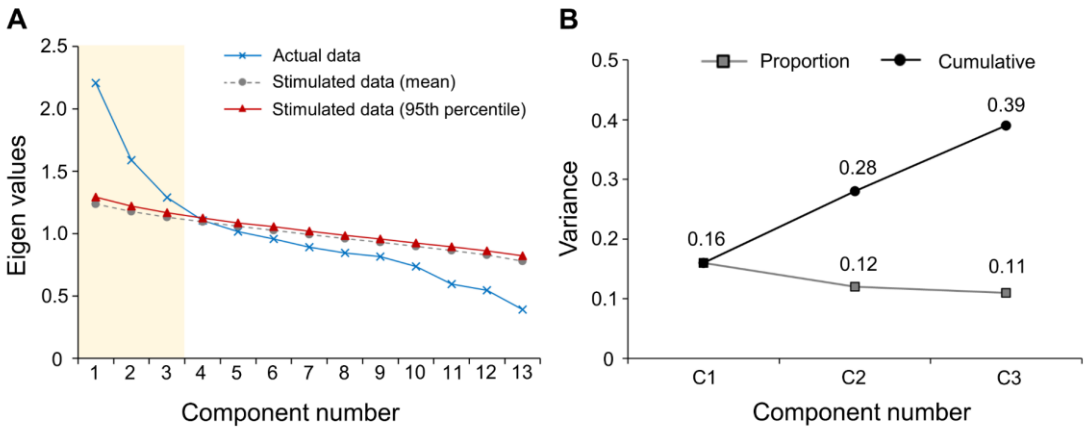
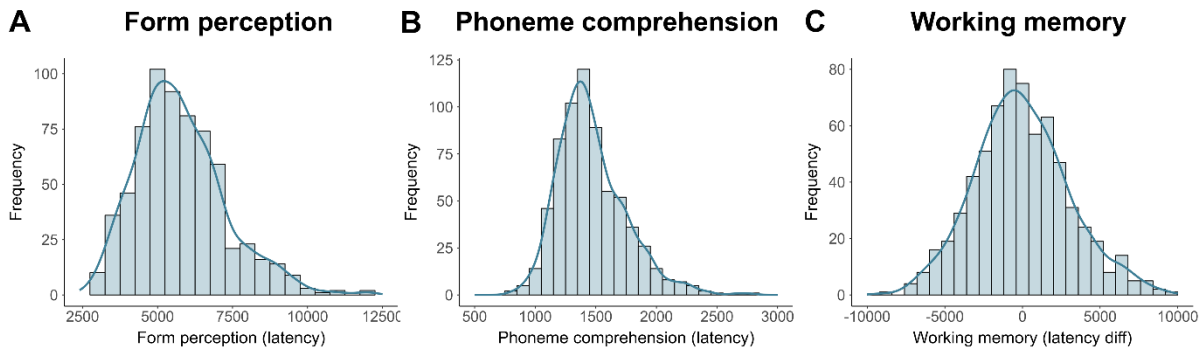
7.3 Supplementary Figures



SFigure 7.1 Participant inclusion criteria in Chapter 2. *For cognitive data reduction analyses and the investigation of cognitive reserve, per site, from the PREVENT–Dementia program.*



SFigure 7.2 Data reduction of cognitive information. *(A) Scree plot and parallel analysis. Eigenvalues of the principal components obtained from the actual data (in blue line) were compared to those of random simulated data (mean values in grey line and 95th percentile in red line). Eigenvalues larger than 95th percentile of the randomly generated 500 eigenvalues (simulation) determined the number of components. (B) The three extracted components were rotated to be uncorrelated with each other. The proportion of variance explained by each component, and the cumulative variance explained by the three components are presented for the cognitive analysis cohort. Abbreviations: C1 = component 1; C2 = component 2; C3 = component 3.*



SFigure 7.3 Distribution for latency measures. *Histogram and density plots for (A) form perception (latency), (B) phoneme comprehension (latency), and (C) working memory (latency difference). On the x axis, higher values represent longer reaction times (worse performance) in form perception/phoneme comprehension/working memory. Abbreviation: diff, difference.*

7.4 Supplementary Tables

STable 7.1 Complete list of risk factors and tests obtained in the PREVENT cohort.

PREVENT–Dementia program	
Risk factor	
APOE4 (Missing = 6)	
Neuropsychological assessments	
COGNITO (Missing = 1)	
Working memory	Name-face association
Narrative recall	Form perception
Description recall	Phoneme comprehension
Implicit memory	Verbal fluency
VSTMBT (Missing = 30)	
Lifestyle activities	
Lifetime of Experiences Questionnaire	

STable 7.2 Description of cognitive tasks and measures

Cognitive Tasks	Measures	Task Description	Descriptive Statistics (N = 669)
Description recall	Total number of correct answers	The subject must recall a series of elements which have a visual sequence (a short description).	Mean = 13.42 SD = 4.41 Range = 27 Missingness = 0
Narrative recall	Total number of correct answers	The subject must recall a series of elements which have a logical sequence (a short story).	Mean = 14.07 SD = 4.34 Range = 26 Missingness = 0
Name-face association	The number of correctly recognized faces and their corresponding names	The subject must decide whether a face on the screen appeared before and if yes, what the person's name is.	Mean = 5.24 SD = 2.12 Range = 9 Missingness = 0
Verbal fluency	Total number of correct answers	The subject must name all the words they can think of within one minute based on semantic and phonetic cues.	Mean = 27.66 SD = 6.66 Range = 46 Missingness = 0
Form perception	Mean time (ms) for correct answers	The subject must discriminate form and line orientation by matching a sample complex figure to one of six figures. Distractor figures are designed to detect visuospatial field neglect and difficulties with line orientation.	Mean = 5766.43 SD = 1503.80 Range = 9556 Missingness = 0
Phoneme comprehension	Mean time (ms) for correct answers	The subject must choose an object illustrating a presented word among 6 objects which include	Mean = 1464.74 SD = 279.54

		shape, phonetic and semantic distractors.	Range = 1951 Missingness = 0

STable 7.2 Description of cognitive tasks and measures (continued)

Form perception	Total number of correct answers	The subject must discriminate form and line orientation by matching a sample complex figure to one of six figures. Distractor figures are designed to detect visuospatial field neglect and difficulties with line orientation.	Mean = 6.36 SD = 1.16 Range = 7 Missingness = 0
Phoneme comprehension	Total number of correct answers	The subject must choose an object illustrating a presented word among 6 objects which include shape, phonetic and semantic distractors.	Mean = 8.61 SD = 0.60 Range = 3 Missingness = 0
VSTMBT-shape only	Total number of correct answers	The subject must recall stimuli that were shapes after a short period of retention.	Mean = 0.85 SD = 0.17 Range = 1.94 Missingness = 30
VSTMBT-shape colour binding	Total number of correct answers	The subject must recall stimuli that were combinations of shapes and colours after a short period of retention.	Mean = 0.48 SD = 0.23 Range = 1.63 Missingness = 30
Working memory	Total number of correct answers	Dual task: The subject must locate the targeted shapes and count the sounds.	Mean = 9.81 SD = 0.61 Range = 11 Missingness = 1
Implicit memory	Difference between the number of names never seen and the number of names already learned	The subject must recognize as soon as possible a name which is constructed progressively on the screen.	Mean = 1.03 SD = 0.68 Range = 8.2 Missingness = 0

Working memory	Mean time (ms) difference in milliseconds between the dual task and a simple form recognition task	Dual task: The subject must locate the targeted shapes and count the sounds. Simple task: Subject must locate the targeted shapes only.	Mean = -42.18 SD = 3037.56 Range = 18238 Missingness = 0

Note: The colors in this table correspond to the main Figure 2.1, illustrating the major loadings for each PCA component. The four highest loading measures for episodic and relational memory are shown in orange, the four highest loading measures for multisensory processing are in blue, and the two highest loading measures for short-term memory binding are in purple. Measures that contributed minimally to any of the three components are shown in white. VSTMBT, visual short-term memory binding test; SD, standard deviation.

STable 7.3 Regression coefficients for the model including 2-way interaction of menopause × occupational attainment on episodic and relational memory in females

Model summary	R^2	F	*p* value
	0.14	9.90	<0.001

DV	IV	β (SE)	95% CI	*p* value
Episodic and relational memory	Menopause	-0.16 (0.14)	[-0.43, 0.11]	0.24
	Occupational attainment	0.01 (0.02)	[-0.02, 0.04]	0.38
	Stimulating activities	0.06 (0.01)	[0.03, 0.08]	<0.001
	Years of education	0.06 (0.02)	[0.03, 0.09]	<0.001
	Age	-0.02 (0.01)	[-0.04, 0.01]	0.15
	Menopause*Occupation	0.02 (0.02)	[-0.02, 0.07]	0.37

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals.

