COGNITIVE AGING TRAJECTORIES: CARDIOVASCULAR RISK, WHITE MATTER, AND MEDICATION PREDICTORS

By

LINDSAY J. ROTBLATT

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To my parents, thank you for everything.

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By

Lindsay J. Rotblatt

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Increases in the older adult population have resulted concomitant increases in cardiovascular disease (CVD) prevalence, which is a known risk factor for cognitive decline and related cerebrovascular dysfunction. While pharmacological treatment has made substantial advances in reductions of CVD-related events (e.g., heart attack, stroke, lowering cholesterol), there remain considerable gaps in the field's collective knowledge regarding the effects of pharmacological treatment on cognitive outcomes. While the fundamental relationships proposed in this study have been investigated prior (CVD, WMH, cognition, medications), the current research extends extant literature by, (a) expanding sample size, (b) expanding longitudinal occasions, (c) looking at a full continuum of cognition, from normal to impaired, and (d) examining all proposed aspects of the research model in a combined statistical model, including mediator and moderator effects.

The proposed study will utilize a subsample of 24,239 participants, aged 60 years and older, drawn from the National Alzheimer's Coordinating Center (NACC). NACC participants along the cognitive continuum (e.g., cognitively normal through dementia) with 2-10 years of follow-up will be included. This current study seeks to

investigate the 10-year longitudinal associations between CVD (including both risk factors like hypertension and comorbidities like myocardial infarction), vascular neuropathology (white matter hyperintensities in regions of interest), and trajectories of change in four cognitive domains (Memory, Attention, Executive Function/Processing Speed, and Language). Thus, the proposed study has two specific aims: (1) To confirm that participants' level and longitudinal rate of change in CVD is associated with level and rate of change in the four cognitive domains over the subsequent decade; and to further investigate whether pharmacological treatment of CVD moderates that association, and (2) in a subset of participants for whom structural MRI data were collected at baseline, to determine whether baseline indicators of vascular neuropathology mediate the relationship between baseline CVD on level and rate of change in cognition over time.

CHAPTER 1
STATEMENT OF THE PROBLEM

Overview

Recent literature in the areas of neuropsychology as well as cardiovascular medicine have demonstrated considerable associations between cardiovascular disease (CVD), and related comorbidities, such as blood pressure and cognition (Hughes & Sink, 2016; Nation et al., 2010; Qiu, Winblad, & Fratiglioni, 2005). While pharmacological treatment has made significant advances in reductions in CVD-related events (e.g., heart attack, stroke), there remain considerable gaps in the literature regarding its effect on cognition (Boockvar, Song, Lee, & Intrator, 2019; Habes et al., 2016; Liao et al., 1997). Furthermore, studies investigating the effect of pharmacological treatment of CVD have primarily relied on only global measures of cognition such as the Mini-Mental Status Exam and/or have only followed participants for shorter periods of time (Streit, Poortvliet, Elzen, Blom, & Gussekloo, 2019; Vazirinejad et al., 2019). In addition, numerous studies have explored the relationships between white matter hyperintensity (WMH) burden and vascular risk factors/CVD as well as WMH and cognition, however few studies have examined these relationships together.

Thus, using longitudinal analyses, this study sought to extend extant literature by investigating the effect of CVD, comprised of cardiovascular risk factors (e.g. hypertension, type 2 diabetes, etc.) and comorbidities (e.g. myocardial infarction, heart failure, etc.), on trajectories of domain-specific changes in cognition in a diverse sample of older adults over a 10-year period. It also sought to investigate whether pharmacological treatment of CVD served to attenuate the potential effect of CVD on cognition. Of central interest to this study was examining the potential mechanisms

through which CVD may affect specific cognitive trajectories. Anatomically, CVD has been frequently associated with the presence of white matter abnormalities, referred to as white matter hyperintensities (WMH) in the literature due to their hyperintense, bright white presence on brain magnetic resonance (MR) imaging (H. M. A. Abraham et al., 2016; Stanek et al., 2011; Tamura & Araki, 2015). This current study additionally sought to explore whether these regional indicators of vascular neuropathology, as measured by WMH volume, served as a potential mediator between initial CVD risk and changes in cognition. A particular focus of this study was to elucidate a possible intervening pathway by which CVD might affect late life cognition, leveraging the longitudinal data available in in the National Alzheimer's Coordinating Center database.

This proposed study leverages the extensive repository of data available in the NACC database, encompassing older adults with structural MRI data with up to 10 years of follow-up data. The NACC database offers an unusually rich source of data in which to investigate these questions because of sample size, longitudinal occasions, broad sampling of individuals, concurrent imaging on a subset of individuals, and detailed medication inventories on all participants. In addition, the NACC database utilizes a Uniform Data Set (UDS), which is a common battery implemented across all NIH-funded Alzheimer's Disease Research Centers. With data collected since 2000, the current data set, downloaded September 2019, includes over 41,559 participants at baseline (42.8% men, 57.2% women. The proposed analyses will include approximately 24,239 participants at baseline aged 60 and older who meet inclusionary/exclusionary criteria. Cognition will be measured utilizing composites of neuropsychological measures within the following cognitive domains: (1) Memory, (2) Attention; (3)

Executive Function/Processing Speed, and (4) Language. White matter hyperintensity volume will be initially calculated on the aggregate but will be further be divided into periventricular and deep white matter for post-hoc analyses.

The present study examined the following aims:

Pre-Aim

Aim 0.

This is a descriptive aim and has no hypotheses. The goal of this aim is to characterize the total sample (N= 22,684) and subsample of participants with neuroimaging data at baseline (N= 1,049) and to describe the bivariate correlations among cognitive, demographic, cardiovascular, medication, and neuroimaging measures. This aim will also present the unconditional growth models for the targeted cognitive outcomes in this study, to characterize normative change and individual differences in such change.

Specific Aims

Aim 1.

(a) To evaluate whether participants' level and longitudinal rate of change in CVD is associated with level and rate of change in the four cognitive domains over the subsequent decade, and to (b) further investigate whether overall level and rate of change in CVD medication affects these associations.

Hypothesis 1.

(a) It was hypothesized that baseline CVD will be associated with lower initial cognitive abilities and greater 10-year cognitive decline. Similarly, worsening of CVD over time would be associated with greater 10-year cognitive decline. Based on prior research, it was further hypothesized that associations would be strongest in Attention

and Executive Function domains. (b) It was further hypothesized that since pharmacological treatment should theoretically reduce level of disease, higher overall CVD medication use would be associated with higher overall level of cognition and less declines in cognition over time.

Aim 2.

(a) In a subset of participants for whom structural MRI data were collected at baseline, to determine whether baseline indicators of vascular neuropathology (e.g. white matter hyperintensities) mediate the relationship between baseline CVD on level and rate of change in cognition over time, and (b) to explore whether CVD medication use moderated the effect of CVD risk on cognitive decline trajectories.

Hypothesis 2.

(a) It is hypothesized that having greater vascular neuropathology (i.e., white matter hyperintensity volume) at baseline will partially mediate the relationship between baseline CVD on initial cognitive level and subsequent rate of change in cognition over 10-years. (b) It is further hypothesized that medication will moderate the relationships between CVD risk and both initial cognitive level and rate of change in cognition over time.

CHAPTER 2
LITERATURE REVIEW

Introduction

As described in the Statement of the Problem, this proposed study seeks to examine the dynamic longitudinal relationships between cardiovascular disease (CVD) and associated risk factors on cognitive trajectories (Memory, Attention, Executive Function/Processing Speed, and Language) in a broad sample of cognitively diverse older adults. This study also aims to assess the extent to which a brain-based indicator of vascular neuropathology (e.g. white matter hyperintensity burden) may serve as a potential mediator between initial CVD and changes in cognition. The study will further investigate whether pharmacological treatment (e.g. cardiovascular medication) influences cognitive decline trajectories. This study is motivated by a particular focus on illuminating possible intervening pathways by which CVD might influence late life cognition.

To understand the relationships between cardiovascular risk factors, cardiovascular medication use, and brain-based indicators of cerebrovascular injury on older adult cognition, the conceptual model in Figure 2-1 below guided this proposal. The model was adapted from Figure 1-2 in R. A. Cohen and Gunstad (2010) and serves as a heuristic that lays out key constructs of interest and their putative relationships, while not addressing the time-varying associations or additional covariates discussed below. Variables with dark outlines represent constructs addressed in this proposed study and review. The exogenous variables of interest are cardiovascular risk (CVD) which reflects the aggregate of an individual's overall risk factors and frank disease, which have been shown to be important predictors of both

cerebrovascular injury and cognition. In accordance with current literature, indicators of vascular neuropathology, such as white matter hyperintensities (WMHs), have also been shown to be important predictors of cognition in aging (Bennett & Madden, 2014; Grueter & Schulz, 2012) and thus are included in this model as a potential mediator of the relationship between cardiovascular risk and cognition. Pharmacological treatment of underlying CVD is included in the conceptual model as both a moderator on the path between CVD and cognition, due to the hypothesized effect CVD medication may have on attenuating negative cognitive sequalae of CVD and vascular pathology. CVD mediation is also included as a path through CVD, modeling the hypothesized effect treatment may have on overall CVD burden.

This current review seeks to provide a summary and integration of the extant literature pertinent to the proposed study. Specific studies were chosen to be highlighted for their primary focus on late-life predictors of cognitive decline and their relevance to the available predictors within the National Alzheimer's Coordinating Center database for this present proposal.

In accordance with our aims, first an overview of age-related changes in cognition and cardiac structure and functioning is considered. Next the effects of CVD, both risk factors and disease, on cognitive decline and dementia will then be explored. Following, a brief review of pharmacological interventions for CVD will be addressed and their effects on cognitive outcomes will then be discussed. Next, the structural and metabolic changes of the aging brain will be reviewed, followed by a review of the effect of vascular risk factors and CVD on WMH burden. Lastly, literature regarding the effects of WMH burden on cognitive decline and dementia risk will be discussed.

Age-Related Changes in Cognition

When we think of these older adults, certain archetypes come to mind. Often these images include an older adult likely with graying hair and wrinkled skin. They may be frail, unable to engage in tasks with the same vigor as before. They may have trouble remembering certain names, navigating spaces, or remembering where they put their keys. These gradual declines associated with aging across a number of cognitive areas are well-established (Drag & Bieliauskas, 2010). While aspects of cognition related to acquired knowledge (e.g. implicit memory, semantic/verbal knowledge, aspects of language, for example) are relatively spared in normal aging, areas most affected by the aging process include attention, executive function, working memory, processing speed, and visuospatial functioning, among others. Horn and Cattell (1966) first published on this phenomenon and coined the terms *fluid intelligence* which referred to age-sensitive cognitive abilities and *crystalized intelligence* for those aspects of cognition less affected by age. This work was expanded upon by Baltes (1987) which described these two intelligences as “fluid” *mechanics* and “crystalized” *pragmatics* (see Figure 2-2a). The mechanics, Baltes argued, referred to the “basic architecture of information processing and problem solving” while pragmatics “concerns the context- and knowledge-related application of the mechanics of intelligence”. More recently, large population-based cohort and longitudinal studies have provided additional support for these age-related changes in *fluid (mechanics)* and *crystallized (pragmatics)* of cognition. As seen in Figure 2-2b, Park et al. (2002) show further support for these previous models of aging; while verbal knowledge remained generally stable, working memory, short-term memory, and speed of processing all demonstrate age-related decline.

Aging of the Cardiovascular System

By 2030, one in five adults will be 65 or older (United States Census Bureau), with nearly one billion new older adults expected worldwide between 2010 and 2050, especially in developing nations (United Nations, 2010). Despite the societal benefits from increased longevity, there will be a concomitant increase in the prevalence of age-associated morbidities, including cognitive and cerebrovascular dysfunction. It is projected that by 2035, approximately 45% of the United States population will be living with at least one cardiovascular disease or related risk factor (CVD) (American Heart Association, 2017). Economic costs are substantial; CVD has projected 2035 costs upward of $1.1 trillion dollars in the United States alone. Importantly, CVD disproportionately affects older adults. While CVD and related risk factors, such as hypertension, diabetes, among others, affect all age groups, increasing age is considered the most potent risk factor for emergent CVD (North & Sinclair, 2012).

The mechanisms through which aging affects cardiac function are vast and include molecular and cellular alterations that lead to structural and functional changes, ultimately predisposing the heart to cardiovascular disease including atrial fibrillation and heart failure (review; Steenman & Lande, 2017). At the molecular level, alterations in mitochondrial function have been observed in the aging heart. Mitochondria play an important role in providing energy, in the form of ATP, to cardiac muscle. Review of the pertinent literature on the role of mitochondria and oxidative stress in the aging heart by Martin-Fernandez and Gredilla (2016) reveal increased mitochondrial DNA instability, enhanced apoptosis (e.g. cellular death), and loss of homeostasis, leading to impairments in cellular respiration (e.g. reduced ATP generation) and inflammatory processes that ultimately produce cardiac dysfunction. Another age-related molecular

mechanism affecting the aging heart pertains to the calcium channel. Calcium plays an important role in cardiac muscle contraction and maintenance of blood pressure. Studies have demonstrated an association with aging and functional decline of L-type calcium channels in cardiac myocytes, leading to slower inactivation of calcium channel and reduced cardiac myocyte function (Feridooni, Dibb, & Howlett, 2015).

Cellular-level changes include the formation of excessive tissue (e.g., fibrosis) and reductions of cardiomyocytes and pacemaker cells. Increases in fibrosis, particularly within the left ventricle have been shown to increase diastolic dysfunction (Keller & Howlett, 2016). Post-mortem histopathological studies have also demonstrated a strong correlation between advanced age and presence of amyloid deposition within the heart (Tanskanen et al., 2008). Both left ventricular fibrosis and cardiac amyloidosis have been found to be associated with heart failure with preserved ejection fraction (Mesquita, Jorge, Souza, & Andrade, 2017; Steenman & Lande, 2017). Increased cardiac amyloidosis is also believed to predispose the heart to the later development of atrial fibrillation, as is the reduction of pacemaker cells within the sinoatrial node (Steenman & Lande, 2017).

Effects of Vascular Risk Factors on Cognitive Outcomes in Older Adults

While aging itself is associated with changes in both brain and heart health, not all older adults experience clinically significant manifestations of these age-related changes. The presence of certain vascular risk factors through adulthood have been shown to be associated with increases in later cardiovascular disease, white matter abnormalities, and ultimately cognitive dysfunction.

Numerous studies have demonstrated the associations between CVDs and increased risk of incipient cognitive decline, mild cognitive impairment (MCI), vascular

cognitive impairment (VCI), vascular dementia (VaD), and Alzheimer's disease (AD) (K. Blom, Emmelot-Vonk, & Koek, 2013; Gorelick et al., 2011; Gottesman et al., 2017; Viswanathan, Rocca, & Tzourio, 2009). While variability exists in clinical and research differentiation between VaD and AD, there is a growing body of literature supporting the effects of vascular risk factors and CVD on later AD risk (de la Torre, 2010; Kivipelto et al., 2001) as well as cerebrovascular dysfunction in the those with AD (Farkas & Luiten, 2001). It remains unclear at present the extent to which vascular risk factors and subsequent vascular neuropathology increase susceptibility to sporadic AD development (Kalback et al., 2004) and, or if AD pathology itself produces discrete cerebrovascular dysfunction (Kimbrough, Robel, Roberson, & Sontheimer, 2015). Nonetheless, there is a clear body of evidence to support underlying vascular risk factors and CVD affecting cognition and dementia prognosis in older adults. As such, the following is a review of the relevant literature regarding vascular risk factors, followed by CVD, included in this proposed study and their associations with cognitive decline and dementia risk. A summary of the primary articles examined, and their main findings is presented in Table 2-1.

Obesity and High BMI

Obesity, defined as by body mass index (BMI) of 30 or greater, is a common medical condition within the United States. Between 2007 and 2010, approximately 35% of older adults were considered obese (Fakhouri, Ogden, Carroll, Kit, & Flegal, 2012). Obesity has also been found to be associated with increases in cardiovascular disease and other related risk factors. In a review by Mandviwala, Khalid, and Deswal (2016) examining the effects of BMI and obesity on subsequent CVD risk found that a one-unit increase in BMI was associated with a 4% increase in risk of ischemic stroke, a 4%

increase in risk of atrial fibrillation, a 5% and 7% increase in risk of heart failure in men and women, respectively, and a 6% increased risk of hemorrhagic stroke. Obesity has also been shown to affect aspects of cognition through hormonal dysregulation and inflammatory processes (R. A. Cohen & Gunstad, 2010). While there is substantial evidence regarding high BMI and obesity on increased risk of other CVD, the effects of obesity on cognitive function have been mixed. Numerous longitudinal studies have explored the effect on obesity/high BMI in midlife, typically defined as age 40-60, on later cognitive decline and dementia risk (Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005; Xu et al., 2011). Results from these studies have demonstrated a clear relationship between obesity/high BMI in midlife (or prior to age 65) and increased incidence of dementia (Pedditzi, Peters, & Beckett, 2016) and cognitive decline across domains (Hassing, Dahl, Pedersen, & Johansson, 2010). Other studies have found that higher BMI at baseline was associated with lower mean cognitive performance over time, with steeper declines seen in tests of attention/executive function and memory (Gunstad, Lhotsky, Wendell, Ferrucci, & Zonderman, 2010). However, this study examined adults across the lifespan (aged 19-93) at baseline, so conclusions regarding the effect of increased BMI in older adulthood on cognition are difficult to ascertain. Nonetheless, other studies have demonstrated obesity being strongly correlated with reduced global cognition, as measured by Mini-Mental Status Exam (MMSE) Korean version (Jeong, Nam, Son, Son, & Cho, 2005). In a large longitudinal study with over 3,800 older adults at baseline, small positive effects of increased BMI on rate of cognitive decline were found over a 6-year period, however this result was only significant for participants with MMSE scores of 24 points or less at

baseline (Sturman et al., 2008). Another study following adults aged 55+ at baseline found that being obese was associated with reductions in global cognition, working memory, and spatial ability, however this was only found to be significant for men and not women (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003). While obesity in midlife is clearly a stronger predictor for late life cognitive decline and dementia compared to late life obesity, there is strong evidence that obesity in later life effects other aspects of CVD health, which may have secondary effects on cognitive decline.

Diabetes Mellitus

Diabetes Mellitus or type 2 diabetes (which will be referred to as simply diabetes moving forward) is increasing in prevalence through the United States and the globe. Notably, the prevalence of diabetes has been shown to be increasing with age. In 2000, approximately 12% of older adults aged 65-70 were diagnosed with diabetes, with over 15% of persons aged 80 and older having the disease (Wild, Roglic, Green, Sicree, & King, 2004). Along with an increased prevalence in older adults, research has demonstrated a strong link between diabetes and vascular risk factors, including dyslipidemia, hypertension, and obesity. Furthermore, it has been well-established that diabetes is also associated with cardiovascular disease (e.g. diabetic cardiomyopathy, heart failure) and mortality (Leon & Maddox, 2015).

Diabetes has been shown to be associated with cognitive dysfunction (see Table 2-1). Comprehensive systematic review of prospective observational studies regarding diabetes and cognition by Cukierman, Gerstein, and Williamson (2005) found that diabetes conferred an increased odds of both cognitive decline and increased dementia risk for adults aged 55 years and older. The odds of increased MCI and dementia were found to be even greater women with diabetes in their 60s (Yaffe et al., 2004). While

studies have found this negative correlation between diabetes and global cognition as measured by the MMSE (Cukierman et al., 2005; Nguyen, Black, Ray, Espino, & Markides, 2002), others have examined discrete cognitive outcomes and found similar results. A longitudinal study following 705 adults aged 55 and older found that having diabetes was associated with significant declines in verbal memory and verbal fluency over a 5-year period (Callisaya et al., 2019). In another longitudinal study of over 900 adults aged 59 years and older at baseline found that over 4-years, adults with diabetes performed worse on measures of executive function, verbal memory, and psychomotor speed compared to those without diabetes (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001). As such, having diabetes in both midlife and later adulthood has been found to be associated with increased cognitive dysfunction and dementia risk.

High Cholesterol/Dyslipidemia

Another cardiovascular risk factor associated with age are lipid abnormalities. Elevated levels of blood lipids, such as low density lipoprotein cholesterol (LDL-C), are known risk factors for cardiovascular disease (Barter et al., 2007; Nelson, 2013), particularly atherosclerosis, coronary heart disease, and ischemic stroke (Félix-Redondo, Grau, & Fernández-Bergés, 2013). While the relationship between dyslipidemia and other CVDs has been well-established, its effect on cognition is less clear. A number of studies have demonstrated an association between increased cholesterol levels and AD risk (Hall et al., 2006; Reitz, Tang, Luchsinger, & Mayeux, 2004), while others have found this association only when high cholesterol and dyslipidemia was measured in midlife (Kivipelto et al., 2002; Notkola et al., 1998). Another study with a cross-sectional design found that high serum cholesterol and LDL were associated with increased risk of Alzheimer's disease, but only for older adults

who did not carry the apolipoprotein (APOE) E4 allele. Notably, APOE plays an important role of transporting cholesterol in the brain, and its E4 allele has been found to be associated with increased Alzheimer's disease risk (de Chaves & Narayanaswami, 2008). Interestingly, some studies have demonstrated higher levels of cholesterol in late life to be associated with reduced risk of dementia, however this finding is not universal (Mielke et al., 2005). Overall, while there is substantial support regarding dyslipidemia affecting cognitive functioning in older adults, the incremental effect of late life dyslipidemia remains unclear.

Cigarette Use and History of Smoking

Cigarette smoking is strongly associated with a host of cardiovascular diseases, including coronary artery disease, peripheral vascular disease, and atherosclerosis. In addition, a history of smoking has been shown to increase the negative effects of high cholesterol, hypertension, and diabetes on cardiovascular disease risk (Lakier, 1992). As such, a history of, and current smoking status as been associated with cognitive dysfunction and dementia in older adults (see Table 1-1).

In a large meta-analysis of prospective studies examining the effects of smoking on cognition, it was found that current older adults smokers had increased risk for both incident vascular dementia (OR= 1.27) and Alzheimer's disease (OR= 1.78), and also demonstrated greater declines on the MMSE (Anstey, von Sanden, Salim, & O'Kearney, 2007). Nonetheless there is some variability in findings regarding smoking and cognitive outcomes. While Luchsinger et al. (2005) found current smoking imparting over a 2 times increase in possible and probably Alzheimer's disease, a smaller longitudinal study found only a trend of increased risks for vascular dementia or Alzheimer's disease, however these findings were not significant (Yoshitake et al., 1995). Larger

longitudinal studies exploring the effects of current smoking status in the elderly found increased rates of MMSE errors (Launer, Feskens, Kalmijn, & Kromhout, 1996) and faster rates of cognitive decline for male smokers across global measures of cognition and executive function (Sabia et al., 2012). Conversely, a study investigating over 800 older adults aged 50 and older found no significant differences between smokers and non-smokers across memory, reasoning, and processing speed tasks (Whittington & Huppert, 1997). The differences in these findings may be accounted for by the younger age range included at baseline in this study and cognitive outcomes measured. Despite this variability, late-life smoking appears to be a unique risk factor for cognitive decline and dementia risk in older adults.

Hypertension

The prevalence of high blood pressure (BP) and hypertension increases with age and is a known risk factor for cardiovascular disease. The Joint National Committee (8^{th}) guidelines define hypertension as >140/90 mmHg and prehypertension as 120-139/80-89 mmHg (James et al., 2014). In a review of prospective studies, Kokubo and Matsumoto (2017) found strong associations between heart failure, atrial fibrillation, coronary heart disease, aortic valvular disease, sudden cardiac death, sick sinus syndrome, abdominal aortic aneurysm, and left ventricular hypertrophy; these associations were found to be stronger for men than women. In a subset of participants from the Framingham Study followed for 9 years, it was found that even prehypertension incurred increased risk for myocardial infarction and coronary artery disease (Qureshi, Suri, Kirmani, Divani, & Mohammad, 2005). Given the systemic effect of high BP on the cardiovascular system and its increased prevalence in older adults,

there have been numerous studies examining whether or not increased BP/hypertension is associated with poorer cognition in older adulthood.

A review of large prospective studies regarding hypertension and cognition yields varied findings, primarily due to study design (e.g. cross-sectional vs. longitudinal), the nature of measurement (e.g. hypertension as a cut score or change in BP), cognitive outcome assessed (e.g. MMSE score, cognitive domains, or diagnosis), and time of measurement (e.g. midlife or late life). Notably, the majority of literature supports midlife hypertension/high BP being most effective on later cognitive decline of fluid abilities, worsening executive function, and dementia risk (Abell et al., 2018; S. Debette et al., 2011; Gottesman et al., 2017; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995; Qiu et al., 2005). Nonetheless, there have been a number of studies exploring the effects of late life hypertension/high BP on cognition.

Across cross-sectional studies examining the associations between high BP/hypertension and cognitive outcomes in older adults, elevated BP (=/>160/90 mmHg) was associated with worse reaction times, slower processing speed (D. L. Harrington, Smith, Zhang, Carlozzi, & Paulsen, 2012), and worse performance on delayed word recognition and spatial memory (Kuo et al., 2004). Longitudinal studies exploring hypertension in older adults, have found late-life hypertension associated with increased risk of mild cognitive impairment (MCI), believed to be a potential prodromal state of dementia, and probable dementia for women (Haring et al., 2016), and reductions in overall global cognitive performance for men (Elias, Wolf, D'Agostino, Cobb, & White, 1993). Another longitudinal study found that systolic BP of greater than 160 mmHg in older adult women reduced performance on a measure of executive

function over a nine-year period (Yasar, Ko, Nothelle, Mielke, & Carlson, 2011). While a number of studies have found conflicting results (e.g. lower BP/cognition relationships, no relationship), the majority of these studies reported only MMSE score, use of MMSE score as a cut-off for MCI, or explored only Alzheimer's disease and the primary cognitive outcome variable, instead of probable dementia or VaD. Furthermore, while some studies have found lower BP to be associated worse cognitive outcomes, the bulk of these studies only reported MMSE as their primary outcome of interest and (review; Qiu et al., 2005). There is also a growing body of literature regarding the effects of low BP on cognition, as well as evidence supporting reduced blood pressure following the development of dementia. Other studies have demonstrated a U-shaped relationship (Waldstein, Manuck, Ryan, & Muldoon, 1991). While the relationship between BP and cognition in later life is clearly more complex than previously thought, the majority of evidence supports midlife hypertension affecting cognition and dementia prognosis, with some support for later life hypertension affecting cognition.

Transient Ischemic Attack & Stroke

Transient ischemic attacks (TIA) and strokes are common within adults and the aging population (Benjamin et al., 2019). TIAs are sometimes referred to as silent strokes due to their short-acting nature; oftentimes people are unaware that they even occurred. TIAs are often preceded by stroke occurrence (Alberts & Atkinson, 2004). While the literature regarding the long-term cognitive effects of TIA and stroke is somewhat limited, there is a growing body of evidence supporting cognitive decline (Ganzer, Barnes, Uphold, & Jacobs, 2016). In a recent study of 140 older adults with a recent history of TIA or minor stroke found impairments on measures of processing speed and executive function (Soros, Harnadek, Blake, Hachinski, & Chan, 2015).

Another study demonstrated longitudinal impairments in TIA and stroke survivors on the Montreal Cognitive Assessment (MoCA) (Pendlebury, Cuthbertson, Welch, Mehta, & Rothwell, 2010). Another longitudinal study by the same group, found that after 5 years, older adult who experienced transient cognitive impairment acutely post-TIA and stroke were at significantly increased odds for later cognitive impairment and dementia (Pendlebury, Wadling, Silver, Mehta, & Rothwell, 2011). Recent reports from the same cohort have found further support for increased dementia risk following TIA/Stroke, however severe stroke was associated with the highest risk of 1-year dementia incidence, followed by minor strokes, and then TIA (Pendlebury & Rothwell, 2019). A recent systematic review of the literature on cognitive decline following mixed support for domain-specific and global cognitive decline. While there is clearly evidence supporting the effect of TIA and stroke on negative cognitive outcomes in elders, the precise effect remains imprecise (Tang et al., 2018).

Sleep Apnea

Obstructive sleep apnea (OSA) occurs in approximately 3-7% of the general population (Punjabi, 2008) and estimates range from 5-67% among community dwelling older adults (Ancoli-Israel et al., 1991). OSA is considered a chronic condition where the upper airways collapse during sleep, which can affect oxygen intake. Given its effect on oxygen consumption, sleep-disordered breathing (SDB) and OSA have been shown to negatively affect cognition in older adults (Gosselin, Baril, Osorio, Kaminska, & Carrier, 2019). A large comprehensive review of the literature on cognitive sequalae of OSA found support for untreated OSA being associated with impairments in attention, executive functioning, memory, and psychomotor speed compared to controls (Aloia, Arnedt, Davis, Riggs, & Byrd, 2004). In a recent longitudinal study, older adult women

with SDB were found to have increased odds of developing both MCI and dementia five years post-baseline compared to controls (Yaffe et al., 2011). Similar findings were found recently in a cross-sectional study of the Alzheimer's disease Neuroimaging Initiative (ADNI) cohort. Results showed that SDB was associated with earlier MCI and dementia onset (Osorio et al., 2015). While these findings are promising, a large longitudinal study of older adults demonstrated only small changes in the attention domain over an 8-year period in otherwise healthy older adults (M. S. Martin, Sforza, Roche, Barthelemy, & Thomas-Anterion, 2015). A recent systematic review and meta-analysis examining the effect of OSA on older adult's cognition found similar findings in that a small association was found between overall neuropsychological performance and cognition, as well as negative associations in memory and processing speed domains (Cross et al., 2017). Overall, sleep apnea and sleep disordered breathing appears to be a small, but significant predictor of cognitive decline and dementia.

Effects of Cardiovascular Disease on Cognitive Outcomes in Older Adults

While vascular risk factors have been associated with cognitive decline and dementia in older adults, there is also a substantial body of literature supporting the negative cognitive effects of frank CVD. A summary of the primary articles examined, and their main findings is presented in Table 2-2.

Atrial Fibrillation

Atrial fibrillation (AFib) causes irregular heart rhythm that can affect cardiac functioning and blood flow. The prevalence of AFib increases with age, with approximately 7% of women and 10% of men 80 years and older diagnosed (Go et al., 2001). A review of the recent literature demonstrates AFib is associated with both cognitive decline and dementia risk (Alonso & Arenas de Larriva, 2016). Prospective

longitudinal studies have found incident AFib being associated with steeper rates of global cognitive decline in older adults (Marzona et al., 2012; Thacker et al., 2013). Another study found similar results, however found domain-specific declines in processing speed and verbal fluency in AFib patients who subsequently developed subclinical cerebral infarcts (Chen et al., 2014). This study is notable in that it links incident AFib and cognitive decline with neurovascular injury.

A number of longitudinal prospective studies have also demonstrated AFib with increased incidence of dementia and AD (Alonso & Arenas de Larriva, 2016). While Dublin et al. (2011) found incident AFib being associated with increased risk for all-cause dementia and AD, another more recent study with a longer follow-up period found that this increased risk was only true for participants who developed AFib earlier than 67 years of age (de Bruijn et al., 2015). These findings were generally support by a meta-analysis of 21 studies, which found AFib was associated with higher risk of cognitive impairment and these effects were consistent in a population with and without stroke history (Kalantarian, Stern, Mansour, & Ruskin, 2013). A similar finding was found for AFib and associated dementia though limited evidence supported associates with specific dementia types.

Heart Failure

Heart failure (HF) is a clinical syndrome related to structural or functional alterations of the heart which impede the ability of the ventricle to fill or eject blood properly (Yancy et al., 2013). HF prevalence increases with age; population-based prevalence of HF ranges from 5.7-6.2% from ages 60-79, up to 13.4-14.1% of older adults 80 years and up (Benjamin et al., 2019). Given its ubiquity with age and effect on blood flow, there is a strong body of literature examining its effect on cognitive decline

and dementia risk. Given the breadth of research, more recent studies will be highlighted (see Table 2-2) along with a focus on overarching findings from published systematic reviews and meta-analyses.

