The role of cerebrovascular reactivity in the ageing brain: Investigating the vascular link between midlife dementia risk and later-life brain and cognitive health



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Abstract

There is growing interest in preventing dementia by targeting modifiable lifestyle risk factors, particularly in midlife. However, the mechanisms through which these factors contribute to neurodegeneration and cognitive decline remain unclear. Cerebrovascular dysfunction, particularly reduced cerebrovascular reactivity (CVR), is a promising but understudied marker of dementia pathology. This thesis investigates whether CVR, as a dynamic indicator of brain vascular reserve, serves as a mechanistic link between midlife dementia risk and later-life brain structure and cognitive performance.

This work includes a systematic review and empirical studies using data from 163 participants in the Whitehall II Heart and Brain Study. Participants were assessed for lifestyle and clinical risk factors in midlife (mean age 52.5 years), and later underwent multimodal brain magnetic resonance imaging and cognitive assessments at two time points approximately nine years apart (mean ages 68 and 77). CVR was measured during the last timepoint of data collection, using the blood-oxygen-level dependent response to a hypercapnic air mixture containing 5% carbon dioxide during a functional magnetic resonance imaging scan.

Three objectives guided the analyses: (1) to examine associations between dementia risk and later-life CVR; (2) to investigate how CVR relates to structural brain markers of dementia and cognitive decline; and (3) to test whether CVR mediates the relationship between midlife risk and later cognitive outcomes.

We found that higher midlife dementia risk was associated with lower CVR, particularly in the

default mode network. Lower CVR, especially in the hippocampus, was associated with smaller grey matter volume, poorer white matter microstructure, and greater cognitive decline. Mediation analyses revealed that higher midlife dementia risk contributed to poorer episodic and visuospatial memory in later life through a pathway involving reduced CVR and smaller grey matter volume in the left hippocampus. These findings support the potential mechanistic role of hippocampal CVR in the pathological processes underlying neurodegeneration and cognitive decline. Given that impairments in CVR are potentially modifiable, we propose that hippocampal CVR may be a valuable marker identifying at-risk individuals and guiding preventive strategies for reducing dementia risk.

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List of Abbreviations

AAIC	Alzheimer's Association International Conference
ACME	Average causal mediation effect
AD	Alzheimer's disease
ADE	Average direct effect
ANU-ADRI	The Australian National University Alzheimer's Disease Risk Index
APOE ε4	Apolipoprotein ε4
ASL	Arterial spin labelling
AUC	Area under the curve
Aβ	Amyloid-β
BH	Benjamini-Hochberg
BNT	Boston Naming Test
BOLD	Blood oxygen level-dependent
CADASIL	Hereditary stroke disorder
CAIDE	The Cardiovascular Risk Factors, Aging, and Incidence of Dementia
CATCH	Critically Attained Threshold of Cerebral Hypoperfusion
Ca^{2+}	Calcium
CBF	Cerebral blood flow
CSF	Cerebrospinal fluid
CVR	Cerebrovascular reactivity
DCOC	Digit Coding
DMN	Default mode network
DSB	Digit Span backward
DSF	Digit Span forward
DSS	Digit Span sequencing
DTI	Diffusion tensor imaging
EMCI	Early mild cognitive impairment
FA	Fractional anisotropy
FDR	False discovery rate
FLAIR	Fluid-Attenuated Inversion Recovery
FLU_C	Category Fluency
FLU_L	Letter Fluency
fMRI	Functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
GHQ	General Health Questionnaire
GMV	Grey matter volume
HBM	Human Brain Mapping
HBS	Heart and Brain Study
HC	Healthy control
HVLT_DR	Hopkins Verbal Learning Test delayed recall
HVLT_IR	Hopkins Verbal Learning Test immediate recall
HVLT_RDI	Hopkins Verbal Learning Test recognition

Hpc	Hippocampus
K^+	Potassium
L1	Axial diffusivity
LMCI	Late mild cognitive impairment
LOAD	Probable Alzheimer's disease patient
log%WMH	Log-transformed percentage of total white matter hyperintensities volume
Max	Maximum
MCI	Mild Cognitive Impairment
MD	Mean diffusivity
MEMP	Multi-Echo MPRAGE
Min	Minimum
MPFC	Medial prefrontal cortex
MP-RAGE	Magnetisation Prepared - RApid Gradient Echo
MRI	Magnetic resonance imaging
NFTs	Neurofibrillary tangles
PCA	Principal component analysis
PCC	Posterior cingulate cortex
PET	Positron Emission Tomography
PVE	Partial volume estimates
PVS	Perivascular spaces
RCF_DF	Rey Complex Figure (delayed reproduce)
RCF_IF	Rey Complex Figure (immediate reproduce)
RD	Radial diffusivity
ROIs	Regions of interest
SD	Standard deviation
SMCs	Smooth muscle cells
T1	Longitudinal relaxation time
TBI	Traumatic brain injury
TE	Echo time
3T	3 Tesla
TI	Inversion time
TMT_A	Trail Making Test A
TMT_B	Trail Making Test B
TOPF	Test of Premorbid Functioning
TPJ	Temporoparietal junction
TR	Repetition time
UKBDRS	UK Biobank Dementia Risk Score
WH	Whitehall
WHII	Whitehall II
WHO	World Health Organization
WM	White matter
WMHs	White matter hyperintensities
WMLs	White matter lesions

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List of Publications and Presentations

Publications arising from this Thesis

- **Wang, C.**, Reid, G., Mackay, C. E., Hayes, G., Bulte, D. P., & Suri, S. (2023). A Systematic Review of the Association Between Dementia Risk Factors and Cerebrovascular Reactivity. *Neuroscience & Biobehavioral Reviews*, 105140.
- **Wang, C.**, Jobbins, L., Reid, G., Hobden, G., Patel, R., Pint, J., Bulte, D., Ebmeier, K., Mackay, C., Kivimäk, M., Singh-Manoux, A., Suri, S. The Relationship between Hippocampal Cerebrovascular Reactivity and Brain Structure in Older Age, *Human Brain Mapping (under revision).*
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Other publications during the DPhil period

- **Wang, C.**, Pearce, E., Jones, R., & Lloyd-Evans, B. (2022). 'Kindness by Post': A Mixed-Methods Evaluation of a Participatory Public Mental Health Project. *Frontiers in Psychology*, *12*, 6700.
- Hayes, G., Pinto, J., Sparks, S. N., **Wang, C.**, Suri, S., & Bulte, D. P. (2022). Vascular smooth muscle cell dysfunction in neurodegeneration. *Frontiers in Neuroscience*, *16*.
- Shan, D., **Wang, C.**, Crawford, T., & Holland, C. (2024). Association between COVID-19 infection and new-onset dementia in older adults: a systematic review and meta-analysis. *BMC geriatrics*, *24*(1), 1-15.
- Shan, D., Li, Z., & **Wang, C.** (2024). New four year direct entry medical degree: prudence is needed. *BMJ: British Medical Journal (Online)*, *386*, q1598.
- Hobden, G., Reid, G., Chiesa, S. T., **Wang, C.**, Jobbins, L., Mackay, C. E., ... & Suri, S. (2025). Associations of aortic and carotid artery health with cerebrovascular markers and cognition in older adults from the Whitehall II imaging study. *BMC medicine*, 23(1), 330.
- Patel, R., Gillis, G., Mackay, C. E., Griffanti, L., **Wang, C**., Ebmeier, K. P., & Suri, S. (2025). The lifetime accumulation of multimorbidity and its influence on dementia risk: a UK Biobank Study. *Brain Communications*, 7(4), fcaf222.

Conference Presentations

- Associations between Later-life Cerebrovascular Reactivity and Brain Structure and Cognitive Decline: A Longitudinal Study in an Aging Cohort with Varying Dementia Risks

Poster presentation: The Alzheimer's Association International Conference, 2024

- Cerebrovascular Reactivity, Brain Structure, and Cognition in Aging: Insights from the Heart and Brain Study

Poster presentation: Organization for Human Brain Mapping Annual Meeting, 2024

- Associations of Mid-Life Dementia Risks with Later-Life Brain Vascular Health, Longitudinal Brain Structure, and Cognitive Function in Healthy Aging

Oral presentation: The 13th Annual Oxford Neuroscience Symposium, 2024

- The relationships between hippocampal cerebrovascular reactivity, hippocampal volume, and episodic memory in healthy ageing

Poster presentation: The Alzheimer's Association International Conference, 2023

- Associations of the novel UK Biobank Dementia Risk Score with longitudinal brain atrophy, cerebrovascular and cognitive decline in ageing

Oral presentation: Dementias Platform UK, 2023 Neuroimaging Symposium, 2023

- A systematic review of the association between dementia risk factors and cerebrovascular reactivity

Poster presentation: The 12th Annual Oxford Neuroscience Symposium, 2023

Poster presentation: Alzheimer's Research UK Thames Valley Network Dementia Research Day, 2022

Chapter 1: Introduction

1.1 The global burden of dementia

Dementia is a progressive neurodegenerative syndrome. The most representative symptom of dementia is decline in cognitive function, such as difficulties with memory, language, thinking, and trouble in processing information (Chertkow et al., 2013; Gaugler et al., 2016). This cognitive dysfunction goes beyond the usual consequences of biological ageing (Alzheimer's Disease Facts and Figures, 2025). Alzheimer's disease (AD) is the leading cause of dementia, accounting for up to 75% of all cases (Qiu et al., 2009). Other subtypes include vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and mixed dementia, which involves features of more than one underlying pathology (Elahi & Miller, 2017; Hugo & Ganguli, 2014). These underlying diseases typically develop in a slow and progressive manner, often with a silent onset (Grand et al., 2011; Robinson et al., 2015). As a result, dementia, which refers to a collection of clinical symptoms arising from these conditions, is characterised by a gradual progression. For example, the cognitive decline often begins subtly and worsens over time. Individuals may initially experience subjective memory complaints, followed by Mild Cognitive Impairment (MCI), during which one or more cognitive difficulties are present. At this stage, people are still able to independently perform their daily activities, although with greater effort. Over time, the condition progresses through mild, moderate, and eventually severe dementia (Albert et al., 2011). As the syndrome advances, cognitive, behavioural, and physical

abilities decline steadily, ultimately leading to full dependence in daily living (Reisberg & Franssen, 1999). Given the progressive nature of dementia, identifying individuals at risk during the preclinical stages, before the onset of overt symptoms is critical for early strategies to slow down dementia progression and preserve cognitive health.

Dementia is a rapidly growing global health challenge. In 2021, an estimated 57 million people were living with dementia worldwide (World Health Organization [WHO], 2025). These numbers are projected to rise steeply, particularly in low- and middle-income countries, with an estimation of 78 million people who will live with the condition by 2030 (World Alzheimer Report 2021). In high-income countries, it affects around 5-10% of individuals aged 65 and older (Hugo & Ganguli, 2014). There is also a huge economic burden due to dementia, with estimated global costs reaching US$1.3 trillion in 2019 from informal care provided by family members or friends (Cheng, 2017; Shon & Yoon, 2021; World Health Organization, 2025). The increasing prevalence of dementia, combined with its substantial economic and social burden highlights the urgent need for effective strategies to slow disease progression and address the anticipated rise in cases globally.

1.2 Modifiable lifestyle factors in dementia prevention

Although our understanding of Alzheimer's and vascular dementia has deepened over recent

decades, effective treatments remain limited. Several medications have been developed based on the key pathological features including amyloid plaques, tau tangles, neuroinflammation, glutamate excitotoxicity and abnormal autophagy (Zhang et al., 2024). However, most approved medications for dementia, such as acetylcholinesterase inhibitors and memantine can only provide short-term improvements in cognition and daily functioning but fail to slow disease progression (Edwards & Corkill, 2023; McShane et al., 2019). Newer agents like Lecanemab have shown modest benefits in the early stage of dementia, but have been associated with serious adverse events, which raises concerns about its safety (Edwards & Corkill, 2023). Additionally, genetic risks such as the Apolipoprotein E (APOE) ε4 allele are among the major identified genetic risk factors for dementia (Kwon & Koh, 2024). However, it is not a direct cause of the disease, as many individuals carrying ε4 never develop dementia and the genetic trait itself cannot be directly modified. This increases the importance of preventive strategies to slow the underlying progression of the disease pathology before the onset of dementia.

Recently, growing evidence has suggested that the management of lifestyle and health-related factors plays a critical role in the prevention of dementia. In a recent Lancet review, Livingston and colleagues identified **14 potentially modifiable risk factors** associated with dementia across the life course. These include less education, head injury, physical inactivity, smoking, excessive alcohol consumption, hypertension, obesity, diabetes, hearing loss, depression, infrequent social contact, and air pollution, and more recently, factors such as high cholesterol

and vision loss (Livingston et al., 2017, 2020, 2024). Addressing these risk factors could potentially prevent or delay up to 40-45% of dementia cases worldwide (Bobrow et al., 2021; Livingston et al., 2020, 2024). Other large-scale studies and meta-analyses have consistently supported these findings, which have suggested that cardiovascular, psychosocial and behavioural factors are closely linked to dementia risk (Barnes & Yaffe, 2011; Montero-Odasso et al., 2020; Noach et al., 2023; Wesselman et al., 2019). There is therefore a growing need to investigate when and how these risk factors may affect brain and cognitive health. Understanding this relationship may offer effective strategies to preserve neurocognitive function in order to prevent or delay dementia.

1.3 Vascular health may link modifiable lifestyle risk and dementia

Among the aforementioned dementia risk factors, many of them are also well-established risk factors for poor brain vascular health. For example, chronically hypertensive status, type 2 diabetes, and physical inactivity have all been linked to impaired cerebral microvasculature, leading to endothelial dysfunction (Daniele et al., 2022) and compromised blood-brain barrier integrity (Iadecola, 2010). Such vascular changes can reduce intracranial arterial flow and cerebral blood supply and increase susceptibility to lacunar infarctions (Cui et al., 2016; Zhou et al., 2014), white matter lesions and strokes (Clark et al., 2019). Over time, these cumulative vascular impairments may also promote pathological processes such as amyloid deposition and neuroinflammation (Ungvari et al., 2021), which are key mechanisms in the development

of dementia. Indeed, cerebrovascular pathology is frequently observed in individuals diagnosed with AD and even MCI (Berman et al., 2015; Eisenmenger et al., 2022; Gorelick et al., 2011). About a quarter of AD cases have been found to have small vessel infarcts, and 61% of these cases also showed white matter hyperintensities (WMHs). Over half of the MCI individuals are also present with WMHs (Scott et al., 2018). These vascular changes contribute to brain atrophy and may exacerbate neurodegenerative processes (Fiford et al., 2017). Overall, brain vascular health is not only influenced by a range of modifiable lifestyle and clinical risk factors but is also closely linked to the onset and progression of dementia. In other words, vascular health may underlie the relationship between modifiable lifestyle factors and dementia risk. Understanding these associations may provide crucial insight into how vascular dysfunction contributes to cognitive decline in ageing.

Several previous studies have demonstrated that dementia risk factors, especially vascular risk factors can accelerate the progression of AD and other dementias. De la Torre proposed the **Critically Attained Threshold of Cerebral Hypoperfusion (CATCH) hypothesis,** which suggests that chronic cerebral hypoperfusion, reflected by persistently reduced cerebral blood flow (CBF) is a key initiating factor leading to neurodegeneration and dementia (De La Torre, 2000a). According to this model, normal ageing is accompanied by a gradual decline in CBF (Pantano et al., 1984; Strandgaard, 1991). However, this reduction is typically within a physiological range and does not in itself lead to neuronal failure. When CBF progressively declines and falls below a critical threshold, the brain can no longer sustain adequate energy

delivery to support normal neuronal function. Once this threshold is crossed, it triggers a cascade of pathological changes of neuronal energy crisis, including synaptic dysfunction, neuronal loss, as well as neurodegenerative changes such as accumulated Amyloid-β plaques and neurofibrillary tangles (NFTs), which contribute to cognitive impairment and dementia (de la Torre, 2018; De La Torre, 2012). The presence of vascular risk factors such as hypertension, diabetes, or atherosclerosis may accelerate this process by further impairing cerebral haemodynamics and pushing perfusion below the critical point, thereby triggering microcirculatory disturbances and other structural brain pathologies (de la Torre, 2010; De La Torre, 2013; de la Torre, 2016). These vascular and structural pathologies accelerate the transition from normal ageing to MCI and ultimately contribute to AD or vascular dementia (***Figure 1.1***). The CATCH hypothesis highlights the critical role of chronic cerebral hypoperfusion as an early event that may link vascular risk factors to the progression of dementia.

1.4 Hypothesis and overall thesis objective

While we now know a lot about the role of CBF in the pathology of dementia, there is more to understand other dynamic markers of cerebrovascular health. One emerging but understudied marker of brain vascular health is **cerebrovascular reactivity (CVR),** which reflects the ability of cerebral blood vessels to dilate in response to vasoactive stimuli (Liu et al., 2019). CVR offers a physiological index of microvascular integrity where lower CVR indicates reduced

vascular reserve and impaired cerebral perfusion capacity (Liu et al., 2019).

This thesis investigates **the role of CVR as a potential intermediary between dementia risk and brain and cognitive decline.** Understanding this is important because a) CVR changes may precede CBF changes as impairments in CVR can be detected even when CBF remains unaltered (Kim et al., 2021; Lin et al., 2018; Weijs et al., 2023; Yezhuvath et al., 2012) and (b) early evidence suggests that CVR is potentially modifiable and therefore could inform risk stratification or preventative interventions.

Figure 1.1 illustrates the overarching hypothesis of this thesis. We hypothesise that:

1) Potentially modifiable risk factors (such as hypertension, type 2 diabetes, depression etc.) can impair CVR.

2) Lower CVR can contribute to a cascade of structural brain changes, including white matter lesions, grey matter atrophy, and lower white matter microstructural connectivity, ultimately leading to cognitive decline.

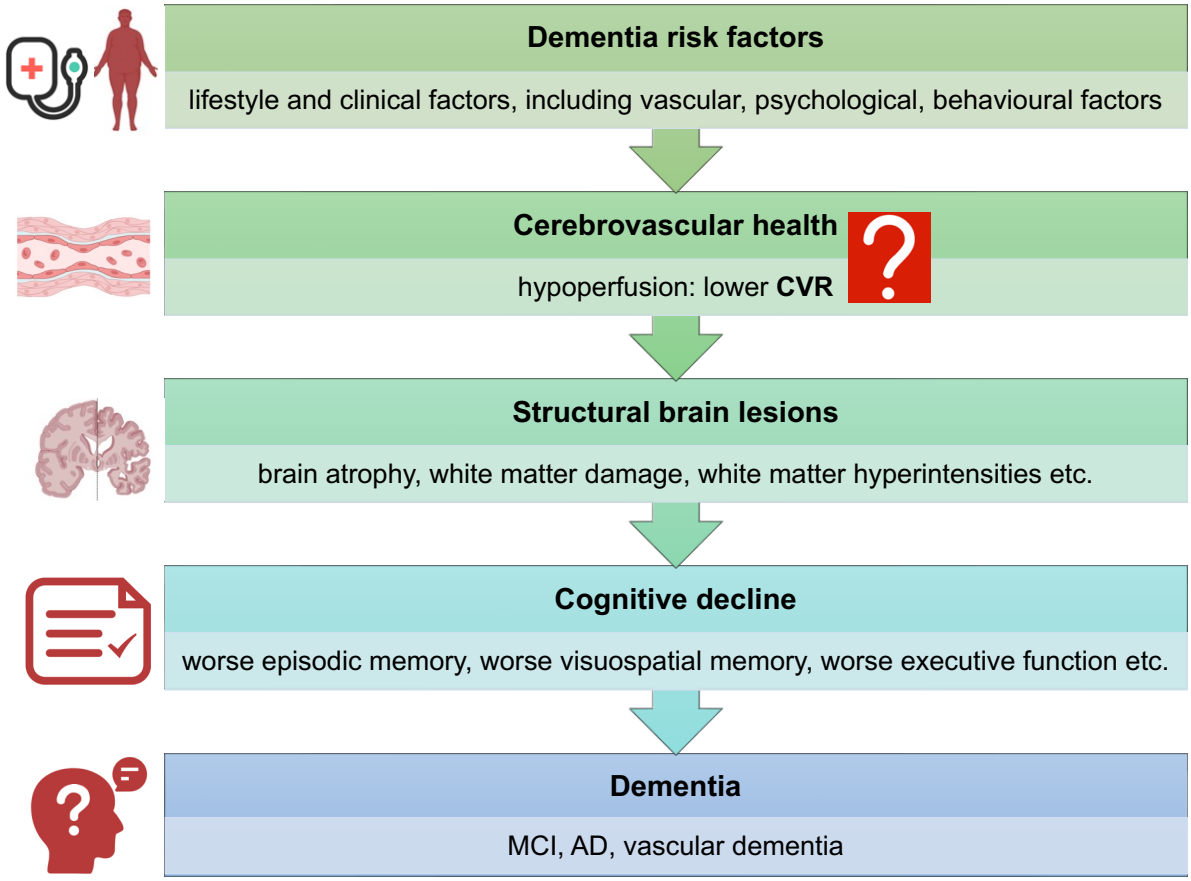


Figure 1.1: A conceptual pathway linking dementia risk factors to cerebrovascular dysfunction and cognitive decline in this thesis

Lifestyle and clinical dementia risk factors may lead to impaired cerebrovascular health such as reduced CVR. This may contribute to brain injury and structural neurodegeneration, like brain atrophy, and eventually lead to cognitive decline and dementia.

The framework is adapted from the CATCH hypothesis by (De La Torre, 2013), which describes a cascade from ageing and increased vascular risk to chronic cerebral hypoperfusion, such as reduced cerebral blood flow, leading to neurodegeneration and cognitive impairment. The role of CVR in this pathway has been understudied, therefore this thesis addresses this gap by investigating whether lower CVR may reflect vascular dysfunction linking dementia risk to later brain and cognitive decline.

Specifically, we aim to address the following three questions:

1. **Does dementia risk influence CVR?**
2. **Is CVR associated with brain structural biomarkers of dementia and cognitive performance, as well as their longitudinal declines?**
3. **Does CVR mediate the relationship between dementia risk and cognitive performance?**

In this introductory chapter, we begin by briefly reviewing existing literature that supports the rationale for these three questions. We then outline the chapter-wise objectives and approach taken in this thesis.

1.5 Question 1: Does dementia risk influence CVR?

As discussed in Section 1.3, several dementia risk factors are closely linked to CBF or perfusion. CBF refers to the amount of blood delivered to brain tissue per unit time (Zazulia et al., 2011). Numerous studies have shown that dementia risk factors, not only those vascular risk factors, but also psychological and behavioural factors are associated with reduced or dysregulated CBF, particularly in brain regions vulnerable to neurodegeneration. For instance,

hypertension has been consistently linked to lower CBF. Compared to healthy controls, individuals with hypertension show reduced CBF, with untreated patients exhibiting even greater reductions in CBF; a significant negative correlation between blood pressure and CBF has also been reported in hypertensive patients (Christie et al., 2022; Nobili et al., 1993). Type 2 diabetes has also been associated with reduced CBF particularly in brain regions critical for cognitive function such as the temporal and frontal cortices (Liu et al., 2018). Similarly, physical inactivity has been linked to lower CBF in both lateral and medial frontal brain regions (Zlatar et al., 2019). Obesity is linked to global CBF reductions; however, this association may be mitigated by higher levels of physical activity (Knight et al., 2021). In terms of psychological factors, a systematic review has reported that reduced CBF is commonly observed in individuals with depression, particularly in the anterior cingulate and prefrontal cortices (Chithiramohan et al., 2022). Trait depression and exposure to stressful events have also been associated with lower CBF, especially in the cingulate gyrus and frontal white matter (Chiappelli et al., 2023). Altogether, these findings suggest that a wide range of dementia risk factors are strongly associated with compromised cerebrovascular health, as reflected by reduced CBF.

While several studies have examined CBF in relation to dementia risk factors, the associations between CVR and these risk factors remain comparatively underexplored. CVR is an index that complements vascular measures such as CBF and cerebral blood volume by providing insight into vascular reserve. While CBF reflects the static level of blood supply to brain tissue under resting conditions, CVR captures the dynamic capacity of cerebral vessels to respond

to physiological stimuli and increase flow in regions requiring higher metabolic demand (Motlagh et al., 2024), which mimics the process of cognitive functioning. A common method for eliciting a CVR response is through inhaling carbon dioxide (CO_2) -rich air (i.e., hypercapnic air) (Juttukonda & Donahue, 2019). The molecular mechanism underlying this is that an increase in CO_2 levels in the blood lowers pH and promotes vasodilation by relaxing vascular smooth muscle cells (SMCs). This occurs through the opening of potassium (K^+) channels, which hyperpolarises SMCs, reduces calcium influx, and decreases intracellular calcium, thereby facilitating dilation (Brayden, 1996; Peng et al., 1998; Yoon et al., 2000). Additionally, increased CO_2 and lower pH activate nitric oxide synthase in endothelial cells, leading to the production of nitric oxide, which diffuses into SMCs to further promote relaxation and vessel dilation (Fathi et al., 2011; Xu et al., 2004). These dilated blood vessels have a greater capacity to boost blood flow to brain tissue in response to an elevated CO_2 stimulus, which helps maintain metabolic homeostasis. This relative increase in blood flow following a hypercapnic challenge is referred to as cerebrovascular reactivity (CVR). A reliable and robust method of measuring CVR non-invasively is by using a hypercapnic stimulus delivered during a blood oxygen level-dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) scan.

CVR remains relatively understudied in dementia research, in part because it is a relatively new marker, but also because of the technical set-up and expertise required to deliver the CO_2 stimulus, as well as lack of knowledge about the tolerability of hypercapnia in older adults. We therefore know little about how dementia risk factors influence CVR. This thesis thus will

address this critical gap in two ways:

In ***Chapter 2***, I will present a systematic review of existing literature examining the associations between CVR and various dementia risk factors, including non-modifiable, modifiable, and clinical factors,

In ***Chapter 3***, I will then introduce a new MRI cohort for which I acquired CVR fMRI scans in 163 older adults: the **Heart & Brain cohort**. In ***Chapter 4***, I will use data from this cohort to investigate how midlife dementia risk contributes to CVR in older age.

1.6 Question 2: Is CVR associated with brain structural biomarkers of dementia and cognitive performance, as well as their longitudinal declines?

Biomarkers of dementia are measurable indicators of underlying neuropathology that can help detect disease processes before clinical symptoms emerge (Strimbu & Tavel, 2010). Amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau are the two core and well-established biomarkers of AD (Blennow & Zetterberg, 2018; Mahaman et al., 2022; Wang et al., 2024). These pathological changes are typically measured through cerebrospinal fluid (CSF) or Positron Emission Tomography (PET) imaging, which are either invasive or less accessible (Buerger et al., 2006; Dulewicz et al., 2022; Olsson et al., 2016; Tapiola et al., 2009).

In addition to these well-established CSF pathological markers, several **non-invasive neuroimaging markers** of brain structural integrity are linked to cognitive impairment and dementia. **Brain atrophy** is one of the most established indicators in AD, with significant grey matter volume (GMV) loss observed in AD patients (Colliot et al., 2008; Gosche et al., 2002; Jack et al., 2011; Pini et al., 2016). GMV reduction is also present in cognitively normal ageing individuals, with faster cognitive decline linked to reduced volumes in medial temporal and hippocampal regions (Fleischman et al., 2013; Nation et al., 2019). **Hippocampus volume** is one of the first to decline in the early stage of dementia (Pini et al., 2016), and smaller left hippocampal volume in MCI patients can also predict later conversion to AD (Eckerström et al., 2008). Additionally, **white matter microstructure** is crucial for efficient neural communication, and compromised white matter microstructure is also recognised as a biomarker for dementia. Ageing has consistently been associated with the white matter diffusion metrics that indicate demyelination and axonal loss especially in frontal white matter regions (Abe et al., 2008; Bosch et al., 2012; Hakun et al., 2015; Huang et al., 2012; O'Dwyer et al., 2011; Salami et al., 2012; Zhang et al., 2011). White matter microstructural damage in AD is observed in temporal, parietal, and prefrontal white matter, as well as in limbic structures such as the fornix, cingulate gyrus, and corpus callosum, and subcortical regions including the thalamus and caudate nucleus (Nowrangi et al., 2012; Teipel et al., 2012; Yin et al., 2015). In healthy ageing, worse white matter microstructure is correlated with slower processing speed, reduced working memory, and declines in reasoning and cognition flexibility (Borghesani et al., 2013; Kennedy & Raz, 2009). Moreover, **white matter hyperintensities** (WMHs) have also be recognised as

a pathological marker of dementia. WMH is a marker to indicate vascular lesions and is typically associated with small vessel disease. Larger WMH volumes are observed in individuals with AD as compared with health controls (Damulina et al., 2019; Vipin et al., 2018; Yoshita et al., 2006). Even among cognitively healthy adults, higher WMH volumes have been shown to predict subsequent cognitive decline in longitudinal studies (Carmichael et al., 2010). These brain structural markers can be non-invasively assessed via MRI, which is generally better tolerated and more widely available than PET imaging (Johnson et al., 2012; van Oostveen & de Lange, 2021). For this reason, this thesis focuses on non-invasive MRI neuroimaging biomarkers of brain health.

Although these biomarkers are essential for clinical diagnosis, by the time they are observed, neurons are often already severely damaged and less likely to recover (Blennow & Zetterberg, 2018; Dulewicz et al., 2022; Hurtle et al., 2024; Kamatham et al., 2024). Some structural changes, such as brain atrophy and white matter microstructural damage, are also largely irreversible, limiting the potential for early intervention to prevent dementia progression (Pini et al., 2016). Therefore, it is important to identify early biomarkers when interventions are more likely to be effective, and neuronal injury may still be preventable. In a data driven modelling research, Iturria-Medina and colleagues observed that vascular dysregulation emerged earlier and more strongly than other pathological factors in the progression of AD (Iturria-Medina et al., 2016). Reduced CBF emerged as the earliest in the mechanistic pathway, whereas amyloid deposition, metabolic dysfunction, and structural atrophy appeared after (***Figure 1.2***). This

patten suggests that vascular abnormalities may arise prior to the classical CSF and structural biomarkers of AD, highlighting the potential of cerebrovascular health as an early marker to identify individuals at high risk. Understanding the role of CVR in this pathophysiological pathway to dementia is therefore of importance, especially since cerebrovascular health is modifiable and may serve as a promising target for early intervention.

This also raises questions about how CVR relates to cognitive decline prior to the onset of clinical symptoms. Current literature suggests a link between impaired CVR and dementia. Several studies have shown that **people with AD or vascular dementia have significantly lower CVR compared to healthy controls** (Alwatban et al., 2019; Gao et al., 2013; Keeling et al., 2024; Vicenzini et al., 2007). AD patients demonstrate reduced CVR in key brain regions such as the precuneus (X. Tang et al., 2025), prefrontal and anterior cingulate cortices (Yezhuvath et al., 2012), and medial temporal areas (Kapoor et al., 2025). Furthermore, CVR reductions are also observed in early stages of dementia, such as MCI. Lower CVR has been observed in MCI patients compared to healthy controls, particularly in the parahippocampal gyrus and medial temporal lobe, and these CVR impairments were also linked to poorer memory performance such as verbal and visual memory deficits (Engstrom et al., 2024; Glass Umfleet et al., 2023; Kapoor et al., 2025). Moreover, CVR also appears to play a predictive role in disease progression. Lower hippocampal CVR has been associated with a higher risk of progressing from normal cognition to MCI (Aslanyan et al., 2022, 2023). Even among cognitively healthy older adults, lower CVR is associated with poorer processing speed and

episodic memory (Catchlove, Pipingas, et al., 2018; Peng et al., 2018). However, the literature on CVR-cognition associations remains mixed. A systematic review found that only six out of ten studies reported significant CVR-cognition relationships (Catchlove, Pipingas, et al., 2018). Inconsistencies may arise from variations in vasodilatory methods, imaging modalities, and cognitive assessments. Therefore, the authors recommend that future research should employ multi-domain cognitive assessments alongside standardised hypercapnia challenges during MRI to better clarify the relationship between CVR and specific cognitive domains, particularly in cognitively healthy older adults in prodromal stages of dementia.

To address these research gaps, in Chapter 5, I will explore the associations between CVR and (1) MRI-based structural brain biomarkers of dementia and (2) multiple cognitive domains using the Heart and Brain Study cohort.

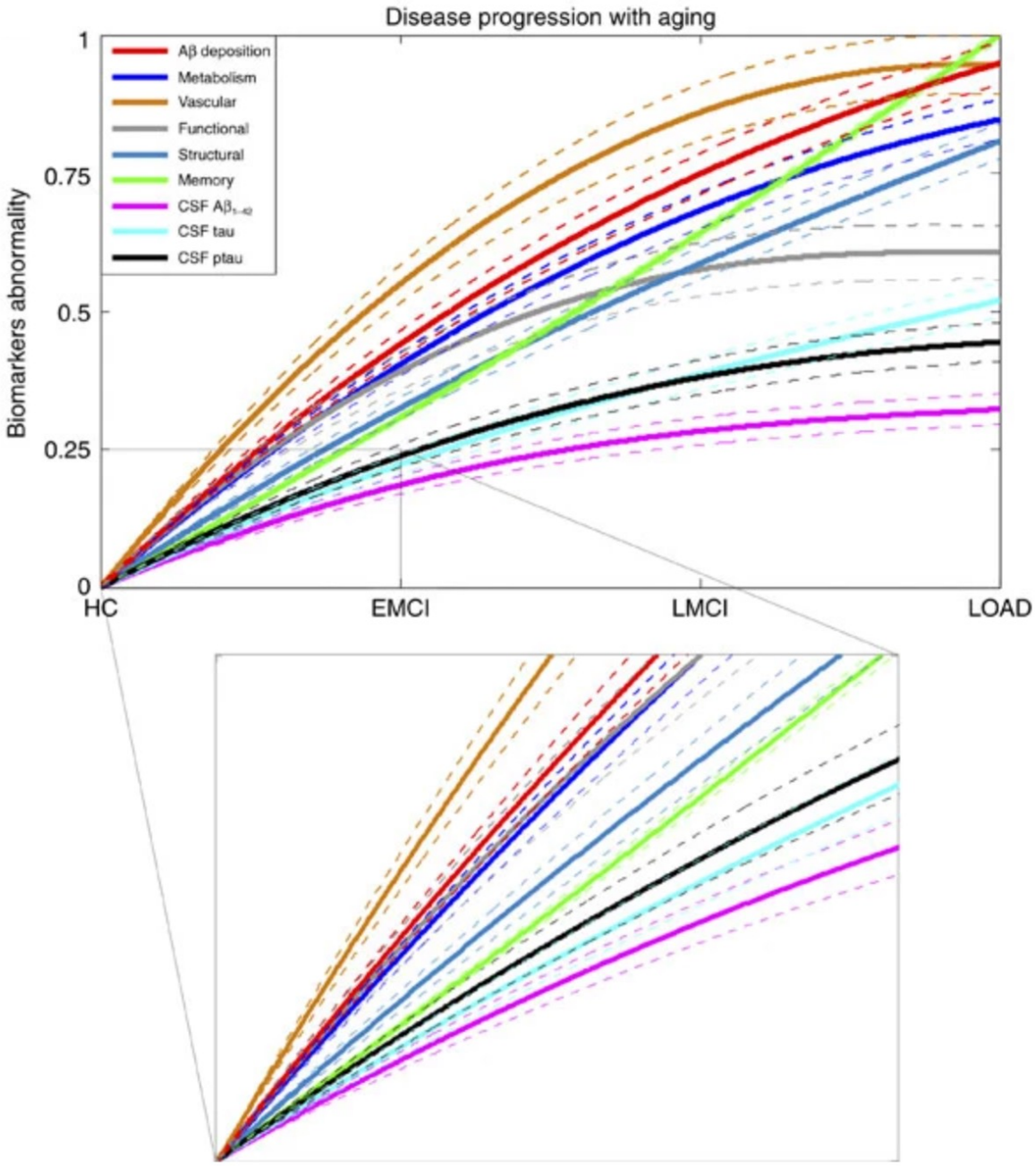


Figure 1.2: Temporal trajectory of vascular and neurodegenerative biomarkers across the progression from healthy ageing to Alzheimer's disease

The plot displays the multifactorial temporal ordering of abnormality trajectories across biomarkers during the transition from healthy control (HC) to early mild cognitive impairment (EMCI), to late mild cognitive impairment (LMCI), and to probable Alzheimer's disease patient (LOAD). Notably vascular dysregulation (orange line) emerges earliest and exerts stronger effects than amyloid, metabolic, functional, or structural changes. The inset figure highlights the prodromal stages of AD, where the vascular component begins to diverge from other biomarkers, while Aβ, metabolism, and functional dysregulation remain closely aligned. Although CVR has not been well studied and was not included in this model, the observed

pattern supports our hypothesis that reduced CVR, as an early marker of vascular dysfunction, may play a mechanistic role in driving neurodegenerative changes. (Figure was adapted from Iturria-Medina et al., 2016 under the terms of the Creative Commons CC BY license).

1.7 Question3: Does CVR mediate the relationship between dementia risk and cognitive performance?

As introduced in the CATCH hypothesis earlier (De La Torre, 2000a), several studies propose that cerebrovascular dysregulation may act not only as an early marker of vulnerability but also as a mechanistic driver of later structural brain changes. Early vascular insults can impair neurovascular coupling, leading to energy deficits that trigger oxidative stress and neuronal loss, particularly in high-demand regions such as the hippocampus, and eventually cause widespread neurodegeneration. These neurovascular complications may accelerate the progression from MCI to AD (Eisenmenger et al., 2022; Solis, et al., 2020). This may also explain why cerebral hypoperfusion may predict conversion from MCI to AD (Duan et al., 2021; Lacalle-Aurioles et al., 2014).

Therefore, we propose that CVR, as a dynamic marker of cerebrovascular health, may also play a mechanistic role linking midlife dementia risk factors to later-life brain atrophy and, ultimately, accelerated cognitive decline (***Figure 1.1***). Building on the results of the associations between dementia risk factors and CVR in **Chapter 4**, as well as the associations between CVR, structural brain biomarkers, and cognitive decline in **Chapter 5**, **Chapter 6** will

integrate all the results and investigate whether CVR mediates the path from midlife dementia risk to later-life cognitive decline (***Figure 1.3***).

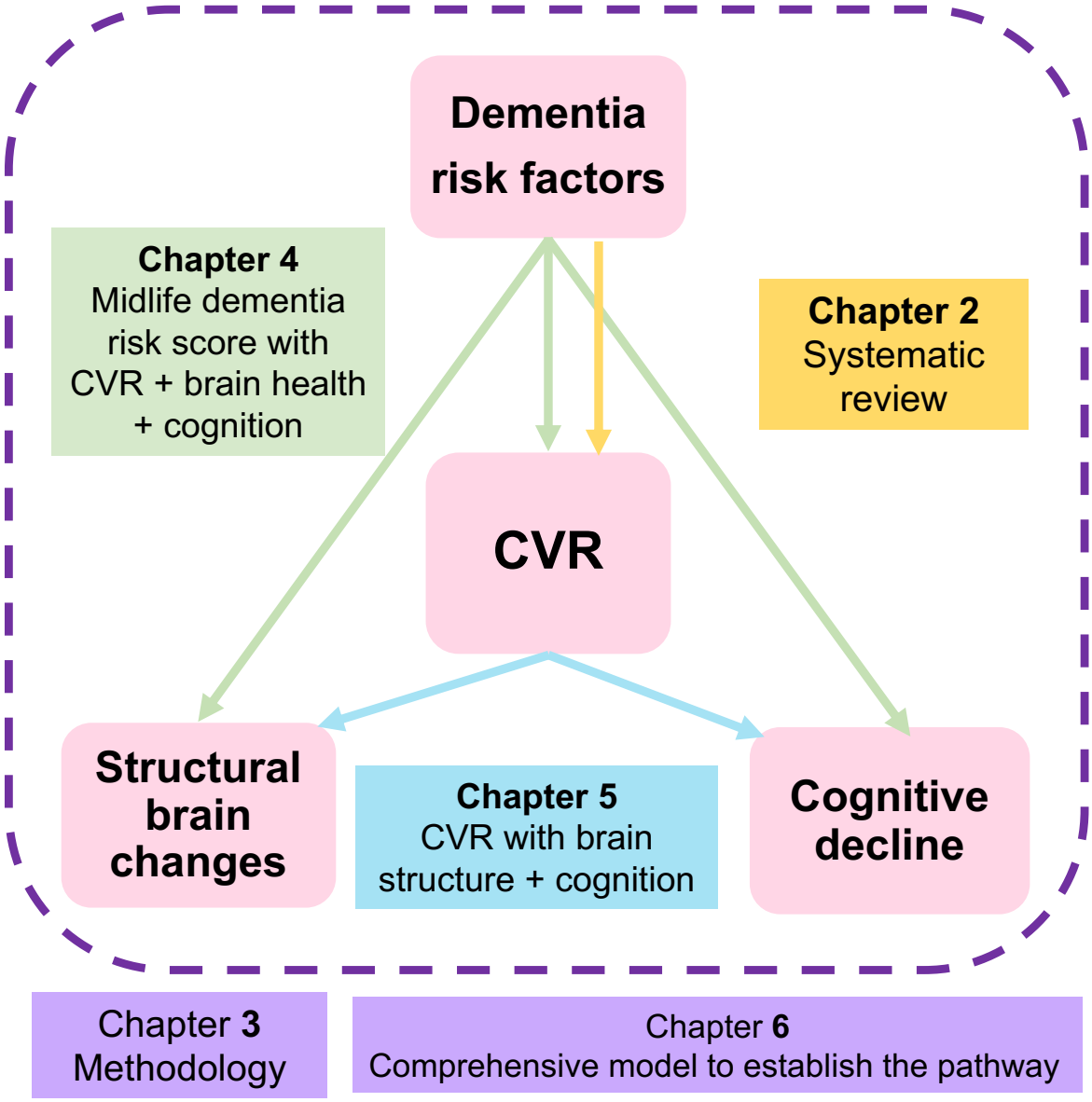


Figure 1.3: Thesis structure and chapter-wise overview

1.8 Summary of thesis chapters

This thesis draws on data from the Heart and Brain Study, a sub-study of the longitudinal Whitehall II cohort, which has tracked participants for over 30 years. The dataset includes repeated assessments of lifestyle and clinical health factors in **midlife (mean age ~52.5 years)**, as well as repeated assessments of brain MRI and cognitive function in later life, first **at ~68 years** and **again at ~77 years**, with the addition of CVR data at the second wave (further details are described in **Chapter 3**). This rich longitudinal design enables the investigation of how midlife dementia risk relates to subsequent trajectories of brain and cognitive ageing across two time points. Capturing risk exposures during midlife is particularly valuable, as midlife represents a critical window for identifying and potentially modifying risk. The Lancet review also suggests that several modifiable risk factors emerge during midlife (Livingston et al., 2020, 2024). Large scale studies across ethnicities also suggests that risk exposure between ages 44 and 54 shows the strongest associations with dementia incidence up to 25 years later (Gottesman et al., 2017), underscoring the importance of early intervention during this age. In addition, the project focuses on the prodromal stages of dementia, specifically targeting older adults who have not yet been diagnosed with MCI or dementia but may already exhibit subtle vascular or cognitive vulnerabilities. This stage represents a critical window for detecting preclinical changes with the goal of informing strategies for timely intervention to slow or prevent the onset of dementia.

Here I present the chapter-wise objectives using data from the Heart and Brain Study to

address the three research questions outlined in Sections 1.5 to 1.7. The framework of the thesis for **Chapters 2-6** is summarised in ***Figure 1.3***. The overarching pathway examined across the empirical chapters explores how midlife dementia risk may influence later-life cognitive decline, potentially via cerebrovascular dysfunction and structural brain changes (i.e., midlife dementia risk → CVR → brain structure → cognition).

- **Chapter 2** aims to address the current gap in understanding the relationship between various dementia risk factors and CVR. We present a systematic review of the literature examining associations between CVR and a range of dementia risk factors, including non-modifiable, modifiable, and clinical factors. This chapter has been **published in *Neuroscience and Biobehavioural Reviews*** *(Wang et al., 2023)* and was presented at the *Alzheimer's Research UK Thames Valley Network Dementia Research Day 2022* and the *Oxford Neuroscience Symposium 2023*.
- **Chapter 3** introduces the Whitehall II Heart and Brain Study cohort and describes the methodology employed across the thesis, including MRI protocols, image pre-processing, and statistical approaches. To study the cumulative effect of multiple midlife risk factors, we recently developed a cohort-specific composite dementia risk score called the UK Biobank Dementia Risk Score (UKBDRS) which will be described in this chapter.
- **Chapter 4** investigates how this midlife dementia risk score (UKBDRS) is associated with CVR in older age, as well as with brain structure (grey matter volume, white matter microstructure, white matter hyperintensities), and cognitive performance. This work has

been presented at the *Dementia Platform UK Neuroimaging Symposium 2023* and the *Oxford Neuroscience Symposium 2024*.

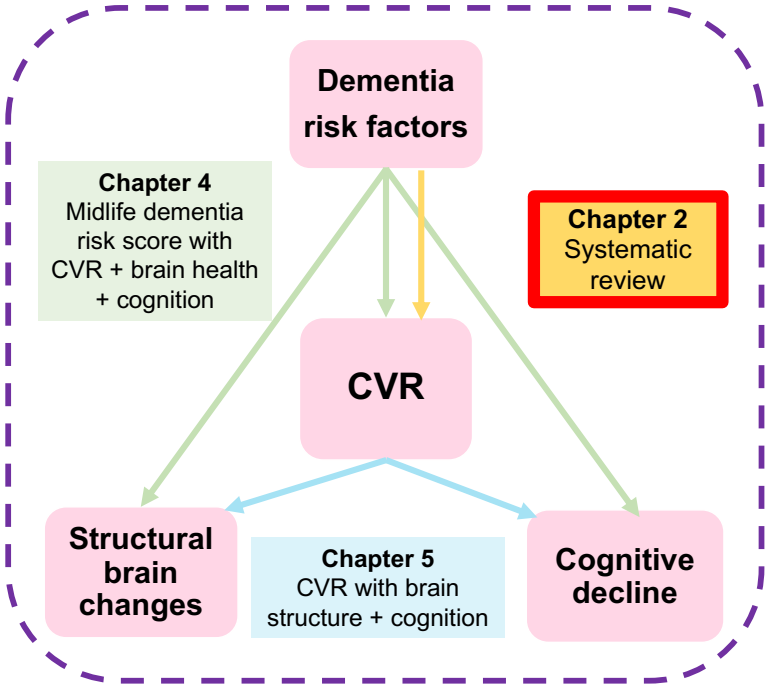
- **Chapter 5**, we investigate the associations between CVR and both brain structure and cognitive function. This work has been presented at the *Alzheimer's Association International Conference (AAIC) 2024* and the *Human Brain Mapping (HBM) 2024 conference* and is currently under revision at the journal *Human Brain Mapping* ***(Wang et al., in revision, HBM)*****.**

- **Chapter 6** explores the potential mechanistic pathways linking midlife dementia risk to later-life cognitive performance, with a specific focus on the mediating role of CVR and brain structure. A modified version of **Chapters 4 and 6** has been prepared as manuscript for submission ***(Wang et al., in submission)***.

- Lastly, **Chapter 7** presents an overall summary of the thesis results, a discussion of our findings in the context of current literature, and recommendations for future work.

Chapter 2: A systematic review of the association between dementia risk factors and cerebrovascular reactivity

Cerebrovascular reactivity (CVR) has been increasingly studied as an indicator of dynamic marker of cerebral perfusion and cerebral vascular health, and impaired CVR has been found among people with dementia. However, it remains unclear how dementia risk factors influence CVR. Understanding this relationship is crucial for clarifying the early disease mechanisms and for identifying potential opportunities for prevention. This chapter presents a systematic review to examine how CVR, measured by magnetic resonance imaging (MRI), is affected by established dementia risk factors, including modifiable, non-modifiable, and clinical factors. This review has been published in Neuroscience and Biobehavioral Review (Wang et al., 2023) and has been modified for this chapter.



2.1 Introduction

2.1.1 The need for dementia prevention and risk factors for dementia

Global estimates indicate that the prevalence of dementia is either increasing or remaining stable in most countries (Stephan et al., 2018). Given that the population is ageing, the number of older adults living with dementia is predicted to increase drastically in the future (Cao et al., 2020; Jia et al., 2020; Nichols et al., 2022; United Nations, 2019). In the absence of disease modifying treatments, lowering the risk of dementia in older adults is a critical step for improving quality of life.

There are a number of modifiable or behavioural factors that can increase the risk of developing dementia, and in particular Alzheimer's or vascular dementia. These include low education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury (TBI), and exposure to air pollution (Livingston et al., 2020; Mendez, 2017; Peters, Ee, et al., 2019; W. Xu et al., 2017). Targeting these risk factors may help prevent around 40% of dementia cases worldwide (Livingston et al., 2020). Additionally, genetic factors such as carrying at least one copy of the apolipoprotein ε4 (APOE ε4) allele can lead to a 3-fold (heterozygous ε4) to 15-fold (homozygous ε4) increase in the risk for Alzheimer's disease (Yin et al., 2018). Clinical

risk factors, such as peripheral artery diseases (Newman et al., 2005; Tasci et al., 2018), or cerebrovascular lesions, such as strokes, infarcts, and white matter hyperintensities (WMHs) can also increase the chances of developing Alzheimer's or vascular dementia (Scott et al., 2018). Recent research has focused on cerebrovascular reactivity (CVR) as a promising biomarker of these early pathological changes that precede the onset of dementia (Bokkers et al., 2011; Gupta et al., 2012; Ribigan et al., 2016; Suri et al., 2015; Wolters, de Bruijn, et al., 2016).

2.1.2 Cerebrovascular reactivity as a marker for cerebral vascular health

CVR refers to the ability of cerebral vessels to dilate in response to vasoactive stimuli (Liu et al., 2019). CVR is considered as a more sensitive indicator of cerebrovascular regulation than static measures such as baseline cerebral blood flow (CBF) or structural assessments of vascular integrity. Unlike baseline CBF, which captures resting perfusion, CVR assesses the capacity of the brain's microvasculature to increase blood flow in response to a vasoactive stimulus, such as carbon dioxide (CO_2) and thus reflects the dynamic flexibility of vascular autoregulation (Juttukonda & Donahue, 2019; Liu et al., 2019). This responsiveness of the cerebral vasculature under hypercapnia condition acts as a functional "stress test" for cerebral circulation, which allows early detection of subclinical vascular dysfunction (Glodzik et al., 2013).