STable 7.4 Multicollinearity assessment for reserve contributors

IV	Tolerance	VIF
Years of education	0.912	1.097
Stimulating activities	0.944	1.059
Occupational attainment	0.787	1.271
Sex	0.951	1.051
Age	0.807	1.239

Note: IV, independent variable; VIF, variance inflation factor.

STable 7.5 Number of participants in each group of the sex × APOE4 factorial design

Group	N
Female APOE4+	155
Female APOE4-	253
Male APOE4+	97
Male APOE4-	155

STable 7.6 Regression coefficients for the main effects of reserve contributors on episodic and relational memory adjusting for additional covariates

	Model summary	R^2	F	p value
		0.16	9.63	<0.001

DV	IV	β (SE)	95% CI	p value
Episodic and relational memory	Years of education	0.05 (0.01)	[0.02, 0.07]	<0.001
	Stimulating activities	0.05 (0.01)	[0.03, 0.07]	<0.001
	Occupational attainment	-0.001 (0.01)	[-0.02, 0.02]	0.91
	Sex	0.41 (0.08)	[0.26, 0.57]	<0.001
	Age	-0.02 (0.01)	[-0.03, -0.003]	0.02
	Race	0.54 (0.18)	[0.18, 0.90]	0.004
	BMI	0.01 (0.01)	[-0.01, 0.02]	0.38
	Hypertension	-0.10 (0.11)	[-0.31, 0.10]	0.32
	Hyperlipidemia	-0.01 (0.09)	[-0.18, 0.17]	0.93
	Sleep	-0.06 (0.08)	[-0.21, 0.09]	0.42
	Alcohol	0.17 (0.10)	[-0.03, 0.36]	0.10
	Smoking status	-0.07 (0.16)	[-0.39, 0.24]	0.65

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; BMI, body mass index. Additional analysis showing that the main effect of stimulating activities was retained after controlling for a number of additional potential confounding variables (i.e., BMI, race, hypertension, hyperlipidemia, sleep, alcohol, smoking status), in addition to controlling for the effects of age and the other two contributors (education and occupation).

STable 7.7 Regression coefficients for model including 2-way interaction of IVs on episodic and relational memory adjusting for additional covariates

Model summary	R^2	F	p value
	0.16	9.14	<0.001

DV	IV	β (SE)	95% CI	p value
Episodic and relational memory	Occupational attainment	-0.09 (0.06)	[-0.21, 0.04]	0.17
	Sex	0.40 (0.08)	[0.24, 0.56]	<0.001
	Sex*Occupational attainment	0.13 (0.08)	[-0.02, 0.29]	0.088
	Years of education	0.05 (0.01)	[0.02, 0.07]	<0.001
	Stimulating activities	0.05 (0.01)	[0.03, 0.07]	<0.001
	Age	-0.02 (0.01)	[-0.03, -0.002]	0.03
	Race	0.56 (0.18)	[0.20, 0.92]	0.003
	BMI	0.01 (0.01)	[-0.01, 0.02]	0.41
	Hypertension	-0.09 (0.11)	[-0.30, 0.11]	0.37
	Hyperlipidemia	-0.01 (0.09)	[-0.19, 0.17]	0.91
	Sleep	-0.05 (0.08)	[-0.20, 0.10]	0.52
	Alcohol	0.17 (0.10)	[-0.02, 0.37]	0.08
	Smoking status	-0.08 (0.16)	[-0.40, 0.23]	0.61

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; APOE4, Apolipoprotein E4 genotype; BMI, body mass index. Additional analysis showing that the trend interaction between sex and occupational attainment was retained after controlling for a number of additional potential confounding variables (i.e., BMI, race, hypertension, hyperlipidemia, sleep, alcohol, smoking status), in addition to controlling for the effects of age and the effects of the three reserve contributors.

STable 7.8 Regression coefficients for model including 3-way interaction of IVs on episodic and relational memory adjusting for additional covariates

	Model summary	R^2	F	p value
		0.18	7.70	<0.001

DV	IV	β (SE)	95% CI	p value
Episodic and relational memory	APOE4	0.05 (0.13)	[-0.20, 0.29]	0.71
	Sex	0.32 (0.10)	[0.12, 0.52]	0.002
	Occupational attainment	-0.02 (0.08)	[-0.18, 0.14]	0.80
	APOE4*Sex	0.20 (0.16)	[-0.11, 0.51]	0.21
	APOE4*Occupational attainment	-0.20 (0.12)	[-0.44, 0.05]	0.11
	Sex*Occupational attainment	-0.001 (0.10)	[-0.19, 0.19]	0.99
	APOE4*Sex*Occupational attainment	0.39 (0.16)	[0.07, 0.71]	0.017
	Years of education	0.04 (0.01)	[0.02, 0.07]	<0.001
	Stimulating activities	0.05 (0.01)	[0.03, 0.07]	<0.001
	Age	-0.01 (0.01)	[-0.03, 0.001]	0.07
	Race	0.60 (0.18)	[0.24, 0.97]	0.001
	BMI	0.01 (0.01)	[-0.01, 0.02]	0.34
	Hypertension	-0.12 (0.11)	[-0.32, 0.09]	0.27
	Hyperlipidemia	-0.01 (0.09)	[-0.19, 0.16]	0.87
	Sleep	-0.05 (0.07)	[-0.19, 0.10]	0.55
	Alcohol	0.18 (0.10)	[-0.04, 0.35]	0.12
	Smoking status	-0.09 (0.16)	[-0.41, 0.22]	0.54

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; APOE4, Apolipoprotein E4 genotype; BMI, body mass index. Additional analysis showing that the significant three way interaction between APOE4, sex and occupational attainment was retained after controlling for a number of additional potential confounding variables (i.e., BMI, race, hypertension, hyperlipidemia, sleep, alcohol, smoking status), in addition to controlling for the effects of age, the main effects of the three reserve contributors, of APOE4 and sex and two-way interactions.

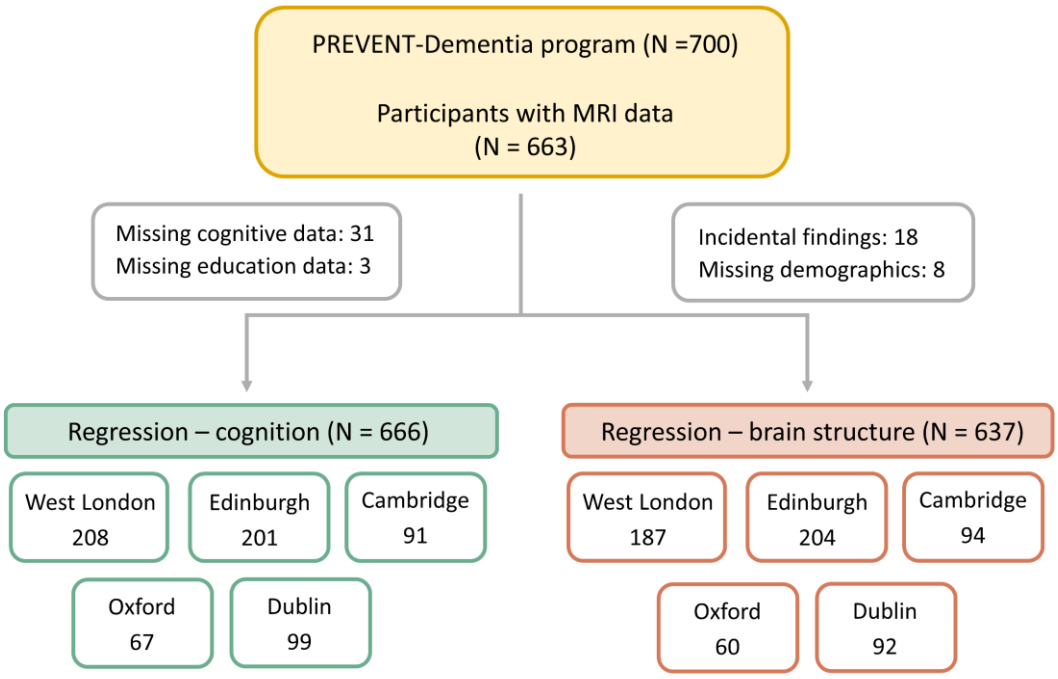
8. Appendix II: Supplementary information for Chapter 3