A longitudinal study following older adults for two years found patients with HF demonstrated greater declines on the Cambridge Cognitive Examination of the Elderly (CAMCOG) compared to healthy controls without coronary artery disease (CAD); though similar patterns of decline were found for both HF and CAD groups in this study (Almeida et al., 2012). In a larger study of community-dwelling elders, self-reported HF at baseline was found to be associated with greater declines in reasoning abilities compared to older adults with no HF over a 5-year period (Alwerdt, Edwards, Athilingam, O'Connor, & Valdes, 2013). More recently, Hammond et al. (2018) found that global cognition (as measured by the 3MSE) declined faster following diagnosis of HF compared to older adults who never had HF and that this association became stronger as participants aged. While a large population-based cohort study found increased risks of all-cause dementia and VaD among patients with HF (Adelborg et al., 2017), there was no increased risk found for AD. However, longitudinal finings support both increased risk for dementia and AD (Qiu et al., 2006). Large systematic reviews of the literature report similar findings. Using meta-analytic techniques, Vogels, Scheltens, Schroeder-Tanka, and Weinstein (2007) pooled data from 22 studies and found the odds ratio for neurocognitive impairment across neuropsychological measures was 1.62 for adults with HF compared to controls. In another systematic review of the literature, Cannon et al. (2017) pooled data from 4 prospective cohort studies and found greater cognitive decline trajectories in HF patients compared to those without. Given the body

of literature, HF appears to be strongly associated with poorer cognitive outcomes including dementia in older adults.

Myocardial Infarction

Myocardial infarction (MI) is the medical term used for the colloquial *heart attack*. MI typically occurs when the coronary arteries develop a block (by plaque, cholesterol, fats, or white blood cell buildup) which prevents proper blood flow into the heart. Subsequent damage occurs to the heart's tissues due to limited oxygen supply (L. Lu, Liu, Sun, Zheng, & Zhang, 2015). Due to involvement of the coronary artery, MI is often grouped together with coronary heart disease (CHD), which is a top cause of mortality within the United States (Benjamin et al., 2019). CHD prevalence is strongly associated with age, with prevalence ranging from 15.1-23.9% for older adults 60 years of age and older (Yazdanyar & Newman, 2009). While there are many studies regarding the effects of CVD (as a composite) on cognitive impairment, few studies have explored the association between MI/CHD on cognitive outcomes (Santos et al., 2017).

While there clearly is a need for more literature within this area, a large study of over 5,000 middle-aged adults found that both MI and CHD were associated with poorer cognitive performance across measures of semantic fluency, verbal reasoning, memory, and vocabulary; CHD was also associated with poorer performances on measures of numerical reasoning and phonemic fluency, though all effect sizes were quite small (Singh-Manoux, Britton, & Marmot, 2003). Another more recent longitudinal study of adults aged 24 – 82 found that MI was associated with declines in verbal memory performance (Schievink et al., 2017). Perhaps the strongest support comes from a recently published study that found over a 12-year median follow-up period incident diagnosis of CHD was associated with steeper rates of cognitive decline across

measures of global cognition, verbal memory, and temporal orientation. With regards to dementia risk, a recent population-based study of over three-hundred thousand older adults with MI found and increased risk for VaD, but not AD or other dementias (Sundboll et al., 2018). Putting these findings together, a recent systematic review and meta-analysis of 10 prospective cohort studies that included at least one-year follow-up and participants of at least 45 years of age demonstrated that CHD was indeed associated with increased risk of cognitive decline or dementia (OR= 1.45) (Deckers et al., 2017). Overall, there appears to be modest evidence supporting MI role in cognitive decline and dementia with more support leaning toward CHD, however more research is needed in this area.

Summary

As reviewed, there remains variability between vascular risk factors and their effect on cognitive decline trajectories and dementia. There was strong support for negative cognitive sequelae related to the majority of cardiovascular diseases, particularly for HF and AFib. Similarly, there was generally good support across vascular risk factors, however obesity, diabetes, dyslipidemia, and hypertension appear to have stronger effects on cognitive outcomes when occurring in midlife.

What Medications Are Used to Treat Vascular Risk Factors and Cardiovascular Disease?

Hypertension, obesity, and dyslipidemia are the most prevalent vascular risk factors among adults within the United States. At the same time, CVDs including heart failure and myocardial infarction, among others continue to be the leading cause of death (Benjamin et al., 2019). Given the high morbidity and mortality rates related to CVD, the past half century has brought about expansive growth in the treatment of

vascular risk factors and CVD. Pharmacological treatment and management of CVD is so pervasive that simvastatin, generally prescribed for hypercholesterolemia (a known CVD risk factor), was the most commonly used single medication by adults in 2011. Concomitantly, the same 2011 study found that eight out of the top ten most commonly used medications were for treatment of CVD, hypertension, diabetes, and other vascular risk factors (Kantor, Rehm, Haas, Chan, & Giovannucci, 2015). This proposal seeks to examine the effect of expanding medications regimens and their effect on cognitive decline trajectories. While the brief review to follow discusses the use of the overarching medication classes included in this study, it is important to keep in mind that pharmacological treatment may serve both as a disease modifier and potential indicator of more advanced health concerns.

Antihypertensive Medications

Hypertension and high blood pressure are extremely common vascular risk factors, particularly in the elderly. While hypertension can be controlled to some extent through certain lifestyle modifications such as dietary changes, stopping smoking, and increased physical exercise (Yang et al., 2017), behavioral change can be challenging and more often than not adults are prescribed antihypertensive medications to assist with stabilizing their BP. Antihypertensives are considered a broad class of medications used to control BP and include the following subclasses: beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium-channel blockers, diuretics, and antiadrenergic agents. For a comprehensive review on mechanisms of action and side effects see Laurent (2017). It is important to note that drugs included under this class of antihypertensives have also been used to treat other vascular risk factors and CVD beyond hypertension including arrhythmias/atrial

fibrillation, heart failure, myocardial infarction, and diabetes (Casu & Merella, 2015; N. Martin, Manoharan, Thomas, Davies, & Lumbers, 2018; Steenman & Lande, 2017).

Beta-blockers. Discovered in 1973, propranolol was the first beta-blocker to market and since there has been a continuous rate of innovation in this area (Kotchen, 2011; Laurent, 2017). Beta-blockers are considered a somewhat heterogenous class of medications that are either non-vasodilating with or without beta-1 adrenergic receptor activity. There are also newer classes of beta-blockers than have vasodilating effects, which were brought to market to help increase their efficacy in stroke prevention and decrease negative effect (e.g. dyslipidemia, diabetes, etc.) (Wu, 2007). Beta-blockers act indirectly on epinephrine, which decreases heart rate, and lowers blood pressure. Beta-blockers are considered a first-line treatment for hypertension, but have also been used to treat heart failure, atrial fibrillation, and coronary artery disease (Dézsi & Szentes, 2017).

Calcium-channel blockers. Another commonly prescribed class of medications are the calcium-channel blockers (CCBs). There are two main subclasses of CCBs that included dihydropyridine and non-dihydropyridine medications (Laurent, 2017). Generally speaking, CCBs aid in vasodilation by reducing peripheral vascular pressure and subsequently increasing blood flow. CCBs are commonly prescribed for hypertension, and have also been indicated in the treatment of coronary artery disease and arrhythmias (Sica, 2006).

Angiotensin Converting Enzyme (ACE) Inhibitors. Part of the renin-angiotensin system, angiotensin II plays an important role in increasing peripheral blood pressure through a number of mechanisms (e.g. vasoconstriction, activation of the

sympathetic nervous system, etc.) (Fyhrquist, Metsarinne, & Tikkanen, 1995). Broadly speaking, ACE inhibitors work by indirectly targeting an enzyme that converts angiotensin I into angiotensin II, thereby modulating the effects of angiotensin II in the body and widening blood vessels (Laurent, 2017). ACE inhibitors have also been used to treat heart failure and acute myocardial infarction (Nasution, 2006).

Angiotensin II receptor blockers (ARBs). Similar to ACE inhibitors, ARBs ultimately reduce blood pressure through vasodilation and reduction of peripheral resistance; they do not effect cardiovascular output unlike some other antihypertensive medications. Mechanistically, they achieve this aim by ultimately blocking the effects of angiotensin II at the receptor level (Laurent, 2017). In addition to treating hypertension, ARBs have been used to treat heart failure, left ventricular hypertrophy, and post-myocardial infarction (Munger, 2011).

Diuretics. Another broad class of antihypertensive medications includes diuretics. Subclasses of medications used within this class include loop-diuretics, thiazides, and potassium-sparing diuretics. Loop-diuretics work at the level of the kidneys to by inhibiting salt reabsorption, indirectly affecting blood volume, thiazides work similarly to loop diuretics, and potassium-sparing diuretics act on either the kidney interfering with sodium and potassium or indirectly at the aldosterone receptor (Laurent, 2017).

Antihyperlipidemic Medications

As mentioned above statins (HMG CoA reductase inhibitors) are the most commonly prescribed medication in the country. They are considered a first line treatment for hyperlipidemia (high cholesterol), however due to potential side-effects and resistance, patients taking statins are often prescribed other antihyperlipidemic

including reductase inhibitors, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors, among others (Karr, 2017). The mechanisms through which these agents reduce circulating lipids is complex; for a comprehensive review see Pahan (2006). Lipid lowering medications are used to primarily treat dyslipidemia, however they are used to prevent TIA, stroke, and myocardial infarction (Meschia et al., 2014).

Anticoagulant and Antiplatelet Medications

Anticoagulant and antiplatelet medications are used in patients with a number of CVDs to reduce the risk of blood clot, myocardial infarction, and stroke. While their mechanisms vary slightly, anticoagulants and antiplatelet medications work by preventing blood clots by thinning the blood. These drugs are often prescribed to patients with peripheral artery disease often caused by atherosclerosis (Anand et al., 2007; Leng et al., 1996). They have been shown to be beneficial in preventing serious cardiovascular events ("Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients," 2002; Kapil et al., 2017).

Diabetes Medications

Patients with diabetes (mellitus/type 2) lack the ability to break down glucose in the blood effectively, either due to insulin resistance or by reduced insulin production. In the early stages, diabetes may be able to be managed via lifestyle modifications including reductions in sugar intake and exercise. However, oftentimes medications including insulin therapy and other methods (e.g. sulfonylureas, biguanides, dipeptidyl peptidase 4 inhibitors, amylin analogs, incretin mimetics) are used (Wallia & Molitch, 2014). While each of these drugs have differing mechanisms, their primary goal is generally to increase circulating insulin levels to lower blood glucose.

Does Pharmacological Treatment of Vascular Risk Factors and Cardiovascular Disease Affect Cognitive Outcomes?

Despite recent emphases in the treatment guidelines for early identification of risk factors and implementation of lifestyle modifications, prevalence of CVD and pharmacological management remains high (Benjamin et al., 2019). Typical interventions used for treatment of vascular risk factors and CVD often involve complex medication regimens to control and prevent disease progression, as reviewed above. While it is often proposed that proper treatment may improve cognitive outcomes, of the many studies exploring vascular risk factors and CVD on cognition, only a select few include a discussion of pharmacological treatment effects.

The majority of literature within this area comes from examining the effects of antihypertensive medications. Longitudinal findings have demonstrated in older adults with isolated systolic hypertension, antihypertensive treatment was associated with lower incidence of dementia over a 5-year period. However, this same study found no appreciable change in MMSE scores between groups, despite significant effects on lowering BP (Forette et al., 1998). However, this finding is challenged by a double-blind placebo-controlled trial of older adults with hypertension. Peters et al. (2008) found no significant differences in dementia risk at 5-year follow-up for older adults in the antihypertensive treatment group compared to placebo control. In a population-based study of predominantly (98%) older adult males, ARBs were associated with significant reductions in both incidence and progression of AD and dementia when compared to ACE inhibitors and other cardiovascular medications (N. C. Li et al., 2010). While Maxwell and Hogan (2010) discuss these findings as promising, given the sample was with majority males, the findings are not generalizable at this time to other cohorts. An

observational study found modest improvements in cognitive scores on the Standardized MMSE and Quick Mild Cognitive Impairment screener (Qmci), however this study only examined the effects in older adults with diagnosed dementia (Gao et al., 2013). Cross-sectional analysis of scores on the Psychogeriatric Assessment Scale – Cognitive test (PAS-Cog) from nursing home residents found use of any CVD medication was associated with better cognitive scores and a reduced odds of dementia diagnosis. Secondary analyses examining specific medication classes found that cardiac therapy medications, beta-blocking agents, and renin-angiotensin system agents were all associated with better cognitive scores and lower dementia diagnosis (E. Liu et al., 2017).

Systematic reviews and meta-analyses shed further light on this growing area of research. Swiger, Manalac, Blumenthal, Blaha, and Martin (2013) performed a systematic review and meta-analysis of 16 studies (11 studies in quantitative analyses) evaluating the short-term cognitive effects of statin use and the potential long-term effects on incidence of dementia. With regards to effects on cognitive function, no significant differences were found between statin users and placebo groups at follow-up across studies. With respect to longer term reductions in dementia risk, of the eight studies included, five demonstrated use of statins was related to incident dementia and three found no effect. When pooled, the authors report 29% reduction in incident dementia across studies for patients treated with statins. A broader systemic review of the literature explored the effects of treatment on cognitive outcomes in older adults with either hypertension dyslipidemia, obesity, diabetes mellitus, or increased homocysteine levels (Ligthart, Moll van Charante, Van Gool, & Richard, 2010). This review is

particularly helpful in understanding the effects of treatment on cognition due to its inclusion of only randomized controlled trials (RCTs) and its exclusion of studies with younger participants. Results from this systematic review of RCTs found no effect for statin use or controlled diabetes on attenuating cognitive decline. While there was evidence for antihypertensive medication in reducing cognitive decline (as supported above), it was determined that there was inconclusive evidence supporting late-life treatment affecting cognitive decline or dementia risk. With regard to treatment of obesity and lowering of homocysteine, the authors concluded that due to limited studies results, effects of treatment are inconclusive.

There is a growing body of literature regarding supporting the beneficial effects of treatment of vascular risk factors and CVD on cognition. Nonetheless, results for larger systematic reviews and meta-analysis demonstrate modest evidence for antihypertensives, with mixed evidence for statin use, and inconclusive results for treatment of dyslipidemia, obesity, diabetes, and high homocysteine. Interestingly, a small number of studies have found negative cognitive side effects (Marvanova, 2016), even after controlling for potential effects of disease (Nevado-Holgado, Kim, Winchester, Gallacher, & Lovestone, 2016), suggesting that potential expanding medication regimens may have negative iatrogenic effects on cognition or potential be themselves an indicator of worsening CVD disease. Given these findings, there remain significant gaps in the literature regarding the effect of pharmacological treatment of CVD on domain specific cognition in older adults with vascular comorbidities, as well as a need for clarity on interrelationships between vascular risk factor and CVD medication use on long term cognitive trajectories, which this proposal seeks to explore.

The Aging Brain

A secondary aim of this proposal is to examine the effects of cardiovascular disease on cognition and to explore whether these changes are facilitated by potential neural changes within the brain. As such, this next section will demonstrate first the brain changes seen in normal aging, however it will then be argued that in the presence of vascular risk factors and cardiovascular diseases just discussed, there may be accelerated neural loss and cognitive decline.

Structural Changes of the Gray Matter

These cognitive changes observed in older adults are associated with relevant alterations in structural and functional neural networks that support these affected areas of cognition (e.g. Dennis & Cabeza, 2008). Findings from neuroimaging studies using structural magnetic resonance imaging (MRI) have revealed age-related alterations in brain volume, with distinctive regions experiencing differential rates of atrophy. Of all the lobar regions of the brain, the frontal lobes have been found to experience the steepest rate of age-related atrophy, with the prefrontal cortex (PFC) showing the earliest signs of age-related volume reduction (Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). The frontal lobes have been shown to be important in supporting higher-order cognitive processes such as executive functions, along with personality and mood. As such, these age-related changes in PFC volume have been found to be associated with alterations in executive function performance in older adults (Elderkin-Thompson, Ballmaier, Hellemann, Pham, & Kumar, 2008; F. M. Gunning-Dixon & Raz, 2003; Newman, Trivedi, Bendlin, Ries, & Johnson, 2007). More modest age-related declines in parietal and occipital lobe volume have also been observed (DeCarli et al., 2005; Raz et al., 2005; Resnick et al., 2003).

Age-related changes in temporal lobe volume have been focused primarily on medial temporal lobe (MTL) regions due to their known association with memory and Alzheimer's disease (Tromp, Dufour, Lithfous, Pebayle, & Despres, 2015). Longitudinal findings regarding MTL atrophy have demonstrated significant hippocampal volume loss with relatively preserved entorhinal cortex volume (Raz et al., 2005). These relative declines in gray matter volume are helpful in distinguishing normal aging from pathological aging. While normal older adults will demonstrate earlier PFC volume loss compared to MTL volume loss, older adults with Alzheimer's disease will typically show greater volumetric reductions in entorhinal cortex and hippocampus prior to PFC atrophy (Tromp et al., 2015).

Structural Changes of the White Matter

Beyond structural gray matter changes, age-related changes have also been observed at the structural level in white matter (WM), including alterations in WM hyperintensity, volume, and integrity (H. Liu et al., 2017). White matter hyperintensities (WMH), also referred to as leukoarioasis, are abnormal changes in WM observed upon imaging. WMHs show up as small hyperintense/bright white regions on T2 and Fluid-Attenuated Inversion Recovery (FLAIR) scans. While typically of presumed vascular origin, their presence on imaging in healthy normal older adults is common (Wardlaw, Valdes Hernandez, & Munoz-Maniega, 2015). General prevalence of WMHs in the adult population has been found to range from 11-21% for young-older adults (approximately 64 years of age) and increases to approximately 64-94% by 82 years of age (Stéphanie Debette & Markus, 2010; Ylikoski et al., 1995). While presence of WMH alone may not confer cognitive dysfunction, increased WMH burden has been shown to be associated with poorer performance on measures of processing speed, executive function,

immediate and delayed memory, and global cognitive function indices (F. M. Gunning-Dixon & Raz, 2000; Moon et al., 2017; Raz & Rodrigue, 2006). Notably, increased WMH burden was found to be associated with poorer performance on an executive task, independent of PFC volume (F. M. Gunning-Dixon & Raz, 2003).

Alterations in global WM volume have also been shown. Despite WM volume demonstrating increases well into middle-age, a cross-sectional study of young, middle-aged, and older adults found overall WM volume declines precipitously after age 60 (H. Liu et al., 2016). While this decline has been observed at the global level, analyses of longitudinal MRI scans from the Baltimore Longitudinal Study on Aging, showed significant age-related asymmetry in WM volume loss, with greater left temporal lobe volume loss compared to right in healthy older adults (Resnick et al., 2003). Other studies exploring age-related changes in WM integrity using diffusion tensor imaging (DTI) have demonstrated anterior (frontal) regions showing the greatest change in WM integrity compared to posterior regions (Faith M. Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; O'Sullivan et al., 2001; Pfefferbaum & Sullivan, 2003). These findings further support age-related changes in frontal white matter contributing to frontally mediated cognitive dysfunction (e.g. executive function, working memory, and others). While there is considerable evidence that structural gray and white matter changes confer significant functional connectivity modifications, a review of the pertinent literature is beyond the scope of this current review.

Metabolic Changes

Despites its relatively small size, the brain requires approximately 20% of the body’s available oxygen (Cipolla, 2009). Given its high metabolic demand, precise regulation of cerebral blood flow is integral for maintaining proper neural function.

Nonetheless, it has been well-established that aging is associated with marked decreases in overall cerebral blood flow (CBF) (R. A. Cohen & Gunstad, 2010; H. Lu et al., 2011). Given the importance of maintaining cerebral hemodynamic homeostasis, reductions in CBF could potentially alter the brains metabolic rate of oxygen consumption. While it would follow that a global reduction in CBF would necessitate reductions in metabolic demand, studies regarding age-related changes in cerebral metabolic rate have been mixed (Aanerud et al., 2012). In a cross-sectional study examining age-related differences in cerebral hemodynamics, Lu and colleagues (2011) found increased metabolic demands and CBF reductions were associated with increasing age. Conversely, a study examining older adults aged 64+ found a negative relationship between cerebral metabolic rate of oxygen and age, such that as age increased, metabolic rate decreased (Ibaraki et al., 2010). Although it has been postulated that reductions in metabolic demand may be a function of age-related reductions in gray matter and thus reduced metabolic need, reduced frontal metabolism has been observed, over and above of cortical volume loss (Nobler, Mann, & Sackeim, 1999). Despite these changes in CBF and metabolic demand, overall cerebral autoregulation has been found to be spared in aging.

How Do Vascular Risk Factors and Cardiovascular Disease Affect the Brain?

While aging incurs both structural and functional changes to the heart and brain, increased cardiovascular risk factors and disease have both been shown to exacerbate these age-related changes. Increases in white matter burden are a hallmark structural change in the brain of presumed vascular origin and are the primary mediator through which this proposal seeks to examine the relationship between vascular risk factors and CVD on cognitive trajectories. Whereas numerous biomarkers of vascular

neuropathology exist (e.g. white matter abnormalities, lacunar infarcts, perivascular spaces, cerebral microbleeds) this study will primarily explore the relationship between white matter hyperintensities (WMH), vascular risk/CVD, and cognition.

WMH are defined as bright white spots or confluences in white matter regions that appear upon T2 and Fluid Attenuated Inversion Recovery (FLAIR) MRI sequences and are considered clinically relevant biomarkers (F. Moroni et al., 2018). It is important to note that presence of WMH are common among older adults and their underlying pathology is heterogenous in nature and may represent different stages of cerebral small vessel disease (Shi & Wardlaw, 2016). While the mechanisms through which vascular risk factors and CVD effect the brain are multifactorial, ischemia and reductions in cerebral blood flow (CBF) are believed to produce chronic states of hypoperfusion within the brain, contributing to vascular neuropathology and ultimately altered neurocognitive function (R. A. Cohen & Gunstad, 2010). Other potential mechanisms include edema due to blood brain barrier dysfunction (Black, Gao, & Bilbao, 2009; Y. Li et al., 2017), venous pathologies (Moody, Brown, Challa, & Anderson, 1995), and increased immune and inflammatory actions (Nam et al., 2017; Wharton, Simpson, Brayne, & Ince, 2015). The following is a brief review of included vascular risk factors and CVD and their associations with WMH burden and cognitive sequalae.

Vascular Risk Factors and WMH Burden

Given the underlying mechanisms by which WMH are believed to be generated, it is no surprise that vascular risk factors and frank cardiovascular disease have been found to be associated with increased WMH.

Hypertension. Of the vascular risk factors, hypertension has been found to be a strong predictor of overall WMH burden, likely due to its direct effect on CBF. Compared to normotensive older adults, older adults with moderate hypertension have been shown to have increased subcortical and periventricular WMH burden (Wiseman et al., 2004). In a large longitudinal study following 845 adults, aged 59-71 at baseline, it was found that uncontrolled hypertension at baseline was associated with severe WMH burden 4-years later (Dufouil et al., 2001). Other studies have demonstrated hypertensive subjects having more severe deep WMH compared to periventricular WM (Strassburger et al., 1997). Midlife hypertension has also been found to be associated with accelerated rates of WMH burden in nondemented older adults (S. Debette et al., 2011). These increases in WMH burden have been found to be associated with cognitive impairments in older adults. In a large longitudinal study, hypertension was found to be associated with reductions in processing speed and gait speed, and these associations were partially mediated by increased WMH burden (Hajjar et al., 2011). In another longitudinal study, higher baseline WMH burden was strongly associated with severe cognitive decline and dementia in older adults with a history of cerebrovascular disease (Dufouil et al., 2009).

Diabetes mellitus. Diabetes is a known risk factor for other vascular risk factors and cardiovascular disease, however its unique contribution to WMH remains somewhat unclear. Longitudinal studies have demonstrated older adults with diabetes having increased WMH burden over a 2- and 3- year period, suggesting diabetes may increase the rate of WMH progression (Gouw et al., 2008; Taylor et al., 2003). However, other studies have failed to find this same relationship, though sample sizes were

somewhat smaller (van Elderen et al., 2010). While a cross-sectional study found no differences between WMH volume of older adults with diabetes compared to healthy controls, the same study found diabetics having increased number of deep punctate WMH compared to controls (de Bresser et al., 2018). While this is a growing body of literature, the relationship between diabetes and WMH burden in older adults remains inconclusive.

Dyslipidemia. Dyslipidemia is another known risk factor for CVD with a small, but growing literature on its effect on WMH burden. Studies exploring dyslipidemia and WMH have demonstrated reductions in high density lipoprotein levels being significant associated with increased WMH burden in older adults (Dickie et al., 2016) as well as dyslipidemia being associated with increased subcortical WMHs (H. M. Abraham et al., 2016). While a study of over 1,000 older adults demonstrated hyperlipidemia being associated with reductions in WMH burden, this study included only ischemic stroke patients (Jimenez-Conde et al., 2010).

Obesity. Being overweight or obese is a known risk factor for poorer heart health. While the literature regarding obesity and WMH is somewhat limited, support for its effect comes primarily from studies examining the effects of visceral adiposity. BMI and increased abdominal visceral adiposity (measured by waist-to-hip ratio) have been found to be associated with increased WMH burden (Lampe et al., 2019). Another recent study found visceral adipose tissue being associated with increased WMH. Other studies exploring effects on WM have found decreased WM volumes in overweight adults (Raji et al., 2010) as well as decreases in overall WM integrity (van Bloemendaal et al., 2016). While longitudinal studies regarding impacts of obesity on the development

of WMH are lacking, there appears to be at least an established association between obesity and poorer WM outcomes.

Smoking. Smoking is associated with a number of poor health outcomes including stroke, coronary artery disease, peripheral artery disease, and atherosclerosis. There have been a number of cross-sectional studies regarding the interactions between WMH burden and smoking, however results have been somewhat variable. A number of studies have demonstrated a relationship between smoking and increased WMH volume and burden (Fukuda & Kitani, 1996; Jeerakathil et al., 2004; Liao et al., 1997). An age-dependent association between smoking status and WMH has also been demonstrated, with older age smoking conferring increased deep WMHs compared to periventricular WMHs (S. H. Kim et al., 2012). Other studies have failed to find substantial associations (Longstreth et al., 1996; Murray et al., 2005). However, a recent longitudinal study examining the 6-year relationship between smoking status and WMH found a dose-dependent relationship between increased pack-years of smoking and greater risk of WMH progression. Interestingly, this same study found no associations with WMH progression and time since quitting smoking or age at smoking initiation, suggesting overall smoking burden may be more important in determining secondary effects on the brain (Power et al., 2015).

Sleep apnea. Sleep disturbances have been found to be associated with increased cardiovascular risk. In particularly obstructive sleep apnea (OSA) has been found to be associated with increased risk for stroke (Koo, Nam, Thomas, & Yun, 2018), atherosclerosis (Levy et al., 2009), coronary heart disease, heart failure, and atrial fibrillation (Drager, McEvoy, Barbe, Lorenzi-Filho, & Redline, 2017). Given its effect on

the cardiovascular system, a number of studies have explored its effect on WMH in the brain. In a study examining OSA in middle-aged and older adults, both moderate and severe OSA was associated with an increased risk of increased WMH burden, even after controlling for other vascular risk factors (H. Kim et al., 2013). In another cross-sectional study, self-reported measures of sleep disordered breathing (a potential indirect measure of sleep apnea) was found to be associated with increased WMH volume, over and above other demographic and vascular risk factors in a diverse cohort of community-dwelling older adults (Rostanski et al., 2016). While findings regarding the long-term effect of OSA on WMH are limited, a recent study examining WM integrity, OSA, and CPAP intervention has shed some light on the matter. Prior to CPAP intervention, adults with OSA was associated with reductions in WM integrity, as well as impairments across cognitive domains studied. Interestingly, 12-months post CPAP treatment, WM abnormalities were reduced and improvements in memory, attention, and executive function were demonstrated. While interesting, the findings from this study are limited in that only a small sample was used, and only middle-aged adults were included. Therefore, the later life associations between sleep apnea and WMH remains somewhat unclear.

Cardiovascular Disease and WMH Burden

Atrial fibrillation. Atrial fibrillation or AFib causes irregular heart rhythms that can lead to ischemia, blood clots, stroke and heart failure. Given the effect of AFib on overall blood flow and relationship with negative cognitive sequalae, it is no surprise that studies have examined its effect on cerebrovascular function (F. Moroni et al., 2018). In a cross-sectional study, Kobayashi, Iguchi, Shimizu, and Uchiyama (2012) found increased deep WMH burden in older adults with AFib compared with age and sex-

matched controls; there was no difference in periventricular WM between controls and AFib patients. Another study found middle-aged adults with either paroxysmal (intermittent) or persistent AFib had increased WMH burden compared to controls. This same study also found that patients with persistent Afib had increased WMH compared to paroxysmal AFib patients, suggesting increased time spent in this diseased state may be associated with worse WM outcomes (Gaita et al., 2013). However, a more recent study by Shao et al. (2019) exploring the relationship between AFib and WM microstructural changes (measured by fractional anisotropy and mean diffusivity)/WMH found no significant relationships after controlling for other vascular risk factors and covariates. While there is support for an association between AFib and WMH burden, this relationship remains somewhat unclear due to differential findings and limited longitudinal analysis.

Heart failure. Heart failure (HF) occurs when the heart cannot generate enough blood flow to meet the metabolic needs of the body and brain or when it does so, but at the expense of an increased intracardiac pressure (Ponikowski et al., 2016). Heart failure has been associated with poor cognitive outcomes (Hajduk, Kiefe, Person, Gore, & Saczynski, 2013), which has led investigators to explore the relationship between HF and structural brain WM changes. In a cross-sectional study, older adults with HF, without HF, and cardiac controls underwent magnetic resonance imaging. Results from this study found that compared to healthy older adults and cardiac controls, patients with HF had significantly more WMH burden. Another study by Alosco, Brickman, Spitznagel, Griffith, et al. (2013) investigating 48 older adults, found that patients with HF with increased systolic BP and decreased systemic perfusion exacerbated WMH

volume. In a follow-up study, it was found that reduced cerebral perfusion in older adult HF patients was associated with greater WMH burden, this increased burden was also found to be associated with poorer MMSE performance (Alosco, Brickman, Spitznagel, Garcia, et al., 2013).

Transient ischemic attack and stroke. Sometimes referred to as “mini-strokes” transient ischemic attacks (TIAs) are known risk factors for future strokes and can affect oxygen supply to the brain. Both TIA and strokes are very similar, however TIAs tend to last a shorter amount of time compared to a typical stroke. Neurological damage due to TIA and stroke is highly dependent upon location and duration. Nonetheless, despite their heterogeneity, there remains a body of literature supporting the relationship between TIA and stroke and alterations in WM. In a cross-sectional of over 3,000 people, Longstreth and colleagues (1996) found that history of silent stroke (TIA) was associated with increased WMH burden in community-dwelling older adults. Other studies have found stroke patients having significantly increased WMH loads compared to normal controls, such that WMHs may represent a large proportion of ischemic burden in adults with TIA and stroke histories (Wen & Sachdev, 2004). Interestingly, in a longitudinal study examining patients with a history of TIA, increased WMH burden was associated with recurrent TIA, suggesting TIA may not increase WMH load, but may also exacerbate future WMH progression through subsequent TIAs (Ren et al., 2018).

Myocardial infarction. The literature regarding myocardial infarction (MI) on WM in older adults is extremely limited. Using conventional search criteria (e.g. “heart attack”, “myocardial infarction”, “white matter”, etc.), no studies were found exploring the direct effects of MI on WMH in an older adult population. One recent study examined

cardiac biomarkers, and found a relationship between them and WMH burden, however these biomarkers are not specific for myocardial infarction alone (Wei, Zhang, Liu, Yuan, & Liu, 2018).

Summary. The research supporting vascular risk factors and cardiovascular disease affecting WM is varied. Studies reviewed demonstrate good support for the relationships between hypertension, a history of smoking, obstructive sleep apnea, history of transient ischemic attack/stroke, atrial fibrillation, and heart failure on increased WMH burden in older adults. While there was evidence to support associations between WMH with obesity and dyslipidemia, the limited number of longitudinal studies makes a causal association between these vascular risk factors and WMH burden unclear. Lastly, while studies have demonstrated either direct or indirect effects of diabetes and myocardial infarction affecting WMH, very few studies existed regarding these variables, thus their direct effects on WMH in an older population is unclear at present.

How Does Increased White Matter Hyperintensity Burden Affect Older Adults' Cognitive Abilities?

As reviewed, vascular risk factors and CVD have been associated with increased WMH burden in older adults and cognitive dysfunction in older adults. However, the relationships between WMHs and cognitive outcomes has not yet been fully explored in this review. The following will be a brief review of cognitive outcomes associated with increased WMH burden in an older adult population (reviews; Alber et al., 2019; Caunca, De Leon-Benedetti, Latour, Leigh, & Wright, 2019; Prins & Scheltens, 2015).