2.1.3 Methods for inducing CVR responses

There are several approaches to elicit a CVR response. Changes in arterial carbon dioxide partial pressure ($PaCO_2$) induced by hypercapnia challenge is the most widely used (Juttukonda & Donahue, 2019). The vasoactive response can be induced through controlled inhalation of CO_2-enriched gas mixtures or by voluntary breathing tasks such as breath-holding (Liu et al., 2019; Urback et al., 2017). These methods increase CO_2 levels, which trigger vasodilation in cerebral vessels. Since $PaCO_2$ cannot be measured directly, a common alternative is to monitor end-tidal CO_2 ($EtCO_2$), which reflects the maximum partial pressure of exhaled CO_2 at the end of expiration (Sleight et al., 2021). The breath-hold method asks participants to hold their breath for a short period of time, typically followed by a period of paced breathing (Tancredi & Hoge, 2013). This approach does not require any external equipment, thus is simple and cost-effective for eliciting CVR responses. However, it relies heavily on participant cooperation, which can be challenging for older adults or individuals with cognitive impairment (Jahanian et al., 2017). Variability in breath-hold duration and effort across individuals may introduce noise into the data and reduce the reliability of the CVR estimates (Magon et al., 2009). In addition, CO_2 concentration in the lungs cannot be directly measured and there is a gap in the CO_2 time course, which makes it difficult to precisely model the stimulus (Liu et al., 2019). Alternatively, inhalation of CO_2 using a fixed concentration of inspired gas is a widely used method to elicit a CVR response. Participants typically breathe 2-7% CO_2 through a non-rebreathing face mask, which delivers a consistent and robust

vasodilatory stimulus (Liu et al., 2019). Compared to breath-hold approaches, this method is less dependent on participant cooperation and thus produce standard hypercapnic stimulus (Fierstra et al., 2013). Although a key concern with this method is that fixed inspired CO_2 does not guarantee precise control of $PaCO_2$ due to individual differences in ventilation and chemoreflex sensitivity (Ainslie & Duffin, 2009; Fisher, 2016), CO_2 inhalation remains a practical and widely adopted approach for inducing cerebrovascular responses in both research and clinical settings. In addition to these respiratory-based approaches, vasodilation can also be induced pharmacologically using an injection of acetazolamide (Vorstrup et al., 1986), which is a carbonic anhydrase inhibitor that increases cerebral blood flow by inducing a mild metabolic acidosis (Vagal et al., 2009). However, there is considerable variability in the duration and magnitude of individual responses to acetazolamide (Dahl et al., 1995; Ringelstein et al., 1992). Acetazolamide can also produce side effects such as headache, nausea and fatigue, which may reduce tolerability, especially in older participants (Saito et al., 2011). Therefore, compared to the invasive nature of acetazolamide challenge, hypercapnia is considered more tolerable for inducing cerebrovascular vasodilation (Fierstra et al., 2013)

2.1.4 Techniques for measuring CVR

CVR can be assessed non-invasively using several measures. One of the most widely used approaches is blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI). BOLD fMRI does not measure CBF directly, instead it reflects changes in the

concentration of deoxyhemoglobin, which arise from complex interactions among CBF, cerebral blood volume, and oxygen metabolism (Liu et al., 2019). BOLD fMRI offers high spatial resolution and a strong signal-to-noise ratio, which enables mapping of CVR in the brain regions with greater spatial sensitivity (Chen, 2018; Liu et al., 2019; Sleight et al., 2021). This makes it particularly useful for studying regional CVR alterations associated with underlying pathology. Another non-invasive MRI-based technique is arterial spin labelling (ASL), which quantifies CBF by magnetically labelling arterial blood water protons. ASL provides direct measure of CBF and is particularly useful for detecting regional blood flow changes (Zhou et al., 2015). However, it has a relatively lower signal-to-noise ratio compared to BOLD and requires longer acquisition times to allow the labelled protons to reach brain tissue, which may limit temporal resolution (Liu et al., 2019). In contrast, transcranial Doppler (TCD) ultrasound offers excellent temporal resolution to monitor rapid changes in blood flow velocity within large cerebral arteries (Sobczyk et al., 2021). However, unlike cerebral perfusion (e.g., ASL) which measures the blood flow per volume of tissue, TCD only measures blood velocity in arteries (Burley et al., 2021; McDonnell et al., 2013). Measurements of TCD are only taken in single major vessels, which may not always represent local changes in tissue blood supply (McDonnell et al., 2013). By contrast, MRI can map CVR in the brain's micro-vessels, allowing for greater spatial sensitivity (Sleight et al., 2021). Therefore, MRI-based measurements of CVR are more useful for describing the specific brain regions that are associated with dementia risk.

2.1.5 The links between CVR and dementia

As discussed in **Chapter 1**, several studies have shown that CVR is impaired in preclinical rodent models of Alzheimer's disease (Glodzik et al., 2013; Nicolakakis et al., 2008), as well as in patients with mild cognitive impairment (Shim et al., 2015), Alzheimer's disease and vascular dementia (Alwatban et al., 2019; Gao et al., 2013; Vicenzini et al., 2007), even after controlling for common vascular risk factors, such as atherosclerotic disease and hypercholesterolemia (Gongora-Rivera et al., 2018). Reduced CVR has also been shown to correlate with the degree of cognitive impairment (Kim et al., 2021; Silvestrini et al., 2006), and impairments in CVR might predict decline in processing speed and episodic memory, although this relation has not been always consistently observed (see Catchlove, Pipingas et al., 2018 for a review on the relationship between CVR and cognitive impairment; Peng et al., 2018).

2.1.6 Study aims

Although there is considerable evidence that CVR is compromised in dementia, the underlying reasons for this remain unknown. Moreover, the relationship between CVR and well-known risk factors for dementia is poorly understood. Studying this association could help inform preventative interventions aimed at modifying CVR in order to reduce dementia risk (Murrell et al., 2013). This systematic review summarises observational and experimental studies

investigating the associations between CVR (measured using MRI) and dementia risk factors in adults. Specifically, we summarise the associations between CVR and (a) non-modifiable risk factors (age and APOE ε4); (b) the 12[1] aforementioned modifiable/behavioural risk factors; and (c) clinical risk factors. We conclude the chapter by exploring the biological mechanisms underpinning these CVR-dementia risk associations and highlighting avenues for future research.

2.2 Methods

The protocol for this systematic review was pre-registered with PROSPERO (International Prospective Register of Systematic Reviews; ID: CRD42021292793) in 2021, between the stages of our initial search and study screenings. We have followed the PRISMA reporting guidelines for systematic reviews throughout the current paper (Page et al., 2021).

2.2.1 Data sources and searching method

The electronic bibliographic databases including Ovid MEDLINE, Embase and PubMed were searched from inception (1946 for MEDLINE, 1974 for Embase, and 1966 for PubMed) to the

[1] *Two additional modifiable risk factors (high cholesterol and vision loss) were identified in updates published after the completion of this review, and therefore could not be included in this thesis.*

24th of November 2021. The search was limited to studies that were written in English and focused on humans rather than animals.

Three concepts guided the search terms: outcome (CVR) AND population of interest (healthy OR dementia/Alzheimer's disease/Mild Cognitive Impairment adults) AND dementia risk factors. Dementia risk factors were selected based on the literature (Breijyeh & Karaman, 2020; Livingston et al., 2020; Serrano-Pozo et al., 2021). Search terms included both generic expressions (e.g., "dementia risk factor" or "genetic risk factor") as well as specific risk factors (e.g., "diabetes mellitus" or "major depressive disorder"). The following risk factors were selected for this study:

(1) **Non-modifiable risk factors** including age and APOE ε4 status;

(2) **Modifiable/behavioural risk factors** were derived from the 12-risk factor model (Livingston et al., 2020) and included less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution; (*The time when we conducted this review, the latest 14 dementia risk model was not developed (Livingston et al., 2024*).

(3) **Clinical risk factors** including strokes, atrial fibrillation, atherosclerosis, peripheral artery disease, and arterial stiffness.

Details of the search terms are presented in ***Appendix 2.1***.

2.2.2 Inclusion and exclusion criteria

We focussed on studies that measured CVR using MRI, but we did not restrict studies based on their choice of vasodilatory stimuli. Hence, we included studies that used pharmacological stimuli (e.g., acetazolamide) or respiratory challenges (e.g., breath holding, hyperventilation, and inhalation of hypercapnic normoxic gas).

Inclusion criteria:

a) Correlational studies (e.g., observational studies);

b) Experimental studies (e.g., randomized controlled trials and quasi-experiments);

Exclusion criteria:

a) Qualitative studies and case reports studies;

b) Reviews and meta-analyses, conference abstracts and editorial or opinion papers;

c) Studies that involved participants with a non-relevant disease, such as a disease that is not an evidenced risk factor of dementia or cognitive decline;

d) Studies that investigated Lewy body dementia, frontotemporal dementia or Parkinson's dementia;

e) Studies that did not investigate CVR as a variable of interest;

f) Studies that did not investigate risk factors for dementia as a variable of interest;

g) Studies that were not conducted in humans;

h) Studies that were not written in English.

i) Studies that did not associate dementia risk factors with CVR

j) Non-MRI studies, i.e., studies assessing CVR using TCD, Xenon CT (computed tomography), PET (positron emission tomography), or SPECT (single-photon emission computed tomography) were excluded as we sought to avoid procedures that were either less spatially sensitive, more expensive, or involved ionising radiation.

2.2.3 Data selection and data synthesis

2.2.3.1 Study selection

Two reviewers (Congxiyu Wang, CW and Graham Reid, GR) independently conducted literature searches on the same platform using the same search terms in order to agree on the number of articles to be included. The *eliminating duplicates* functions in Ovid and Endnote

were used to remove duplicates. Then, based on the stated inclusion/exclusion criteria, both reviewers separately examined the titles and abstracts and selected the relevant studies for the review. The two reviewers compared and discussed the lists of included studies, and any disagreements about article inclusion were resolved by discussion with a third reviewer (Sana Suri, SS).

2.2.3.2 Data extraction

In a data extraction table, details about the author, title, country, year of publication, study design, participant demographics, study objective, risk factors studied, method of assessing CVR, vasodilatory challenge, and main findings on the association between CVR and dementia risk factors were recorded. The data extraction table was completed by one reviewer (CW), and the extracted data was reviewed by the second reviewer (GR). Disagreements were resolved with the help of a third reviewer (SS).

2.2.3.3 Data synthesis

The main findings were reported using a narrative synthesis technique. The table of data obtained from the studies was structured according to the types of dementia risk factors: non-modifiable, modifiable/behavioural, and clinical risk factors. A formal meta-analysis was not

possible due to considerable methodological heterogeneity between studies.

2.2.3.4 Mini-Meta analysis

In order to investigate quantitative results of the association, we performed a mini-meta-analysis for the associations between age and CVR. The statistical parameters were extracted from the eligible studies. Effect size was analysed using a random-effects model to calculate the overall standard difference in means. Heterogeneity was assessed using the I^2 statistic, with a value greater than 50% indicating substantial heterogeneity (Cochran, 1954). Publication bias was evaluated using a funnel plot and Begg and Mazumdar rank correlation test (Begg & Mazumdar, 1994; Egger & Smith, 1995). The meta-analysis was performed using Comprehensive Meta-Analysis (version 3.7).

2.2.4 Quality assessment

Both reviewers (CW and GR) used the NIH Quality Assessment Tool (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) to determine whether the eligible studies had a risk of bias. This test uses 14 questions to analyse numerous potential sources of bias in a study, including clear research questions, study population eligibility, sample size justification, and the validity and reliability of the study measurements.

Inter-rater discrepancies were resolved by conversations with a third reviewer (SS), and each study was given either a good, fair, or poor-quality rating.

2.3 Results

A total of 4197 studies were identified in the initial search, of which 119 articles met the inclusion criteria at the first screening stage. After reviewing the full texts for the 119 articles, a final sample of 59 studies were included in the review (sample selection in ***Figure 2.1***). The risk of bias evaluation found that no studies had a significant quality risk; only eight out of 59 were rated as “fair” quality, and no study fulfilled the threshold for “poor” quality (***Appendix 2.2***). There was no noticeable difference in the results between the “fair” and “good” quality studies for each risk factor.

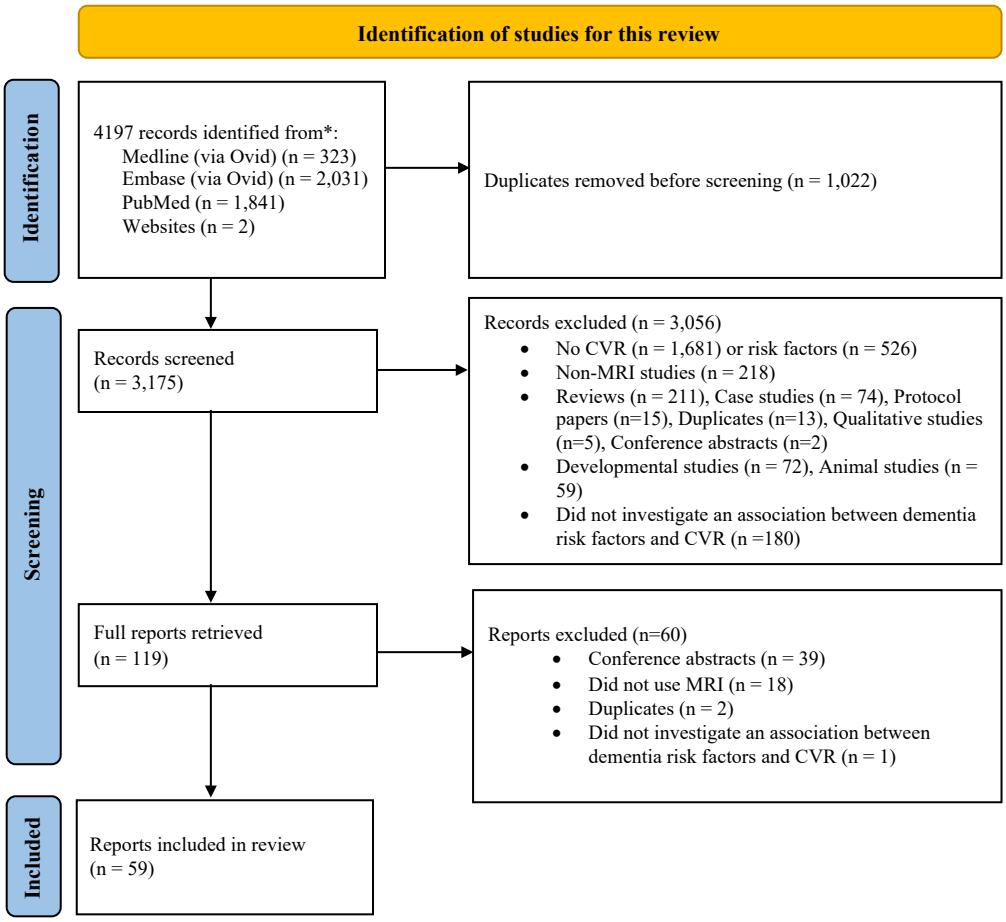


Figure 2.1: Study identification and selection process

**Records shown here were duplicated by Ovid interface and reference manager*

Overall, we found relevant studies investigating the associations between CVR and both non-modifiable factors (i.e., age and APOE ε4), six of the 12 established modifiable/behavioural risk factors (i.e., physical inactivity, obesity, hypertension, diabetes, depression, and TBI), and several known clinical risk factors (e.g., strokes, stroke-related cerebrovascular diseases, small vessel diseases, arterial occlusions or arterial stenosis, and aortic stiffness). Summaries of the studies are reported in ***Appendix Table 2.1 - 2.3***. The number of papers discussing negative or positive associations between each risk factor and CVR can be seen in ***Figure 2.2***.

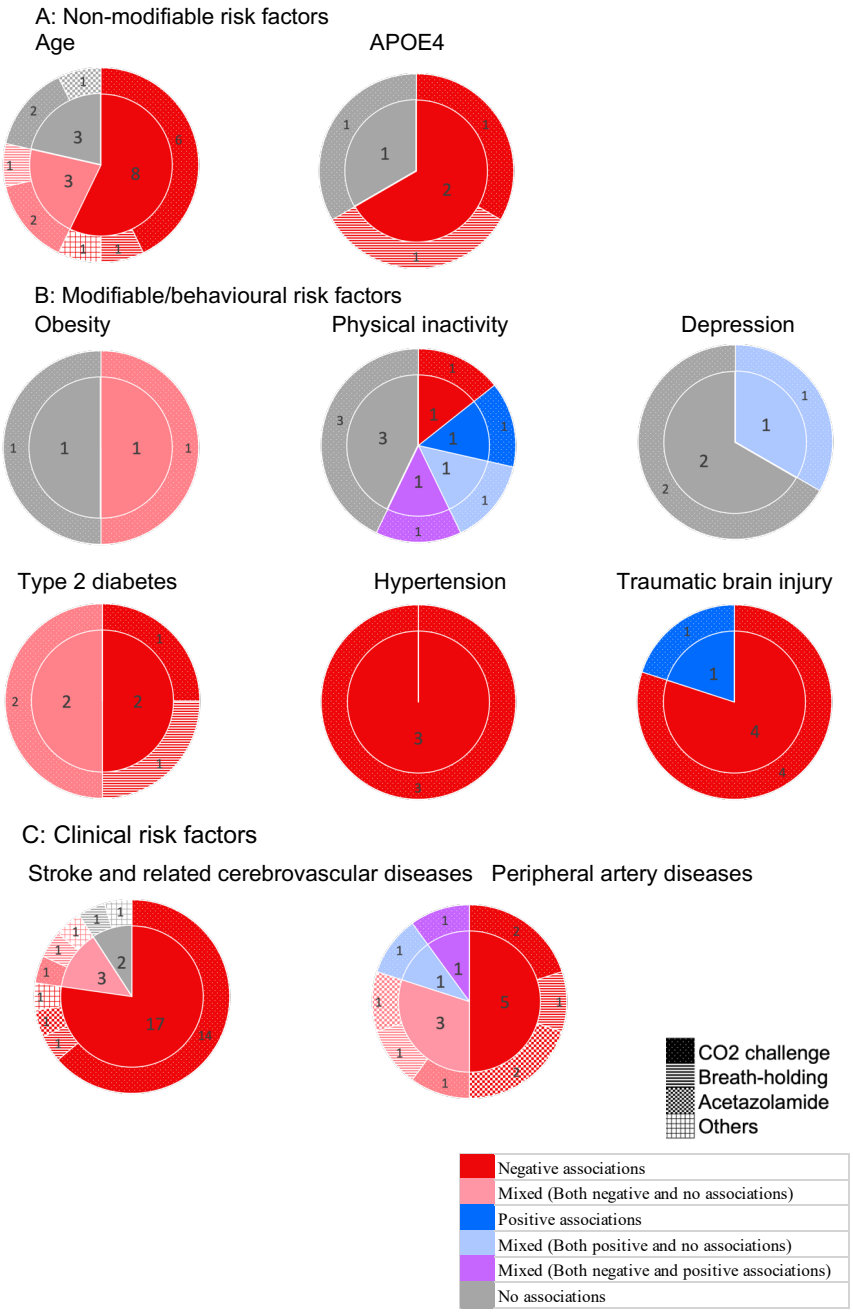


Figure 2.2: Association of dementia risk factors with CVR, showing the number of studies and their choice of vasodilatory stimuli

More details on mixed studies and the *vasodilatory stimuli are presented in Appendix Table 2.1-3. Note: The figures do not account for the sample size or the effect size of the individual studies. 14 studies are represented multiple times as they have looked at multiple risk factors in the same study and hence have overlapping samples. These studies are marked with # in Appendix Table 2.1-3)*

2.3.1 Non-modifiable risk factors

2.3.1.1 Age

14 studies examined age-related changes in CVR. Overall, there were consistent findings of age-related decreases in CVR in 11 studies, while three studies did not find any relationship between age and CVR.

Compared with younger adults (22-30 years old across the 12 studies), older people (55-75 year olds) had lower CVR either in the whole brain (Taneja et al., 2020; Tucker et al., 2020), grey matter (Catchlove, Parrish, et al., 2018; Intzandt et al., 2020; Leoni et al., 2017; Thomas et al., 2013) or in specific regions, such as the temporal lobe (Catchlove, Parrish, et al., 2018; Thomas et al., 2013), cingulum (Catchlove, Parrish, et al., 2018), or occipital cortices (Hund-Georgiadis et al., 2003; Thomas et al., 2013). Some studies also found that older adults had slower hemodynamic responses to CO_2 compared to the younger group (Leoni et al., 2017; Rasmussen et al., 2019). However, Raut et al., (2016) reported that while there was no age-related difference in the amplitude of BOLD signal change to CO_2, the area of activation in the grey matter was larger for young people than older people.

Some studies found age-specific associations in CVR. For instance, one cross-sectional study found that CVR decreased with increasing age in older adults (55-75 years) but not in younger adults (21-45 years; Catchlove, Parrish, et al., 2018). Moreover, a longitudinal study noted that participants' CVR generally declined over the four-year observation period (Peng et al., 2018), but that CVR declined faster in middle-aged participants (41-60 years) compared to older participants (61 years and above). This study also suggested that the quickest declines in CVR were observed in the temporal lobe, followed by the parietal and frontal lobes.

In contrast, two studies observed no age-related differences in CVR in global grey matter with a relatively small effect size of hedges' g=0.03 for BOLD-CVR (Burley et al., 2021), or in the frontal cortex with a large effect size of R^2=0.152 (Gauthier et al., 2015). In addition, one older study with only ten participants used acetazolamide instead of a gas stimulus and found no significant correlations between age and vasoreactivity (Mandai et al., 1994). McKetton et al., (2018) used two types of hypercapnia challenges: step CO_2, in which the $P_{ET}CO_2$ (end-tidal partial pressures of CO_2), was immediately increased to 10 mmHg above baseline, and ramp CO_2, where the $P_{ET}CO_2$ was gradually increased to hypercapnia status. When CO_2 was increased gradually, it was found that CVR was lower in the older group compared to the younger group in the frontal lobe's white matter. As for grey matter CVR, no age-related differences were found when CO_2 was administered gradually. When CO_2 was increased to hypercapnia status immediately without gradation, no age-related differences in CVR were found in either the grey or white matter.

After excluding one study which did not report necessary statistics (Thomas et al., 2013), a meta-analysis of the remaining 13 studies that assessed the associations between age and CVR showed an overall large mean effect size of −1.004 (95% confidence interval (CI) =-1.302 to −0.707, $p < 0.001$; ***Figure 2.3***) suggesting that CVR may decrease with age. However, the studies were significantly heterogeneous ($Q = 25.6$, $p = 0.012$, $I^2 = 53.1$), indicating that the summary effect estimate may not be representative of the true effect. Begg and Mazumdar rank correlation was not significant with $\tau=-0.026$ (two-tailed $p=0.903$) though the meta-analysis was biased towards underestimating the true effect. The funnel plot did not indicate significant publication bias (***Figure 2.3***). Given the heterogeneity of studies in their choice of vasodilatory stimuli, brain regions of interest, and demographics, we did not perform meta-analysis for the other risk factors to avoid misinterpretations.

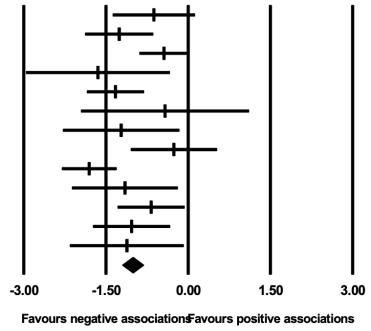
a)

Meta Analysis on Age and CVR

Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Burley et al., 2021	BOLD_CVR	-0.626	0.381	0.145	-1.374	0.121	-1.642	0.101
Catchlove et al., 2018	BOLD_CVR	-1.260	0.316	0.100	-1.879	-0.641	-3.989	0.000
Gauthier et al., 2015	BOLD_CVR	-0.442	0.228	0.052	-0.888	0.005	-1.939	0.053
Hund-Georgiadis et al., 2003	BOLD_CVR	-1.646	0.668	0.446	-2.956	-0.337	-2.465	0.014
Intz et al., 2020	BOLD_CVR	-1.328	0.265	0.070	-1.847	-0.809	-5.016	0.000
Mandai et al., 1994	Combined	-0.423	0.781	0.610	-1.954	1.107	-0.542	0.588
Leoni et al., 2017	Combined	-1.225	0.540	0.291	-2.282	-0.167	-2.269	0.023
McKetton et al., 2018	Combined	-0.261	0.400	0.160	-1.044	0.523	-0.652	0.514
Peng et al., 2018	BOLD_CVR	-1.805	0.253	0.064	-2.302	-1.308	-7.122	0.000
Rasmussen et al., 2019	BOLD_CVR	-1.154	0.492	0.242	-2.118	-0.191	-2.348	0.019
Raut et al., 2016	Combined	-0.676	0.310	0.096	-1.285	-0.068	-2.178	0.029
Taneja et al., 2020	Combined	-1.032	0.357	0.128	-1.733	-0.332	-2.889	0.004
Tucker et al., 2020	BOLD_CVR	-1.120	0.529	0.280	-2.156	-0.083	-2.117	0.034
		-1.010	0.097	0.009	-1.201	-0.820	-10.378	0.000

Statistics for each study

Std diff in means and 95% CI



b)

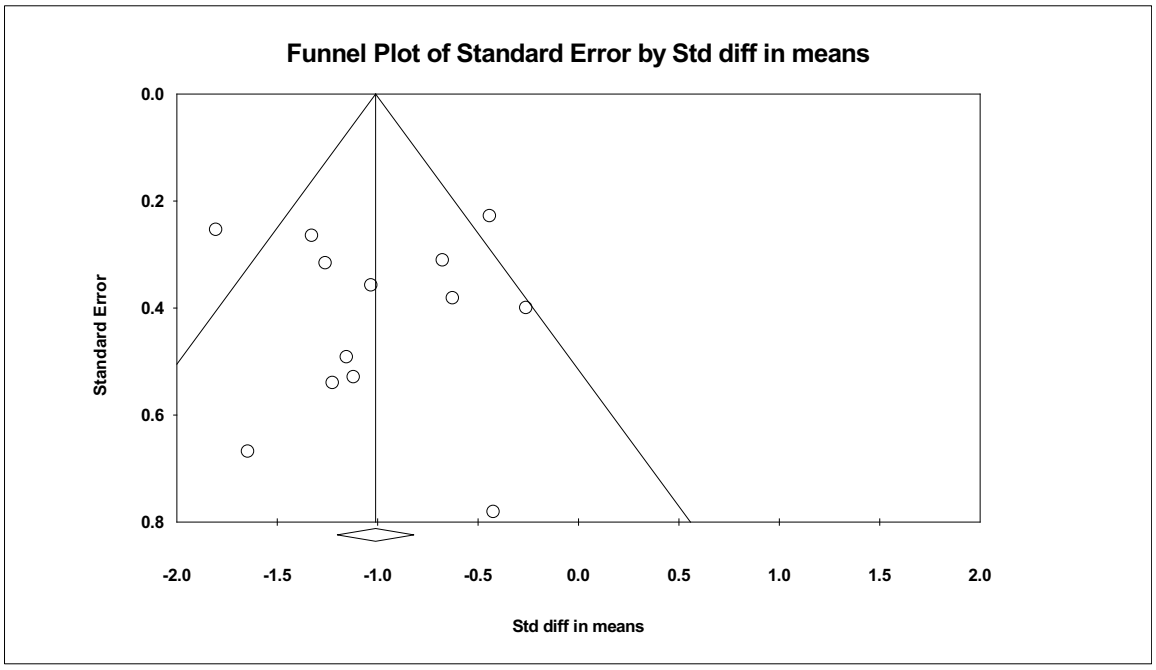


Figure 2.3: a) Statistical summary and forest plot and b) funnel plot of effect size of the meta-analysis on the association between age and CVR

Most studies used BOLD CVR as the outcome, however some used "Combined" as the results combined CVR for different brain regions, or different measurements (e.g., activation volume/magnitude or ramp CVR/step CVR/mean CVR) or different MRI methods (e.g., BOLD-CVR, ASL-CVR).

2.3.1.2 APOE ε4

Three studies have investigated APOE ε4 and two of them reported that carrying the APOE ε4 allele increased the likelihood of having impaired CO_2-CVR regardless of age. In young adults, there was evidence that compared with carriers of the APOE ε2 or ε3 alleles, ε4-carriers had the lowest measures of CVR in widespread brain regions, including the hippocampus (Suri et al., 2015). Similar findings were also demonstrated in middle-aged people (50-60 years). Using a breath-holding task, Rasmussen et al., (2019) found that APOE ε4 carriers had slower peak BOLD responses to hypercapnia relative to ε3 carriers. The third study investigated the interaction between aortic stiffness and APOE on CVR (Jefferson et al., 2018). Although this did not directly compare main effects of APOE on CVR, the authors found that APOE ε4 did not influence the association between temporal lobe CVR and aortic stiffness, both in cognitively healthy adults and in people with mild cognitive impairment.

2.3.2 Modifiable/behavioural risk factors

2.3.2.1 Obesity

Only two studies investigated the association between obesity and CVR. Frosch et al., (2017) found that obese and overweight adults (defined as BMI >25 kg/m^2) had lower CO_2-CVR

compared to healthy weighted controls, and this group difference reached a large effect size of η^2_p =0.174. They also found that higher BMI was linked to lower CVR, but this link was no longer significant after controlling for insulin resistance. In contrast, a small surgical intervention study (N=6 bariatric surgery candidates) found no difference in CVR between obese pre-bariatric surgery patients (BMI >35 kg/m^2) and age-matched controls prior to surgery (Tucker et al., 2020). Interestingly, in this study global CVR did not change following bariatric surgery despite patients losing weight, BMI, and body circumference.

2.3.2.2 Physical inactivity

Due to the lack of studies assessing physical inactivity, we reviewed studies evaluating the associations between exercise or cardiorespiratory fitness and CVR. Foster et al., (2020) found that grey matter CO_2-CVR was positively correlated to aerobic fitness (measured as participants' maximum oxygen consumption; VO_2max). However, Burley et al., (2021) observed no significant differences in either global grey matter CVR (Hedges' g= 0.38) or sub-cortical CVR (Hedges' g= 0.53-0.61) with BOLD MRI between a younger fit group (indicated by VO_2max) and an older unfit group (assessed by physical activity questionnaires). Gauthier et al. (2015) reported a negative association between VO_2max and CVR in frontal regions with a relatively large effect size (R^2= 0.11), but positive correlations in periventricular watershed regions and within the postcentral gyrus.

MRI studies have also reported no immediately beneficial effects of exercise interventions on CVR. For instance, CVR did not change after a 3-month physical exercise training programme, and there was no significant difference in CVR between groups who completed physical exercise training and those who completed cognitive training (Chapman et al., 2016). However, there was also no change in VO_2max after the physical training intervention, which might either be due to participant's prior sedentary lifestyle or the fact that the intervention was too short. Similarly, Steventon et al., (2020) performed MRI scans at baseline and 25 minutes post-exercise and observed no changes in CVR before and after 20 minutes of cycling.

Two studies have also reported negative associations between lifelong physical activity and CVR in older adults. Master athletes (who were ranked in regional or national running competitions) showed lower whole-brain CVR than sedentary age-matched individuals, and there was a negative association between global CVR and fitness (VO_2max; Thomas et al., 2013). Additionally, Intzandt et al., (2020) showed that there were negative relationships between cardiovascular fitness and BOLD-CVR in grey matter throughout the cortex for elderly subjects, whereas there was no link for younger adults.

2.3.2.3 Depression

Depression was the only psychiatric risk factor for dementia included in this review, and there

were consistent results of no relationships between depression and CVR. Abi Zeid Daou et al., (2012) reported no differences in CVR between people with and without depression and there was also no significant association between depression severity and CVR. Similarly, Moreton et al., (2018) used another depression scale and found that though CADASIL patients with depressive symptoms had lower CVR relative to those without depression, this was not statistically significant. Furthermore, an interventional study in individuals with depression found that there was no correlation between baseline depression severity and CVR in any fronto-cingulate regions (Abi Zeid Daou et al., 2017). However, higher CVR in the caudal medial frontal gyrus was related to less effective response to antidepressants.

2.3.2.4 Type 2 Diabetes

People with type 2 diabetes had lower CVR than healthy controls, according to three out of the four selected studies. Last et al., (2007) observed reduced CVR in the frontal, temporal, parieto-occipital, and cortical regions in patients with diabetes. People with diabetes also had accelerated impairments in CVR than non-diabetic controls after a two-year follow-up (Chung et al., 2015), and this effect had a large effect size with r^2_{adj}=0.16-0.53 for various brain regions. Furthermore, in those with pre-existing hypertension, people who with co-morbid diabetes had decreased CVR in the bilateral lingual gyrus, cuneus and precuneus, parietal areas, and right lateral occipital regions (Tchistiakova et al., 2014). However, Jor'dan et al., (2014) found no difference in CVR between type 2 diabetes and non-diabetic groups. Nevertheless, they found

that those with a slow gait speed had a lower CVR in the diabetes group (r^2_{adj}= 0.13), but not in the healthy controls.

2.3.2.5 Hypertension

Three studies assessed the association between hypertension and CVR. There were consistent results that hypertension was associated with lower CVR (Blair et al., 2020; Hajjar et al., 2010; Peng et al., 2018), predominantly in the frontal and parietal areas with large effect seizes of η^2>0.3 (Hajjar et al., 2010). Interestingly, Peng et al., (2018) noted that while cross-sectional hypertension was linked to worse CVR outcomes, the longitudinal changes in CVR over four years were unrelated to hypertensive status (Peng et al., 2018). For people with stroke, CVR was lower in the white and grey matter if their systolic blood pressure was high (Blair et al., 2020).

2.3.2.6 Traumatic brain injury (TBI)

Four studies observed associations between TBI and impaired CVR, but one study found the opposite. Amyot et al., (2018) suggested that TBI patients had a lower amplitude of CVR in the whole grey and white matter, as well as higher volume of abnormal CVR, as compared with healthy controls. Cohen's d >0.7 suggested large effect sizes in all cortical regions (Amyot et

al., 2018). Later, with both BOLD MRI and functional near-infrared spectroscopy, the same team verified this association with a relatively older cohort (Amyot et al., 2020). According to a recent study by this team, individuals with persistent TBI had lower whole-brain CVR, and the more severe the headache, the lower the CVR (Amyot et al., 2021). Furthermore, Haber et al., (2018) demonstrated that chronic TBI had a long-term negative influence on both whole-brain CVR and CVR in normal-appearing tissue. However, Champagne et al., (2019) reported that compared to football players without concussions, those with concussions had significantly higher BOLD-CVR and ASL-CVR in regions of the right visual cortex, left superior and inferior parietal lobules, left premotor motor cortex, right supplementary cortex, and right parietal operculum. The authors suggested that the football players' improved CVR could have arisen from pre-existing differences in the resting metabolic factors (e.g., oxygen extraction and vessel morphology) between the two groups.

Of the 12 examined modifiable/behavioural risk factors, we found no MRI studies examining associations between CVR and levels of education, smoking, air pollution, hearing impairment, social isolation or alcohol consumption. We note that there are transcranial Doppler studies that have examined effects of smoking and exercise on CVR (Burley et al., 2021; Silvestrini et al., 1996), but these were outside the scope of this review.

2.3.3. Clinical risk factors

2.3.3.1 Stroke and related cerebrovascular diseases

We reviewed five studies investigating CVR in stroke patients. Thrippleton et al., (2018) observed lower CVR in the grey matter of stroke patients compared to healthy controls. Krainik et al., (2005) noted that impaired CVR in stroke patients was largely observed in the lesioned hemisphere. Moreover, compared with single stroke patients, people with recurrent stroke episodes had lower CVR in the stroke-affected hemisphere, but not in the contralateral hemisphere (Goode et al., 2016; Papassin et al., 2021). In contrast, Raut et al., (2016) used a breath-holding vasodilatory stimulus and found that patients with acute stroke had similar CVR to age-matched controls.

Our literature search also resulted in seventeen studies which investigated stroke-related cerebrovascular disease, such as infarcts, perivascular spaces (PVS), microbleeds, white matter hyperintensities (WMH) and Moyamoya disease. In patients with a hereditary stroke disorder (CADASIL), a higher number of lacunes or lower brain volume was associated with impaired CVR (Moreton et al., 2018). Two studies found reduced CVR in the arterial territories (Zhao et al., 2009) and lesioned areas (Geranmayeh et al., 2015) of individuals with cerebral infarcts. However, Conijn et al., (2012) found no significant differences in global CVR between people with and without lacunar infarcts. Five MRI studies also examined CVR in Moyamoya patients. In general, CVR was lower in Moyamoya patients compared to healthy controls (Donahue et al., 2014, 2013; Ladner et al., 2012). Higher Moyamoya scores (i.e., more severe

Moyamoya) were associated with reduced CVR (Heyn et al., 2010), and regions with less advanced stages of Moyamoya disease had higher CVR (Donahue et al., 2013, 2014). Studies have therefore suggested that interventions, such as uniliteral revascularisation, could improve CVR in both affected and non-affected hemispheres (Sam et al., 2015). For people with intracranial stenosis, impairments in CVR have been observed in both the stenosed and contralateral hemispheres (Mandai et al., 1994). Two studies with patients who had atherosclerosis and Moyamoya disease showed that CVR was lower in the stenosed hemispheres compared to the non-stenosed hemispheres (Donahue et al., 2014; Juttukonda et al., 2021).

Two studies have reported that CVR was reduced in the presence of microbleeds (Conijn et al., 2012; Hund-Georgiadis et al., 2003), whereas one study found no differences in CVR between patients with microbleeds and healthy controls (Akoudad et al., 2016). Moreover, three studies found that reduced CVR was associated with WMH (Atwi et al., 2019; Blair et al., 2020; Last et al., 2007). Blair et al., (2020) also noted lower levels of CVR with total small vessel disease (SVD) burden and more PVS. Similarly, Atwi et al., (2019) found that people with moderate and severe WMH, as well as those diagnosed with CADASIL, had lower white-matter CVR but not grey-matter CVR when compared to healthy controls. In contrast, Conijn et al., (2012) observed no associations between CVR and white matter lesions. One study showed that patients with hypertensive intracerebral haemorrhages had lower CVR than healthy controls (Lee et al., 2021).

2.3.3.2 Peripheral artery diseases

We reviewed ten studies examining peripheral artery phenotypes, such as stiffening (hardening), stenosis (narrowing), and occlusions (blockage) of the aorta and the carotid arteries, all of which have been shown to increase the risk of developing dementia (Iulita et al., 2018; Kang et al., 2020; Lee et al., 2017; M. P. Pase et al., 2012; Sun et al., 2022).

Two MRI studies examined associations between aortic stiffness and CVR. Surprisingly, Jefferson et al., (2018) reported a relatively preserved CVR despite increasing levels of aortic stiffness (measured as pulse wave velocity) in cognitively healthy adults (however they found no association between CVR and aortic stiffness in participants with mild cognitive impairment). One explanation for this could be underlying sex differences in this association. Although the authors did not report any interactions with sex, another study noted that sex modulated the correlations between CVR and aortic stiffness, with females having lower CVR and males having higher CVR with increasing aortic stiffness (Sabra et al., 2021).

There were also consistent results showing that patients with carotid artery stenosis had impaired CVR (Campos Herrera et al., 2016; Hartkamp et al., 2012). In fact, Sobczyk et al., (2020) showed that CVR reduced as the severity of stenosis increased. However, (Hartkamp

et al., 2018) only noted impairments in CVR in symptomatic but not asymptomatic patients with internal carotid artery (ICA) stenosis, suggesting that CVR might be preserved for asymptomatic stenosed patients. Most studies have consistently found CVR reductions mainly in the hemisphere of the stenosed or occluded vessels (Bokkers et al., 2011; de Vis et al., 2015; Hartkamp et al., 2018; Kaczmarz et al., 2021; Sam et al., 2014). However, Kaczmarz et al., (2021) reported that CVR of stenosed patients was also lower in the grey matter of the contralateral hemisphere but was comparable to healthy controls in the white matter. Hartkamp et al., (2018) found that CVR was compromised in both hemispheres of patients with ICA occlusion. De Vis (et al., 2015) showed that CVR was lower in ICA occlusive patients compared to healthy controls, and CVR was lower in the ipsilateral than in the contralateral MCA territory. However, this difference was only observed using BOLD CVR but not with ASL CVR.

2.3.3.3 Vasodilatory stimulus

Most studies used CO_2 challenge as the vasodilator, with acetazolamide and breath-holding being relatively less common approaches (***Figure 2.2***). For most risk factors, contradictory studies used a lesser common vasodilatory stimulus. For example, for studies on stroke and related cerebrovascular diseases, 77% of studies (17/22) consistently reported a negative association with CVR of which 82% (14/17) used CO_2. Conversely, 80% (4/5) of the studies that found no association or mixed results used breath-holding and other less common vasoactive stimuli (***Figure 2.2C***). However, inconsistencies also existed between studies using

CO_2 alone as in the case of the TBI where both negative (4/5 studies) and positive associations (1/5 studies) were observed using CO_2.

2.4 Discussion

2.4.1 Summary of the results

In this review, we summarised 59 MRI studies investigating the associations between CVR and non-modifiable, modifiable/behavioural, and clinical risk factors for dementia. Overall, we found reasonably strong and consistent evidence that CVR decreases as people get older. APOE ε4 carriers also had lower CVR than those without the ε4 risk allele. Nevertheless, we note that the number of MRI studies on CVR and APOE was limited (i.e., only 3 studies). Surprisingly, most studies found that physical activity was not associated or even inversely associated with CVR in older adults. Thomas et al., (2013) suggested that lifelong exposure to high level aerobic exercise may desensitise the cerebrovascular system and suppress the vaso-regulatory response to carbon dioxide, resulting in lower CVR in athletic individuals. However, the physical activity studies were largely inconsistent both in terms of the directionality of the associations and the affected brain regions. We also note that the studies included in this review mainly focused on CVR in physically active people, such as athletes, or people with physical training, and we identified almost no studies examining the associations

between physical inactivity and MRI-based CVR. Thus, it is difficult to draw a clear conclusion about the associations between physical inactivity and CVR. Most studies examining other modifiable/behavioural risk factors, such as type 2 diabetes, hypertension and TBI consistently found associations with impaired CVR, but the affected brain regions varied between studies. We noted that one study found a higher CVR in football players with history of sport-related concussions compared to those without concussions (Champagne et al., 2019), however in a subsequent follow-up the authors also found lower resting cerebral blood flow (CBF) in the concussion group compared to the controls (Champagne et al., 2021). The authors therefore suggested that the higher CVR in the concussed group was likely due to their preserved dilatory capacity of the cerebrovasculature, as their lower baseline CBF suggested greater tone, resulting in a greater shift in blood flow and higher CVR. Results on obesity were variable and limited. The reviewed literature also showed no associations between depression and CVR except one intervention study which found that patients with higher CVR exhibited less change in depression severity with sertraline treatment (Abi Zeid Daou et al., 2017).

As for clinical risk factors, there was consistent evidence that people with stroke, Moyamoya syndrome, peripheral artery occlusions or stenosis had lower CVR. In general, impairments in CVR were seen in widespread brain regions for patients with internal carotid artery occlusion and cerebral infarctions. However, people with carotid artery stenosis had greater reductions in CVR in the area ipsilateral to the stenosis than that in the contralateral area. There was mixed evidence for the associations between microbleeds, WMHs and CVR.

2.4.2 Mechanisms underlying the associations between dementia risk and CVR

While the exact mechanisms by which dementia risk factors may affect CVR are unclear, there are some possible biological explanations. The first would be endothelial dysfunction. For example, there is an increase in the production or release of vasoconstrictive proteins like endothelin-1 in older individuals, as well as a reduction in the release of vasodilatory substances like nitric oxide (NO; Kalaria, 1996). This change can result in a diminished ability for vasodilatation or possibly hyper-constriction of the vessels, eventually leading to insufficient responses to higher metabolic demands (Catchlove, Parrish, et al., 2018). Lower endothelial NO production has been observed in hypertensive patients and is believed to reduce the cerebral response to CO_2 (Hajjar et al., 2010). Moreover, hyperglycaemia and insulin resistance in diabetes can cause inflammation, which can contribute to endothelial dysfunction (Chung et al., 2015). The association between TBI and impaired CVR might also arise from endothelial damage resulting from the brain injury (Amyot et al., 2018). Increased capillary thickness, microangiopathy, and altered endothelial permeability may all have a deleterious impact on CVR (Chung et al., 2015).

The second explanation may be attributed to abnormalities in the blood vessels, such as arterial stenosis (narrowing), arterial occlusion (blockage), and arteriosclerosis (stiffening of the artery walls). These structural abnormalities are often attributed to risk factors such as

ageing, high blood pressure, obesity, or smoking (Barton et al., 2012; Livingston et al., 2017, 2020; Rahman & Laher, 2007; Rubio-Ruiz et al., 2014): all of which are also risk factors for dementia (Livingston et al., 2017, 2020). These arterial abnormalities can reduce the capacity of the brain-feeding arteries to supply blood to neurons, thereby affecting the vasodilatory response (Hartkamp et al., 2018). For instance, the decline in CVR for elderly people could, at least in part, be due to the increase in rigidity and decrease in elasticity of the body's vessels, which is commonly observed in ageing (Catchlove, Parrish, et al., 2018). Eventually, impairments in CVR can result in a chronic inability to regulate blood supply to meet the brain's high metabolic demands. This persistent hypoperfusion can potentially lead to the neurological and cognitive decline typically seen in dementia (De La Torre, 2012).

The impaired CVR observed in most of the risk groups could also be attributed to dysfunctions of vascular smooth muscle cells (SMCs) in the arteries (Hayes et al., 2022). Extracellular pH drops in the presence of CO_2, causing vascular SMC membrane hyperpolarization and $Ca2^+$ channel inactivation. These events may trigger a decrease in intracellular $Ca2^+$ levels, relaxing smooth muscle tone (Duffin et al., 2018; Fisher & Mikulis, 2021). As a result, vascular SMC relaxation leads to vasodilation, which increases blood flow. It is possible that the dementia-risk groups (e.g., APOE ε4, Moyamoya diseases, CADASIL) with lower CVR may have impairments in this cellular mechanism, therefore reducing the ability of the arterial walls to vasodilate (Lin et al., 2012; Pfefferkorn et al., 2001).

2.4.3 Sex differences in the associations between dementia risk and CVR

Although sex was not examined as a dementia risk factor in the published review, we discuss the importance of examining sex differences in CVR in this section. The prevalence of dementia is higher in females (Cao, et al., 2020; Fiest et al., 2015), however, several established dementia risk scores identify male sex as a risk factor for dementia (Anatürk et al., 2023; Kivipelto et al., 2006; Wang et al., 2022). Previous studies have reported sex differences in CVR. For example, (Kassner et al., (2010) reported higher CVR in females compared with males across both grey and white matter using a controlled respiratory challenge. Similarly, Tallon et al., (2020) observed higher CVR in females relative to males. A study in a larger cohort of older adults (mean age ~ 70 years) also reported higher CVR in females, which aligns with evidence showing generally higher cerebral blood flow in women (Engstrom et al., 2025).

Despite these observations, most studies included in our systematic review did not explicitly examine sex differences in the association between dementia risk and CVR. These studies either lacked formal interaction tests between sex and risk factors on CVR or did not perform sex-stratified analyses to compare risk-CVR associations across groups. A few studies tested for sex differences in CVR but reported no significant effects (Catchlove, Parrish, et al., 2018; Gauthier et al., 2015; Leoni et al., 2017; McKetton et al., 2018). Only one study found that female sex was associated with lower CVR (Conijn et al., 2012). However, none of these studies directly examined sex differences in CVR in relation to dementia risk factors. One notable exception was the study by (Sabra et al., 2021), which demonstrated sex-specific

associations between aortic stiffness and CVR, whereby higher arterial stiffness was associated with higher CVR in males but lower CVR in females. The authors suggested that these opposing associations may reflect sex differences in vascular ageing trajectories. In females, arterial stiffness tends to increase more rapidly after menopause due to estrogen depletion. In contrast, males experience a more gradual progression of arterial stiffening, which may lead to different vascular adaptations and consequently different CVR responses. Given the lack of consistent findings, the role of sex in moderating the associations between dementia risk factors and CVR remains unclear and requires further investigation.

2.4.4 Methodological heterogeneity across studies

While most of the risk factors had consistent associations with CVR, there were few studies which reported contradictory results. This variation could, in part, be due to the between-study differences in CVR measurements. For example, unlike the majority of studies that used CO_2 as the vasodilatory stimulus, one study used intravenous acetazolamide (a carbonic anhydrase inhibitor that causes acidosis) and found no correlation between age and CVR (Mandai et al., 1994). It has been suggested that acetazolamide might not be as suitable a vasodilatory stimulus as CO_2 due to considerable individual variability in the response to and tolerability of acetazolamide (Fierstra et al., 2013). This could affect the reproducibility of stimulus-response relationships in acetazolamide studies. Furthermore, while most of the stroke-related research found a link between the occurrence of stroke and lower CO_2-CVR, two studies that used

breath-holding to assess CVR did not find such a relationship (Conijn et al., 2012; Raut et al., 2016). In contrast to the CO_2 delivery method, it is difficult to precisely monitor the CO_2 within arteries using breath-holding due to the variability of respiratory responses between individuals (Catchlove, Parrish, et al., 2018). Moreover, participants may also show considerable variability in head motion during breath-holding, which could affect the quality of the imaging data (Raut et al., 2016). However, contradictory results can be found even with CO_2 inhalation, and the inconsistency of results cannot be attributed entirely to the heterogeneity of the vasodilators. Other possible explanations include variations in CO_2 inhalation paradigm, gas delivery apparatus, measurement of CO_2 time course, or CO_2 concentration (Liu et al., 2019). Additionally, while BOLD and ASL measures of CVR are complementary techniques (Zhou et al., 2015), there are assumptions depending on the sequence used (e.g., inversion efficiency, arrival time) that may contribute to some of the methodological heterogeneity (Aslan et al., 2010; Sanvito et al., 2021).

2.4.5 Implications of the findings

This review has raised several considerations for future research. 1) The majority of studies in this review were cross-sectional, so it is still unclear whether impairments in CVR worsen dementia risk factors or whether the cerebral vasodilatory capability is worsened in the presence of the risk factor itself (Conijn et al., 2012; Intzandt et al., 2020). Therefore, longitudinal studies are needed to address the causal relationship. 2) Some reviewed studies

had relatively small sample sizes (e.g., fewer than 10 participants in all subgroups; Hund-Georgiadis et al., 2003; Krainik et al., 2005; Tucker et al., 2020), highlighting the need for larger studies with greater statistical power (Button et al., 2013). 3) Future studies should carefully consider the choice of confounding or moderating variables. For instance, Sam et al., (2014) noted that diabetes mellitus and depression might potentially confound the association between arterial stenosis and CVR. Consumption of caffeine might also introduce bias to the vasodilatory results (Peng et al., 2018). 4) Given the lack of CVR studies investigating education, smoking, air pollution, hearing impairment, social isolation, and alcohol consumption, future MRI studies should focus on these important dementia risk factors. Moreover, as most dementia risk factors are present in midlife (Livingston et al., 2024), understanding association of midlife dementia risk with later-life CVR may offer valuable insights for early intervention strategies. 5) Studies should investigate if managing dementia risk factors can preserve or reverse CVR decline. For instance, it has been suggested that CVR deficits can be reversed by restoring the blood supply of stroke patients through surgery (Mandell et al., 2011). Surgical revascularisation could increase total brain blood supply and restore perfusion in haemodynamically compromised brain tissue, therefore improving CVR (L. McKetton et al., 2019). Treatments of Moyamoya disease have been linked to improvements or recovery of CVR (Sam et al., 2015). One study also found that treated hypertensive patients had significantly higher CVR than those with poorly controlled blood pressure (Peng et al., 2018). Moreover, even though acute physical training (i.e., 20-min aerobic cycling) may not improve CVR (Steventon et al., 2020), lifelong aerobic exercise has been known to have a positive effect on cerebral blood flow (Bailey et al., 2013; Thomas et al., 2013). Nonetheless,

the evidence for interventions is still limited.