8.1 Supplementary Results

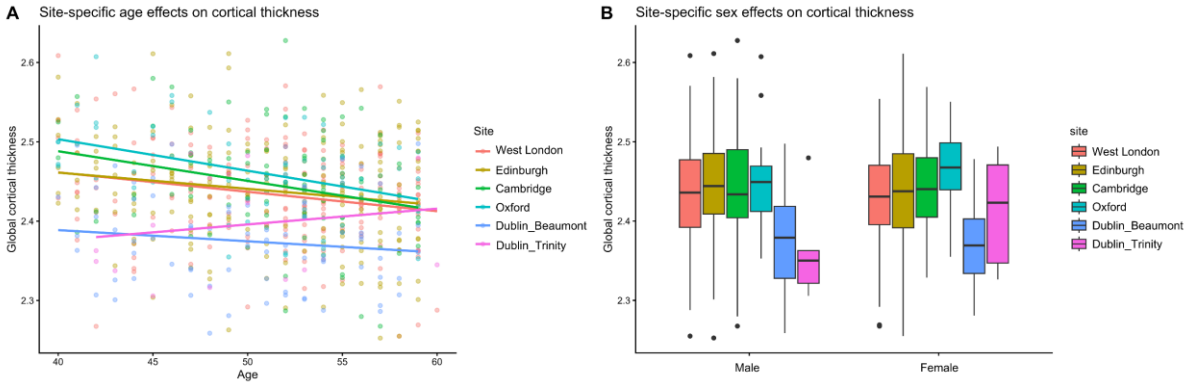
8.1.1 ComBat assumptions assessments

Prior to ComBat harmonization, site-level characteristics were examined to assess whether key assumptions for harmonization were reasonably satisfied. The majority of sites showed broadly consistent negative associations between age and cortical thickness. However, Dublin site (Trinity) displayed a differing pattern, with a positive age-related slope (SFigure 8.2). This site also had the smallest sample size (N = 17), suggesting that this deviation may reflect sampling variability rather than a true difference in underlying biological effects. While some degree of imbalance in sample size and sex distribution was present across sites (STable 8.11), such variability is common in multi-site studies. Importantly, age distributions across sites showed substantial overlap within the targeted mid-life age range (40–60 years). Although some variability in distribution shape was observed across sites (e.g., slight shifts towards younger or older age ranges), no site showed a completely distinct or non-overlapping age profile (SFigure 8.3).

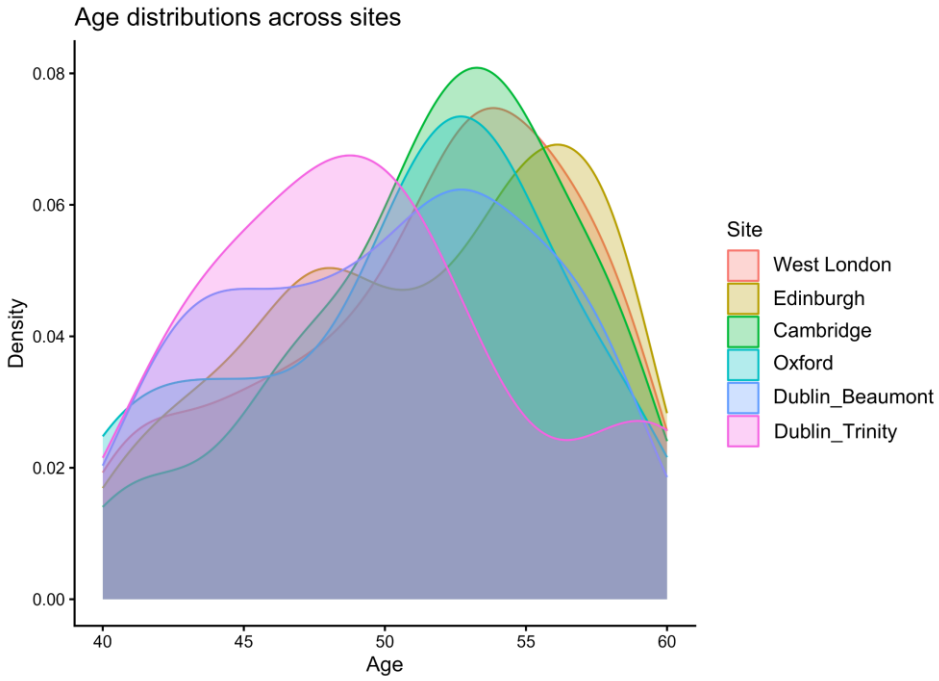
8.2 Supplementary Figures



SFigure 8.1 Participant inclusion criteria in Chapter 3. For the regression analyses of cognitive data and brain structural data, per site, from the PREVENT–Dementia program.



SFigure 8.2 Site-specific covariate effects on global cortical thickness. (A) Age effects, and (B) sex effects on global cortical thickness across six scan sites.



SFigure 8.3 Age distributions across scan sites.

8.3 Supplementary Tables

STable 8.1 Regression coefficients for the model including 3-way interaction of sex × education × stimulating activities on episodic and relational memory

Model summary		R^2	F	*p* value
		0.15	9.14	<0.001
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Episodic and relational memory	Education (Medium level)	0.16 (0.16)	[-0.16, 0.47]	0.32
	Education (High level)	0.09 (0.18)	[-0.26, 0.44]	0.62
	Stimulating activities	0.08 (0.04)	[-0.01, 0.17]	0.08
	Sex	0.19 (0.17)	[-0.14, 0.52]	0.27
	Occupational attainment	0.007 (0.01)	[-0.01, 0.02]	0.45
	Age	-0.03 (0.01)	[-0.04, -0.01]	<0.001
	Education (Medium)*stimulating activities	-0.03 (0.05)	[-0.13, 0.06]	0.50
	Education (High)*stimulating activities	-0.01 (0.06)	[-0.13, 0.10]	0.81
	Education (Medium)*sex	0.30 (0.20)	[-0.09, 0.69]	0.13
	Education (High)*sex	0.34 (0.22)	[-0.09, 0.76]	0.12
	Stimulating activities*sex	0.01 (0.05)	[-0.09, 0.11]	0.82
	Education (Medium)*stimulating activities*sex	0.01 (0.06)	[-0.10, 0.13]	0.81
	Education (High)*stimulating activities*sex	-0.06 (0.07)	[-0.20, 0.07]	0.34

STable 8.2 Regression coefficients for the model including 3-way interaction of sex × education × stimulating activities on short-term memory binding

Model summary	R^2	F	*p* value
	0.03	1.74	0.049

DV	IV	β (SE)	95% CI	*p* value
Short-term memory binding	Education (Medium level)	0.04 (0.17)	[-0.30, 0.38]	0.82
	Education (High level)	-0.15 (0.19)	[-0.52, 0.22]	0.43
	Stimulating activities	0.01 (0.05)	[-0.09, 0.11]	0.79
	Sex	-0.07 (0.18)	[-0.42, 0.29]	0.72
	Occupational attainment	0.007 (0.01)	[-0.01, 0.03]	0.45
	Age	-0.03 (0.01)	[-0.04, -0.01]	0.001
	Education (Medium)*stimulating activities	-0.02 (0.05)	[-0.09, 0.12]	0.73
	Education (High)*stimulating activities	0.01 (0.06)	[-0.11, 0.13]	0.89
	Education (Medium)*sex	-0.23 (0.21)	[-0.65, 0.19]	0.28
	Education (High)*sex	0.16 (0.23)	[-0.30, 0.62]	0.50
	Stimulating activities*sex	0.02 (0.06)	[-0.09, 0.13]	0.75
	Education (Medium)*stimulating activities*sex	-0.03 (0.06)	[-0.16, 0.09]	0.58
	Education (High)*stimulating activities*sex	-0.04 (0.07)	[-0.18, 0.10]	0.57

STable 8.3 Regression coefficients for the model including 3-way interaction of sex × education × occupational attainment on episodic and relational memory

Model summary	R^2	F	*p* value
	0.16	9.29	<0.001

DV	IV	β (SE)	95% CI	*p* value
Episodic and relational memory	Education (Medium level)	0.20 (0.15)	[-0.09, 0.49]	0.17
	Education (High level)	0.09 (0.18)	[-0.26, 0.43]	0.63
	Occupational attainment	-0.01 (0.02)	[-0.06, 0.04]	0.63
	Sex	0.23 (0.15)	[-0.08, 0.53]	0.14
	Stimulating activities	0.06 (0.01)	[0.03, 0.08]	<0.001
	Age	-0.02 (0.01)	[-0.04, -0.01]	<0.001
	Education (Medium)*occupational attainment	-0.01 (0.03)	[-0.07, 0.04]	0.69
	Education (High)*occupational attainment	0.03 (0.04)	[-0.04, 0.10]	0.36
	Education (Medium)*sex	0.25 (0.19)	[-0.12, 0.62]	0.19
	Education (High)*sex	0.29 (0.21)	[-0.13, 0.71]	0.17
	Occupational attainment *sex	0.06 (0.03)	[-0.01, 0.12]	0.09
	Education (Medium)*occupational attainment *sex	-0.01 (0.04)	[-0.09, 0.06]	0.72
	Education (High)*occupational attainment *sex	-0.08 (0.05)	[-0.17, 0.01]	0.07

