RACIAL DIFFERENCES, COGNITIVE OUTCOMES, AND THE ROLE OF SOCIOECONOMIC STATUS AND CARDIOVASCULAR RISK

by

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(Under the Direction of L. Stephen Miller)

ABSTRACT

Cognitive aging and associated functional decline are a growing area of focus due to the rapidly expanding older adult population. There are also known racial differences in the severity of cognitive decline in aging, with Black/African American older adults displaying greater cognitive impairment and greater risk of dementia compared to White older adults. We sought to evaluate these racial differences in the context of important risk factors for cognitive decline, as African Americans tend to display higher levels of negative risk factors for decline, including cardiovascular risk (CVR), while also displaying fewer protective/reserve factors, like higher educational and occupational attainment due to historic socioeconomic disparities. We applied a sequential mediation model to assess the serial effect of cognitive reserve (education and occupational intensity), and CVR on cognitive performance (Chapter 3), white matter hyperintensity volume (WMHs), and diffusion tensor imaging (DTI) metrics (Chapter 4) in a matched sample of Black and White older adults. Our results revealed significant differences in executive performance between Black and White older adults, as well as significant differences in CVR scores across racial groups, with Black participants displaying lower average executive performance and greater CVR. While educational attainment and occupational intensity did not

differ across groups, CVR partially mediated the relationship between racial group membership and executive performance. There was significant unexplained variance in this model. There were no significant differences between WMH and DTI metrics across racial groups, however, greater CVR was associated with greater WMH volume. In exploratory DTI analyses, greater CVR was related in some regions with greater white matter integrity (greater anisotropic and less isotropic water movement), but this was based on analyses in a small sample. Our results suggest that racial disparities in CVR partially explain differences in cognitive performance, even though these differences do not appear related to differences in white matter structure. These findings highlight that modifiable risk factors like CVR may be a focus of intervention/prevention, particularly among historically disadvantaged groups, as well as the need to better understand other possible mechanisms that contribute to disparities in cognitive outcomes among racial groups.

INDEX WORDS: cognitive aging, cardiovascular health, cognitive reserve, racial disparities white matter hyperintensities (WMH), diffusion tensor imaging (DTI)

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

The rapidly expanding older adult population both in the United States and worldwide, presents significant public health concerns due to the burdens associated with cognitive and functional impairment in late life. Older adults are now the fastest growing age group in the United States, with the proportion of individuals 65 and older expected to rise from 16 to 23 percent by 2060 (Colby & Ortman, 2017). Numerous efforts and resources are directed to understanding, preventing, and treating the course of cognitive and functional decline in older adults. Research focused on risk and protective factors for cognitive decline in normal and pathological aging, has identified various genetic, physical health, and socio-environmental/lifestyle risk and protective factors. With the focus on risk reduction and prevention, and with the availability of neuroimaging, there is greater opportunity to understand how these risk factors, particularly cardiovascular disease, may affect neural integrity and thus cognitive function. However, there is also evidence of differences in late life cognitive performance across racial groups, including evidence of grater cognitive impairment and greater risk of degenerative disease (e.g., Alzheimer's dementia) among Black/African American older adults (Weuve et al., 2018). Importantly, Black/African Americans are more likely to be burdened with the negative health risk factors for pathological cognitive aging, particularly cardiovascular risk, while displaying fewer of the protective and reserve factors associated with the maintenance of cognitive and functional status (e.g., higher educational and occupational

attainment) (Kurian & Cardarelli, 2007; Barnes et al., 2011; Schwartz et al, 2004). The relationship between these factors has been well studied in multiple health fields, suggesting that lower education and socioeconomic status are linked to greater risk for negative health outcomes and cardiovascular disease, as they often represent related disparities in access to quality health care and resources (Winkleby, Jatulis, Frank &Fortman, 1992). Given the breadth of evidence suggesting racial/ethnic disparities in these important risk and protective factors, there is reason to evaluate the relation between racial group membership and cognitive outcomes in late life as a result of a trajectory of socioeconomic and physical health risk factors which also impact neuronal integrity. The purpose of the current analysis was to evaluate if observed racial differences in cognitive performance of Black and White older adults are better explained by differential attainment of socioeconomic risk/protective factors, and subsequent disparity in cardiovascular risk leading to poorer cognitive function and greater neurological indicators of disease burden. These analyses may better explicate the observed racial differences in cognitive outcomes by revealing factors associated with racial group membership which contribute to increased risk.