WMH Burden and Cognitive Decline

Numerous cross-sectional studies have found significant relationships between increased WMH and reduced global and domain-specific (e.g., executive function, processing speed, delayed memory) cognition in elders (Arvanitakis et al., 2016; Bolandzadeh, Davis, Tam, Handy, & Liu-Ambrose, 2012; F. M. Gunning-Dixon & Raz, 2003; Haynes et al., 2017; Smith et al., 2011). Nevertheless, prospective longitudinal studies provide better support for potential causal associations. One of these such studies was the Rotterdam Scan Study, a large population-based study investigating longitudinal change in brain structure and neuropsychological function in 668 older adults. Results from this study found that progression of periventricular WMH was associated with declines in processing speed, general cognition, and declines in MMSE. Interestingly subcortical WMH progression was not associated with cognitive decline (van Dijk et al., 2008). In another large population-based study called the Australian Stroke Prevention Study, increasing WMH volume over a 3- and 6- year period was associated with declines across memory, conceptualization, and visuo-practical skills, as well as reductions in brain volume. The negative effects of WMH burden progression on cognition was explained by reductions in total brain volume, which was associated with increasing WMH burden (Schmidt et al., 2005). In a larger study examining the complex interplay between changes in WMH and cognition found increased WMH burden on serial MRI scans (5-years apart) was associated with greater declines in MMSE score and on a measure of processing speed, after controlling for effects of TIA and stroke between time points (Longstreth et al., 2005). In a more recent large longitudinal study of non-demented older adults, Vemuri et al. (2015) found that greater vascular pathology (measured as both WMH and infarcts) served as an independent

predictor of steeper rates of cognitive decline across a global cognition z-score, which was similar to the association between amyloid burden and cognitive decline trajectory. Similarly, another population-based longitudinal study found WMH volume was associated with 6-year steeper rates of cognitive decline across global cognition, working memory, episodic memory, semantic memory, and perceptual speed, as well as increased risk of MCI. Notably, these effects persisted after controlling for total brain gray matter volume, vascular risk factors, and CVD (Boyle et al., 2016). A number of systematic reviews and meta-analyses have been conducted to determine the overall unique contribution WMHs play in cognitive decline trajectories. Overall findings support somewhat small, but persistent effects of WMH across cognitive domains, with progression of WMH associated with worse attention and executive functioning (Kloppenborg, Nederkoorn, Geerlings, & van den Berg, 2014).

WMH Burden and Dementia Risk

As described above, increased WMH burden has been found to be associated with impairments in cognitive functioning and cognitive decline trajectories. As such, there is a parallel body of literature growing regarding the effects of baseline WMH burden and changes in WMH on subsequent dementia risk. Looking at baseline predictors, the Rotterdam Scan Study found higher baseline burden of periventricular (but not subcortical) WMH increased 5-year follow-up risk for dementia independent of other known dementia risk factors (Prins et al., 2004). Interestingly, a study investigating MCI stability and progression found that higher baseline levels of deep subcortical WHM was associated with increased odds of conversion from MCI to AD (Prasad, Wiryasaputra, Ng, & Kandiah, 2011). In another longitudinal study of older adults, Brickman et al. (2015) explored the relationship between WMH burden, hippocampal

volumes, and measures of cortical thickness in areas related to AD. Findings from this study demonstrated higher baseline parietal lobe WMH and progression of parietal WMH were independent predictors of progression to AD over and above typical AD-related neurodegenerative alterations. Other studies have found limited support for baseline WMH burden but have demonstrated that progression of WMHs was strongly associated with VaD (Verdelho et al., 2010). Given these findings and support from other reviews of the literature, there is clearly an effect of increased WMH burden on dementia and AD risk (Mortamais, Artero, & Ritchie, 2014), however precise contributions of region-specific (i.e., parietal, deep subcortical, periventricular) WMH remains to be established.

Contributions of the Current Study

It has been well-established that an individual's overall cardiovascular health is an important predictor of both cerebrovascular injury and cognition. In accordance with current literature, indicators of vascular pathology (WMH) have also been shown to be important predictors of cognition in aging. Although pharmacological treatment of underlying vascular risk factors and cardiovascular diseases have been proposed as a potential mechanism to attenuate cardiovascular-related cognitive decline, literature regarding its effect is inconclusive with treatment potentially representing higher disease burden and/or a potential intervening pathway toward better overall CVD health and cognitive function. As the constituent relationships proposed in this study have been investigated before, (e.g., vascular risk factors, CVD, cognition, medications), this proposal seeks to expand past research by (a) increasing sample size, (b) expanding longitudinal occasions, (c) looking across a full continuum of cognition, from normal to

impaired, and (d) examining all proposed aspects of the research model (Figure 2.1) in a combined statistical model, including mediator and moderator effects.

Table 2-1. Selected Studies of Vascular Risk Factors and Their Association with Cognitive Dysfunction in Older Adults

Study Authors	Vascular Risk Factor	Participants	Main Findings
Xu et al. (2011)	Obesity/Higher BMI	8,534 twins, 64+ years old	Obesity in midlife was related to increased risk of dementia, VaD, and AD (OR= 3.88)
Whitmer et al. (2005)	Obesity/Higher BMI	10,276 adults, age 40-45 at baseline, followed for 27 years	Obesity in midlife was associated with increased risk of later dementia diagnosis (HR= 1.74) after adjusting for demographic and other health factors
Jeong et al. (2005)	Obesity/Higher BMI	467 adults, 65+ years old	Obesity was strongly associated with poor cognition as measured by the Korean MMSE
Gunstad et al. (2010)	Obesity/Higher BMI	1,703 adults, 19-93 years old at baseline	Higher BMI was associated with lower mean cognitive performance across domains over time. Steeper declines found in tests of attention/executive function and memory
Hassing et al. (2010)	Obesity/Higher BMI	417 adults aged 50-60 age baseline, followed for 30 years	Higher BMI in midlife was associated with lower test performance across long-term, short-term, speed, verbal, and spatial memory measures 30 years later, though not associated with steeper rates of decline
Elias et al. (2003)	Obesity/Higher BMI	1,423 adults aged 55-88 at baseline, followed for 6 years	Being obese at baseline was associated with reduced global cognitive function, working memory ability, and spatial ability in men but not women
Sturman et al. (2008)	Obesity/Higher BMI	3,885 older adults aged 65+ at baseline, followed for 10 years	Small positive effect of increased BMI on rate of cognitive decline over a 6-year period; but this result was only significant for participants with reduced MMSE scores at baseline
Pedditzi et al. (2016)	Obesity/Higher BMI	Meta-analysis of 21 longitudinal studies on midlife obesity	Being obese before age 65 was associated with increased dementia incidence (RR= 1.41), but a reduction in dementia incidence was noted for obesity after 65 (RR= 0.83)

Table 2-1. Continued

Study Authors	Vascular Risk Factor	Participants	Main Findings
Callisaya et al. (2019)	Diabetes	705 participants with and without diabetes, 55+ years old at baseline, followed for 4.6 years	Significant diabetes by time interactions found for verbal memory (β= -0.06) and verbal fluency (β= -0.03) after adjusting for other vascular risk factors
Nguyen et al. (2002)	Diabetes	1,759 Mexican American participants, 65+ at baseline, followed for 5 years	Diabetes was associated with an increased risk (OR= 1.2) of cognitive decline, measured by a drop in MMSE score (3 points, or falling below 17 points)
Yaffe et al. (2004)	Diabetes	564 women with diabetes, mean age of 66.2, followed for 4 years	Over 4 years, diabetes was associated with an increased risk in dementia (OR= 2.38) and MCI (OR= 1.78) for older women
Fontbonne et al. (2001)	Diabetes	926 adults aged 59-71 at baseline, followed for 4 years	Over 4 years, adults with diabetes performed worse on measures of executive function, verbal memory, and psychomotor speed compared to those without diabetes.
Cukierman et al. (2005)	Diabetes	Systematic review of 25 articles	Over time, adults with diabetes had 1.2-1.5 greater change in cognitive function and 1.6 greater odds for later dementia
Kivipelto et al. (2002)	High Cholesterol/Dyslipidemia	1,449 older adults, aged 65+ at final assessment, followed for ~21 years	Elevated cholesterol in midlife was associated with increased risk of Alzheimer's disease in later life
Notkola et al. (1998)	High Cholesterol/Dyslipidemia	444 men, aged 40-59 at baseline, followed for 25 years	High serum cholesterol at baseline was a strong predictor of Alzheimer's disease (OR= 3.1) after controlling for age
Mielke et al. (2005)	High Cholesterol/Dyslipidemia	392 older adults, 70 years of age at baseline, followed for ~18 years	High cholesterol levels in late life was associated with decreased risk of dementia (HR= 0.70 -0.77)

Table 2-1. Continued

Study Authors	Vascular Risk Factor	Participants	Main Findings
Reitz et al. (2004)	High Cholesterol/Dyslipidemia	4,316 older adults, 65+ years old	Higher levels of non-HDL-C (OR= 1.6) and lower levels of HDL-C were associated with increased prevalence of vascular dementia, but not Alzheimer's disease
Hall et al. (2006)	High Cholesterol/Dyslipidemia	1,075 older adults, 70+ in Nigeria, followed for ~ 10 years	Increased levels of cholesterol and LDL were associated with an increased risk of Alzheimer's disease, but only for those without the APOE-E4 allele
Sabia et al. (2012)	Cigarette Use/History of Smoking	7,236 adults, mean age 56 at baseline, followed for 10 years	Faster cognitive decline was found for current male smokers compared to those who had never smoked in global cognition (-0.09); recent ex-smokers demonstrated greater declines in executive function (-0.08)
Launer et al. (1996)	Cigarette Use/History of Smoking	333 men, mean age 75.1 at baseline, followed for 3 years	Current smoking was associated with 20% more errors on the MMSE than those who never smoked
Luchsinger et al. (2005)	Cigarette Use/History of Smoking	1,138 older adults, aged 65+ at baseline, followed for ~ 11 years	Current smoking imparted an increased risk for possible and probable Alzheimer's disease (HR= 2.0) in older adults
Whittington and Huppert (1997)	Cigarette Use/History of Smoking	862 older adults, aged 50+ at baseline, followed for 7 years	No significant differences reported between smokers and non-smokers across memory, reasoning, simple reaction time, or choice reaction time after adjusting for age, education, and lung function
Yoshitake et al. (1995)	Cigarette Use/History of Smoking	828 older adults, aged 65+, followed for 7 years	Smoking was associated with an increased risk ratio of vascular dementia and Alzheimer's disease; however, this was not statistically significant after adjusting for age and sex

Table 2-1. Continued

Study Authors	Vascular Risk Factor	Participants	Main Findings
Cerhan et al. (1998)	Hypertension/High Blood Pressure	13,840 adults, aged 45-69	Hypertension (=/>160/95 mmHg) was associated with lower scores on processing speed and verbal fluency measures
F. Harrington, Saxby, McKeith, Wesnes, and Ford (2000)	Hypertension/High Blood Pressure	107 untreated hypertensives and 116 normotensives, aged 70-89	Hypertension (=/>160/90 mmHg) was associated with slower reaction times and worse performance in measures of delayed word recognition and spatial memory
Kuo et al. (2004)	Hypertension/High Blood Pressure	70 healthy older adults, aged 65+	Impairments on an executive function task was found in older adults with supine systolic BP> than 135 mmHg
Haring et al. (2016)	Hypertension/High Blood Pressure	6,426 women, aged 65+, followed for ~9 years	Hypertension was associated with an increased risk for developing MCI or probable dementia (HR 1.20)
Elias et al. (1993)	Hypertension/High Blood Pressure	1,420 adults, aged 55-88, followed 4-6 years	Hypertension (=/>140/90 mmHg) was associated with lower total cognitive composite performance in me, but not women
Waldstein, Giggey, Thayer, and Zonderman (2005)	Hypertension/High Blood Pressure	847 adults, mean age 70.6 at baseline, followed for 11 years	Higher systolic BP (and low SBP) was associated with (1) poorer cognitive performance on measures of executive function, confrontation naming, particularly for adults with less education; declines in nonverbal memory and confrontation naming for individuals with higher SBP
Yasar et al. (2011)	Hypertension/High Blood Pressure	337 women, aged 70+ at baseline, followed for 9 years	Higher systolic BP (=/> 160 mmHg), particularly for older woman (76+) was associated with worse performance on a measure of executive function
Soros et al. (2015)	Transient Ischemic Attack/Stroke	140 older adults, with history of TIA/minor stroke	Older adults with a history or TIA/minor stroke were in the impaired range on a measure of processing speed and executive function

Table 2-1. Continued

Study Authors	Vascular Risk Factor	Participants	Main Findings
Pendlebury et al. (2010)	Transient Ischemic Attack/Stroke	413 older adults with a history of TIA/stroke, followed for 6 months or 5 years	Older adults with a history of TIA/stroke were impaired on the MoCA, particularly in areas of executive function, attention, and delayed recall
Pendlebury et al. (2011)	Transient Ischemic Attack/Stroke	280 older adults with an acute history of TIA/ minor stroke followed for 5 years	Older adults who experienced transient cognitive impairment acutely post-TIA/stroke were at increased odds of cognitive impairment (OR= 4.3) and dementia (4.9) 5 years later
Pendlebury and Rothwell (2019)	Transient Ischemic Attack/Stroke	2080 older adults with a history of TIA and stroke, followed for 5 years	Incidence of 5-year post-event dementia was highest for older adults with severe stroke, followed by minor stroke, and then TIA
Yaffe et al. (2011)	Obstructive Sleep Apnea	298 women with and without sleep-disordered breathing (SDB), followed for ~ 5 years	Older women with SDB were more 31% more likely to develop MCI and 44.8% more likely to develop dementia compared to controls.
Osorio et al. (2015)	Obstructive Sleep Apnea	1,610 older adults with MCI or Dementia	Reported SDB was associated with earlier age at MCI and AD dementia onset
M. S. Martin et al. (2015)	Obstructive Sleep Apnea	559 older adults, followed for 8 years	SDB at baseline accounted for only small longitudinal changes only in attention (not in executive function or memory) after controlling for multiple comorbidities

Table 2-2. Selected Studies of Cardiovascular Disease and Their Association with Cognitive Dysfunction in Older Adults

Study Authors	Cardiovascular Disease	Participants	Main Findings
Marzona et al. (2012)	Atrial Fibrillation	31,506 older adults, followed for ~ 5 years	AFib was associated with increased risk of cognitive decline as measured by MMSE score (HR= 1.14) and incipient dementia (HR= 1.30)
Thacker et al. (2013)	Atrial Fibrillation	5,150 older adults, followed for 7 years	Average modified MMSE score (3MSE) experienced steeper rates of decline following incident AFib compared to older adults with AFib
Chen et al. (2014)	Atrial Fibrillation	935 older adults, followed for ~ 10 years	Incident AFib with was associated with greater annual decline in processing speed and verbal fluency for older adults who developed subclinical cerebral infarcts
Dublin et al. (2011)	Atrial Fibrillation	3,045 older adults, followed for ~7 years	AFib was associated with higher risk of developing all-cause dementia (HR= 1.38) and possible/probable AD (HR= 1.50)
de Bruijn et al. (2015)	Atrial Fibrillation	6,196 older adults, followed for ~ 13 years	Prevalence of AFib was associated with increased risk of dementia in participants under 67 (HR= 1.81) years of age, but not in participants older than 67
Almeida et al. (2012)	Heart Failure	231 older adults, followed for 2 years	Older adults with HF demonstrated greater 2-year decline on the Cambridge Cognitive Examination of the Elderly (CAMCOG) compared to controls without coronary artery disease
Alwerdt et al. (2013)	Heart Failure	2,790 older adults, followed for 5 years	Over 5-years, older adults with self-reported HF at baseline demonstrated declines in reasoning abilities over time
Hammond et al. (2018)	Heart Failure	4,864 healthy older adults, followed for ~5 years	Global cognition (measured by 3MSE) was found to decline faster after a diagnosis of HF compared older adults without HF; this association was stronger as age increased
Qiu et al. (2006)	Heart Failure	1,301 older adults, followed for 9 years	HF was associated with increased risk for dementia (HR= 1.84) and AD (HR= 1.80)
Adelborg et al. (2017)	Heart Failure	324,418 older adults with HF, 1,622,079 older adults without HF	Older adults with HF and increased risk for all-cause dementia (HR=1.21), with stronger associations found for men and patients under 70; HF patients also had higher risk for vascular dementia (HR= 1.49), though no increased risk was found for AD (HR=1.00)

Table 2-2. Continued

Study Authors	Cardiovascular Disease	Participants	Main Findings
Singh-Manoux et al. (2003)	Myocardial Infarction/ Coronary Heart Disease	5,822 adults aged 46-68	MI was associated with poorer cognitive performance on measures of semantic fluency, verbal reasoning, memory, and vocabulary; CHD was associated with poorer cognitive performances across all measures (numerical reasoning, phonemic fluency) though all effect sizes were small
Schievink et al. (2017)	Myocardial Infarction/ Coronary Heart Disease	1,823 adults aged 24-82, followed for 12 years	Post-hoc analysis found MI was associated with declines in verbal memory
Xie, Zheng, Yan, and Zhong (2019)	Myocardial Infarction/ Coronary Heart Disease	7,888 older adults, followed for ~ 12 years	In older adults following incident diagnosis of CHD, cognitive decline was accelerated across measures of global cognition, verbal memory, and temporal orientation
Sundboll et al. (2018)	Myocardial Infarction/ Coronary Heart Disease	314,911 patients with MI and 1,573,193 matched controls (older adults), followed for 35 years	MI was associated with increased risk for VaD (HR= 1.35), but not all-cause dementia, AD, or other dementias; this association was stronger in patients with history of stroke

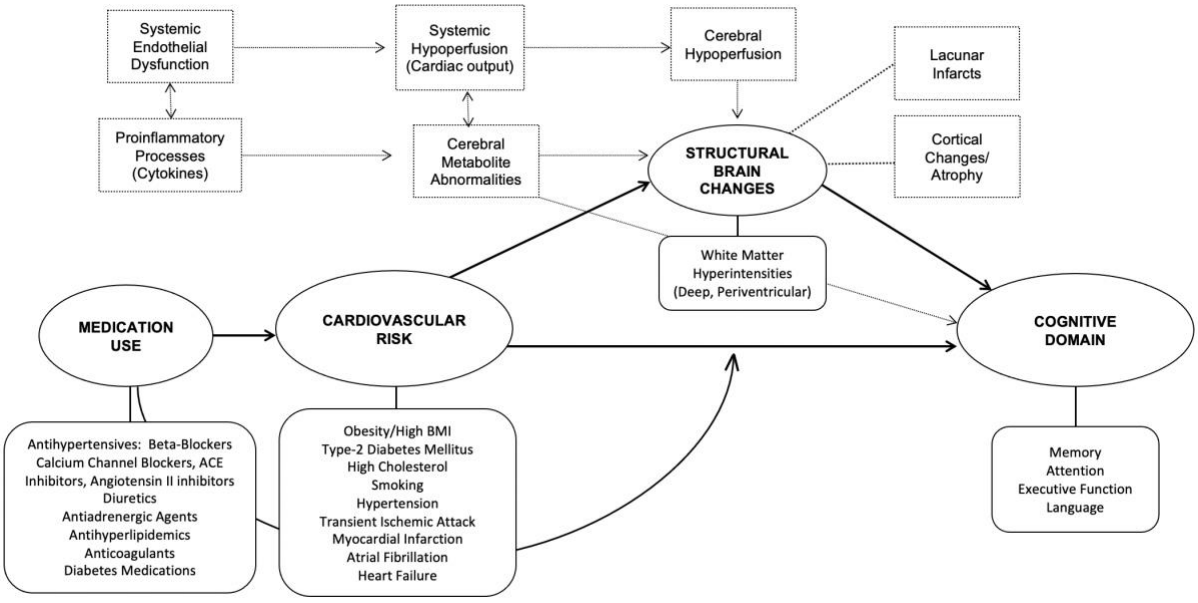


Figure 2-1. Conceptual Model of Cardiovascular Influences on Cognition

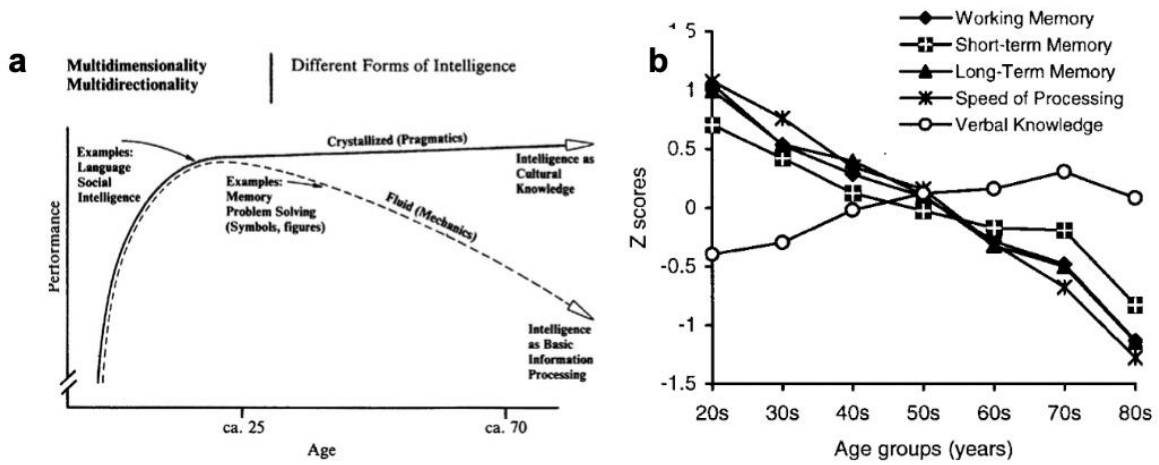


Figure 2-2. Fluid and Crystallized Abilities: a) Conceptual Model of Different Forms of Intelligence (Baltes, 1987); b) Lifespan Performance Across Measures (Park et al., 2002)

CHAPTER 3
RESEARCH DESIGN AND METHODS

Overview

The purpose of the present study, entitled Cognitive Aging Trajectories: Cardiovascular Risk, White Matter, and Medication Predictors, was to examine the longitudinal associations between cardiovascular disease/related comorbidities (CVD) and cognition in a cognitively diverse sample of older adults, as well as to explore whether pharmacological treatment of CVDs moderated these associations. In addition, this study endeavored to evaluate whether baseline indicators of vascular neuropathology (e.g., white matter hyperintensities) mediated the relationship between baseline CVD on initial level and rate of change in cognition over a 10-year period. The present study utilized a subset of participants recruited by Alzheimer's disease Centers (ADCs) across the country who submitted their data to the National Alzheimer's Coordinating Center (NACC) database, a national repository combining neuropsychological testing data from Uniform Data Set (UDS) and neuroimaging data to evaluate these aims.

The following sections describe participant recruitment and eligibility, reviews general study procedures, details measures included in this study, presents the statistical power analysis and missing data plan, and outlines the statistical analyses employed. This study was approved as Exempt by the University of Florida Institutional Review Board (IRB#: IRB-2019-00828).

Participants

Participant recruitment occurred from 2005 through 2019. Participants were recruited at individual ADCs in the following states: Arizona, California, Connecticut,

Florida, Georgia, Illinois, Indiana, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Minnesota, Missouri, New York, North Carolina, Oregon, Pennsylvania, Texas, Washington, and Wisconsin. Each ADC utilized the Uniform Data Set (UDS), a standardized neuropsychological evaluation, as well as additional site-specific neuropsychological and experimental measures. The maintenance of potentially identifiable data in the NACC repository is covered by the University of Washington IRB approval, while the individual ADC sites that collected the human subject's data have their own approvals that they maintain. All individual ADCs obtained informed consent from participants prior to study enrollment.

This study utilized a subsample of the NACC database, who met inclusion/exclusion criteria (defined below) irrespective of neuroimaging data available. Data for this sample was collected from 2005 through the December 2019 data freeze.

Eligibility

Only individuals who met both inclusion and exclusion criteria were included in the total sample. Specific exclusion criteria are listed below.

Inclusion Criteria.

- 60 years of age or older at first visit (baseline)
- Completion of at least a baseline and one follow-up visit of neuropsychological testing of Uniform Data Set (UDS) measures
- For our aim examining WMH volume, having both T1 and Fluid-Attenuated Inversion Recovery (FLAIR) sequences acquired +/- 6 months following baseline UDS visit and passed conversion for processing

Exclusion Criteria.

- History of primary etiologic diagnoses of: Lewy body disease, multiple systems atrophy, progressive supranuclear palsy, corticobasal degeneration, frontotemporal lobar degeneration, essential tremor, Down syndrome, Huntington's disease, prion disease, traumatic brain injury, normal pressure hydrocephalus, epilepsy, CNS neoplasm, HIV, other neurologic/ genetic/ infectious condition, depression, bipolar disorder, schizophrenia or other psychosis, anxiety disorder, delirium, PTSD, other psychiatric disease, or cognitive impairment due to alcohol abuse/other substance abuse/other specified reasons at baseline
- Evidence of any of the following dementia syndromes at baseline: primary progressive aphasia, posterior cortical atrophy, or Lewy body dementia
- Vision or hearing loss that would impair successful completion of neuropsychological testing

Characterization of the Baseline Sample

The baseline sample consisted of 22,718 cognitively diverse (normal cognition through dementia) older adults aged 60 and greater with an average of 15.24 years of education. Following outlier trimming (34 excluded, age =/> 98), the final baseline sample consisted of 22,684 participants and the final neuroimaging subsample consisted of 1,049 participants. Between the baseline total sample and neuroimaging subsample, there were significant differences with regards to average age, race, ethnicity, and CDR cognitive status. For complete demographic data with comparison to neuroimaging subsample see Table 3-1. Figure 3-2 represents a CONSORT diagram

between the two samples used in analyses. Briefly, compared to the neuroimaging subsample, the total sample was slightly older, had a higher proportion of Black/African American participants, a lower proportion of Asian American/ Hawaiian Native/Pacific Islander participants, and a smaller proportion of participants who identified as Other race. Compared to the total sample, the neuroimaging subsample had a significantly higher proportion of Hispanic participants at baseline; this was likely due to the 1Florida ADRC, which focused on the recruitment of Hispanic elders, and which attempted to obtain imaging data on all participants. Lastly, the total sample had a higher proportion of participants with no cognitive impairment as measured by the CDR, a lower proportion of participants with Questionable Impairment, but again a higher proportion of participants with Mild-Severe Impairment. There were no significant differences between samples associated with sex, education, or score.

Procedures

Study Design

The Uniform Data Set (UDS) was first implemented in 2005 as a way for ADCs across the country to collect data that could be combined across sites. Despite the heterogeneity of neuropsychological measures administered across ADC sites depending on time at enrollment, cognitive measures included in this study were grouped by domain in accordance with a previous factor analysis of the UDS battery (Hayden et al., 2011) with the inclusion of additional variables validated by the NACC Crosswalk Study (Monsell et al., 2016). Additionally, NACC included a broad list of covariates (e.g., demographics, health, medication) collected via questionnaire or in-person interview, some of which were restricted to baseline measures (e.g., sex/gender, education), and some of which were time-varying and collected annually (e.g.,

cardiovascular disease, cognition. medication). As a proportion of the sample meets criteria for mild cognitive impairment or dementia, self-report measures were administered with caregivers present to safeguard accuracy of data. While missing data is unavoidable in longitudinal analyses, to avoid potential bias, list-wise deletion was not employed, and participants were included until their exit from the study, even when they had partial or complete missing data at specific occasions. Details regarding missing data handling is outlined in the Analysis section.

Baseline Measures

The following characterization of participants is derived from the total sample at baseline (N=22,684).

Education. Total years of education was collected at baseline. Participants were asked to select 12 years if they completed high school or obtained a GED, 16 years for a bachelor's degree, 18 years for a master's degree, and 20 for a doctorate. If unknown, participants were asked to estimate the total number of years of education, which within this sample ranged from 0 – 30. The average number of years of education for the total sample at baseline was 15.24 years (SD = 3.43). Given this wide range and skewness, for the purposes of analysis, education was dichotomized into participants who had up to a high school education (0 – 12 years; 24.9%) and those who had at least some college or greater (13+ years; 75.1%).

Race and Ethnicity. Participants were asked to self-identify their race to the testing administrator. Racial categories utilized in this study included Black or African American, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander/Asian, or Other. For analyses, the following four dummy variables were created and included in all models as covariates: Black/African American (14.6%); White

(80.6%); AAPI (2.5%), which included both Asian and Native Hawaiian or Pacific Islanders; and Other (1.4%), which included American Indian or Alaskan Native and Other unspecified races. Participants were also asked to report if they identified as Hispanic/Latino (7.4%) ethnicity (i.e., having origins from a mainly Spanish-speaking Latin American country).

Depression. Participants were excluded in this study if they had a primary etiological diagnosis of depression at baseline. Nonetheless, depressive symptomology has been found to be associated with history of CVD, including stroke and myocardial infarction (Kanellopoulos et al., 2020; Ziegelstein, 2001). Depression has also been demonstrated to significantly affect cognitive performance (Morimoto, Kanellopoulos, & Alexopoulos, 2014). As such, this study included the Geriatric Depression Scale - short form (GDS-SF, Sheikh & Yesavage, 1986) at baseline to control for potential effects of depression on cognitive outcomes. The GDS-SF is a 15-item self-report measure that is commonly used to identify depression within an older adult population. One point is given for each affirmative response (Yes/No); thus, scores range from 0-15. The total score is then doubled to utilize clinical cutoff scores, as follows: 0-9: Normal; 10-19: Mild-Moderate Depression; 20-30: Severe Depression. Participants in the baseline sample had an average GDS score of 1.79 (SD = 2.28). Approximately 9% of the sample met criteria for Mild-Moderate Depression and 0.9% met criteria for Severe Depression.

***APOE* Genotype**. The *APOE* gene, which is responsible for encoding apolipoprotein E (ApoE), assists with cholesterol and lipid transport within the brain. *APOE* exists in three polymorphic alleles, ε2, ε3, and ε4. Specifically, the *APOE* ε4

allele has been shown to be a strong biomarker for Alzheimer's disease risk (C.-C. Liu, Liu, Kanekiyo, Xu, & Bu, 2013), and functions in a dose-dependent fashion (Corder et al., 1993). As such, this study included the number of the *APOE* ε4 alleles (0-2) as covariate. Of the participants in the total sample at baseline, 59.6% had no ε4 alleles, 33.3% had only one, while 6.6% had two copies.

Clinical Dementia Rating Scale (CDR). While not formally included as a covariate in analyses, the CDR score is useful for understanding the cognitive heterogeneity of the current sample. The CDR (Berg, 1988) is clinician administered instrument that utilizes both a semi-structured interview and 5-point rating scale on six domains to characterize functional and cognitive status. Following, a CDR Global Score is determined using the following clinical cut-offs: 0: No Impairment; 0.5: Questionable Impairment; 1: Mild Impairment; 2: Moderate Impairment; 3: Severe Impairment. Within our total baseline sample, 47.4% had No Impairment, 35.1% had Questionable Impairment, 12.7% had Mild Impairment, 3.3% had Moderate Impairment, and 1.4% had Severe Impairment.

Cognitive Measures

NACC determined cognitive domains and their associated neuropsychological tests based upon existing literature on cognitive aging and expert consensus and are described below (Weintraub et al., 2009). Table 3-2 presents a complete list of cognitive measures employed across UDS versions 1.2 through 3 that were used in this study to determine cognitive domain composite scores. In March 2015, ADCs across the country adopted a new neuropsychological test battery in which previous proprietary tests were replaced with similar, rights-free measures. Prior to administration, NACC conducted a crosswalk study to determine the correlations between measures, which established

feasibility for transitioning to new neuropsychological tests (Monsell et al., 2016). See Table 3-3 for Spearman correlation coefficients for old and new measures. This study coalesced measures according to the published crosswalk, as detailed below. This permitted the largest possible dataset for the current sample, and cognitive composites were constructed with all available coalesced data.

Specifically, this current utilized the published equipercentile equating conversion tables to coalesce scores across older and newer tests, and thus allow newer UDS tests to be converted into an score that was equivalent (i.e., on the same raw score scale as the tests that had been administered in earlier UDS phases (Monsell et al., 2016). To concretize this process, let's say a participant received a score of 13 on the Craft Story 21 Immediate Recall (described below). Using the equipercentile tables provided, this score was converted to an 11, which was the Logical Memory Immediate Recall equivalent. Equipercentile equivalent tests were then coalesced at each occasion (i.e., the person's final logical memory was either the Logical Memory Immediate Recall score, or the equipercentile equated Logical Memory Immediate estimated score based on the Craft Story). In rare circumstances where participants received both tests at the same occasion, scores were averaged. All variables underwent normalizing transformation prior to construction of cognitive domains (G. Blom, 1958).