STable 8.4 Regression coefficients for the model including 3-way interaction of sex × education × occupational attainment on multisensory processing

Model summary		R^2	F	*p* value
		0.02	1.02	0.43
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Multisensory processing	Education (Medium level)	-0.25 (0.16)	[-0.56, 0.07]	0.13
	Education (High level)	-0.13 (0.19)	[-0.51, 0.24]	0.48
	Occupational attainment	-0.02 (0.03)	[-0.04, 0.07]	0.55
	Sex	-0.10 (0.17)	[-0.43, 0.23]	0.55
	Stimulating activities	0.02 (0.01)	[-0.01, 0.04]	0.14
	Age	-0.01 (0.01)	[-0.03, 0.004]	0.15
	Education (Medium)*occupational attainment	-0.03 (0.03)	[-0.10, 0.03]	0.30
	Education (High)*occupational attainment	-0.06 (0.04)	[-0.14, 0.02]	0.13
	Education (Medium)*sex	0.20 (0.21)	[-0.21, 0.60]	0.34
	Education (High)*sex	-0.03 (0.23)	[-0.49, 0.42]	0.89
	Occupational attainment *sex	-0.01 (0.03)	[-0.08, 0.05]	0.69
	Education (Medium)*occupational attainment*sex	0.03 (0.04)	[-0.05, 0.12]	0.42
	Education (High)*occupational attainment*sex	0.07 (0.05)	[-0.02, 0.17]	0.13

STable 8.5 Regression coefficients for the model including 3-way interaction of sex × education × occupational attainment on short-term memory binding

Model summary		R^2	F	*p* value
		0.04	2.18	0.009
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Short-term memory binding	Education (Medium level)	0.01 (0.16)	[-0.30, 0.32]	0.93
	Education (High level)	-0.21 (0.19)	[-0.58, 0.15]	0.25
	Occupational attainment	-0.03 (0.03)	[-0.08, 0.02]	0.27
	Sex	-0.16 (0.17)	[-0.48, 0.17]	0.33
	Stimulating activities	0.02 (0.01)	[-0.003, 0.04]	0.10
	Age	-0.03 (0.01)	[-0.04, -0.1]	<0.001
	Education (Medium)*occupational attainment	0.02 (0.03)	[-0.04, 0.09]	0.48
	Education (High)*occupational attainment	0.05 (0.04)	[-0.03, 0.12]	0.20
	Education (Medium)*sex	-0.14 (0.20)	[-0.54, 0.26]	0.49
	Education (High)*sex	0.27 (0.23)	[-0.18, 0.71]	0.25
	Occupational attainment *sex	0.01 (0.03)	[-0.06, 0.08]	073
	Education (Medium)*occupational attainment*sex	0.03 (0.04)	[-0.06, 0.11]	0.53
	Education (High)*occupational attainment*sex	-0.02 (0.05)	[-0.11, 0.08]	0.74

STable 8.6 Regression coefficients for the model including 3-way interaction of sex × education × stimulating activities on total grey matter volume

Model summary	R^2	F	*p* value
	0.76	140.4	<0.001

DV	IV	β (SE)	95% CI	*p* value
Total grey matter volume	Education (Medium level)	5316 (4821)	[-4152, 14784]	0.27
	Education (High level)	2818 (5397)	[-7781, 13417]	0.60
	Stimulating activities	3090 (1261)	[613.8, 5566]	0.01
	Sex	-26110 (5273)	[-36467, -15758]	<0.001
	Occupational attainment	-152.5 (269.1)	[-680.9, 375.8]	0.57
	Age	-1061 (227.5)	[-1508.1, -614.7]	<0.001
	TIV	0.25 (0.008)	[0.23, 0.26]	<0.001
	Education (Medium)*stimulating activities	-2499 (1424)	[-5295, 297.4]	0.08
	Education (High)*stimulating activities	-2117 (1649)	[-5356, 1121]	0.20
	Education (Medium)*sex	-6623 (6035)	[-17374, 6328]	0.36
	Education (High)*sex	-371.1 (6610)	[-13352, 12610]	0.96
	Stimulating activities*sex	-2487 (1535)	[-5502, 527.3]	0.11
	Education (Medium)*stimulating activities*sex	2479 (1769)	[-994.1, 5953]	0.16
	Education (High)*stimulating activities*sex	3430 (2005)	[-508.1, 7367]	0.09

STable 8.7 Regression coefficients for the model including 3-way interaction of sex × education × occupational attainment on total grey matter volume

Model summary	R^2	F	*p* value
	0.76	140.1	<0.001

DV	IV	β (SE)	95% CI	*p* value
Total grey matter volume	Education (Medium level)	8916 (4473)	[-132.1, 17699]	0.05
	Education (High level)	8282 (5583)	[-2682, 19246]	0.14
	Occupational attainment	485.4 (738.3)	[-964.4, 1935]	0.51
	Sex	-21900 (4857)	[-31438, -12361]	<0.001
	Stimulating activities	1006 (320.2)	[377.1, 1635]	0.002
	Age	-1086 (227.5)	[-1533, -639.1]	<0.001
	TIV	0.25 (0.008)	[0.23, 0.26]	<0.001
	Education (Medium)*occupational attainment	-539.8 (930.8)	[-2368, 1288]	0.56
	Education (High)*occupational attainment	-1304 (1142)	[-3546, 938.5]	0.25
	Education (Medium)*sex	-9620 (5774)	[-20958, 1718]	0.10
	Education (High)*sex	-5093 (6739)	[-18327, 8141]	0.45
	Occupational attainment *sex	-798.8 (969.4)	[-2703, 1105]	0.41
	Education (Medium)*occupational attainment*sex	346.9 (1215)	[-2040, 2734]	0.76
	Education (High)*occupational attainment*sex	2289 (1420)	[-499.3, 5077]	0.11

STable 8.8 Regression coefficients for the model including 3-way interaction of sex × education × occupational attainment on global cortical thickness

Model summary	R^2	F	*p* value
	0.08	3.78	<0.001

DV	IV	β (SE)	95% CI	*p* value
Global cortical thickness	Education (Medium level)	0.02 (0.01)	[0.005, 0.04]	0.01
	Education (High level)	0.03 (0.01)	[0.01, 0.06]	0.01
	Occupational attainment	-8e-06 (0.002)	[-0.003, 0.003]	0.99
	Sex	0.02 (0.01)	[0.003, 0.04]	0.03
	Stimulating activities	-1e-04 (0.001)	[-0.002, 0.001]	0.83
	Age	-0.001 (5e-04)	[-0.003, -0.001]	<0.001
	TIV	4e-08 (1e-08)	[8e-09, 8e-08]	0.02
	Education (Medium)*occupational attainment	-0.002 (0.002)	[-0.01, 0.002]	0.26
	Education (High)*occupational attainment	-0.004 (0.003)	[-0.01, 0.001]	0.09
	Education (Medium)*sex	-0.003 (0.01)	[-0.06, -0.01]	0.02
	Education (High)*sex	-0.03 (0.01)	[-0.06, 0.001]	0.06
	Occupational attainment *sex	0.001 (0.002)	[-0.004, 0.004]	0.79
	Education (Medium)*occupational attainment*sex	0.002 (0.003)	[-0.004, 0.01]	0.55
	Education (High)*occupational attainment*sex	0.004 (0.003)	[0.003, 0.01]	0.26

STable 8.9 Number of participants in each group of the sex × education factorial design

Group	N
Cognitive analyses	666
Females	
High education	136
Medium education	178
Low education	100
Males	
High education	69
Medium education	121
Low education	62
Structural analyses	637
Females	
High education	129
Medium education	174
Low education	92
Males	
High education	63
Medium education	118
Low education	61

STable 8.10 Number of participants in each group of the CAIDE × education factorial design in structural analyses in males

Group	N
Mean CAIDE - 1SD group	
High education males	35
Medium education males	57
Low education males	25
Mean CAIDE group	
High education males	15
Medium education males	28
Low education males	9
Mean CAIDE + 1SD group	
High education males	13
Medium education males	33
Low education males	27

STable 8.11 Demographics in all harmonization sites

	West London	Edinburgh	Cambridge	Oxford	Dublin (Beaumont hospital)	Dublin (Trinity)
N	187	204	94	60	75	17
Age range (y)	40–60	40–59	40–59	40–59	40–59	42–60
Mean age (SD)	51.4 (5.4)	51.3 (5.5)	51.7 (5.0)	50.5 (5.6)	50.2 (5.4)	49.7 (5.7)
Sex (Female%)	70.1%	57.8%	60.6%	78.3%	41.3%	64.7%