2.4.6 Strengths and limitations of the review

To our knowledge, this is the first systematic review to investigate the relationship between dementia risk factors and CVR. The study included as wide a range as possible of the commonly established risk factors for dementia or mild cognitive impairment. However, there are several limitations of the review. In order to prioritise methodological consistency across studies, and to describe specific brain regions affected by dementia risk, we only included studies that utilised MRI to assess CVR. However, TCD is also a commonly used technique to measure CVR. Previous studies have noted agreements in the CVR values measured by TCD and MRI within the same participants (Burley et al., 2021; Campos Herrera et al., 2016; Moreton et al., 2018). However, the TCD and MRI studies do not always find the same directionality of correlations between CVR and various dementia risk factors (Campos Herrera et al., 2016; Intzandt et al., 2020). Especially for physical activity, most TCD studies suggested a positive association between aerobic exercise and CVR (Bailey et al., 2013; Foster et al., 2020; Murrell et al., 2013). However, this was not the case for the MRI studies reported here (Chapman et al., 2016; Gauthier et al., 2015; Intzandt et al., 2020; Steventon et al., 2020; Thomas et al., 2013). TCD measures variations in blood velocity in the arteries, whereas BOLD MRI predominantly measures changes in deoxy-haemoglobin concentration in the venules and veins, resulting in possible discrepancies between CVR evaluated by the two methods (Burley

et al., 2021). Therefore, evidence merely in terms of MRI data might not be sufficient to draw strong conclusions for our research questions. Finally, we note that grey literature (e.g., conference publications or publications outside traditional academic databases) was not included in this review, and hence we may have missed studies that failed to find statistically significant results (Egger et al., 2003).

2.5 Conclusion

We reviewed studies investigating the associations between a range of well-established risk factors for dementia and CVR measured by MRI. There were consistent reports that older adults have lower CVR than younger adults. Clinical factors, such as stroke and artery stenosis-occlusive diseases, were also strongly associated with decreased CVR. The evidence also suggested that carrying APOE ε4 allele, being diagnosed with hypertension, diabetes or TBI were all related to impaired CVR. However, the associations between CVR and obesity, aortic stiffness, microbleeds, white matter hyperintensities and physical exercise were mixed. While limited in number, the evidence suggested that CVR was not affected in people with depression. We also found no MRI studies examining associations between CVR and education, smoking, air pollution, hearing impairment, social isolation, or alcohol consumption. Mixed results could be attributed to variability in choice of vasodilatory stimulus, study design, and sample size. Overall, this review offers valuable insights into how CVR is affected by modifiable/behavioural and clinical risk for dementia. It is possible that timely

intervention and management of such risk factors may have beneficial effects on cerebrovascular health, and in turn potentially help delay or prevent dementia.

While we propose several avenues for future research, this thesis addresses four key limitations of existing CVR studies: 1) it uses a larger sample than most prior work (average N = 35, our N = 163); 2) it applies a robust and reliable hypercapnic BOLD-CVR protocol; 3) it incorporates a composite dementia risk score combining multiple lifestyle and clinical (albeit not all mentioned above) risk factors; 4) it leverages a longitudinal cohort to examine how midlife dementia risk relates to later-life CVR, a critical window for early intervention.

Chapter 3: Study cohort and methodology of the key variables

In order to further investigate the role of cerebrovascular reactivity (CVR) in the progression of brain ageing and cognitive decline, we conducted a longitudinal study using data from the Whitehall II Heart and Brain Study. This study was carried out between 2019 and 2023 as part of my DPhil research. This is a methodology chapter which outlines the timeframe of the longitudinal study, the assessment of lifestyle and clinical risk factors in midlife, as well as neuroimaging and cognitive measures in later life. It also describes the preprocessing pipelines for the imaging data. These methodological details provide essential information for analysing and interpreting the results presented in the subsequent chapters.

3.1 Introduction

The systematic review in **Chapter 2** revealed consistent associations between cerebrovascular reactivity (CVR) and certain modifiable risk factors, such as hypertension, diabetes, and stroke (Wang et al., 2023). However, other modifiable dementia factors such as education and depression remained under-investigated. As these risk factors are highly correlated with each other, analysing their individual relationships with dementia related outcomes can lead to multicollinearity issues, reduced statistical power, and potential model overfitting (Dormann et al., 2013; Franke, 2010; Kim, 2019). To address these methodological

challenges, researchers have increasingly turned to use **comprehensive lifestyle risk scores** that combine multiple risk factors into a single predictive measure (D. E. Barnes et al., 2009; Kivipelto et al., 2006; Schiepers et al., 2018).

To robustly investigate the long-term associations between midlife dementia risk factors and late-life brain health, a longitudinal cohort with repeated assessments is essential. Specifically, a study design that captures lifestyle risk profiles in the critical midlife period a stage (typically ~40 to ~65 years) when many modifiable risk factors begin to exert measurable effects and can be effectively addressed through intervention (Livingston et al., 2020, 2024), and follows individuals over decades to assess cerebrovascular health, brain structural changes, and cognitive performance in later life is particularly valuable (Sedaghat et al., 2023).

In this chapter, we describe the cohort used in this thesis and the development of a composite dementia risk score based on midlife dementia risk factors (the UK Biobank Dementia Risk Score, UKBDRS). We then detail the acquisition and pre-processing methods of the neuroimaging data. The MRI protocol included CVR scans that were derived from blood-oxygen-level-dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) under a hypercapnic challenge, structural imaging metrics including grey matter volume (GMV) via T1-weighted structural MRI, white matter microstructure via diffusion tensor imaging (DTI), and white matter hyperintensities (WMHs) via Fluid-Attenuated Inversion Recovery (FLAIR) scans. Finally, we present the neuropsychological assessments used to characterise cognitive

performance across domains in later-life. The methods outlined here form the foundation for investigating the interplay associations between midlife dementia risks, brain vascular and structural health, and cognitive decline in the subsequent chapters.

3.2 Design and Cohort

3.2.1 The Whitehall II cohort

All the following chapters in this thesis utilised data from the Heart and Brain Study (HBS), a sub-study of the Whitehall II (WHII) Stress & Health Study. WHII is a longitudinal project with original recruitment of 10,308 British civil servants, established in 1985. This study conducted repeated assessments of clinical, psychological, socioeconomic, and health-related data approximately every five years (across 13 waves) at the University College London (Ben Hassen et al., 2022; Marmot & Brunner, 2005). The detailed phenotyping and consistent longitudinal follow-up of this cohort make it one of the most well-characterised data frames for investigating brain health, ageing, and cognitive decline. A timeline of data collection is presented in ***Figure 3.1***. In this thesis, WHII data waves are referred to as WH-Waves. Retrospective records of midlife risk factors were drawn from **WH-Waves 3 to 9** and were used to derive a midlife dementia risk score.

3.2.2 Whitehall imaging sub-study (MRI-Wave 1)

A total of 775 participants from the 6,035 individuals attending WH-Wave 11 (2012-2013) were recruited for the Whitehall Imaging sub-study (2012-2016), during which vascular risk profiles, comprehensive neuropsychological assessments, and neuroimaging data were collected at the Oxford Centre for Functional MRI of the Brain, University of Oxford. The imaging protocol included T1-weighted structural scans, DTI, and FLAIR sequences (protocol is available in Filippini et al., 2014). Written informed consent was obtained from all participants before the MRI scan, and the study was approved by the University of Oxford Central University Research Ethics Committee (Reference: MSD-IDREC-C1-2011-71). In this thesis, we refer to the imaging data collected during this wave as **MRI-Wave 1**, which serves as the baseline assessment for brain structure and cognitive performance.

3.2.3 Heart and brain study (MRI-Wave 2)

The Heart and Brain Study (HBS; protocol is available in Suri et al., 2021) is a neuroimaging follow-up of the Whitehall II imaging sub-study (MRI-Wave 1). It involved 163 participants who had previously completed MRI-Wave 1 and were subsequently re-invited for a second MRI session after around 8.7 years, and thereafter, referred as **MRI-Wave 2** (2019-2023) at Oxford Centre for Human Brain Activity, University of Oxford. MRI-Wave 2 followed the same

neuroimaging and cognitive protocol as MRI-Wave 1, with the addition of BOLD functional MRI to measure CVR. Exclusion criteria for the HBS consisted of contraindications to MRI (e.g., claustrophobia), respiratory contraindications to the CVR scan (e.g., severe asthma), and clinical diagnosis of dementia. **No participants were classified as having severe cognitive impairments**, based on self-report at screening as well as relative performance across cognitive domains. The study was approved by the University of Oxford Medical Sciences Interdivisional Research Ethics Committee (Reference: R57135/RE006), and all participants provided written informed consent at their visit to collect imaging data.

3.2.4 Data used in this thesis

This thesis uses data from 163 participants (Male: n = 121, 87%) who underwent longitudinal neuroimaging and cognitive assessments at MRI-Wave 1 (first imaging assessment/baseline) and MRI-Wave 2 (final imaging assessment/follow-up), with CVR additionally measured during MRI-Wave 2 at the University of Oxford from the HBS. They also had midlife dementia risk factors assessed during the previous WHII study waves (WH-Waves 3-9) at University College London. The study uses a retrospective cohort design.

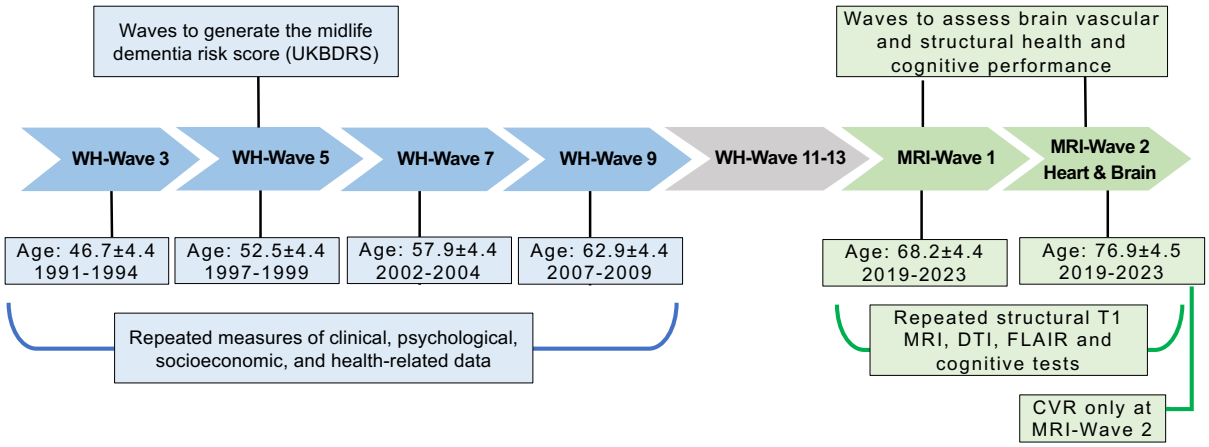


Figure 3.1: Timeline of data collection and key measures in each wave of the Heart and Brain cohort

Note: The mean age (± standard deviation) shown for each wave reflects the 163 participants included in the final sample for the thesis. Time points include midlife dementia risk assessments (the UK Biobank Dementia Risk Score [UKBDRS]), and later-life imaging and cognitive data. WH = Whitehall; MRI = Magnetic Resonance Imaging; DTI = Diffusion Tensor Imaging; FLAIR = Fluid-Attenuated Inversion Recovery; CVR = Cerebrovascular Reactivity; UKBDRS = UK Biobank Dementia Risk Score.

3.3 Dementia risk scores

3.3.1 The UK Biobank Dementia Risk Score

Our lab has recently created the UK Biobank Dementia Risk Score (UKBDRS) for dementia risk prediction (Anatürk et al., 2023). It was developed using the extensive UK Biobank cohort and externally validated in the WHII cohort. The UKBDRS incorporates eight modifiable and three non-modifiable risk factors including age, education, parental history of dementia, socioeconomic status, and multiple health conditions including type 2 diabetes, stroke,

depression, hypertension, and high cholesterol (Anatürk et al., 2023). The score combines these measures from midlife to assess the likelihood of developing dementia in the next 14 years. In the original training model based on the UK Biobank cohort, the UKBDRS was developed using data from individuals aged 50 to 73. It was later validated in the WHII cohort, which included individuals with a median age of 57 (Min = 40 years old). We have previously shown that the UKBDRS demonstrates strong predictive accuracy with an area under the curve (AUC) of 0.80 in the UK Biobank development cohort and 0.77 in the WHII validation cohort. The UKBDRS also performed better than other commonly used dementia risk scores, including Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE; AUC = 0.60 for UK biobank and AUC=0.69 for WHII) and the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI; AUC = 0.57 for UK biobank and AUC = 0.52 for WHII) (Anatürk et al., 2023). Given its good predictive performance, and that it has already been validated in the WHII cohort, we opted to use this score to assess dementia risk in this thesis (additional explanation in **Chapter 4**).

3.3.2 Calculation of the UKBDRS for the HBS cohort

We calculated the UKBDRS based on measurements collected in **WH-Wave 5** of the WHII study (1997-1999), when participants were approximately **52.5 ± 4.4 years old**, as done during the original development and validation of the score (Anatürk et al., 2023). If the risk variables were missing for WH-Wave 5, we used the information from WH-Wave 3 (Mean age 46.7 ± 4.4

years), 7 (Mean age 57.9 ± 4.4 years), or 9 (Mean age 62.9 ± 4.4 years) as long as the participant was still in the midlife age range (40 - 65 years) at that wave (substitute from WH-Waves 3 - 9 are provided in ***Table 3.1***). We set the minimum age at 40 as the UKBDRS was validated in WHII participants aged over 40, and the upper limit at 65, consistent with the age range commonly defined as midlife in dementia risk research (Anatürk et al., 2023; Kivipelto et al., 2006; Livingston et al., 2024). The score includes age, level of education, parental history of dementia, material deprivation as measured by Townsend deprivation index (Townsend, 1987), type 2 diabetes, current/history of stroke, depression, hypertension, high total cholesterol, male sex and lower household occupancy (Anatürk et al., 2023). Although dementia is generally more prevalent in women (Beam et al., 2018; Gong et al., 2023), the UKBDRS identified male sex as a risk factor, which is consistent with the higher dementia incidence observed in the UK Biobank cohort (Anatürk et al., 2023; Gong et al., 2021). Except age and education level, each factor was classified as either presenting a risk (scored as 1) or not (scored as 0), following predefined cut-off guidelines. These binary scores were then combined using a validated formula to produce an overall dementia risk score (see ***Table 3.2***). However, due to a high number of missing responses (n = 29) for the household occupancy variable at WH-Wave 5 and no substitute from the other WH-Waves, and with the consideration to preserve statistical power by avoiding the exclusion of a large number of participants, we excluded this factor in the final risk calculation. Given its relatively minor weighting (0.141, with all factor weights ranging from 0.041 to 0.655), its omission was not expected to significantly impact the accuracy of the overall risk score. The final dementia risk score was log-transformed to reduce skewness and ensure a normal distribution for use in statistical analyses throughout

this thesis.

Table 3.1: Number of risk variables used from each wave to calculate the UKBDRS for 163 participants of the study

Risk factors were primarily drawn from WH-Wave 5 for most of the participants. Missing values were substituted using data from WH-Wave 7, and then WH-Wave 3 or 9 if within the midlife age range (40-65 years old).

Risk factor	Wave 3	Wave 5	Wave 7	Wave 9
Parental history of dementia	163	-	-	-
Education	-	163	-	-
Diabetes	-	159	4	-
Depression	-	151	11	1
Stroke	-	163	-	-
Material deprivation	-	163	-	-
Hypertension	-	163	-	-
Total cholesterol level	2	156	5	-
Sex	-	163	-	-
Age	-	163	-	-

Table 3.2: Formula and criteria used for binary coding of each variable in calculating the UKBDRS (adapted from Anatürk et al., 2023)

"Yes" indicates the presence of the corresponding risk factor according to predefined cut-off guidelines. Variables marked with an asterisk (*) were continuous and directly input into the calculation. β coefficients indicate the relative weight assigned to each risk factor within the UKBDRS model. The final UKBDRS that was used in the analysis was log transformed. In the original development of the score UKBDRS cut-offs of 1.843% and 3.201% correspond to 80% sensitivity and specificity, respectively, for dementia prediction (note that this original development included the household occupancy variable, which was not included in this thesis) (Anatürk et al., 2023). General Health Questionnaire is a self-report screening tool designed to detect psychological distress, including symptoms of depression. Total cholesterol level was measured by blood samples taken after at least five hours of fasting (Marmot et al., 1991).

Risk factor	**Guideline for binary coding (yes=1, no=0)**	**β coefficient**
Parental history of dementia (yes)	Participant has at least one parent diagnosed with dementia	0.431
Education (years)*	Total years of education	−0.041
Diabetes (yes)	Self-reported diagnosis of diabetes	0.536
Depression (yes)	GHQ (General Health Questionnaire) score ≥5	0.556
Stroke (yes)	Self-reported diagnosis of stroke	0.655
Material deprivation (yes)	Highest level of material deprivation with Townsend deprivation index >0.758	0.228
Hypertension (yes)	Systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg, or currently taking antihypertensive medication	0.159
High cholesterol (yes)	Total blood cholesterol level >6.2 mmol/L	0.104
Sex (yes)	Male participants	0.169
Age*	Age while taking the questionnaire	0.178
Formula to calculate the UKBDRS		
• UKBDRS Linear Predictor=0.178×(Age−59.97)+0.431×(Parental Dementia History)−0.041×(Years of Education−13.54)+0.536×(Diabetes)+0.228×(Material Deprivation)+0.556×(Depression)+0.655×(Stroke)+0.159×(Hypertension)+0.104×(High Cholesterol)+0.169×(Male Sex) • Predicted Probability=$1-0.9916195^{\exp(\text{UKBDRS Linear Predictor})}$ • Predicted UKBDRS=Predicted Probability×100		

3.4 Brain imaging measures

Participants received 3 Tesla (3T) T1-weighted structural MRI, DTI, FLAIR at MRI-Waves 1 and 2, as well as a CO_2-CVR scan only at MRI-Wave 2. Scan protocols were closely matched between MRI-Waves; however, they were conducted on different scanners (MRI-Wave 1: 3T Verio; MRI-Wave 2: 3T Prisma). Detailed sequence parameters for these scans are provided in the HBS protocol paper (Suri et al., 2021), as well as in ***Table 3.3***. The sequence parameters were selected based on previous protocols for CVR imaging and were validated for image quality and participant tolerability in our pilot testing (Liu et al., 2019; Suri et al., 2021). All imaging data were collected and processed by the author. Imaging pre-processing was performed using FMRIB Software Library (FSL) tools (Jenkinson et al., 2012). Details about pre-processing of GMV, CVR, white matter microstructure and WMH scans are described in the HBS protocol paper (Suri et al., 2021) and presented here in detail.

Table 3.3: MRI acquisition parameters for the two MRI-Waves (adapted from the protocol paper (Suri et al., 2021)

MRI: Magnetic resonance imaging, BOLD: Blood oxygenation level dependent, TR: Repetition time, TE: Echo time, TI: Inversion time, DTI: Diffusion tensor imaging, A: Anterior, P: Posterior, FLAIR: Fluid-attenuated inversion recovery, MP-RAGE: Magnetisation Prepared - RApid Gradient Echo, MEMPR: Multi-Echo MPRAGE

MRI	**MRI-Wave 1 3T Verio**	**MRI-Wave 2 3T Prisma**
Duration	April 2012-December	October 2019-May 2023
Head coil	32-channel	64-channel
Respiratory-calibrated BOLD functional MRI (CVR)		
Voxel, mm^3	--	2.4×2.4×2.4
TR/TE, ms	--	800/30
Flip angle, ◦	--	52
Field of view, mm	--	216
Multi-band acceleration factor *N*	--	6
N volumes	--	450
Acquisition time	--	6min 8s
T1		
Sequence	MEMPR	MPRAGE
Voxel, mm^3	1×1×1	1×1×1
TR, ms	2,530	1,900
TE, ms	1.79/3.65/5.51/7.37	3.97
TI, ms	1,380	904
Flip angle, ◦	7	8
Field of view, mm	256	192
Acquisition time	6min 12s	5 min 31 s
DTI		
Voxel, mm^3	2×2×2	2×2×2
TR/TE, ms	8,900/91.2	8,900/91.2
b-value, s/mm^2	1,500	1,500
N volumes (A >> P)	60 + 5*b* = 0 s	60 + 5*b* = 0 s
N volumes (P >> A)	1*b* = 0	1*b* = 0
Field of view, mm	192	192
Acquisition time	9min 56s	10min 5s
FLAIR		
Voxel, mm^3	0.4×0.4×3.0	0.4×0.4×3.0
TR/TE, ms	9,000/73	9,000/73
TI, ms	2,500	2,500
Flip angle, ◦	150	150
Field of view, mm	220	220
Acquisition time	4min14s	4min 14s

3.4.1 Grey matter volume (GMV)

Grey matter is primarily composed of neuronal cell bodies, dendrites, and axon terminals, and plays a critical role in processing and integrating information essential for cognitive functions (Mercadante & Tadi, 2023). Structural MRI, such as T1-weighted sequences acquired at 3T, offers high-resolution anatomical images that enable the quantification of grey matter volume (GMV) across the whole brain and within specific cortical or subcortical regions. T1-weighted MRI generates anatomical contrast based on differences in the longitudinal relaxation time (T1) of various tissue types (Brown et al., 2014; Mitchell & Cohen, 2004). In T1-weighed scan, grey matter typically appears relatively grey while white matter appears brighter, and cerebrospinal fluid appears the darkest. The clear contrast between tissue types enables accurate tissue segmentation and volumetric analysis, making T1-weighted imaging a widely used, non-invasive method for studying brain structure.

In this study, GMV was measured using 3T T1-weighted structural MRI scans collected at both MRI-Waves. Pre-processing of the T1 images was conducted using a rigorous pipeline based on tools from FSL. Initially, all T1-weighted images were defaced using “FSL_DEFACE” to remove facial features and ensure participant anonymity. Gradient distortion correction (intensity inhomogeneities in MRI images caused by imperfections in the scanner hardware or variations in tissue composition) (Doran et al., 2005) was then applied using a custom Python script. This was followed by bias field correction and brain extraction using the “FSL_ANAT”

tool to improve tissue contrast. Due to scanner differences between MRI-Wave 1 and 2, intensity clipping was applied to remove any signal intensities exceeding that of white matter, which commonly arise from bright vascular structures. This step was implemented to improve the accuracy of tissue segmentation. Brain tissue was segmented into grey matter, white matter, and cerebrospinal fluid using "FSL_FAST" (Zhang et al., 2001), which generates partial volume estimates (PVE) to minimise tissue boundary contamination, and the segmentations were visually inspected using FSLeyes. Segmentation of bilateral hippocampus was performed using "FSL_FIRST" based on the patrial volume estimates, and the final segmentations were visually inspected for accuracy (Patenaude et al., 2011). To minimise misclassification during tissue segmentation, white matter hyperintensities (WMHs) regions that are often appearing with signal intensities similar to grey matter on T1-weighted images, were excluded from grey matter volume estimates. Details of the WMHs segmentation are described in the following methodological section.

Although the sample size of 163 is relatively large for CVR studies, it remains underpowered for voxel-wise analyses. Therefore, this thesis focused on *a priori* defined regions to maximise statistical power. The regions included **total grey matter**, and **six key nodes of the default mode network (DMN)** that are known to be first affected in cognitive impairment and dementia (Beason-Held, 2011; Grieder et al., 2018; Pini et al., 2016): **left and right hippocampi, the posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and bilateral temporoparietal junction (TPJ) and precuneus** (***Figure 3.2***). The DMN supports higher-

order cognitive functions and internally directed processes that are disengaged from external stimuli, such as autobiographical memory retrieval, future thinking, and self-referential reflection (Buckner et al., 2008). Converging evidence suggests that DMN, particularly its medial temporal and posterior midline subsystems is disrupted early in Alzheimer's diseases (AD). Structural imaging studies reveal accelerated atrophy in the medial temporal lobe and posterior cingulate cortex even in preclinical stages (Buckner et al., 2005; Neufeld et al., 2022; Ramanoël et al., 2018). Among DMN nodes, the hippocampus is particularly critical to dementia progression. It plays a critical role in the formation and consolidation of episodic memories (Rao et al., 2022), and decline in episodic memory is often the first sign of cognitive deterioration in both normal ageing and AD (Tromp et al., 2015). Multiple neuroimaging studies have showed that hippocampal atrophy is one of the earliest and most reliable biomarkers for AD and mild cognitive impairment (MCI) conversion and is also detectable in healthy elderly with future cognitive decline (Dang et al., 2023; Guo et al., 2014; Perrotin et al., 2015; Van De Mortel et al., 2021; Wu et al., 2021; Zanchi et al., 2017).

ROI masks for the PCC, MPFC, and bilateral TPJ were obtained from a publicly available dataset (https://identifiers.org/neurovault.collection:6262). The precuneus was defined using the Harvard-Oxford Cortical Structural Atlas (Desikan et al., 2006). All masks were first registered from standard space to each participant's T1 space using FSL's linear ("FSL_FLIRT"; (Jenkinson et al., 2002; Jenkinson & Smith, 2001) and nonlinear ("FSL_FNIRT"; (Andersson et al., 2007) registration tools. These masks were then applied to each participant's grey matter

PVE. GMV was extracted using “FSL_STATS”, and all volume measurements were converted from mm^3 to cm^3 for subsequent statistical analyses.

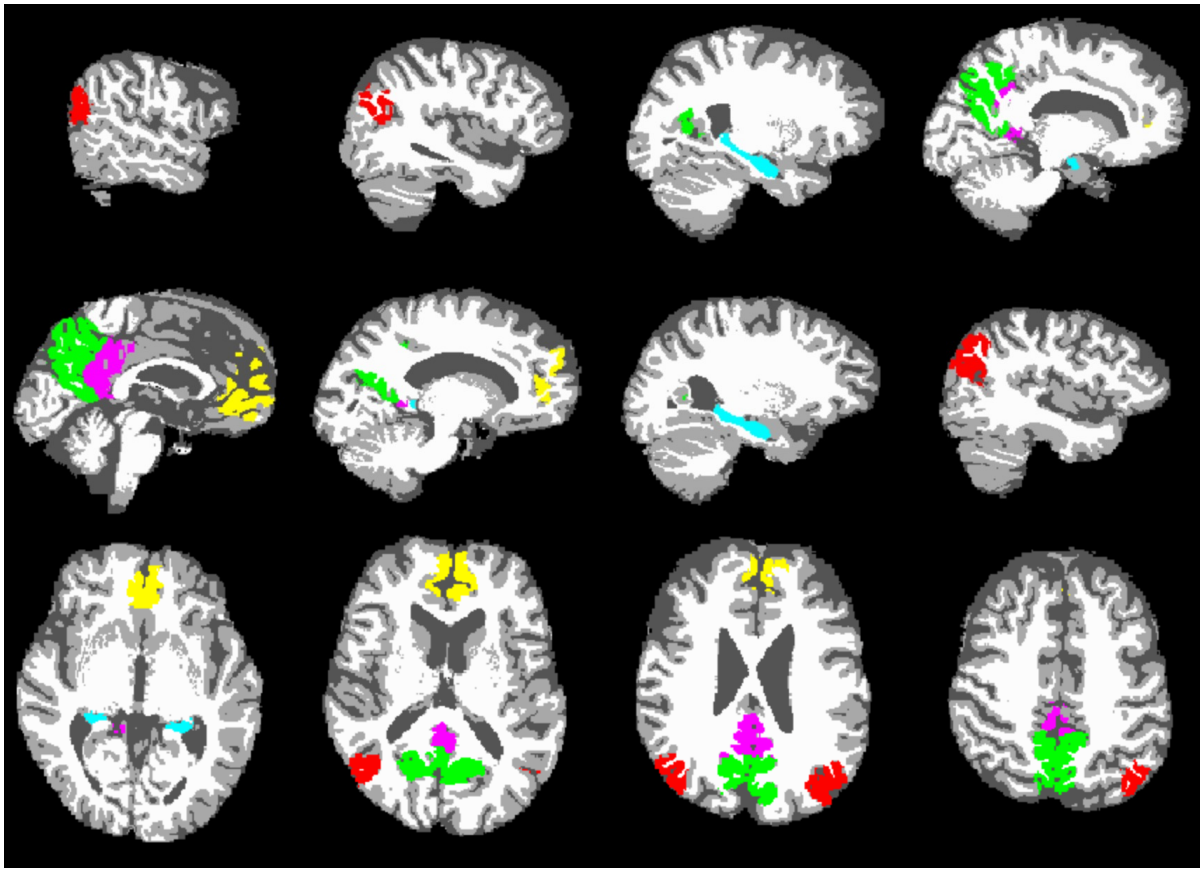


Figure 3.2: Regions of Interest (ROIs) for extracting grey matter volume and cerebrovascular reactivity

Note: Masks are overlaid on the segmented brain of a single participant of the cohort derived from “FSL FAST”. Regions include Medial prefrontal cortex (MPFC; yellow), Posterior cingulate cortex (PCC; purple), Temporoparietal junction (TPJ; red), Precuneus (green), and left and right hippocampi (blue).

3.4.2 Cerebrovascular reactivity (CVR)

BOLD fMRI is a widely used technique to measure brain activity based on changes in blood oxygenation. The BOLD signal arises from differences in the magnetic properties of oxygenated and deoxygenated haemoglobin. As deoxygenated haemoglobin is paramagnetic, it leads to a reduction in the local MR signal intensity (Ogawa et al., 1990). When a specific brain region becomes active in response to a stimulus, it triggers a neurovascular response that increases cerebral blood flow. As a result, vessels deliver more oxygenated blood than is metabolically required. This overcompensation leads to a reduction in local deoxygenated haemoglobin concentration, thereby increasing the MR signal. BOLD fMRI captures these signal fluctuations over time, which provides information about the underlying neural activity across active brain regions.

In this study, we used the principles of BOLD fMRI to measure CVR at MRI-Wave 2. We used hypercapnia challenge where participants were fitted with an anaesthetic face mask through which they inhaled controlled levels of gases. The face mask was connected to a custom-built unidirectional breathing circuit (University of Oxford, parts from Inter-surgical Ltd., UK). Gases were delivered at a rate of 15 L/min via solenoid-controlled flow meters (The Gas Safety Co., UK), which was connected to cylinders of synthetic medical air (BOC Ltd., UK) and mixed air of 5% CO_2 (BOC Ltd., UK), regulated by Gasarc Tech-Master pressure regulators (ESAB, UK). The hypercapnia paradigm consisted of an initial 60 seconds of medical air, followed by two

75-second blocks of 5% CO_2 in medical air, interleaved with 75-second blocks of medical air. This paradigm was extensively piloted and optimised (Suri et al., 2021) and has been shown to produce cerebrovascular responses comparable to longer continuous CO_2 challenges while allowing for minimal participant discomfort, particularly suitable for the older cohort in this study (Liu et al., 2019; Yezhuvath et al., 2009).

Inspired and expired gases were continuously recorded via a gas analyser (ML206, AD Instruments, New Zealand) and PowerLab acquisition system (ADInstruments), which recorded a full respiratory trace. The end-tidal CO_2 ($EtCO_2$, the maximum CO_2 concentration at the end of an exhaled breath, ***Figure 3.3***) was extracted using a customised MATLAB script from the data collected for the respiratory trace (Bulte et al., 2012; Suri et al., 2021). $EtCO_2$ reached a steady state within each CO_2 challenge block, and the baseline after each block remained comparable to the initial baseline (Suri et al., 2021; ***Figure 3.3***). For each participant, the normalised $EtCO_2$ was calculated by subtracting the baseline mean and dividing by the maximum $EtCO_2$.

Raw fMRI data was pre-processed by “FSL_FEAT”, which included removing non-brain tissue by “FSL_BET” (S. M. Smith, 2002), motion correction using MCFLIRT (Jenkinson et al., 2002), gradient distortion correction with an echo-planar imaging (EPI) echo spacing of 0.51 ms and echo time of 30 ms, and unwarping applied in the negative phase-encode (-y) direction to correct susceptibility-induced distortions. Images were spatially smoothed using a Gaussian

kernel with a full-width half-maximum of 4 mm. A temporal high-pass filter (cur-off of 210 s) was applied to remove low-frequency drifts. Voxels exhibiting more than 10% signal loss were excluded.

The normalised $EtCO_2$ then served as regressors in a general linear model to assess how changes in CO_2 were associated with changes in the BOLD signal (Woolrich et al., 2001) CVR was quantified as the percentage change in BOLD signal per unit change in $EtCO_2$ (%BOLD/$\Delta EtCO_2$ mmHg, where $\Delta EtCO_2$ represents the difference between normocapnic levels and the average of the maximum changes during the two hypercapnic blocks). ***Figure 3.4*** shows a CVR image for an example participant.

The mean CVR was extracted from the selected ROIs which included total grey matter and the six key nodes of DMN using “Featquery”. All the masks of the selected regions were derived from each participant's T1-weighted masks and then registered to CVR space to ensure alignment between the regions used for GMV and CVR extraction. This approach enabled direct comparisons between CVR and GMV in the same anatomical regions.

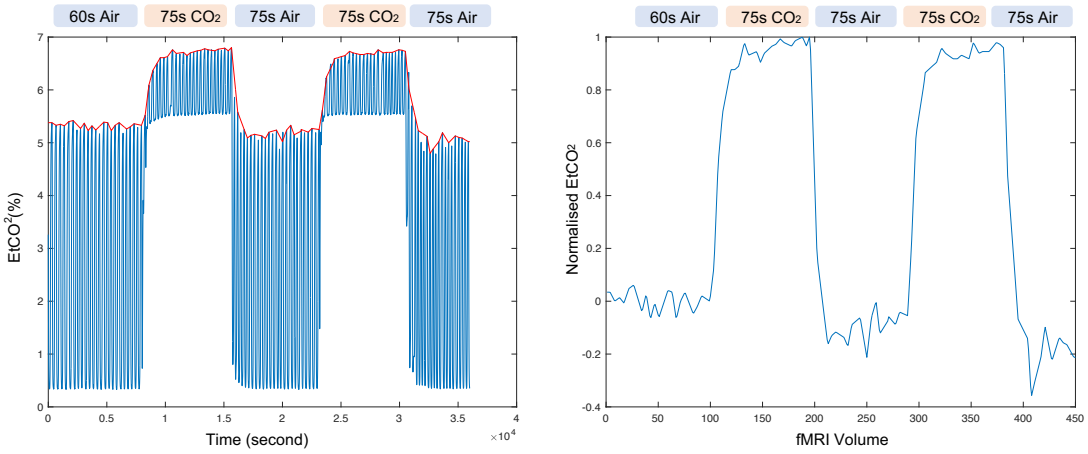


Figure 3.3: End-tidal CO_2 trace and normalised regressor during the hypercapnia challenge of a representative participant

Note: Left: Raw end-tidal CO_2 ($EtCO_2$) trace throughout the hypercapnia challenge. Each blue peak corresponds to a single breath, and the red line represents the detected $EtCO_2$ at the end of expiration. The red trace was resampled at each fMRI repetition time (TR) to align with BOLD data. The breathing paradigm consisted of alternating blocks of medical air (0.04% CO_2) and hypercapnic gas (5% CO_2 in air), with 60 seconds of baseline air followed by two 75-second blocks of CO_2, interleaved with air. Right: The $EtCO_2$ values resampled at each TR and normalised for each participant (by subtracting the baseline and dividing by the maximum value). This trace was used as the explanatory variable in the general linear model to compute CVR.

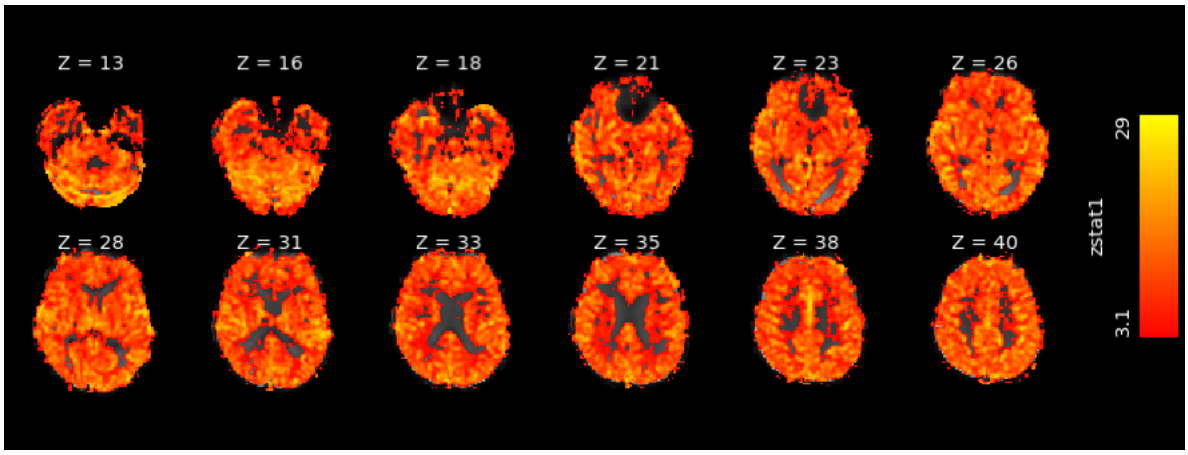


Figure 3.4: Thresholded CVR map showing BOLD signal response to CO_2 challenge in a representative participant.

The maps show excellent signal to noise, with nearly full brain coverage of relative increase in BOLD signal in response to hypercapnia.

To assess tolerability of the CVR scan, participants completed a post-scan questionnaire evaluating discomfort during the scan, including mask-wearing, breathing gases, breathlessness, dizziness, claustrophobia, anxiety, and being inside the scanner. Of the 103/163 participants who completed the questionnaire, we found that overall, the scan was well tolerated, with most participants reporting low discomfort across all domains during the 5% CO_2 inhalation phase (***Figure 3.5***). More than 95% of the participants reported none-to-low levels (<5) of claustrophobia or dizziness. Notably, those who reported higher discomfort during the CVR scan also tended to report elevated discomfort with general MRI-related factors such as claustrophobia and breathlessness. This suggests that intolerance was likely related to pre-existing discomfort with the scanning environment rather than the gas challenge itself.

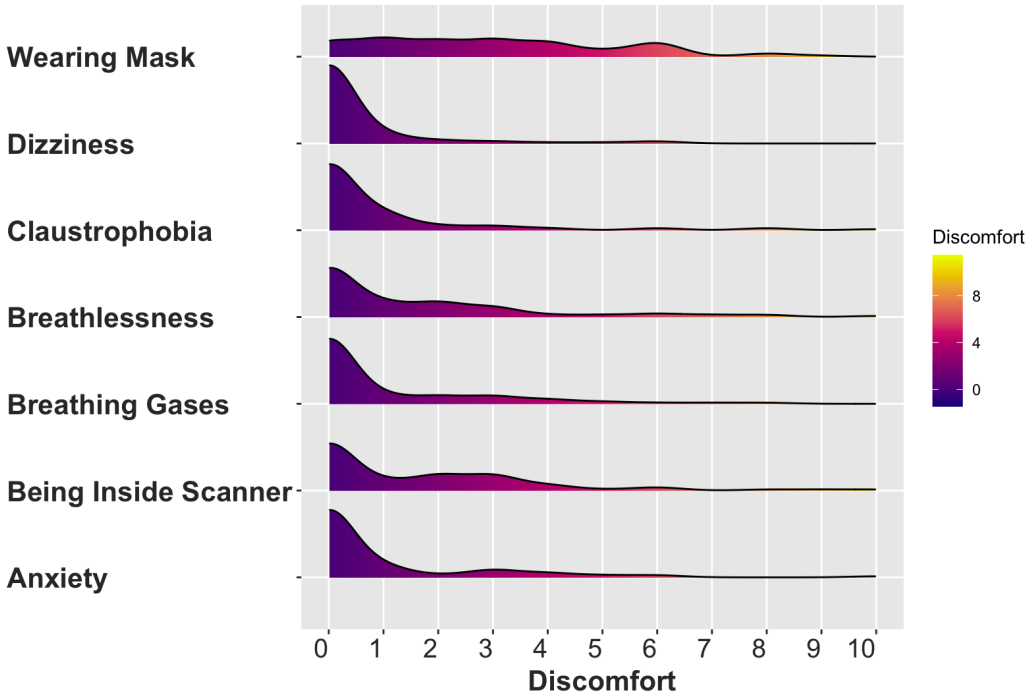


Figure 3.5: Distribution of self-reported discomfort scores across various domains during the CVR scan

Note: The distribution reflects responses from all participants of the Heart and Brain study who completed the self-report questionnaire. Most participants reported low discomfort during the CVR of 5% CO_2 inhalation phase.

3.4.3 White matter (WM) microstructure

White matter (WM) microstructure reflects the integrity of myelinated axonal fibres that facilitate efficient communication between brain regions. Diffusion tensor imaging (DTI) is an MRI technique that measures the directional diffusion of water molecules in tissue. This movement is modelled as a tensor which provides quantitative information about how strong the diffusion is, the degree of anisotropy, and the orientation of diffusion anisotropy. These properties give us valuable information about the structure and integrity of white matter in the brain (Alexander

et al., 2007).

There are four commonly used metrics in WM microstructure analysis: fractional anisotropy (FA, ranging from 0-1), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (L1). FA reflects the degree of directional preference in water molecule diffusion, which indicates the integrity of the axon (Basser & Pierpaoli, 1996). MD measures the overall magnitude of molecular motion independent of tissue directionality (Basser et al., 1994; Pierpaoli et al., 1996). Lower FA and higher MD are commonly used metrics to indicate compromised fibre structure. Two additional DTI metrics, radial diffusivity (RD) and axial diffusivity (L1), provide further insights: RD measures diffusion perpendicular to the primary fibre direction and is associated with demyelination (Song et al., 2002), and L1 quantifies diffusion along the main fibre orientation, offering information on axonal injury or loss (Pierpaoli et al., 2001). All these white matter diffusion metrics together provide a comprehensive profile of WM microstructure and have been widely used to investigate age-related cognitive decline (Madden et al., 2012).

In our study, WM microstructure was assessed by the diffusion metrics derived from DTI scans at both MRI-Wave 1 and 2. These scans were processed with the FMRIB Diffusion Toolbox. Raw diffusion-weighted images were first corrected for susceptibility-induced distortions using FSL_TOPUP. These distortions are spatial misalignment along the phase-encoding direction due to local magnetic inhomogeneities. “FSL_TOPUP” estimates a susceptibility-induced field map by comparing images acquired with opposing phase-encoding directions and applies a

warping correction to unwarp the distortions (Andersson et al., 2003). Next, motion correction and eddy current induced distortion were corrected by “FSL_EDDY”. Eddy currents occur when rapidly switched magnetic field gradients, inducing a secondary magnetic field in the scanner. These residual fields distort the main magnetic field, leading to spatial distortions in the acquired images as well as inaccuracies in estimates of the diffusion metrics (Chan et al., 2014). “FSL_EDDY” corrects diffusion data by integrating signals across multiple diffusion-weighted images, detecting and modelling outliers and distortions to produce reliable datasets for subsequent analysis (Andersson & Sotiropoulos, 2016). Brain extraction was performed with “FSL_BET” (Brown, 2009), and gradient distortion correction was applied using gradient unwarp scripts adapted from the Human Connectome Project pipeline. The pre-processed data were then fitted to the diffusion tensor model using “DTIFIT” (S. M. Smith et al., 2006), which estimates the diffusion tensor at each voxel and generates voxel-wise maps of diffusion metrics. These maps were entered into Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) for the computation of FA, MD, RD and L1.

Region of interests (ROIs) masks were derived from the Johns Hopkins University (JHU) ICBM-DTI 81 white matter atlas (Mori et al., 2008), encompassing 25 tracts for each hemisphere. We selected **four principal white matter tracts** that are related to cognitive decline in dementia: **corpus callosum, fornix, cingulum bundle, and internal capsule** (Jin Thong et al., 2014; Suri et al., 2014). Although these four white matter tracts were selected for their relevance to dementia, they also play critical roles in other clinical conditions, including

mental health and neurodevelopmental disorders such as depression or attention-deficit/hyperactivity disorder (Bracht et al., 2015; Chiang et al., 2015; Henderson et al., 2013). For each tract, masks of individual segments were combined into a single tract mask (e.g., body, genu and splenium of corpus callosum were combined to form a corpus callosum tract; ***Figure 3.6***). The combined mask was then used to extract the values of FA, MD, RD, and L1 from the TBSS-derived skeleton for each participant at each timepoint. Global skeleton values across the entire white matter were also extracted for all four metrics using the mean FA skeleton mask.

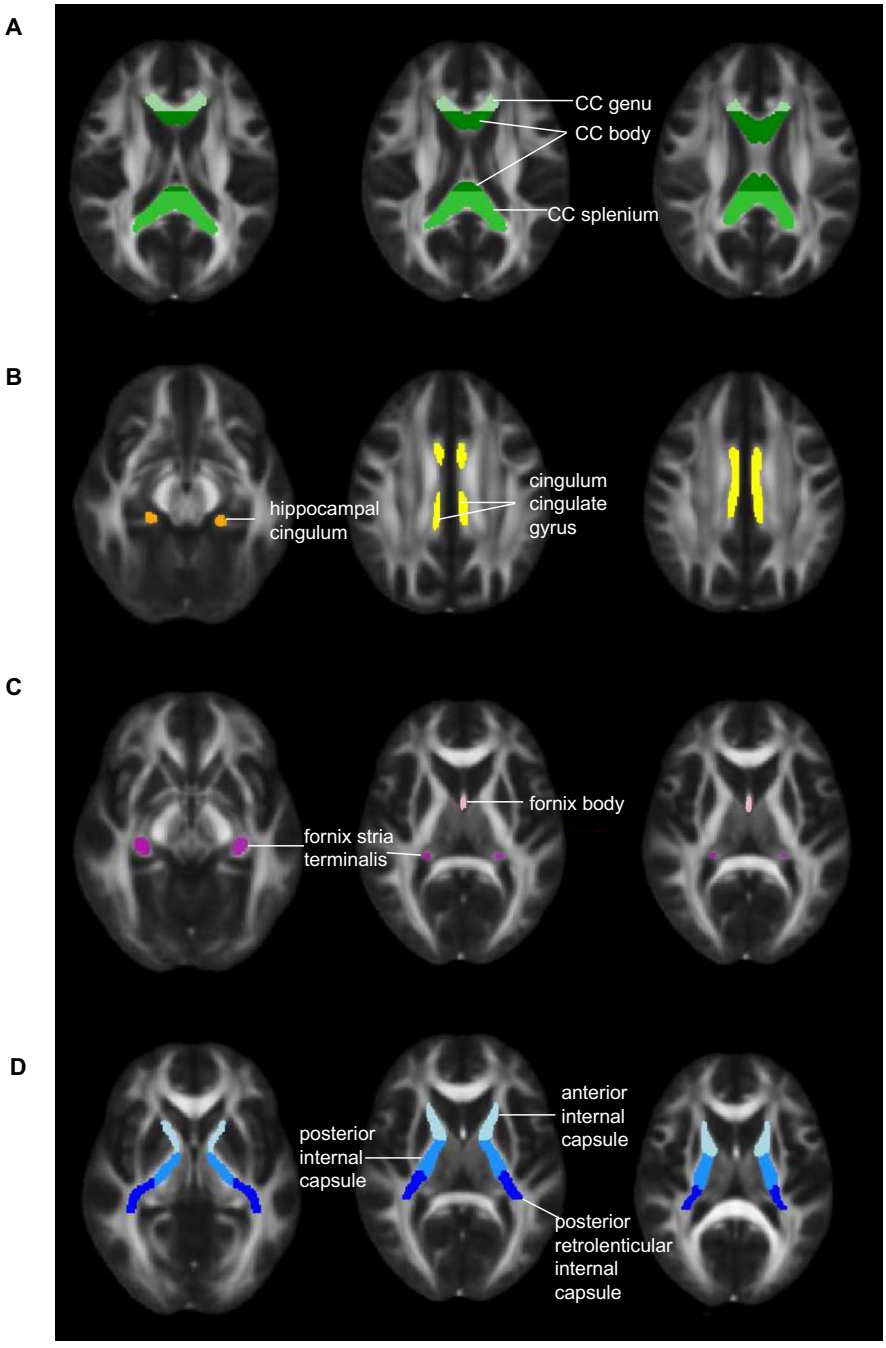


Figure 3.6: Regions of interests for four major white matter tracts

Masks are overlaid FMRIB58_FA image. A: Corpus Callosum: body (dark green), splenium (green), genu (light green). B: Cingulum Bundle: bilateral hippocampal cingulum (orange), bilateral cingulate gyrus (yellow). C: Fornix: bilateral fornix stria terminalis (purple), fornix body (pink). D: Internal Capsule: bilateral anterior (light blue), bilateral posterior (blue), bilateral posterior retrolenticular (dark blue).

3.4.4 White matter hyperintensities (WMHs)

Fluid-Attenuated Inversion Recovery (FLAIR) is an MRI technique designed to improve the visibility of abnormalities in the brain tissue. It works by applying a 180-degree inversion pulse that flips the direction of proton magnetisation. After a long inversion time (TI), the signal from CSF becomes fully suppressed by the time the image is taken. As a result, FLAIR makes it easier to detect tissue abnormalities that have higher water content, such as white matter hyperintensities (WMHs) adjacent to the ventricles and within white matter by cancelling out CSF signals (Hajnal et al., 1992; Saranathan et al., 2017). These WMHs often appear as bright (hyperintense) spots on the images, standing out clearly against the darker background of normal white and grey matter.

In this study, WMHs were quantified from T2-weighted FLAIR scans acquired at both MRI-Wave 1 and MRI-Wave 2. Pre-processing of FLAIR images was performed using a customised pipeline. Firstly, T1-weighted images were linearly registered to native FLAIR space using “FSL_FLIRT” (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Brain extraction was then applied using masks derived from the co-registered T1 scans. Bias field correction was performed using “FAST”. White matter masks were generated from T1 segmentations accounting for partial volume effects, and then registered to FLAIR space to constrain the WMH classification. Finally, the registered, white matter masked FLAIR images were

transformed into standard MNI152 space. Then, WMH probability maps were generated using FSL_BIANCA (Brain Intensity Abnormality Classification Algorithm; Griffanti et al., 2016), which employs a supervised k-nearest-neighbour algorithm trained using manually labelled examples (Griffanti et al., 2016). The outputs were visually inspected in FSLeyes. To reduce false positives, a threshold of 0.9 was applied to the probability maps, such that only voxels with ≥90% probability of being WMH were included (see ***Figure 3.7)***.

The binarised maps were then used to calculate total WMH volume, which was expressed as a percentage of total brain volume (sum of grey matter, white matter, and CSF volumes derived from “FSL_FAST” tissue segmentation). To reduce skewness and ensure normalised distribution for statistical analyses, the WMH% values were log-transformed at both waves separately (***Figure 3.8***), as has been done before in this cohort (Hobden et al., 2025).