Cognitive domain construction. Cognitive measures, coalesced as discussed in the last section, were used to construct cognitive domains by replicating a previously published factor analysis (Hayden et al., 2011), which reported invariance of four factors across cognitive groups defined in terms of their CDR score (e.g., Normal Cognition, MCI, Dementia). As such, a confirmatory factory analysis (CFA) was conducted using the statistical software package lavaan in RStudio (Rosseel, 2012), to evaluate the fit of a four cognitive domain solution

(Memory, Attention, Executive Function, Language) in the current sample, using full-information maximum likelihood (FIML) estimation. Both baseline and follow-up (Visit 2) data were used to determine factor structure invariance across time. Given metric invariance in past studies and also reported below, factor scores were derived using a common set of scoring coefficients across all occasions and groups. This preserved changes in mean level and variability across time. Model fit was determined to be strong using conventional standards for goodness of fit (e.g., ratio of $\chi 2$ to degrees of freedom 2:1 or less, RMSEA less than .05 and non-significant, and CFI and TLI above 0.9 (Browne & Cudeck, 1992; Hu & Bentler, 1995). Following the CFA, factor scores were saved for each cognitive domain using a regression-based approach produced by lavaan and are used in subsequent analyses as primary outcome variables of interest. See Appendix A for details regarding the final CFA, including factor loadings, correlations, and fit.

Memory. Given the focus of NACC on Alzheimer's disease (AD), episodic memory was included as it has been shown to decline with age (Shaie, 1996) and is considered the hallmark cognitive domain associated with AD (Albert, 1996). In NACC, episodic memory was assessed with the Wechsler Memory Scale – Revised Edition Logical Memory subtest (WMS-R LM; Wechsler, 1987) and Craft Story 21 (Craft et al., 1996) a similar measure, introduced after March 2015. For the WMS-R Logical Memory, participants were instructed to listen carefully to two short stories one at a time. Immediately following they were asked to recall the stories in as close to the same phrasing. Immediate recall scoring was out of a total of 50 points. Following a 30-minute delay, participants were asked to recall the two short stories read to them earlier. Delayed recall scoring was out of 50 points. For Craft Story 21 participants were instructed to listen and to remember a short story read to them. After the administrator completed the story, they were asked to recall the story in as much detail as they could remember. Immediate recall verbatim scoring was out of a total of 44 points; administrators also scored based on participants paraphrasing to produce an immediate recall paraphrase score out of a total of 25

points. Following a 20-minute delay, participants were then asked to recall the previous learned story. Both verbatim and paraphrased scores were calculated for delayed recall.

Attention. This cognitive domain was evaluated by the WMS-R Digit Span subtest (WMS-R DS; Wechsler, 1987) and the Number Span test (post March 2015). The WMS-R Digit Span task involves participants listening to successively longer strings of numbers and repeating those strings back, just as they heard them. Number spans were randomly generated with adjacent sequence restrictions requiring no digit to be one lower or one higher (e.g., a “5” would not be preceded or succeeded by a 6 or 4). Excluding area codes was also attempted as part of the random number generator. For both WMS-R Digit Span and Number Span measures, participants were administered trials until they failed to accurately recall both trials of the same span length. Both measures employed a forward span, which was scored as the number of trials the participant correctly repeated a string of numbers forward. Participants also completed a backwards span, which required participants to listen to a string of numbers read forward and to immediately repeat them backwards. The backwards span is generally considered a measure of working memory.

Executive function. Executive function was assessed in NACC with the Trail Making Test (TMT; Reitan & Wolfson, 1993) Part B. This task required participants to draw a line from a number to a letter in alternating alpha-numeric order as quickly as possible. The time to complete the task was recorded. Processing speed was assessed by the TMT Part A, a task requiring rapid sequencing of numbers, and with the Wechsler Adult Intelligence Test – Revised (WAIS-R; Weschler, 1981) Digit Symbol subtest, a task requiring participants to rapidly match a series of symbols with their associated digits. For TMT Part A, participants total time to complete the task was recorded and considered their total score. For the WAIS-R Digit Symbol, the total number of items completed before 90 seconds elapsed was the total score.

Language. To test confrontation naming, a shortened version of the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) was constructed using the 30 odd-

numbered items. Test discontinuation occurred following 6 consecutive failures. Total score on the BNT consisted of the total number of correctly named items plus the number of items correctly named following a semantic cue. After March 2015, NACC adopted the Multilingual Naming Test (MINT; Gollan, Weissberger, Runnqvist, Montoya, & Cera, 2012; Ivanova, Salmon, & Gollan, 2013) a 32-item confrontation naming test, also sensitive to impairment in AD. Total score on the MINT consisted of the total number of correctly named items plus the total number of correctly named items following semantic cue. Category fluency measures were included in UDS versions 1-3, however for UDS version 3, letter fluency was added. For category fluency, participants had one minute to name as many members of a particular category for two separate trials (i.e., animals, vegetables). Letter fluency tasked participants with one minute to generate as many words as they could beginning with a particular letter (i.e., F, L). The total number of words generated to semantic category and letter serve as the total scores.

Cardiovascular Health Measures

Data regarding cardiovascular health was collected in NACC at each annual wave through clinician-assessed subject health history (UDS versions 1-3, Form A5) and via clinician-assessed medical conditions (UDS versions 1-3, Form D2). Cardiovascular risk and comorbidity variables for this current study were selected based on inclusion in previously published cardiovascular indices (Allan, Garrison, & McCormack, 2014; R. B. D'Agostino et al., 2000) and being known risk factors for cardiovascular disease (CDC, 2017; Fryar, Chen, & Li, 2012; Tonstad & Andrew Johnston, 2006; van Rooy & Pretorius, 2014), as well as availability across NACC UDS versions. Health history measures included endorsement of the following: (1) heart attack/cardiac arrest; (2) atrial fibrillation; (3) congestive heart failure; (4) stroke; (5) transient ischemic attack (TIA); (6) history/current type 2 diabetes; (7) high cholesterol; (8) history of smoking (100 cigarettes or more); and (9) current smoking status. Clinician-assessed medical conditions include: (1) obesity (BMI of 30 or greater); and (2) systolic hypertension (systolic blood pressure of 140 mm/Hg or greater). These CVD variables were included in creation of a

CVD risk composite (described in *Statistical Analysis Plan*) at baseline and each successive annual wave. While sleep apnea has been shown to be associated with increased risk of congestive heart failure, stroke, and coronary artery disease, clinician-assessed history of sleep apnea was only completed for UDS version 3. As such, history of sleep apnea was not included in the final cardiovascular composite. As shown on Table 3-4, of the baseline total sample, 21.1% were obese, 13.2% had diabetes, 52.8% had high cholesterol, 36.5% had systolic hypertension, 3.7% currently smoked, though 45.3% had a history of smoking, 5.1% had a history of TIA, 4.6% had a history of stroke, 5.7% had a history of heart attack, 2.3% had a history of heart failure, and 7.2% had a history of atrial fibrillation.

Cardiovascular Treatment Measures

Raw medication data was collected at each annual wave for each participant. Preliminary work regarding this measure informed the use of a global total cardiovascular medication count with the inclusion of the following medication classes: (1) Antihypertensives (ACE Inhibitors, antiadrenergic agent, beta-adrenergic blocking agent, calcium channel blocking agent, angiotensin II inhibitor, vasodilator, diuretic);(2) Anticoagulant and Antiplatelet Agents; (3) Lipid Lowering Agents (HMG-COA reductase inhibitors, antihyperlipidemic agents, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors); and (4) Diabetes Medications (insulin, sulfonylureas, biguanides, dipeptidyl peptidase 4 inhibitors, amylin analogs, incretin mimetics). Medication class data was reported dichotomous for the four classes (treated/untreated). As such, the cardiovascular medication variable used within this study ranges of 0 through 4 to capture expanding treatment regimens at baseline and across each annual wave.

Neuroimaging Data Acquisition

Neuroimaging acquisition and data collection protocols vary by ADC. The neuroimaging data available is voluntarily submitted from ADCs, and thus only a subset of our sample had complete baseline neuroimaging data (i.e., T1 and FLAIR sequences) available. Neuroimaging

data was acquired via cloud computing technologies using the CyberDuck application from the NACC repository as DICOM files. All DICOM files were then converted to Neuroimaging Informatics Technology Initiative (nifti) file format using the dcm2nii program (available at https://people.cas.sc.edu/rorden/mricron/install.html). Once converted to nifit format, files were uploaded to a HiPerGator, a supercomputer, where they were they were separated into 20 batches of approximately 100 files each. Due to variable nomenclature used across ADC sites, a Bash script was utilized on the command line to convert proprietary naming into appropriate convention for processing in UBO Detector. See Appendix B for sample script. Following renaming, T1 and FLAIR files were organized via sequence type into separate folders for processing. Of the 2,068 individual nifiti files from NACC, 847 were excluded prior to processing due to missing either T1, FLAIR, both scans and/or due to file corruption. See Figure 3-2 for CONSORT diagram. Processing of all 1,221 T1 and FLAIR scans was completed using the OnDemand platform for HiPerGator (available at https://ondemand.rc.ufl.edu) using the CNS software containing UBO Detector, MATLAB v. 2019a, SPM v. 12b, and FSL v. 5.0.5. (see below for more information).

White Matter Quantification. Quantification of WMH volumes was conducted using UBO Detector (Jiang et al., 2018). Developed at the University of New South Wales Centre for Health Brain Ageing (CHeBA), the Unidentified Bright Object (UBO) Detector is a cluster-based, fully automated processing pipeline that is readily available for public use in graphical user interface (GUI) format. UBO Detector uses a built-in, validated training set to optimize the algorithm for quantification of WMH volumes. For the purposes of this study, all scans were run using the Older Australian Twins Study (OATS) training set, which was validated for older adults with cognitive impairment ages 65-75. For a detailed description of the UBO Detector processing pipeline, see Jiang et al. (2018). Described in brief, UBO Detector uses integrations with SPM 12 (Ashburner, 2009) and FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) packages for preprocessing (e.g. co-registration and segmentation) of raw FLAIR and T1-

weighted MR images. These packages run on MATLAB. It then applies a machine learning algorithm using k-nearest neighbors (k-NN) to differentiate WMHs from non-WMHs. UBO Detector employs a quality control stop-point which uses a visual rating mask (see Appendix C for preliminary example). Once WMH masks are determined to be acceptable, post-processing of WMH maps are further segmented into periventricular WMHs (PVWMH) and deep WMHs (DWMH) to quantify total and region-specific WMH volume. UBO Detector uses SPM's Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) space, as such, adjustment for total intracranial volume was not employed for individual or group comparisons (Ashburner, 2008). See Figure 3-2 for a graphical representation of the described processing which is adapted from the published pipeline from Jiang and colleagues (2018). For a step-by-step tutorial for running UBO Detector, see Appendix D.

Quality Control. Following processing, all WMH masks were examined for feasibility. Of the 1,221 initial images, 145 failed quality control measures due to presence of motion artifacts, missing half image, and/or poor contrast. It was also noted during quality control, that some participants had missing borders around their scans. Typically, these were thin black margins that only affected very outer portions of the scan. As such, participants these participants were included in final analyses to preserve sample size, but this should be noted as a limitation. In addition, duplicate scans were found for 26 participants (one of whom had three total scans). As such, 27 scans were excluded post-processing due to duplication. Following quality control, 1,049 total participants passed all stops and were included for analysis in Aim 2.

Statistical Analysis Plan

Power and Sample Size Considerations

The current retrospective study had a sample size on the lower bound of 1,049 (for participants with neuroimaging data) to an upper bound of 22,684 total participants at baseline. This study has been powered significantly to detect effects that might be characterized as "small" (Cohen's d=0.1) or better. There are several indications of generally adequate power,

with some caveats (described below). First, the proposed sample sizes fall well within Bollen's (1989) suggestion of at least "several cases per free parameter". The sample further falls well above the N=100 – 500 minimums suggested by other researchers (Anderson & Gerbing, 1984; Boomsma, 1982; Stevens, 2001; Tabachnick & Fidell, 2006). Additionally, using a published sample size calculator for structural equation modeling or SEM (Soper, 2018), the minimally acceptable sample size to detect an effect in a model with 5 latent variables and 30 observed variables, given alpha = 0.05, power of 0.8, is 1,599, which is well under our total sample size of 22,684 (J. Cohen, 1988; Westland, 2010). However, our total neuroimaging sample was approximately 66% of the optimal sample size needed, and thus was likely underpowered. It should be noted however, that this subsample is larger than most previous neuroimaging studies, and additional participants will be added in the future as the NACC sample size increase.

Missing Data

Given the longitudinal and multi-site nature of this study, missing data were inevitable due to attrition and potentially participant death. However, removing subjects with incomplete or missing data from the analyses can introduce unnecessary biases. See Table 3-5 for summary of neuropsychological test data across 10 annual waves. As described, by the third annual wave 75.1% of the baseline sample remained, 43.6% by wave 5, and only 9.63% by wave 10. At baseline, we were missing the following proportion of data: 0% for sex, 0.3% for Hispanic ethnicity, 0.4% for education, 17.1% for number of APOE4 alleles, 0.1% for cardiovascular risk, and 1.3% for cardiovascular medication. To account for missing data, we used full-information maximum likelihood (FIML) estimation methods with missing data, assessing first whether data are Missing Completely at Random, or including covariates (when adjusted) make the data closer to Missing at Random. The FIML approach is fully integrated into lavaan, provides a reduction in prediction bias, works well even in small datasets, and is the preferable method to

multiple imputation or mean substitution in regard to handling missingness (Rosseel, 2012; Schafer & Graham, 2002).

Cardiovascular Risk Composite

This study utilized a composite score for cardiovascular risk, using variables similar to those included in the Framingham CVD composite (R. B. D'Agostino, Sr. et al., 2008), in lieu of exploration of individual predictors. This was done to explore the potential combined effects cardio- and cerebrovascular risk factors and frank disease have on the older adult brain and cognition. The overall cardiovascular risk composite was constructed by combining a participant's total number of cardiovascular diseases and vascular risk factors present at each annual wave. Dichotomous predictors included: 1) cardiovascular diseases: comprised of a history of heart attack/cardiac arrest, congestive heart failure, and atrial fibrillation and 2) vascular risk factors: comprised of a history/current obesity/high BMI, diabetes, high cholesterol, systolic hypertension, history of smoking, current smoking status, transient ischemic attack, and stroke. While missing data was inevitable, to avoid listwise deletion, which may introduce unnecessary bias, each participant was required to have at least two valid cases at each annual wave. Sleep apnea was unable to be included due to insufficient data across waves as it was only collected in the most recent version of the Uniform Data Set.

Statistical Analyses

The analytical framework for the study relied heavily on structural equation modeling (SEM) which was selected to due to its ability to model latent constructs, multiple growth outcomes, and ability to handle missing data using full-information maximum likelihood estimation (FIML). Prior to statistical analysis, all variables assessed for normality and outliers. Any outliers, defined here as exceeding three standard deviations above or below the mean, were assessed for plausibility and removed. Most analyses below were premised on the assumption of multivariate normality; Blom-normalizing transformation (G. Blom, 1958) or estimators for non-normal variables were employed when univariate normality was not found. All

aims were analyzed first with specific variables of interest and then with the inclusion of age, sex, education, race, ethnicity, geriatric depression scale score, and number of ApoE4 alleles. However, due to significant reductions in sample size after inclusion of additional covariates and thus poor model fit, individual predictors used within the final models varied by aim. A summary of aims and analyses appears below.

Aim 0.

This was a descriptive aim and has no hypotheses. The goal of this aim is to characterize the total sample (N= 22,684) and subsample of participants with neuroimaging data at baseline (N= 1,049) and to describe the bivariate correlations among cognitive, demographic, cardiovascular, medication, and neuroimaging measures. This aim also presents the unconditional growth models for the targeted cognitive outcomes in this study, to characterize normative change and individual differences in such change.

Analytical Approach 0. Bivariate correlations were run to explore the associations between age, sex, education, ethnicity, *APOE* ε4 allele count, GDS score, and the four cognitive factor scores. This section also included unconditional growth models to characterize the typical change in each of the four cognitive domains, as well as individual differences in level and change.

Aim 1.

To confirm that participants' level and longitudinal rate of change in CVD is associated with level and rate of change in the four cognitive domains over the subsequent decade, controlling for covariates including age, sex, race, Hispanic ethnicity, education ApoE4 status, depression symptoms, and cardiovascular medication use; and to further investigate whether a participant's initial level and rate of change in cardiovascular medication use is associated with level and rate of change of cognition over time.

Analytical Approach 1. A series of random intercepts and slopes (RIS) predict RIS latent growth curve models (LGCM) were run for each cognitive domain using FIML estimation

to address Aim 1. Data was analyzed using the lavaan package (Rosseel, 2012) for R (R Core Team, 2014) with the "growth" function. We estimated intercept, linear, and quadratic parameters for each cognitive growth process, and intercept and linear parameters for CVD risk and CVD medication growth processes. To characterize growth trajectories for cognitive factor, CVD burden, and CVD medication variables, LGCMs were estimated with CVD acting as both a predictor of our cognitive outcomes and as a potential mediator between CVD medication and cognitive outcomes. The final models (described below) included the baseline age, education, race, Hispanic ethnicity sex, GDS depression score, and number of apolipoprotein E4 (*APOE* ε4) alleles, all of which were allowed to freely estimate intercept, linear, and quadratic growth factors the four cognitive growth processes. Residual mean and variance terms were freely estimated. Regression weights and correlations between factor intercepts and slopes were examined to assess the relationship between CVD and cognitive domains initially over ten years. However, due to having fewer than 10% of participants with follow-up data by wave 10, growth models were restricted to 7 waves of data (6 years). Evaluation of mediation paths between intercept and linear slope of CVD medications, intercept and linear CVD risk, and intercept, linear, and quadratic cognition was conducted to determine if CVD risk mediated the relationship between CVD medication use and cognitive trajectories. Both direct and indirect paths were estimated between CVD medication use and cognitive trajectories, though CVD risk. To evaluate significance of indirect effects, product terms of Blom-transformed variables were created and we employed bootstrapping methods (1000 bootstrapped samples) with bias-corrected confidence intervals (Mackinnon, Lockwood, & Williams, 2004). LGCM for each cognitive growth process, as well as model fit information, are shown in Table 4-1.

Aim 2.

In a subset of participants for whom structural MRI data were collected at baseline, to determine whether baseline indicators of vascular neuropathology (i.e., white matter hyperintensities) mediate the relationship between baseline CVD on level and rate of change in

cognition over time, and to explore whether CVD medication use moderated the effect of CVD risk on cognitive decline trajectories.

Analytical Approach 2. First, bivariate correlations were run between age, education, and baseline cognitive factor scores with both whole brain WMH volumes derived by UBO Detector (UBO-WMH) and WMH volumes quantified for NACC (NACC-WMH) by the Imaging of Dementia and Aging (IDeA) Lab at the University of California Davis (Director: Charles DeCarli, M.D). Methods used by NACC/Dr. DeCarli were similar to those used by the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol and may be found at https://www.alz.washington.edu/WEB/adni_proto.pdf. This reliability check demonstrated strong correlations between whole brain NACC-WMH and UBO-WMH volumes (r = 0.882, p < .001). Both WMH variables also demonstrated similar bivariate correlational patterns between cognitive factor scores at baseline and age. While NACC-WMH was not associated with education, UBO-WMH was found to be weakly and negatively correlated education in this sample (r = -0.081, p < .001). For the remainder of this study, UBO-WMH will be used and simply referred to as WMH.

Statistical evaluation of the proposed mediation model utilized the recommended approaches of Baron and Kenny (1986) and Preacher and Hayes (2008) using a structural equation model framework with maximum likelihood estimation as represented in Figure 6. Prior to analyses, CVD risk, CVD medication, and WMH volumes (whole brain, deep, and periventricular) underwent Blom-normalizing transformation (G. Blom, 1958) to ensure multivariate normality. Following, a product term was created between CVD medication and CVD risk to explore moderation. Data was again analyzed using the lavaan package (Rosseel, 2012) for R (R Core Team, 2014) with the "growth" function. Like Aim 1, to characterize growth trajectories for all cognitive factors both intercept and linear slope were estimated for the four cognitive domains over a 5-year period and served as outcome variables. While it was originally

proposed to explore cognitive growth processes over 10 annual waves, due to limited data at later waves, growth models were restricted to 6 waves of data (5 years) for this aim.

LGCMs were estimated with baseline CVD acting as both a predictor of our cognitive outcomes and as a potential mediator between baseline CVD medication and cognitive outcomes. The final models (described below) included the baseline age, education, race, Hispanic ethnicity, and sex, all of which were allowed to freely estimate intercept and linear growth factors for the four cognitive growth processes, along with white matter hyperintensity (WMH) volume, and baseline CVD risk. Due to listwise deletion causing a significant reduction in sample size, covariates GDS depression score, number of apolipoprotein E4 (*APOE* ε4) alleles, and total intracranial volume were excluded from our final model. See Appendix E for supplementary analysis output. Residual mean and variance terms were freely estimated. Evaluation of mediation paths between baseline CVD medications, CVD risk, and WMH volume on intercept and linear cognition were also conducted through use of direct and indirect paths with bias-corrected bootstrapped confidence intervals to assist in evaluation of significance (Mackinnon et al., 2004).

Table 3-1. Mean (SD) or N (%) of Demographic Data from the Baseline Total and Neuroimaging Sample

	Total Sample	Neuroimaging Sample	*t* or χ^2	*p* value
	(N=22,684)	(N=1,049)		
Age	74.44 (7.83)	73.86 (7.26)	2.351	.018
Sex			1.513	.218
Female	13,304 (58.6%)	594 (56.7%)		
Male	9,380 (41.4%)	453 (43.3%)		
Education (years)	15.24 (3.43)	15.13 (3.65)	1.012	.311
Race (%)			25.228	<.001
White	18,277 (80.6%)	891 (85.3%)	-	-
Black/ African American	3,297 (14.6%)	104 (10.0%)	-	-
American Indian/ Alaskan Native	157 (0.7%)	8 (0.8%)	-	-
Asian American/ Hawaiian Native/ Pacific Islander	556 (2.5%)	35 (3.4%)	-	-
Other	308 (1.4%)	6 (0.6%)	-	-
Ethnicity (%)			69.198	<.001
Hispanic	1,681 (7.4%)	151 (14.5%)	-	-
Non-Hispanic	20,928 (92.3%)	892 (85.5%)	-	-
GDS	1.79 (2.28)	1.82 (2.35)	0.415	.678
CDR Cognitive Status			46.187	<.001
No Impairment	10,762 (47.4%)	447 (42.7%)	-	-
Questionable Impairment	7,969 (35.1%)	470 (44.9%)	-	-
Mild-Severe Impairment	3,953 (17.4%)	130 (12.4%)	-	-

Note. P-values are based on group differences between Total and Neuroimaging sample based on T-test (two-tailed) for age, education, and GDS score, and Chi-Square test for Sex, Race, Ethnicity, and Cognitive Status. Age and Education variables are presented in total years. Abbreviations: GDS = Geriatric Depression Scale (Yesavage, 1983), MCI = Mild Cognitive Impairment. CDR Cognitive Status = Clinical Dementia Rating global score cut offs.

Table 3-2. Cognitive Measures by Domain

Cognitive Composite	Neuropsychological Measures	Source
Memory	Logical Memory: Immediate Recall*; Delayed Recall*	NACC UDS v1- 3 NACC UDS v3
	Craft Story: Immediate Recall; Delayed Recall	
Attention	Digit Span Forward: Longest Sequence, Total Correct*	NACC UDS v1- 3
	Digit Span Backward: Longest Sequence, Total Correct*	NACC UDS v1- 3 NACC UDS v3
	Number Span Forward: Longest Sequence, Total Correct	NACC UDS v3
	Number Span Backward: Longest Sequence; Total Correct	
Executive Function/ Processing Speed	Trail Making Test B*	NACC UDS v1- 3
	Trail Making Test A	NACC UDS v1- 3
	WAIS-R Digit Symbol – Total*	NACC UDS v1- 3
Language	Boston Naming Test – Total*	NACC UDS v1-3
	Multilingual Naming Test – Total	NACC UDS v3
	Vegetable List Generation – Total*	NACC UDS v1-3
	Animal List Generation – Total*	NACC UDS v1-3

* = Neuropsychological measure included as part of Hayden et al. (2011) factor analysis of UDS Data

Table 3-3. Spearman Correlation Coefficients Between Test Pairs (from Monsell et al., 2016)

Old Test	New Test	ρ
BNT	MINT	0.76
Logical Memory IA, Immediate	Craft Story 21, Immediate — paraphrase	0.73
Logical Memory IIA, Delayed	Craft Story 21, Delayed — paraphrase	0.77
Digit Span Forward — trials correct	Number Span Forward — trials correct	0.75
Digit Span Forward — length	Number Span Forward — length	0.68
Digit Span Backward — trials correct	Number Span Backward — trials correct	0.78
Digit Span Backward — length	Number Span Backward — length	0.72

Abbreviations: BNT = Boston Naming Test, MINT = Multilingual Naming Test, MMSE = Mini Mental State Examination, MoCA = Montreal Cognitive Assessment, UDS = Uniform Data Set.

Table 3-4. N (%) of Individual Vascular Risk Factors and Cardiovascular Disease Present in the Baseline Total Sample (N=22,684)

Current Smoker	Total Sample
Vascular Risk Factor	(N=22,684)
Obesity	4,794 (21.1%)
Diabetes	2,994 (13.2%)
High Cholesterol	11,972 (52.8%)
Current Smoker	850 (3.7%)
History of Smoking	10,286 (45.3%)
Systolic Hypertension	8,277 (36.5%)
History of TIA	1,156 (5.1%)
History of Stroke	1,041 (4.6%)
Cardiovascular Disease	
History of Heart Attack	1,284 (5.7%)
History of Heart Failure	524 (2.3%)
History of Atrial Fibrillation	1,633 (7.2%)

Note. History implies either active or inactive history of vascular risk factor or disease.
Abbreviations: TIA = transient ischemic attack

Table 3-5. Total Number of Participants Across Annual Waves and Associated Neuropsychological Measures

	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Total Participants	22,718	22,718	17,050	13,025	9,901	7,606	5,756	4,171	2,998	2,188
Memory										
Logical Memory (immediate)	18,015	16,449	12,010	8,802	6,325	4,646	3,310	2,104	1,219	616
Craft Story (immediate)	3,189	3,876	2,852	2,364	1,997	1,657	1,495	1,386	1,302	1,211
Logical Memory (delayed)	18,023	16,366	11,979	8,779	6,310	4,632	3,296	2,094	1,217	616
Craft Story (delayed)	3,176	3,850	2,837	2,352	1,981	1,644	1,479	1,379	1,294	1,206
Executive Function/ Processing Speed										
Trail Making Test A	21,027	19,819	14,433	10,816	8,076	6,149	4,691	3,404	2,478	1,803
Trail Making Test B	19,639	18,175	13,270	9,983	7,530	5,765	4,409	3,211	2,354	1,709
Digit Symbol (WAIS-R)	17,132	15,356	11,119	8,032	5,635	4,009	2,794	1,678	770	138
Attention										
Digit Span (forward)	18,185	16,566	12,067	8,831	6,344	4,646	3,313	2,106	1,218	619
Number Span (forward)	3,212	3,912	2,867	2,385	2,006	1,670	1,509	1,389	1,307	1,221
Digit Span (backward)	18,159	16,525	12,046	8,812	6,332	4,636	3,305	2,097	1,216	619
Number Span (backward)	3,211	3,900	2,859	2,380	2,005	1,666	1,507	1,389	1,306	1,218
Language										
Boston Naming Test	18,085	16,454	11,967	8,751	6,284	4,616	3,295	2,099	1,216	618
Multilingual Naming Test	3,184	3,862	2,842	2,364	1,993	1,656	1,486	1,373	1,289	1,202
COWA Vegetables	21,360	20,418	14,894	11,183	8,330	6,306	4,809	3,494	2,528	1,843
COWA Animals	21,575	20,524	14,957	11,228	8,367	6,332	4,830	3,505	2,538	1,847

Abbreviations: COWA = Controlled Oral Word Association Test; MMSE = Mini-Mental Status Exam; MoCA = Montreal Cognitive Assessment. Data download October 2018, these values represent data mi

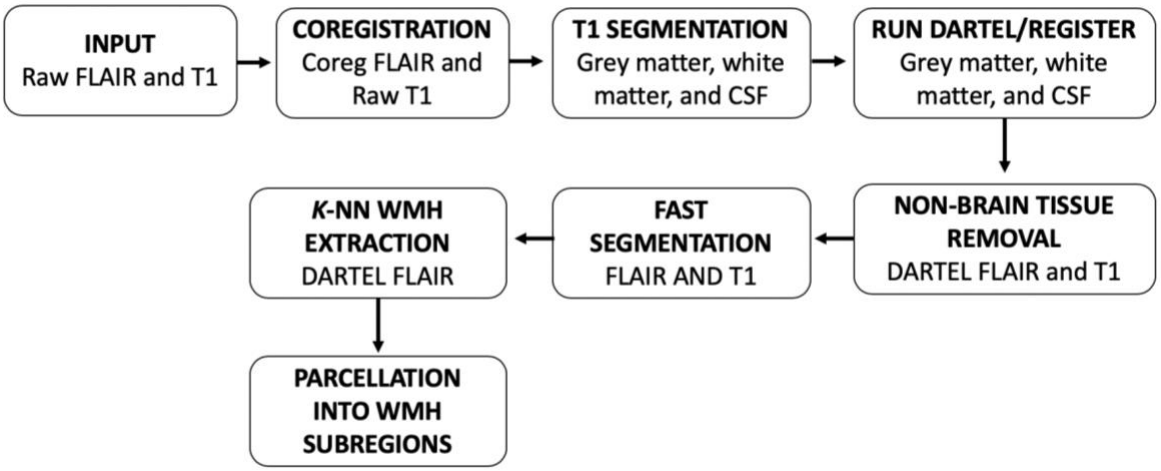


Figure 3-1. Adapted UBO Detector Processing Pipeline.

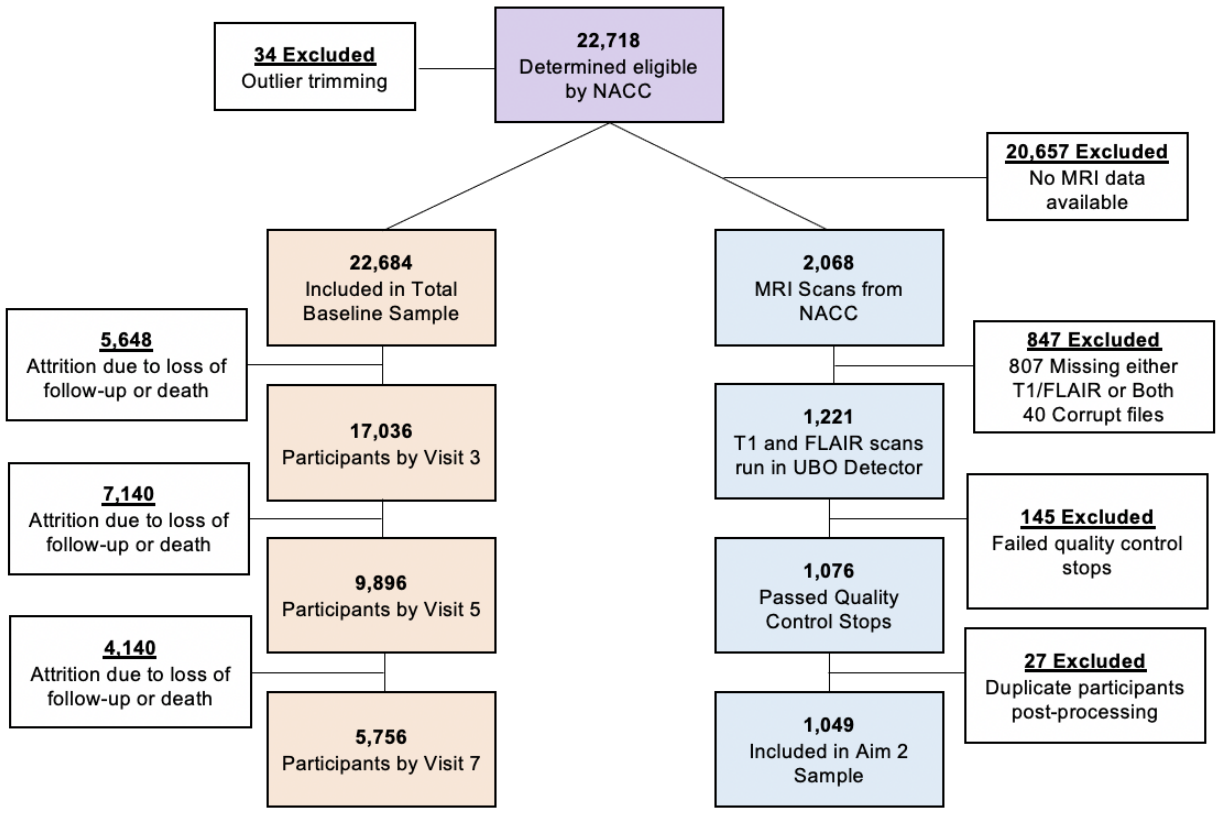


Figure 3-2. CONSORT diagram describing the flow of participants from eligibility assessment through post-processing of neuroimaging data. Orange refers to those included in Aim 1 analyses, while blue refers to neuroimaging data included in Aim 2 analyses.