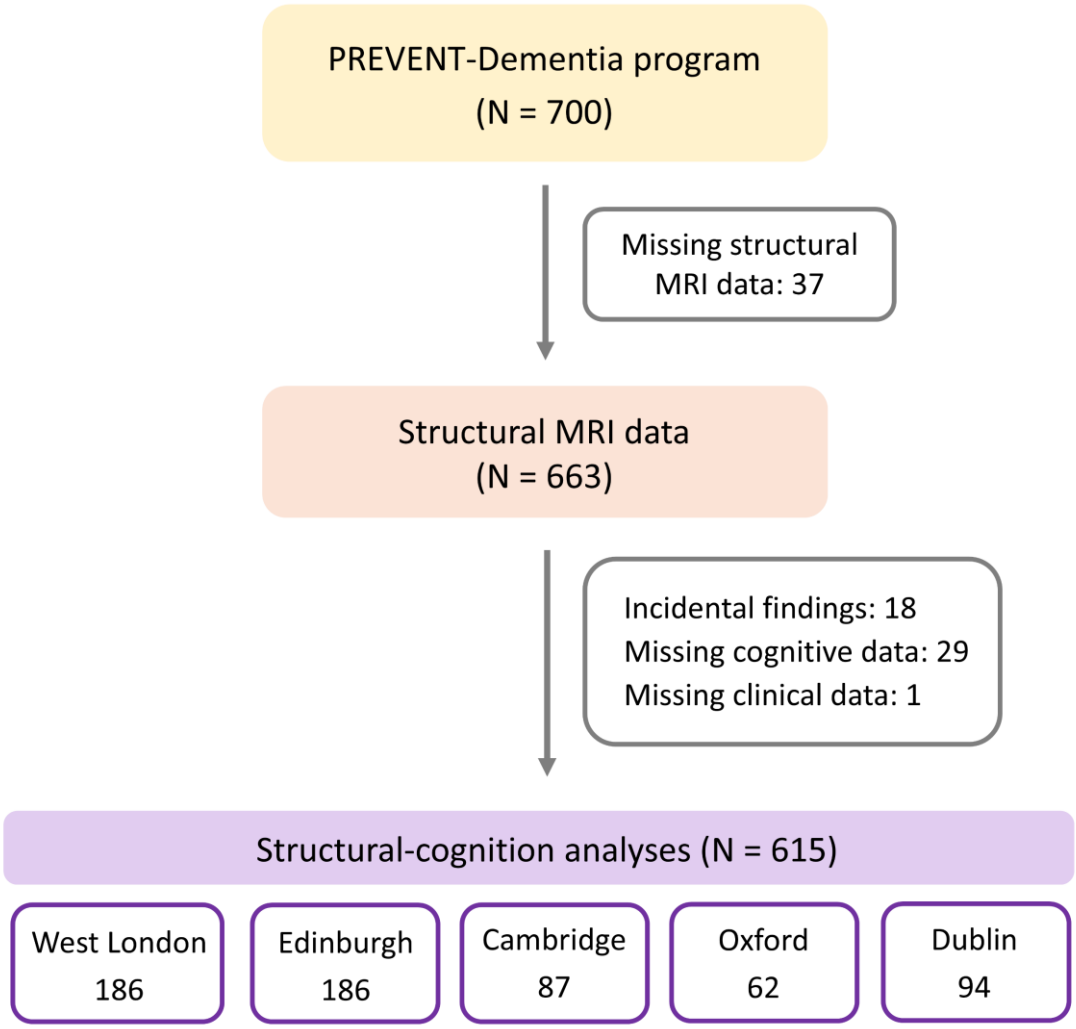
STable 8.12 Regression coefficients for the model including 3-way interaction of sex × education × stimulating activities on global cortical thickness using data without ComBat

Model summary	R^2	F	*p* value
	0.20	7.87	<0.001

DV	IV	β (SE)	95% CI	*p* value
Global cortical thickness	Education (Medium) (reference = low education)	0.01 (0.01)	[-0.01, 0.03]	0.33
	Education (High) (reference = low education)	0.01 (0.01)	[-0.01, 0.04]	0.28
	Stimulating activities	0.01 (0.003)	[0.002, 0.01]	0.009
	Sex	0.006 (0.01)	[-0.02, 0.03]	0.58
	Occupational attainment	-0.001 (0.001)	[-0.002, 0.0003]	0.11
	Age	-0.002 (<0.001)	[-0.003, -0.001]	<0.001
	TIV	<0.001 (<0.001)	[3e-09, 7e-08]	0.014
	Education (Medium vs. Low)*stimulating activities	-0.008 (0.003)	[-0.01, -0.002]	0.014
	Education (High vs. Low)*stimulating activities	-0.01 (0.004)	[-0.02, -0.001]	0.020
	Education (Medium vs. Low)*sex	-0.003 (0.01)	[-0.04, 0.01]	0.30
	Education (High vs. Low)*sex	-0.01 (0.01)	[-0.03, 0.03]	0.79
	Stimulating activities*sex	-0.01 (0.003)	[-0.02, -0.003]	0.005
	Education (Medium vs. Low)*stimulating activities*sex	0.01 (0.004)	[0.002, 0.017]	0.012
	Education (High vs. Low)*stimulating activities*sex	0.01 (0.004)	[0.002, 0.019]	0.015

9. Appendix III: Supplementary information for Chapter 4

9.1 Supplementary Figures



SFigure 9.1 Participant inclusion criteria in Chapter 4*. For the investigation of brain structure and cognition, per site, from the PREVENT–Dementia program.*

9.2 Supplementary Tables

STable 9.1 Regression coefficients for models including 3-way interaction on episodic and relational memory

DV	Interaction term	β (SE)	95% CI	t	*p* value
Episodic and relational memory	APOE4*sex*global CT	0.17 (0.15)	[-0.12, 0.47]	1.14	0.253
	CAIDE*sex*global CT	-0.04 (0.07)	[-0.18, 0.10]	-0.52	0.605
	APOE4*sex*precuneus CT	0.13 (0.16)	[-0.18, 0.44]	0.81	0.421
	CAIDE*sex*precuneus CT	-0.05 (0.07)	[-0.19, 0.09]	-0.70	0.486

Note: Unstandardized coefficients β and standard error (SE) were reported. Each row denotes a separate model. Models including APOE4 controlled for age, sex, education, TIV, and scan sites, and models including CAIDE adjusted for TIV and scan sites. CI, confidence intervals; APOE4, Apolipoprotein E4 genotype; CAIDE, Cardiovascular Risk Factors, Aging and Dementia; CT, cortical thickness.

STable 9.2 Multicollinearity assessment for brain structural measures

IV	Tolerance	VIF
TGM	0.310	3.223
TIV	0.368	2.715
Age	0.951	1.051
Sex	0.593	1.686
Years of education	0.934	1.071
Site	0.915	1.093

Note: TGM, total grey matter volume; TIV, total intracranial volume; IV, independent variable; VIF, variance inflation factor.

10. Appendix IV: Supplementary information for Chapter 5

10.1 Supplementary Methods

10.1.1 Framewise Displacement Calculation

Differentiating head realignment parameters across frames yields a six dimensional timeseries that represents instantaneous head motion, which can then be summarised as a scalar quantity, framewise displacement (FD), using the formula (Equation (1)). Specifically, this measure was calculated as the sum of the absolute values of the derivatives of the 6 realignment parameters (Power et al., 2012). Rotational displacements were converted from degrees to millimetres by calculating the displacement on the surface of a sphere with a radius of 50 mm, which is approximately the mean distance from the cerebral cortex to the centre of the head.

$$\boldsymbol{FD_i} = |\Delta \boldsymbol{d_{ix}}| + |\Delta \boldsymbol{d_{iy}}| + |\Delta \boldsymbol{d_{iz}}| + |\Delta \boldsymbol{\alpha_i}| + |\Delta \boldsymbol{\beta_i}| + |\Delta \boldsymbol{\gamma_i}| \qquad (\mathbf{1})$$

Where $\Delta \boldsymbol{d_{ix}} = \boldsymbol{d_{(i-1)x}} - \boldsymbol{d_{ix}}$ and similarly for the other rigid body parameters $[\boldsymbol{d_{iy}}, \boldsymbol{d_{iz}}, \boldsymbol{\alpha_i}, \boldsymbol{\beta_i}, \boldsymbol{\gamma_i}]$.

10.1.2 Associations of mean framewise displacement with episodic and relational memory and biological sex

After carefully censoring the motion-contaminated data, mean FD was not significantly associated with episodic and relational memory across all participants, within female-only group and male-only group (All participants: r = -0.01, p = 0.89; female-only group: r = -0.04, p = 0.49; male-only group: r = 0.09, p = 0.24). These results suggest that head movement did not significantly influence our results. Furthermore, we found no significant difference in mean FD between females and males (Mann-Whitney U = 25242.00, Z = 1.30, p = 0.19).