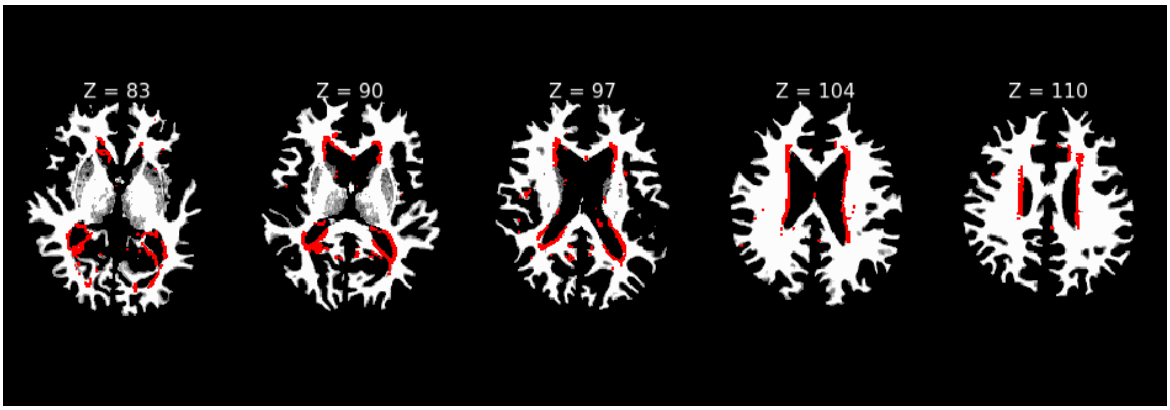


Figure 3.7: WMH mask overlaid on white matter volume in a representative participant

Note: Voxels with WMH probability greater than 90% were binarised to create a WMH mask, which is shown in red.

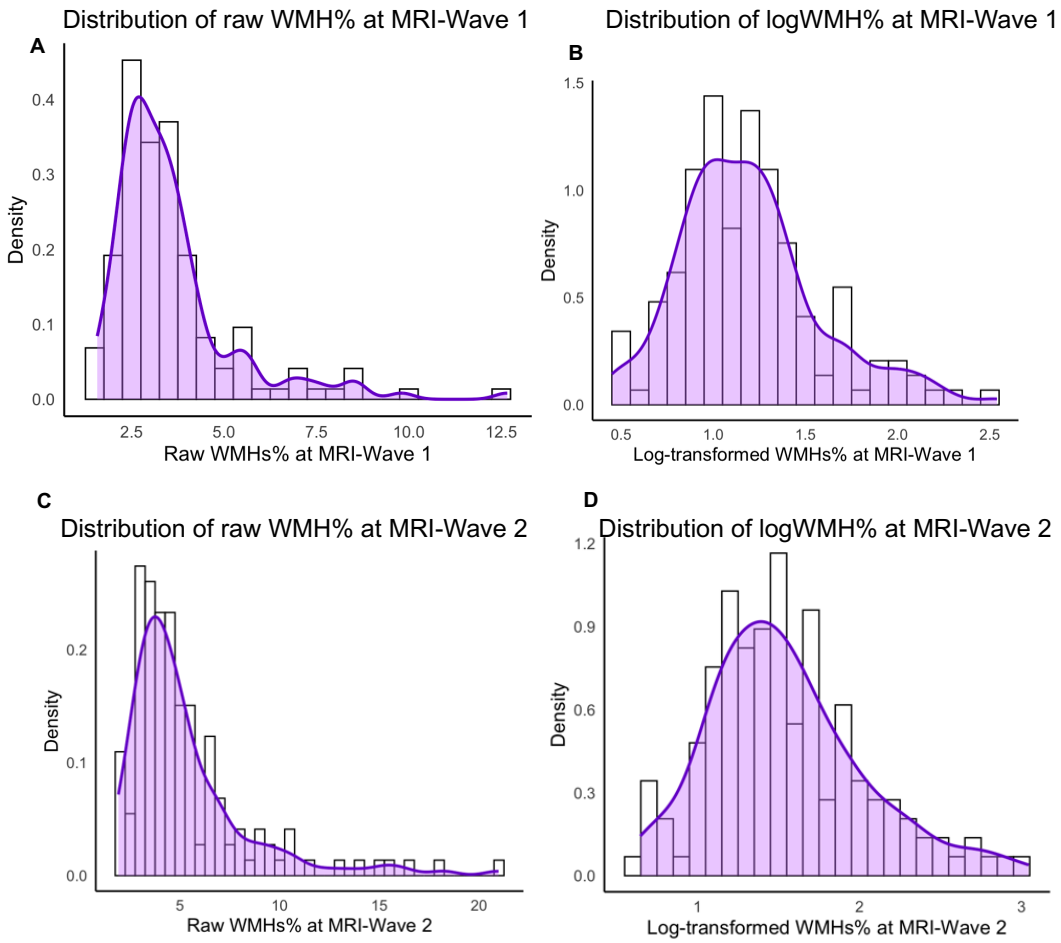


Figure 3.8: Distribution of white matter hyperintensity values before and after log transformation to reduce skewness

3.4.5 Longitudinal change in brain structure

To account for inter-scanner variability between MRI-Waves 1 and 2, we standardised (z-scored) the GMV and WM diffusion metrics values within each wave using the R “scale” function to ensure that the measures were comparable between the waves. Longitudinal changes in GMV/WM diffusion metrics were calculated as the difference between standardised values from MRI-Wave 2 and MRI-Wave 1 (e.g., ΔGMV = standardised GMV at MRI-Wave 2 - standardised GMV at MRI-Wave 1; ΔFA = standardised FA at MRI-Wave 2 - standardised FA at MRI-Wave 1 and similarly for MD, RD, L1). Since we are using standardised values, the changes do not reflect absolute change at the individual level but rather the relative amount of change for an individual compared to others within the cohort. This approach enables assessment of relative change (i.e., whether a person underwent more/less change in GMV relative to other participants) but does not allow inferences about absolute volumetric change (i.e., whether the volume of a person increased/decreased from MRI-Wave 1 to 2). It is reasonable to assume, based on extensive literature, that in the age range of 70 to 80 years, hippocampal volume and FA within our selected tracts are more likely to decrease than increase (J. Barnes et al., 2009; Damoiseaux et al., 2009), while diffusivity (MD, RD, L1) is more likely to increase (Madden et al., 2012; Sullivan & Pfefferbaum, 2006).

Thus, for ***GMV and FA***, we can reasonably conclude that ***more negative*** standardised Δ

values reflect ***more change*** (i.e., more atrophy and reduced WM microstructure) relative to the rest of the group. In contrast, for **MD, RD, L1, *more positive*** standardised Δ values reflect ***more change*** (i.e., reduced WM microstructure) relative to the rest of the group (see ***Figure 3.9*** for distributions of Δ values across all dependent variable measures).

We did not standardise WMHs values at each MRI wave because we have previously shown that the performance of the FSL_BIANCA tool is consistent over the two scanners (as described in the cohort protocol paper (Suri et al., 2021). Longitudinal change in WMHs volumes between waves was therefore calculated as the absolute difference in log-transformed %WMH values (ΔWMH = MRI-Wave 2 logWMH% - MRI-Wave 1 logWMH%), i.e., positive values represent an increase in WMH volumes from MRI-Wave 1 to 2.

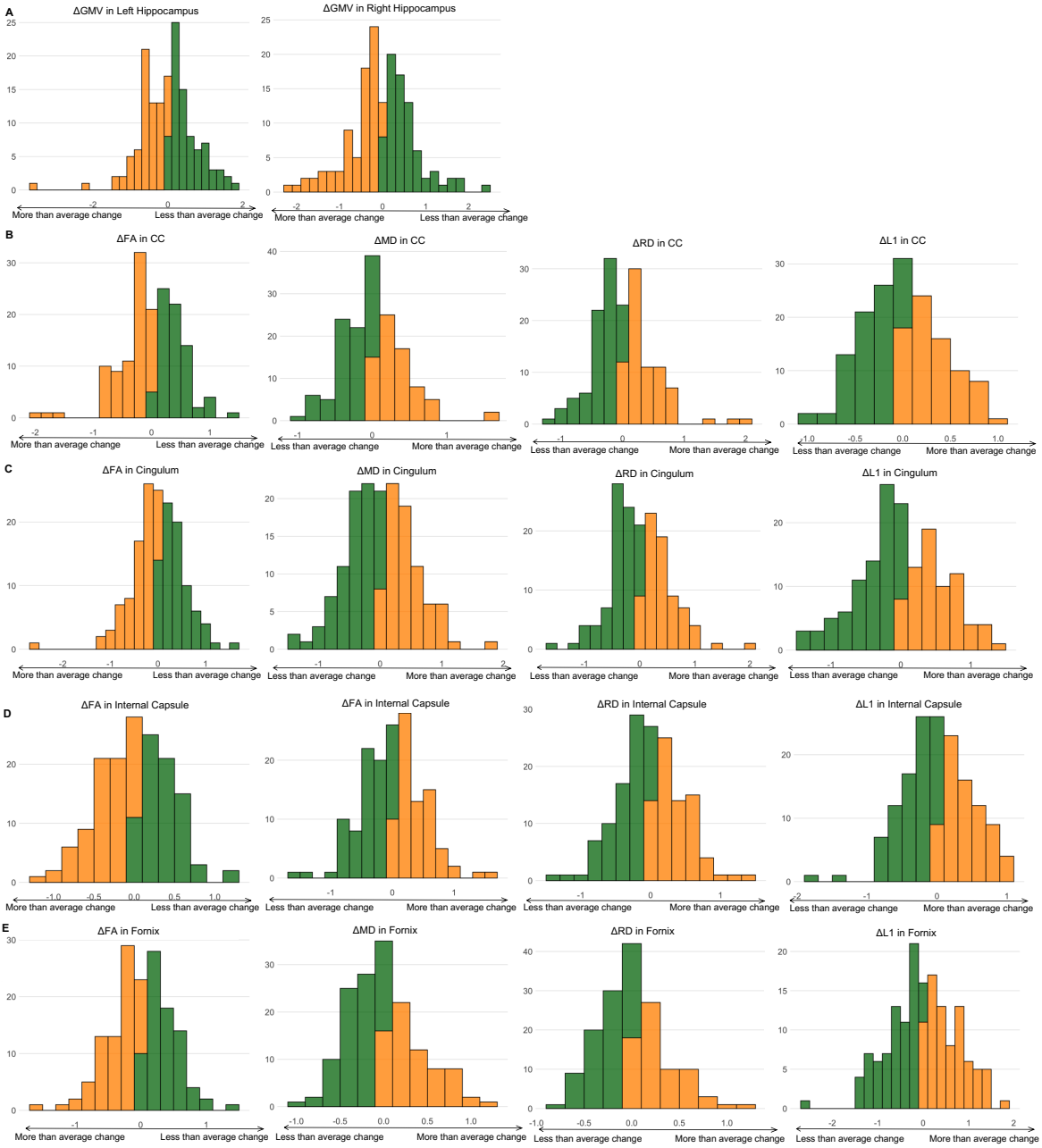


Figure 3.9: Distribution of standardised changes in grey matter volume and white matter diffusion metrics between MRI-Wave 1 and 2

Y axis represents number of participants. X axis represents relative change in (A) hippocampal volume and white matter diffusion metrics within the (B) corpus callosum (C) cingulum (D) internal capsule and (E) fornix between MRI-Wave 1 and MRI-Wave 2. Orange represents potentially relatively greater degeneration in the MRI measures including more negative standardised ΔFA and ΔGMV values relative to others in the cohort, and more positive standardised ΔMD, ΔRD, and ΔL1. Green represents potentially relatively less degeneration in the MRI measures including more positive standardised Δ values for FA and GMV, and more negative standardised Δ values for MD, RD, and L1. CC = Corpus Callosum, FA = fractional anisotropy, GMV = grey matter volume, L1 = axial diffusivity, MD = mean diffusivity, RD = radial diffusivity.

3.5 Cognitive Measures

3.5.1 Cognitive test battery

Participants completed a battery of cognitive tests on the day of the MRI scan at both MRI-Waves (described in ***Table 3.4***). These cognitive tests are widely used in studies investigating neurodegenerative conditions, including Alzheimer's disease, as they reliably capture impairments across key cognitive domains (Filippini et al., 2014).

Table 3.4: Description of cognitive tests

Tests marked with an asterisk (*) indicate that higher scores reflect poorer performance (e.g., RCF forgetting score, TMT completion time). As discussed below, the cognitive domain scores that included these tests were reversed in sign so that higher values consistently represent better cognitive performance across all cognitive domains.

Cognitive Test	**Task Description**
Trail Making Test* (Tombaugh, 2004)	TMT-A: Time taken to connect sequentially numbered circles in order quickly and accurately (seconds) TBT-B: Time taken to alternately connect numbered and lettered circles (1-A-2-B-3-C) quickly and accurately (seconds)
Hopkins Verbal Learning Test Revised (HVLT-R) (Brandt, 1991)	Immediate recall of word list (HVLT-IR), recall after a delay (HVLT-DR), and recognition discrimination (HVLT-RDI)
Digit Span (DS) (Wechsler, 2008)	Recall digit sequences in original order (DS-forward), in reverse order (DS-backward), and in ascending numerical order (DS-sequencing).
Digit Coding (DCOD) (Wechsler, 2008)	Quickly match and transcribe symbols associated with digits
Category Fluency (FLU_C) (Mioshi et al., 2006)	Generate as many names of a pre-defined categorify as possible in 1 minute (here, the category was animals)
Letter Fluency (FLU_L) (Mioshi et al., 2006)	Generate as many words as possible beginning with a specific letter in 1 minute (here, the letter F)
Rey Complex Figure * (Jerskey & Meyers, 2011)	Copy a complex figure then reproduce from memory immediately (RCF-IF) and after a delay (RCF-DF). Here we calculated scores representing the degree of forgetting
Boston Naming Test (BNT) (Kaplan et al., 1983)	Name visually presented objects shown as black-and-white line drawings
Test of Premorbid Functioning (TOPF) (Wechsler, 2011)	Read out words to estimate premorbid intellectual function that can be calculated from the raw score, adjusted for sex and years of education

3.5.2 Principal component analysis (PCA)

To reduce dimensionality and group related cognitive measures across the 15 sub-scores, we performed a principal component analysis (PCA) with oblimin rotation (Brown, 2009; Jackson, 2005). This method was chosen to allow for potential correlations among cognitive domains. We examined the scree plot that displayed the eigenvalues of each component in descending order to determine the optimal number of components to retain. Specifically, we identified the point at which the slope of the curve levels off (i.e., the “elbow” point, Cattell, 1966; Hayton et al., 2004; Springer, 2002). The scree plot indicated a potential elbow at five components (***Figure 3.10***). However, further inspection of this factor structure indicated that the Test of Premorbid Functioning loaded similarly across two principal components, and Digit Span scores loaded onto different components when we kept five components (***Appendix Figure 3.1A***), which reduced the clarity of domain interpretation. To improve interpretability of the factor structure, an additional component was retained beyond the elbow point, which solved the cross-loading and allowed each test to load predominantly onto a single cognitive domain (***Appendix Figure 3.1B***). As a result, we identified **six cognitive domains: episodic memory, visuospatial memory, executive function, working memory, fluency, and lexical retrieval.**

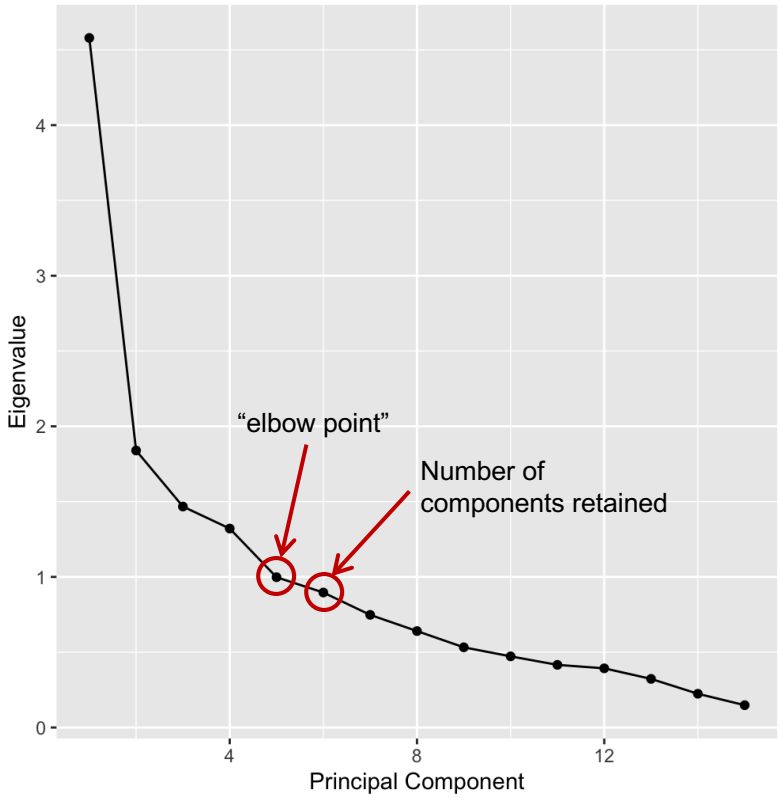


Figure 3.10: Scree plot showing eigenvalues for principal component analysis of *cognitive test scores*

Note: Although the elbow suggested five components, six were retained to improve interpretability and reduce cross-loading.

To derive composite cognitive domain scores, we applied a loading threshold based on the absolute value greater than 0.4 to the normalised PCA loadings (see ***Figure 3.11*** for original loading of each cognitive test score, and ***Table 3.5*** for loading of cognitive test score included to compute cognitive domain score). This ensured that only tests with meaningful contributions to the cognitive domain were included. The selected loadings were then used as weights to compute cognitive domain scores. Specifically, for each cognitive domain, the raw scores of the selected cognitive tests were multiplied by their corresponding loadings and summed to

produce a weighted composite score. This approach ensured that the cognitive indices reflected the most representative tests for each domain while maintaining interpretability on the original measurement scale. We reversed the signs for the executive function and visuospatial memory factors in order to maintain consistency in interpretation with other domains such that **higher factor scores indicate better performance across all domains.**

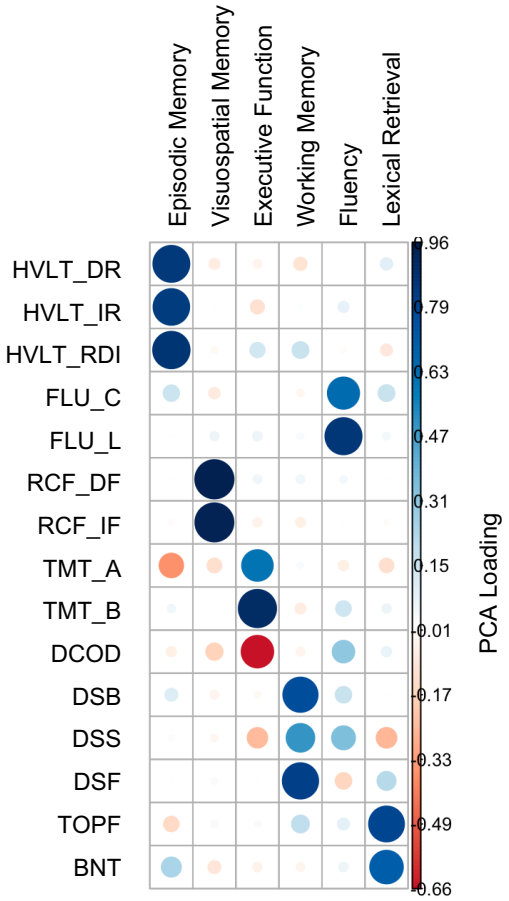


Figure 3.11: PCA loadings of cognitive test scores across six cognitive domains

Note: This figure illustrates the raw principal component loadings of individual cognitive test scores onto six derived cognitive domains. Blue indicates positive loadings, and red indicates negative loadings. Abbreviations are explained in table above.

Table 3.5: Factor loadings for each cognitive domain in PCA

** Scores for visuospatial memory and executive function were reversed in the analysis, so higher values indicate better cognitive performance, consistent with other domains.*

Cognitive Domain	Tests included (Normalised factor loadings)
Episodic Memory	HVLT Delayed Recall (0.848), HVLT Immediate Recall (0.832), HVLT Recognition (0.868)
Visuospatial Memory*	RCF Immediate Forgetting Score (0.946), RCF Delayed Forgetting Score (0.956)
Executive Function*	TMT-A second (0.907), TMT-B second (0.618), Digit Coding (-0.656)
Working Memory	Digit Span Forward (0.817), Digit Span Backward (0.768), Digit Span Sequence (0.506)
Fluency	Category Fluency (0.641), Letter Fluency (0.854)
Lexical Retrieval	Boston Naming Test (0.698), TOPF Full-scale IQ (0.798)

3.5.3 Longitudinal cognitive outcomes

To assess longitudinal changes in cognitive function, we examined domain scores across both MRI waves. PCA was conducted separately at MRI-Wave 1 and MRI-Wave 2 to inspect the stability of the factor structure over time. The normalised component loadings for the cognitive test scores were found to be highly consistent across waves, which indicated that the cognitive loading constructs were comparable across waves. Therefore, the factor loadings derived from the recent MRI-Wave 2 were selected as the reference structure and applied uniformly to compute cognitive domain scores at both waves. This method was previously applied in other related research (Kimura et al., 2023), which ensured consistency in the weighting of each test within its respective cognitive domain. Change scores (Δ Cognition) for each domain were then

calculated by subtracting the baseline (MRI-Wave 1) domain score from the follow-up (MRI-Wave 2) domain score (e.g., Δ Episodic memory = Episodic memory at MRI-Wave 2 − Episodic memory at MRI-Wave 1). As cognitive performance typically declines with age, **more negative delta values** (MRI-Wave 2 minus MRI-Wave 1) in the cognitive domain scores **indicate greater cognitive decline over time**.

3.5.4 Statistical analysis

All statistical analyses were conducted in RStudio (version 4.3.0). Prior to hypothesis testing using regression models, the Shapiro-Wilk test was used to assess the model residuals to satisfy the assumption of normality for linear regression models (Shapiro & Wilk, 1965). Outliers were identified and excluded based on the criterion that observations with an absolute deviation from the median exceeding six times the median absolute deviation were removed. Analyses were performed using complete case data. Participants with missing values in any variables included in a given model were excluded from that specific analysis. Detailed statistical models are described in each chapter of the thesis.

3.6 Summary

Chapter 3 described the measures used in this thesis as described in summary ***Table 3.6***.

Table 3.6: Summary of measures in the Heart and Brain study

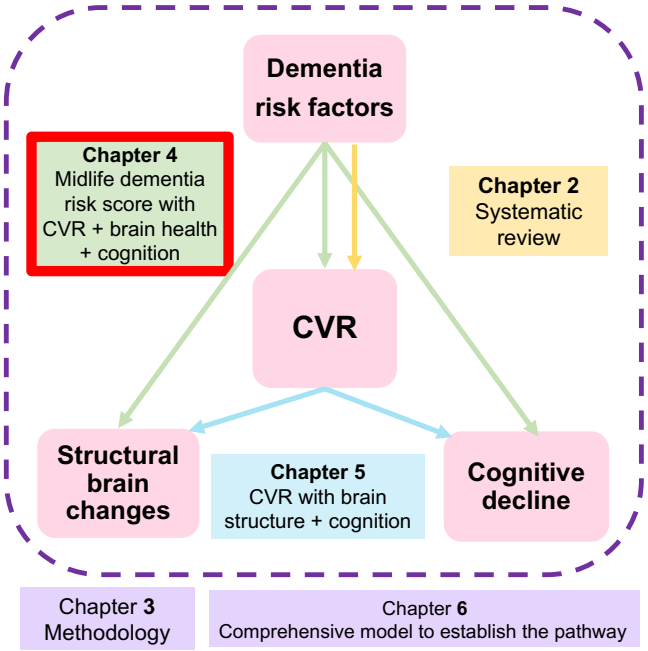
The variables are colour coded by modality: green= GM = Grey Matter, pink = White Matter microstructure, yellow = WMH = White Matter Hyperintensity, grey = cognition; blue = CVR = Cerebrovascular Reactivity, DMN = Default Mode Network, FA = Fractional Anisotropy, MD = Mean Diffusivity, RD = Radial Diffusivity, L1 = Axial Diffusivity, UKBDRS = UK Biobank Dementia Risk Score, Δ = Change between Wave 2 and Wave 1, HVLT-R = Hopkins Verbal Learning Test Reversed, FLU_C = Category Fluency, FLU_L = Letter Fluency, RCF = Rey Complex Figure, TMT = Trail Making Test Part, DCOC = Digit Coding, TOPF = Test of Premorbid Functioning, BNT = Boston Naming Test.

Measure	Description	Units or interpretation
UKBDRS	UK Biobank Dementia Risk Score based on 10 midlife risk factors	logUKBDRS, higher score = higher dementia risk
GM	Grey matter volume in whole brain and 6 DMN ROIs	cm^3
ΔGM	Change in grey matter volume (MRI-Wave2 - MRI-Wave1)	more negative Δ = more atrophy
CVR	Cerebrovascular reactivity in whole brain and 6 DMN ROIs	%BOLD/mmHg
FA	Fractional anisotropy in 4 white matter tracts and whole brain	Unitless, ranging from 0 (lower structural integrity) to 1
ΔFA	Change in FA (MRI-Wave2 - MRI-Wave1)	more negative Δ = more degeneration
MD	Mean diffusivity in 4 white matter tracts and whole brain	mm^2/s
ΔMD	Change in MD (MRI-Wave2 - MRI-Wave1)	more positive Δ = more degeneration
RD	Radial diffusivity in 4 white matter tracts and whole brain	mm^2/s
ΔRD	Change in RD (MRI-Wave2 - MRI-Wave1)	more positive Δ = more degeneration)
L1	Axial diffusivity in 4 white matter tracts and whole brain	mm^2/s
ΔL1	Change in L1(MRI-Wave2 - MRI-Wave1)	more positive Δ= more degeneration
WMH	White matter hyperintensity volume	Log-transformed % of total brain

		volume
ΔWMH	Change in WMH (MRI-Wave2 - MRI-Wave1)	more positive ΔlogWMH% = more increase
Episodic Memory	PCA-derived score from the HVLT-R test	higher score = better performance
ΔEpisodic Memory	Change in episodic memory (MRI-Wave2 - MRI-Wave1)	more negative Δ= more decrease
Working Memory	PCA-derived score from Digit Span tests	higher score = better performance
ΔWorking Memory	Change in working memory (MRI-Wave2 - MRI-Wave1)	more negative Δ= more decrease
Visuospatial Memory	PCA-derived score from the RCF test	higher score = better performance
ΔVisuospatial Memory	Change in visuospatial memory (MRI-Wave2 - MRI-Wave1)	more negative Δ= more decrease
Executive Function	PCA-derived score from DCOD, TMT (A&B)	higher score = better performance
ΔExecutive Function	Change in executive function (MRI-Wave2 - MRI-Wave1)	more negative Δ= more decrease
Fluency	PCA-derived score from FLU_C and FLU_L	higher score = better performance
ΔFluency	Change in fluency (MRI-Wave2 - MRI-Wave1)	more negative Δ= more decrease
Lexical Retrieval	PCA-derived score from TOPF and BNT	higher score = better performance
ΔLexical Retrieval	Change in lexical retrieval (MRI-Wave2 - MRI-Wave1)	more negative Δ= more decrease

Chapter 4: Associations between midlife dementia risk and later-life brain vascular and structural health and cognitive decline

This chapter examines how the UK Biobank Dementia Risk Score (UKBDRS), a composite measure of midlife dementia risk, relates to CVR, especially in regions relevant to cognitive function. As discussed in **Chapter 3**, the UKBDRS is a validated score that predicts risk for dementia, and combines a range of midlife dementia risk factors, including psychosocial and behavioural factors that are often under-studied. In addition to assessing the association between UKBDRS and CVR, we also investigate the association of this score with later-life brain structural health and cognitive decline. A modified version of this chapter, in combination with Chapter 6, has been prepared as a manuscript entitled "The role of cerebrovascular reactivity in the pathway from midlife dementia risk to cognitive decline" (***Wang et al., in submission***).



4.1 Introduction

4.1.1 The importance of targeting midlife for dementia prevention

As discussed in earlier chapters, there is growing evidence that lifestyle modifications can help lower the risk of developing dementia (Livingston et al., 2020, 2024). Midlife represents a critical window for dementia prevention, as it is the period when modifiable risk factors such as hypertension, obesity, and type 2 diabetes commonly emerge (Kivipelto et al., 2018; Livingston et al., 2020, 2024). While the definition of midlife varies from study to study, for the purposes of this thesis we define midlife as ranging from 40 to 65 years of age. These factors also feature prominently in cardiovascular health assessments and have been linked to accelerated cognitive decline and greater dementia risk (Gardener et al., 2016; Sabia et al., 2019; Samieri et al., 2018). Therefore, midlife offers a unique opportunity to identify individuals at higher risk of dementia and implement early intervention strategies. To inform early prevention, it is essential to understand how dementia risk contributes to the underlying pathological processes that lead to cognitive decline and dementia before the onset of clinical symptoms.

4.1.2 Midlife dementia risk score: UKBDRS

While individual risk factors offer valuable insight into the development of dementia, they often

occur together and interact in complex ways. To better capture the cumulative effect of multiple exposures, several composite dementia risk scores have been developed by combining multiple risk factors. For example, the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score is one of the most widely used tools. CAIDE was developed with the data from the Finnish population of participants aged 39-64 years. This score incorporates age, education level, systolic blood pressure, body mass index, total cholesterol levels, and physical activity (Kivipelto et al., 2006). The CAIDE score has demonstrated robust predictive validity for dementia risk up to 20 years in advance (Exalto et al., 2014; Salinas-Contreras et al., 2020). Additionally, the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) offers another comprehensive approach to dementia risk assessment. This risk score is based on both protective and additional modifiable risk factors other than CAIDE, including depression, smoking, cognitive stimulating activities, physical activity (Anstey et al., 2014). Compared to CAIDE that is useful for midlife, the ANU-ADRI was developed to predict dementia in older cohorts (i.e., older than 65 years old; Anstey et al., 2014), and can also predict the risk of progression from cognitive normal to MCI or cognitive decline in ageing (Andrews et al., 2017; Hall et al., 2024). These risk scores provide scalable, evidence-based tools to estimate dementia risk for individual, which helps identify people at risk for preventive interventions.

While CAIDE and ANU-ADRI both incorporate several well-established dementia risk factors, the recently developed UK Biobank Dementia Risk Score (UKBDRS) extends these models

by including additional psychosocial and behavioural factors such as type 2 diabetes, depression and socioeconomic deprivation (Anatürk et al., 2023). Many of these factors have been individually associated with increased dementia risk. For example, diabetes mellitus has been linked to a 1.5- to 2.5-fold increased risk of developing dementia and is also associated with accelerated cognitive decline (Barbiellini Amidei et al., 2021; Ninomiya, 2014; Xue et al., 2019). Additionally, a systematic review revealed that depression is a significant risk factor for dementia (Almeida et al., 2017; Prince et al., 2015). With integration of the factors that are underrepresented in other risk scores, but are modifiable and socially relevant, the UKBDRS may enhance its ability to capture a comprehensive risk profile, identify individuals at high risk of dementia, and support more accessible lifestyle-based interventions to reduce risk from midlife. More importantly, the UKBDRS was developed using UK Biobank data and has been externally validated in the Whitehall II cohort (Anatürk et al., 2023), which is the same cohort used in this thesis. In addition, the UKBDRS has also demonstrated more predictive accuracy for dementia prevalence compared to other scores like the CAIDE and ANU-ADRI within UK-based cohorts, including within the cohort used in this thesis (Anatürk et al., 2023). Based on this we opted to use the UKBDRS to encapsulate midlife risk for dementia.

4.1.3 Dementia risk scores and brain structure and vascular health

Although dementia risk scores were developed to estimate future dementia risk, emerging evidence suggests that they may also be associated with preclinical markers of

neurodegeneration and brain ageing. Several structural MRI biomarkers are known to precede the clinical onset of dementia by many years and offer potential for early detection of brain vulnerability. As discussed in **Chapter 1**, grey matter atrophy, particularly in the hippocampus and regions within the default mode network (DMN), (Buckner et al., 2005, 2008; Dang et al., 2023; Hafkemeijer et al., 2014; Neufeld et al., 2022; Pini et al., 2016; Van De Mortel et al., 2021; Wu et al., 2021), white matter microstructural degeneration (Bergamino et al., 2021; Gold et al., 2012; Kantarci et al., 2014; Peter et al., 2025; Power et al., 2019), and white matter hyperintensities (WMHs) (Chutinet & Rost, 2014; D'arbeloff et al., 2019; Debette & Markus, 2010; Hu et al., 2021) are all consistently associated with increased dementia risk and cognitive decline.

Several studies have demonstrated that the commonly used dementia risk scores such as CAIDE and ANU-ADRI are associated with these neuroimaging biomarkers. For example, in cognitively healthy adults, higher CAIDE scores have been linked to lower grey matter volume (GMV) in the temporal, occipital, and ventral visual cortices, as well as faster longitudinal grey matter atrophy in posterior parietal and occipital cortex (Xulin Liu et al., 2021). Higher CAIDE scores were also related to reduced total grey matter and hippocampal volume, and lower cortical thickness (Stephen et al., 2017, 2021). CAIDE can also predict atrophy in medial temporal lobe up to 30-year follow-up period (Vuorinen et al., 2015). Similarly, higher ANU-ADRI scores are associated with lower cortical grey matter, particularly in DMN regions (Cherbuin et al., 2019). CAIDE scores have also been associated with more severe WMHs,

greater progression of both periventricular and deep WMHs up to 20 years from midlife (Low et al., 2022; Vuorinen et al., 2015), the presence of cerebral infarctions (Hooshmand et al., 2018), as well as increased small vessel disease burden, including microbleeds and lacunes (Low et al., 2022). These findings suggest that composite dementia risk scores can capture early brain structural and vascular changes associated with neurodegeneration. However, to our knowledge, no study has yet investigated how the UKBDRS relates to these neuroimaging biomarkers. Moreover, we know very little about the association between composite dementia risk scores and white matter microstructure or CVR.

4.1.4: Dementia risk score in relation to cognitive performance

Dementia risk scores can not only predict the likelihood of developing dementia in later life but have also been shown to be associated with cognitive performance across multiple domains. For example, higher CAIDE scores have been associated with poorer global cognition (as measured by the Montreal Cognitive Assessment) and reduced verbal fluency in cognitively healthy individuals (Tolea et al., 2021), as well as with lower performance in episodic and working memory, language, attention, processing speed, executive function, and visuospatial abilities among those with all types of dementia. Similarly, Ecay-Torres et al. (2018) reported associations between lower CAIDE scores and worse executive function, visual perception, and constructional abilities in cognitively normal older adults. Furthermore, it was suggested that higher CAIDE scores also predicted slower processing speed in the cognitive normal

individuals (Stephen et al., 2017). These findings suggest that dementia risk scores may capture early cognitive changes in the prodromal phase. However, to our knowledge, the predictive validity of the UKBDRS for specific cognitive outcomes and longitudinal cognitive decline in later life has not yet been established.

4.1.5 Study aims and hypotheses

To address these research gaps, this chapter aims to examine the long-term associations between midlife dementia risk, as measured by the UKBDRS, and key neuroimaging and cognitive outcomes known to be associated with dementia that were assessed in later life. We focus on four key domains of brain health as discussed above: CVR, GMV, white matter (WM) microstructure, and white matter hyperintensities (WMHs). In addition, to assess whether the UKBDRS can predict domain-specific cognitive decline during the prodromal phase of dementia in a healthy ageing population, we also examine its associations with cognitive performance across six domains, including episodic memory, executive function, visuospatial memory, working memory, fluency and lexical retrieval. We further investigate whether midlife dementia risk is associated with longitudinal changes in GMV, WM microstructure, WMH burden, and cognitive decline, measured across the two imaging time points of the study (MRI-Wave 1 and MRI-Wave 2, approximately nine years apart).

We hypothesise that individuals with higher midlife UKBDRS scores will have lower CVR, reduced GMV, poorer WM microstructural integrity, greater WMHs volume, and poorer cognitive performance in older age. Regarding longitudinal change, we expect that those with higher midlife dementia risk will show more pronounced reductions in GMV and WM microstructure, a greater increase in WMHs burden, and faster declines in cognitive performance over time.

4.2. Methods

Full details of the study design and MRI pre-processing pipeline are available in **Chapter 3** with a timeline presented in ***Figure 3.1***. Here, we briefly summarise the key steps relevant to this chapter.

4.2.1 Timeline and outcomes

This study included 163 participants from the Heart and Brain Study, who had midlife risk variables collected during Whitehall II Study Waves 3 to 9 (1991-2009), and a comprehensive MRI protocol at two timepoints, referred to as MRI-Wave 1 (baseline, 2012-2016) and MRI-Wave 2 (follow-up, 2019-2023). At MRI-Wave 1, imaging included a T1-weighted structural scan to assess GMV, diffusion tensor imaging to evaluate WM microstructure, and a T2-

weighted FLAIR scan to quantify WMHs. These same imaging scans were repeated at MRI-Wave 2. In addition, participants underwent a functional BOLD fMRI scan to measure CVR, using a 5% carbon dioxide inhalation challenge to elicit vascular response at MRI-Wave 2. Cognitive performance was assessed at both timepoints using a comprehensive battery of ten neuropsychological tests, which were grouped into six cognitive domains using Principal component analysis (PCA).

Dementia risk score: We calculated **the UKBDRS** for all participants based on the midlife measures from WH-Wave 5. We log-transformed the UKBDRS to correct for positive skewness and normalise the distribution for statistical analysis (**Chapter 3, *Figure 4.1***). As a result, the transformed values no longer reflect an absolute probability of developing dementia, but rather indicate relative risk across the cohort. **Higher log-transformed UKBDRS values correspond to higher midlife dementia risk within the cohort.**

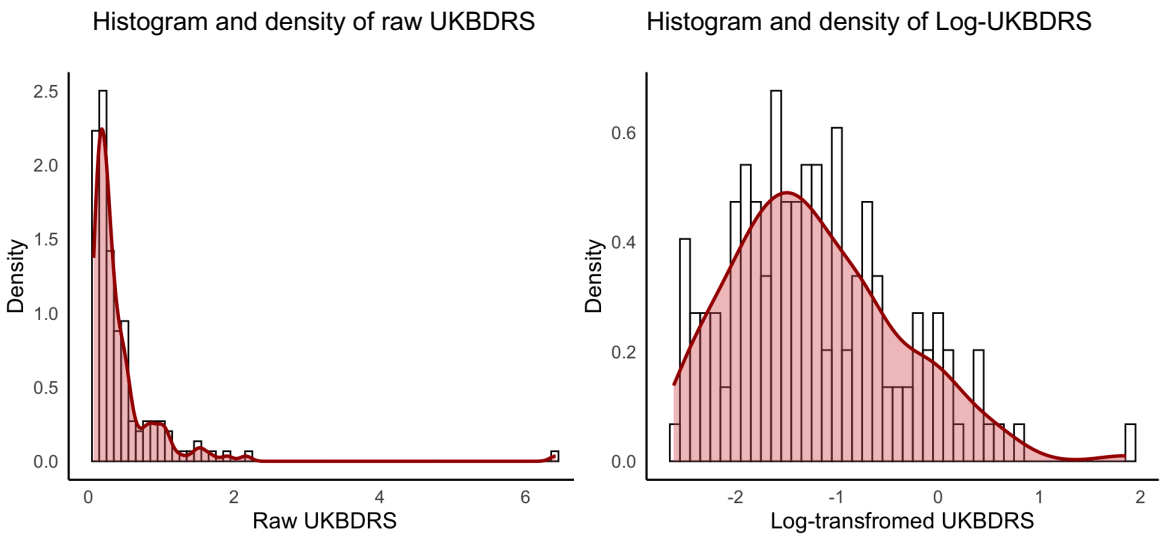


Figure 4.1: Distribution of UKBDRS before and after log transformation

Note: The left figure shows the positively skewed distribution of raw UKBDRS, and the right figure displays the log-transformed values of UKBDRS, which exhibit reduced skewness and approximate a normal distribution.

ROIs for grey matter and CVR: we selected six core regions of the DMN as regions of interest (ROIs), in addition to total grey matter volume. These regions included the hippocampus (left and right), bilateral temporoparietal junction (TPJ), medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and the precuneus. The same anatomical masks, derived from the T1-weighted structural images, were used to extract **mean CVR** values in these ROIs. As a secondary analysis, we also examined the association between the UKBDRS and mean hippocampal CVR, defined as the average of left and right hippocampal CVR values.

ROIs for white matter microstructure: we examined four diffusion metrics: fractional

anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (L1) to indicate integrity of WM microstructure. These metrics were extracted from four major white matter tracts known to be involved in cognitive function: the corpus callosum, cingulum bundle, internal capsule, and fornix, as well as the whole brain metrics.

White matter hyperintensities: we used the percentage of total WMHs volume out of total brain volume (%WMH). Due to positive skewness, %WMH was log-transformed (log%WMH) for statistical analyses.

Cognitive performance: we assessed six cognitive domains derived using PCA: episodic memory, executive function, visuospatial memory, working memory, fluency and lexical retrieval (higher factor scores = better performance)

Longitudinal outcomes: For the longitudinal outcomes, we used the standardised difference between MRI-Wave 2 and Wave-1 for GMV and WM diffusion metrics (FA, MD, RD and L1), the difference in logWMH%, and the difference in cognitive domain scores from MRI-Wave 1 to 2. All details regarding standardisation procedures and the computation of these difference values are provided in **Chapter 3**.

4.2.2 Statistical analysis

To test the association of midlife UKBDRS with later-life brain and cognitive outcomes at MRI-Wave 2, we used linear regression models with UKBDRS as the predictor and CVR, GMV, WM diffusion metrics, WMHs and cognition as the outcomes. As sex, midlife age and education are already components of the UKBDRS, they were not included as covariates to avoid over-adjustment. We adjusted for the time interval between the age at which UKBDRS was calculated in midlife, and the age at MRI-Wave 2, in order to account for variability in the interval between risk exposure and outcome measurement. For analyses involving regional GMV, total GMV at MRI-Wave 2 was included as an additional covariate to control for individual differences in brain size (***Equation 4.1***).

Equation 4.1: Model of UKBDRS and later life outcomes

$$\boxed{Y = \beta_0 + \beta_1 logUKBDRS + \beta_2 D + (\beta_3 GMV_{total}) + \varepsilon}$$

- β_0 = Intercept
- Y = MRI outcome (CVR, GMV, WM diffusion metrics, logWMH%) and cognitive outcome at MRI-Wave 2
- D = Duration from midlife to MRI-Wave 2
- β_3 GMV_{total} (total GMV at MRI-Wave 2 is only included when Y is regional GMV)
- ε = Error term

Next, we examined whether UKBDRS was associated with longitudinal changes in brain and cognitive measures. In these regression models, the change of the outcome including ΔGMV, ΔWM diffusion metrics, ΔlogWMH% and ΔCognition were treated as the dependent variable.

Covariates included the time interval between midlife age and MRI-Wave 1, and the time interval between MRI-Wave 1 and MRI-Wave 2. We did not include chronological age in the models, as midlife age is already incorporated in the UKBDRS. Including age as an additional covariate could absorb some of the variance explained by the UKBDRS, potentially diminishing its effect. It may also introduce collinearity and lead to over-adjustment (***Figure 4.2***). In models involving regional GMV change, baseline (MRI-Wave 1) total GMV was included to account for individual differences in brain size at the baseline MRI measures (***Equation 4.2***). As the logWMH% and cognitive domain scores were not standardised, we used paired-sample t-tests to examine whether there was a significant change from MRI-Wave 1 to MRI-Wave 2.

Equation 4.2: Model of UKBDRS and change in later-life outcomes

$$\boxed{\Delta Y = \beta_0 + \beta_1 logUKBDRS + \beta_2 D_1 + \beta_3 D_2 + (\beta_4 GMV_{total1}) + \varepsilon}$$

- β0 = intercept
- ΔY = Change in outcome (ΔGMV, ΔWM diffusion metrics, ΔlogWMH% and Δcognition) between MRI-Wave 1 and MRI-Wave 2
- D_1 = Duration from midlife to MRI-Wave 1
- D_2 = Duration between MRI-Wave 1 and 2
- GMV_{total1}= Baseline total GMV at MRI-Wave 1 (only included when Y is DMN ΔGMV)
- ε = Error term

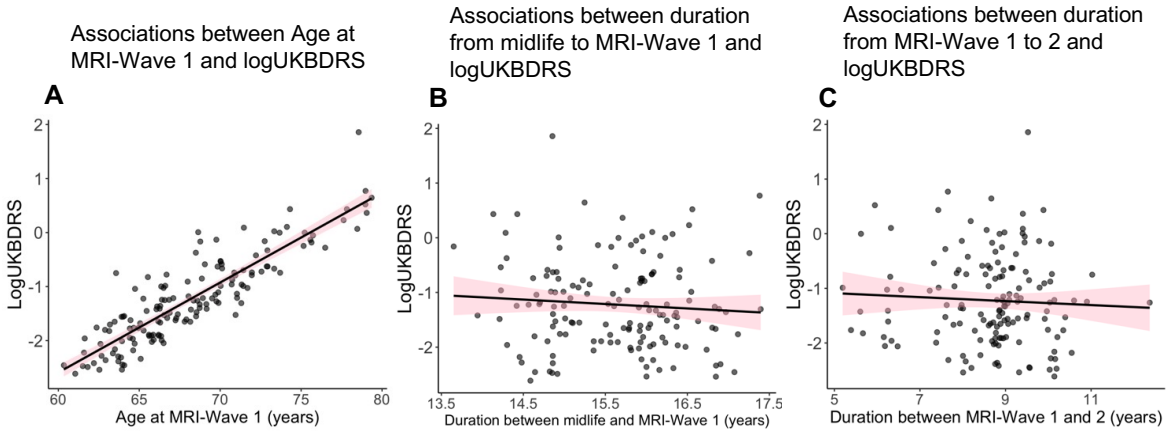


Figure 4.2: Associations between logUKBDRS and age-related variables to inform covariate selection for the model of the change in later-life outcomes

Note: Figure A-C show the associations between logUKBDRS and age and duration in order to decide covariates in the changes model. Age at MRI-Wave 1 is highly collinear with logUKBDRS, and thus was not included for adjustment.

To correct for multiple comparisons, we applied the Benjamini-Hochberg (BH) false discovery rate (FDR) procedure within each category of analysis (Benjamini & Hochberg, 1995). This included correction across the six nodes of DMN nodes for CVR and GMV separately, across the four white matter tracts for each diffusion metric, and across the six cognitive domains. The

BH method uses a ranking-based approach to control FDR and is widely used in neuroimaging research (Clark et al., 2020; Genovese et al., 2002; Sun et al., 2025). Statistical significance was defined as $p_{corr} < 0.05$. For completeness, uncorrected p-values are also reported and discussed alongside corrected values. Cohen's f^2 of the whole regression model as well as the individual predictor were used to assess effect size for significant associations.

4.3 Results

4.3.1 Demographic results

A total of 163 participants were initially included in the study, of whom 155 had complete and good quality CVR scans. Seven participants were identified as outliers (four for CVR, three for executive function). In order to keep the sample consistent throughout the analysis for this thesis, people with outliers were excluded from the analysis. The final sample for analysis for all subsequent chapters comprised **148 participants**, of whom 110 were male (74.3%) and 38 were female (25.7%).

The mean age at midlife, when the UKBDRS was calculated, was 52.6 years (SD = 4.3). The mean age at the first assessment of outcomes (MRI-Wave 1) was 68.2 years (SD = 4.4), and the mean age at the final timepoint (MRI-Wave 2) was 76.9 years (SD = 4.4). The average

interval between midlife assessment and MRI-Wave 1 was 15.6 years (SD = 0.8), and the duration between MRI-Wave 1 and MRI-Wave 2 was 8.7 years (SD = 1.2; ***Figure 4.3***). The mean total duration between midlife and MRI-Wave 2 was 24.3 years (SD = 1.2).

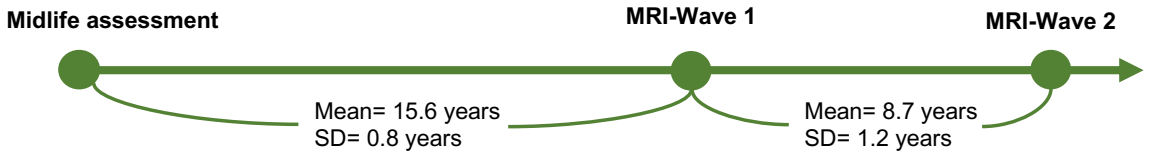


Figure 4.3: Duration between UKBDRS assessments and MRI acquisitions

The distributions of each risk factor for the UKBDRS are reported in ***Table 4.1*** (note that the UKBDRS in thesis excludes the house occupancy variable due to several missing cases for this variable). Participants had a mean/median predicted risk of dementia of 0.442%/0.268% (SD = 0.622%, UKBDRS ranging from 0.073% to 6.410%, prior to log transformation). For reference, a UKBDRS risk of 1.843% predicts dementia with 80% sensitivity, and a risk of 3.201% corresponded to 80% specificity (according to the original development of the score in UK Biobank). Therefore, even though the values are numerically low values, they reflect a clinically meaningful probability of dementia risk. In the Heart and Brain sample, only three of the 121 participants exceeded the 1.843% predicted risk cut-off, which suggests that, at 80% sensitivity, only few individuals in this cohort are likely to develop dementia.

Table 4.1: Summary of dementia risk factors used in the UKBDRS

UKBDRS = UK Biobank Dementia Risk Score; GHQ = General Health Questionnaire; SD = standard deviation; n = number of participants. Distribution reported for the cohort used in the statistical analysis.

Risk factor	**Distribution**
Parental history of dementia	No: n=140 (94.6%), Yes: n=8 (5.4%)
Education (years)	Mean=16.3, SD=4.2
Diabetes	No: n=146 (98.6%), Yes: n=2 (1.4%)
Depression (GHQ score)	Mean=3.1, SD=5.3
Stroke	No: n=142 (95.9%), Yes: n=6 (4.1%)
Material deprivation	Not deprived: n=144 (97.3%), Deprived: n=4 (2.7%)
Hypertension	No: n=128 (86.5%), Yes: n=20 (13.5%)
Total cholesterol level (mmol/L)	Mean=5.9, SD=4.2
Sex	Male: n=110(74.3%), Female: n=38 (25.7%)
Age (years)	Mean=51.9, SD=4.3

Summary of the demographic information, MRI and cognitive measures at MRI-Wave 2 are in ***Table 4.2***.

Table 4.2: Demographics, MRI markers and cognitive performance at MRI-Wave 2

Summary statistics are presented for the 148 participants included in the final analysis. This table presents either the mean and standard deviation (SD) for continuous variables, or the number and percentage for categorical measures. CVR = cerebrovascular reactivity, FA = fractional anisotropy, GMV = grey matter volume, L1 = axial diffusivity, MD = mean diffusivity, Min = minimum, Max = maximum, SD = Standard deviation. Note that GMV, FA, MD, RD, L1, WMHs and cognition were also acquired at MRI-Wave 1. However, some of these values were standardised as descried in the Methods and therefore not presented below.