CHAPTER 4
RESULTS

Overview

The present study investigated the relationship between vascular risk factors, cardiovascular disease, and pharmacological treatment on cognitive trajectories in a large, national sample of older adults from the National Alzheimer's Coordinating Center (NACC). While this study originally intended to explore cognitive trajectories over 10 annual visits, the proportion of the sample available at visit 10 was less than 10% of the original sample. As such, latent growth curve models for the cognitive trajectories were run examining model fit across visits with the final models utilizing 6 years of cognitive, cardiovascular, and medication data for Aim 1 and 5 years of cognitive data for Aim 2. This study also examined whether increased vascular neuropathology, as measured by white matter hyperintensity volume (including whole brain, deep and, and periventricular) mediated the relationship between baseline vascular risk factors and cardiovascular disease (CVD), CVD medication use, and cognitive trajectories. It further explored whether medication use attenuated potential negative effects of CVD on overall cognitive performance and change over time.

Aim 0: Characterization of the Baseline Sample

Prior to conducting study analyses, we examined bivariate associations among measured variables at baseline, both to ascertain strength of univariate relationships, and as a data check (i.e., to confirm that associations were in expected directions). As seen in Tables 4-1 and 4-2, cognition (i.e., Memory, Attention, Executive Function, and Language) in general was negatively related to white matter hyperintensities (WMH) volume (whole brain, deep, and periventricular), CVD, and CVD medications. Older age, greater number of APOE ε4 alleles, and higher GDS score were also negatively related to cognition (but positively related to CVD medications, CVD, and WMH volume), while Hispanic ethnicity was negatively associated with cognition, WMH volume, but positively associated with CVD. Higher educational attainment was

positively associated with cognition, while sex (being a woman) was positively associated with Memory, Executive Function, and Language, but not Attention.

Model-implied trajectories for the four cognitive growth models, in a random selection of 50 individuals (to aid visibility of individual trajectories), can be found in Figure 4-1 (A: Memory; B: Attention; C: Executive Function; D: Language. Examination of these four growth models revealed generally similar trends across cognitive factors. All unconditional growth models had significant variance in intercept and slope, meaning there were individual differences across overall level and linear and quadratic rate of change, which is clearly observed across figures

Aim 1: Does Cardiovascular Risk and its Treatment Influence Overall Level and Rate of Change in Cognition Over Time?

The first study aim was to describe change in participants' cardiovascular risk burden (CVD) and medication use on cognitive trajectories over time, and to determine if CVD mediated the relationship between CVD medication on cognition over time. Analyses were conducted via latent growth curve modeling (LGCM) which relies upon a structural equation modeling (SEM) framework. Overall (intercept), linear, and quadratic growth curves were modeled separately for cognitive factors Memory, Attention, Executive Function, and Language, which served as outcome variables. Both overall (intercept) and linear growth curves were modeled for CVD and CVD medication use. Covariates included baseline age, sex, education, dummy-coded race, Hispanic ethnicity, Geriatric Depression Scale (GDS) score, and number of APOE ε4 alleles. As described in Methods, analyses used full-information maximum likelihood estimation and included all available cases (under the assumption that any missing data were missing at random).

Associations Among Overall Level and Rate of Change in Each Cognitive Domain

Table 4-3 shows the correlations among overall level and rate of change in each of the cognitive domains. After adjustment for age, education, sex, race, Hispanic ethnicity, GDS score, and number of APOE ε4 alleles, overall Memory performance was associated with less

linear decline in Memory (r = 0.393, p < .001), and reduction in rate of decline at later waves (r = -0.456, p < .001). In addition, greater linear declines in Memory were associated with accelerated rate of decline at later waves (r = 0.244, p < .001). Likewise, higher overall Attention was associated with less linear decline in Attention (r = 0.282, p < .001), and a reduction in rate of decline in Attention at later waves (r = -0.538, p < .001). Higher overall level of Executive Function was also associated with less linear decline in Executive Function (r = 0.521, p < .001) and reduction in rate of decline at later waves (r = -0.476, p < .001). Finally, higher overall Language was associated with less linear decline in Language (r = 0.662, p < .001) and reduction in rate of decline in Language at later waves (r = -0.474, p < .001). Though, while small, less linear decline in language was associated with accelerated rate of decline in Language at later waves (r = -0.081, p < .01). Speaking generally, people with higher Memory experienced less linear or quadratic decline, while those with lower Memory experienced more dramatic decline, though the lowest low experienced a sort of plateauing at later occasions, probably representing floor effects. Attention showed a similar trend to Memory, however people at the higher end of the distribution didn't experience as must decline as those at the bottom. Likewise, higher Executive Function was associated with less decline, while those in the middle tended to decline more rapidly, and those at the bottom again demonstrate some plateauing. Similar trends were observed for the Language factor as well.

Effects of Demographic and Health Covariates on Cognitive Outcomes

Effects of background covariates, including b-weights and significance tests, are show in Table 4-4. In general, older age at baseline was associated with poorer overall Memory, Attention, Executive Function, and Language performance and greater linear

decline over the 6-year period. Higher educational attainment (13+ years or more) was associated with greater overall Memory, Attention, Executive Function, and Language and reduced rate of change in Memory, Attention, and Language over the 6-year period. Compared to Other (American Indian/Alaskan Native, Other unspecified), White and Black/African American participants demonstrated accelerated change in Attention, Asian/Hawaiian Native/Pacific Islander participants demonstrated greater overall Executive Function performance, while White participants demonstrated greater overall Attention, Executive Function, and Language, greater linear decline in Executive Function, and reduced linear decline in Language. With regards to depression, higher GDS scores at baseline were associated with poorer overall Memory, Attention, Executive Function, and Language and greater linear declines across domains. There was a small, but significant effect of higher GDS score predicting accelerated change in Memory, Attention, and Language over the 6 years. Finally, having a higher number of ApoE4 alleles was associated with both poorer overall and linear rate of change across all four cognitive domains. While small, more ApoE4 alleles was also associated with accelerated change in Memory, but not other cognitive domains measured.

Cardiovascular Disease, Medication, and Cognitive Trajectories over 6 Years

A primary aim of this study was to explore the relationships between overall cardiovascular disease and vascular risk burden (CVD), and its pharmacological treatment (CVD Medication), on cognitive trajectories over time. As such, four latent growth curve models (LGCM) were run to explore these effects, one for each of Memory, Attention, Executive Function, and Language. As outlined in Table 4-4, all four models demonstrated good model fit and converged without error.

Memory. *(a) CVD.* There were no significant associations between level or linear rate of change in CVD across overall level, linear, or quadratic change in Memory over the 6-year period. *(b) CVD Medication.* In contrast to the absence of relationships between cardiovascular risk factors/disease and memory, many associations were found between cardiovascular medications and memory. Greater overall CVD Medication was associated with higher overall Memory performance ($b = 0.034$, $p < .01$) and reductions in rate of decline at later waves ($b = -0.062$, $p < .05$). Greater linear increases in CVD Medication were also associated with higher overall level ($b = 0.068$, $p < .001$), less negative change ($b = 0.115$, $p < .001$) and less accelerated decline in Memory over the 6-year period ($b = 0.086$, $p < .01$).

Attention. *(a) CVD.* Higher overall level of CVD burden was associated with poorer overall performance ($b = -0.024$, $p < .05$) and greater linear declines in Attention over time ($b = -0.068$, $p < .05$). *(b) CVD Medication.* While higher overall CVD Medication was associated with reduction in rate of decline in Attention at later waves ($b = -0.077$, $p < .05$), greater linear increases in CVD Medication were associated with both higher overall level ($b = 0.042$, $p < .01$), and attenuated linear decline in Attention over the 6-year period ($b = 0.057$, $p < .01$).

Executive Function. *(a) CVD.* Higher overall CVD burden was associated with poorer overall level of Executive Function performance ($b = -0.039$, $p < .001$), but not linear or quadratic change over time. However, higher CVD burden over the 6-year period was associated with greater linear decline in Executive Function over the same period ($b = -0.050$, $p < .05$). *(b) CVD Medication.* With regards to treatment, higher CVD Medication was associated with higher overall level of Executive Function performance

(b = 0.035, p < .01), as well as less linear decline in Executive Function over time (b = 0.047, p < .01). Furthermore, greater increase in CVD Medication over 6-years was associated with higher overall level of Executive Function (b = 0.058, p < .001) and less linear decline in Executive Function over the same period (b = 0.098, p < .001).

Language. *(a) CVD.* As with Memory, there were no significant associations between CVD burden overall, linear, or quadratic rate of change in Language performance over time. *(b) CVD Medication.* However, overall CVD Medication was associated with both higher overall level (b = 0.043, p < .001) and less linear decline in Language performance over the 6 years (b = 0.054, p < .01). Likewise, higher linear increases in CVD Medication were also associated with higher overall level of Language performance (b = 0.067, p < .001) and less linear decline over the 6-year period (b = 0.116, p < .001).

Aim 2: Does Whole Brain White Matter Hyperintensity Volume Mediate the Relationships Between Cardiovascular Risk and Cognition and Does Medication Matter?

The purpose of this aim was two-fold: (1) First we endeavored to explore whether baseline whole brain white matter hyperintensity (WMH) volume served as a potential mediator through which baseline CVD risk exerted its effect on overall cognition and its change over time, and (2) we examined whether treatment of underlying vascular risk factors and cardiovascular disease (CVD medication) attenuated the effect of CVD on overall cognitive performance and change over time and/or if CVD medication had direct or indirect effects on WMH volume through CVD. As described in *Methods*, overall level (intercept) and linear growth curves were modeled separately for all four cognitive factors using LGCM with full-information maximum likelihood estimation. Additional LGCM exploring the effects of whole brain WMH volume with additional

covariates (GDS score, APOE4, and total intracranial volume) not included in the following models as these were only available on approximately 60% of the sample and thus for inclusion, reduced the sample size and substantially degraded statistical power. Because these effects were of importance, we nonetheless included these covariates in additional exploratory models and are shown in Appendix E. To reduce table redundancy, we only show these results from our Memory model, although their estimation was a part of all four cognitive models. Beyond trivial sampling variation, the direction and magnitude of the relationships between our covariates and cognitive level/slope were consistent and similar in each of the four models. As demonstrated in Tables 4-6 though 4-9, all models exhibited good model fit.

Relationships Between Cardiovascular Risk, White Matter Hyperintensity Volume, and Cognitive Factors

As described in Table 4-5, after controlling for the effects of age, sex, education, race, and Hispanic ethnicity there were significant effects of CVD on WMH, such that higher CVD risk was associated with greater whole brain WMH (b = 0.116, p < .001), as well as both deep (b = 0.092, p < .001) and periventricular WMH (b = 0.108, p < .01). Additionally, greater whole brain WMH volume was associated with both poorer overall Memory (b = -0.273, p < .001), Attention (b = -0.246, p < .001), Executive Function (b = -0.291, p < .001), and Language (b = -0.283, p < .001) and greater linear declines in Memory (b = -0.219, p < .001), Attention (b = -0.223, p < .001), Executive Function (b = -0.288, p < .001), and Language (b = -0.219, p < .001) over the 5-year period.

Direct and Indirect Effects of Cardiovascular Risk on Cognitive Factors

(a) *Direct effects.* Paralleling what we had observed in the full sample for Memory and Language, there were no significant direct effects observed between CVD on level

or rate of change in any of the four cognitive factors; in this smaller subset, CVD was also not directly related to Attention or Executive function. (b) *Indirect effects.* All indirect effects reported are standardized with confidence intervals (CI) from 1,000 bootstrapped samples. Indirect associations were observed however between CVD on overall Memory (*IND* = -0.032, *p* = .002, bootstrapped CI [-0.051, -0.013]), Attention (*IND* = -0.029, *p* = .002, bootstrapped CI [-0.030, -0.008]), Executive Function (*IND* = -0.034, *p* = .002), and Language (*IND* = -0.033, *p* = .002) through whole brain WMH volume. Indirect effects of CVD through whole brain WMH were also observed for rate of decline in Memory (*IND* = -0.026, *p* = .011, bootstrapped CI [-0.006, -0.001]) and Executive Function (*IND* = -0.033, *p* = .003). While similar findings were found for Attention (*IND* = -0.026, *p* = .025) and Language (*IND* = -0.025, *p* = .006), after examination of bias-corrected bootstrapped confidence intervals, neither indirect effects Attention, CI [-0.003, 0.000] nor Language CI [-0.002, 0.001] remained significant. In general, what these results suggest is that greater CVD was associated with more WMH, which in turn was associated with poorer cognitive level and more negative cognitive change, although the magnitude of these effects were uniformly low.

Direct and Indirect Effects of Medication on Cardiovascular Risk, White Matter, Hyperintensity Volume, and Cognitive Factors

(a) *Direct effects of medication use on CVD risk.* As described in Table 4-5, across all models, higher CVD medication use at baseline was associated with greater baseline CVD risk (*b* = 0.523, *p* < .001). (b) *Direct effects of medication use on cognition.* However, there were no significant direct effects of CVD medication on level or rate of change in any of the four cognitive factors. (c) *Direct effects of medication use on WMH.* Additionally, there was no effect of CVD medication on either whole brain,

deep, or periventricular WMH volume. (d) *Indirect effects of medication use on cognition or WMH.* Nor were there any indirect effects of CVD medication on cognitive level or rate of change through WMH (whole brain, deep, and periventricular) for any of the cognitive domains. (e) *Moderating effects of medication use on the relationship between CVD and cognition.* Moderating effects of CVD medication on CVD was tested by inclusion of an interaction term. In the final models (presently described), medication did not significantly moderate the association between CVD and cognitive level or rate of change across cognitive factors.

Follow-Up Analyses

Overview

Following analysis the two primary aims of this study, three supplementary follow-up analyses were run.

Follow-Up Analysis 1: Do Deep or Periventricular White Matter Hyperintensity Volumes Differ from Whole Brain on Relationships Between Cardiovascular Risk, Medication and Cognition? Our first follow-up analysis was conducted as a supplement to Aim 2, which described the relationships between CVD risk, CVD medication, and whole brain WMH volume on overall level and rate of change in Memory, Attention, Executive Function, and Language. As described in *Literature Review*, most studies examining WMH typically explore whole brain WMH. However, UBO detector was selected as the preferred neuroimaging method due to the addition of specific WMH regional volumes (i.e., periventricular, deep) and WMH types (i.e., focal, punctate, medium, and confluent). While literature is still inconclusive regarding differences in etiology and pathology between deep and periventricular WMH (Wardlaw et al., 2015), studies examining the unique effects of deep and/or periventricular on

cognition have found differential effects on cognition in both healthy older adults and those with dementia (see *Literature Review*). Thus, we re-examined our Aim 2 analyses substituting deep and periventricular WMH volumes in lieu of whole brain WMH to explore whether different patterns of relationships emerged for the four cognitive constructs. This exploratory analysis utilized the same LGCM modeling approach as described for Aim 2, above.

Follow-Up Analysis 2: Exploring Medication as a Moderator in a Simple Latent Growth Curve Model without Covariates. Our second follow-up analysis was run to confirm whether there was in fact no moderation of the relationship between CVD and cognition by CVD medication (as observed in Aim 2), or whether this moderation was unobservable due to multi-collinearity upon the addition of covariates. As such, four simple models were run without addition of covariates on the four cognitive domains and whole brain WMH volume.

Follow-Up Analysis 3: Associations Between Baseline and Incident Vascular Risk and Cardiovascular Disease on Cognitive Factors over 6-years. Lastly, our third follow-up analysis was run to explore the associations between individual vascular risk factors and cardiovascular diseases on overall level and rate of change in cognition. This model was run without the addition of covariates. Latent growth curves were modeled for the four cognitive domains (intercept, linear slope) over a 6-year period. Regressions were run on intercept and linear slope with baseline risk factor and risk factor after baseline. To determine emergent (after baseline) presence of each risk factor, we evaluated whether each individual participant had each risk factor present between waves 2-7. By including both predictors in the regression models we

were able to explore whether after controlling for baseline risk factors, whether newly emergent CVD (incident CVD) was associated with our cognitive variables of interest.

Analyses

Follow-Up Analysis 1: Do Deep or Periventricular White Matter Hyperintensity Volumes Differ from Whole Brain on Relationships Between Cardiovascular Risk, Medication and Cognition?

In the first follow-up analysis we examined the association of deep or periventricular white matter hyperintensities with cognition in two separate models for each cognitive domain (i.e., for each cognitive domain as outcome, one exploring including periventricular white matter as the predictor, and another including deep white matter). Covariates were age, sex, education, race, and Hispanic ethnicity. As described in Table 4-5, there were significant effects of CVD on WMH, such that higher CVD risk was associated with greater deep (b = 0.092, p < .001) and periventricular WMH volume (b = 0.108, p < .01). Additionally, as described in Tables 4-13 through 4-20, and consistent with Aim 2 findings, greater deep WHM volumes were associated with poorer overall level of Memory (b = -0.249, p < .001), Attention (b = -0.216, p < .001), Executive Function (b = -0.246, p < .001), and Language (b = -0.239, p < .001) and greater linear declines in Memory (b = -0.244, p < .001), Attention (b = -0.244, p < .001), Executive Function (b = -0.247, p < .001), and Language (b = -0.192, p < .001) over the 5-year period. Likewise, greater periventricular WMH volumes were also associated with poorer overall level of Memory (b = -0.244, p < .001), Attention (b = -0.221, p < .001), Executive Function (b = -0.273, p < .001), and Language (b = -0.264, p < .001) along with greater linear declines in Memory (b = -0.172, p < .01), Attention (b = -0.176, p < .05), Executive Function (b = -0.258, p < .001), and Language (b = -0.190, p < .001) over the 5-year period. Comparing to earlier results using whole brain WMH,

relationships with deep or periventricular were generally of the same magnitude and significance; no clear evidence emerged that either deep or periventricular white matter was more important for predicting cognitive level or change.

Follow-Up Analysis 2: Exploring Medication as a Moderator in a Simple Latent Growth Curve Model without Covariates

See Tables 4-10 through 4-13 for summary of findings. In these models, no covariates were included. Cognitive level and slope were regressed on CVD medication and CVD, with and additional product term interaction (CVD medication * CVD) added to evaluate moderation. Results from these no-covariate models showed small, but significant positive interaction effects between CVD medication and CVD for Memory (b = 0.065, $p < .05$) and Language (b = 0.074, $p < .001$) as well as shallower linear declines in Language (b = 0.093, $p < .05$) over the 5-year period. There were no significant interactions found for Attention or Executive Function domains. As seen in Figure 4.2, for the two variables with significant interactions, Memory and Language, there was a match-vs-mismatch effect. Specifically, highest overall level and least linear decline were predicated in those who had low CVD and low CVD medication or high CVD and high CVD medication. These were situations where medication and cardiovascular health appeared matched. However, the lowest overall level and steepest decline was predicted in those who had low CVD and high medication (over-treatment) and high CVD but low CVD medication (under-treatment).

Follow-Up Analysis 3: Associations Between Baseline and Incident Vascular Risk and Cardiovascular Disease on Cognitive Factors over 6-years

See Table 4-22 for standardized regression weights and significance values. To obtain these values: (a) for each risk factor/disease, two indicators (presence or

absence at baseline; presence or absence after baseline) were simultaneously entered. This permits the interpretation of the second indicator as the effects of incident risk factor/after controlling for the baseline value of the indicator; (b) separate models were run for each risk factor/disease. Results from this follow-up analysis revealed significant associations between baseline and incident CVD and with our four cognitive domains of interest, however it should be noted effect sizes were quite small.

Vascular Risk Factors. (i) *Obesity.* Obesity at baseline was associated with higher overall level of Memory and Language, and less linear decline across memory, Executive Function, and Language. After controlling for baseline obesity, incident obesity was associated with higher overall level of Memory, Executive Function, and Language. (ii) *Diabetes.* Diabetes at baseline was associated with lower overall level across all four cognitive factors. There were no significant associations between incident diabetes and cognition. (iii) *High cholesterol.* High cholesterol at baseline was associated with lower overall level of Memory and Executive Function, and greater linear declines in Language, while incident high cholesterol was associated with high overall level of Memory and Language, as well as less linear decline in Language. (iv) *Current smokers.* People who were current smokers at baseline had lower overall level of Executive Function and Language, while incident current smoking was associated with less linear declines in Language. (v) *History of smoking.* History of smoking at baseline was associated with higher overall level of Memory, Executive Function, and Language. There were no significant associations between incident history of smoking. (vi) *Systolic hypertension.* Systolic hypertension at baseline was associated was associated with poorer overall level and greater linear decline in all four cognitive

domains, while incident systolic hypertension after baseline was associated with higher overall level across cognitive domains, and less linear decline in Memory, Executive Function, and Language. (vii) *TIA.* History of TIA at baseline was associated with less linear decline in language, while incident TIA history was associated with lower overall level and greater linear declines across all four cognitive factors. (viii) *Stroke.* While of stroke at baseline was associated with lower overall level of all four cognitive factors, incident stroke history was associated with lower overall level of Memory and Executive function and greater linear decline in Memory, Executive Function, and Language.

Cardiovascular Disease. *(i) Heart attack.* Baseline history of heart attack was associated with lower overall level across all four cognitive factors. There were no significant associations between incident heart attack history and cognitive factors. *(ii) Heart failure.* Like heart attack, baseline history of heart failure was associated with lower overall level across all four cognitive factors, while incident heart failure history was associated with greater linear declines in Memory and Executive Function. *(iii) Atrial fibrillation.* Finally, baseline history of atrial fibrillation was associated with lower overall level across all four cognitive factors, while incident atrial fibrillation history was associated with higher overall level of Memory, Attention, and Language, but greater linear decline in Attention and Executive Function.

Table 4-1. Bivariate Correlations between Cognitive Factors, Cardiovascular Risk, Medication and Other Variables (N=22,684)

		1	2	3	4	5	6	7	8	9	10	11	12
1	CVD Meds (22,396)	1.00											
2	CVD (22,670)	0.50	1.00										
3	Age (22,684)	0.08	0.04	1.00									
4	Sex (22,684)	-0.16	-0.10	-0.03	1.00								
5	Education (22,590)	-0.04	-0.14	-0.10	-0.18	1.00							
6	Hispanic (22,609)	0.02	0.04	-0.04	0.05	-0.33	1.00						
7	*APOE* ε4 (18,801)	0.01	0.00	-0.12	-0.03	-0.01	-0.04	1.00					
8	GDS (21,529)	0.06	0.09	0.00	-0.01	-0.14	0.12	0.05	1.00				
9	Memory (21,649)	-0.06	-0.05	-0.20	0.11	0.28	-0.11	-0.25	-0.17	1.00			
10	Attention (21,649)	-0.07	-0.09	-0.16	0.01	0.37	-0.22	-0.12	-0.17	0.56	1.00		
11	Executive Function (21,649)	-0.09	-0.12	-0.33	0.04	0.38	-0.20	-0.15	-0.23	0.68	0.74	1.00	
12	Language (21,649)	-0.08	-0.09	-0.30	0.07	0.35	-0.17	-0.18	-0.22	0.80	0.70	0.89	1.00

Note. Correlations greater that |0.02| are significantly greater than zero, $p < .05$. Values in parentheses represent the sample size for that variable. CVD = summation of vascular risk factors and cardiovascular disease; CVD Medication = total number of medications used to treat CVD; *APOE* ε4 = number of *APOE* ε4 alleles; GDS = Geriatric Depression Scale total score. Memory / Attention / Executive / Language represent cognitive factor scores.

Table 4-2. Bivariate Correlations between White Matter Hyperintensity Volumes, Cognitive Factors, and Other Variables (N=1,049)

		1	2	3
1	Whole Brain WMH (1,047)	1.00		
2	Deep WMH (1,047)	0.91	1.00	
3	Periventricular WMH (1,047)	0.94	0.72	1.00
4	CVD Meds (1,047)	0.10	0.08	0.11
5	CVD (1,047)	0.13	0.10	0.13
6	Age (1,047)	0.35	0.23	0.40
7	Sex (1,047)	0.01	-0.03	0.04
8	Education (1,039)	-0.08	-0.05	-0.09
9	Hispanic (1,043)	-0.08	-0.06	-0.08
10	*APOE* ε4 (915)	0.06	0.06	0.05
11	GDS (1,020)	0.08	0.06	0.08
12	Memory (1,039)	-0.26	-0.21	-0.26
13	Attention (1,039)	-0.18	-0.15	-0.18
14	Executive (1,039)	-0.28	-0.23	-0.29
15	Language (1,039)	-0.31	-0.25	-0.32

Note. Correlations greater that |0.04| are significantly greater than zero, $p < .05$. Values in parentheses represent the sample size for that variable. WMH = White matter hyperintensity volume; CVD = summation of vascular risk factors and cardiovascular disease; CVD Medication = total number of medications used to treat CVD; *APOE* ε4 = number of *APOE* ε4 alleles; GDS = Geriatric Depression Scale total score. Memory / Attention / Executive / Language represent cognitive factor scores.

Table 4-3. Latent Growth Curve Correlations for Cognitive Outcomes (N=22,684)

	Linear Change	Quadratic Change
Memory		
Level	0.393**	-0.456**
Linear Change	-	0.244**
Quadratic Change	-	-
Attention		
Level	0.282**	-0.538**
Linear Change	-	-0.018
Quadratic Change	-	-
Executive Function		
Level	0.521**	-0.476**
Linear Change	-	0.014
Quadratic Change	-	-
Language		
Level	0.662**	-0.474**
Linear Change	-	-0.081*
Quadratic Change	-	

Note. Correlation coefficients adjusted for baseline age, education, sex, race, Hispanic, GDS score, and number of *APOE* ε4 alleles**.** *$p < .01; **$p < .001.

Table 4-4. Summary of Growth Models Predicting Change in Memory, Attention, Executive Function, and Language over 6-years (N=22,684)

	Memory			Attention			Executive			Language		
Variables	Level	Linear Change	Quad Change	Level	Linear Change	Quad Change	Level	Linear Change	Quad Change	Level	Linear Change	Quad Change
Intercept	2.028***	3.080***	-0.329	1.440***	1.701***	-0.242	2.808***	1.586***	-0.347	2.372***	1.973***	0.142
CVD												
Level	0.009	-0.016	0.015	-0.024*	-0.068*	0.034	-0.039***	-0.032	0.009	-0.016	-0.023	0.018
Linear	0.018	-0.046	-0.027	0.027	-0.044	-0.064	0.019	-0.050*	-0.034	0.026	-0.036	-0.067
CVD Meds												
Level	0.034**	0.018	-0.062*	0.018	0.037	-0.077*	0.035**	0.047**	-0.034	0.043***	0.054**	-0.04
Linear	0.068***	0.115***	0.086**	0.042**	0.057*	0.034	0.058***	0.098***	0.027	0.067***	0.116***	0.052
Age	-0.289***	-0.314***	0.019	-0.228***	-0.234***	-0.017	-0.365***	-0.221***	0.016	-0.327***	-0.267***	-0.052
Sex	0.130***	0.001	-0.050*	0.071***	0.035	-0.044	0.080***	0.031*	-0.037	0.098***	0.025*	-0.045**
Education	0.183***	0.036*	-0.012	0.197***	0.043*	0.043	0.167***	0.022	0.018	0.168***	0.027*	0.008
Race												
Black/ AfAm	-0.009	0.009	0.07	-0.007	0.126	0.204*	-0.017	0.040	0.034	-0.002	0.070	0.085
AAPI	0.000	-0.038	-0.037	0.013	0.026	0.065	0.029**	-0.027	-0.021	0.000	0.008	0.005
White	0.036	-0.081	0.021	0.113***	0.018	0.218*	0.091***	-0.098*	0.026	0.067**	-0.066	0.072
Hispanic	-0.049***	-0.002	0.003	-0.138***	0.008	-0.014	-0.087***	0.050**	-0.022	-0.066***	0.044**	0.000
GDS	-0.170***	-0.136***	0.052*	-0.155***	-0.116***	0.069*	-0.187***	-0.116***	0.045	-0.184***	-0.144***	0.055*
APOE ε4	-0.316***	-0.236***	0.078***	-0.223***	-0.312***	0.026	-0.268***	-0.331***	0.042	-0.283***	-0.350***	0.010

Model Fit	df	AIC	BIC	RMSEA	CFI	TLI	χ^2
Memory	378	454,277.727	454,768.760	0.033	0.969	0.967	7,870.118***
Attention	378	405,041.703	405,532.736	0.033	0.967	0.966	7,830.025***
Executive	378	399,659.654	400,150.687	0.033	0.973	0.971	7,973.207***
Language	378	370,914.135	371,405.168	0.033	0.973	0.972	7,895.596***

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve models. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; Quad = Quadratic change; Executive = Executive Function; CVD = summation of vascular risk factors and cardiovascular disease; CVD Medication = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; GDS = Geriatric Depression Scale total score; *APOE* ε4 = number of alleles; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index

Table 4-5. Summary of Relationships Between Baseline CVD, White Matter Hyperintensities, and Covariates (N=22,684)

Variables	CVD Baseline[a]	Whole Brain WMH Volume[a]
CVD Baseline	-	0.116***
CVD Meds	0.523***	0.007
Race		
Black/AfAm	0.164*	-0.585***
AAPI	0.00	-0.334***
White	0.076	-0.72***
Hispanic	-0.012	-0.123***
Age	0.002	0.231***
Sex	-0.026	-0.023
Education	-0.104***	-0.137***

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve models for Memory factor models. [a]From model summarized in Table 4-6; *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified.

Table 4-5. Summary of Relationships Between Baseline CVD, White Matter Hyperintensities, and Covariates (N=22,684)

Variables	Deep WMH Volume[b]	Periventricular WMH Volume[c]
CVD Baseline	0.092***	0.108**
CVD Meds	0.008	0.010
Race		
Black/AfAm	-0.502***	-0.592***
AAPI	-0.285***	-0.347***
White	-0.591***	-0.748***
Hispanic	-0.110***	-0.121***
Age	0.204***	0.232***
Sex	-0.061*	-0.007
Education	-0.118***	-0.132***

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve models for Memory factor models. [b]From model summarized in Table 4-7; [c]From model summarized in Table 4-8. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified.