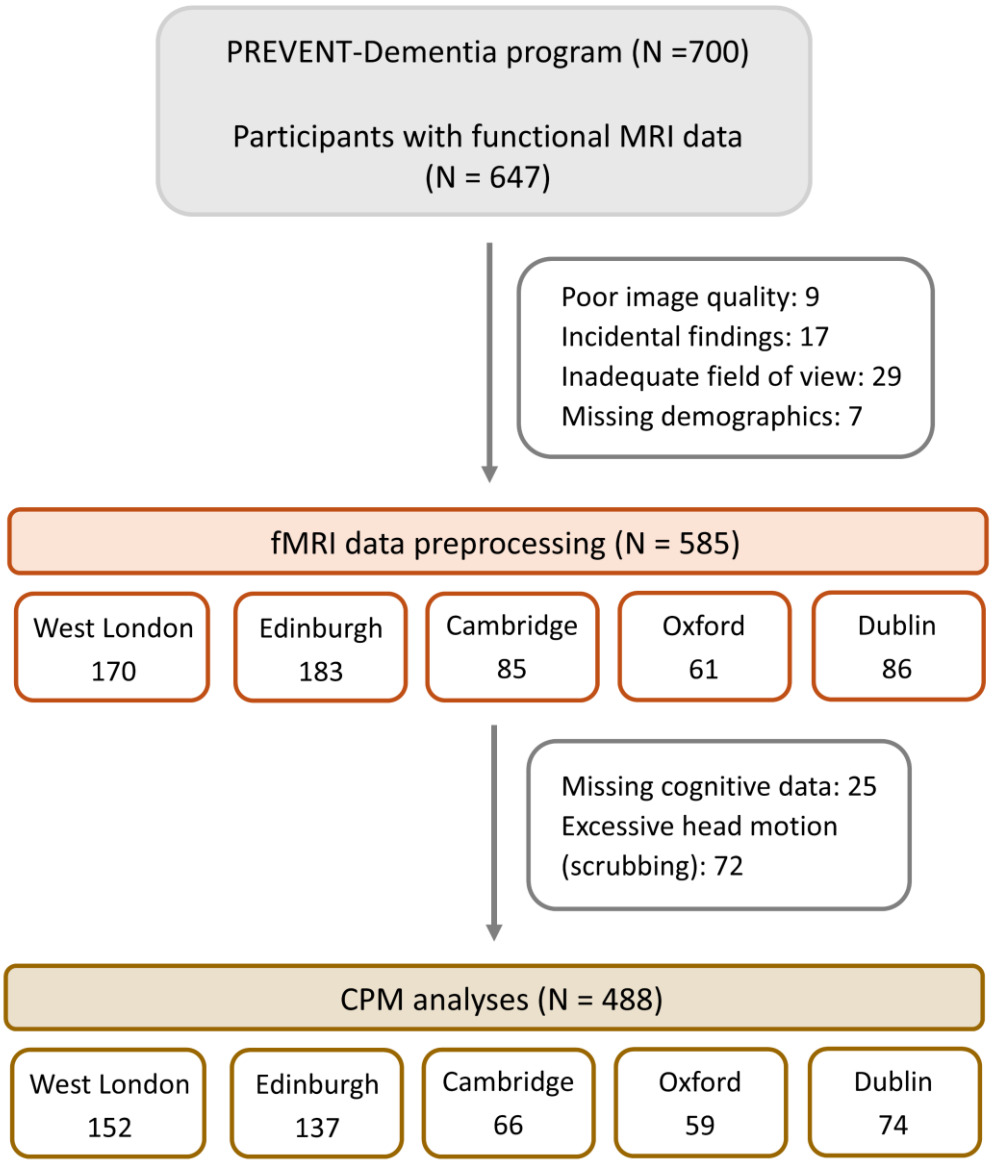
10.2 Supplementary Results

10.2.1 ComBat assumptions assessments before CPM analyses

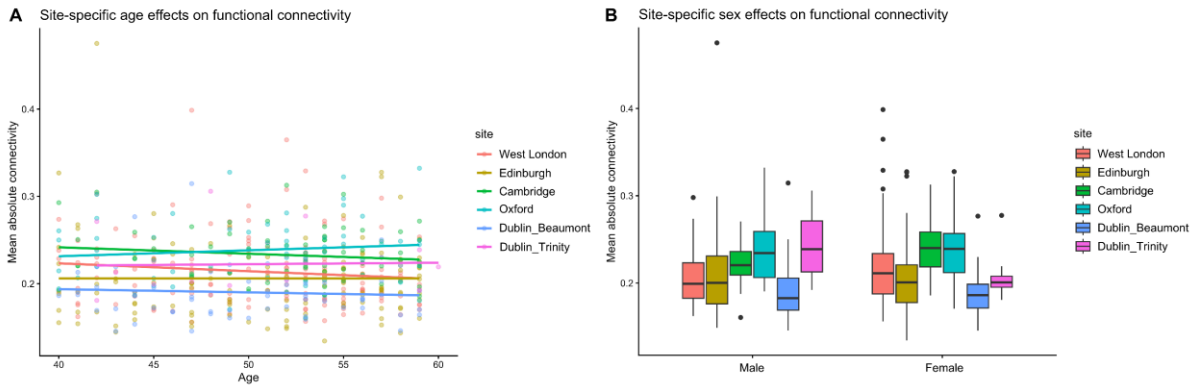
For the functional connectivity analyses, the assumptions underlying ComBat were assessed using summary measures derived from the non-harmonized connectivity data prior to harmonization. Given the high dimensionality of the connectivity matrices, covariate effects were not examined at the level of individual edges. Instead, site-specific associations between age/sex and functional measure were examined using mean absolute connectivity.

The majority of sites showed broadly consistent associations between age and mean absolute connectivity. However, Oxford and Dublin (Trinity) sites displayed differing patterns (SFigure 10.2). Dublin (Trinity) site also had the smallest sample size (N = 13), suggesting that this deviation may reflect sampling variability rather than a true difference in underlying biological effects. While some degree of imbalance in sample size and sex distribution was present across sites (STable 8.16), such variability is common in multi-site studies. Importantly, age distributions across sites showed substantial overlap within the targeted mid-life age range (40–60 years). Although some variability in distribution shape was observed across sites (e.g., slight shifts towards younger or older age ranges), no site showed a completely distinct or non-overlapping age profile (SFigure 10.3).

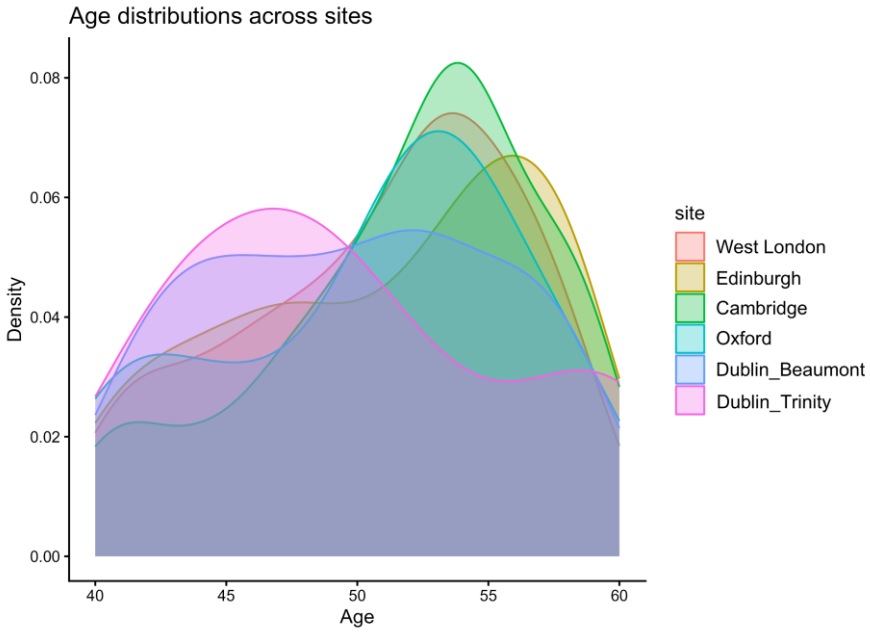
10.3 Supplementary Figures



SFigure 10.1 Participant inclusion criteria in Chapter 5. *For fMRI data preprocessing and the CPM analyses, per site, from the PREVENT-Dementia program.*



SFigure 10.2 Site-specific covariate effects on mean absolute functional connectivity. (A) Age effects, and (B) sex effects on mean absolute functional connectivity across six scan sites.



SFigure 10.3 Age distributions across scan sites.