Measures		**Mean (SD) or n (%)**
Sex		Male: n=110 (74.3%), Female: n=38 (25.7%)
Age (years)		76.88 (4.40)
Education (years)		17.50 (5.20)
Body mass index (kg/m^2)		25.77 (4.20)
Systolic blood pressure (mmHg)		149.50 (19.57)
Diastolic blood pressure (mmHg)		78.72 (11.12)
Current smoking status		Yes: n=3 (2.00%), No: n=144 (98.00%)
Type 2 Diabetes		Yes: n=11 (7.48%), No: n=136 (92.52%)
CVR (%/mmHg)	**Whole Brain**	0.28 (0.07)
	Left Hippocampus	0.21 (0.07)
	Right Hippocampus	0.20 (0.07)
	Medial Prefrontal Cortex	0.23 (0.07)
	Posterior Cingulate Cortex	0.35 (0.10)
	Temporoparietal Junction	0.23 (0.07)
	Precuneus	0.33 (0.10)
GMV (cm^3)	**Whole Brain**	533.11 (44.65)
	Left Hippocampus	2.93 (0.43)
	Right Hippocampus	3.09 (0.40)
	Medial Prefrontal Cortex	8.73 (1.28)
	Posterior Cingulate Cortex	6.14 (0.91)

	Temporoparietal Junctions	9.12 (1.72)
	Precuneus	19.33 (2.44)
FA	**Whole Brain**	0.47 (0.02)
	Corpus Callosum	0.72 (0.03)
	Cingulum Bundle	0.60 (0.03)
	Internal Capsule	0.64 (0.02)
	Fornix	0.50 (0.04)
MD x10^{-4} (mm^2/s)	**Whole Brain**	6.98 (0.29)
	Corpus Callosum	6.93 (0.41)
	Cingulum Bundle	6.55 (0.29)
	Internal Capsule	6.27 (0.26)
	Fornix	8.44 (0.66)
RD x10^{-4} (mm^2/s)	**Whole Brain**	5.00 (0.32)
	Corpus Callosum	3.10 (0.44)
	Cingulum Bundle	3.84 (0.33)
	Internal Capsule	3.44 (0.28)
	Fornix	5.99 (0.82)
L1 x10^{-4} (mm^2/s)	**Whole Brain**	10.93 (0.28)
	Corpus Callosum	14.60 (0.48)
	Cingulum Bundle	11.97 (0.42)
	Internal Capsule	11.92 (0.36)
	Fornix	13.33 (0.49)
White Matter Hyperintensity (logWMH%)		1.54 (0.48)
Episodic Memory (factor score)		34.92 (7.33)
Visuospatial Memory (factor score)		30.55 (11.22)
Fluency (factor score)		28.33 (7.23)
Executive Function (factor score)		33.23 (33.61)
Working Memory (factor score)		20.74 (4.00)
Lexical Retrieval (factor score)		132.73 (9.08)

4.3.2 Associations between UKBDRS and CVR

Higher logUKBDRS in midlife was significantly associated with lower CVR in the MPFC (β = -0.017, 95% CI [-0.031, -0.003], p = 0.018, p_{corr} = 0.037), PCC (β = -0.021, 95% CI [-0.041, -0.001], p = 0.043, p_{corr} = 0.065), left hippocampus (β = -0.017, 95% CI [-0.030, -0.004], p = 0.012, p_{corr} = 0.037), and right hippocampus (β = -0.016, 95% CI [-0.029, -0.003], p = 0.018, p_{corr} = 0.037). All associations except for the PCC survived corrections for multiple comparisons. Detailed results are displayed in ***Table 4.3, Figure 4.4 A***. In the secondary analysis, higher logUKBDRS was significantly associated with lower mean hippocampal CVR (β = -0.016, 95% CI [-0.029, -0.004], p = 0.010).

4.3.3 Associations between UKBDRS and GMV

Higher logUKBDRS was significantly associated with lower GMV in the total grey matter (β = -11.791, 95% CI [-20.415, -3.168], p = 0.008), left hippocampus (β = -0.131, 95% CI [-0.210, -0.053], p = 0.001, p_{corr} = 0.007), and right hippocampus (β = -0.085, 95% CI [-0.158, -0.011], p = 0.024, p_{corr} = 0.073). However, the associations with right hippocampal CVR did not remain significant after correction for multiple comparisons. Results are presented in ***Table 4.3 and Figure 4.4 B***.

In terms of **longitudinal change**, higher logUKBDRS was significantly associated with greater reduction in total GMV (β = -0.134, 95% CI [-0.221, -0.046], p = 0.003), as well as greater volume loss in both the left (β = -0.194, 95% CI [-0.308, -0.080], p = 0.008, p_{corr} = 0.009) and right **hippocampus** (β = -0.243, 95% CI [-0.386, -0.100], p = 0.001, p_{corr} = 0.006), **MPFC** (β = -0.159, 95% CI [-0.270, -0.049], p = 0.005, p_{corr} = 0.007), in **PCC** (β = -0.132, 95% CI [-0.220, -0.045], p = 0.003, p_{corr} = 0.007), and in **TPJ** (β = -0.178, 95% CI [-0.297, -0.060], p = 0.003, p_{corr} = 0.007). No significant association was observed for the precuneus. All these associations survived after correction for multiple comparisons (***Table 4.4 and Figure 4.5 A***).

4.3.4 Associations between UKBDRS and WM microstructure

Across the whole brain white matter, higher logUKBDRS was associated with lower FA (β = -0.007, 95% CI [-0.011, -0.003], p < 0.001), higher MD (β = $1.228x10^{-5}$, 95% CI [$6.785x10^{-6}$, $1.777x10^{-5}$, p < 0.001), higher RD (β = $1.312x10^{-5}$, 95% [$7.228x10^{-6}$, $1.901x10^{-5}$], p < 0.001), and higher L1 (β = $1.060x10^{-5}$, 95% CI [$5.346x10^{-6}$, $1.586x10^{-5}$], p < 0.001).

Higher logUKBDRS scores were also significantly associated with lower integrity of WM microstructure in **corpus callosum**, as indicated by significant associations with lower FA (β = -0.011, 95% CI [-0.017, -0.006], p < 0.001, p_{corr} < 0.001), and higher MD (β = $2.209x10^{-5}$, 95% CI [$1.465x10^{-5}$, $2.953x10^{-5}$], p < 0.001, p_{corr} < 0.001), higher RD (β = $2.034x10^{-5}$, 95% CI

[1.220×10^{-5}, 2.849×10^{-5}], $p < 0.001$, $p_{corr} < 0.001$), and higher L1 ($\beta = 2.559 \times 10^{-5}$, 95% CI [$1.689 \times 10^{-5}$, 3.429×10^{-5}], $p < 0.001$, $p_{corr} < 0.001$). In the **fornix**, higher logUKBDRS was significantly associated with lower FA ($\beta = -0.012$, 95% CI [-0.019, -0.005], $p < 0.001$, $p_{corr} = 0.001$), and higher MD ($\beta = 2.015 \times 10^{-5}$, 95% CI [$7.810 \times 10^{-6}$, 3.250×10^{-5}], $p = 0.002$, $p_{corr} = 0.002$) and higher RD ($\beta = 2.779 \times 10^{-5}$, 95% CI [$1.220 \times 10^{-5}$, 4.338×10^{-5}], $p < 0.001$, $p_{corr} = 0.001$). In the **cingulum**, higher logUKBDRS was significantly associated with lower FA ($\beta = -0.006$, 95% CI [-0.012, -0.001], $p = 0.030$, $p_{corr} = 0.040$), as well as higher MD ($\beta = 6.134 \times 10^{-6}$, 95% CI [$4.587 \times 10^{-7}$, 1.181×10^{-5}], $p = 0.034$, $p_{corr} = 0.034$), and higher RD ($\beta = 8.153 \times 10^{-6}$, 95% CI [$1.816 \times 10^{-6}$, 1.449×10^{-5}], $p = 0.012$, $p_{corr} = 0.016$). In the **internal capsule**, higher logUKBDRS was significantly associated with higher MD ($\beta = 8.455 \times 10^{-6}$, 95% CI [$3.593 \times 10^{-6}$, 1.332×10^{-5}], $p < 0.001$, $p_{corr} = 0.002$), higher RD ($\beta = 5.603 \times 10^{-6}$, 95% CI [$1.357 \times 10^{-6}$, 1.107×10^{-5}], $p = 0.045$, $p_{corr} = 0.045$), and higher L1 ($\beta = 1.416 \times 10^{-5}$, 95% CI [$7.417 \times 10^{-6}$, 2.090×10^{-5}], $p < 0.001$, $p_{corr} < 0.001$). Results are summarised in ***Table 4.3 and Figure 4.4 D-G***.

In terms of **longitudinal ~9 year changes** in WM microstructure, higher logUKBDRS was significantly associated with larger deteriorations in WM microstructure in the whole brain, as indicated by more reduction in FA ($\beta = -0.132$, 95% CI [-0.217, -0.046], $p = 0.003$), larger increase in MD ($\beta = 0.079$, 95% CI [0.008, 0.150], $p = 0.028$) and larger increase in RD ($\beta = 0.100$, 95% CI [0.027, 0.173], $p = 0.008$).

In the **corpus callosum**, higher logUKBDRS was significantly associated with larger reduction

in FA (β = -0.207, 95% CI [-0.301, -0.113], p < 0.001, p_{corr} < 0.001), and larger increase in MD (β = 0.108, 95% CI [0.030, 0.186], p = 0.007, p_{corr} = 0.027) and larger increase in RD (β = 0.185, 95% CI [0.097, 0.273], p < 0.001, p_{corr} < 0.001). In the **cingulum**, higher logUKBDRS was significantly associated with a larger reduction in FA (β = -0.202, 95% CI [-0.303, -0.102], p < 0.001 p_{corr} < 0.001) and larger increase in RD (β = 0.153, 95% CI [0.055, 0.251], p = 0.002, p_{corr} = 0.005). However, higher logUKBDRS was associated with larger decrease in L1 (β = -0.143, 95% CI [-0.257, -0.028], p = 0.015, p_{corr} = 0.058), which represents a reverse direction to what would typically be expected but was no longer significant after multiple comparison correction. In the **internal capsule**, higher logUKBDRS was associated with larger reduction in FA (β = -0.102, 95% CI [-0.186, -0.018], p = 0.018, p_{corr} = 0.024), larger increase in MD (β = 0.113, 95% CI [0.025, 0.201], p = 0.012, p_{corr} = 0.017), while RD and L1 showed no significant associations. There were no significant associations observed in the fornix. Results are summarised in ***Table 4.4, Figure 4.5 C-F***.

4.3.5 Associations between UKBDRS and WMHs

Higher logUKBDRS was significantly associated with larger volumes in WMHs **(logWMH%)** at MRI-Wave 2 (β = 0.136, 95% CI [-0.042, 0.229], p = 0.005).

WMHs significantly increased from MRI-Wave 1 to Wave 2, as indicated by a paired t-test

(mean difference = -0.35, $p < 0.001$). However, there was no significant association between logUKBDRS and change in WMH volume ($p = 0.516$).

4.3.6 Associations between UKBDRS and Cognition

Higher logUKBDRS was significantly associated with poorer performance in episodic memory ($\beta = -2.42$, 95% CI [-3.81, -1.04], $p = 0.001$, $p_{corr} = 0.002$), executive function ($\beta = -14.49$, 95% CI [-20.64, -8.34], $p < 0.001$, $p_{corr} < 0.001$) and visuospatial memory ($\beta = -2.314$, 95% CI [-4.446, -0.183], $p < 0.034$, $p_{corr} = 0.067$) at MRI-Wave 2. Detailed results are displayed in ***Table 4.3 and Figure 4.4 C***.

Results from paired t-test showed that between MRI-Wave 1 and Wave 2, there were significant reductions across all cognitive domains ($p < 0.001$), except for the fluency domain, which showed a slight but non-significant decrease at Wave 2 compared to Wave 1 ($p = 0.285$).

Higher logUKBDRS was significantly associated with larger declines across several cognitive domains: episodic memory ($\beta = -1.765$, 95% CI [-3.052, -0.478], $p = 0.008$, $p_{corr} = 0.013$), visuospatial memory ($\beta = -3.198$, 95% CI [-5.568, -0.829], $p = 0.009$, $p_{corr} = 0.013$), executive function ($\beta = -6.363$, 95% CI [-10.760 -1.967], $p = 0.005$, $p_{corr} = 0.013$) as well as lexical retrieval ($\beta = -1.389$, 95% CI [-2.407, -0.371], $p = 0.008$, $p_{corr} = 0.013$). No significant associations were

observed for changes in fluency (p = 0.977) or working memory (p = 0.886). Detailed results are demonstrated in ***Table 4.4 and Figure 4.5 B***.

Table 4.3: Associations between midlife dementia risk (logUKBDRS) with CVR, GMV, WM microstructure, WMH and cognitive performance at MRI-Wave 2

β = coefficient of the linear regression models, Cohen's f^2 to indicate effect size for significant results, (table displays both Cohen's f^2 for the overall model as well as the Cohen's f^2 for the individual independent variable); Correction for multiple comparisons was performed for the six DMN nodes for CVR and GM analyses and for four predefined tracts for WM analyses; and corrected p-values reflect this correction. p_{corr} = significance level after Benjamini-Hochberg correction for multiple comparisons, with $p_{corr} < 0.05$ indicating a significant association after correction. Associations with p < 0.05 (uncorrected) and either surviving multiple comparison correction or not requiring correction are highlighted in orange. Associations with p < 0.05 (uncorrected) but not surviving multiple comparison correction are highlighted in yellow. CVR = cerebrovascular reactivity, GMV = grey matter volume; MPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; TPJ = temporoparietal junction; FA = fractional anisotropy, GMV = grey matter volume, L1 = axial diffusivity, MD = mean diffusivity, RD = radial diffusivity, WM = white matter, WMH = white matter hyperintensity. 95%CI = 95% confidence interval.

Outcome	**β [95% CI]**	**p**	**p_{corr}**	**Cohen's f^2 for overall model (Independent variable)**
CVR				
Total GM	-0.010 [-0.024, 0.004]	0.163		
MPFC	-0.017 [-0.031, -0.003]	**0.018**	**0.037**	0.050 (0.040)
PCC	-0.021 [-0.041, -0.001]	**0.043**	0.065	0.051 (0.029)
TPJ	-0.008 [-0.022, 0.006]	0.240		
Precuneus	-0.005 [-0.024, 0.015]	0.628		
Left Hippocampus	-0.017 [-0.030, -0.004]	**0.012**	**0.037**	0.068 (0.045)
Right Hippocampus	-0.016 [-0.029, -0.003]	**0.018**	**0.037**	0.044 (0.039)
GMV				
Total GM	-11.791 [-20.415, -3.168]	**0.008**		0.053 (0.049)

MPFC		-0.008 [-0.200, 0.184]	0.937		
PCC		0.042 [-0.092, 0.176]	0.534		
TPJ		-0.080 [-0.369, 0.210]	0.587		
Precuneus		-0.132 [-0.474, 0.210]	0.447		
Left Hippocampus		-0.131 [-0.210, -0.053]	**0.001**	**0.007**	0.248 (0.075)
Right Hippocampus		-0.085 [-0.158, -0.011]	**0.024**	0.073	0.261 (0.036)
WM microstructure					
FA	Whole Brain	-0.007 [-0.011, -0.003]	**<0.001**		0.086 (0.082)
	Corpus Callosum	-0.011 [-0.017, -0.006]	**<0.001**	**<0.001**	0.115 (0.112)
	Cingulum	-0.006 [-0.012, -0.001]	**0.030**	**0.040**	0.033 (0.032)
	Internal Capsule	-0.001 [-0.006, 0.003]	0.587		
	Fornix	-0.012 [-0.019, -0.005]	**<0.001**	**0.001**	0.093 (0.080)
MD (β x10^{-5})	Whole Brain	1.228 [0.685, 1.777]	**<0.001**		
	Corpus Callosum	2.209 [1.465, 2.953]	**<0.001**	**<0.001**	0.234 (0.231)
	Cingulum	0.613 [0.046, 1.181]	**0.034**	**0.034**	0.031 (0.031)
	Internal Capsule	0.846 [0.359, 1.332]	**<0.001**	**0.002**	0.087 (0.079)
	Fornix	2.015 [0.781, 3.250]	**0.002**	**0.002**	0.081 (0.070)
RD (β x10^{-5})	Whole Brain	1.312 [0.722, 1.901]	**<0.001**		0.134 (0.130)
	Corpus Callosum	2.034 [1.220, 2.849]	**<0.001**	**<0.001**	0.167 (0.163)
	Cingulum	0.815 [0.182, 1.449]	**0.012**	**0.016**	0.044 (0.043)
	Internal Capsule	0.056 [0.014, 1.107]	**0.045**	**0.045**	0.030 (0.028)
	Fornix	2.779 [1.220, 4.338]	**<0.001**	**0.001**	0.097 (0.083)

L1 (β x10^{-5})	Whole Brain	1.060 [0.535, 1.586]	**<0.001**		0.108 (0.107)
	Corpus Callosum	2.559 [1.689, 3.429]	**<0.001**	**<0.001**	0.227 (0.227)
	Cingulum	0.210 [-0.626, 1.045]	0.621		
	Internal Capsule	1.416 [0.742, 2.090]	**<0.001**	**<0.001**	0.129 (0.116)
	Fornix	0.488 [-0.485, 1.460]	0.324		
WMH					
logWMH%		0.136 [0.042, 0.229]	**0.005**		0.061 (0.056)
Cognition					
Episodic Memory		-2.423 [-3.808, -1.038]	**0.001**	**0.002**	0.090 (0.078)
Visuospatial Memory		-2.314 [-4.446, -0.183]	**0.034**	0.067	0.046 (0.031)
Fluency		-1.002 [-2.410, 0.407]	0.162		
Executive Function		-14.488 [-20.640, -8.335]	**<0.001**	**<0.001**	0.148 (0.146)
Lexical Retrieval		-0.208 [-1.939, 1.523]	0.813		
Working Memory		-0.108 [-0.881, 0.665]	0.782		

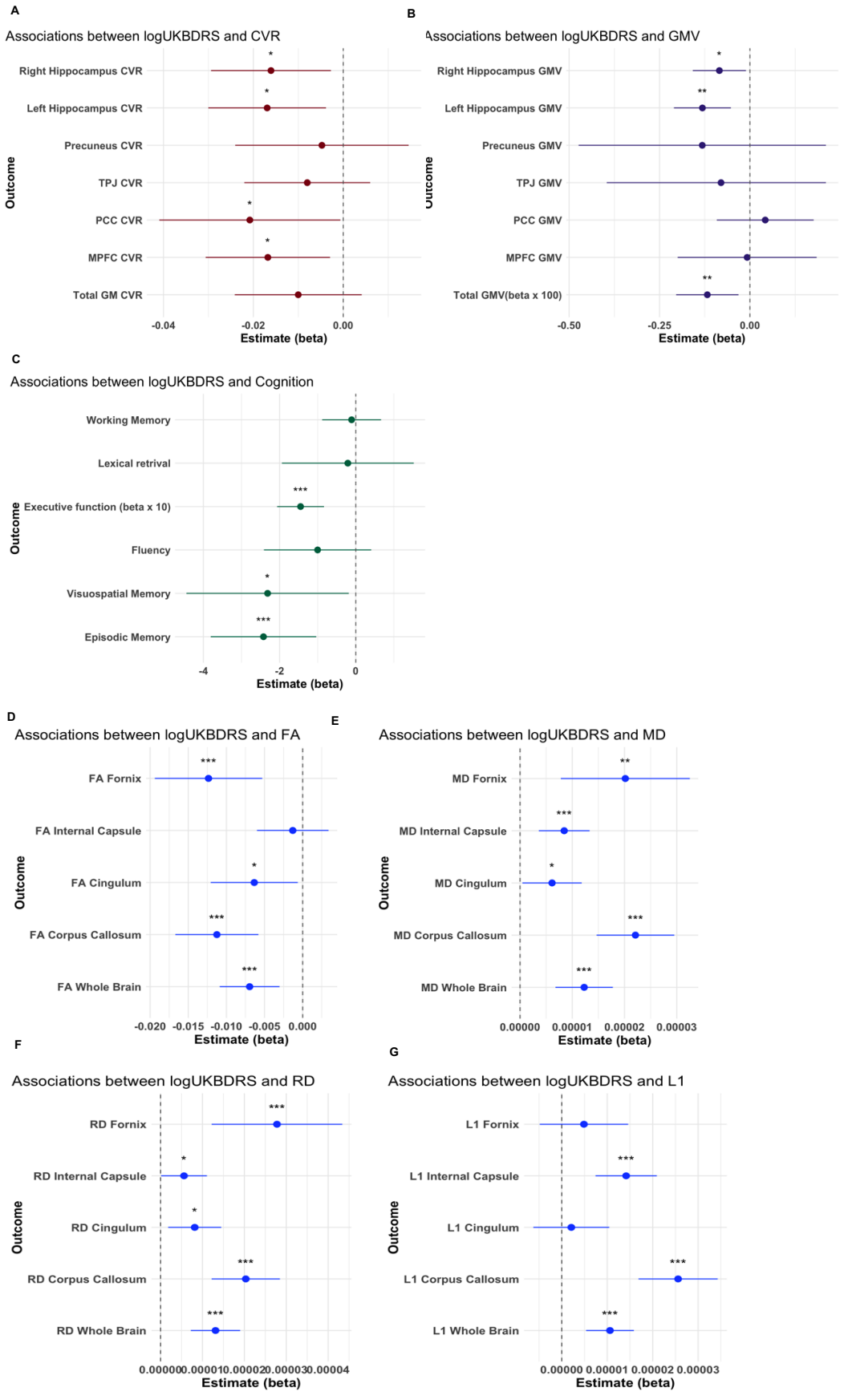


Figure 4.4: Forest plots showing the associations between midlife logUKBDRS and

brain and cognitive outcomes at MRI-Wave 2

*Associations with (A) CVR, (B) GMV, (C) cognitive performance, and (D-G) white matter microstructure as measured by diffusion metrics: FA, MD, RD, and L1. Bars represent 95% confidence intervals of beta coefficients. Asterisks indicate levels of statistical significance: * represents p < 0.05, ** represents p < 0.01, *** represents p < 0.001.*

Table 4.4: Associations between midlife dementia risk (logUKBDRS) with change in GMV, WM microstructure, WMH and cognitive performance from MRI-Wave 1 to 2

β = coefficient of the linear regression models, Cohen's f^2 to indicate effect size for significant results, (table displays both Cohen's f^2 for the overall model as well as the Cohen's f^2 for the individual independent variable); Correction for multiple comparisons was performed for the six DMN nodes for CVR and GM analyses and for four predefined tracts for WM analyses; and corrected p-values reflect this correction. p_{corr} = significance level after Benjamini-Hochberg correction for multiple comparisons, with $p_{corr} < 0.05$ indicating a significant association after correction. Associations with $p < 0.05$ (uncorrected) and either surviving multiple comparison correction or not requiring correction are highlighted in orange. Associations with $p < 0.05$ (uncorrected) but not surviving multiple comparison correction are highlighted in yellow. GMV = grey matter volume; MPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; TPJ = temporoparietal junction; FA = fractional anisotropy, GMV = grey matter volume, L1 = axial diffusivity, MD = mean diffusivity. RD = radial diffusivity, WM = white matter, WMH = white matter hyperintensity. 95%CI = 95% Confidence interval.

Outcome		**Beta [95% CI]**	**p**	**p_{corr}**	**Cohen's f^2 Overall model (Independent variable)**
ΔGMV					
Total GM		-0.134 [-0.221, -0.046]	**0.003**		0.096 (0.063)
MPFC		-0.159 [-0.270, -0.049]	**0.005**	**0.007**	0.163 (0.057)
PCC		-0.182 [-0.220, -0.045]	**0.003**	**0.007**	0.083 (0.062)
TPJ		-0.178 [-0.297, -0.060]	**0.003**	**0.007**	0.078 (0.062)
Precuneus		-0.075 [-0.199, 0.049]	0.232		
Left Hippocampus		-0.194 [-0.335, -0.052]	**0.008**	**0.009**	0.141 (0.052)
Right Hippocampus		-0.243 [-0.386, -0.100]	**0.001**	**0.006**	0.210 (0.081)
ΔWM microstructure					
FA	Whole Brain	-0.132 [-0.217, -0.046]	**0.003**		0.125 (0.064)
	Corpus Callosum	-0.207 [-0.301, -0.113]	**<0.001**	**<0.001**	0.204 (0.131)
	Cingulum	-0.202 [-0.303, -0.102]	**<0.001**	**<0.001**	0.151 (0.111)
	Internal Capsule	-0.102 [-0.186, -0.018]	**0.018**	**0.024**	0.067 (0.040)
	Fornix	-0.058 [-0.149, 0.034]	0.213		

MD	Whole Brain	0.079 [0.008, 0.150]	**0.028**		0.070 (0.034)
	Corpus Callosum	0.108 [0.030, 0.186]	**0.007**	**0.027**	0.138 (0.052)
	Cingulum	0.038 [-0.066, 0.142]	0.471		
	Internal Capsule	0.081 [-0.015, 0.176]	0.098		
	Fornix	0.065 [-0.016, 0.146]	0.113		
RD	Whole Brain	0.100 [0.027, 0.173]	**0.008**		0.101 (0.051)
	Corpus Callosum	0.185 [0.097, 0.273]	**<0.001**	**<0.001**	0.200 (0.120)
	Cingulum	0.153 [0.055, 0.251]	**0.002**	**0.005**	0.101 (0.066)
	Internal Capsule	0.113 [0.025, 0.201]	**0.012**	**0.017**	0.078 (0.044)
	Fornix	0.050 [-0.019, 0.119]	0.154		
L1	Whole Brain	0.032 [-0.045, 0.110]	0.410		
	Corpus Callosum	0.026 [-0.054, 0.106]	0.522		
	Cingulum	-0.143 [-0.257, -0.028]	**0.015**	0.061	0.058 (0.042)
	Internal Capsule	0.058 [-0.037, 0.153]	0.229		
	Fornix	0.112 [-0.033, 0.256]	0.129		
ΔWMH					
ΔlogWMH%		-0.015 [-0.063, 0.032]	0.516		
ΔCognition					
Δ Episodic Memory		-1.765 [-3.052, -0.478]	**0.008**	**0.013**	0.095 (0.051)
Δ Visuospatial Memory		-3.198 [-5.568, -0.829]	**0.009**	**0.013**	0.073 (0.051)
Δ Fluency		-0.017 [-1.155, 1.122]	0.977		
Δ Executive Function		-6.363 [-10.760, -1.967]	**0.005**	**0.013**	0.109 (0.059)
Δ Lexical Retrieval		-1.389 [-2.407, -0.371]	**0.008**	**0.013**	0.142 (0.052)
Δ Working Memory		0.042 [-0.542, 0.626]	0.886		

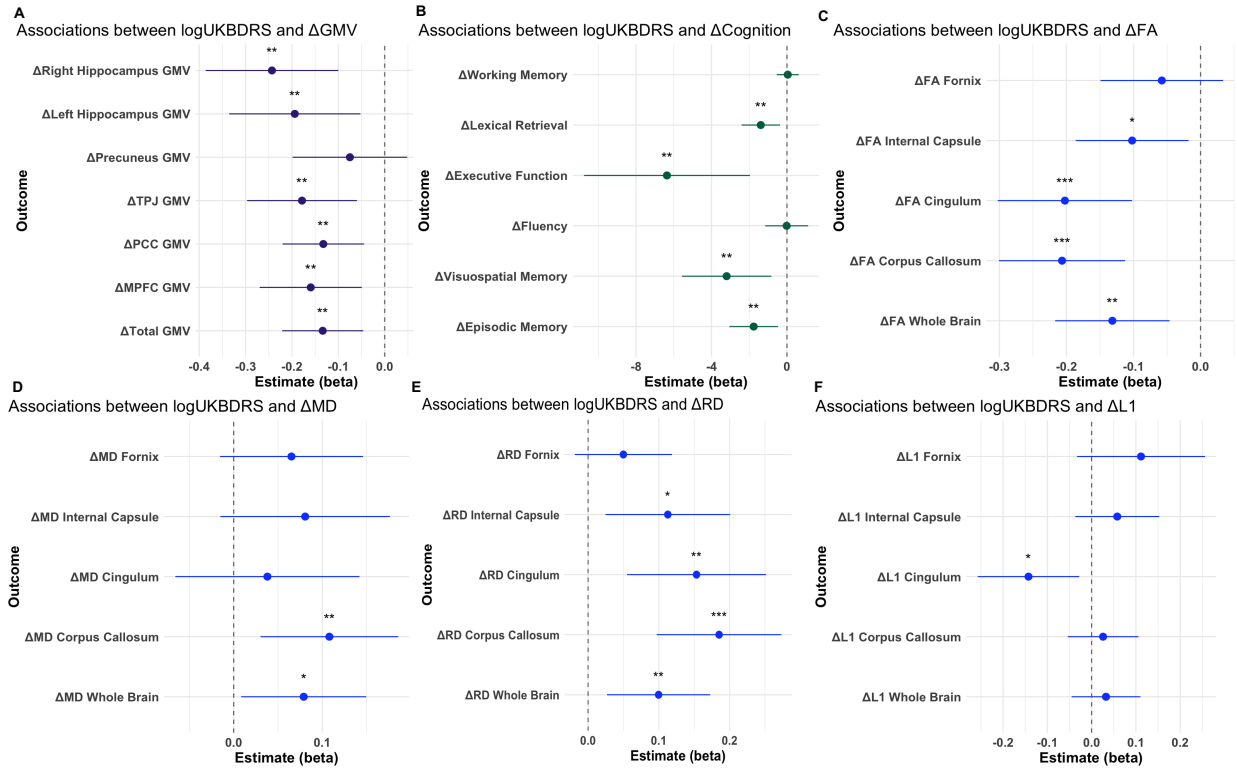


Figure 4.5: Associations between midlife UKBDRS and longitudinal changes in brain structure and cognitive performance from MRI-Wave 1 to MRI-Wave 2

*Forest plots show associations between logUKBDRS with longitudinal changes in (A) GMV, (B) Cognition, (C) FA, (D) MD, (E) RD, and (F) L1. Bars represent 95% confidence intervals of beta coefficients. Asterisks indicate levels of statistical significance: * represents p < 0.05, ** represents p < 0.01, *** represents p < 0.001.*

4.4 Discussion

4.4.1 Summary of the findings

This study examined how midlife dementia risk relates to brain structural, vascular, and cognitive health in later life, approximately 24.3 years later. The findings suggest that individuals with higher midlife dementia risk, as measured by the novel UK Biobank Dementia Risk Score (UKBDRS), had lower CVR in the hippocampus, MPFC and PCC. These associations remained significant after correction for multiple comparisons, with the exception of the association with PCC CVR. Individuals with higher UKBDRS also exhibited smaller total grey matter and bilateral hippocampal volumes, although only the association with left hippocampal volume remained significant after correction for multiple comparisons. They also underwent greater grey matter atrophy in older age, between ~68 to ~77 years of age, in most of the DMN including PCC, MPFC, TPJ, and hippocampus, and all of these associations survived multiple comparisons correction. Higher midlife risk was also associated with poorer WM microstructure in later life, as well as greater longitudinal decline in WM microstructure in whole brain and most of the major white matter tracts, including the corpus callosum, cingulum and internal capsule. Most WM microstructural associations remained significant after correction for multiple testing, except for the association with change in L1 in the cingulum. People with higher midlife dementia risk also had greater white matter hyperintensity volumes, although there was no evidence that they experienced a greater increase in WMHs over time.

In terms of cognitive function, higher midlife dementia risk was linked to poorer performance in episodic memory, executive function and visuospatial memory, and faster longitudinal decline in all of these domains. Although the association with later-life visuospatial memory did not survive correction for multiple comparisons, all other cognitive associations remained significant after correction. This study provides promising preliminary evidence that the UKBDRS captures preclinical processes relevant to brain and cognitive health decades before clinical symptoms may present.

4.4.2 The UKBDRS and brain vascular health

First, we found that higher midlife dementia risk (at age ~52 years), as assessed by the UKBDRS, was associated with lower CVR in later life (at age ~77 years). The UKBDRS captures a range of modifiable cardiovascular and lifestyle risk factors, such as hypertension and type 2 diabetes, many of which have been previously linked to impaired brain vascular health in older age. Prior studies have consistently shown that a greater burden of these risk factors is associated with reduced cerebral blood flow and perfusion, both globally and regionally (Bangen et al., 2014; Iadecola & Gottesman, 2019; Suri et al., 2019). Vascular risk has also been linked to lower flow velocities in major arteries supplying the brain, including the common carotid and middle cerebral arteries (Matthew P. Pase et al., 2012). These vascular alterations may precede the onset of structural brain pathology and reflect early metabolic decline in vulnerable regions (Fujishima et al., 1995). Building on this evidence, our study

extends the literature by examining CVR, a dynamic and functionally sensitive marker of neurovascular health. Our findings suggest that the cumulative effect of multiple risk factors may compromise cerebrovascular function before significant cognitive impairment becomes apparent or the clinical diagnosis of dementia. We specifically found higher midlife dementia risk scores were linked with lower CVR in the MPFC, PCC, and bilateral hippocampus. These brain regions are particularly relevant for cognitive function. The MPFC is crucial for working/spatial memory, decision-making, and social cognition (Euston et al., 2012; Grossmann, 2013; Jobson et al., 2021), and the PCC is involved in integrating autobiographical memories, and regulating attention (Leech & Sharp, 2013). The hippocampus, which is critical for episodic memory and spatial navigation, is particularly vulnerable to vascular insults and is amongst the earliest brain regions to show atrophy in Alzheimer's disease (Ji et al., 2021; Pini, Pievani, Bocchetta, Altomare, Bosco, Cavedo, Galluzzi, Marizzoni, & Giovanni B. Frisoni, 2016a; Schuff et al., 2009). Therefore, the compromised CVR due to higher risks factors cumulating from midlife may be one of the factors contributing to cognitive decline (Wolters et al., 2017).

4.4.3 The UKBDRS and brain structure

We observed that higher midlife dementia risk was associated with accelerated GMV loss in nearly all DMN regions examined in this study, with the exception of the precuneus. These findings align with previous research highlighting the vulnerability of DMN in dementia. Several

studies have found abnormalities of functional connectivity in DMN (Grieder et al., 2018; Hafkemeijer et al., 2012). A meta-analysis further suggested that GM atrophy in AD predominantly affects functionally connected DMN regions, especially the prefrontal, limbic, and temporal cortices (Wang et al., 2015). Our study adds to this literature by demonstrating that midlife dementia risk may contribute to earlier structural decline in DMN, even before clinical diagnosis. Notably, we found both smaller hippocampal volume and greater longitudinal GMV loss in the hippocampus, which emphasises its greater susceptibility to early neurodegeneration. This aligns with prior studies showing that hippocampal atrophy is among the earliest and most robust neuroimaging markers of cognitive decline and dementia (Jack et al., 2010; Pini, Pievani, Bocchetta, Altomare, Bosco, Cavedo, Galluzzi, Marizzoni, & Giovanni B. Frisoni, 2016). In contrast, we did not observe accelerated GMV loss in the precuneus in individuals with higher risk. Although prior work has shown that cognitively healthy individuals exhibit stronger precuneus connectivity compared to those with AD (Jones et al., 2011), other studies suggest that volume loss in this region may occur more slowly than in other areas of the brain during disease progression (Goto et al., 2015). Our findings may therefore reflect a relative structural resilience to these specific dementia risk factors in the precuneus compared to other DMN nodes.

We found that higher midlife dementia risk was associated with poorer WM microstructure as well as faster decline in this measure. Diffusion metrics capture different aspects of tissue integrity, in that lower FA and higher MD generally reflect compromised white matter structure.

RD is sensitive to demyelination (Song et al., 2002), while L1 reflects axonal injury and WM maturation (Pierpaoli et al., 2001). In our study, individuals with high-risk scores demonstrated lower FA, higher MD, RD, and L1 in both the whole-brain and the corpus callosum, which indicates widespread degeneration involving both myelin and axonal injury. These results reflect more severe and diffuse white matter damage in this key WM tract, highlighting its vulnerability to ageing processes linked with cardiovascular and lifestyle risks from midlife. In the fornix and cingulum, we observed significant reductions in FA and increases in MD and RD, but no significant associations with L1, which is also a common patten in age-related research (Wheeler-Kingshott & Cercignani, 2009). This suggests predominant demyelination with relative preservation of axonal structure in these limbic tracts. In the internal capsule, we did not detect significant associations with FA, but found elevated MD, RD, and L1. This pattern suggests a more complex microstructural degeneration, possibly involving axonal disorganisation or damage that does not substantially affect anisotropy. However, it could also be because the diffusivity measures may be more sensitive to white matter integrity differences than FA (Bennett & Madden, 2013).

Longitudinal analyses revealed that higher midlife dementia risk was associated with a greater decline in WM microstructure over time, particularly in the corpus callosum, cingulum, and internal capsule. Both the cingulum and internal capsule showed greater reductions in FA and greater increases in RD, indicating a progressive demyelination (Barrick et al., 2010). In the corpus callosum, we additionally observed a larger increase in MD over time, suggesting more

widespread microstructural disruption. Given that the corpus callosum is a major commissural tract essential for interhemispheric communication (Matsunami et al., 1994), these findings underscore its particular vulnerability to ageing processes linked to midlife dementia risk factors.

People with higher midlife dementia risk had higher WMH volumes in later life. This finding aligns with previous studies showing that individual dementia risk factors are linked with WMH burden. For instance, midlife blood pressure and hypertension is strongly associated with WMH burden (Debette et al., 2011; Wartolowska & Webb, 2021). Similarly, raised cholesterol and diabetes mellitus are also important risk factors for WMH (Wang et al., 2020; Wardlaw et al., 2015). In addition to individual risk factors, Low et al. (2022) found that higher CAIDE score was associated with greater WMH burden in later life. WMHs play an important role in dementia pathology through several mechanisms. First, WMHs are a result of chronic hypoperfusion, impaired blood-brain barrier dysfunction, which can lead to demyelination, axonal damage, and microglial activation (Alber et al., 2019; Dallaire-Théroux et al., 2017). Another mechanism would be that WMHs in regions such as the periventricular white matter, hippocampus, and associative cortex may disrupt neurotransmitter systems, particularly cholinergic signalling, thereby compounding cognitive decline (Chen et al., 2016). Additionally, Garnier-Crussard et al., (2023) also suggested that WMHs share common genetic risk loci with Alzheimer's diseases, which suggests a potential shared pathophysiological basis. Therefore, we suggest that midlife dementia risk may contribute to cognitive decline via increased WMH burden. Low

et al. (2022) also reported that higher CAIDE scores were associated with greater progression of WMH burden, particularly in periventricular and deep white matter region, however we did not observe significant associations between midlife UKBDRS and changes in WMH volume over our follow-up period. This discrepancy may be partly explained by the fact that our cohort may have been relatively healthy compared to clinical samples, potentially limiting our ability to detect clinically meaningful changes in WMH progression over the follow-up period. Taken together, these findings support the view that midlife dementia risk may contribute to brain structural degenerations including grey matter atrophy, white matter microstructural degeneration and increase WMH burden, a well before clinical onset.

4.4.4 The UKBDRS and cognition

The observed association between midlife risk factors and later-life cognitive function, particularly in episodic memory, executive function and visuospatial memory, aligns with longitudinal studies demonstrating that midlife hypertension, diabetes, obesity, and other vascular risk factors predict domain-specific cognitive decline (Debette et al., 2011; Whitmer et al., 2005). Episodic memory is the capacity to form and retrieve conscious memories of specific past events (e.g., recall what happened during a particular birthday party, including who was involved, where it happened, and the sequence of events; Tulving, 2002). It is one of the first memory systems to decline in both normal and pathological ageing and thus be considered a hallmark of early AD pathology (Irish et al., 2011; Tromp et al., 2015). Similarly,

executive function refers to higher-order cognitive processes such as mental set shifting, information updating and monitoring and inhibition of automatic responses (Miyake et al., 2000). It has also been increasingly recognised as an early marker of cognitive decline, even in cognitively healthy older adults (Guarino et al., 2019; Idowu & Szameitat, 2023). Visuospatial memory involves both visual perception and the interpretation of spatial relationships in one's environment (de Bruin et al., 2016). Previous studies have shown that patients with AD, Lewy bodies dementia, and vascular dementia all performed significantly worse than healthy controls on tests of object and space perception (Pal et al., 2016), and impairments in visuospatial function have been observed even in the prodromal stages of AD (Quental et al., 2013). Our findings support the relevance of the use of the UKBDRS to capture cognitive decline, particularly in domains known to be affected early in dementia. Moreover, our findings also extend previous research validating the UKBDRS as a predictive tool for dementia risk. While Anatürk et al., (2023) demonstrated that the UKBDRS predicts incident dementia diagnoses, our study shows that this risk score also associates with general cognitive decline as well as other relevant biomarkers of dementia in ageing individuals without clinical dementia.

4.4.5 Implications

This study has several important implications. Firstly, our findings support the increase in focus towards midlife as a critical window for intervention in order to help preserve brain health and reduce the risk of cognitive decline and dementia in later life. The UKBDRS captures a range

of modifiable midlife risk factors, such as hypertension, diabetes, depression, and material deprivation, and many of which can be managed through lifestyle changes, medical treatment, or social support. Early identification and management of these risks could potentially affect vascular and structural brain changes that emerge decades later, though intervention studies may be needed to confirm their effects. Secondly, we identified several vulnerable brain regions that appear particularly sensitive to midlife risk exposure, including the hippocampus, multiple DMN nodes, and major white matter tracts such as the corpus callosum, cingulum, and internal capsule. These regions may serve as important targets for longitudinal monitoring aimed at identifying at-risk individuals, slowing or preventing the progression of dementia.

4.4.6 Strengths and limitations

This study has several notable strengths. It is the first to examine associations between the novel UK Biobank Dementia Risk Score (UKBDRS) and several known dementia biomarkers, including GMV, WM microstructure, WMHs, and domain-specific cognitive decline in a healthy ageing cohort. With the addition of CVR which is a dynamic and sensitive vascular index, this study adds important evidence to the emerging literature linking midlife risk profiles to later-life brain vascular health. Secondly, the study benefits from a longitudinal design with over 20 years of follow-up, which enables a better understanding of the temporal dynamics between modifiable risk factors and age-related vascular, structural and functional brain changes in later-life.

We discuss general limitations of the cohort demographics and study design in **Chapter 7**, however specific limitations that apply to this chapter are acknowledged here. Although we found that higher UKBDRS in midlife was associated with impaired CVR in later life, this composite score reflects the combined influence of multiple risk factors. To an extent, these findings help address the evidence gap identified in **Chapter 2**, where our systematic review showed limited and inconsistent evidence regarding the relationship between certain lifestyle factors, such as depression or education with CVR. However, our analysis remains limited in its ability to determine their individual contributions to later-life CVR. Additionally, due to the use of different MRI scanners between MRI-Wave 1 and MRI-Wave 2, we standardised the structural data separately for each wave to account for inter-scanner variability. While necessary, this approach limited our ability to capture absolute changes in brain structural health measures for each participant, but rather focused on capturing an individual's change relative to the rest of the cohort, potentially reducing the sensitivity of our longitudinal findings.

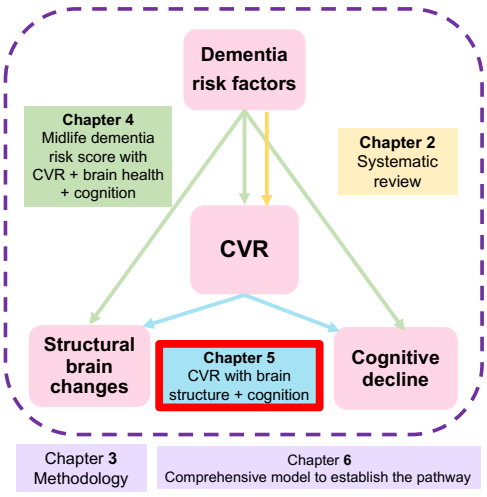
4.5 Conclusion

In conclusion, this study demonstrates that higher midlife dementia risk, as measured by the UKBDRS, is associated with poorer brain vascular and structural health, as well as faster cognitive decline in later life. These findings highlight midlife as a crucial window for intervention, with many modifiable factors included in the UKBDRS. Furthermore, this study

adds to the growing body of evidence supporting the utility of the UKBDRS not only for predicting dementia but also as a valuable tool for identifying individuals at risk of brain health deterioration and cognitive decline before clinical symptoms emerge. Lastly, our findings suggest that midlife dementia risk may contribute to later-life cognitive decline through progressive changes in cerebrovascular function and brain structure, which could be a potential mechanism underlying how dementia risk factor contribute to dementia and cognitive decline.

Chapter 5: Cerebrovascular reactivity and its associations with brain structure and cognition in older age

In **Chapter 4**, we showed that higher midlife dementia risk, as quantified by the UK Biobank Dementia Risk Score (UKBDRS), was significantly associated with lower CVR in key regions of the default mode network (DMN), as well as with neurodegeneration and cognitive decline. However, despite growing interest in CVR as a vascular marker of dementia risk, relatively little is known about whether impairments in CVR can directly influence brain structural and cognitive changes in ageing. In this chapter, we examined the association of CVR with our predefined structural brain imaging markers (grey matter volume, white matter degeneration and white matter hyperintensities), as well as domain-specific cognitive decline. A modified version of this chapter has been prepared as a manuscript entitled “The relationship between hippocampal cerebrovascular reactivity and brain structure in older age” and submitted to Human Brain Mapping (***Wang et al., under revision***).



5.1 Introduction

5.1.1 Impaired CVR and neurodegeneration in ageing

As discussed in **Chapter 1,** impaired CVR reflects dysfunction in the regulation of blood flow, which can lead to inadequate cerebral perfusion, chronic hypoxia and neuroinflammation (Iadecola, 2017; Ryman et al., 2023), all of which can accelerate cognitive decline and dementia progression. Numerous studies have demonstrated that CVR declines with ageing and is further reduced in individuals with dementia. For example, people with Alzheimer's disease (AD) or vascular dementia exhibit significantly lower CVR compared to healthy controls (Alwatban et al., 2019; Gao et al., 2013; Keeling et al., 2024; Vicenzini et al., 2007). Reduced CVR has been observed in several brain regions that are involved in memory and executive function, such as the precuneus (X. Tang et al., 2025), prefrontal and anterior cingulate cortices (Yezhuvath et al., 2012), and medial temporal areas (Kapoor et al., 2025). It has also been noted that impairments in CVR may even accelerate subsequent cognitive decline in patients with dementia (Cantin et al., 2011; Gao et al., 2013; Glodzik et al., 2013; Nicolakakis et al., 2008; Silvestrini et al., 2006; Vicenzini et al., 2007; Yezhuvath et al., 2012). Similarly, individuals with mild cognitive impairment (MCI) have also been observed to have lower CVR than healthy controls (Cantin et al., 2011; Engstrom et al., 2024; Larissa McKetton et al., 2019; Shim et al., 2015; Sur et al., 2020), which suggests that CVR dysfunctions may occur early in the course of dementia. Additionally, higher CVR in AD-signature regions,

including the hippocampus, parahippocampus, precuneus, temporal gyrus, and angular gyrus, has been associated with a lower risk of conversion from cognitively normal status to MCI among individuals with hypertension (Aslanyan et al., 2023). These findings all support the notion that impaired CVR is an early vascular signature of dementia vulnerability,

However, little is known about the association of CVR with brain structural and cognitive outcomes in “healthy” ageing, particularly in relation to the biomarkers outlined in **Chapter 1** (grey matter volume, white matter microstructure and white matter hyperintensities). Much of the existing cerebrovascular literature in this area has focused on cerebral blood flow (CBF). For example, lower baseline CBF has been associated with greater brain atrophy over time (Ghaznawi et al., 2020; Zonneveld et al., 2015). Lower CBF in the left posterior cingulate cortex was related with smaller GMV (Agnollitto et al., 2023). Similarly for white matter microstructure, CBF reduction has been observed in parietal and temporal cortices in which regions that exhibit microstructural abnormalities, and lower CBF has been associated with higher mean diffusivity (MD) and lower fractional anisotropy (FA) across multiple cortical regions (Chen et al., 2013; Niu et al., 2023; Yin et al., 2019). Reduced CBF has also been reported in individuals with a higher WMHs burden (Huang et al., 2021), although this association was attenuated after adjusting for age (Han et al., 2022). These studies consistently highlight the role of CBF in maintaining brain structural health (de la Torre, 2018; De La Torre, 2000b). Investigating how CVR relates to these established neuroimaging markers of dementia would enhance our understanding of the role of CVR in neurodegenerative pathway.

Similarly, in order to determine whether CVR has an early role in the pathological process of dementia, it is also essential to investigate whether it relates to cognitive decline before the onset of clinical symptoms. Current literature suggests a close link between CVR and cognitive decline (Catchlove, Pipingas, et al., 2018). Several studies have shown that individuals with cognitive impairment exhibit lower CVR compared with cognitively normal controls (Calviere et al., 2010; Metzger et al., 2018), and that higher CVR is positively associated with better global cognition, as measured by the Mini-Mental State Examination (Cantin et al., 2011; Kim et al., 2021; Richiardi et al., 2015). In addition, higher CVR has been positively associated with performance in executive function, processing speed, and both verbal and episodic memory (Catchlove, Parrish, et al., 2018; Chung et al., 2015; Launer et al., 2015; Peng et al., 2018), and lower baseline CVR has predicted greater declines in Stroop reading and interference tasks in people carrying the APOEε4 allele (Wolters, De Bruijn, et al., 2016). However, other studies have reported no significant associations between CVR and executive function or processing speed (Gauthier et al., 2015; Tchistiakova et al., 2014). Such inconsistencies may arise from variations in the cognitive tasks used to assess specific domains across studies as well as differences in how CVR is measured (e.g., BOLD MRI, ASL vs TCD etc.) or which region CVR was measured from (whole brain vs regional measures).

Overall, while most existing studies that examine the associations between CVR and cognitive decline have been conducted in individuals with cognitive impairments or other clinical

conditions, evidence in healthy older adults is limited and mixed, particularly in relation to longitudinal changes in cognition. Therefore, further work is needed to clarify the associations between regional CVR and domain-specific cognitive decline.

5.1.2 Aims and hypotheses

This chapter **aims** to fill these gaps in the literature by investigating the associations between global and regional CVR with brain structural and cognitive outcomes. We examine these associations both cross-sectionally and longitudinally between MRI-Waves 1 and 2 in the Heart and Brain cohort. It is important to note that CVR was measured only at MRI-Wave 2, whereas changes in brain structure and cognition were evaluated retrospectively over the preceding decade. Therefore, the longitudinal analyses in this chapter should be interpreted as reflecting retrospective changes rather than prospective predictions.