Table 4-6. Summary of Growth Model Predicting Memory, Whole Brain WMH Volume, and CVD Relationships (N=1,049)

Variables	Memory Level	Memory Linear Change
Intercept	1.287**	2.615**
Whole Brain WMH	-0.273***	-0.219***
CVD	0.022	0.000
CVD Meds	0.032	0.043
CVD x CVD Meds	0.038	0.002
Race		
Black/AfAm	0.066	-0.084
AAPI	0.018	-0.012
White	0.025	-0.222
Hispanic	-0.023	0.049
Age	-0.220***	-0.208***
Sex	0.115***	-0.024
Education	0.08*	-0.121*
Model Fit Statistics		
AIC	11220.854	
BIC	11453.09	
RMSEA	0.046	
CFI	0.974	
TLI	0.962	
χ^2 (df)	218.965*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-7. Summary of Growth Model Predicting Attention, Whole Brain WMH Volume, and CVD Relationships (N=1,049)

Variables	Attention Level	Attention Linear Change
Intercept	0.586	0.809
Whole Brain WMH	-0.246***	-0.223**
CVD	-0.048	-0.038
CVD Meds	0.019	0.042
CVD x CVD Meds	-0.002	0.073
Race		
Black/AfAm	-0.006	0.051
AAPI	-0.039	0.005
White	0.034	-0.098
Hispanic	-0.212***	0.111
Age	-0.138***	-0.15*
Sex	0.086**	0.092
Education	0.159***	-0.097
Model Fit Statistics		
AIC	8681.39	
BIC	8913.626	
RMSEA	0.034	
CFI	0.983	
TLI	0.975	
χ^2 (df)	149.147*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-8. Summary of Growth Model Predicting Executive Function, Whole Brain WMH Volume, and CVD Relationships (N=1,049)

Variables	Executive Function Level	Executive Function Linear Change
Intercept	1.840***	0.545
Whole Brain WMH	-0.291***	-0.288***
CVD	-0.009	0.03
CVD Meds	0.03	0.012
CVD x CVD Meds	0.013	0.026
Race		
Black/AfAm	-0.052	-0.035
AAPI	-0.018	-0.090
White	-0.024	-0.215
Hispanic	-0.153***	0.093*
Age	-0.246***	-0.072
Sex	0.094**	0.043
Education	0.113***	-0.126***
Model Fit Statistics		
AIC	8510.267	
BIC	8742.503	
RMSEA	0.052	
CFI	0.975	
TLI	0.963	
χ^2 (df)	263.002*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-9. Summary of Growth Model Predicting Language, Whole Brain WMH Volume, and CVD Relationships (N=1,049)

Variables	Language Level	Language Linear Change
Intercept	1.450**	0.784
Whole Brain WMH	-0.283***	-0.219***
CVD	0.013	0.004
CVD Meds	0.036	0.034
CVD x CVD Meds	0.049	0.053
Race		-0.039
Black/AfAm	0.034	
AAPI	0.009	-0.006
White	0.033	-0.188
Hispanic	-0.082*	0.05
Age	-0.232***	-0.112*
Sex	0.100**	0.038
Education	0.093**	-0.073
Model Fit Statistics		
AIC	6741.765	
BIC	6974.001	
RMSEA	0.04	
CFI	0.986	
TLI	0.979	
χ^2 (df)	181.192*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-10. Simple Latent Growth Curve Model Examining Effects of CVD, Medication, and Whole Brain WMH Volume on Memory (N=1,049)

	Memory Level	Memory Linear Change	Whole Brain WMH	CVD
Intercept	-0.398***	-0.0345***	-	-
Whole Brain WMH	-0.370***	-0.290***	-	-
CVD	0.012	0.034	0.136***	-
CVD Meds	-0.006	0.014	0.045	0.536***
CVD x CVD Meds	0.065*	0.041	-	-
Model Fit Statistics				
AIC	9158.060			
BIC	9252.217			
RMSEA	0.000			
CFI	1.000			
TLI	1.001			
χ^2 (df)	35.551 (41)			

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from basic latent growth curve model without covariates. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-11. Simple Latent Growth Curve Model Examining Effects of CVD, Medication, and Whole Brain WMH Volume on Attention (N=1,049)

	Attention Level	Attention Linear Change	Whole Brain WMH	CVD
Intercept	-0.300***	-0.794***	-	-
Whole Brain WMH	-0.312***	-0.267***	-	-
CVD	-0.085	0.034	0.136***	-
CVD Meds	-0.005	0.014	0.045	0.536***
CVD x CVD Meds	0.008	0.041	-	-
Model Fit Statistics				
AIC	11642.037			
BIC	11736.194			
RMSEA	0.034			
CFI	0.991			
TLI	0.990			
χ^2 (df)	91.727*** (41)			

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from basic latent growth curve model without covariates. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-12. Simple Latent Growth Curve Model without Covariates Examining Effects of CVD, Medication, and Whole Brain WMH Volume on Executive Function (N=1,049)

	Executive Function Level	Executive Function Linear Change	Whole Brain WMH	CVD
Intercept	-0.330***	-0.788***	-	-
Whole Brain WMH	-0.399***	-0.294***	-	-
CVD	-0.040	0.067	0.136***	-
CVD Meds	-0.007	-0.017	0.045	0.536***
CVD x CVD Meds	0.036	0.070	-	-
Model Fit Statistics				
AIC	9094.452			
BIC	9188.608			
RMSEA	0.049			
CFI	0.986			
TLI	0.985			
χ^2 (df)	142.741*** (41)			

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from basic latent growth curve model without covariates. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-13. Simple Latent Growth Curve Model without Covariates Examining Effects of CVD, Medication, and Whole Brain WMH Volume on Language (N=1,049)

	Language Level	Language Linear Change	Whole Brain WMH	CVD
Intercept	-0.399***	-0.827***	-	-
Whole Brain WMH	-0.385***	-0.244***	-	-
CVD	-0.005	0.029	0.136***	-
CVD Meds	-0.004	0.008	0.045	0.536***
CVD x CVD Meds	0.074*	0.093*	-	-
Model Fit Statistics				
AIC	7203.869			
BIC	7298.026			
RMSEA	0.022			
CFI	0.997			
TLI	0.997			
χ^2 (df)	61.501*(41)			

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from basic latent growth curve model without covariates. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-14. Summary of Growth Model Predicting Memory, Deep WMH Volume, and CVD Relationships (N=1,049)

Variables	Memory Level	Memory Linear Change
Intercept	1.625**	2.776**
Deep WMH	-0.249***	-0.244***
CVD	0.013	-0.004
CVD Meds	0.033	0.044
CVD x CVD Meds	0.035	0.002
Race		
Black/AfAm	0.066	-0.094
AAPI	0.017	-0.019
White	0.031	-0.229
Hispanic	-0.024	0.044
Age	-0.25***	-0.217***
Sex	0.099**	-0.036
Education	0.084*	-0.12*
Model Fit Statistics		
AIC	11276.12	
BIC	11508.356	
RMSEA	0.039	
CFI	0.981	
TLI	0.972	
χ^2 (df)	176.83*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-15. Summary of Growth Model Predicting Attention, Deep WMH Volume, and CVD Relationships (N=1,049)

Variables	Attention Level	Attention Linear Change
Intercept	0.920	1.061
Deep WMH	-0.216***	-0.224**
CVD	-0.057	-0.043
CVD Meds	0.02	0.043
CVD x CVD Meds	-0.005	0.073
Race		
Black/AfAm	-0.004	0.045
AAPI	-0.039	0.000
White	0.041	-0.101
Hispanic	-0.213***	0.108
Age	-0.168***	-0.170*
Sex	0.072*	0.079
Education	0.163***	-0.094
Model Fit Statistics		
AIC	8737.567	
BIC	8969.802	
RMSEA	0.023	
CFI	0.992	
TLI	0.988	
χ^2 (df)	105.885*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-16. Summary of Growth Model Predicting Executive Function, Deep WMH Volume, and CVD Relationships (N=1,049)

Variables	Executive Function Level	Executive Function Linear Change
Intercept	0.770***	0.862***
Deep WMH	-0.246***	-0.247***
CVD	-0.020	0.020
CVD Meds	0.031	0.013
CVD x CVD Meds	0.010	0.024
Race		
Black/AfAm	-0.047	-0.032
AAPI	-0.018	-0.092
White	-0.013	-0.206
Hispanic	-0.152***	0.092*
Age	-0.285***	-0.110**
Sex	0.078**	0.027
Education	0.118***	-0.120**
Model Fit Statistics		
AIC	8575.027	
BIC	8807.263	
RMSEA	0.046	
CFI	0.98	
TLI	0.971	
χ^2 (df)	222.322*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-17. Summary of Growth Model Predicting Language, Deep WMH Volume, and CVD Relationships (N=1,049)

Variables	Language Level	Language Linear Change
Intercept	1.850***	1.079
Deep WMH	-0.239***	-0.192***
CVD	0.002	-0.004
CVD Meds	0.037	0.035
CVD x CVD Meds	0.045	0.051
Race		
Black/AfAm	0.04	-0.037
AAPI	0.01	-0.006
White	0.044	-0.181
Hispanic	-0.082*	0.049
Age	-0.270***	-0.139**
Sex	0.084**	0.026
Education	0.097**	-0.07
Model Fit Statistics		
AIC	6807.538	
BIC	7039.774	
RMSEA	0.031	
CFI	0.991	
TLI	0.987	
χ^2 (df)	138.632*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-18. Summary of Growth Model Predicting Memory, Periventricular WMH Volume, and CVD Relationships (N=1,049)

Variables	Memory Level	Memory Linear Change
Intercept	1.351**	2.757**
Periventricular WMH	-0.244***	-0.172**
CVD	0.017	-0.006
CVD Meds	0.033	0.044
CVD x CVD Meds	0.037	0
Race		
Black/AfAm	0.076	-0.07
AAPI	0.021	-0.007
White	0.033	-0.209
Hispanic	-0.02	0.052
Age	-0.23***	-0.226**
Sex	0.117***	-0.024
Education	0.084*	-0.117*
Model Fit Statistics		
AIC	11228.294	
BIC	11460.529	
RMSEA	0.047	
CFI	0.972	
TLI	0.959	
χ^2 (df)	229.881+ (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-19. Summary of Growth Model Predicting Attention, Periventricular WMH Volume, and CVD Relationships (N=1,049)

Variables	Attention Level	Attention Linear Change
Intercept	0.636	0.942
Periventricular WMH	-0.221***	-0.176**
CVD	-0.053	-0.044
CVD Meds	0.020	0.044
CVD x CVD Meds	-0.004	0.070
Race		
Black/AfAm	0.004	0.066
AAPI	-0.036	0.011
White	0.041	-0.083
Hispanic	-0.209***	0.116
Age	-0.146***	-0.168*
Sex	0.089**	0.093
Education	0.162***	-0.093
Model Fit Statistics		
AIC	8686.263	
BIC	8918.499	
RMSEA	0.035	
CFI	0.981	
TLI	0.972	
χ^2 (df)	158.509*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. *$p < .05$; ** $p < .01$; ***$p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-20. Summary of Growth Model Predicting Executive Function, Periventricular WMH Volume, and CVD Relationships (N=1,049)

Variables	Executive Function Level	Executive Function Linear Change
Intercept	1.854***	0.594
Deep WMH	-0.273***	-0.258***
CVD	-0.014	0.024
CVD Meds	0.031	0.014
CVD x CVD Meds	0.012	0.024
Race		
Black/AfAm	-0.042	-0.021
AAPI	-0.016	-0.085
White	-0.017	-0.203
Hispanic	-0.15***	0.096*
Age	-0.251***	-0.081
Sex	0.098**	0.047
Education	0.116***	-0.124**
Model Fit Statistics		
AIC	8516.196	
BIC	8748.432	
RMSEA	0.054	
CFI	0.973	
TLI	0.961	
χ^2 (df)	273.926*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 4-21. Summary of Growth Model Predicting Language, Periventricular WMH Volume, and CVD Relationships (N=1,049)

Variables	Language Level	Language Linear Change
Intercept	1.468***	0.851
Periventricular WMH	-0.264***	-0.190***
CVD	0.008	-0.001
CVD Meds	0.037	0.035
CVD x CVD Meds	0.048	0.052
Race		
Black/AfAm	0.043	-0.029
AAPI	0.011	-0.003
White	0.038	-0.179
Hispanic	-0.08**	0.052
Age	-0.237***	-0.122**
Sex	0.104**	0.04
Education	0.096**	-0.07
Model Fit Statistics		
AIC	6746.274	
BIC	6978.51	
RMSEA	0.042	
CFI	0.984	
TLI	0.977	
χ^2 (df)	193.051*** (69)	

Note. Table contains parameter estimates (standardized b-weights) and approximate *p*-values from final latent growth curve model. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$. Abbreviations: Level = intercept; Linear = linear change; WMH = white matter hyperintensity volume; CVD = baseline summation of vascular risk factors and cardiovascular disease; CVD Meds = total number of medications used to treat CVD; Age = baseline age in years; Sex = Man, Woman; Education = 0-12 years; 13+ years; Race = dummy-coded race variables; White = white; Black/AfAm= Black/African American; AAPI = Asian, Hawaiian Native/Pacific Islander; Reference is Other = American Indian/Alaskan Native, Other unspecified; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; RMSEA = Root-Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index

Table 4-22. Summary of Baseline and Incident Vascular Risk Factors and Cardiovascular Disease on Cognitive Level and Rate of Change (N=22,684)

	Memory Level	Memory Slope	Attention Level	Attention Slope	Executive Function Level	Executive Function Slope	Language Level	Language Slope
Vascular Risk Factors								
Obesity at BL	0.047***	0.063***	0.004	0.085***	0.020	0.083***	0.037**	0.073***
Obesity after BL	0.031*	0.046*	-0.006	0.029	0.028*	0.040*	0.034**	0.053***
Diabetes at BL	-0.062***	-0.035	-0.080***	0.006	-0.079***	-0.008	-0.063**	-0.005
Diabetes after BL	0.022	0.043	-0.026	-0.002	-0.008	0.040	0.005	0.036
High Cholesterol at BL	-0.045**	-0.007	-0.022	0.021	-0.026*	-0.027	-0.039**	-0.037*
High Cholesterol after BL	0.032*	0.011	0.007	-0.041	0.020	0.029	0.034**	0.048**
Current Smoker at BL	-0.021	-0.012	-0.019	-0.013	-0.028*	0.000	-0.025*	-0.021
Current Smoker after BL	0.015	0.007	0.001	-0.007	0.010	0.017	0.017	0.029*
Smoking History at BL	0.068*	0.042	0.0108	0.070	0.073*	0.000	0.077**	0.035
Smoking History after BL	-0.04	-0.039	-0.063	-0.091	-0.054	0.000	-0.056	-0.039
Systolic Hypertension at BL	-0.083***	-0.066***	-0.089***	-0.045***	-0.097**	-0.050***	-0.090***	-0.049***
Systolic Hypertension after BL	0.050***	0.040**	0.027**	0.002	0.049***	0.045***	0.057***	0.059***
TIA History at BL	-0.013	-0.003	-0.006	-0.006	-0.013	0.018	-0.013	0.032*
TIA History after BL	-0.039**	-0.063**	-0.051***	-0.067**	-0.071***	-0.067***	-0.053***	-0.073***
Stroke History at BL	-0.037**	0.006	-0.050**	-0.046	-0.047***	0.047**	-0.045***	0.022
Stroke History after BL	-0.058***	-0.086*	-0.005	-0.036	-0.105***	-0.085***	-0.081	-0.076***
Cardiovascular Disease								
Heart Attack History at BL	-0.036*	0.002	-0.050**	-0.046	-0.042**	-0.031	-0.044**	-0.027
Heart Attack History after BL	-0.00	-0.041	-0.005	-0.036	-0.021	-0.011	-0.005	-0.009
Heart Failure History at BL	-0.027*	0.012	-0.032**	0.007	-0.033**	0.001	-0.030**	0.006
Heart Failure History after BL	-0.004	-0.044**	-0.020	-0.037	-0.047***	-0.027	-0.019	-0.014
Atrial Fibrillation History at BL	-0.065***	-0.016	-0.044***	-0.012	-0.062***	-0.013	-0.061**	-0.027
Atrial Fibrillation History after BL	0.048***	-0.022	0.042**	-0.049*	0.019	-0.031*	0.039**	-0.009

Note. * p < .05, ** p < .01, *** p < .001. For each risk factor/diagnosis, baseline and post-baseline measures were entered simultaneously, so the post-baseline association can be considered the association of incident disease/risk. Values shown represent standardized regression weights. Cognitive measures were included as regression-based factor scores derived from unconditional growth models. Abbreviations: Slope = linear slope; BL = baseline; TIA = transient ischemic attack.

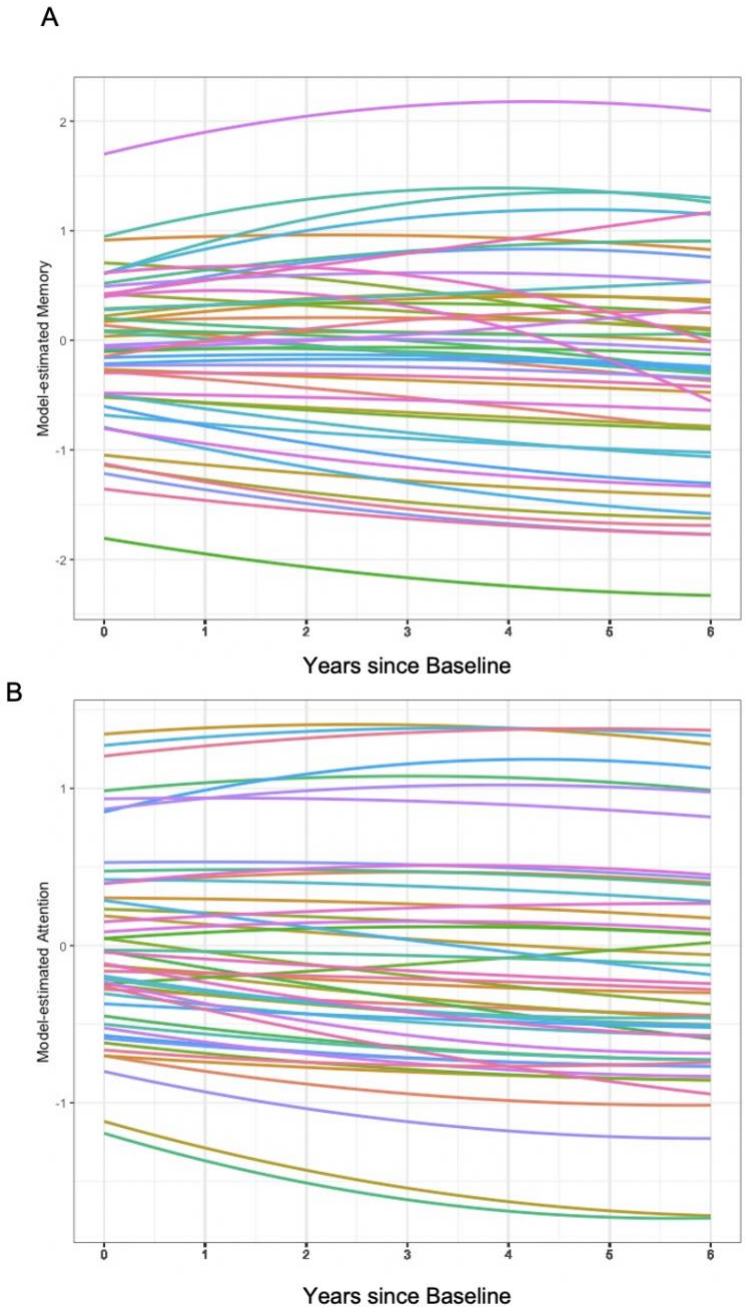


Figure 4-1. Model-implied trajectories of cognitive change from unconditional growth models. X-axes: Occasion; Y-axes: Cognitive factor in Z-score (Blom normalized) metric (N=50, random subset for ease of plotting).

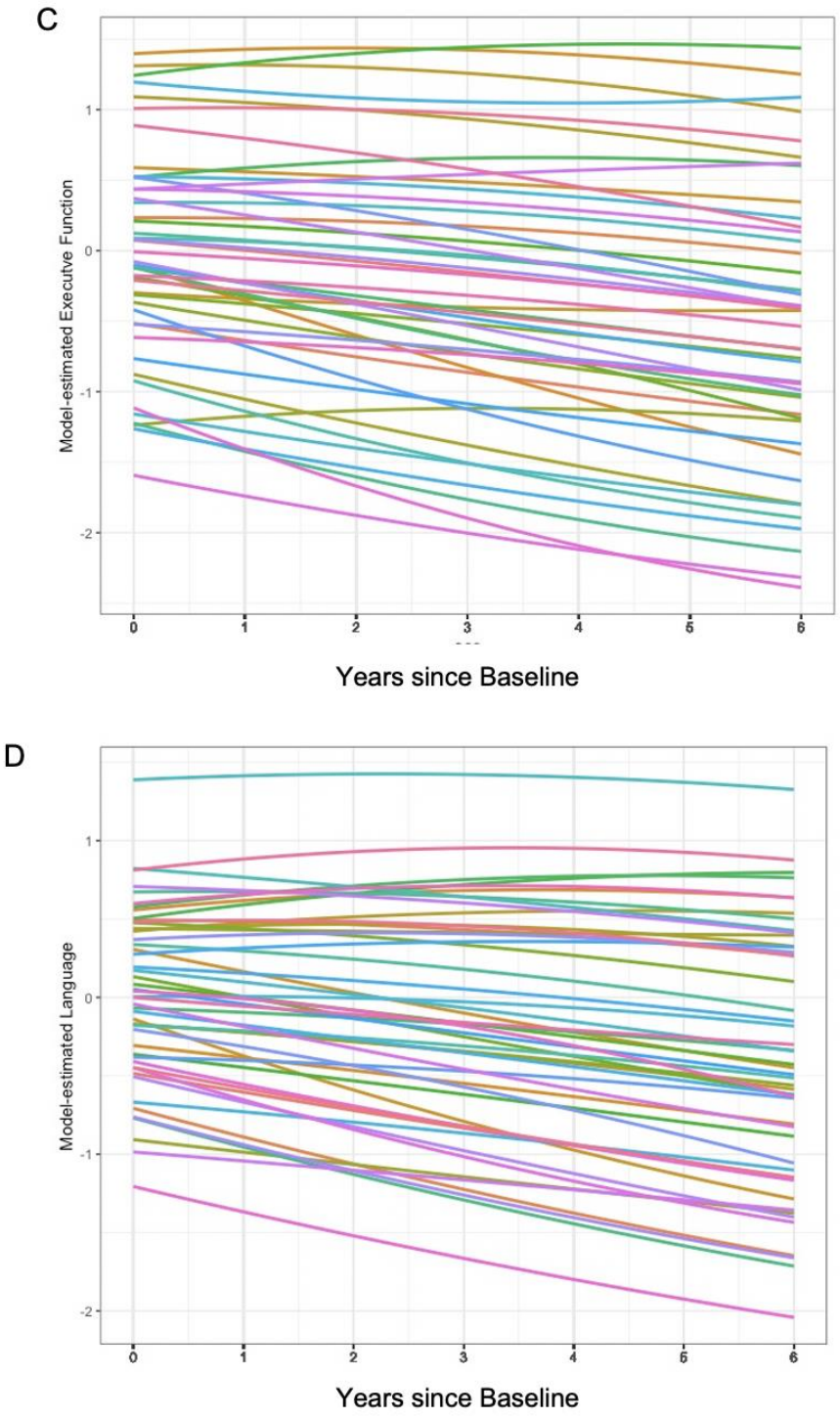


Figure 4-1. Continued.

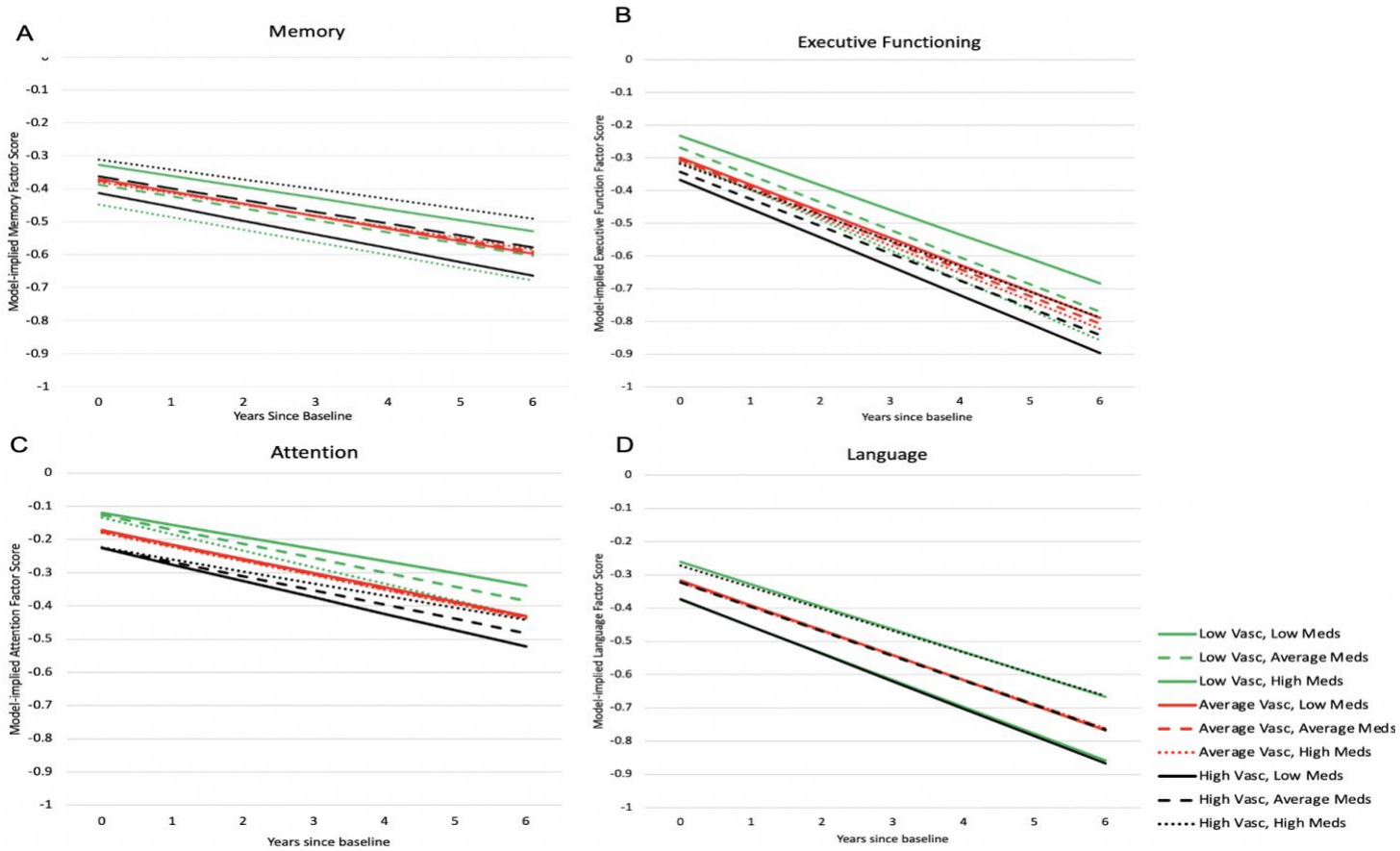


Figure 4-2. Decomposing the interaction between cardiovascular risk and medication use in simple latent growth models. X-axes: Year since Baseline; Y-axes: Model-implied cognitive factor in Z-score (Blom normalized) metric, N=1,049.

CHAPTER 5
DISCUSSION

This chapter is organized into four sections. First, we review key findings regarding the study aims and post-hoc analyses. Second, we consider the theoretical and conceptual implications of the findings. Third, we review specific advantages and limitations of the NACC data set to answer the questions explored herein. Fourth, we consider big picture conclusions that might be drawn from the study, along with potential future directions suggested by the results of this study.

Key Findings

This present study was conducted to examine the overarching relationships between vascular risk factors/cardiovascular disease (CVD) and its treatment (CVD medication) on cognition and cognitive decline in a large sample of older adults. This study also endeavored to explore these relationships with the inclusion of brain-based indicators of vascular insult, as measured by white matter hyperintensity (WMH) volume. Important features of this study included the use of time-varying associations between CVD, treatment, and cognition, as well as the inclusion of WMH volume within our models. To our knowledge, no studies to date have examined the time-varying associations between expanding medication regimens and CVD risk on cognitive decline trajectories in an older adult population. Furthermore, few studies have examined clinic-derived CVD risk variables, pharmacological treatment, and vascular neuropathology measures in tandem on cognition and decline trajectories in elders. Findings provide both support for known relationships and new insights into the complex interplay between CVD, treatment, WMH burden, and cognitive decline. Key findings of the current study are described below.

Mixed support for the negative effects of concurrent CVD on overall cognition and cognitive decline. It was hypothesized that higher overall level and greater longitudinal increases in CVD would be associated with poorer overall level and greater declines in cognitive abilities over time, and that these associations would be strongest in Attention and Executive Function domains. These hypotheses were directionally supported, however we found no significant associations between level/rate of change in CVD with level/rate of change in either Language or Memory domains (supporting the stronger association of CVD with Executive Function and Attention). Specific to Executive Function, while we failed to find a significant association between higher overall level of CVD on change in Executive Function over time, we did find that greater linear increases in CVD over time were associated with greater linear declines. The important caveat here is effect sizes were uniformly low. The largest standardized b-weight was observed between overall level of CVD and linear decline in Attention (b=-0.068), and the smallest b-weight that was still statistically significant was observed between overall level of CVD and overall level of Attention (b=-0.024), suggesting very weak unique relationships (after all covariates had been accounted for).

While these findings support the known association between CVD and their negative effects on cognition, when white matter hyperintensity (WMH) volume was also included in our models, we found no significant remaining unique direct associations between baseline CVD on level or rate of change across all four cognitive factors. Instead, we found support suggesting that CVD had small, but significant, *indirect* effects on overall level of Memory, Attention, Executive Functioning and Language.

Whole brain WMH volume served as the mediator of this relationship, as it did for an indirect effect of baseline CVD on rate of decline in Memory and Executive Function.

The effects of CVD medication use on cognition were inconsistent across cognitive outcomes. Based on the premise that pharmacological treatment of CVD should theoretically reduce the negative cognitive sequalae of CVD, it was hypothesized that greater CVD medication use would be associated with better overall cognitive performance and less decline. The results varied across outcomes.

In models where we considered relationships without the inclusion of WMH burden, greater overall CVD medication use was associated with better overall performance across Memory, Executive Function, and Language domains, along with reduced linear declines in Executive Function and Language, and deceleration in rate of decline in Memory and Attention at later waves. Furthermore, greater linear increases in CVD medication over the 6-year period were associated with greater overall level and less linear decline across all four cognitive domains, as well as decelerated decline in Memory at later waves. Taken together, these findings are suggestive of a potential benefit of CVD treatment on cognition and cognitive trajectories in late life.

We found no indirect effects of CVD medication use on cognition through CVD (i.e., that the route of action might be for medications to be associated with less cardiovascular disease, which in turn is associated with better cognition). In part, this may be because diagnoses would continue to be endorsed (e.g., hypertension) even after they are treated.

In models where we explored these relationships with the inclusion of WMH burden (representing a sample size reduction from over 22,000 participants to 1,049

participants), no significant direct or indirect effects were found between baseline CVD medication use and overall level or rate of change across all four cognitive factors, likely in part due to the lack of power to detect such small effects. Likewise, potential moderating effects of CVD medication use on the relationship between CVD and cognition were small, and only found when we explored such associations in models without the addition of any covariates. When decomposed, the interaction between CVD and medications found a complex miss-match between disease and treatment. Lower overall level and greater rate of were observed for both Memory and Language domains for both older adults who had (a) low CVD and high medication use and for older adults with (b) high CVD but fewer medications. Conversely, higher overall level and slower rates of decline in Memory and Language were observed for older adults with higher CVD and higher medication use, as well as those with low CVD and taking few medications. While these associations were small, findings suggest potential benefits of adequate treatment, but also highlight potential negative cognitive consequences for both under-treated and over-treated older adults.

Higher CVD risk is associated with greater WMH burden. This study also found significant associations (but small – range of significant associations was 0.092 to 0.116) between higher CVD risk and greater vascular neuropathology, as measured by whole brain WMH volume.

In follow-up analyses, we further examined whether CVD and cognitive measures might be differentially related to subcortical deep WMH (which are thought to represent more ischemic/chronic hypoxic damage(Fernando et al., 2006), versus periventricular WMH (which are believed to be of nonischemic metabolic and/or

inflammatory origin; (Fazekas et al., 1993; Griffanti et al., 2018). Owing in part to the strong association between deep and periventricular WMH in this study (r=0.72) higher WMH burden in both deep and periventricular regions were similarly related to CVD measures and cognitive outcomes, with no clear evidence of stronger relationships with one or the other.

Overall cognition and trajectory of change is affected by greater WMH burden. We expected, based on previous studies, that higher WMH burden should be associated with poorer cognition, particularly in areas of attention and executive function. Consistent with this expectation, whole brain, deep, and periventricular WMH burden were all negatively correlated with the overall level of our four cognitive constructs as well as with greater 5-year linear declines across Memory, Attention, Executive Function, and Language.

Individual vascular risk factors/cardiovascular disease show differential associations with cognition and rate of change, but these unique effects are small. Follow-up analyses examined the association of individual vascular risk factors and cardiovascular conditions with cognitive level and slope, further breaking these CVD variables into baseline versus incident disease. Several observations emerged: (a) First, many risk and disease factors occurred with relatively low frequency: Current smoking, TIA, stroke, heart attack, heart failure and atrial fibrillation all occurred in less than 10% of the sample; thus, range restriction may have suppressed correlations; (b) Obesity, diabetes, high cholesterol, smoking history and systolic hypertension, however, occurred with high frequency in the sample (13-53%), yet relationships were not much stronger with any of the cognitive constructs. No single standardized b-weight was even

as large as |0.1| and separate inspection, not shown, confirmed that this was also true for simple bivariate correlations.

Theoretical and Conceptual Considerations

The literature review introduced several theoretical and conceptual ideas that informed the study specific aims. This next section briefly considers how findings from this study might extend extant literature and our understanding of the relationships between cardiovascular risk factors/disease, its pharmacological treatment, neuropathology of presumed vascular origin, and cognitive decline.

Consistency with prior research. Significant negative relationships between higher CVD and poorer overall Attention and Executive Function and decline were generally consistent with and extend findings from prior studies (Jefferson et al., 2015; Kaffashian et al., 2013; Samieri et al., 2018). While we did not find significant associations between overall CVD level on rate of change in Executive Function (which other studies have previously supported), we did however observe that greater increases in CVD risk in late-life evinced greater linear declines in Executive Function over a 6-year period. Given that fronto-parietal networks are highly susceptible to vascular insults in healthy aging (Veldsman et al., 2020), it is no surprise that increasing CVD burden in late-life would be most deleterious in the Executive Function domain in a heterogenous sample of older adults. While direct relationships between baseline CVD and cognition no longer remained after inclusion of baseline WMH volume, small, but significant indirect associations between CVD risk and cognition through WMH were observed, with WMH volume serving as mediator. While one cannot make causal assertions from mediation models in the absence of strict rules for causal inference (Pearl, 2010), the results are suggestive that some of the effect of CVD on late life

cognitive level and change may be by increasing WMH burden, which in turn is associated with poorer overall level and greater declines in cognition.