10.4 Supplementary Tables

STable 10.1 Participant characteristics in Cam-CAN dataset

Participant characteristics	Cam-CAN cohort
N	161
Age (y)	48.0 (10.0)
Sex (% Female)	51.6%
Years of education	16.0 (4.0)
Episodic memory	0.14 (1.1)
Mean FD	0.15 (0.05)

NOTE: median (interquartile range, IQR) was reported for non-normal distributed continuous variables. Mean (SD) was reported for normal distributed continuous variables. Abbreviations: FD, frame-wise displacement.

STable 10.2 Top 20 nodes of positive network predicting episodic and relational memory for all participants

No.	Degree	Region	Network	MNI coordinates		
				x	*y*	*z*
1	17	Precentral gyrus	Sensorimotor	44	-11	38
2	14	Basal ganglia	Cingulo-opercular	11	-24	2
3	13	Frontal	Sensorimotor	53	-3	32
4	13	Basal ganglia	Cingulo-opercular	-6	17	34
5	12	Mid insula	Sensorimotor	33	-12	16
6	12	ACC	Cingulo-opercular	-2	30	27
7	12	Inf temporal	Default mode	-61	-41	-2
8	11	dlPFC	Frontoparietal	40	36	29
9	11	dACC	Cingulo-opercular	9	20	34
10	11	Occipital	Visual	-34	-60	-5
11	11	Med cerebellum	Cerebellum	-16	-64	-21
12	10	Angular gyrus	Default mode	51	-59	34
13	10	Inf temporal	Default mode	-59	-25	-15
14	10	Occipital	Default mode	-2	-75	32
15	9	Fusiform	Cingulo-opercular	54	-31	-18
16	9	Angular gyrus	Default mode	-48	-63	35
17	9	vmPFC	Default mode	-11	45	17
18	9	vlPFC	Default mode	46	39	-15
19	9	Post occipital	Visual	33	-81	-2
20	8	Parietal	Sensorimotor	-47	-12	36

Notes: ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; dACC, dorsal anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex.

STable 10.3 Top 20 nodes of negative network predicting episodic and relational memory for all participants

No.	Degree	Region	Network	MNI coordinates		
				x	*y*	*z*
1	10	Basal ganglia	Cingulo-opercular	-20	6	7
2	6	vlPFC	Frontoparietal	39	42	16
3	5	vPFC	Cingulo-opercular	34	32	7
4	5	vFC	Cingulo-opercular	-46	10	14
5	5	Angular gyrus	Default mode	-48	-63	35
6	5	Lat cerebellum	Cerebellum	-34	-57	-24
7	4	dlPFC	Frontoparietal	-44	27	33
8	4	dlPFC	Frontoparietal	46	28	31
9	4	Mid insula	Sensorimotor	-42	-3	11
10	4	Ant insula	Cingulo-opercular	38	21	-1
11	4	Post cingulate	Default mode	-5	-43	25
12	4	Post occipital	Visual	-29	-88	8
13	3	Mid insula	Sensorimotor	-36	-12	15
14	3	Temporal	Sensorimotor	-41	-37	16
15	3	Mid insula	Cingulo-opercular	32	-12	2
16	3	Ant insula	Cingulo-opercular	-36	18	2
17	3	vmPFC	Default mode	9	51	16
18	2	IPL	Frontoparietal	-41	-40	42
19	2	Vent aPFC	Frontoparietal	-43	47	2
20	2	dFC	Frontoparietal	-42	7	36

Notes: vlPFC, ventrolateral prefrontal cortex; vPFC, ventral prefrontal cortex; vFC, ventral frontal cortex; dlPFC, dorsolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; IPL, inferior parietal lobule; dFC, dorsal frontal cortex.

STable 10.4 Top 20 nodes of positive network predicting episodic and relational memory for female-only group

No.	Degree	Region	Network	MNI coordinates		
				x	*y*	*z*
1	18	Med cerebellum	Cerebellum	-11	-72	-14
2	15	Precuneus	Default mode	11	-68	42
3	14	dlPFC	Frontoparietal	40	36	29
4	14	Mid insula	Sensorimotor	33	-12	16
5	14	Basal ganglia	Cingulo-opercular	-6	17	34
6	12	Sup temporal	Cingulo-opercular	42	-46	21
7	12	Inf temporal	Default mode	-61	-41	-2
8	12	aPFC	Default mode	-25	51	27
9	11	Ant insula	Cingulo-opercular	-36	18	2
10	11	vmPFC	Default mode	6	64	3
11	11	Precuneus	Default mode	-3	-38	45
12	11	Post occipital	Visual	27	-91	2
13	10	Post cingulate	Default mode	-5	-43	25
14	10	Med cerebellum	Cerebellum	5	-75	-11
15	9	Temporal	Sensorimotor	59	-13	8
16	9	ACC	Cingulo-opercular	-2	30	27
17	9	Temporal	Cingulo-opercular	43	-43	8
18	9	Occipital	Default mode	-42	-76	26
19	9	Post occipital	Visual	33	-81	-2
20	8	Occipital	Visual	19	-66	-1

Notes: dlPFC, dorsolateral prefrontal cortex; aPFC, anterior prefrontal cortex; vmPFC, ventromedial prefrontal cortex; ACC, anterior cingulate cortex.

STable 10.5 Top 20 nodes of negative network predicting episodic and relational memory for female-only group

No.	Degree	Region	Network	MNI coordinates		
				x	*y*	*z*
1	8	dlPFC	Frontoparietal	-44	27	33
2	6	aPFC	Frontoparietal	-29	57	10
3	6	vPFC	Cingulo-opercular	34	32	7
4	5	Post cingulate	Default mode	-5	-43	25
5	5	Precuneus	Default mode	9	-43	25
6	3	vent aPFC	Frontoparietal	-43	47	2
7	3	dlPFC	Frontoparietal	40	36	29
8	3	Temporal	Sensorimotor	-41	-37	16
9	3	Basal ganglia	Cingulo-opercular	14	6	7
10	3	Thalamus	Cingulo-opercular	-12	-3	13
11	3	Parietal	Cingulo-opercular	-55	-44	30
12	3	vFC	Cingulo-opercular	51	23	8
13	3	Basal ganglia	Cingulo-opercular	-20	6	7
14	3	Angular gyrus	Default mode	-48	-63	35
15	3	Post occipital	Visual	-29	-88	8
16	2	IPL	Frontoparietal	54	-44	43
17	2	aPFC	Frontoparietal	29	57	18
18	2	vlPFC	Frontoparietal	39	42	16
19	2	vPFC	Frontoparietal	-52	28	17
20	2	IPL	Frontoparietal	-53	-50	39

Notes: dlPFC, dorsolateral prefrontal cortex; aPFC, anterior prefrontal cortex; vPFC, ventral prefrontal cortex; vFC, ventral frontal cortex; IPL, inferior parietal lobule; vlPFC, ventrolateral prefrontal cortex.

STable 10.6 Top 20 nodes of positive network predicting episodic and relational memory for male-only group

No.	Degree	Region	Network	MNI coordinates		
				x	*y*	*z*
1	15	aPFC	Frontoparietal	-29	57	10
2	9	vmPFC	Default mode	9	51	16
3	9	vmPFC	Default mode	-11	45	17
4	7	Precentral gyrus	Sensorimotor	44	-11	38
5	6	dFC	Frontoparietal	-42	7	36
6	6	Med cerebellum	Cerebellum	-6	-60	-15
7	6	Med cerebellum	Cerebellum	-16	-64	-21
8	5	Post cingulate	Cingulo-opercular	-4	-31	-4
9	5	IPS	Default mode	-36	-69	40
10	5	vmPFC	Default mode	8	42	-5
11	5	ACC	Default mode	9	39	20
12	4	dFC	Frontoparietal	44	8	34
13	4	Vent aPFC	Frontoparietal	42	48	-3
14	4	dlPFC	Frontoparietal	-44	27	33
15	4	IPL	Frontoparietal	-53	-50	39
16	4	IPL	Frontoparietal	-48	-47	49
17	4	Parietal	Sensorimotor	46	-20	45
18	4	Post insula	Cingulo-opercular	-30	-28	9
19	4	Ant insula	Cingulo-opercular	-36	18	2
20	4	Lat cerebellum	Cerebellum	21	-64	-22

Notes: aPFC, anterior prefrontal cortex; vmPFC, ventromedial prefrontal cortex; dFC, dorsal frontal cortex; IPS, intraparietal sulcus; ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobule.