We examined three established MRI biomarkers of dementia: grey matter volume (GMV), white matter (WM) microstructure, and white matter hyperintensities (WMHs). Consistent with **Chapter 4**, we selected six nodes of the DMN for regional CVR and GMV analysis: the left and right hippocampi, medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), temporoparietal junction (TPJ), and precuneus. For WM microstructure, we focused on four white matter tracts defined a priori (the fornix, cingulum, internal capsule, and corpus callosum)

which are known to be critical for higher-order cognitive processes and commonly disrupted in dementia (Suri et al., 2014). Cognitive performance was grouped into six domains: episodic memory, visuospatial memory, executive function, working memory, fluency, and lexical retrieval.

We **hypothesised** that lower CVR at MRI-Wave 2 would be associated with poorer structural and cognitive outcomes at the same timepoint, including smaller GMV, reduced white matter (WM) microstructure, greater white matter hyperintensity (WMH) burden, and worse cognitive performance. Furthermore, we expected that lower CVR at MRI-Wave 2 would be associated with greater decline in these outcomes over the preceding nine years (between MRI-Waves 1 and 2), including more pronounced grey matter atrophy, WM microstructure degeneration, increased WMH volume, and faster cognitive decline.

5.2 Methods

The dataset, imaging pre-processing, and computation of longitudinal measures of the MRI and cognitive outcomes were detailed in **Chapter 3**. Here we only describe statistical analysis.

5.2.1 Statistical analysis for associations between CVR and MRI and cognitive outcomes at MRI-Wave 2

Statistical analyses were conducted using RStudio (version 4.3.0). We used multiple linear regression models to examine the cross-sectional associations between CVR and MRI and cognitive outcomes at MRI-Wave 2.

We assessed the associations between CVR in total grey matter and six regions of DMN (MPFC, PCC, TPJ, precuneus, left and right hippocampi) with the following MRI-based outcomes:

- GMV in the corresponding brain regions (i.e., total grey matter CVR with total GMV, MPFC CVR with MPFC GMV, etc.).
- WM microstructure as indicated by FA, MD, RD, and L1 in the whole brain and in four predefined white matter tracts (corpus callosum, fornix, internal capsule, cingulum).
- Whole-brain WMH volume as indicated by logWMH%.

For GMV, left and right hippocampi were analysed separately. In the WM microstructure and WMHs analysis, hippocampal CVR was defined as the average of CVR values from the left and right hippocampi. This is because most major white matter tracts, such as the corpus callosum, extend across both hemispheres, and our analyses of WMHs focused on whole-brain volume, thus it was considered more appropriate to use the mean CVR from the left and right hippocampi. The linear regression model used for these analyses is shown as ***Equation***

5.1.

Equation 5.1: CVR --> Brain Structure

$$\boxed{Y = \beta_0 + \beta_1 CVR + \beta_2 Sex + \beta_3 Age + \varepsilon}$$

- Y = MRI outcomes of GMV (whole brain and six DMN regions), WM microstructure (FA/MD/RD/L1 of whole brain and four WM tracts) or logWMH%
- β_0 = intercept
- ε = Error term

We also tested associations between whole brain and six regional CVR and six domain-specific cognitive scores (episodic memory, visuospatial memory, executive function, working memory, fluency, and lexical retrieval) assessed at MRI-Wave 2. The corresponding model is given in ***Equation 5.2***.

Equation 5.2: CVR --> Cognition

$$\boxed{Y = \beta_0 + \beta_1 CVR + \beta_2 Sex + \beta_3 Age + \beta_4 Education + \varepsilon}$$

- Y = Six cognitive domain scores
- β_0 = intercept
- ε = Error term

All regression models were adjusted for age (at MRI-Wave 2) and sex. For the cognitive analyses, we additionally included total years of education as a covariate.

5.2.2 Statistical analysis for associations between CVR and changes in MRI and cognitive outcomes from MRI-Wave 1 to 2

We next examined how CVR measured at MRI-Wave 2 was associated with longitudinal changes in MRI and cognitive outcomes from MRI-Wave 1 to MRI-Wave 2.

Specifically, we assessed the associations between CVR in total grey matter and six DMN regions and changes in the following MRI outcomes:

- ΔGMV in corresponding regions (i.e., MPFC CVR with MPFC ΔGMV; total grey matter CVR with total ΔGMV etc.).
- White matter microstructure metrics (ΔFA, ΔMD, ΔRD, ΔL1) in the whole brain and four predefined tracts.
- ΔWMH, calculated as change in ΔlogWMH%.

The regression model used to examine these longitudinal MRI associations is presented in ***Equation 5.3***.

Equation 5.3: CVR --> ΔBrain Structure

$$\boxed{\Delta Y = \beta_0 + \beta_1 CVR + \beta_2 Sex + \beta_3 Age_1 + \beta_4 D + \varepsilon}$$

- ΔY = changes in the MRI outcomes of GMV (whole brain and six DMN regions), WM

microstructure (FA/MD/RD/L1 of whole brain and four WM tracts) or logWMH%

- β_0 = intercept
- Age_1 = age at MRI-Wave 1
- D = time interval from MRI-Wave 1 to MRI-Wave 2
- ε = Error term

We also tested associations between total and six regional CVR and longitudinal change in the six cognitive outcomes from MRI-Wave 1 to 2. The model is shown in ***Equation 5.4***.

Equation 5.4: **CVR --> ΔCognition**

$$\boxed{\Delta Y = \beta_0 + \beta_1 CVR + \beta_2 Sex + \beta_3 Age_1 + \beta_4 D + \beta_5 Education + \varepsilon}$$

- ΔY = Six cognitive domain scores
- β_0 = intercept
- Age_1 = age at MRI-Wave 1
- D = time interval from MRI-Wave 1 to MRI-Wave 2
- ε = Error term

All longitudinal models adjusted for age at MRI-Wave 1, sex, and time interval between MRI waves. For the cognition models, total years of education was additionally included as a covariate.

Associations with $p < 0.05$ were considered statistically significant and reported in the results. We additionally corrected for multiple comparisons using the Benjamini-Hochberg (BH)

correction (Benjamini & Hochberg, 1995), with significance level of $p_{corr} < 0.05$. For CVR-GMV analysis, correction was applied across the six DMN CVR-GMV associations tested. In the CVR-WM microstructure analysis, corrections were applied across five CVR regions and four and white matter tracts for each diffusion metric (e.g., FA across five CVR regions and four tracts) (*note that the WM microstructure analysis included five CVR regions because left and right hippocampus was merged*). For cognitive analyses, correction was applied across the six cognitive domains for total grey matter CVR. For DMN CVR, correction was applied across six DMN CVR regions and six cognitive domains. Cohen's f^2 of the whole regression model as well as the individual independent variable were used to assess effect size for significant associations.

5.2.3 Interpreting longitudinal analyses

As discussed in **Chapter 3**, GMV and white matter microstructure generally decline with age, while WMHs tend to increase with age from MRI-Wave 1 to 2. Thus, a **positive β value for GMV indicates that lower CVR is associated with greater GMV decline,** whereas a **negative β for WMH indicates that lower CVR is linked to greater WMH accumulation over time**. For white matter microstructure, FA typically decreases, while diffusivity measures (MD, RD, L1) increase with age. Accordingly, a **positive β for FA suggests that lower CVR is related to a greater reduction in FA,** and a **negative β for MD, RD, or L1 suggests that lower CVR is associated with greater increases in these diffusivity metrics**, which reflects

more pronounced white matter deterioration. Cognitive performance also declines with age. Thus, a **positive β means that lower CVR is associated with greater cognitive decline**, and a negative β suggests relative preservation of function.

5.3 Results

As described in **Chapter 4**, 148 participants were included in the statistical analyses from an original cohort of 163 people in the Heart and Brain Study. Participants were excluded from the analysis due to invalid CVR scans or outlier values in CVR or cognitive measures. Age and sex distributions, as well as descriptive statistics for all neuroimaging and cognitive measures, have been reported in detail in **Chapter 4**.

5.3.1 Associations between CVR and GMV

In cross-sectional analyses at MRI-Wave 2, lower CVR in the left hippocampus was significantly associated with smaller GMV in this region (β = 1.212, 95% CI [0.234, 2.190], p = 0.016, p_{corr} = 0.093). However, this association was not significant after corrections for multiple comparisons. No other significant associations were observed between CVR and GMV at MRI-Wave 2 in the other regions (***Table 5.1, Appendix Table 5.1, Figure 5.1)***.

In longitudinal analysis, lower CVR in the MPFC at MRI-Wave 2 was significantly associated with greater GMV decline in the MPFC from MRI-Wave 1 to 2, and this association did not survive after corrections for multiple comparisons ($\beta = 1.530$, 95% CI [0.245, 2.814], $p = 0.020$, $p_{corr} = 0.120$). No significant associations were found between CVR and GMV change for any of the other regions (***Table 5.1, Appendix Table 5.1, Figure 5.1***).

Table 5.1: Significant associations between CVR at MRI-Wave 2 and GMV measured at MRI-Wave 2 and the change in GMV from MRI-Wave 1 to 2

Only significant associations between CVR and GMV are summarised here (for full table with all associations see Appendix Table 5.1). Positive beta value reflects that lower CVR is associated with greater GMV decline. 95% CI = 95% confidence interval; bolded p-values highlight significant results ($p < 0.05$), p_{corr} indicates the Benjamini-Hochberg corrected p-value and is reported only for results with uncorrected $p < 0.05$ (yellow highlights). Multiple comparisons were conducted across DMN regions, separately for the cross-sectional and longitudinal analyses. Cohen's f^2 is reported for two components: the overall model (reflecting the effect size of the full model including all covariates), and the independent variable (CVR) alone (reflecting its unique contribution to explaining variance in the outcome).

Exposure	Outcome	Beta [95% CI]	p-value	p_{corr}	Cohen's f^2 Overall model (Independent variable)
MPFC CVR	MPFC GMV	2.689 [-0.175, 5.553]	0.066		
	ΔMPFC GMV	1.530 [0.245, 2.814]	**0.020**	0.120	0.165 (0.039)
Left Hippocampus CVR	Left Hippocampus GMV	1.212 [0.234, 2.190]	**0.016**	0.093	0.221 (0.038)
	ΔLeft Hippocampus GMV	1.328 [-0.431, 3.087]	0.138		

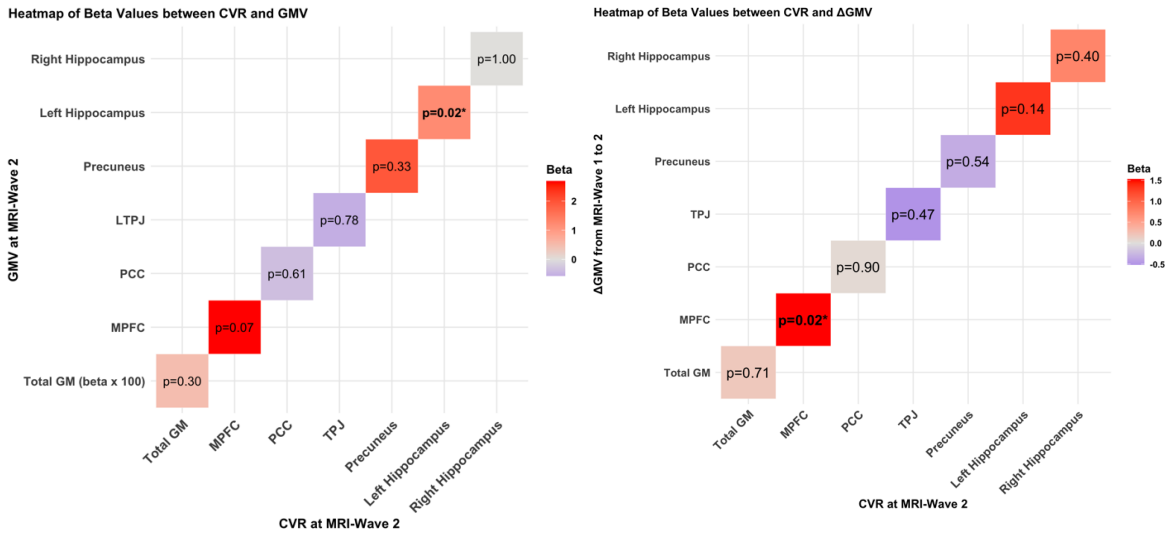


Figure 5.1: Heatmap of the associations between CVR and GMV at MRI-Wave 2 and change in GMV from MRI-Wave 1 to 2

Cell colour reflects only the magnitude and direction of the beta coefficient, not its significance. Red indicates a more positive beta, blue/purple a more negative beta. Statistical significance is shown within each cell, and bolded values with asterisks denote $p < 0.05$.

5.3.2 Associations between CVR and WM microstructure

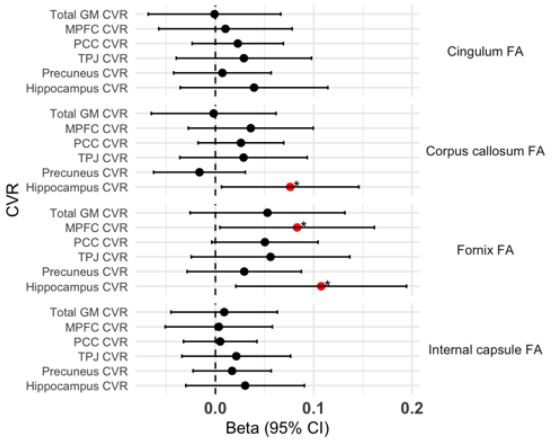
Lower hippocampal CVR was significantly associated with poorer WM diffusion metrics at MRI-Wave 2 in the fornix (lower FA: $\beta = 0.108$, $p = 0.016$, $p_{corr} = 0.255$; higher RD: $\beta = -2.139 \times 10^{-4}$, $p = 0.032$, $p_{corr} = 0.322$), corpus callosum (lower FA: $\beta = 0.076$, $p = 0.033$, $p_{corr} = 0.255$; higher MD: $\beta = -1.170 \times 10^{-4}$, $p = 0.016$, $p_{corr} = 0.162$; higher RD: $\beta = -1.256 \times 10^{-4}$, $p = 0.018$, $p_{corr} = 0.322$), and the internal capsule (higher MD: $\beta = -7.742 \times 10^{-5}$, $p = 0.016$, $p_{corr} = 0.162$; higher L1: $\beta = -1.127 \times 10^{-4}$, $p = 0.013$, $p_{corr} = 0.255$). Lower MPFC CVR was significantly associated lower FA in the fornix ($\beta = 0.083$, $p = 0.038$, $p_{corr} = 0.255$). In contrast, lower precuneus CVR was significantly associated with lower L1 in the cingulum ($\beta = 8.071 \times 10^{-5}$, $p = 0.026$, p_{corr}

=0.263). These associations did not survive correction for multiple comparisons ($p_{corr} > 0.05$).

Details can be found in ***Table 5.2, Appendix Table 5.2, Figure 5.2***.

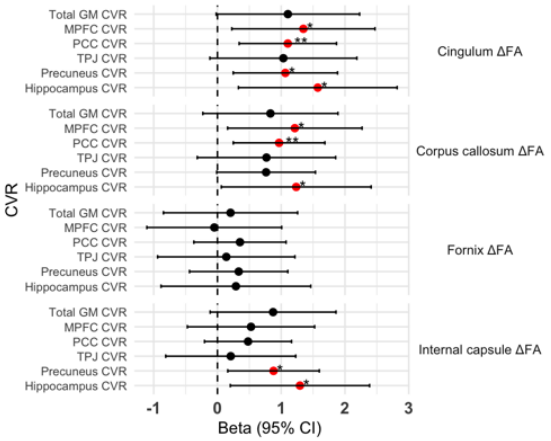
A: Cross-sectional associations

Associations between CVR and FA

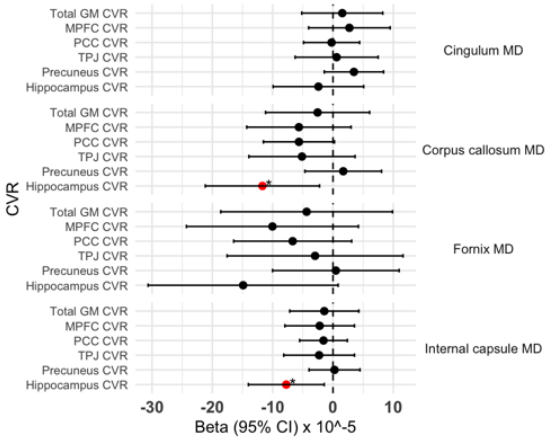


B: Longitudinal associations

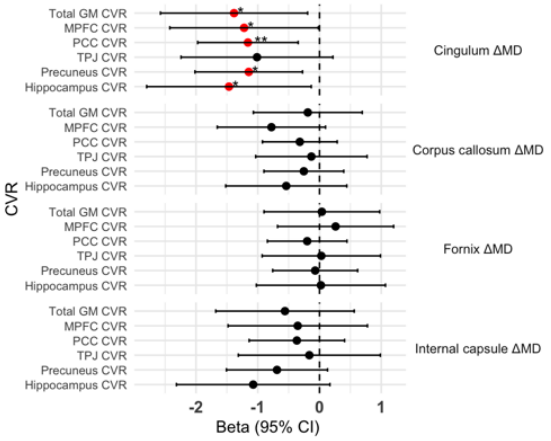
Associations between CVR and Δ FA



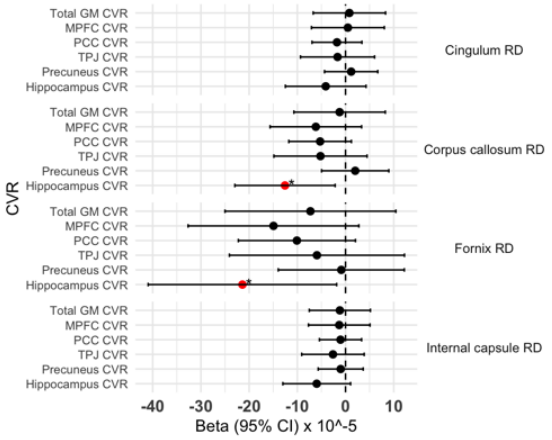
Associations between CVR and MD



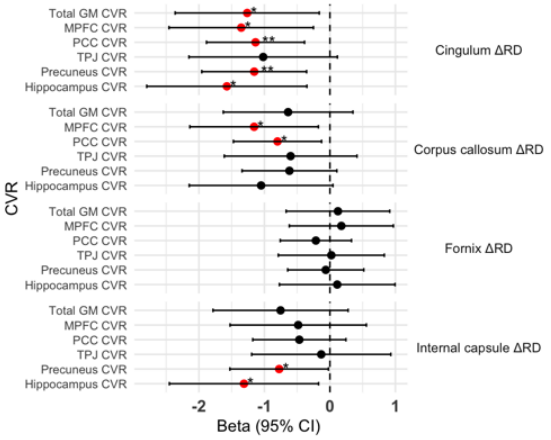
Associations between CVR and Δ MD



Associations between CVR and RD



Associations between CVR and Δ RD



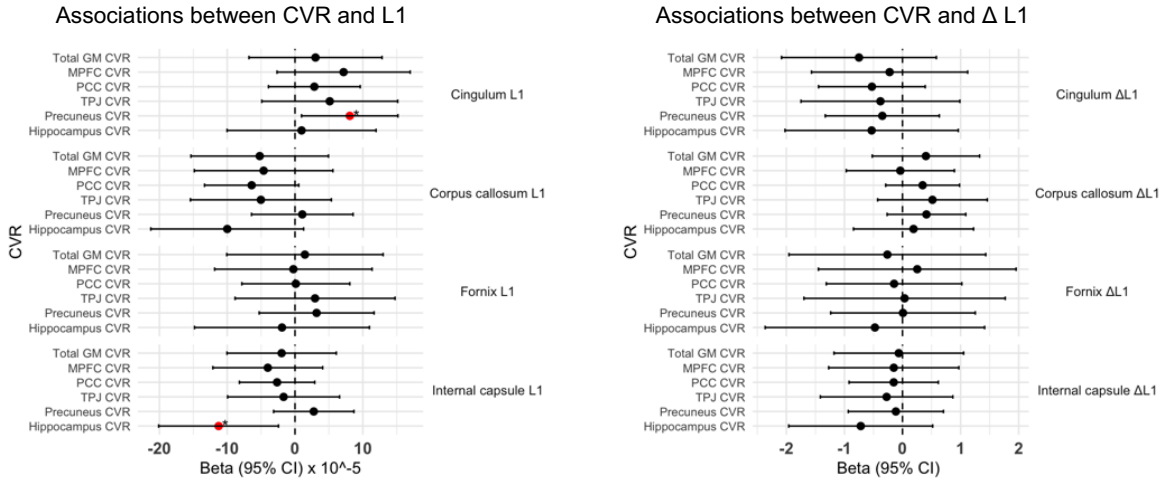


Figure 5.2: Forest plots of associations between CVR at MRI-Wave 2 and WM diffusion metrics at MRI-Wave 2 and changes from MRI-Wave 1 to 2

*Panel A shows the cross-sectional associations between CVR and WM diffusion metrics at MRI-Wave 2 and Panel B shows the associations of CVR with the changes in WM diffusion metrics from MRI-Wave 1 to 2. FA generally decreases with age, so a more negative change indicates greater decline. In contrast, diffusivity metrics (MD, RD, L1) typically increase with age, so a more positive change reflects greater increase. Therefore, a positive beta for FA indicates that lower CVR is associated with greater FA decline, whereas a negative beta for MD/RD/L1 indicates that lower CVR is associated with greater increases in these diffusivity measures. Red dots indicate statistically significant associations. Asterisks denote significance levels: * p < 0.05, ** p < 0.01. Error bars represent 95% confidence intervals around the beta estimates from linear regression models.*

Table 5.2: Associations between CVR at MRI-Wave 2 and WM diffusion metrics measured at MRI-Wave 2

Only significant associations between CVR and WM tracts are summarised here (for full table with all associations see Appendix Table 5.2). 95% CI = 95% confidence interval; p_{corr} refers to the significance level after correction for multiple comparisons using the Benjamini-Hochberg approach and is only presented for the associations with uncorrected p < 0.05 (yellow highlights). For total grey matter CVR, corrections were applied across the four white matter tracts within each diffusion metric (e.g., FA in all tracts). For regional CVR, corrections were applied across all CVR regions and tracts within each diffusion metric (e.g., all FA values across five CVR regions and four tracts). Cohen's f^2 is reported for two components: the overall model (reflecting the effect size of the full model including all covariates), and the independent variable (CVR) alone (reflecting its unique contribution to explaining variance in the outcome). Hpc = Hippocampus

Exposure	Outcome		Beta [95% CI] *Beta (e^{-5}) for MD/RD/L1*	p-value	p_{corr}	Cohen's f^2 Overall model (Independent variable)
MPFC CVR	Fornix	FA	0.083 [0.005, 0.162]	**0.038**	0.255	0.200(0.031)
		MD	-10.044 [-24.302, 4.215]	0.166		
		RD	-14.944 [-32.655, 2.767]	0.098		
		L1	-0.242 [-11.852, 11.368]	0.967		
Precuneus CVR	Cingulum	FA	0.007 [-0.042, 0.057]	0.777		
		MD	3.469 [-1.448, 8.386]	0.165		
		RD	1.168 [-4.354, 6.690]	0.676		
		L1	8.071 [0.964, 15.178]	**0.026**	0.263	0.036(0.035)
Hpc CVR	Corpus callosum	FA	0.076 [0.006, 0.146]	**0.033**	0.255	0.189(0.029)
		MD	-11.702 [-21.174, -2.230]	**0.016**	0.162	0.323(0.043)
		RD	-12.555 [-22.957, -2.153]	**0.018**	0.322	0.252(0.038)
		L1	-9.996 [-21.264, 1.272]	0.082		
	Internal capsule	FA	0.030 [-0.030, 0.091]	0.323		
		MD	-7.742 [-14.031, -1.452]	**0.016**	0.162	0.161(0.035)
		RD	-5.977 [-13.001, 1.047]	0.095		

		L1	-11.271 [-20.103, -2.438]	**0.013**	0.255	0.182(0.046)
	Fornix	FA	0.108 [0.021, 0.194]	**0.016**	0.255	0.214(0.043)
		MD	-14.900 [-30.657, 0.856]	0.064		
		RD	-21.390 [-40.940, -1.839]	**0.032**	0.322	0.208(0.031)
		L1	-1.922 [-14.816, 10.972]	0.769		

There were also several associations between CVR at MRI-Wave 2 and longitudinal change in WM microstructure in the preceding ~ 9 years. Specifically, **lower total grey matter CVR** was associated with larger deterioration of WM microstructure in the cingulum, reflected by greater increases in MD (β = -1.384, p = 0.023, p_{corr} = 0.093) and RD (β = -1.263, p = 0.025, p_{corr} = 0.099). **Lower MPFC CVR** was significantly associated with a larger decline in FA (β = 1.348, p = 0.019, p_{corr} = 0.059) and greater increases in MD (β = -1.221, p = 0.047, p_{corr} =0.233) and RD (β = -1.354, p = 0.016, p_{corr} = 0.069) in the cingulum. Lower MPFC CVR was also significantly associated with larger decline in FA (β = 1.214, p = 0.024, p_{corr} = 0.061) and a greater increase in RD (β = -1.157, p = 0.021, p_{corr} = 0.069) in the corpus callosum. However, these associations did not survive the strict corrections for multiple comparisons.

Lower PCC CVR was significantly associated with larger deterioration in the cingulum, as indicated by a larger decline in FA (β = 1.104, p = 0.005, p_{corr} =0.059) and greater increases in MD (β = -1.159, p = 0.006, p_{corr} = 0.103) and RD (β = -1.136, p = 0.003, p_{corr} = 0.049). Lower PCC CVR was also associated with a larger decline in FA (β = 0.967, p = 0.009, p_{corr} = 0.059) and greater increase in RD (β = -0.800, p = 0.020, p_{corr} = 0.069) in the corpus callosum.

Lower precuneus CVR was significantly associated with a larger decline in FA (β = 1.066, p = 0.011, p_{corr} = 0.059) and greater increases in MD (β = -1.146, p = 0.010, p_{corr} = 0.103) and RD (β = -1.156, p = 0.005, p_{corr} = 0.049) in the cingulum. It was also significantly associated with a larger decline in FA (β = 0.880, p = 0.017, p_{corr} = 0.059) and greater increase in RD (β = -0.775, p = 0.044, p_{corr} = 0.109) in internal capsule.

Lower hippocampal CVR was significantly associated with a larger decline in FA (β = 1.574, p = 0.014, p_{corr} = 0.059) and greater increases in MD (β = -1.466, p = 0.031, p_{corr} = 0.209) and RD (β = -1.573, p = 0.012, p_{corr} = 0.069) in the cingulum. Hippocampal CVR was also associated with a larger decline in FA (β = 1.294, p = 0.021, p_{corr} = 0.059) and greater increase in RD (β = -1.312, p = 0.024, p_{corr} =0.069) in internal capsule and a larger decline in FA (β = 1.236, p = 0.039, p_{corr} = 0.088) in the corpus callosum.

Statistical results are summarised in ***Table 5.3, Figure 5.2***.

Table 5.3: Associations between CVR at MRI-Wave 2 and change in WM diffusion metrics measured from MRI-Wave 1 to 2

Only significant associations between CVR and WM tracts tare summarised here (for full table with all associations see Appendix Table 5.3). Positive beta values for FA indicate that lower CVR is associated with greater FA decline, whereas negative beta values for MD/RD/L1 indicate that lower CVR is associated with greater increases in these diffusivity measures. 95% CI = 95% confidence interval; p_{corr} refers to the significance level after correction for multiple comparisons using the Benjamini-Hochberg procedure and is only presented for associations with uncorrected p < 0.05. For total grey matter CVR, corrections were applied across the four white matter tracts within each diffusion metric (e.g., FA in all tracts). For regional CVR, corrections were applied across five CVR regions and four tracts for each diffusion metric. Associations with p < 0.05 (uncorrected) and surviving multiple comparison correction are highlighted in orange. Associations with p < 0.05 (uncorrected) but not surviving multiple comparison correction are highlighted in yellow. Cohen's f^2 is reported for two components: the overall model (reflecting the effect size of the full model including all covariates), and the independent variable (CVR) alone (reflecting its unique contribution to explaining variance in the outcome). Hpc = Hippocampus

Exposure	Outcome		Beta [95% CI]	p-value	p_{corr}	Cohen's f^2 Overall model (Independent variable)
Total GM CVR	Cingulum	ΔFA	1.105 [-0.020, 2.230]	0.054		
		ΔMD	-1.384 [-2.576, -0.192]	**0.023**	0.093	0.073 (0.037)
		ΔRD	-1.263 [-2.363, -0.162]	**0.025**	0.099	0.203 (0.036)
		ΔL1	-0.750 [-2.083, 0.583]	0.268		
MPFC CVR	Corpus callosum	ΔFA	1.214 [0.159, 2.269]	**0.024**	0.061	0.328 (0.036)
		ΔMD	-0.779 [-1.656, 0.098]	0.081		
		ΔRD	-1.157 [-2.139, -0.176]	**0.021**	0.069	0.342 (0.038)
		ΔL1	-0.037 [-0.968, 0.894]	0.937		
	Cingulum	ΔFA	1.348 [0.226, 2.471]	**0.019**	0.059	0.273 (0.039)
		ΔMD	-1.221 [-2.424, -0.019]	**0.047**	0.233	0.064 (0.028)
		ΔRD	-1.354 [-2.457, -0.251]	**0.016**	0.069	0.209 (0.041)
		ΔL1	-0.222 [-1.567, 1.122]	0.744		

PCC CVR	Corpus callosum	ΔFA	0.967 [0.248, 1.686]	**0.009**	0.059	0.345 (0.049)
		ΔMD	-0.319 [-0.924, 0.287]	0.300		
		ΔRD	-0.800 [-1.473, -0.127]	**0.020**	0.069	0.343 (0.039)
		ΔL1	0.346 [-0.289, 0.982]	0.283		
	Cingulum	ΔFA	1.104 [0.340, 1.868]	**0.005**	0.059	0.295 (0.057)
		ΔMD	-1.159 [-1.973, -0.345]	**0.006**	0.103	0.092 (0.055)
		ΔRD	-1.136 [-1.884, -0.387]	**0.003**	**0.049**	0.234 (0.063)
		ΔL1	-0.527 [-1.445, 0.391]	0.259		
Precuneus CVR	Cingulum	ΔFA	1.066 [0.247, 1.884]	**0.011**	0.059	0.282 (0.046)
		ΔMD	-1.146 [-2.017, -0.275]	**0.010**	0.103	0.084 (0.047)
		ΔRD	-1.156 [-1.956, -0.356]	**0.005**	**0.049**	0.228 (0.057)
		ΔL1	-0.348 [-1.330, 0.634]	0.485		
	Internal capsule	ΔFA	0.880 [0.162, 1.598]	**0.017**	0.059	0.088 (0.041)
		ΔMD	-0.689 [-1.507, 0.130]	0.098		
		ΔRD	-0.775 [-1.527, -0.022]	**0.044**	0.109	0.094 (0.029)
		ΔL1	-0.115 [-0.934, 0.705]	0.783		
Hpc CVR	Corpus callosum	ΔFA	1.236 [0.061, 2.411]	**0.039**	0.088	0.321 (0.030)
		ΔMD	-0.539 [-1.519, 0.441]	0.279		
		ΔRD	-1.051 [-2.148, 0.046]	0.060		
		ΔL1	0.190 [-0.844, 1.223]	0.717		
	Cingulum	ΔFA	1.574 [0.329, 2.819]	**0.014**	0.059	0.278 (0.044)
		ΔMD	-1.466 [-2.798, -0.133]	**0.031**	0.209	0.069 (0.033)
		ΔRD	-1.573 [-2.796, -0.351]	**0.012**	0.069	0.214 (0.045)
		ΔL1	-0.531 [-2.023, 0.960]	0.482		
	Internal capsule	ΔFA	1.294 [0.201, 2.387]	**0.021**	0.059	0.085 (0.038)
		ΔMD	-1.074 [-2.317, 0.168]	0.090		
		ΔRD	-1.312 [-2.451, -0.173]	**0.024**	0.069	0.102 (0.036)

ΔL1	-0.719 [-1.959, 0.521]	0.253

5.3.3 Associations between CVR and WMHs

No significant associations were observed between CVR and WMHs at MRI-Wave 2 or the change from MRI-Wave 1 to 2 across all CVR regions examined (all p-values > 0.05, ***Appendix Table 5.4***).

5.3.4 Associations between CVR and Cognition

There were no significant cross-sectional associations between CVR and cognitive performance across any brain region or cognitive domain.

Lower MPFC CVR was associated with greater decline in executive function (β = 61.016, 95% CI [10.361, 111.672], p = 0.019, p_{corr} = 0.335), and with greater decline in visuospatial memory (35.467, 95% CI [7.709, 63.225], p = 0.013, p_{corr} = 0.335). Additionally, **lower right hippocampus CVR** was also associated with greater decline in visuospatial memory (β = 30.696, 95% CI [1.523, 59.869], p = 0.039, p_{corr} = 0.423). In contrast, **lower CVR in total grey matter** was significantly associated with smaller decline in lexical retrieval over time (β = -12.934, 95% CI [-23.975, -1.893], p = 0.022, p_{corr} =0.132). Other longitudinal associations between CVR and cognitive change were not statistically significant. Details about the results can be found in ***Table 5.4, Appendix Table 5.5, Figure 5.3*.**

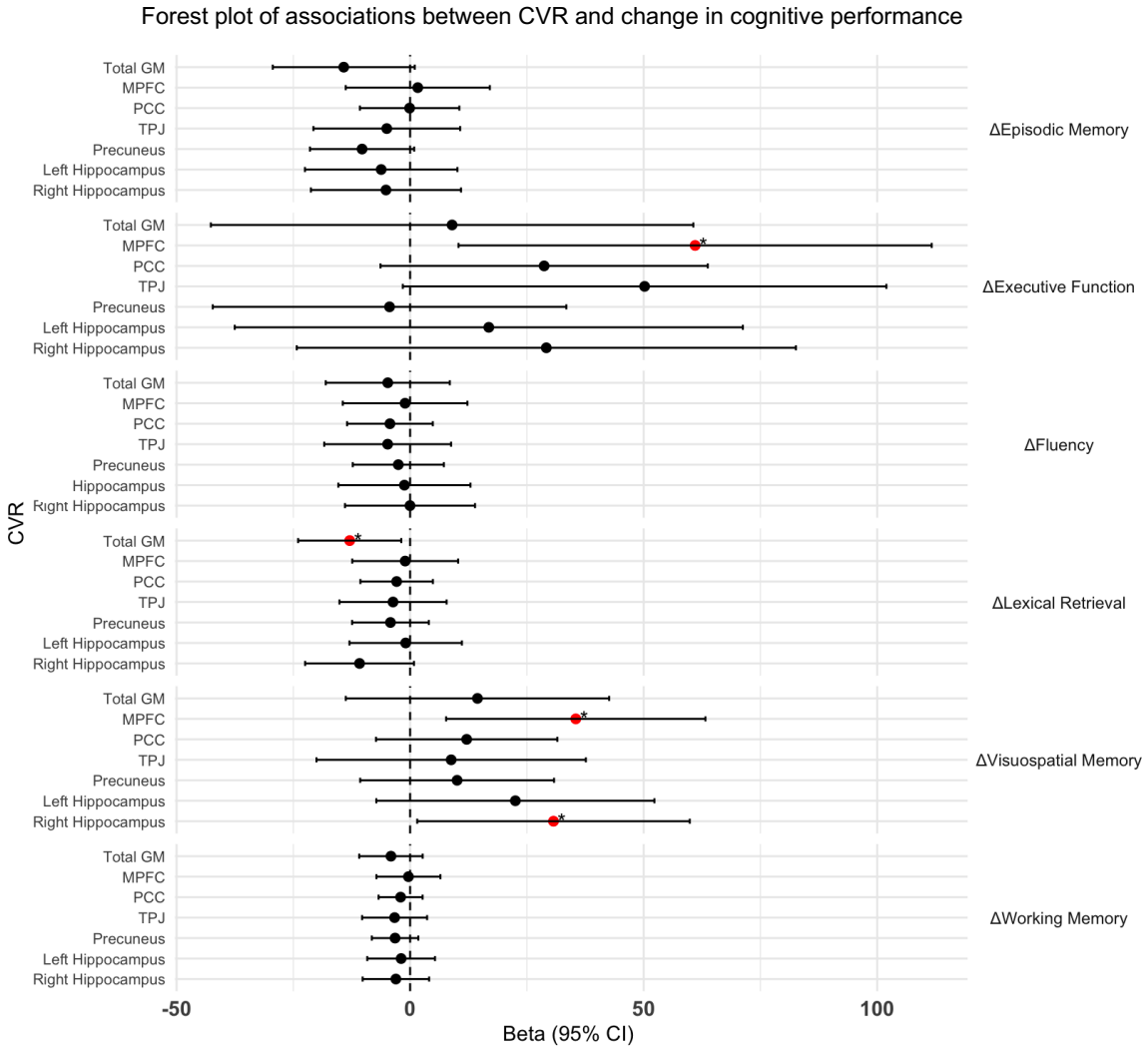


Figure 5.3: Forest plots of associations between CVR at MRI-Wave 2 and changes in cognition from MRI-Wave 1 to 2

*Note: As cognitive performance generally declines from MRI-Wave 1 to Wave 2, the change in cognitive scores (MRI-Wave 2 - MRI-Wave 1) tends to be negative. Therefore, a larger (i.e., more negative) Δ value indicates greater cognitive decline, whereas a smaller (i.e., less negative) Δ value reflects less decline. Positive beta means that lower CVR is associated with greater cognitive decline, and a negative beta suggests lower CVR is associated with smaller cognitive decline. Red dots indicate statistically significant associations. Asterisks denote significance levels: * p < 0.05, ** p < 0.01. Error bars represent 95% confidence intervals around the beta estimates from linear regression models.*

Table 5.4: Associations between CVR at MRI-Wave 2 and change in cognition from MRI-Wave 1 to 2

Only significant associations between CVR and cognition tare summarised here (for full table with all associations see Appendix Table 5.5). Positive beta means that lower CVR is associated with greater cognitive decline, and a negative beta suggests lower CVR is associated with smaller cognitive decline. 95% CI = 95% confidence interval; p_{corr} refers to the significance level after correction for multiple comparisons using the Benjamini-Hochberg approach and only presents for associations with uncorrected p < 0.05 (yellow highlighted). Correction was applied across the six cognitive domains for total grey matter CVR, and across all six Cognitive domains x CVR in six DMN regions for cross only presented for statistically significant associations. Cohen's f^2 is reported for two components: the overall model (reflecting the effect size of the full model including all covariates), and the independent variable (CVR) alone (reflecting its unique contribution to explaining variance in the outcome)

Exposure	**Outcome**	**Beta [95% CI]**	**p-value**	**p_{corr}**	**Cohen's f^2 Overall model (Independent variable)**
Total GM CVR	Δlexical Retrieval	-12.934 [-23.975, -1.893]	**0.022**	0.132	0.355(0.039)
MPFC CVR	Δvisuospatial Memory	35.467 [7.709, 63.225]	**0.013**	0.335	0.115(0.047)
	Δexecutive Function	61.016 [10.361, 111.672]	**0.019**	0.335	0.177(0.041)
Right Hippocampus CVR	Δvisuospatial Memory	30.696 [1.523, 59.869]	**0.039**	0.423	0.099(0.032)

5.4 Discussion

5.4.1 Summary of the findings

This chapter examined how CVR relates to dementia brain structural markers and cognitive outcomes in older age. Our findings revealed that people with lower CVR in the left hippocampus and MPFC tended to have smaller GMV and a greater atrophy in these regions over time. People with lower CVR were also more likely to have poorer WM microstructure in the corpus callosum and fornix, as well as greater WM microstructure decline over the preceding decade in the corpus callosum, cingulum, and internal capsule. Overall, the corpus callosum emerged as the most consistently affected tract, and hippocampal CVR showed the most widespread associations across WM metrics. In terms of cognition, people with lower MPFC CVR showed greater decline in executive function and visuospatial memory, and those with lower right hippocampal CVR also exhibited more pronounced decline in visuospatial memory. However, CVR was not significantly associated with cerebrovascular lesions as measured by WMHs. Many of these associations had small-to-moderate effect sizes and did not survive strict corrections for multiple comparisons. However, they support the emerging role of CVR as a marker of brain anatomical and cognitive decline, and as a mechanism within the neurodegenerative pathway.

5.4.2 Hippocampal and MPFC CVR with grey matter atrophy

Impaired CVR may disrupt neurovascular coupling and contribute to neural dysfunction. These impairments can reduce cerebral autoregulation and lead to chronic cerebral hypoperfusion, which has been linked to microvascular damage and structural brain atrophy (Pillai & Mikulis, 2015; Zonneveld et al., 2015). In our study, we observed significant associations between lower CVR in the left hippocampus and smaller GMV in later life, as well as between lower CVR in the MPFC and greater GMV atrophy over time. Although not statistically significant, similar trends were found between left hippocampal CVR and longitudinal GMV decline, and between MPFC CVR and cross-sectional GMV. These findings highlight the potential vulnerability of the MPFC and left hippocampus to vascular mechanisms involved in dementia pathology. The MPFC is a region critically involved in executive control, attention and working and spatial memory, and its abnormalities in functional connectivity precede structural changes and may be driven by ageing-related vascular mechanisms (Jobson et al., 2021). Similarly, the hippocampus is an important region that is involved in episodic memory, working memory, processing speed and executive function in older adults (O'Shea et al., 2016), and is among the first regions to exhibit atrophy in AD (Jack et al., 2000, 2011; Pini et al., 2016). The hippocampus has relatively low vascular density, with micro-vessels spaced further apart (Ji et al., 2021), which makes it more vulnerable to even minor declines in vascular autoregulation and perfusion. The susceptibility of both the MPFC and left hippocampus to vascular compromise may partly reflect their high metabolic demand and vital role in cognitive

processing. A previous study in hypertensive patients found no association between CVR and hippocampal volume (Aslanyan et al., 2023), while another study in individuals with multiple sclerosis reported that lower CVR was linked to greater grey matter atrophy (Marshall et al., 2014). Our findings are in line with the latter but extend current knowledge by demonstrating that, even in cognitively healthy individuals without severe cerebrovascular burden, lower CVR is associated with reduced GMV and atrophy specifically in the left hippocampus and MPFC, both of which are key regions for episodic memory, including encoding object-context associations and retrieving past events (Morici et al., 2022). This may suggest that CVR-related vulnerability is more pronounced in memory-related regions with higher metabolic demand, which makes them particularly vulnerable to vascular insults.

It Is Important to note that significant CVR-GMV associations were found only in the left, but not the right hippocampus. While the exact mechanism underlying this asymmetry remains unclear, the observed associations only in left hippocampus might be explained by its greater susceptibility to age-related neurodegeneration. Previous studies suggest functional lateralisation within the hippocampus: the right hippocampus is more involved in spatial memory, while the left is linked to episodic memory, the latter being one of the earliest cognitive functions affected in both ageing and dementia (Ezzati et al., 2016; Tromp et al., 2015). Consistently, studies have shown greater volume reduction in the left hippocampus compared to the right in individuals with MCI and AD (Shi et al., 2009). It is possible that grey matter atrophy, which is often a result of neuronal loss (Kril et al., 2004; Scheff & Price, 2003), may

be exacerbated by impaired CVR, particularly in the left hippocampus, eventually compromising perfusion in this region (Nur et al., 2009). This vascular sensitivity may impact both GMV and neuronal function and contribute to subsequent cognitive decline (Johnson, 2023; Nur et al., 2009).

5.4.3 CVR and WM microstructure

We found that lower CVR, especially hippocampal CVR was associated with poorer WM microstructure in the corpus callosum and fornix, along with larger WM microstructure decline in the corpus callosum, cingulum and internal capsule between ~70 to ~80 years of age. In addition to hippocampal CVR, we also observed significant associations between changes in WM diffusion metrics and CVR in other DMN regions, including the MPFC and PCC and precuneus. While most associations did not survive multiple comparison correction (except for PCC CVR and precuneus CVR associations with change in RD in the cingulum, which survived correction), their consistent direction and significance before correction indicate potential underlying relationships and are worth discussing. The affected WM tracts in our study align with previous studies showing similar white matter changes in the corpus callosum, fornix, internal capsule, and cingulum bundle in AD and MCI patients, as well as in healthy older adults (Bennett et al., 2017; Bosch et al., 2012; Huang et al., 2012; Zhang et al., 2011). Specifically, we noted associations with higher diffusivity alongside lower FA, which together indicate a structural loss of myelin in these tracts. The fornix and cingulum are key hippocampal tracts;

the fornix connects the hippocampus to other limbic regions essential for memory and emotional regulation (Chen et al., 2015), whereas the cingulum, which links the cingulate gyrus with the hippocampus and other cortical regions, is involved in executive control, emotion, and episodic memory (Bubb et al., 2018). Interestingly, we also noted associations of CVR with two distal WM tracts that are not directly connected to the hippocampus but are known to be affected in AD and MCI: the corpus callosum, which is a heavily myelinated tract and regulates inter-hemispheric cognitive integration (Abe et al., 2004; Barbaresi et al., 2024), and the internal capsule, which is involved in sensorimotor control (Xiuxiu Liu et al., 2021). The longitudinal findings in our study highlight the progressive vulnerability of these tracts over time, and the microstructure of these output tracts is closely linked to the vascular health of the DMN regions. While our study is not designed to infer causality, one possible interpretation is that impairments in cerebrovascular reserve could, over time, lead to axonal hypoperfusion and ischemia (Chen et al., 2013; Van Beek et al., 2008), thus disrupting axon-glia integrity (McQueen et al., 2014). Others have shown that such disruptions are often accompanied by a decrease in the density of oligodendrocytes (the cells responsible for myelination), which further exacerbates myelin loss (Arai, 2020; McIver et al., 2010). These findings underscore a potentially critical role of DMN CVR, especially hippocampal CVR in preserving the microstructure of the key WM tracts and, potentially, their associated cognitive functions.

5.4.4 CVR and WM lesion burden

Although previous studies have found CVR to be lower in individuals with more pronounced WMH, or within WMH lesions compared to contralateral normal-appearing white matter in people with leukaoraisis (Marstrand et al., 2002; Ni et al., 2021; Sam et al., 2016), we found no association of whole brain or regional CVR with WMH in our study. This might be because our cohort did not include anyone with diagnosed cerebrovascular pathology, and therefore generally had lower WMH volumes compared to individuals with more pronounced leukoaraiosis. Given that the role of WMH in dementia primarily depends on lesion severity (Frisoni et al., 2007; Van Der Flier et al., 2005), the lack of association in our study might be explained by the relatively low WMH burden in our cohort.

5.4.5 CVR and longitudinal cognitive decline

We did not find any significant cross-sectional associations between CVR and cognitive performance in any domain. Although CVR has often been linked with AD and vascular dementia (Cantin et al., 2011; Glodzik et al., 2013), its cross-sectional associations with cognition in preclinical older adults have been mixed (Catchlove, Pipingas, et al., 2018). Some studies report positive CVR-cognition associations in subjective memory or processing speed (Catchlove, Parrish, et al., 2018; Kim et al., 2021), while others find no significant relationships with cognitive performance (Gauthier et al., 2015b; Tchistiakova et al., 2014; Thomas et al., 2016). There are several possible reasons why we did not observe significant cross-sectional associations. First, our cognitive measures may not have been sufficiently sensitive to detect

subtle individual variations in cognitive performance that are indicative of underlying vascular dysfunction. Second, cross-sectional cognitive assessments provide only a snapshot of cognitive function at a single time point, which may not fully capture ongoing decline related to impaired cerebrovascular health. Indeed, our longitudinal analyses did reveal relationships between CVR and faster longitudinal declines across several cognitive domains, highlighting the importance of examining cognitive performance longitudinally. Specifically, we found that lower MPFC CVR was associated with greater decline in visuospatial memory and executive function over the preceding 9 years, and that lower right hippocampal CVR was also linked to greater decline in visuospatial memory. These findings add to prior evidence suggesting that temporal and frontal CVR are positively associated with episodic memory and processing speed (Peng et al., 2018). The regions showing associations with CVR in our study are both functionally linked to spatial memory, with the MPFC also supporting executive control (Ezzati et al., 2016; Jobson et al., 2021). Our findings are consistent with the functional specialisation of these brain regions. Importantly, the observed association between lower CVR in the MPFC and reduced GMV, as well as changes in WM microstructure within cognitive-relevant tracts, was consistent with the finding that lower MPFC CVR also linked with greater longitudinal cognitive decline. This convergence across structural and cognitive outcomes strengthens the interpretation that cerebrovascular dysregulation in these regions may represent an early mechanism underlying dementia processes. In contrast, we observed a surprisingly opposite association whereby lower total grey matter CVR was linked to a smaller decline in lexical retrieval. This unexpected direction may reflect the possibility that lexical retrieval is more resistant to age-related decline compared to other cognitive domains. Lexical retrieval in our

study was assessed using the Test of Premorbid Functioning and the Boston Naming Test. Lexical retrieval, as reflected by performance on these tasks, is often more preserved in the ageing process, and older adults may rely on their larger vocabulary to support this ability as they age (Kavé et al., 2009). Moreover, individuals with stronger baseline lexical retrieval may have greater cognitive reserve and show less decline in the cognitive domain (Baciu et al., 2021; Connor et al., 2004), which could have influenced the observed direction of the CVR-cognition association in our study.

5.4.6 Limitations of this study

Several limitations of the study should be acknowledged. First, some significant results did not withstand multiple comparison adjustments, likely due to the sample size and small effect sizes (Cohen's $f^2 < 0.15$, Cohen, 2013). Although the effect sizes in our study were small, they appear comparable to other studies with similar sample sizes investigating the associations between CVR and cerebral perfusion (Jefferson et al., 2018). Additionally, as in previous chapters, we standardised the structural MRI data separately for each wave to mitigate the impact of using different scanners at MRI-Wave 1 and 2. As a result, the longitudinal analyses in this chapter only reflect relative rather than absolute changes in brain structure. Therefore, caution is warranted when interpreting the associations between CVR and longitudinal brain structural outcomes, as the estimates in the associations only reflect relative trends rather than exact estimates of anatomical deterioration. Finally, CVR was measured only at follow-up, whereas

changes in brain structure and cognition were evaluated retrospectively over the preceding decade. This temporal limitation prevents us from establishing CVR as a predictive marker of these longitudinal changes or inferring directionality and causality in these associations; rather, our results reflect only concurrent associations between CVR and ongoing brain structural and cognitive decline. Thus, although we observed associations between CVR and GMV, we cannot exclude the possibility that lower CVR may itself be a result of reduced vascular density due to grey matter atrophy. However, given that previous studies have suggested that cerebrovascular dysfunction may precede structural changes in the ageing brain (Iturria-Medina et al., 2016), we suggest that our follow-up measurement of CVR is very likely indicative of chronic vascular health status and shows a consistent association with brain structure throughout older age. Future work should investigate longitudinal assessments of CVR in larger cohorts to verify the retrospective findings from this study. Additionally, as we did not observe cross-sectional associations between CVR and cognitive performance, future research could explore potential non-linear relationships using quadratic or other non-linear models to capture more complex associations between CVR and cognitive outcomes.