Congruent with previous literature, this study found strong associations between CVD risk and greater WMH burden (Francesco Moroni et al., 2018). However, unlike other studies, these associations were also found even after controlling for the potential effects of baseline CVD treatment. Additionally, these findings were not only true for whole brain WMH, but similar associations were also found for deep and periventricular regions. We also found similar patterns of associations between whole brain WMH burden and our cognitive constructs as demonstrated in previous studies (Arvanitakis et al., 2016; Boyle et al., 2016; F. M. Gunning-Dixon & Raz, 2003; Puzo et al., 2019). For example, a large meta-analysis of 23 cross-sectional and 14 longitudinal studies examining the associations between WMH burden across cognitive domains found small, yet significant effects of WMH burden on all cognitive domains, which was consistent with our findings (Kloppenborg et al., 2014). Similarly, effect sizes were within comparable range to those derived meta-analytically.

While prior research has demonstrated differential associations between progression of deep versus periventricular WMH on decline in MMSE, global cognition and processing speed (van Dijk et al., 2008), this study found that both deep and periventricular WMH were both associated with poorer cognitive outcomes across domains. While deep and periventricular WMH are believed to represent differential etiologies (Griffanti et al., 2018), the emergence of similar relationships across cognitive constructs may represent age-associated reductions in representations at the neural level, also known as *dedifferentiation* (S.-C. Li, Lindenberger, & Sikström, 2001). Due to

dedifferentiation, profiles of previously observed strengths and weaknesses that used to distinguish abilities (e.g., strong attentional abilities, but poorer semantic retrieval) break down, and the correlations among domains become stronger and stronger (as we found in our correlations across cognitive domains). As we age, our brain tends to recruit additional regions to compensate. Further described by Cabeza (2002), hemispheric asymmetry reduction in older adulthood (HAROLD) leads to more bilateral recruitment, especially in frontal and parietal regions to support increasing task demands (Huang, Polk, Goh, & Park, 2012). Age-associated reductions in white matter and increases in white matter hyperintensity volume decrease interneural signal transduction speed (F. M. Gunning-Dixon & Raz, 2000) and likely contribute, at least partially, to the increased recruitment of additional compensatory regions. Cognitive reserve likely plays a protective role as well, though we did not explore the interactive effects of education and WMH on cognition in this study. As such, dedifferentiation may explain, at least in part, similar patterns of associations of cognitive constructs with regional and whole brain WMH burden.

No direct or indirect relationships between treatment and CVD risk when we controlled for the effects of vascular neuropathology through inclusion of WMH volumes, though moderation yielded interesting findings. Literature regarding the interrelationships between vascular risk/cardiovascular disease, treatment, WMH, and cognitive decline are limited and inconclusive. As such, findings from this study add to this small, but developing body of literature. Notably, when vascular neuropathology wasn't considered, more treatment of vascular risk factors and cardiovascular disease was associated with better overall cognitive performance,

reduced cognitive decline, and less acerated decline at later waves. Thus, in general, this argued for a protective effect of cardiovascular medications, with the caveat of low effect sizes (range of significant standardized b-weights was 0.034 to 0.116). Nonetheless, when we included (and controlled for) the effects WMH in our models, there were no direct or indirect associations observed between baseline CVD, treatment, and cognitive change. This null finding suggests that while treatment may affect cognition though other potential mechanism (i.e., reductions in neuroinflammatory processes, decreased oxidative stress, improved cerebrovascular perfusion) we failed to find substantial support for positive benefit of treatment on WMH burden in an older adult population. This finding, however, isn't entirely surprising. Notably, relationships between cardiovascular burden, treatment, and WMH volumes were only explored between baseline predictors so we could not explore more time-varying associations between disease onset and accumulation of WMH burden. It is likely that treatment of underlying vascular risk factors and cardiovascular conditions are more neuroprotective in earlier periods prior to onset of older adulthood and before the onset of other neurodegenerative processes including Alzheimer's disease (AD) pathology (D. Kim et al., 2020; Lennon, Makkar, Crawford, & Sachdev, 2019; McGrath et al., 2017).

The lack of direct and indirect associations between CVD, treatment and cognition are further qualified by small, but significant interaction found between CVD and treatment when we removed additional covariates from the model. This complex interaction found that a mismatch between level of disease and treatment put individuals at elevated risk for lower cognitive level and increased cognitive decline. Specifically, (1) low CVD risk/low treatment and high CVD risk/high treatment were

associated with higher overall level and slower rates of decline in Memory and Language while, (2) lower CVD risk/high treatment and high CVD risk/low treatment was associated with poor overall Memory and Language and steeper rates of decline.

These mismatch findings are somewhat consistent with previously mixed findings; excess or inappropriate treatment in some instances may have iatrogenic consequences (fueling the geriatric deprescribing movement) *and* there are likely potential negative consequences of undertreatment in older age (Krishnaswami et al., 2019). It should also be noted that the majority of literature supporting treatment effects comes from exploration of treatment of hypertension in cognitively normal (or free of dementia) populations (Gottesman et al., 2017; Gottesman et al., 2014; Gupta et al., 2020). As such, our current study was likely more cognitively diverse and older than previous and likely experienced greater mixed pathologies contributing to differential effects of treatment of underlying CVD.

Use of self-report of medical conditions may have reduced reliability and validity of diagnoses and attenuated associations with CVD composite. As discussed in *Literature Review*, numerous studies have found relationships between vascular risk factors/cardiovascular condition and cognitive decline/dementia. While associations are generally in the moderate range, associations found within this study when exploring the unique relationships between CVD and individual CVD predictors were smaller than expected. One potential reason for this finding may have been due to the inclusion of both recent/active (i.e., if any conditions required active management and/or medication) and remote/inactive (i.e., existed at least a year prior, but not currently treated) history for conceptualization for numerous vascular risk factors and

cardiovascular conditions. In doing so, simple diagnosis likely masked the underlying range of severity of each risk factor and disease. Furthermore, due to treatment considerations in determination of “active” disease, our ability to distinguish unique and interactive effects of CVD treatment may have also been attenuated. In addition, in this data set, information about health conditions was generally taken from history interviews with participants and/or their proxies, and not from objective laboratory values or medical record abstracts. Known biases to self-report (van Berkel et al., 2020) and proxy report (Gruters et al., 2019; Seebauer, Fleiß, & Schweighart, 2017) could further have reduced reliability and validity of cardiovascular health data, though there is some evidence to suggest, specific to cardiovascular health measures, that self-report has good sensitivity and specificity when compared with “gold standard” biomedical examination (Kivimäki et al., 2017).

Positive selection likely contributed to null findings with CVD. This study leveraged data collected at Alzheimer’s disease Research Centers from across the United States. While participants are usually identified through neurology or other medical referral, recruitment of cognitively normal older adults may involve the inclusion of caregivers or community-dwelling older adults interested in research participation. The sample also likely consists of an overrepresentation of older adults with Alzheimer’s disease (AD), that may be in nature, less susceptible to vascular effects compared to older adults with mixed or vascular dementia. As such, it is likely that certain recruitment factors may have influenced the generalizability of our sample as are indications that the current sample may have been positively selected with regards to AD and health factors. For example, the prevalence of diabetes in this sample was 13%, which is half

the rate (26%) in population of American adults over 65 years (CDC, 2017). Prevalence of obesity in the sample was 21%, which is substantially less than the 35% estimated in the population of adults 65+ (Fakhouri et al., 2012). Hypertension was substantially lower in this sample (36.5%) than in epidemiological representative samples (70% of those over 65 years of age) (Benjamin et al., 2019). Only two of the vascular risk factors had prevalence roughly similar to what would be expected based on past research. High cholesterol was recorded for 53% of participants and history of smoking (45%) were both roughly consistent with population estimates. (Félix-Redondo et al., 2013) These last comparisons raise the question of whether the NACC sample has a lower rate of cardiovascular burden than one might expect in a truly representative sample, and whether this might have attenuated relationships.

Along with health variables that may have contributed to a positive selected sample, there was additional support for positively biased sample due to higher educational attainment than compared to the population. Within the NACC sample, at baseline approximately 50% of the sample had almost an undergraduate degree (15 years of education). Furthermore, approximately 79% of the sample had a high school education (including technical school, community college, and so forth), and 47% of the sample had at least a bachelor's degree or higher. When compared to population-based estimates, our sample had 16% more elders with bachelor's degree or higher, supporting a positively biased sample within NACC (Services, 2019).

In addition, survivor bias may constrain and further attenuate variability. There are several components to this. First, in all longitudinal studies, the remaining sample in a longitudinal study tends to be healthier and more positively selected as time goes on,

reflecting both active dropout and selective mortality. But, more generally, the selection criteria for the ADRCs tend to be more focused on identifying either participants with existing impairment, or control participants who are free of impairment. These control participants are likely to increase the representation of positively selected survivors who may convert to cognitive impairment at lower rates than in the population overall.

Positive Study Design Features

Prior to consideration of the limitations of this study, it is important to enumerate several ways in which this study attempted to address gaps raised by previous literature, along with unique considerations of the study. *(1) More comprehensive cognitive battery than many previous studies.* As discussed extensively in the *Literature Review*, numerous studies have explored the relationships between vascular risk factors, cardiovascular disease, WMH burden, on cognition. However, while many studies exploring cognitive change rely on cognitive screening tools, such as the MMSE to serve as proxy for global cognition, this study utilized a comprehensive neuropsychological battery. *(2) Inclusion of pharmacological treatment as effect modifier.* Many studies neglect to explore the unique effects of treatment, or only explore treatment effects when examining individual risk factors (e.g., antihypertensive treatment of hypertension). *(3) Longitudinal models and correlated change.* Few studies to date have explored the effects cardiovascular risk, treatment, and WMH on cognitive decline trajectories within the same model. We believe our analytic approach was a particular strength as it allowed for us to explore the complex interplay between these variables of interest while also controlling for the potential effects of one another. While other studies have explored cognitive trajectories of change, this study also included exploration of time-varying associations of not just cognition, but also medication and its

treatment. Additionally, we believe the inclusion of moderation and direct/indirect paths via mediation was a value-added component of this study, as it allowed for us to explore additional pathways of association.

Limitations and Future Directions

Limitations of the vascular risk and cardiovascular health variables. One area of criticism of the current study that we were unable to overcome was the lack of information about duration, severity, or age of onset of vascular risk factors and their associated treatment. While we attempted to elucidate the compounding effects of both remote/inactive and recent/active disease states, were unable to fully quantify each person's true level of disease burden, which would have required laboratory values and clinical data. This is a common challenge in large, multisite, longitudinal studies. Future studies may benefit from the inclusion of questionnaires surveying not only if the risk factor of interest was present in the past, but age of onset, as this would help bolster the utility of late-life self-report measures. In addition, corroboration of disease onset and duration could be accomplished through the use of the electronic medical record and/or Medicare data which provided more precise measurement of chronicity of disease states. This also serves to highlight the need for aging research to begin observation of health and other factors prior to late life. As demonstrated in our review of the literature, associations between vascular risk factors and cardiovascular conditions tend to be stronger predictors of later life cognition when they emerged within midlife. The importance of understanding sensitive time points when treatment and/or additional interventions may be most beneficial cannot be understated. Without this understanding we are unable to precisely address the best course of actions for both older adults cardiovascular, but also cognitive health.

Use of a composite measure of cardiovascular risk/disease may have constrained our ability to find unique associations between treatment, WMH burden, and cognitive decline. Another unique consideration of our study was the use of a cardiovascular risk composite. CVD composites are used throughout the research world to explore the cumulative effects of multiple VRFs/disease states on various outcomes of interest (R. B. D'Agostino, Sr. et al., 2008; Harrison et al., 2017). Given that older adult populations are more likely to have multiple vascular health challenges, we felt the inclusion of a composite variable in lieu of individual risk factors would provide a more real-world estimate of vascular burden on the aging brain and cognition. Similar challenges emerged for conceptualization of treatment effects (as this was also a composite variable of different categories). Nonetheless, problems arise with the use of an overall index, as it can wipe out effects of specific individual risk factors that may be more contributory to cognitive changes. It is worth noting that in this study, the composite index had more variability than single disease indicators, and thus tended to have stronger relationships than seen with single factors. The composite also allowed us to examine change in overall cardiovascular disease via growth modeling. Studies exploring univariate associations between individual risk factors and cognitive decline without the inclusion of other vascular risk factors may also be problematic, as vascular risk and cardiovascular conditions do not act upon the brain in a vacuum. However, given recent findings regarding positive benefit of treatment of hypertension in mid-life (Gottesman et al., 2017), future studies will focus specifically on antihypertensives for hypertension on WMH burden and cognitive decline in an aging sample.

Positively selected sample and self-report. In both sample size and heterogeneity, the current sample exceeds that of many other investigations in this content domain. Nonetheless, a factor that may have contributed to our lower relationships between CVD and cognition may have been due to positive selection bias present in the sample (e.g., healthier older adults than expected) and with higher educational attainment than the general population. In addition, healthy controls within NACC may represent a positively selected convenience sample (e.g., spouses of enrolled participants with cognitive impairment). As such, propensity methods may be needed to construct a sample that better mirrors the demographic characteristics of the parent population and should be explored in future studies.

In addition to positive selection bias, we cannot rule out the fact the specific vascular risk factors and cardiovascular conditions may be more important than cumulative/overall burden on WMH burden and cognitive trajectories (e.g., Guo et al., 2020). This study also relied on self-report measures, which as described above, may produce unreliable estimates of disease. Inclusion of blood-based measures (e.g., lipid profile, glucose, hormone levels, LDL/HDL ratios) or more precise biomarkers of cardiovascular and metabolic factors (e.g., VO2 max, ejection fraction, central adiposity) would have improved reliability of the cardiovascular construct but were not feasible for a large, multisite study.

Use of a cognitively diverse sample is a double-edged sword. This study examined relationships of interest in a large sample of older adults with varying cognitive abilities at baseline and throughout the study. Cognition ranged from unimpaired, through severely impaired (indicative of late-stage dementia) at baseline.

While we chose to initial explore these relationships this way to improve potential generalizability of observed relationships, in doing so, our cognitive outcome variables likely suffered floor effects (as shown in unconditional growth slopes). These floor effects in turn likely limited our ability to detect more subtle relationships between our variables of interest on cognitive decline trajectories, as well as make more definitive statements regarding these relationships for a more cognitively health population at advanced age. Future analyses will explore primary study aims within a sample of cognitively normal older adults at baseline. Doing so will better allow us to understand how cardiovascular risk and treatment effect decline, as well as better understand if greater WMH burden in a cognitively health sample at baseline is predictive of poorer cognitive outcomes. In addition, to exploration of these relationships on adults who are cognitively normal at baseline, future studies will also investigate whether consensus-conference based diagnostic categories (instead of decline trajectories) are more sensitive to cardiovascular risk, treatment, and WMH burden.

Limited follow-up data at later waves despite large sample. This study originally endeavored to explore cognitive trajectories across 10 annual waves of data to better understand cognitive decline in late life. Despite starting with over 22,000 older adults at baseline, we were unable to explore trajectories of change beyond 5-6 years due to significant attrition (approximately 600 cases at wave 10). Despite our use of full-information maximum likelihood estimation, we were unable to find statistically identifiable solutions that could converge (according to conventional maximum likelihood criteria) for growth models with longer follow-up. While signification sample attrition isn't unique to the NACC, it is indeed a considerable hurdle for aging and

dementia research. It is important to add that this attrition is not so much a failure of good clinical practice/research methods, but an inherent issue in samples with advanced age and neurodegenerative disease.

Use of only whole brain, deep, and periventricular regions to explore WMH relationships. Given the focused nature of this dissertation and parent NRSA fellowship, this study chose to explore only whole brain, and subsequently deep and periventricular WMHs due to their frequency in the literature with cognitive and cerebrovascular associations. Nonetheless, through processing FLAIR/T1 MRIs, we also in the processing quantified hemispheric and regional specific WMH volumes. We also were able to quantify focal, medium, punctate, and confluent WMH clusters which may be of interest in future studies due to their differential associations with various pathologies. It would also be interesting to see whether white matter intensities could be grouped across regions of interest that conform to common white matter tracts or functional networks, and whether such a grouping could reveal stronger and more specific relationships with cognition. This would likely require a re-engineering of the UBO detector algorithm used in this study.

More refined methods to mediation analysis may be more appropriate for future studies. While we explored whether vascular neuropathology (WMHB) served as a potential intervening pathway from which CVD effects cognitive decline, we acknowledge the potential limitations of mediation with cross-sectional data (O'Laughlin, Martin, & Ferrer, 2018). To better control for potential confounders, future studies should explore the utility of (a) cross-lagged dual-change method; and/or (b) directed acyclic graphs (DAGs) to either augment and/or replace mediation modeling. Bivariate

dual-change score modeling is employed when examining two changing constructs, or to examine effects from prior change on subsequent trajectories (Grimm, An, McArdle, Zonderman, & Resnick, 2012). This method may be employed to examine time-varying CVD and cognition. DAGs look similar to path models but are more general models of non-parametric SEMs. They have been shown to be particularly useful modeling whether associations are spurious or causal and thus may be a more appropriate means for our stated analyses than classical mediation (Elwert, 2013).

Unique neuroimaging considerations. The multisite nature of this study meant that neuroimaging protocols and scanner type varied across participants. While UBO Detector has been validated across various scanner types and scan qualities, it is possible that site/scanner variable did introduce potential unmeasured bias within our results. Furthermore, while UBO Detector uses DARTEL space and theoretically does not require corrections for total intracranial volume (ICV), doing so may produce more unique associations between WMH burden irrespective of overall head size. While this study did include the inclusion of total ICV in supplementary models (with similar findings), doing so substantially reduced our sample size due to ICV being previously quantified (and thus certain cases we were able to run were missing ICV totals). There are also unknown selection factors that may have drove who underwent neuroimaging (e.g., younger participants, less with dementia, more with mild cognitive impairment), and other factors that were unable to explore. Additionally, geography and functional status may have also biased the sample in unknown ways and thus may constrain generalizability of findings. Indeed, in response to the wide heterogeneity of imaging in NACC, the National Institute on Aging has newly funded an option program for ADRCs

to standardized imaging protocols (i.e., sites agree to the use of a single scanner, using calibrated scanning parameters and quality control to ensure consistent images across sites) and imaging processing methods (National Institute on Aging, 2019). This program is modeled off of the Alzheimer's disease Neuroimaging Initiative (ADNI: http://adni.loni.usc.edu/methods/documents/mri-protocols/) and will provide imaging funding (not currently included as part of ADRCs) to sites that agree to participate.

Conclusion

This current study was designed to explore the complex relationships among time-varying vascular risk factors/cardiovascular conditions and time-varying treatment on cognitive decline in a large, multisite, cognitively diverse sample of older adults from NACC. A predominant focus of this study was also to explore these relationships when neuropathology of presumed vascular origin (i.e., white matter hyperintensity volume) was included. Findings from this study were generally consistent with previous literature examining these relationships. Additionally, results from our study add to the small, but growing body of work linking cardiovascular health measures, pharmacological treatment data, and brain-based measures on cognitive decline in an older adult sample. Results from this study support the need for additional research in areas of cardiovascular risk and WMH burden to determine sensitive windows of opportunity for intervention. While middle-age is likely an appropriate target for exploration of intervention effects, giving our findings, it is also important for future studies to continue to investigate these relationships in an older adult population so that potential later-life windows of opportunity are not missed.

APPENDIX A
COMMAND LINE SCRIPT FOR NEUROIMAGING PREPROCESSING

1. **To search for nomenclature for naming; run the following in each of the batch folders to determine renaming convention**

```
find . -name "*.nii.gz"
```

2. **To remove duplicate files run the following for files:**

```
for subject in `cat subjects1.txt` ; do cd ${subject}; rm
*Post*.nii.gz ; rm *Post*.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; rm
*a*.nii.gz ; rm *a*.json ; cd .. ; done
```

3. **To rename T1 files use the following, depending on what file naming you have for your batch:**

```
for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*FSPGR*.nii.gz ${subject}_T1.nii.gz ; mv *FSPGR*.json
${subject}_T1.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*MPRAGE*.nii.gz ${subject}_T1.nii.gz ; mv *MPRAGE*.json
${subject}_T1.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv *MP-
RAGE*.nii.gz ${subject}_T1.nii.gz ; mv *MPRAGE*.json
${subject}_T1.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*mprage*.nii.gz ${subject}_T1.nii.gz ; mv *mprage*.json
${subject}_T1.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*SPGR*.nii.gz ${subject}_T1.nii.gz ; mv *SPGR*.json
${subject}_T1.json ; cd .. ; done
```

4. **For additional T1 file nomenclature, use the following:**

```
for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*_GRADIENT_T1*.nii.gz ${subject}_T1.nii.gz ; mv
*_GRADIENT_T1*.json ${subject}_T1.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*SAG_T1*.nii.gz ${subject}_T1.nii.gz ; mv *SAG_T1*.json
${subject}_T1.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*__T1_AX*.nii.gz ${subject}_T1.nii.gz ; mv *__T1_AX*.json
${subject}_T1.json ; cd .. ; done
```

```
for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*AX_SE_T1*.nii.gz ${subject}_T1.nii.gz ; mv *AX_SE_T1*.json
${subject}_T1.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*T1TFE*.nii.gz ${subject}_T1.nii.gz ; mv **T1TFE*.json
${subject}_T1.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*T1_PRE*.nii.gz ${subject}_T1.nii.gz ; mv *T1_PRE*.json
${subject}_T1.json ; cd .. ; done
```

5. **To rename FLAIR files use the following:**

```
for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*FLAIR*.nii.gz ${subject}_FLAIR.nii.gz ; mv *FLAIR*.json
${subject}_FLAIR.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*T2*FLAIR*.nii.gz ${subject}_FLAIR.nii.gz ; mv *T2*FLAIR*.json
${subject}_FLAIR.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*flair*.nii.gz ${subject}_FLAIR.nii.gz ; mv *flair*.json
${subject}_FLAIR.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*FlAIR*.nii.gz ${subject}_FLAIR.nii.gz ; mv *FlAIR*.json
${subject}_FlAIR.json ; cd .. ; done

for subject in `cat subjects1.txt` ; do cd ${subject}; mv
*Flair*.nii.gz ${subject}_FLAIR.nii.gz ; mv *Flair*.json
${subject}_FLAIR.json ; cd .. ; done
```

Note: You may need to add more to these options to capture all FLAIR and T1 files - there may be duplicates, requires some looking into the number of files converted.

```
find . -name "*FLAIR.nii.gz"

find . -name "*T1.nii.gz"
```

6. **To delete FSPGR duplicates search for the following and then remove with the following commands:**

```
find . -name "*FSPGR*-BACKUP_*.nii.gz"

for subject in `cat subjects1.txt` ; do cd ${subject}; rm
*FSPGR*-BACKUP_*.nii.gz ; rm *FSPGR*-BACKUP_*.json ; cd .. ; done
```

Note: Following you may have to delete remaining duplicates. To do this run the find command and then cd into subject's directory to delete duplicate. You must go back to the previous command to rename them before moving forward.

7. **When you are done renaming and have confirmed final count of T1 and FLAIR FILES, in each batch folder run the following:**

```
mkdir -p UBO1{T1,FLAIR}
```

8. **To move T1 and FLAIR files into their appropriate folder do the following:**

```
for subject in `cat subjects1.txt` ; do cp
./${subject}/${subject}_T1.nii.gz ./UBO1/T1/ ;  cp
./${subject}/${subject}_FLAIR.nii.gz ./UBO1/FLAIR/ ; done
```

9. **If you have a file with a missing T1 or FLAIR you must delete the unmatched file to prevent UBO detector errors, to check look in each folder using these codes, and then remove unmatched files with rm function:**

```
find . -name "*FLAIR.nii.gz"

find . -name "*T1.nii.gz"

rm VARIABLE NAME HERE
```

APPENDIX B
CONFIRMATORY FACTOR ANALYSIS OF COGNITIVE CONSTRUCTS

	Factor Loadings (Standardized Regression Coefficients)	Residual Variances
Memory		
LM Immediate Recall	0.968	0.064
LM Delayed Recall	0.945	0.106
Attention		
Digits Forward	0.681	0.536
Digits Forward Length	0.63	0.603
Digits Backward	0.905	0.182
Digits Backward Length	0.868	0.247
Executive Function		
Trails A	0.856	0.290
Trails B	0.966	0.175
WAIS Digit Symbol	0.902	0.221
Language		
BNT	0.724	0.419
COWA Animals	0.806	0.248
COWA Vegetables	0.867	0.345
Model Fit Statistics		
X^2 test, p-value, *df*	9501.508, p< .001, *df*= 46	
CFI	0.991	
TLI	0.987	
RMSEA	0.046	

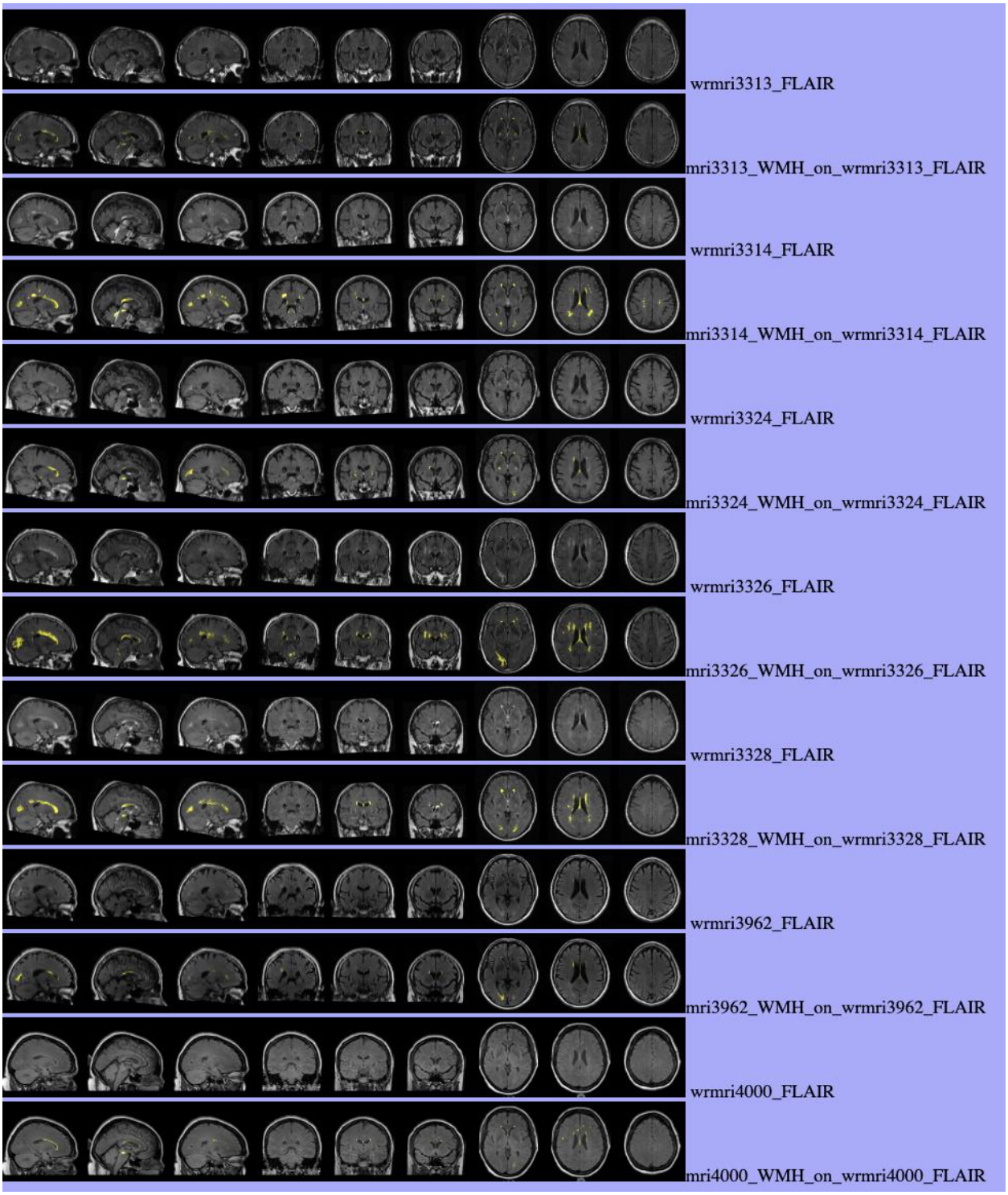
Note. Final model parameters fixed variances to 1 and means to 0. Intercepts, factor loadings, and residual variances were allowed to be freely estimated. All factor loadings and correlations were significant, p<.001. Abbreviations: LM = Logical Memory; WAIS = Weschler Adult Intelligence Scale; BNT = Boston Naming Test, COWA = Controlled Oral Word Association.

FACTOR CORRELATION MATRIX

Factor	Memory	Attention	Executive Function	Language
Memory	-	0.532	0.656	0.764
Attention	-	-	0.686	0.641
Executive Function	-	-	-	0.828
Language	-	-	-	-

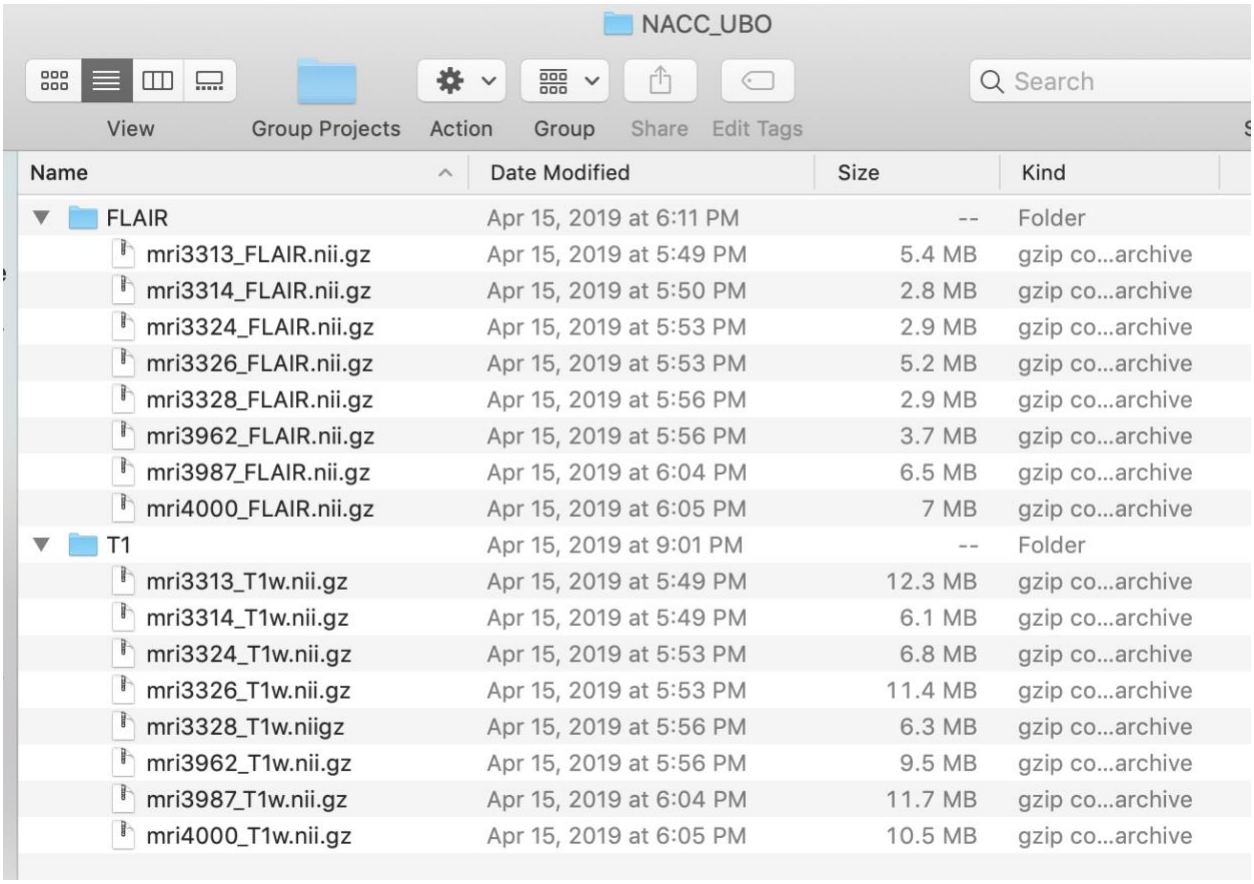
Note. All correlations were significant at p< .001.