STable 10.7 Top 20 nodes of negative network predicting episodic and relational memory for male-only group

No.	Degree	Region	Network	MNI coordinates		
				x	*y*	*z*
1	23	Lat cerebellum	Cerebellum	-28	-44	-25
2	22	Basal ganglia	Cingulo-opercular	-20	6	7
3	21	vmPFC	Default mode	-11	45	17
4	19	vFC	Cingulo-opercular	-46	10	14
5	18	vmPFC	Default mode	9	51	16
6	18	ACC	Default mode	9	39	20
7	17	vPFC	Cingulo-opercular	34	32	7
8	15	Sup temporal	Cingulo-opercular	42	-46	21
9	15	Mid insula	Cingulo-opercular	37	-2	-3
10	15	Occipital	Visual	9	-76	14
11	15	Med cerebellum	Cerebellum	-16	-64	-21
12	13	Mid insula	Cingulo-opercular	32	-12	2
13	13	Temporal	Cingulo-opercular	51	-30	5
14	13	Occipital	Visual	-44	-63	-7
15	12	Temporal	Sensorimotor	-53	-37	13
16	12	Thalamus	Cingulo-opercular	11	-12	6
17	12	Ant insula	Cingulo-opercular	-36	18	2
18	11	dFC	Frontoparietal	44	8	34
19	11	Vent aPFC	Frontoparietal	42	48	-3
20	11	vPFC	Frontoparietal	-52	28	17

Notes: vmPFC, ventromedial prefrontal cortex; vFC, ventral frontal cortex; ACC, anterior cingulate cortex; vPFC, ventral prefrontal cortex; dFC, dorsal frontal cortex.

STable 10.8 Regression coefficients for the effect of CAIDE on negative network strength

Model summary		R^2	F	*p* value
		0.08	19.97	<0.001
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Negative network strength	CAIDE	-0.09 (0.08)	[-0.26, 0.07]	0.258
	Mean FD	17.96 (2.85)	[12.35, 23.56]	<0.001

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; FD, framewise displacement.

STable 10.9 Regression coefficients for the effect of APOE4 on positive network strength

Model summary		R^2	F	*p* value
		0.09	8.98	<0.001
DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Positive network strength	APOE4	2.65 (1.60)	[-0.49, 5.79]	0.098
	Years of education	-0.05 (0.07)	[-0.56, 0.37]	0.683
	Sex	-0.06 (0.49)	[4.14, 10.50]	<0.001
	Age	-0.09 (0.05)	[-0.62, -0.07]	0.014
	Mean FD	17.89 (2.89)	[19.20, 57.75]	<0.001

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; FD, framewise displacement.

STable 10.10 Regression coefficients for the effect of APOE4 on negative network strength

Model summary	R^2	F	*p* value
	0.08	8.48	<0.001

DV	IV	β (SE)	95% CI	*p* value
Negative network strength	APOE4	-0.09 (0.47)	[-1.01, 0.84]	0.854
	Years of education	-0.04 (0.07)	[-0.17, 0.10]	0.594
	Sex	-0.13 (0.48)	[-1.06, 0.81]	0.793
	Age	-0.08 (0.04)	[-0.16, 0.002]	0.057
	Mean FD	17.70 (2.89)	[12.03, 23.37]	<0.001

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; FD, framewise displacement.

STable 10.11 Regression coefficients for the effects of lifestyle activities on negative network strength

	Model summary	R^2	F	*p* value
		0.08	7.15	<0.001

DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Negative network strength	Stimulating activities	0.02 (0.07)	[-0.11, 0.15]	0.748
	Occupational attainment	0.04 (0.06)	[-0.07, 0.14]	0.502
	Years of education	-0.05 (0.07)	[-0.19, 0.09]	0.511
	Sex	-0.06 (0.49)	[-1.02, 0.90]	0.907
	Age	-0.09 (0.05)	[-0.18, -0.002]	0.044
	Mean FD	17.89 (2.89)	[12.21, 23.57]	<0.001

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; FD, framewise displacement.

STable 10.12 Regression coefficients for model including 2-way interaction of occupation × sex on positive network strength

	Model summary	R^2	F	*p* value
		0.12	8.91	<0.001

DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Positive network strength	Occupational attainment	2.09 (2.89)	[-3.59, 7.77]	0.470
	Sex	7.76 (1.65)	[4.53, 11.00]	<0.001
	Stimulating activities	0.85 (0.22)	[0.41, 1.29]	<0.001
	Years of education	-0.35 (0.24)	[-0.82, 0.12]	0.147
	Age	-0.55 (0.15)	[-0.85, -0.25]	<0.001
	Mean FD	40.35 (9.71)	[21.27, 59.43]	<0.001
	Occupation * sex	-0.18 (1.65)	[-3.43, 3.06]	0.911

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; FD, framewise displacement.

STable 10.13 Regression coefficients for model including 2-way interaction of occupation × sex on negative network strength

	Model summary	R^2	F	*p* value
		0.08	6.21	<0.001

DV	IV	β (SE)	95% CI	*p* value
Negative network strength	Occupational attainment	0.84 (0.86)	[-0.86, 2.54]	0.332
	Sex	-0.01 (0.49)	[-0.97, 0.96]	0.991
	Stimulating activities	0.02 (0.07)	[-0.11, 0.16]	0.720
	Years of education	-0.04 (0.07)	[-0.19, 0.10]	0.537
	Age	-0.10 (0.05)	[-0.19, -0.01]	0.038
	Mean FD	18.07 (2.90)	[12.37, 23.76]	<0.001
	Occupation * sex	-0.40 (0.49)	[-1.37, 0.57]	0.420

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; FD, framewise displacement.

STable 10.14 Regression coefficients for model including 3-way interaction of occupation × sex × APOE4 on positive network strength

	Model summary	R^2	F	*p* value
		0.13	6.27	<0.001

DV	**IV**	**β (SE)**	**95% CI**	***p* value**
Positive network strength	Occupational attainment	3.69 (3.51)	[-3.20, 10.58]	0.293
	Sex	5.56 (2.10)	[1.44, 9.68]	0.008
	APOE4	-6.76 (5.80)	[-18.16, 4.64]	0.244
	Stimulating activities	0.82 (0.23)	[0.38, 1.26]	<0.001
	Years of education	-0.35 (0.24)	[-0.83, 0.12]	0.141
	Age	-0.52 (0.15)	[-0.83, -0.22]	<0.001
	Mean FD	39.98 (9.74)	[20.84, 59.12]	<0.001
	Occupation * sex	-1.16 (2.01)	[-5.11, 2.79]	0.564
	Occupation * APOE4	-4.95 (5.96)	[-16.66, 6.77]	0.407
	Sex * APOE4	5.68 (3.37)	[-0.93, 12.29]	0.092
	Occupation * sex * APOE4	2.90 (3.47)	[-3.92, 9.72]	0.404

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; FD, framewise displacement.

STable 10.15 Regression coefficients for model including 3-way interaction of occupation × sex × APOE4 on negative network strength

	Model summary	R^2	F	*p* value
		0.09	4.20	<0.001

DV	IV	β (SE)	95% CI	*p* value
Negative network strength	Occupational attainment	0.11 (1.05)	[-2.06, 2.08]	0.992
	Sex	0.09 (0.63)	[-1.14, 1.32]	0.886
	APOE4	0.08 (1.74)	[-3.33, 3.50]	0.962
	Stimulating activities	0.03 (0.07)	[-0.10, 0.16]	0.657
	Years of education	-0.04 (0.07)	[-0.18, 0.10]	0.592
	Age	-0.10 (0.05)	[-0.19, -0.01]	0.034
	Mean FD	18.48 (2.92)	[12.74, 24.22]	<0.001
	Occupation * sex	0.15 (0.60)	[-1.04, 1.33]	0.807
	Occupation * APOE4	2.51 (1.79)	[-1.00, 6.03]	0.160
	Sex * APOE4	-0.22 (1.01)	[-2.20, 1.77]	0.831
	Occupation * sex * APOE4	-1.65 (1.04)	[-3.69, 0.40]	0.114

Note: Unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CI, confidence intervals; FD, framewise displacement.

STable 10.16 Demographics in all harmonization sites in CPM analyses

	West London	**Edinburgh**	**Cambridge**	**Oxford**	**Dublin (Beaumont hospital)**	**Dublin (Trinity)**
N	152	137	66	59	61	13
Age range (y)	40–59	40–59	40–59	40–59	40–59	42–60
Mean age (SD)	50.8 (5.3)	51.0 (5.8)	51.8 (5.3)	50.5 (5.7)	49.9 (5.6)	49.8 (6.4)
Sex (Female%)	74.3%	59.1%	63.6%	79.7%	41.0%	61.5%

STable 10.17 CPM results using data without ComBat

Data	Groups	Positive network		Negative network		Combined network	
		r	*p*	r	*p*	r	*p*
Data without Combat	All participants	0.254	**<0.001**	0.238	**<0.001**	0.185	**<0.001**
	Female-only	0.226	**<0.001**	0.167	**0.003**	0.184	**0.002**
	Male-only	0.054	0.269	0.182	0.030	0.151	0.053

Note: Bold font indicates *p* value survived after Bonferroni correction.

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