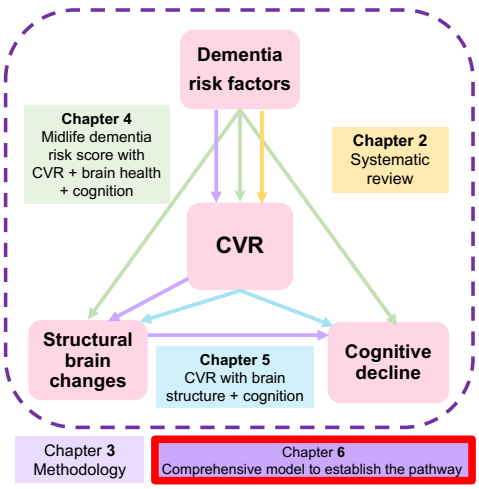
5.5 Conclusion

In summary, this chapter highlights the importance of CVR and its links with brain structure and cognitive health in later life. Lower CVR, particularly in the hippocampus and MPFC, was consistently associated with greater brain atrophy and white matter microstructural

degeneration. These structural changes also aligned with greater decline in executive function and visuospatial memory among individuals with lower CVR. Taken together, our findings add to growing evidence that CVR reflects cerebrovascular reserve and may play a key role in the vascular mechanisms underlying brain and cognitive ageing.

Chapter 6: Investigating the mediating effects of brain structure and cerebrovascular reactivity on the pathways from midlife dementia risk to later cognition

So far, we have presented empirical evidence for associations between midlife dementia risk , (the UK Biobank Dementia Risk Score), and cerebrovascular reactivity (CVR), as well as brain atrophy and cognitive decline (risk --> CVR/brain structure, cognitive decline, **Chapter 4**). We then observed that lower CVR was related to structural brain atrophy and cognitive decline in older age (CVR --> brain structure/cognitive decline; **Chapter 5**). This chapter examines whether CVR mediates the associations between midlife dementia risk and later-life brain and cognitive outcomes. This chapter integrates the findings from all previous analyses to test the mediating role of CVR in the dementia risk pathway. A modified version of this chapter, in combination with **Chapter 4**, has been prepared as a manuscript entitled “Cerebrovascular reactivity and brain structure as pathways linking midlife dementia risk to age-related cognitive decline” (***Wang et al., in submission***).



6.1 Introduction

6.1.1 What we have found in previous chapters

In previous chapters, we examined how midlife dementia risk and brain vascular health contribute to later-life cognitive outcomes. In **Chapter 4**, we found that higher midlife dementia risk, as assessed by the UK Biobank Dementia Risk Score (UKBDRS), was associated with poorer performance in executive function, visuospatial memory, and episodic memory in later life. Higher dementia risk was also linked with lower cerebrovascular reactivity (CVR) in the hippocampus, medial prefrontal cortex (MPFC), and posterior cingulate cortex (PCC). In addition, higher UKBDRS scores were associated with some established biomarkers of dementia, including reduced hippocampal grey matter volume (GMV), lower fractional anisotropy (FA), and higher diffusivity in several major white matter tracts. In **Chapter 5**, we extended this work by examining CVR as a potential neurovascular marker of later-life brain structural health. We found that lower CVR in the left hippocampus and MPFC was associated with reduced GMV and compromised white matter (WM) microstructure, particularly in the corpus callosum and fornix. These findings suggest that midlife dementia risk may influence both cerebrovascular and structural brain changes in shaping cognitive decline in ageing.

6.1.2 Research gap in understanding potential mechanistic pathways

Although the UKBDRS can predict both clinical dementia and cognitive decline in pre-clinical older people, a major gap remains in our understanding of how these midlife risk factors contribute to neurodegenerative changes and cognitive impairment in later life (Anatürk et al., 2023). In other words, the underlying pathways that mediate this midlife risk-later life cognitive decline relationship remain poorly understood. One plausible mechanism is that dementia risk factors, especially those related to vascular health, exert chronic stress on the brain's vascular health such as insufficient perfusion or blood supply, leading to degeneration in brain structure (De La Torre, 2012). These vascular and structural alterations may in turn lead to the cognitive deficits that develop in old age.

The rationale to include CVR in this proposed pathway is based on the fact that several dementia risk factors comprising the UKBDRS, such as type 2 diabetes and hypertension, high cholesterol are also known to compromise cerebrovascular health through mechanisms such as endothelial dysfunction, chronic hypoperfusion, blood-brain barrier disruption, and capillary dysfunction, all of which may ultimately contribute to neurodegeneration and cognitive decline (De La Torre, 2012; Jefferson, 2014; Luchsinger et al., 2005; Suri et al., 2019; Yang & Webb, 2025). Therefore, cerebrovascular dysfunction may represent a key intermediate pathway linking midlife dementia risk to later-life cognitive impairment.

In addition to cerebrovascular health, brain structure also plays a critical role in linking

dementia risk to later-life cognitive decline. Previous studies have shown that vascular and metabolic risk factors, such as hypertension, diabetes, dyslipidaemia, and adiposity, as well as composite dementia risk scores can contribute to brain atrophy (e.g., reduced total and grey matter volume in the hippocampus and the default mode network) (Akinyemi et al., 2013; Cherbuin et al., 2019; C. Tang et al., 2025). These risk factors have also been associated with reduced white matter integrity, as indicated by lower FA and higher mean diffusivity (MD) (Wassenaar et al., 2019). Therefore, the brain structure may also be a critical role in the proposed pathway linking dementia risk to later life cognitive decline (Pham et al., 2025; Schipper et al., 2023).

Previous studies have suggested interactive effects between dementia risk factors, cerebrovascular health, brain structure, and cognitive decline. A growing body of research has examined the mediating roles of cerebral blood flow (CBF) and brain structure in these pathways. For example, Guiney et al. (2015) found that increased physical activity may improve inhibitory control through enhanced CBF. Similarly, it has been reported that reduced CBF was associated with poorer cognitive performance, but only in individuals with elevated vascular risk burden, which suggest an interaction between vascular risk and CBF on predicting cognitive outcomes (Bangen et al., 2014). Additionally, several studies have demonstrated that brain structural changes mediate the impact of vascular risk on cognition. C. Tang et al. (2025) identified hippocampal atrophy as a key mediator linking cerebrovascular pathology to cognitive decline. It has also been shown that white matter integrity loss,

particularly in anterior regions, partially mediated the association between vascular burden and processing speed (Chen et al., 2023; Moran et al., 2025). Midlife obesity as indicated by waist-hip ratio, has also been associated with poorer working memory and executive function through the mediating effect of white matter connectivity (Jensen et al., 2025). All these results underscore the combined influence of cerebrovascular and brain structural health in the link between dementia risk and cognitive decline. Despite this, the existing literature has primarily focused on CBF, very few studies have examined the mechanistic role of CVR in mediating the associations between dementia risk and later-life outcomes. Our findings in **Chapters 2-5** showed that CVR appears to be not only associated with midlife dementia risk factors but also directly related to later-life brain and cognitive health. Therefore, this chapter aims to integrate findings from previous chapters and test the potential mediating role of CVR in linking midlife dementia risk to brain structural changes and cognitive decline in later life.

6.1.3 Study aims and hypotheses

This study aimed to investigate the role of brain vascular in linking midlife dementia risk to later life brain/cognitive decline. As vascular health typically precedes structural brain changes (Govindpani et al., 2019; Iturria-Medina et al., 2016), we propose a mechanistic pathway whereby midlife dementia risk influences cognitive outcomes via CVR and brain structural degeneration (**risk -->CVR-->brain structure-->cognition**). Specifically, we test this via a two-stage mediation pathway: first, whether CVR mediates the associations between dementia risk

and brain structure (**risk-->CVR-->brain structure**) and second, whether brain structure mediates the associations between CVR and cognitive outcomes (**CVR-->brain structure-->cognition**).

6.2 Methods

6.2.1 Proposed mediation models and temporal assumptions

Our initial objective was to test a full serial mediation model in which midlife dementia risk (measured by the UKBDRS) would affect later-life cognition through two sequential mediators: CVR and brain structure (e.g., GMV or WM microstructure) (i.e., test the entire risk--> CVR-->structure-->cognition pathway together). However, due to limited statistical power arising from a small sample size and relatively small effect sizes (as shown in previous chapters), it was not feasible to estimate a full serial mediation model or a structural equation modelling, particularly given the number of parameters and covariances involved (Boomsma, 1985; Fritz & MacKinnon, 2007; Wolf et al., 2013). Therefore, we tested two separate mediation models, with each model examining one stage of the proposed pathway. This approach allows us to qualitatively link the serial mediators according to the direction proposed in our hypothesis.

In this study, we explored mediations **only if** there was a total effect from independent variable

(X) to mediator (M), even if no direct effect from X to dependent variable/outcome (Y). Previous studies have suggested that total mediations can be examined even if there is no direct effect from X to Y (O'Rourke & MacKinnon, 2017; O'Rourke & Mackinnon, 2018). Therefore, even though we observed no direct association between CVR and cognition cross-sectionally (**Chapter 5**), we still tested mediating pathways of CVR --> GM/WM -->cognition because we found significant relationships between CVR -->GM/WM. Therefore, we tested the following four hypothesised pathways:

Path 1: UKBDRS --> CVR --> GM/WM

- **Path 1.1**: Whether CVR mediated the effect of UKBDRS on GMV (UKBDRS-->CVR-->GMV);
- **Path 1.2**: Whether CVR mediated the effect of UKBDRS on WM microstructure (UKBDRS-->CVR-->WM microstructure);

Path 2: CVR --> GM/WM --> cognition

- **Path 2.1**: Whether GMV mediated the association between CVR and cognition (CVR-->GMV-->Cognition);
- **Path 2.2**: Whether WM microstructure mediated the association between CVR and cognition (CVR--> WM microstructure -->Cognition).

The **temporal assumptions** for mediation say that the independent variable (X) should

precede or occur concurrently with the mediator (M) and outcome (Y). Hence as CVR was only measured at MRI-Wave 2, **we restricted all mediation models to cross-sectional outcomes at MRI-Wave 2, rather than using change scores from MRI-Wave 1 to 2 (thus although we found associations between CVR and ΔCognition, we did not test these because the change in cognition was retrospective and violated assumptions of the mediation model).** Although CVR, GMV and WM microstructure were measured concurrently, our mediation model was specified based on theoretical and empirical evidence suggesting that cerebrovascular dysfunction may precede neurodegeneration of brain structure (Iturria-Medina et al., 2016; Nation et al., 2019). Therefore, we tested whether the associations between CVR and cognition could be statistically explained by GMV and WM microstructure.

6.2.2 Statistical analysis

We used the 'mediation' package in R with 5000 bootstrap simulations for the mediation analysis (Imai et al., 2010). Each mediation analysis consisted of two models: a mediator model predicting the mediator from the independent variable, and an outcome model predicting the outcome from both the independent variable and the mediator. Covariates were included as follows:

- For **Path 1**, models were adjusted for the time interval between midlife risk measurement and MRI-Wave 2. In addition, total GMV was included as a covariate in the outcome model of Path 1.1 (to account for differences in total GMV when regional GMV is the outcome).

- For **Path 2**, models were adjusted for age and sex at MRI-Wave 2 in both mediator and outcome models, and for years of education in the outcome model.

We did not adjust for age, sex, or education in Path 1, as these variables are already components of the UKBDRS. Including them as additional covariates would lead to collinearity and over-adjustment.

6.2.3 Selection of variables for the mediation model

Variables included in the mediation models were selected based on the significant associations reported in **Chapters 4 and 5**. These are summarised in ***Table 6.1***, which indicates the independent variables, mediators, outcomes, and whether we would run the mediation models.

Two selection criteria were used to reduce model complexity and avoid testing multiple overlapping pathways.

1. As stated above, we only tested mediations if we previously found **a total effect from independent variable (X) to mediator (M)**, even if no direct effect from X to dependent variable/outcome (Y).
2. For mediation models involving WM microstructure as the mediator: if multiple WM microstructure metrics within the same tract (e.g., FA/MD/RD of corpus callosum) were all significantly associated with a given regional CVR, then we selected **one**

representative WM microstructure metric with the largest Cohen's f^2 effect size

for mediation analysis (e.g., just MD of corpus callosum)

Table 6.1: Summary of proposed mediation models

Note: This table summarises the variables considered for mediation analysis. If we observed significant associations between the independent variable (X) and the mediator (M) in Chapters 4 and 5, we considered them for mediation analyses. UKBDRS = UK Biobank dementia risk score, CVR = Cerebrovascular reactivity, MPFC = Medial prefrontal cortex, PCC = Posterior cingulate cortex, GMV = Grey matter volume, WM = White matter, FA = Fractional anisotropy, MD = Mean diffusivity, RD = Radial diffusivity, L1 = Axial diffusivity

Independent variable	Mediator	Outcome	Included in mediation analysis?	Reasons for exclusion
Path 1.1: UKBDRS->CVR->GMV				
UKBDRS	MPFC CVR	MPFC GMV	Yes	
	PCC CVR	PCC GMV	Yes	
	Left Hippocampus CVR	Left Hippocampus GMV	Yes	
	Right Hippocampus CVR	Right GMV	Yes	
Path 1.2: UKBDRS->CVR->WM microstructure				
UKBDRS	MPFC CVR	FA/MD of four WM tracts	Yes	
	PCC CVR		Yes	
	Mean Hippocampal CVR		Yes	
Path 2.1: CVR->GMV->Cognition				
Left Hippocampus CVR	Left Hippocampus GMV	Six cognitive domains	Yes	
Path 2.2: CVR->GWM microstructure->Cognition				
MPFC CVR	Fornix FA	Six cognitive domains	Yes	
Precuneus CVR	Cingulum L1		Yes	

Hippocampal CVR	Corpus callosum FA		No	Cohen's f^2=0.029, smaller than that in MD (Cohen's f^2=0.043)
	Corpus callosum MD		Yes	
	Corpus callosum RD		No	Cohen's f^2=0.038, smaller than that in MD (Cohen's f^2=0.043)
	Internal capsule MD		No	Cohen's f^2=0.035, smaller than that in L1 (Cohen's f^2=0.046)
	Internal capsule L1		Yes	
	Fornix FA		Yes	
	Fornix RD		No	Cohen's f^2=0.031, smaller than that in FA (Cohen's f^2=0.043)

6.3 Results

6.3.1 Path 1.1: UKBDRS-CVR-GMV

Left hippocampal CVR significantly and partially mediated the association between logUKBDRS and left hippocampal volume, as the indirect effect via CVR was statistically significant (ACME: β = -0.018, 95% CI [-0.043, 0.0003], p = 0.045). Specifically, higher logUKBDRS was linked to lower CVR (β = -0.017, p = 0.011), which was in turn associated with lower GMV (β = 1.032, p = 0.038). The direct effect of logUKBDRS on GMV remained significant (ADE: β = −0.118, p = 0.003), and the total effect was also significant (β = -0.136, p < 0.001), supporting a partial mediation pathway (***Figure 6.1A***). The other three mediation pathways for Path 1.1 were not significant.

6.3.2 Path 1.2: UKBDRS-CVR-WM microstructure

Hippocampal CVR significantly mediated the associations between logUKBDRS and several WM microstructure metrics (***Table 6.2***).

Hippocampal CVR significantly mediated the association between logUKBDRS and FA in the

corpus callosum (ACME: β = -1.265x10^{-3}, 95% CI [-0.031, −0.0003], p = 0.041). Specifically, higher logUKBDRS was associated with lower hippocampal CVR (β = -0.017, p = 0.010), which was in turn associated with lower FA (β = 0.077, p = 0.035). The direct effect of logUKBDRS on FA remained significant (ADE: β = -0.009, p = 0.001), and the total effect was also significant (β = -0.011, p < 0.001), supporting a partial mediation pathway (***Figure 6.1B***).

Hippocampal CVR also significantly mediated the association between logUKBDRS and MD in the corpus callosum (ACME: β = 1.878x10^{-6}, 95% CI [1.325x10^{-7}, 4.489x10^{-6}], p = 0.028). Higher logUKBDRS was associated with lower CVR (β = -0.017, p = 0.010), which in turn was associated with higher MD (β = -1.143x10^{-4}, p = 0.022). The direct effect of logUKBDRS on MD remained significant (ADE: β = 1.930x10^{-5}, p < 0.001), and the total effect was also significant (β = 2.118x10^{-5}, p < 0.001), supporting a partial mediation pathway (***Figure 6.1C***).

Hippocampal CVR significantly mediated the association between logUKBDRS and FA in the fornix (ACME: β = -0.002, 95% CI [-0.004, -1.205x10^{-4}], p = 0.025). Higher logUKBDRS was associated with lower hippocampal CVR (β = -0.017, p = 0.010), which in turn was linked to lower FA (β = 0.106, p = 0.021). The direct effect of logUKBDRS on FA remained significant (ADE: β = -0.009, p = 0.012), and the total effect was also significant (β = -0.011, p = 0.002), indicating a partial mediation (***Figure 6.1D***).

Finally, hippocampal CVR significantly mediated the association between logUKBDRS and MD in the internal capsule (ACME: $\beta = 1.273x10^{-6}$, 95% CI [$1.019x10^{-7}$, $3.017x10^{-6}$], $p = 0.025$). Higher logUKBDRS was associated with lower hippocampal CVR ($\beta = -0.017$, $p = 0.010$), which was in turn associated with higher MD ($\beta = -7.748x10^{-5}$, $p = 0.019$). The direct effect remained significant (ADE: $\beta = 7.128x10^{-6}$, $p = 0.005$), and the total effect was also significant ($\beta = 8.401x10^{-6}$, $p < 0.001$), indicating a partial mediation (***Figure 6.1E***).

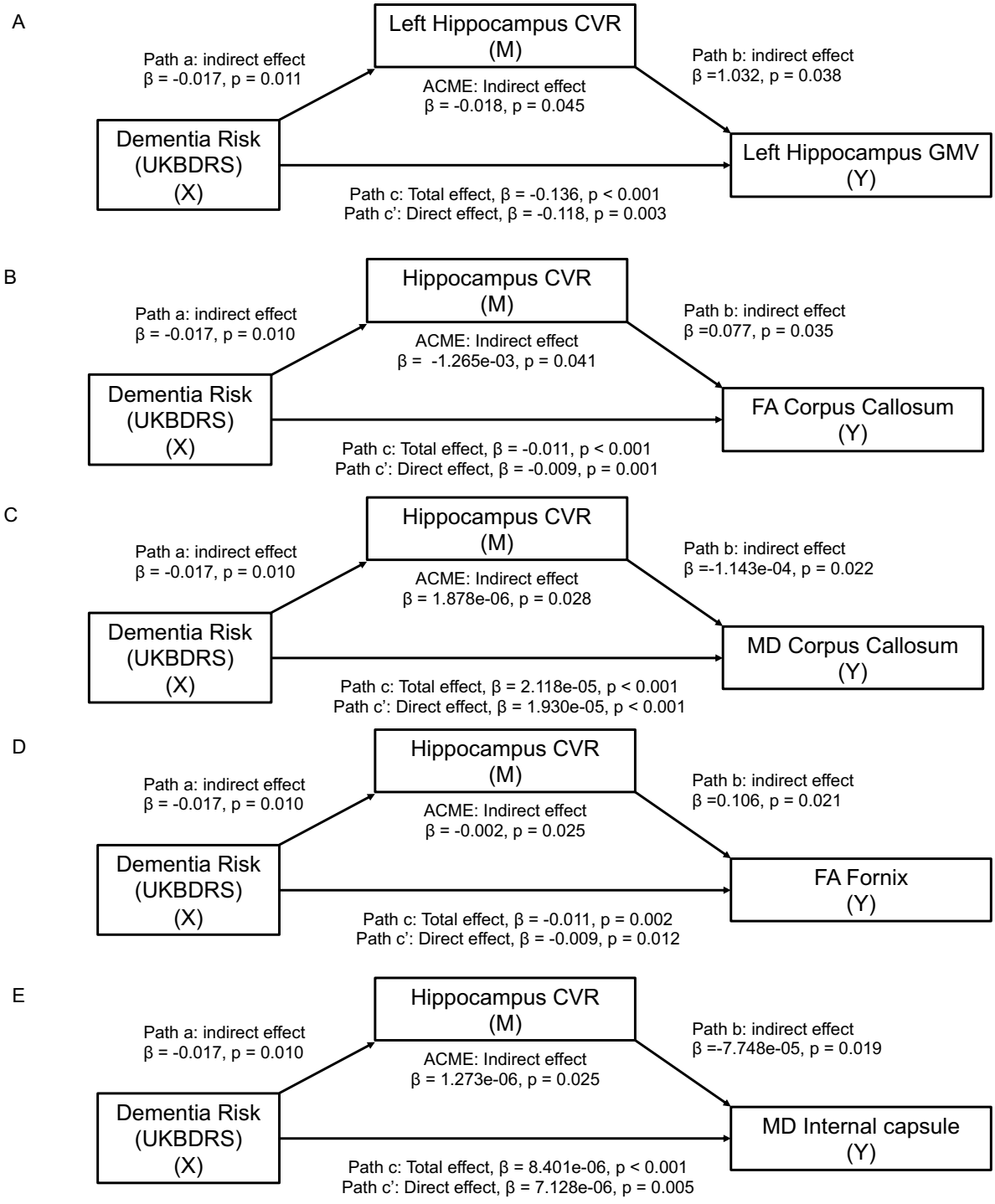


Figure 6.1: Significant mediation pathways for Path 1: UKBDRS-CVR-structure

Note: Path a represents the association between the independent variable and the mediator. Path b represents the association between the mediator and the outcome. Path c' indicates the direct effect of the independent variable on the outcome after accounting for the mediator. Indirect effects (ACME) reflect the mediated pathway through mediator.

6.3.3 Path 2.1: CVR-GMV-Cognition

Left hippocampal volume significantly mediated the association between left hippocampal CVR and episodic memory (ACME β = 4.491 [0.321, 10.459], p = 0.028). Lower CVR was significantly associated with smaller GMV in the left hippocampus (β = 1.212, p = 0.016), which in turn was significantly associated with worse episodic memory (β = 3.686, p = 0.013). The direct effect from CVR to episodic memory was not significant (ADE β = -7.440, p = 0.401), nor was the total effect (β = -2.949, p = 0.401), which suggested a full mediation via GMV from CVR to episodic memory (***Figure 6.2A***).

Left hippocampal GMV also significantly mediated the association between CVR and visuospatial memory. The indirect effect (ACME) was significant (β = 8.603, 95% CI [1.070, 19.042], p = 0.016). Lower CVR was associated with smaller GMV (β = 1.243, p = 0.013), which in turn was related to worse visuospatial memory (β = 6.884, p = 0.005). The direct effect from CVR to visuospatial memory was not significant (ADE β = 3.363, p = 0.804), and the total effect was also not significant (β = 11.966, p = 0.410), indicating a full mediation pathway through GMV (***Figure 6.2B***).

6.3.4 Path 2.2: CVR-WM microstructure-Cognition

White matter microstructure did not significantly mediate the associations between CVR and any cognitive domains.

All details of the significant mediation models are summarised in ***Table 6.2***, and the full set of results is presented in ***Appendix Table 6.1***.

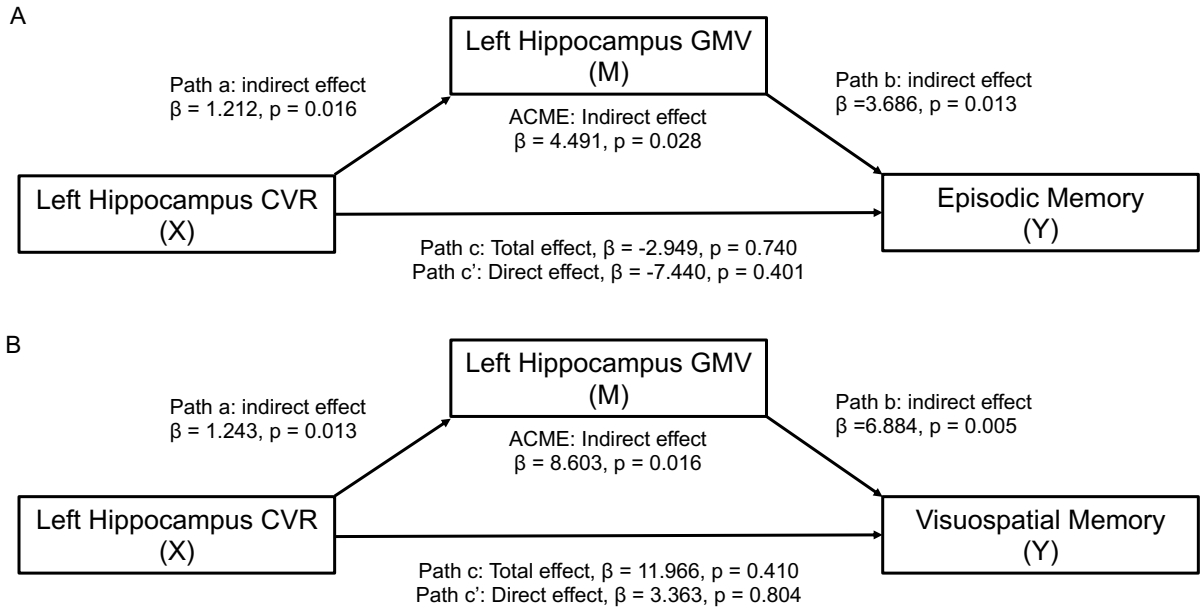


Figure 6.2: Significant mediation pathways for Path 2: CVR-structure-cognition

Note: Path a represents the association between the independent variable and the mediator. Path b represents the association between the mediator and the outcome. Path c' indicates the direct effect of the independent variable on the outcome after accounting for the mediator. Indirect effects (ACME) reflect the mediated pathway through mediator.

Table 6.2: Summary of significant mediation models

Note: These tables present the mediation models where the independent variable and mediator showed a significant indirect effect (shaded in yellow) on the outcome, indicated by an ACME p-value < 0.05. Hpc = hippocampus. Full mediation results can be found in Appendix Table 6.1.

Path 1.1: UKBDR-CVR-GMV				
Independent Variable	**Mediator**	**Outcome**	**ACME β [95% CI]**	**ACME p**
UKBDRS	**Left Hpc CVR**	**Left Hpc GMV**	**-0.018 [-0.043, -0.0003]**	**0.045**
Path 1.2: UKBDRS-CVR-WM microstructure				
Independent variable	**Mediator**	**Outcome**	**ACME β [95% CI] x 10^{-4}**	**ACME p**
UKBDRS	Hpc CVR	**FA Corpus Callosum**	**-12.646 [-31.047, -0.315]**	**0.041**
		FA Cingulum	-6.961 [-23.696, 5.325]	0.279
		FA Internal Capsule	-5.697 [-19.366, 4.329]	0.278
		FA Fornix	**-17.384 [-41.114, -1.205]**	**0.025**
		MD Corpus callosum	**0.019 [0.001, 0.045]**	**0.028**
		MD Cingulum	0.003 [-0.009, 0.018]	0.582
		MD Internal capsule	**0.013 [0.001, 0.030]**	**0.025**
		MD Fornix	0.024 [-0.002, 0.063]	0.085
Path 2.1: CVR-GMV-Cognition				
Independent Variable	**Mediator**	**Outcome**	**ACME β [95% CI]**	**ACME p**
Left Hpc CVR	Left Hpc GMV	**Episodic Memory**	**4.491 [0.321, 10.459]**	**0.028**
		Visuospatial Memory	**8.603 [1.070, 19.042]**	**0.016**

6.4 Discussion

6.4.1 Summary of the findings

We observed several novel mediation pathways, many of which point towards a central role for hippocampal CVR in particular. We demonstrated that left hippocampal CVR mediated the association between UKBDRS and left hippocampal GMV. Additionally, hippocampal CVR significantly mediated the associations between UKBDRS and several WM microstructure metrics in the corpus callosum, fornix, and internal capsule. Furthermore, although CVR was not directly associated with episodic or visuospatial memory performance cross-sectionally, we observed an indirect pathway from left hippocampal CVR to these cognitive domains via GMV. While CVR and GMV were measured concurrently, the mediation models were specified based on prior conceptual work proposing that cerebrovascular dysfunction may precede neurodegenerative structural changes. Taken together, these findings highlight a novel neurovascular pathway through which midlife risk may impact later-life episodic and visuospatial memory decline via reductions in hippocampal CVR and volume.

6.4.2 Linking midlife dementia risk to cognitive decline via hippocampal CVR and grey matter atrophy

Through two-stage mediation analyses, we identified a potential pathway by which individuals with higher UKBDRS may experience poorer episodic and visuospatial memory in later life via lower CVR in the left hippocampus and a smaller hippocampal GMV. These findings suggest that hippocampal vascular dysregulation and atrophy may serve as potential mechanisms underlying the associations between midlife dementia risk and later-life cognitive decline. Interestingly, as reported in **Chapter 5**, we did not observe direct associations between CVR and cognitive performance, aligning with previous studies reporting mixed or null findings regarding CVR-cognition links in healthy adults (Catchlove, Pipingas, et al., 2018; Gauthier et al., 2015; Tchistiakova et al., 2014; Thomas et al., 2016). However, in this chapter, we found that lower CVR in the left hippocampus was indirectly linked to worse episodic and visuospatial memory via reduced hippocampal volume. This finding suggests that reduced cerebrovascular reserve, particularly in the left hippocampus, may contribute to cognitive vulnerability via hippocampal atrophy. CVR and GMV were assessed concurrently and therefore this mediation pathway does not imply causality or indicate a temporal ordering of events per se. Rather, it reflects a potential mechanistic sequence supported by theoretical and empirical literature proposing that vascular dysfunction may precede brain structural changes in ageing and contribute to cognitive decline (see Figure 1.2; (Iturria-Medina et al., 2016). Our findings highlight the importance of structural mediators influencing the CVR-cognition relationship,

which may help explain prior inconsistencies found in the CVR-cognition literature.

6.4.3 The role of the left hippocampus in vascular and neurodegenerative pathways

Interestingly, we observed these mechanistic pathways specifically in the left hippocampus, rather than in right hippocampus or other default mode network regions. This lateralised finding may reflect both the functional specialisation and vascular vulnerability of the left hippocampus in the ageing process, which has been discussed in **Chapter 5**. It has been suggested that the left hippocampus may serve as a more sensitive region than the right hippocampus for early neurodegenerative progression (Shi et al., 2009). Furthermore, previous studies have shown that the left hippocampus plays a central role in verbal episodic memory and works in conjunction with the right hippocampus to support visuospatial memory, particularly through the sequential and egocentric encoding of spatial information (Ezzati et al., 2016; Iglói et al., 2010). By focusing on domain-specific outcomes, we showed that reduced hippocampal CVR was also associated with larger decline in visuospatial memory in **Chapter 5**, which are closely linked to hippocampal function and known to be among the earliest affected in Alzheimer's disease through smaller grey matter volume (Cheng, 2013; Coughlan et al., 2018; Eichenbaum, 2017; Kossowska-Kuhn et al., 2024). Therefore, the observed mediation pathways further reinforce that hippocampal cerebrovascular reserve, a dynamic marker of cerebrovascular responsiveness, may have a critical role in linking midlife dementia risk, to cognitive decline. This adds valuable evidence over and above the vast literature that has previously focussed

on more passive markers of cerebral perfusion such as CBF (Bangen et al., 2014; Guiney et al., 2015; C. Tang et al., 2025).

6.4.4 Vascular contributions to WM microstructure

This study also proposed a pathway by which midlife dementia risk may affect WM microstructure through impaired CVR in the hippocampus. Specifically, higher midlife dementia risk, as assessed by the UKBDRS, was associated with lower FA and higher MD in the corpus callosum, lower FA in the fornix, and higher MD in the internal capsule. Mediation analyses revealed that hippocampal CVR partially mediated these relationships, suggesting that cerebrovascular dysfunction may account for some, but not all, of the associations between midlife dementia risk and later-life WM microstructural degeneration. CVR may decline over time as a result of ageing and the chronic accumulation of vascular and metabolic insults associated with dementia risk factors (C Wang et al., 2023). This reduced cerebrovascular reserve limits the ability of hippocampal vessels to respond to metabolic demand, eventually contributing to ischemic injury in surrounding white matter, and leading to demyelination, axonal loss, and gliosis (Hainsworth & Markus, 2008; Sam et al., 2016). These microstructural changes can result in measurable increases in diffusivity and reduced white matter integrity. In addition, the vascular supply connections between the hippocampus and these white matter tracts may help explain why we found the mediation pathway in these tracts. The fornix, positioned as the outflow tract of the hippocampus, is particularly vulnerable to hippocampal

vascular dysfunction (Srisaikaew et al., 2020). Other white matter tracts also share vascular supply territories with the hippocampus, which is primarily supplied by branches of the posterior cerebral artery (Goldstein et al., 2023; Hacking & D'Souza, 2008; Johnson, 2023; Maingard et al., 2014; Vitosević et al., 2005). Therefore, if midlife dementia risk leads to impaired hippocampal CVR, the resulting cerebral dysregulation may compromise the vascular supply to the connected white matter tracts, accelerating structural degeneration in these regions.

It is interesting to note that although hippocampal CVR mediated the pathway from midlife dementia risk to MD in the corpus callosum (risk-CVR-WM microstructure; Path 1), we did not observe any significant mediation pathways from hippocampal CVR through WM microstructure to cognitive outcomes (i.e., no CVR-WM microstructure-cognition pathway; Path 2). These findings suggest that WM microstructure may not serve as a primary mediator between hippocampal CVR and cognition in this cohort and that this serial pathway may be more closely linked to hippocampal grey matter volume as discussed above. Previous studies have reported that WM microstructure mediates the associations between cognition and other vascular markers. For example, white matter hyperintensity burden or broader cerebral small vessel disease are associated with poorer executive function and information processing speed through WM integrity (Chen et al., 2022; Li et al., 2025; Sui et al., 2025). In contrast, it is possible our study did not find such mediation pathways for CVR-WM microstructure-cognition because of the relatively low cerebral vascular burden in this cohort.

6.4.5 Strengths and Limitations

This study offers several notable strengths. Firstly, whereas most previous research has examined CBF or broader cerebrovascular burdens such as vascular disease, few studies have investigated the role of CVR in the mechanistic pathways linking dementia risk and cognitive decline. This study provides novel identification of hippocampal CVR as a potential mechanistic link between midlife dementia risk, brain structural changes, and later-life cognitive outcomes. Moreover, while previous research has established the role of hippocampal atrophy in cognitive decline (Chen et al., 2020; Korf et al., 2004; Yao et al., 2020), our findings advance the field by introducing hippocampal CVR rather than other broader vascular markers such as white matter hyperintensities or cerebral blood flow, as a region-specific vascular marker in linking midlife dementia risk to later life cognitive decline. This adds to the growing literature emphasising the contribution of vascular health in the neurodegenerative pathology. Additionally, we examined multiple cognitive domains, allowing for a comprehensive assessment of cognitive functions beyond global cognition. Finally, by focusing on a priori grey matter regions and white matter tracts that had previously been associated with CVR in this cohort, our analyses enabled more region-specific inferences regarding the associations between vascular dysfunction, brain structure, and cognition.

Nonetheless, some limitations should be acknowledged. First, as noted above, GMV, WM microstructure, cognitive performance, and CVR were assessed concurrently in this cohort.

Despite suggesting a temporal sequence in our pathways (i.e., midlife dementia risk --> CVR --> GMV --> cognition), we cannot make any causal inferences with the observational and cross-sectional study design. However, we structured the two-stage mediation models based on extensive literature suggesting that vascular dysfunction precedes structural atrophy and cognitive decline (Appelman et al., 2008; Iturria-Medina et al., 2016). Second, the modest sample size limited our ability to test sequential mediation models, so we separated the pathway into two linked models. Larger sample sizes would be necessary to satisfy the statistical power to comprehensively evaluate these pathways with multiple mediators and covariates (Schoemann et al., 2017; Sim et al., 2021). Despite this, future research should address these limitations through larger, more diverse cohorts with repeated measures of the brain and cognitive outcomes.

6.5 Conclusion

Our study highlights a potential pathway through which midlife dementia risk factors impact brain ageing and episodic and visuospatial memory via impaired hippocampal CVR and atrophy. While we also observed that hippocampal CVR mediated the associations from midlife dementia risk to later life WM microstructure integrity, these associations did not significantly relate to cognitive performance. This suggests that hippocampal grey matter atrophy may play a more central role in linking dementia risk to cognitive decline through CVR. In conclusion, these findings underscore the importance of hippocampal CVR and structural brain health in

understanding how midlife vascular risk may contribute to later-life cognitive vulnerability and emphasise the potential value of targeting modifiable risk factors to preserve brain and cognitive health in ageing.

Chapter 7: Discussion

This thesis presents the first comprehensive investigation into the role of cerebrovascular reactivity (CVR) as a dynamic marker of cerebrovascular health that may serve as an intermediate mechanism linking midlife dementia risk to later-life brain structure and cognition. This thesis draws on a longitudinal dataset with repeated measures from midlife dementia risk to later-life structural brain health, and cognitive performance, alongside assessment of CVR in later-life. We conducted non-invasive fMRI-based CVR measures, which enabled us to investigate regional CVR, particularly in brain regions that are critical for cognitive function. Overall, our results supported our two key hypotheses that 1) greater burden of modifiable factors is linked to lower CVR and 2) lower CVR relates to poor measures of brain structure and greater cognitive decline. In this final chapter, I revisit the three primary research questions proposed in **Chapter 1** and synthesise key findings across research chapters. I also outline strengths and limitations of this project, reflect on implications of the findings, and finally consider future directions for research.

7.1 Question 1: Does dementia risk influence CVR?

A key objective of this thesis was to examine the relationship between dementia risk and CVR. In **Chapter 2,** we conducted a novel systematic review of 59 studies to examine the existing

evidence on the associations between dementia risk factors and CVR measured using MRI (Wang et al., 2023). The review included a comprehensive range of well-established dementia risk factors including modifiable, non-modifiable, and clinical risk factors, as suggested by the Lancet Commission review (Livingston et al., 2020). In this review, we found consistent evidence that people with several vascular and clinical risk factors, such as type 2 diabetes, hypertension, traumatic brain injury, stroke, and carotid artery occlusion or stenosis had lower CVR compared to individuals without these conditions. Similarly, older adults consistently showed reduced CVR relative to younger individuals, aligning with known age-related vascular changes. Individuals carrying the apolipoprotein ε4 (APOE-ε4) risk allele for Alzheimer's disease also exhibited lower CVR in several studies, suggesting that vascular dysfunction may be one pathway through which genetic risk contributes to neurodegeneration. In contrast, findings for obesity, physical activity, and depression were mixed and often inconsistent, with considerable variability in affected brain regions and directionality of associations. Notably, we found no MRI-based CVR studies examining five modifiable risk including air pollution, social isolation, hearing impairment, alcohol consumption, and low education.

Although the precise mechanisms remain uncertain, our review suggested several biological pathways through which dementia risk factors may impair CVR. These include endothelial dysfunction (Hajjar et al., 2010; Kalaria, 1996), vascular inflammation (Chung et al., 2015), structural abnormalities of the vessels (Hartkamp et al., 2018; Rahman & Laher, 2007), and impaired vascular smooth muscle cell function (Fisher & Mikulis, 2021; Hayes et al., 2022).

While the thesis did not directly examine these mechanisms, future research using animal models or molecular approaches may further explore these biological pathways in more detail.

Our review highlighted a few important methodological inconsistencies in the literature, which were addressed in subsequent thesis chapters. First, given that CVR is itself a marker of cerebrovascular health, it was perhaps unsurprising that most consistently associated dementia risk factors identified in our review were vascular or clinically vascular in nature. In contrast, we noted that the psychosocial risk factors (e.g., depression, education) were either not associated with CVR in existing studies or had been examined in only a small number of studies. We highlighted the importance of addressing this gap in the literature given the potential for preventative interventions to target these risk factors.

Second, although we limited our review to studies using MRI-based assessment techniques, we found substantial variation in results depending on the type of vasoactive stimulus used. For example, responses to acetazolamide vary across individuals in both timing and intensity due to differences in drug sensitivity. Breath-holding tasks require participant cooperation, which can be influenced by individual differences in task compliance and breath control. Such variability can compromise the reliability of CVR measurements. Therefore, we suggested to prioritise the use of controlled hypercapnia challenges via administered CO_2 inhalation (Fierstra et al., 2013; Juttukonda & Donahue, 2019; Liu et al., 2019), which offers a standardised and non-invasive approach that is both tolerable for participants and less

susceptible to task-related variability. This is not to suggest that results obtained through this method are entirely free from limitations, but rather that this approach may help reduce certain systematic errors. We demonstrate in subsequent chapters that this approach was stable, had high signal to noise, and most importantly, was tolerable in older participants (>70 years old). Notably 95% of our participants reported none-to-low levels of claustrophobia, and 97% reported none-to-low level of dizziness during the CO_2 scan.

In **Chapters 4-6**, we aimed to take the results of our systematic review forward by conducting an empirical analysis using data from the Heart and Brain Study. which employed a standardised CO_2 inhalation BOLD fMRI protocol for CVR assessment. We focused specifically on dementia risk factors measured in midlife, as this period represents the time when many risk factors exert their strongest and most lasting effects on brain and vascular health (Kivipelto et al., 2018). Notably, we included several behavioural factors that were underrepresented in the existing literature, such as education, depression, and socioeconomic deprivation. Rather than examining individual risk factors, we considered the relative contribution of each factor by using a composite midlife risk score called the UKBDRS, which has been previously validated in this cohort for predicting dementia specifically (Anatürk et al., 2023).

In **Chapter 4,** we showed that individuals who were more vulnerable to midlife dementia risk factors, as indicated by **higher UKBDRS, exhibited lower CVR approximately 25 years**

later, particularly in brain regions closely associated with cognitive function, including the bilateral hippocampus, posterior cingulate cortex (PCC), and medial prefrontal cortex (MPFC). This is the first study to examine the association between the UKBDRS and regional CVR. Although our study does not disentangle the individual effects of each risk factor, it provides exciting new evidence that elevated measures of a **dementia-specific risk score** in midlife are associated with reduced CVR in later life (**Wang et al., in submission).** This risk profile includes contributions from ten factors, and many of which are modifiable (e.g., depression, material deprivation, hypertension etc.). The findings support the idea that managing dementia risk in midlife, particularly through interventions targeting the factors captured by the UKBDRS, may contribute to the preservation of CVR in later life.

7.2 Question 2: Is CVR associated with brain structural biomarkers of dementia and cognitive performance, as well as their longitudinal declines?

In **Chapter 5**, we used data from the Heart and Brain cohort to examine the associations between CVR and grey matter volume (GMV), white matter microstructure, and white matter hyperintensities (WMHs), both cross-sectionally and in relation to the changes over the preceding ~9 years. We presented exciting new evidence showing associations between CVR and declines in brain structure (**Wang et al., under revision HBM**). First, we note that **lower CVR was associated with smaller GMV** cross-sectionally, particularly in the left hippocampus. We also found that lower CVR was related to greater GMV decline over the preceding years

in the MPFC. These findings suggest that lower CVR in the left hippocampus and MPFC may be linked with faster grey matter atrophy.

Second, **lower CVR was associated with lower fractional anisotropy (FA) and higher diffusivity,** particularly in the corpus callosum and fornix. These associations were most observed for **hippocampal CVR**. Longitudinally, impaired CVR at follow-up was also linked to greater microstructural decline over the preceding 9 years, indicated by **more pronounced reductions in FA and increases in diffusivity over time** particularly in the cingulum, corpus callosum, and internal capsule. These associations were widely observed for CVR in MPFC, posterior cingulate cortex (PCC), precuneus, and hippocampus. These findings suggest that lower CVR may reflect or contribute to faster deterioration of white matter microstructure, particularly in tracts that support cognition, such as the corpus callosum.

However, unexpectedly, we did **not find significant associations between CVR and WMHs**, either cross-sectionally or longitudinally. This null finding may be due to the use of whole brain WMH measures or the relatively low WMH burden in this healthy cohort, and future studies should examine periventricular WMHs volume among people with higher burden of white matter lesions.

Although we found that CVR was associated with structural biomarkers of dementia, these

links should not be interpreted as causal associations. However, drawing on previous literature suggesting that vascular dysfunction may precede structural brain changes in the ageing process (de la Torre, 2018; De La Torre, 2000b; Eisenmenger et al., 2022; Iturria-Medina et al., 2016), we propose that lower CVR may reflect chronic hypoperfusion and impaired regulation of cerebral blood flow in response to metabolic demands. Over time, this may contribute to neurodegenerative processes, as observed in grey matter atrophy and white matter microstructural damage.

We also observed that **lower CVR at follow up was associated with faster decline in visuospatial memory and executive function** over the preceding 9 years, particularly for CVR in the MPFC and right hippocampus. MPFC CVR was linked to decline in both domains, while right hippocampal CVR was specifically associated with visuospatial memory. This finding suggests that lower CVR may contribute to progressive cognitive decline, which may occur alongside changes in structural biomarkers of dementia and in brain regions involved in cognitive function. Therefore, CVR, particularly in the hippocampus and MPFC, may serve as a potential early marker of age-related and dementia-related structural brain changes, and may also reflect vulnerability to cognitive decline. Interestingly, we did not find cross-sectional associations between CVR and cognitive performance at follow-up. This may indicate that the relationship between CVR and cognition is more complex than a simple direct link. It is also possible that our sample of relatively healthy, well-educated individuals may have shown ceiling effects in cognitive performance, which could have limited the variability needed to

detect significant associations.

7.3 Question 3: Does CVR mediate the relationship between dementia risk and cognitive performance?

To better understand the mechanisms linking midlife dementia risk to later-life brain and cognitive outcomes, we first examined the direct associations between UKBDRS and neuroimaging and cognitive measures in **Chapter 4.** We found that higher UKBDRS was associated with smaller GMV, particularly in the hippocampus and total grey matter, as well as greater atrophy over time in regions of the default mode network, including the bilateral hippocampus, PCC, TPJ, and MPFC. UKBDRS was also related to poorer white matter microstructure, both globally and within selected tracts including fornix, cingulum, corpus callosum, and internal capsule.

In terms of cognitive outcomes, higher midlife UKBDRS was associated with worse performance in executive function, visuospatial memory, and episodic memory about 25 years later, and with faster decline over time in these same domains. Based on these findings, and the associations reported in **Chapter 5** between lower CVR and both structural brain changes and cognitive decline, in **Chapter 6,** we further formally tested the **hypothesis that CVR may mediate the relationship between midlife dementia risk and later-life cognitive outcomes**.

Although there was no cross-sectional association observed between CVR and cognitive performance in **Chapter 5**, the key findings from **Chapter 6** suggest that intermediate cerebrovascular and structural mechanisms may link midlife dementia risk to later-life cognitive decline. Sequential mediation models showed that 1) CVR in the left hippocampus partially mediated the association between UKBDRS and left hippocampal GMV, and 2) GMV fully mediated the association between CVR and both episodic memory and visuospatial memory **(higher UKBDRS --> lower left hippocampus CVR --> smaller left hippocampus GMV --> worse cognitive performance)**. This result suggests that CVR may play a mechanistic role in pathological pathway linking midlife dementia risk to cognitive decline, although the mediation was tested cross-sectionally and does not imply causal or temporal direction. Our model aligns with emerging vascular contributions to Alzheimer's disease, such as the CATCH hypothesis (De La Torre, 2000b, 2012) and the two-hit vascular hypothesis (Eisenmenger et al., 2022; Nelson et al., 2015; Zlokovic, 2011), both of which suggest that vascular dysfunction, driven by ageing and vascular risk factors, may lead to metabolic failure and structural brain damage, and this will trigger the neurodegenerative process. Our study extends this existing evidence, and suggests that **CVR, a relatively understudied but physiologically relevant marker, may serve as a key mechanism in the pathway linking midlife dementia risk to later-life neurodegeneration.**

Furthermore, UKBDRS was associated with lower FA and higher MD in the corpus callosum,

lower FA in the fornix, and higher MD in the internal capsule, through reduced CVR in the hippocampus (higher risk --> lower hippocampal CVR --> poor white matter microstructure). This finding suggests that hippocampal CVR may be involved in the vascular mechanisms linking midlife dementia risk to neurodegenerations in white matter microstructure. Although we found robust associations between CVR and white matter microstructural decline in **Chapter 5**, this did not extend to cognitive outcomes. Previous study has shown that the relationship between executive function and frontoparietal white matter integrity is mediated by cerebrovascular burden in patients with stroke (Veldsman et al., 2020). In contrast, our relatively healthy cohort may have limited sensitivity to detect subtle cognitive effects of white matter damage. It is also possible that CVR mediates the relationship from white matter microstructure to cognition, rather than white matter microstructure mediates the relationship from CVR to cognition, which need to be further investigated.

7.4 General strengths and limitations of this thesis

This thesis has several **strengths**. First, its **longitudinal design** enables the investigation of how midlife dementia risk factors relate to brain vascular function, structural brain changes, and cognitive outcomes approximately 25 years later. The longitudinal measures of brain structure and cognition (from ~68 years to ~77 years old) further allows us to explore how these risk factors contribute to trajectories of neurodegeneration and cognitive decline over time in later-life. Second, we used a comprehensive **multi-modal neuroimaging** approach,

including T1-weighted imaging, DTI, FLAIR, and BOLD-fMRI. This integration of diverse imaging modalities allows for a more comprehensive understanding of the ageing brain and its vulnerability to dementia. Third, the Heart and Brain study benefits from a rich set of **midlife lifestyle and clinical risk profiles**, which enables us to examine a broad spectrum of modifiable and non-modifiable dementia risk factors using the validated UKBDRS. Fourth, as discussed earlier, a methodological strength is the use of a **standardised BOLD-based CVR measure** with controlled CO_2 inhalation. This method offers high spatial sensitivity for assessing regional CVR, particularly in subcortical areas like the hippocampus, as well as minimises variability from participant compliance or delivery methods, making the results more reliable. Finally, we chose to use **Benjamini-Hochberg false discovery rate (FDR) correction** to account for multiple comparisons. While traditional approaches such as the Bonferroni correction are effective in controlling Type I error (false positives), they are highly conservative and can increase the risk of Type II errors (false negative), which makes it potentially miss true effects, especially for relatively small sample sized study (Perneger, 1998). In contrast, the Benjamini-Hochberg method adjusts the significance threshold based on the rank of individual p-values. It provides a more balanced control of false positive while preserving sensitivity to detect meaningful associations (Benjamini & Hochberg, 1995; Menyhart et al., 2021). This is particularly important in a study like ours that involves a large number of hypothesis tests across multiple brain regions and cognitive outcomes. The Benjamini-Hochberg correction enhanced the robustness and interpretability of our findings.