APPENDIX C
UBO DETECTOR QUALITY CONTROL OUTPUT FOR WHITE MATTER MASKS

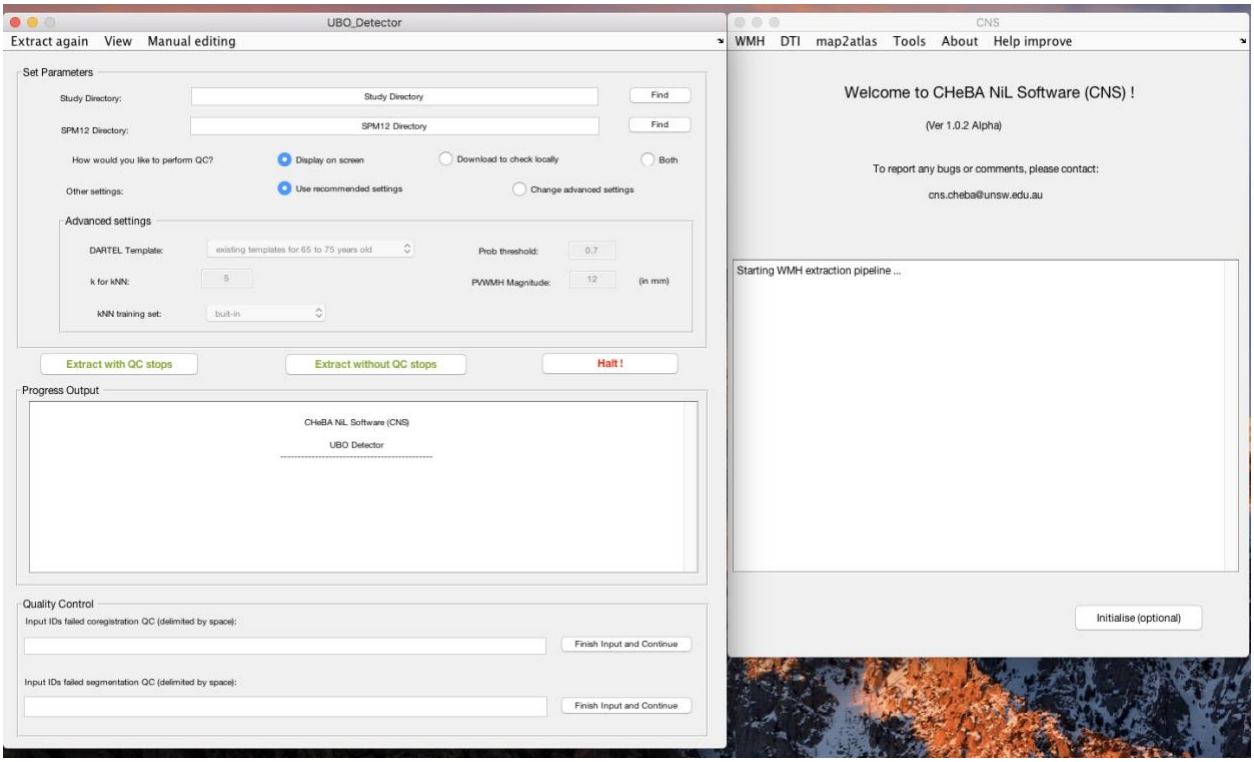


APPENDIX D
ADAPTED UBO DETECTOR SET-UP INSTRUCTIONS

Data Preparation. For UBO Detector to operate properly, all files should be labeled with unique subject IDs and sequence names (e.g., *mri3811_flair.nii.gz*) and stored in two folders under the study folder as such:



WMH Extraction. The following outlines the steps needed to run the GUI program. A visual representation can be seen below.



Step 1: In MATBLAB, addpath ('/path/to/CNS') and run CNS

Step 2: Open the UBO Detector trough WMH -> Extract WMH

Step 3: Find the Study Directory by clicking *Find*.

Step 4: *Find spm12* folder.

Step 5: Specify how you would like to view the coregistration, segmentation, and final results for quality control (QC).

Display on screen - Results will be displayed in MATLAB web browser by calling the *web* function in MATLAB.

Download to check locally - Results will be exported into a HTML webpage, and compressed for download

Both - both *Display on screen* and *Download*

Step 6: *Extract with QC stops* if you want to exclude scans failed coregistration or segmentation QC, or *Extract without QC stops* if you want to complete the extraction without stops. "*Extract without QC stops*" will not allow you to exclude any subjects from

the process but will generate the same QC figures as "*Extract with QC stops*" (i.e. coregistration, segmentation, final QC), which is stored in the *<studyFolder>/subjects/QC* folder.

Step 7: If selected "Extract with QC stops" in Step 6. The pipeline will generate QC webpage after coregistration. Depending on the means of viewing the results specified in Step 5, the coregistration results will be either displayed as a webpage on screen, or available for download, or both display and download. Please input the IDs failed coregistration QC (separated by space) in the Quality Control section and click *Finish and continue*.

Step 8: If selected "Extract with QC stops" in Step 6. The pipeline will generate QC webpage after segmentation. The segmentation results will be available according to what you specified in Step 5. Input the IDs failed segmentation QC (separated by space) in the Quality Control section and click *Finish and continue*.

Step 9: The final results will be available according to Step 5 after finishing all the extraction steps.

Output. UBO Detector will provide output for WMH extraction in excel format and images of extracted white matter for comparison (see next page).

APPENDIX E
SUPPLEMENTAL ANALYSES FOR AIM 2 GROWTH MODELS WITH ADDITIONAL COVARIATES

Memory Factor – Model Fit and Regression Output

```
lavaan 0.6-8 ended normally after 178 iterations

  Estimator                                         ML
  Optimization method                           NLMINB
  Number of model parameters                        64
  Number of equality constraints                     5

                                                  Used       Total
  Number of observations                           607        1049
  Number of missing patterns                        19

Model Test User Model:

  Test statistic                               164.923
  Degrees of freedom                            81
  P-value (Chi-square)                           0.000

Model Test Baseline Model:

  Test statistic                              4272.643
  Degrees of freedom                           124
  P-value                                        0.000

User Model versus Baseline Model:

  Comparative Fit Index (CFI)                    0.980
  Tucker-Lewis Index (TLI)                       0.969

Loglikelihood and Information Criteria:

  Loglikelihood user model (H0)              -3231.433
  Loglikelihood unrestricted model (H1)             NA

  Akaike (AIC)                                6580.866
  Bayesian (BIC)                              6840.969
  Sample-size adjusted Bayesian (BIC)         6653.658
```

Root Mean Square Error of Approximation:

RMSEA	0.041
90 Percent confidence interval - lower	0.032
90 Percent confidence interval - upper	0.050
P-value RMSEA <= 0.05	0.943

Standardized Root Mean Square Residual:

SRMR	0.017

Parameter Estimates:

Standard errors	Standard
Information	Observed
Observed information based on	Hessian

Regressions:

	Estimate	Std.Err	z-value	P(>|z|)	Std.lv	Std.all
mem_i ~						
blmWhlWMH (b1)	-0.255	0.037	-6.814	0.000	-0.282	-0.289
blmTtlV.1 (b3)	0.071	0.043	1.669	0.095	0.078	0.075
bCVDM_T.1	0.011	0.045	0.247	0.805	0.012	0.012
blom_nt_1	0.014	0.036	0.398	0.691	0.016	0.016
race_blck	0.272	0.429	0.634	0.526	0.300	0.097
race_aapi	-0.105	0.458	-0.231	0.818	-0.116	-0.020
race_whit	0.077	0.414	0.186	0.853	0.085	0.031
HISPANIC	-0.133	0.117	-1.133	0.257	-0.146	-0.045
NACCAGE.1	-0.027	0.005	-5.215	0.000	-0.030	-0.224
SEX	0.201	0.085	2.370	0.018	0.222	0.111
EDUC_2lvl	0.174	0.078	2.236	0.025	0.192	0.087
NACCICV	-0.000	0.000	-0.569	0.569	-0.000	-0.028
NACCGDS.1	-0.063	0.013	-4.716	0.000	-0.070	-0.176
NACCNE4S	-0.386	0.054	-7.097	0.000	-0.426	-0.262

mem_s ~						
blmWhlWMH (b2)	-0.021	0.007	-3.088	0.002	-0.215	-0.221
blmTtlV.1 (b4)	0.005	0.008	0.614	0.539	0.049	0.047
bCVDM_T.1	0.005	0.008	0.648	0.517	0.055	0.051
blom_nt_1	-0.004	0.007	-0.611	0.541	-0.042	-0.042
race_blck	-0.024	0.078	-0.303	0.762	-0.237	-0.077
race_aapi	-0.009	0.084	-0.104	0.917	-0.087	-0.015
race_whit	-0.037	0.075	-0.495	0.621	-0.374	-0.135
HISPANIC	0.008	0.021	0.375	0.708	0.079	0.024
NACCAGE.1	-0.003	0.001	-2.945	0.003	-0.029	-0.214
SEX	-0.017	0.016	-1.101	0.271	-0.172	-0.086
EDUC_2lvl	-0.025	0.015	-1.731	0.083	-0.254	-0.114
NACCICV	-0.000	0.000	-1.500	0.134	-0.001	-0.125
NACCGDS.1	-0.010	0.003	-3.976	0.000	-0.101	-0.253
NACCNE4S	-0.030	0.010	-2.931	0.003	-0.297	-0.183
blomWholeWMH ~						
blmTtlV.1 (a1)	0.076	0.048	1.595	0.111	0.076	0.071
bCVDM_T.1 (a2)	-0.006	0.048	-0.127	0.899	-0.006	-0.006
race_blck	-1.982	0.411	-4.826	0.000	-1.982	-0.624
race_aapi	-2.061	0.446	-4.618	0.000	-2.061	-0.340
race_whit	-2.189	0.399	-5.484	0.000	-2.189	-0.771
HISPANIC	-0.486	0.124	-3.911	0.000	-0.486	-0.146
NACCAGE.1	0.047	0.004	10.721	0.000	0.047	0.339
SEX	-0.147	0.080	-1.838	0.066	-0.147	-0.071
EDUC_2lvl	-0.221	0.086	-2.560	0.010	-0.221	-0.097
NACCICV	-0.001	0.000	-3.088	0.002	-0.001	-0.106
NACCGDS.1	0.026	0.015	1.740	0.082	0.026	0.064
NACCNE4S	0.085	0.061	1.408	0.159	0.085	0.051
blomTotalVasc.1 ~						
bCVDM_T.1 (a0)	0.524	0.035	14.959	0.000	0.524	0.508
race_blck	0.943	0.348	2.712	0.007	0.943	0.318
race_aapi	0.306	0.380	0.806	0.420	0.306	0.054
race_whit	0.486	0.340	1.430	0.153	0.486	0.183
HISPANIC	0.065	0.106	0.615	0.539	0.065	0.021
NACCAGE.1	0.002	0.004	0.465	0.642	0.002	0.013
SEX	-0.096	0.068	-1.409	0.159	-0.096	-0.050
EDUC_2lvl	-0.278	0.073	-3.825	0.000	-0.278	-0.131
NACCICV	-0.000	0.000	-1.027	0.304	-0.000	-0.032
NACCGDS.1	0.031	0.013	2.411	0.016	0.031	0.081
NACCNE4S	-0.030	0.052	-0.574	0.566	-0.030	-0.019

```
Covariances:
                   Estimate   Std.Err  z-value  P(>|z|)   Std.lv   Std.all
 .mem_i ~~
   .mem_s             0.044    0.006    7.918    0.000     0.685    0.685


Defined Parameters:
                    Estimate   Std.Err  z-value  P(>|z|)   Std.lv   Std.all
    ind_f_mds_____     0.002    0.012    0.127    0.899     0.002    0.002
    ind_f_cvd_____    -0.019    0.012   -1.553    0.120    -0.021   -0.021
    ind_f_mds_____     0.000    0.001    0.127    0.899     0.001    0.001
    ind_f_cvd_____    -0.002    0.001   -1.417    0.156    -0.016   -0.016
    ind_f_mds_____     0.037    0.022    1.659    0.097     0.041    0.038
    ind_f_mds_____     0.003    0.004    0.614    0.539     0.026    0.024
```

Attention Factor – Model Fit and Regression Output

```
lavaan 0.6-8 ended normally after 165 iterations

  Estimator                                         ML
  Optimization method                           NLMINB
  Number of model parameters                        64
  Number of equality constraints                     5

                                                  Used       Total
  Number of observations                           607        1049
  Number of missing patterns                        19

Model Test User Model:

  Test statistic                               133.581
  Degrees of freedom                                81
  P-value (Chi-square)                           0.000

Model Test Baseline Model:

  Test statistic                              3609.884
  Degrees of freedom                               124
  P-value                                        0.000

User Model versus Baseline Model:

  Comparative Fit Index (CFI)                    0.985
  Tucker-Lewis Index (TLI)                       0.977
```

```
Loglikelihood and Information Criteria:

  Loglikelihood user model (H0)              -2475.519
  Loglikelihood unrestricted model (H1)             NA

  Akaike (AIC)                               5069.038
  Bayesian (BIC)                             5329.142
  Sample-size adjusted Bayesian (BIC)        5141.830

Root Mean Square Error of Approximation:

  RMSEA                                         0.033
  90 Percent confidence interval - lower        0.022
  90 Percent confidence interval - upper        0.042
  P-value RMSEA <= 0.05                         0.999

Standardized Root Mean Square Residual:

  SRMR                                          0.019


Regressions:
                   Estimate   Std.Err  z-value  P(>|z|)   Std.lv   Std.all
  attn_i ~
    blmWhlWMH (b1)    -0.134    0.025   -5.478    0.000   -0.240   -0.247
    blmTtlV.1 (b3)    -0.011    0.028   -0.412    0.680   -0.021   -0.020
    bCVDM_T.1         -0.002    0.030   -0.073    0.942   -0.004   -0.004
    blom_nt_1         -0.008    0.023   -0.358    0.720   -0.015   -0.015
    race_blck         -0.105    0.280   -0.374    0.709   -0.187   -0.061
    race_aapi         -0.265    0.299   -0.884    0.376   -0.474   -0.080
    race_whit         -0.057    0.271   -0.209    0.834   -0.101   -0.037
    HISPANIC          -0.411    0.077   -5.378    0.000   -0.736   -0.228
    NACCAGE.1         -0.012    0.003   -3.402    0.001   -0.021   -0.155
    SEX                0.118    0.056    2.118    0.034    0.211    0.105
    EDUC_2lvl          0.138    0.051    2.702    0.007    0.246    0.111
    NACCICV            0.000    0.000    0.906    0.365    0.000    0.048
    NACCGDS.1         -0.031    0.009   -3.523    0.000   -0.055   -0.140
    NACCNE4S          -0.135    0.036   -3.799    0.000   -0.242   -0.149
```

attn_s ~						
blmWhlWMH (b2)	-0.014	0.005	-2.975	0.003	-0.251	-0.258
blmTtlV.1 (b4)	0.001	0.005	0.151	0.880	0.015	0.014
bCVDM_T.1	0.002	0.006	0.409	0.683	0.042	0.039
blom_nt_1	0.003	0.005	0.683	0.495	0.056	0.057
race_blck	-0.004	0.053	-0.085	0.932	-0.080	-0.026
race_aapi	-0.020	0.057	-0.346	0.729	-0.353	-0.060
race_whit	-0.021	0.051	-0.400	0.689	-0.365	-0.132
HISPANIC	0.008	0.014	0.581	0.562	0.148	0.046
NACCAGE.1	-0.001	0.001	-1.557	0.120	-0.019	-0.138
SEX	-0.004	0.011	-0.377	0.707	-0.072	-0.036
EDUC_2lvl	-0.016	0.010	-1.578	0.115	-0.281	-0.127
NACCICV	-0.000	0.000	-2.604	0.009	-0.002	-0.265
NACCGDS.1	-0.003	0.002	-1.762	0.078	-0.054	-0.137
NACCNE4S	-0.021	0.007	-3.059	0.002	-0.379	-0.233
blomWholeWMH ~						
blmTtlV.1 (a1)	0.076	0.048	1.595	0.111	0.076	0.071
bCVDM_T.1 (a2)	-0.006	0.048	-0.127	0.899	-0.006	-0.006
race_blck	-1.982	0.411	-4.826	0.000	-1.982	-0.624
race_aapi	-2.061	0.446	-4.618	0.000	-2.061	-0.340
race_whit	-2.189	0.399	-5.484	0.000	-2.189	-0.771
HISPANIC	-0.486	0.124	-3.911	0.000	-0.486	-0.146
NACCAGE.1	0.047	0.004	10.721	0.000	0.047	0.339
SEX	-0.147	0.080	-1.838	0.066	-0.147	-0.071
EDUC_2lvl	-0.221	0.086	-2.560	0.010	-0.221	-0.097
NACCICV	-0.001	0.000	-3.088	0.002	-0.001	-0.106
NACCGDS.1	0.026	0.015	1.740	0.082	0.026	0.064
NACCNE4S	0.085	0.061	1.408	0.159	0.085	0.051
blomTotalVasc.1 ~						
bCVDM_T.1 (a0)	0.524	0.035	14.959	0.000	0.524	0.508
race_blck	0.943	0.348	2.712	0.007	0.943	0.318
race_aapi	0.306	0.380	0.806	0.420	0.306	0.054
race_whit	0.486	0.340	1.430	0.153	0.486	0.183
HISPANIC	0.065	0.106	0.615	0.539	0.065	0.021
NACCAGE.1	0.002	0.004	0.465	0.642	0.002	0.013
SEX	-0.096	0.068	-1.409	0.159	-0.096	-0.050
EDUC_2lvl	-0.278	0.073	-3.825	0.000	-0.278	-0.131
NACCICV	-0.000	0.000	-1.027	0.304	-0.000	-0.032
NACCGDS.1	0.031	0.013	2.411	0.016	0.031	0.081
NACCNE4S	-0.030	0.052	-0.574	0.566	-0.030	-0.019

```
Covariances:
                   Estimate   Std.Err  z-value  P(>|z|)   Std.lv   Std.all
 .attn_i ~~
   .attn_s            0.013    0.002    5.240    0.000     0.562    0.562


Defined Parameters:
                    Estimate   Std.Err  z-value  P(>|z|)   Std.lv   Std.all
    ind_f_mds_____     0.001    0.006    0.127    0.899     0.001    0.001
    ind_f_cvd_____    -0.010    0.007   -1.531    0.126    -0.018   -0.017
    ind_f_mds_____     0.000    0.001    0.127    0.899     0.002    0.001
    ind_f_cvd_____    -0.001    0.001   -1.406    0.160    -0.019   -0.018
    ind_f_mds_____    -0.006    0.015   -0.412    0.680    -0.011   -0.010
    ind_f_mds_____     0.000    0.003    0.151    0.880     0.008    0.007
```

Executive Function Factor – Model Fit and Regression Output

```
lavaan 0.6-8 ended normally after 165 iterations

  Estimator                                         ML
  Optimization method                           NLMINB
  Number of model parameters                        64
  Number of equality constraints                     5

                                                  Used       Total
  Number of observations                           607        1049
  Number of missing patterns                        19

Model Test User Model:

  Test statistic                               181.011
  Degrees of freedom                                81
  P-value (Chi-square)                           0.000

Model Test Baseline Model:

  Test statistic                              5494.684
  Degrees of freedom                              124
  P-value                                        0.000

User Model versus Baseline Model:

  Comparative Fit Index (CFI)                    0.981
  Tucker-Lewis Index (TLI)                       0.971
```

```
Root Mean Square Error of Approximation:

  RMSEA                                          0.045
  90 Percent confidence interval - lower         0.036
  90 Percent confidence interval - upper         0.054
  P-value RMSEA <= 0.05                          0.813

Standardized Root Mean Square Residual:

  SRMR                                           0.016


Regressions:
                   Estimate   Std.Err  z-value  P(>|z|)   Std.lv   Std.all
  ef_i ~
    blmWhlWMH (b1)    -0.242    0.036   -6.719    0.000   -0.268   -0.275
    blmTtlV.1 (b3)     0.005    0.041    0.114    0.909    0.005    0.005
    bCVDM_T.1          0.011    0.044    0.242    0.808    0.012    0.011
    blom_nt_1          0.018    0.034    0.523    0.601    0.020    0.020
    race_blck         -0.237    0.413   -0.574    0.566   -0.263   -0.085
    race_aapi         -0.234    0.441   -0.531    0.595   -0.259   -0.044
    race_whit         -0.146    0.400   -0.366    0.714   -0.162   -0.059
    HISPANIC          -0.448    0.113   -3.963    0.000   -0.496   -0.153
    NACCAGE.1         -0.033    0.005   -6.514    0.000   -0.036   -0.269
    SEX                0.202    0.082    2.475    0.013    0.224    0.112
    EDUC_2lvl          0.147    0.075    1.974    0.048    0.163    0.073
    NACCICV            0.000    0.000    0.715    0.475    0.000    0.034
    NACCGDS.1         -0.051    0.013   -3.945    0.000   -0.056   -0.142
    NACCNE4S          -0.322    0.052   -6.154    0.000   -0.356   -0.219
  ef_s ~
    blmWhlWMH (b2)    -0.029    0.006   -4.856    0.000   -0.279   -0.287
    blmTtlV.1 (b4)     0.007    0.007    1.048    0.295    0.069    0.066
    bCVDM_T.1         -0.000    0.007   -0.046    0.963   -0.003   -0.003
    blom_nt_1          0.006    0.006    1.036    0.300    0.058    0.058
    race_blck         -0.036    0.066   -0.539    0.590   -0.350   -0.113
    race_aapi         -0.087    0.071   -1.215    0.224   -0.848   -0.144
    race_whit         -0.070    0.064   -1.087    0.277   -0.684   -0.247
    HISPANIC           0.003    0.018    0.144    0.885    0.025    0.008
    NACCAGE.1         -0.001    0.001   -1.178    0.239   -0.009   -0.071
    SEX                0.002    0.013    0.124    0.902    0.016    0.008
    EDUC_2lvl         -0.028    0.012   -2.238    0.025   -0.270   -0.122
    NACCICV           -0.000    0.000   -0.724    0.469   -0.000   -0.050
    NACCGDS.1         -0.002    0.002   -0.813    0.416   -0.017   -0.042
    NACCNE4S          -0.050    0.009   -5.790    0.000   -0.486   -0.299
```

blomWholeWMH ~						
blmTtlV.1 (a1)	0.076	0.048	1.595	0.111	0.076	0.071
bCVDM_T.1 (a2)	-0.006	0.048	-0.127	0.899	-0.006	-0.006
race_blck	-1.982	0.411	-4.826	0.000	-1.982	-0.624
race_aapi	-2.061	0.446	-4.618	0.000	-2.061	-0.340
race_whit	-2.189	0.399	-5.484	0.000	-2.189	-0.771
HISPANIC	-0.486	0.124	-3.911	0.000	-0.486	-0.146
NACCAGE.1	0.047	0.004	10.721	0.000	0.047	0.339
SEX	-0.147	0.080	-1.838	0.066	-0.147	-0.071
EDUC_2lvl	-0.221	0.086	-2.560	0.010	-0.221	-0.097
NACCICV	-0.001	0.000	-3.088	0.002	-0.001	-0.106
NACCGDS.1	0.026	0.015	1.740	0.082	0.026	0.064
NACCNE4S	0.085	0.061	1.408	0.159	0.085	0.051
blomTotalVasc.1 ~						
bCVDM_T.1 (a0)	0.524	0.035	14.959	0.000	0.524	0.508
race_blck	0.943	0.348	2.712	0.007	0.943	0.318
race_aapi	0.306	0.380	0.806	0.420	0.306	0.054
race_whit	0.486	0.340	1.430	0.153	0.486	0.183
HISPANIC	0.065	0.106	0.615	0.539	0.065	0.021
NACCAGE.1	0.002	0.004	0.465	0.642	0.002	0.013
SEX	-0.096	0.068	-1.409	0.159	-0.096	-0.050
EDUC_2lvl	-0.278	0.073	-3.825	0.000	-0.278	-0.131
NACCICV	-0.000	0.000	-1.027	0.304	-0.000	-0.032
NACCGDS.1	0.031	0.013	2.411	0.016	0.031	0.081
NACCNE4S	-0.030	0.052	-0.574	0.566	-0.030	-0.019

Covariances:

	Estimate	Std.Err	z-value	P(>|z|)	Std.lv	Std.all
.ef_i ~~						
.ef_s	0.047	0.005	9.108	0.000	0.706	0.706

Defined Parameters:

	Estimate	Std.Err	z-value	P(>|z|)	Std.lv	Std.all
ind_f_mds_____	0.001	0.012	0.127	0.899	0.002	0.002
ind_f_cvd_____	-0.018	0.012	-1.552	0.121	-0.020	-0.019
ind_f_mds_____	0.000	0.001	0.127	0.899	0.002	0.002
ind_f_cvd_____	-0.002	0.001	-1.515	0.130	-0.021	-0.020
ind_f_mds_____	0.002	0.021	0.114	0.909	0.003	0.003
ind_f_mds_____	0.004	0.004	1.045	0.296	0.036	0.033

Language Factor – Model Fit and Regression Output

```
lavaan 0.6-8 ended normally after 173 iterations

  Estimator                                         ML
  Optimization method                           NLMINB
  Number of model parameters                        64
  Number of equality constraints                     5

                                                  Used       Total
  Number of observations                           607        1049
  Number of missing patterns                        19

Model Test User Model:

  Test statistic                               131.895
  Degrees of freedom                                81
  P-value (Chi-square)                           0.000

Model Test Baseline Model:

  Test statistic                              5593.859
  Degrees of freedom                               124
  P-value                                        0.000


User Model versus Baseline Model:

  Comparative Fit Index (CFI)                    0.991
  Tucker-Lewis Index (TLI)                       0.986

Loglikelihood and Information Criteria:

  Loglikelihood user model (H0)              -1857.415
  Loglikelihood unrestricted model (H1)             NA

  Akaike (AIC)                                3832.829
  Bayesian (BIC)                              4092.932
  Sample-size adjusted Bayesian (BIC)         3905.621
```

Root Mean Square Error of Approximation:

RMSEA	0.032
90 Percent confidence interval - lower	0.022
90 Percent confidence interval - upper	0.042
P-value RMSEA <= 0.05	0.999

Standardized Root Mean Square Residual:

SRMR	0.015

Regressions:

	Estimate	Std.Err	z-value	P(>|z|)	Std.lv	Std.all
lang_i ~						
blmWhlWMH (b1)	-0.222	0.031	-7.109	0.000	-0.284	-0.292
blmTtlV.1 (b3)	0.034	0.036	0.954	0.340	0.043	0.041
bCVDM_T.1	0.000	0.038	0.012	0.991	0.001	0.001
blom_nt_1	0.043	0.030	1.443	0.149	0.055	0.055
race_blck	0.072	0.359	0.201	0.840	0.092	0.030
race_aapi	-0.105	0.382	-0.274	0.784	-0.134	-0.023
race_whit	0.020	0.347	0.059	0.953	0.026	0.009
HISPANIC	-0.239	0.098	-2.432	0.015	-0.306	-0.095
NACCAGE.1	-0.025	0.004	-5.630	0.000	-0.031	-0.233
SEX	0.204	0.071	2.881	0.004	0.262	0.131
EDUC_2lvl	0.105	0.065	1.624	0.104	0.134	0.061
NACCICV	0.000	0.000	0.709	0.478	0.000	0.034
NACCGDS.1	-0.041	0.011	-3.644	0.000	-0.052	-0.131
NACCNE4S	-0.323	0.045	-7.130	0.000	-0.414	-0.254
lang_s ~						
blmWhlWMH (b2)	-0.019	0.005	-3.960	0.000	-0.222	-0.228
blmTtlV.1 (b4)	0.004	0.006	0.795	0.427	0.051	0.049
bCVDM_T.1	0.002	0.006	0.321	0.748	0.022	0.020
blom_nt_1	0.004	0.005	0.905	0.365	0.049	0.050
race_blck	0.002	0.055	0.033	0.973	0.021	0.007
race_aapi	-0.013	0.060	-0.212	0.832	-0.144	-0.025
race_whit	-0.026	0.054	-0.481	0.630	-0.296	-0.107
HISPANIC	-0.006	0.015	-0.394	0.693	-0.068	-0.021
NACCAGE.1	-0.001	0.001	-1.634	0.102	-0.013	-0.095
SEX	0.004	0.011	0.392	0.695	0.050	0.025
EDUC_2lvl	-0.016	0.010	-1.580	0.114	-0.186	-0.084
NACCICV	-0.000	0.000	-0.728	0.467	-0.000	-0.049
NACCGDS.1	-0.002	0.002	-1.140	0.254	-0.023	-0.058
NACCNE4S	-0.045	0.007	-6.248	0.000	-0.511	-0.314

blomWholeWMH ~						
blmTtlV.1 (a1)	0.076	0.048	1.595	0.111	0.076	0.071
bCVDM_T.1 (a2)	-0.006	0.048	-0.127	0.899	-0.006	-0.006
race_blck	-1.982	0.411	-4.826	0.000	-1.982	-0.624
race_aapi	-2.061	0.446	-4.618	0.000	-2.061	-0.340
race_whit	-2.189	0.399	-5.484	0.000	-2.189	-0.771
HISPANIC	-0.486	0.124	-3.911	0.000	-0.486	-0.146
NACCAGE.1	0.047	0.004	10.721	0.000	0.047	0.339
SEX	-0.147	0.080	-1.838	0.066	-0.147	-0.071
EDUC_2lvl	-0.221	0.086	-2.560	0.010	-0.221	-0.097
NACCICV	-0.001	0.000	-3.088	0.002	-0.001	-0.106
NACCGDS.1	0.026	0.015	1.740	0.082	0.026	0.064
NACCNE4S	0.085	0.061	1.408	0.159	0.085	0.051
blomTotalVasc.1 ~						
bCVDM_T.1 (a0)	0.524	0.035	14.959	0.000	0.524	0.508
race_blck	0.943	0.348	2.712	0.007	0.943	0.318
race_aapi	0.306	0.380	0.806	0.420	0.306	0.054
race_whit	0.486	0.340	1.430	0.153	0.486	0.183
HISPANIC	0.065	0.106	0.615	0.539	0.065	0.021
NACCAGE.1	0.002	0.004	0.465	0.642	0.002	0.013
SEX	-0.096	0.068	-1.409	0.159	-0.096	-0.050
EDUC_2lvl	-0.278	0.073	-3.825	0.000	-0.278	-0.131
NACCICV	-0.000	0.000	-1.027	0.304	-0.000	-0.032
NACCGDS.1	0.031	0.013	2.411	0.016	0.031	0.081
NACCNE4S	-0.030	0.052	-0.574	0.566	-0.030	-0.019

Covariances:

	Estimate	Std.Err	z-value	P(>|z|)	Std.lv	Std.all
.lang_i ~~						
.lang_s	0.041	0.004	10.442	0.000	0.808	0.808

Defined Parameters:

	Estimate	Std.Err	z-value	P(>|z|)	Std.lv	Std.all
ind_f_mds_____	0.001	0.011	0.127	0.899	0.002	0.002
ind_f_cvd_____	-0.017	0.011	-1.556	0.120	-0.022	-0.021
ind_f_mds_____	0.000	0.001	0.127	0.899	0.001	0.001
ind_f_cvd_____	-0.001	0.001	-1.479	0.139	-0.017	-0.016
ind_f_mds_____	0.018	0.019	0.952	0.341	0.023	0.021
ind_f_mds_____	0.002	0.003	0.793	0.428	0.027	0.025

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BIOGRAPHICAL SKETCH

Lindsay Rotblatt graduated from the University of California at Santa Barbara in 2011 with a Bachelor of Science degree in Biopsychology and a minor in Education and Applied Psychology. Following graduation, she went on to San Diego State University where she spent two years working under Dr. Paul Gilbert at the Center for Healthy Aging and Neurodegenerative Disease Research. She earned her Master of Arts degree in Psychology with emphasis in Cognitive and Behavioral Neuroscience at SDSU in 2015. She is currently pursuing her doctorate at the University of Florida in Clinical and Health Psychology, with a specialization in Neuropsychology and minor in Geropsychology. She received the Ruth L. Kirschstein National Research Service Award F31 parent award in 2019. She will receive her degree in summer 2022 after completing her predoctoral internship at VA San Diego Health Care System/University of California, San Diego in Neuropsychology and Inpatient Psychiatry. Broadly speaking, her research interests are in modifiable risk and protective factors affecting long-term age-related changes in cognition. Outside of academic endeavors she has a love for cooking and fermentation. Notably, while a portion of this dissertation was completed during the 2020 Covid-19 pandemic, she, along with her trusty microbiologist partner perfected the elusive sourdough bread.