Study specific **limitations** have been discussed in each chapter (**Chapters 4-6**). The first general limitation is that the demographics of this cohort limit the generalisability of our findings to the wider UK population. The participants in our study are relatively healthy, predominantly well-educated, White British, and 74% of the cohort are male. This broadly reflects the makeup of the British civil service from which this cohort was initially drawn at study inception in 1985. Therefore, the cohort has low representation of individuals from ethnically diverse or socioeconomically disadvantaged backgrounds. As a result, our **findings may not** fully reflect associations in underserved and minority populations, or those with higher vascular or dementia-related risk burden. For instance, the absence of significant associations between CVR and WMHs might be due in part to the low WMH burden in this cohort. Similarly, the modest associations between CVR and cognitive outcomes could reflect a restricted range of cognitive impairment in this healthy and well-educated ageing sample, which leads to potential underestimation of effect sizes. Furthermore, although sex was included as a covariate in the analyses, the predominance of male participants in this cohort (74%) resulted in an unbalanced sex distribution. This limits our ability to meaningfully examine sex differences in CVR, or to determine whether the associations between CVR and brain structure or cognitive outcomes differ by sex.

Second, a key general limitation is that CVR was only measured at the follow-up time point (MRI-Wave 2), with **no CVR measurements at baseline**. This restricted our ability to examine the trajectories of CVR over time or to investigate its temporal precedence in the associations

between CVR and later-life brain and cognitive outcomes. Consequently, the analyses conducted cross-sectionally for CVR do not permit causal inferences or conclusions about the directionality of associations. In other words, we cannot determine whether lower CVR contributes to reduced GMV, or whether smaller grey matter regions simply exhibit a diminished vascular response as reflected by the BOLD signal. Therefore, the association results should be interpreted with caution. Nevertheless, given that vascular dysfunction often precedes a range of structural biomarkers, our findings support the potential of lower CVR as an early indicator of brain structural neurodegenerations and subsequent cognitive decline.

Although, although the **sample size** of the Heart and Brain Study (155 participants with valid CVR scans) is relatively large compared to most CVR studies, which usually include on average 35 participants (there are very few studies with more than 100 participants) (Sleight et al., 2021). However, it is still considered modest for most other neuroimaging studies using other MRI modalities (structure or function) (Lorca-Puls et al., 2018). As a result, we had limited statistical power to reliably to test voxel-wise associations for CVR and had to focus on predefined regions of interest. Additionally, due to power constraints, we could not test more complex serial mediation models linking midlife dementia risk to CVR, then to brain structural integrity and cognitive outcomes in a single model. Instead, we adopted a sequential modelling approach to examine these pathways in two stages. Although several associations identified in this thesis reached nominal statistical significance ($p < 0.05$), many did not survive correction for multiple comparisons. This is not unexpected, as cognitive decline and dementia are driven

by complex, multifactorial processes involving interacting vascular, inflammatory, metabolic, and neurodegenerative mechanisms. The contribution of any single mediator, such as CVR, to these pathways is therefore likely to be modest. It is therefore important to present both corrected and uncorrected results, since the uncorrected findings may highlight emerging trends that warrant further validation in larger samples.

Finally, the imaging data were acquired using different scanners at MRI-Wave 1 (3T Verio) and Wave 2 (3T Prisma). To account for **inter-scanner variability** in the longitudinal analysis of brain structure (including GMV and white matter diffusion metrics), we applied standardisation procedures and expressed changes as z-scores within the cohort for each MRI wave. While this is a common approach in longitudinal neuroimaging studies, it captures relative rather than absolute changes within this cohort (Schwarz, 2021). The change in z-scores from MRI-Wave 1 to 2 only reflect the change in participants' relative position in the cohort, rather than absolute change over time. A participant maintaining a similar z-score across waves may still have experienced structural decline, but at a rate comparable to others. The standardisation approach does not indicate the direction of change at the group level. Therefore, our interpretation relies on the assumption that brain structure typically declines with age from MRI-Wave 1 to 2, which we used to infer that lower CVR may be linked with relatively faster structural deterioration within the cohort. However, this method limits our ability to detect true change trajectories, especially in a relatively healthy cohort, and may underestimate associations in individuals more vulnerable to neurodegeneration.

7.5 Future directions

Building on the findings and limitations of this thesis, several key avenues for future research are warranted. 1) It is essential to better understand how the longitudinal trajectory of CVR (i.e., repeated CVR measurements) influences brain structure and cognitive decline. This would help to establish the temporal relationships between CVR and later-life outcomes in brain structure, cognitive decline, or the other biomarkers of dementia such as the accumulation of amyloid-β and tau. 2) Larger sample sizes are needed to increase statistical power, particularly for voxel-wise analyses that can reveal finer-grained spatial patterns of CVR-brain associations. Greater statistical power would also facilitate more robust mediation models, which enables the exploration of more complex mechanistic pathways. 3) Future work may extend the current findings to clinical populations, such as individuals with mild cognitive impairment or dementia. Examining whether the associations and mechanistic pathways identified in this thesis hold in patients with dementia would provide valuable insights into the role of CVR in the progressive stages of dementia. Although conducting CVR studies in such groups would be challenging, particularly concerning scan tolerability and CO_2 stimulation, these protocols are likely feasible for individuals with subjective cognitive impairment or mild cognitive impairment, given the good tolerability to such protocol of the current cohort with advanced age. 4) Although MRI-based CVR is increasingly available, it remains costly and less accessible in many regions, especially in middle- and low-income countries. Therefore, it

would be valuable to explore alternative techniques, such as transcranial Doppler (TCD) ultrasound or near-infrared spectroscopy (NIRS), which are less expensive and easier to operate. Some studies suggest that CVR assessed by transcranial Doppler (TCD) is highly correlated with MRI-based CVR (Sleight et al., 2021), but further validation is needed to test whether these alternative measures can also reliably reflect cerebrovascular health and predict brain changes and cognitive decline. 5) As the current findings have limited generalisability, future studies should aim to investigate CVR in more heterogeneous cohorts, including individuals from different ethnic backgrounds, lower socioeconomic status, and with higher vascular or cognitive burdens. In addition, future research may also examine whether sex modulates the associations between CVR and brain structure, cognition and dementia risk in cohorts with more balanced sex distribution. 6) Methodological improvements such as using the same scanner across timepoints or applying advanced harmonisation techniques such as "ComBat" (Beer et al., 2020), may enhance the detection of absolute changes in CVR and other neuroimaging markers. This would strengthen the interpretation of longitudinal changes, particularly in relation to disease progression or intervention effects. 7) The UKBDRS also has an alternative version which includes genetic risk for dementia, specifically the APOE genotype (Anatürk et al., 2023). While this thesis focused on modifiable lifestyle factors, future research should investigate how APOE ε4 interacts with lifestyle and vascular risk factors in relation to CVR. Examining such gene-lifestyle interactions may provide deeper insight into individual vulnerability to cerebrovascular dysfunction and dementia-related outcomes. Lastly, future studies may explore the optimal temporal windows during which multiple risk factors exert the strongest influence on CVR and examine whether targeted interventions addressing these risk

factors can preserve or enhance CVR over time.

7.6 Implications

Currently, there is no effective treatment for Alzheimer's disease or other forms of dementia. Therefore, prevention remains a crucial strategy to reduce the growing burden of dementia. Identifying individuals at high risk through early biomarkers during the prodromal stage, before the onset of dementia, provides a critical window for implementing effective interventions. Many commonly used non-invasive biomarkers of dementia, such as brain atrophy and white matter damage, typically reflect later-stage pathology. Extensive neuronal loss and irreversible damage have often already occurred by the time these biomarkers are observed, which limits the potential reversible interventions. Therefore, it is essential to **identify earlier and modifiable biomarkers** that can 1) improve our understanding of mechanisms and 2) inform timely intervention strategies.

Our findings suggest that CVR, particularly in the hippocampus and MPFC, may serve as a promising early marker to indicate vulnerability to structural brain changes, including grey matter atrophy and white matter microstructural damage. There is potential to adopt CVR as a vascular marker to identify individuals at elevated risk of dementia in clinical settings, particularly as more accessible pipelines for its processing have been developed, which may

ease its assessment in both research and clinical settings (Liu et al., 2022). In addition, CVR is influenced by various modifiable factors as suggested by our systematic review and empirical study. Therefore, the preservation of CVR, which may help maintain brain health, could be facilitated by modifiable lifestyle changes and better control of vascular risk. And indeed, **CVR can be improved through different interventions**. Studies have shown that moderate intensity endurance exercise training can increase CVR in both younger and older people (Murrell et al., 2013; Talbot et al., 2023), and treadmill-based aerobic training has been found to increase CVR in stroke survivors and sedentary elderly individuals (Ivey et al., 2011; Vicente-Campos et al., 2012). Non-smokers are also known to have higher CVR suggesting that interventions to smoking may also help to preserve CVR (Silvestrini et al., 1996). In addition to exercise and smoking, pharmacological interventions such as statin therapy have demonstrated significant improvements in CVR among individuals with small vessel disease and those with internal carotid artery occlusion (Reinhard et al., 2011; Sander et al., 2005). Beyond pharmacological approaches, surgical interventions to restore cerebral blood flow by direct unilateral superficial temporal artery-to-middle cerebral artery (STA-MCA) bypass has been shown to enhance CVR in both the MCA territory and in the anterior cerebral artery territory (L. McKetton et al., 2019). Therefore, CVR is modifiable, and interventions or treatments that preserve or improve CVR may help to maintain brain health and potentially reduce the risk of cognitive decline and future dementia. Other lifestyle-based approaches (such as changes in diet or sleep pattens) also warrant further investigation as accessible strategies to support cerebrovascular health. It would be of interest to investigate whether other lifestyle management can influence CVR through randomised controlled trials or longitudinal

cohort studies.

7.7 Concluding remarks

This thesis provides novel and comprehensive evidence for the role of CVR in linking midlife dementia risk factors to later-life brain structure and cognitive outcomes. We found that CVR is associated with multiple dementia risk factors (**risk --> CVR**). In older age, lower CVR is related to poorer brain structural health, which includes greater brain atrophy and reduced white matter microstructure, as well as to greater cognitive decline (**CVR -> brain structure; CVR --> cognitive decline**). Among the examined brain regions, hippocampal CVR appears to be a particularly sensitive marker, which may mediate the association between midlife dementia risk and later-life brain and cognitive outcomes (**risk --> CVR --> brain structure -> cognitive performance**). These findings suggest that hippocampal CVR may serve as a key vascular indicator of the pathological progression leading to dementia. Although longitudinal studies with repeated CVR measurements are required to establish its temporal associations and predictive value as a potential biomarker for dementia, our results highlight the potential of hippocampal CVR to reflect vulnerability in brain and cognitive health. We propose that interventions aimed at preserving or improving CVR, particularly through the management of modifiable risk factors, may contribute to strategies for dementia prevention.

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Appendix

Appendix for Chapter 2

Appendix 2.1: Search terms for systematic review

Concept 1: CVR:

"cerebral vascular reactivity" OR "cerebrovascular reactivity" OR "cerebral vasoreactivity" OR "cvr" OR "cerebral vasomotor reactivity" OR "vasomotor responsiveness" OR "cerebrovascular responsiveness" OR "cerebrovascular CO*"

Concept 2: Population:

2.1 Dementia/AD/vascular dementia/mixed dementia/MCI

"dementia" OR "dement*"OR "alzheimer*" OR "AD" OR "vascular dementia" OR "multi-infarct dementia" OR "multi-infarct" OR "vascular cognitive impairment" OR "vascular" OR "mixed dementia" OR "cognitive impairment" OR "mild cognitive impairment" OR "MCI" OR "neurocognitive disorder" OR "cognitive disorder"

OR

2.2 Healthy aging

"ageing" OR "aging" OR "aged" OR "older" OR "elder*"

Concept 3: Risk factors

"dementia risk factor*" OR "genetic risk factor*" OR "clinical risk*" OR "risk factor" OR

"apolipoprotein" OR "apolipoprotein E" OR "APOE4" OR "APOE*" OR

"stroke" OR "atrial fibrillation" OR "atherosclerosis" OR "peripheral artery disease" OR "aortic stiffness" OR "arterial stiffness" OR "arterial stiffening" OR "pulse wave velocity" OR

"hypertensi*" OR "blood pressure" OR "hypotensi*" OR "systolic" OR "diastolic" OR "antihypertensive" OR

"physical inactivity" OR "exercise" OR "fitness" OR "physical exercise" OR "physical activity" OR "aerobic exercise" OR

"smoking" OR "tobacco" OR "nicotine" OR

"air pollution*" OR "particulate matter" OR "nitrogen dioxide" OR "nitrates" OR "nitric oxide" OR "ozone" OR "ultrafine particulate matter" OR "UFPM" OR "vehicle emission*" OR "road proximity" OR "traffic" or "sulfur dioxide" OR "sulphur dioxide" OR

"less education" OR "education" OR "year of education" OR "years of education" OR "educational attainment" OR

"hearing loss" OR

"diabetes" OR "type 2 diabetes mellitus" OR "diabetes mellitus" OR "prediabetes" OR

"obesity" OR "obese" OR "body weight" OR "overweight" OR "BMI" OR "body mass index" OR "weight loss" OR "waist circumference" OR "hip to waist ratio" OR

"depression" OR "major depressive disorder" OR "depressive disorder" OR "depressed" OR

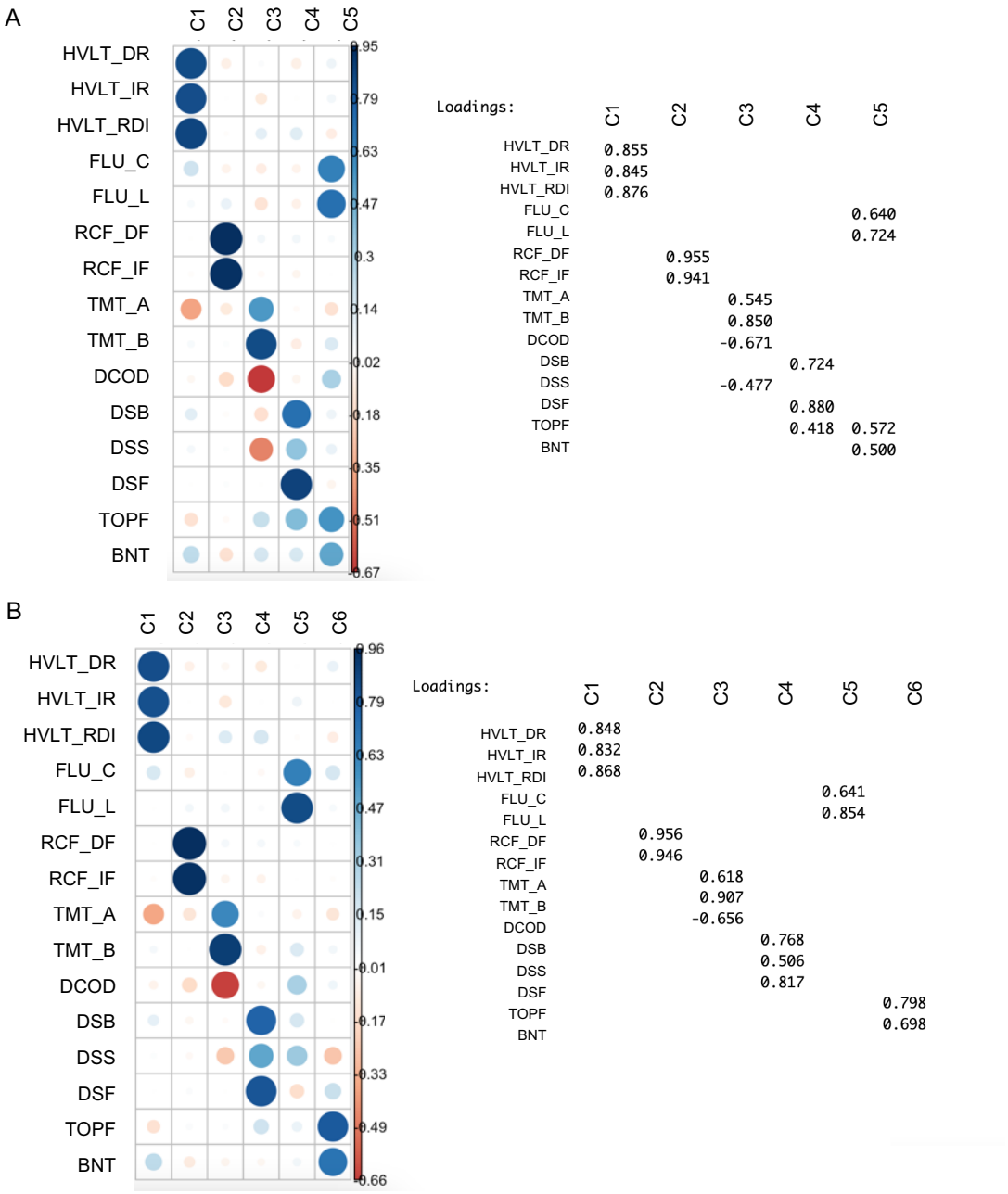
"social contact*" OR "social* isolat*" OR "social* engage*" OR "social* activ*" OR "social participation" OR "social interaction" OR "social support" OR "social environment" OR

"TBI" OR "traumatic brain injury" OR "head injury" OR "brain injury" OR

"alcohol*" OR "units per week"

1 AND 2.1 OR 2.2 AND 3

Limited to human, humans studies and English



Appendix Figure 3.1: Loadings of cognitive test scores on principal components before and after thresholding

Note: Figures on the left show original loadings; figures on the right show normalised loadings thresholded at 0.4. Panel A shows loadings with five retained components. The Test of Premorbid Functioning (TOPF) loaded onto two components, and Digit Span (DS) scores split across domains. Panel B shows loadings with six retained components, which resolved these overlaps and allowed clearer domain interpretation.

Appendix for Chapter 5

Appendix Table 5.1: Associations between CVR at MRI-Wave 2 and GMV measured at MRI-Wave 2 and the change in GMV from MRI-Wave 1 to 2.

Positive beta value reflects that lower CVR is associated with greater GMV decline. 95% CI = 95% confidence interval; bolded p-values highlight significant results ($p < 0.05$), p_{corr} indicates the Benjamini-Hochberg corrected p-value and is reported only for results with $p < 0.05$ (yellow highlights). Multiple comparisons were conducted across DMN regions, separately for the cross-sectional and longitudinal analyses. Cohen's f^2 is reported for two components: the overall model (reflecting the effect size of the full model including all covariates), and the independent variable (CVR) alone (reflecting its unique contribution to explaining variance in the outcome).

Exposure	Outcome	Beta [95% CI]	p-value	p_{corr}	Cohen's f^2 Overall model (Independent variable)
Total GM CVR	Total GMV	48.505 [-42.870, 139.879]	0.296		
	ΔTotal GMV	0.189 [-0.825, 1.203]	0.714		
MPFC CVR	MPFC GMV	2.689 [-0.175, 5.553]	0.066		
	ΔMPFC GMV	1.530 [0.245, 2.814]	**0.020**	0.120	0.165 (0.039)
PCC CVR	PCC GMV	-0.364 [-1.774, 1.046]	0.611		
	ΔPCC GMV	0.048 [-0.671, 0.766]	0.896		
TPJ CVR	TPJ GMV	-0.565 [-4.539, 3.408]	0.779		
	ΔTPJ GMV	-0.516 [-1.929, 0.897]	0.471		
Precuneus CVR	Precuneus GMV	1.932 [-1.999, 5.862]	0.333		
	ΔPrecuneus GMV	-0.329 [-1.401, 0.743]	0.545		
Left Hippocampus CVR	Left Hippocampus GMV	1.212 [0.234, 2.190]	**0.016**	0.093	0.221(0.038)
	ΔLeft Hippocampus GMV	1.328 [-0.431, 3.087]	0.138		
Right Hippocampus CVR	Right Hippocampus GMV	-0.002 [-0.955, 0.955]	0.997		
	ΔRight Hippocampus GMV	0.750 [-0.996, 2.495]	0.397		

Appendix Table 5.2: Associations between CVR at MRI-Wave 2 and WM diffusion metrics measured at MRI-Wave 2.

95% CI = 95% confidence interval; p_{corr} refers to the significance level after correction for multiple comparisons using the Benjamini-Hochberg approach and only presents for the associations with p<0.05 (yellow highlights). For total grey matter CVR, corrections were applied across the four white matter tracts within each diffusion metric (e.g., FA in all tracts). For regional CVR, corrections were applied across all CVR regions and tracts within each diffusion metric (e.g., all FA values across five CVR regions and four tracts). Cohen's f^2 is reported for two components: the overall model (reflecting the effect size of the full model including all covariates), and the independent variable (CVR) alone (reflecting its unique contribution to explaining variance in the outcome).

Exposure	Outcome		Beta [95% CI] *Beta (e^{-5}) for MD/RD/L1*	p-value	p_{corr}	Cohen's f^2 Overall model (Independent variable)
Total GM CVR	Whole brain	FA	0.006 [-0.040, 0.052]	0.800		
		MD	0.660 [-5.870, 7.190]	0.842		
		RD	0.287 [-6.672, 7.246]	0.935		
		L1	1.406 [-4.905, 7.718]	0.660		
	Corpus callosum	FA	-0.002 [-0.065, 0.062]	0.956		
		MD	-2.554 [-11.186, 6.078]	0.560		
		RD	-1.228 [-10.709, 8.252]	0.798		
		L1	-5.206 [-15.352, 4.939]	0.312		
	Cingulum	FA	-0.001 [-0.068, 0.066]	0.980		
		MD	1.539 [-5.182, 8.260]	0.652		
		RD	0.798 [-6.707, 8.304]	0.834		
		L1	3.020 [-6.791, 12.832]	0.544		
	Internal capsule	FA	0.009 [-0.045, 0.063]	0.744		
		MD	-1.443 [-7.176, 4.290]	0.620		
		RD	-1.178 [-7.516, 5.161]	0.714		
		L1	-1.973 [-10.036, 6.090]	0.629		
	Fornix	FA	0.053 [-0.026, 0.132]	0.186		
		MD	-4.368 [-18.608, 9.871]	0.545		
		RD	-7.282 [-25.003, 10.438]	0.418		
		L1	1.460 [-10.070, 12.989]	0.803		
MPFC CVR	Corpus callosum	FA	0.036 [-0.028, 0.100]	0.265		
		MD	-5.651 [-14.302, 3.000]	0.199		
		RD	-6.161 [-15.653, 3.331]	0.202		
		L1	-4.631 [-14.853, 5.591]	0.372		
	Cingulum	FA	0.010 [-0.058, 0.078]	0.766		
		MD	2.716 [-4.040, 9.473]	0.428		
		RD	0.493 [-7.064, 8.050]	0.898		
		L1	7.164 [-2.656, 16.984]	0.151		
	Internal capsule	FA	0.003 [-0.051, 0.058]	0.900		
		MD	-2.210 [-7.975, 3.554]	0.45		
		RD	-1.307 [-7.688, 5.073]	0.686		
		L1	-4.016 [-12.113, 4.081]	0.328		
	Fornix	FA	0.083 [0.005, 0.162]	**0.038**	0.255	0.200(0.031)
		MD	-10.044 [-24.302, 4.215]	0.166		

		RD	-14.944 [-32.655, 2.767]	0.098
		L1	-0.242 [-11.852, 11.368]	0.967
PCC CVR	Corpus callosum	FA	0.026 [-0.018, 0.070]	0.241
		MD	-5.646 [-11.539, 0.248]	0.060
		RD	-5.271 [-11.760, 1.217]	0.111
		L1	-6.395 [-13.345, 0.554]	0.071
	Cingulum	FA	0.023 [-0.024, 0.069]	0.333
		MD	-0.235 [-4.878, 4.408]	0.920
		RD	-1.777 [-6.951, 3.397]	0.498
		L1	2.849 [-3.917, 9.615]	0.407
	Internal capsule	FA	0.005 [-0.032, 0.042]	0.795
		MD	-1.576 [-5.529, 2.376]	0.432
		RD	-1.041 [-5.415, 3.334]	0.639
		L1	-2.647 [-8.201, 2.907]	0.348
	Fornix	FA	0.050 [-0.004, 0.104]	0.068
		MD	-6.687 [-16.468, 3.094]	0.179
		RD	-10.090 [-22.238, 2.058]	0.103
		L1	0.120 [-7.841, 8.081]	0.976
TPJ CVR	Corpus callosum	FA	0.029 [-0.036, 0.093]	0.384
		MD	-5.144 [-13.950, 3.663]	0.250
		RD	-5.199 [-14.868, 4.471]	0.290
		L1	-5.034 [-15.424, 5.356]	0.340
	Cingulum	FA	0.029 [-0.040, 0.098]	0.407
		MD	0.603 [-6.282, 7.488]	0.863
		RD	-1.656 [-9.336, 6.024]	0.671
		L1	5.121 [-4.901, 15.143]	0.314
	Internal capsule	FA	0.021 [-0.034, 0.077]	0.449
		MD	-2.300 [-8.161, 3.562]	0.439
		RD	-2.608 [-9.085, 3.870]	0.427
		L1	-1.684 [-9.940, 6.572]	0.687
	Fornix	FA	0.056 [-0.024, 0.137]	0.171
		MD	-2.971 [-17.558, 11.617]	0.688
		RD	-5.933 [-24.089, 12.223]	0.519
		L1	2.954 [-8.842, 14.749]	0.621
Precuneus CVR	Corpus callosum	FA	-0.016 [-0.063, 0.030]	0.494
		MD	1.697 [-4.657, 8.052]	0.598
		RD	2.009 [-4.962, 8.981]	0.570
		L1	1.074 [-6.418, 8.565]	0.777
	Cingulum	FA	0.007 [-0.042, 0.057]	0.777
		MD	3.469 [-1.448, 8.386]	0.165
		RD	1.168 [-4.354, 6.690]	0.676

		L1	8.071 [0.964, 15.178]	**0.026**	0.263	0.036(0.035)
	Internal capsule	FA	0.017 [-0.023, 0.057]	0.400		
		MD	0.252 [-3.971, 4.475]	0.906		
		RD	-1.005 [-5.669, 3.659]	0.671		
		L1	2.766 [-3.156, 8.688]	0.357		
	Fornix	FA	0.029 [-0.029, 0.087]	0.32		
		MD	0.474 [-10.019, 10.967]	0.929		
		RD	-0.881 [-13.952, 12.191]	0.894		
		L1	3.184 [-5.288, 11.655]	0.459		
Hippocampal CVR	Corpus callosum	FA	0.076 [0.006, 0.146]	**0.033**	0.255	0.189(0.029)
		MD	-11.702 [-21.174, -2.230]	**0.016**	0.162	0.323(0.043)
		RD	-12.555 [-22.957, -2.153]	**0.018**	0.322	0.252(0.038)
		L1	-9.996 [-21.264, 1.272]	0.082		
	Cingulum	FA	0.039 [-0.036, 0.114]	0.302		
		MD	-2.417 [-9.929, 5.095]	0.526		
		RD	-4.109 [-12.477, 4.260]	0.333		
		L1	0.967 [-10.020, 11.953]	0.862		
	Internal capsule	FA	0.030 [-0.030, 0.091]	0.323		
		MD	-7.742 [-14.031, -1.452]	**0.016**	0.162	0.161(0.035)
		RD	-5.977 [-13.001, 1.047]	0.095		
		L1	-11.271 [-20.103, -2.438]	**0.013**	0.255	0.182(0.046)
	Fornix	FA	0.108 [0.021, 0.194]	**0.016**	0.255	0.214(0.043)
		MD	-14.900 [-30.657, 0.856]	0.064		
		RD	-21.390 [-40.940, -1.839]	**0.032**	0.322	0.031(0.208)
		L1	-1.922 [-14.816, 10.972]	0.769		

Appendix Table 5.3: Associations between CVR at MRI-Wave 2 and change in WM diffusion metrics measured from MRI-Wave 1 to 2.

Positive beta values for FA indicate that lower CVR is associated with greater FA decline, whereas negative beta values for MD/RD/L1 indicate that lower CVR is associated with greater increases in these diffusivity measures. 95% CI = 95% confidence interval; p_{corr} refers to the significance level after correction for multiple comparisons using the Benjamini-Hochberg approach and only presents for associations with p<0.05 (yellow highlights for associations not survive correction for multiple comparisons, and orange highlights for associations survive correction). For total grey matter CVR, corrections were applied across

the four white matter tracts within each diffusion metric (e.g., FA in all tracts). For regional CVR, corrections were applied across all CVR regions and tracts within each diffusion metric (e.g., all FA values across five CVR regions and four tracts). Cohen's f^2 is reported for two components: the overall model (reflecting the effect size of the full model including all covariates), and the independent variable (CVR) alone (reflecting its unique contribution to explaining variance in the outcome).

Exposure	Outcome		Beta [95% CI]	p-value	p_{corr}	Cohen's f^2 Overall model (Independent variable)
Total GM CVR	Whole brain	ΔFA	0.458 [-0.539, 1.456]	0.366		
		ΔMD	-0.136 [-0.937, 0.664]	0.737		
		ΔRD	-0.168 [-0.999, 0.663]	0.690		
		ΔL1	-0.035 [-0.933, 0.864]	0.939		
	Corpus callosum	ΔFA	0.831 [-0.229, 1.891]	0.123		
		ΔMD	-0.190 [-1.071, 0.692]	0.671		
		ΔRD	-0.638 [-1.628, 0.352]	0.204		
		ΔL1	0.403 [-0.521, 1.327]	0.390		
	Cingulum	ΔFA	1.105 [-0.020, 2.230]	0.054		
		ΔMD	-1.384 [-2.576, -0.192]	**0.023**	0.093	0.073 (0.037)
		ΔRD	-1.263 [-2.363, -0.162]	**0.025**	0.099	0.203 (0.036)
		ΔL1	-0.750 [-2.083, 0.583]	0.268		
	Internal capsule	ΔFA	0.872 [-0.115, 1.860]	0.083		
		ΔMD	-0.559 [-1.680, 0.562]	0.326		
		ΔRD	-0.753 [-1.785, 0.278]	0.151		
		ΔL1	-0.064 [-1.180, 1.052]	0.910		
	Fornix	ΔFA	0.205 [-0.847, 1.258]	0.700		
		ΔMD	0.038 [-0.899, 0.974]	0.937		
		ΔRD	0.122 [-0.668, 0.913]	0.760		
		ΔL1	-0.261 [-1.954, 1.433]	0.761		
MPFC CVR	Corpus callosum	ΔFA	1.214 [0.159, 2.269]	**0.024**	0.061	0.328 (0.036)
		ΔMD	-0.779 [-1.656, 0.098]	0.081		
		ΔRD	-1.157 [-2.139, -0.176]	**0.021**	0.069	0.342 (0.038)
		ΔL1	-0.037 [-0.968, 0.894]	0.937		
	Cingulum	ΔFA	1.348 [0.226, 2.471]	**0.019**	0.059	0.273 (0.039)
		ΔMD	-1.221 [-2.424, -0.019]	**0.047**	0.233	0.064 (0.028)
		ΔRD	-1.354 [-2.457, -0.251]	**0.016**	0.069	0.209 (0.041)
		ΔL1	-0.222 [-1.567, 1.122]	0.744		
	Internal capsule	ΔFA	0.526 [-0.472, 1.525]	0.299		
		ΔMD	-0.353 [-1.481, 0.776]	0.538		

		ΔRD	-0.484 [-1.524, 0.557]	0.359		
		ΔL1	-0.150 [-1.271, 0.970]	0.791		
	Fornix	ΔFA	-0.049 [-1.107, 1.008]	0.927		
		ΔMD	0.260 [-0.680, 1.200]	0.585		
		ΔRD	0.174 [-0.620, 0.968]	0.665		
		ΔL1	0.254 [-1.448, 1.955]	0.769		
PCC CVR	Corpus callosum	ΔFA	0.967 [0.248, 1.686]	**0.009**	0.059	0.345 (0.049)
		ΔMD	-0.319 [-0.924, 0.287]	0.300		
		ΔRD	-0.800 [-1.473, -0.127]	**0.020**	0.069	0.343 (0.039)
		ΔL1	0.346 [-0.289, 0.982]	0.283		
	Cingulum	ΔFA	1.104 [0.340, 1.868]	**0.005**	0.059	0.295 (0.057)
		ΔMD	-1.159 [-1.973, -0.345]	**0.006**	0.103	0.092 (0.055)
		ΔRD	-1.136 [-1.884, -0.387]	**0.003**	**0.049**	0.234 (0.063)
		ΔL1	-0.527 [-1.445, 0.391]	0.259		
	Internal capsule	ΔFA	0.480 [-0.203, 1.162]	0.167		
		ΔMD	-0.367 [-1.140, 0.406]	0.349		
		ΔRD	-0.467 [-1.179, 0.245]	0.197		
		ΔL1	-0.152 [-0.920, 0.617]	0.697		
	Fornix	ΔFA	0.353 [-0.370, 1.076]	0.336		
		ΔMD	-0.200 [-0.844, 0.445]	0.541		
		ΔRD	-0.214 [-0.758, 0.329]	0.437		
		ΔL1	-0.145 [-1.312, 1.022]	0.806		
TPJ CVR	Corpus callosum	ΔFA	0.769 [-0.317, 1.855]	0.164		
		ΔMD	-0.132 [-1.034, 0.770]	0.773		
		ΔRD	-0.600 [-1.613, 0.413]	0.244		
		ΔL1	0.516 [-0.428, 1.460]	0.282		
	Cingulum	ΔFA	1.034 [-0.119, 2.187]	0.078		
		ΔMD	-1.012 [-2.242, 0.217]	0.106		
		ΔRD	-1.019 [-2.152, 0.114]	0.078		
		ΔL1	-0.380 [-1.748, 0.988]	0.584		
	Internal capsule	ΔFA	0.208 [-0.811, 1.228]	0.687		
		ΔMD	-0.165 [-1.315, 0.985]	0.777		
		ΔRD	-0.133 [-1.195, 0.930]	0.806		
		ΔL1	-0.274 [-1.414, 0.867]	0.636		
	Fornix	ΔFA	0.139 [-0.938, 1.215]	0.799		
		ΔMD	0.029 [-0.929, 0.987]	0.952		
		ΔRD	0.021 [-0.788, 0.830]	0.958		
		ΔL1	0.036 [-1.697, 1.769]	0.967		
Precuneus CVR	Corpus callosum	ΔFA	0.763 [-0.012, 1.538]	0.054		
		ΔMD	-0.254 [-0.900, 0.393]	0.439		
		ΔRD	-0.618 [-1.342, 0.106]	0.094		

		ΔL1	0.412 [-0.265, 1.090]	0.231		
	Cingulum	ΔFA	1.066 [0.247, 1.884]	**0.011**	0.059	0.282 (0.046)
		ΔMD	-1.146 [-2.017, -0.275]	**0.010**	0.103	0.084 (0.047)
		ΔRD	-1.156 [-1.956, -0.356]	**0.005**	**0.049**	0.228 (0.057)
		ΔL1	-0.348 [-1.330, 0.634]	0.485		
	Internal capsule	ΔFA	0.880 [0.162, 1.598]	**0.017**	0.059	0.088 (0.041)
		ΔMD	-0.689 [-1.507, 0.130]	0.098		
		ΔRD	-0.775 [-1.527, -0.022]	**0.044**	0.109	0.094 (0.029)
		ΔL1	-0.115 [-0.934, 0.705]	0.783		
	Fornix	ΔFA	0.333 [-0.438, 1.105]	0.395		
		ΔMD	-0.070 [-0.758, 0.618]	0.840		
		ΔRD	-0.064 [-0.645, 0.517]	0.829		
		ΔL1	0.008 [-1.236, 1.253]	0.989		
Hippocampal CVR	Corpus callosum	ΔFA	1.236 [0.061, 2.411]	**0.039**	0.088	0.321 (0.030)
		ΔMD	-0.539 [-1.519, 0.441]	0.279		
		ΔRD	-1.051 [-2.148, 0.046]	0.060		
		ΔL1	0.190 [-0.844, 1.223]	0.717		
	Cingulum	ΔFA	1.574 [0.329, 2.819]	**0.014**	0.059	0.278 (0.044)
		ΔMD	-1.466 [-2.798, -0.133]	**0.031**	0.209	0.069 (0.033)
		ΔRD	-1.573 [-2.796, -0.351]	**0.012**	0.069	0.214 (0.045)
		ΔL1	-0.531 [-2.023, 0.960]	0.482		
	Internal capsule	ΔFA	1.294 [0.201, 2.387]	**0.021**	0.059	0.085 (0.038)
		ΔMD	-1.074 [-2.317, 0.168]	0.090		
		ΔRD	-1.312 [-2.451, -0.173]	**0.024**	0.069	0.102 (0.036)
		ΔL1	-0.719 [-1.959, 0.521]	0.253		
	Fornix	ΔFA	0.289 [-0.885, 1.463]	0.627		
		ΔMD	0.022 [-1.023, 1.068]	0.967		
		ΔRD	0.112 [-0.771, 0.994]	0.803		
		ΔL1	-0.475 [-2.364, 1.414]	0.620		

Appendix Table 5.4: Associations between CVR at MRI-Wave 2 and WMH volume measured at MRI-Wave 2 and the change in WMH volume from MRI-Wave 1 to 2.
A positive beta indicates that lower CVR is associated with a larger increase in WMHs volume, and a negative beta suggests that lower CVR is associated with a smaller increase in WMHs volume. 95% CI = 95% confidence interval; no p-values reached significance at p < 0.05, therefore corrected p-values and effect size estimates are not reported.

Exposure	Outcome	Beta [95% CI]	p-value
Total GM CVR	logWMH%	0.606 [-0.501, 1.713]	0.281
	ΔlogWMH%	0.192 [-0.357, 0.742]	0.490
MPFC CVR	logWMH%	0.076 [-0.144, 1.192]	0.894
	ΔlogWMH%	0.058 [-0.494, 0.609]	0.837
PCC CVR	logWMH%	0.061 [-0.700, 0.821]	0.875

	ΔlogWMH%	0.032 [-0.408, 0.344]	0.887
TPJ CVR	logWMH%	0.537 [-0.593, 1.667]	0.349
	ΔlogWMH%	0.068 [-0.492, 0.628]	0.811
Precuneus CVR	logWMH%	0.241 [-0.575, 1.058]	0.560
	ΔlogWMH%	-0.059 [-0.463, 0.344]	0.772
Hippocampal CVR	logWMH%	-0.093 [-1.328, 1.142]	0.882
	ΔlogWMH%	-0.242 [-0.851, 0.367]	0.433

Appendix Table 5.5: Associations between CVR at MRI-Wave 2 and cognition measured at MRI-Wave 2 and the change in cognition from MRI-Wave 1 to 2.

Positive beta means that lower CVR is associated with greater cognitive decline, and a negative beta suggests lower CVR is associated with smaller cognitive decline. 95% CI = 95% confidence interval; p_{corr} refers to the significance level after correction for multiple comparisons using the Benjamini-Hochberg approach and is only presented for associations with p<0.05 (yellow highlights). Cohen's f^2 is reported for two components: the overall model (reflecting the effect size of the full model including all covariates), and the independent variable (CVR) alone (reflecting its unique contribution to explaining variance in the outcome)

Exposure	Outcome	Beta [95% CI]	p-value	p_{corr}	Cohen's f^2 Overall model (Independent variable)
Total GM CVR	Episodic Memory	-7.773 [-24.043, 8.498]	0.347		
	ΔEpisodic Memory	-14.209 [-29.411, 0.992]	0.067		
	Visuospatial Memory	4.973 [-21.326, 31.272]	0.709		
	ΔVisuospatial Memory	-14.420 [-13.773, 42.613]	0.314		
	Fluency	1.479 [-15.372, 18.329]	0.863		
	ΔFluency	-4.784 [-18.065, 8.497]	0.478		
	Executive Function	-4.431 [-77.659, 68.796]	0.905		
	ΔExecutive Function	8.986 [-42.664, 60.635]	0.731		
	Lexical Retrieval	7.854 [-7.750, 23.458]	0.321		
	ΔLexical Retrieval	-12.934 [-23.975, -1.893]	**0.022**	0.132	0.355(0.039)
	Working Memory	-6.537 [-15.926, 2.852]	0.171		
	ΔWorking Memory	-4.164 [-21.780, 13.452]	0.234		
MPFC CVR	Episodic Memory	11.300 [-4.997, 27.598]	0.173		
	ΔEpisodic Memory	1.640 [-13.787, 17.066]	0.834		
	Visuospatial Memory	9.143 [-17.271, 35.556]	0.495		
	ΔVisuospatial Memory	35.467 [7.709, 63.225]	**0.013**	0.335	0.115(0.047)
	Fluency	10.163 [-6.691, 27.018]	0.235		
	ΔFluency	-1.076 [-14.419, 12.268]	0.874		
	Executive Function	50.177 [-22.768, 123.121]	0.176		
	ΔExecutive Function	61.016 [10.361, 111.672]	**0.019**	0.335	0.177(0.041)
	Lexical Retrieval	12.024 [-3.651, 27.698]	0.132		
	ΔLexical Retrieval	-1.053 [-12.388, 10.282]	0.855		
	Working Memory	0.871 [-8.627, 10.369]	0.856		
	ΔWorking Memory	-0.361 [-7.208, 6.485]	0.917		
PCC CVR	Episodic Memory	0.487 [-10.826, 11.800]	0.932		
	ΔEpisodic Memory	-0.106 [-10.749, 10.537]	0.984		
	Visuospatial Memory	-4.627 [-22.794, 13.540]	0.615		
	ΔVisuospatial Memory	12.109 [-7.305, 31.523]	0.220		
	Fluency	-0.558 [-12.239, 11.122]	0.925		
	ΔFluency	-4.32 [-13.497, 4.857]	0.354		

	Executive Function	26.570 [-23.467, 76.607]	0.296
	ΔExecutive Function	28.69 [-6.344, 63.724]	0.108
	Lexical Retrieval	4.260 [-6.558, 15.079]	0.438
	ΔLexical Retrieval	-2.887 [-10.649, 4.876]	0.463
	Working Memory	-5.270 [-11.762, 1.223]	0.111
	ΔWorking Memory	-2.037 [-6.748, 2.674]	0.394
TPJ CVR	Episodic Memory	-0.636 [-17.339, 16.067]	0.940
	ΔEpisodic Memory	-4.997 [-20.704, 10.710]	0.530
	Visuospatial Memory	-17.034 [-43.744, 9.675]	0.209
	ΔVisuospatial Memory	8.790 [-20.044, 37.624]	0.548
	Fluency	3.599 [-13.638, 20.835]	0.680
	ΔFluency	-4.811 [-18.391, 8.770]	0.485
	Executive Function	48.759 [-25.196, 122.714]	0.195
	ΔExecutive Function	50.201 [-1.564, 101.966]	0.057
	Lexical Retrieval	15.297 [-0.491, 31.085]	0.057
	ΔLexical Retrieval	-3.659 [-15.127, 7.809]	0.529
	Working Memory	-1.584[-11.253, 8.085]	0.747
	ΔWorking Memory	-3.32 [-10.278, 3.638]	0.347
Precuneus CVR	Episodic Memory	-6.180 [-18.136, 5.776]	0.309
	ΔEpisodic Memory	-10.286 [-21.444, 0.872]	0.071
	Visuospatial Memory	2.626 [-16.764, 22.015]	0.789
	ΔVisuospatial Memory	10.062 [-10.689, 30.812]	0.339
	Fluency	2.826 [-9.555, 15.206]	0.653
	ΔFluency	-2.530 [-12.284, 7.224]	0.609
	Executive Function	-16.137 [-69.830, 37.557]	0.553
	ΔExecutive Function	-4.404 [-42.251, 33.443]	0.818
	Lexical Retrieval	7.331 [-4.095, 18.757]	0.207
	ΔLexical Retrieval	-4.208 [-12.42, 4.004]	0.313
	Working Memory	-4.591 [-11.498, 2.316]	0.191
	ΔWorking Memory	-3.220 [-8.200, 1.761]	0.203
Left Hippocampus CVR	Episodic Memory	-3.137 [-20.485, 14.211]	0.721
	ΔEpisodic Memory	-6.195 [-22.517, 10.127]	0.454
	Visuospatial Memory	11.177 [-16.666, 39.020]	0.429
	ΔVisuospatial Memory	22.532 [-7.236, 52.300]	0.137
	Fluency	2.055 [-15.862, 19.972]	0.821
	ΔFluency	-1.222 [-15.366, 12.921]	0.865
	Executive Function	-1.410 [-78.638, 75.818]	0.971
	ΔExecutive Function	16.848 [-37.544, 71.240]	0.541
	Lexical Retrieval	10.841 [-5.823, 27.506]	0.200
	ΔLexical Retrieval	-0.948 [-12.983, 11.087]	0.876
	Working Memory	-4.009 [-14.038, 6.019]	0.431
	ΔWorking Memory	-1.922 [-9.172, 5.328]	0.601

Right Hippocampus CVR	Episodic Memory	3.208 [-13.883, 20.298]	0.711		
	ΔEpisodic Memory	-5.170 [-21.239, 10.898]	0.526		
	Visuospatial Memory	11.566 [-15.956, 39.089]	0.407		
	ΔVisuospatial Memory	30.696 [1.523, 59.869]	**0.039**	0.423	0.099(0.032)
	Fluency	6.559 [-11.063, 24.180]	0.463		
	ΔFluency	-0.022 [-13.94, 13.895]	0.997		
	Executive Function	37.672 [-38.234, 113.579]	0.328		
	ΔExecutive Function	29.165 [-24.264, 82.594]	0.282		
	Lexical Retrieval	10.696 [-5.640, 27.031]	0.198		
	ΔLexical Retrieval	-10.826 [-22.479, 0.827]	0.068		
	Working Memory	-2.869 [-12.759, 7.021]	0.567		
	ΔWorking Memory	-3.050 [-10.172, 4.073]	0.399		

Appendix for Chapter 6

Appendix Table 6.1: Full results of mediation models

Note: These tables present the mediation models where the independent variable and mediator showed a significant indirect effect on the outcome, indicated by an ACME p-value < 0.05 (yellow highlights).

Path 1.1: UKBDR-CVR-GMV				
Independent Variable	**Mediator**	**Outcome**	**ACME β [95% CI]**	**ACME p**
UKBDRS	MPFC CVR	MPFC GMV	-0.027 [-0.081, 0.010]	0.166
	PCC CVR	PCC GMV	0.014 [-0.008, 0.049]	0.231
	Left Hippocampus CVR	**Left Hippocampus GMV**	**-0.018 [-0.043, -0.0003]**	**0.045**
	Right Hippocampus CVR	Right Hippocampus GMV	0.002 [-0.013, 0.020]	0.760
Path 1.2: UKBDRS-CVR-WM microstructure				
Independent variable	**Mediator**	**Outcome**	**ACME β [95% CI] x 10^{-4}**	**ACME p-value**
UKBDRS	MPFC CVR	FA Corpus Callosum	-5.735 [-20.568, 5.006]	0.307
		FA Cingulum	-1.815 [-15.685, 10.551]	0.749
		FA Internal Capsule	-0.970 [-12.039, 9.265]	0.828
		FA Fornix	-13.409 [-35.088, 0.601]	0.066
		MD Corpus Callosum	0.008 [-0.006, 0.029]	0.274
		MD Cingulum	-0.005 [-0.021, 0.006]	0.366
		MD Internal Capsule	0.003 [-0.007, 0.016]	0.516
		MD Fornix	0.016 [-0.008, 0.050]	0.214
	PCC CVR	FA Corpus Callosum	-5.247 [-18.910, 3.874]	0.294
		FA Cingulum	-5.194 [-19.474, 4.440]	0.332
		FA Internal Capsule	-1.883 [-12.277, 6.705]	0.655
		FA Fornix	-9.195 [-27.969, 2.521]	0.159
		MD Corpus Callosum	0.011 [-0.002, 0.032]	0.126
		MD Cingulum	0.00004 [-0.011, 0.012]	0.998
		MD Internal Capsule	0.003 [-0.005, 0.015]	0.471
		MD Fornix	0.012 [-0.009, 0.043]	0.301
	Hippocampus CVR	**FA Corpus Callosum**	**-12.646 [-31.047, -0.315]**	**0.041**
		FA Cingulum	-6.961 [-23.696, 5.325]	0.279
		FA Internal Capsule	-5.697 [-19.366, 4.329]	0.278
		FA Fornix	**-17.384 [-41.114, -1.205]**	**0.025**
		MD Corpus Callosum	**0.019 [0.001, 0.045]**	**0.028**
		MD Cingulum	0.003 [-0.009, 0.018]	0.582
		MD Internal Capsule	**0.013 [0.001, 0.030]**	**0.025**
		MD Fornix	0.024 [-0.002, 0.063]	0.085

Path 2.1: CVR-GMV-Cognition				
Independent Variable	**Mediator**	**Outcome**	**ACME β [95% CI]**	**ACME p**
Left Hippocampus CVR	Left Hippocampus GMV	**Episodic Memory**	**4.491 [0.321, 10.459]**	**0.028**
		Visuospatial Memory	**8.603 [1.070, 19.042]**	**0.016**
		Fluency	1.837 [-1.893, 6.592]	0.339
		Executive Function	16.167 [-0.891, 41.230]	0.065
		Lexical Retrieval	1.372 [-1.971, 5.497]	0.418
		Working Memory	-0.478 [-3.043, 1.743]	0.665
Path 2.2 CVR-WM microstructure-Cognition				
Independent Variable	**Mediator**	**Outcome**	**ACME β [95% CI]**	**ACME p**
MPFC CVR	FA Fornix	Episodic Memory	0.579 [-2.696, 4.259]	0.693
		Visuospatial Memory	-0.894 [-6.781, 4.022]	0.717
		Fluency	1.508 [-1.571, 5.766]	0.348
		Executive Function	1.994 [-13.675, 18.923]	0.786
		Lexical Retrieval	1.548 [-1.096, 5.502]	0.281
		Working Memory	0.503 [-1.347, 2.720]	0.569
Precuneus CVR	L1 Cingulum	Episodic Memory	1.109 [-1.277, 4.218]	0.362
		Visuospatial Memory	0.978 [-2.986, 5.655]	0.598
		Fluency	-0.217 [-3.086, 2.458]	0.868
		Executive Function	7.676 [-2.578, 22.974]	0.165
		Lexical Retrieval	0.964 [-1.314, 3.901]	0.400
		Working Memory	0.136 [-1.382, 1.729]	0.832
Hippocampus CVR	MD Corpus Callosum	Episodic Memory	2.446 [-1.203, 7.801]	0.209
		Visuospatial Memory	1.216 [-5.431, 8.767]	0.694
		Fluency	2.559 [-1.206, 8.108]	0.204
		Executive Function	9.027 [-8.972, 33.148]	0.325
		Lexical Retrieval	-0.634 [-4.909, 3.248]	0.722
		Working Memory	1.077 [-1.072, 4.017]	0.327
	L1 Internal Capsule	Episodic Memory	1.198 [-2.729, 6.120]	0.540
		Visuospatial Memory	2.710 [-3.272, 10.834]	0.377
		Fluency	0.093 [-4.344, 4.671]	0.972
		Executive Function	7.582 [-9.359, 30.415]	0.378
		Lexical Retrieval	-2.211 [-7.151, 1.238]	0.228
		Working Memory	-0.121 [-2.652, 2.380]	0.912
	FA Fornix	Episodic Memory	1.217 [-2.784, 5.968]	0.526
		Visuospatial Memory	-1.349 [-8.802, 4.847]	0.663
		Fluency	2.179 [-1.717, 7.504]	0.280

		Executive Function	3.753 [-14.858, 24.733]	0.664
		Lexical Retrieval	2.011 [-1.397, 6.839]	0.260
		Working Memory	0.860 [-1.415, 3.671]	0.445