Cognitive Decline in Aging

There is an expected degree of cognitive decline associated with older age. This age-related cognitive decline (ARCD) is known to occur in the absence of neuropathological processes such as in Alzheimer's dementia (AD) or other neurodegenerative diseases (Boyle et al., 2013; Carlo et al., 2000; Ebly, Hogan & Parhad, 1995). This decline is associated with functional impairment in activities of daily living (ADLs), decision-making, and ultimately the ability to live independently (Tucker-Drob, 2011).

ARCD is known to effect multiple cognitive domains, with evidence of decline across attention, processing speed, memory, executive functioning, and spatial processing (Glisky, 2007; Meijer, van Boxtel, van Gerven, van Hooren, & Jolles, 2009; Tucker-Drob, Johnson, & Jones, 2009). The pattern of cognitive decline seen in aging can vary across individuals and depending on disease trajectories, with certain disease processes affecting specific domains of cognition (e.g., AD, Vascular dementia, etc.; Fotenos et al, 2005; Raz et al. 2005). However, the general pattern of cognitive decline in aging appears to follow an anterior-posterior trajectory, meaning that the functions of the anterior portions of the brain appear to be affected first, with corresponding deficits in frontal lobe mediated functions (executive function), in addition to diminished processing speed with age (Raz, 2000; Gonoi et al., 2010; Hoogendam et al., 2014).

Executive function

Older adults often exhibit decline in areas of "higher order" cognitive functions, such as working memory, task monitoring/inhibition, and cognitive flexibility, also known as the executive functions (EF; Diamond, 2013). Executive functions (EF) are comprised of multiple top-down processes which influence goal directed behaviors like reasoning, problem solving, and task planning and monitoring (Miller & Cohen, 2001; Collins & Koechlin, 2012). The general components of EF include inhibitory control, working memory, and cognitive flexibility (Lehto et al. 2003, Miyake et al. 2000). These abilities refer to regulating behavioral responses (e.g., resisting impulses), exercising cognitive inhibition and selective attention (e.g., focusing attention for a goal while filtering irrelevant stimuli), holding and manipulating information in mind for completion of a goal, and adapting or shifting behavior to accommodate changing goals or task demands (Baddely, 1998; Diamond, 2013). Based on these three components, it is clear

how the skills involved in EF are important for integrated functional tasks, like judgment, reasoning, and problem solving.

Research on cognitive aging provides evidence for how adults show increased difficulty on executive tasks as they age (Daniels, Toth & Jacoby, 2006). Comparisons between older and younger adults shows consistent differences in performance on neuropsychological tests of EF between young and old adults, as well as within older adult samples, with individuals older than 74 displaying greater difficulty on EF tasks than older adults below age 74 (Libon et al., 1994; Zelazo, Craik, & Booth; 2004). Common executive tasks include those involving initiation planning and organizing, searching for targets while ignoring salient distractors, or attention switching tasks, where individuals are asked to perform two tasks simultaneously (Gilsky, 2007). Researchers in this area posit that these "higher order" cognitive functions, which arise later in development, are the first to deteriorate with age, while other cognitive abilities, like language, which appear early in cognitive development, are more resilient to the effects of aging (Brickman et al., 2012). There is also substantial neurobiological evidence from multiple neuroimaging methodologies that supports this pattern of cognitive change with age (See **Neuroimaging Correlates of Cognitive Aging** below).

Memory

The ability to acquire and recall information over time is another important cognitive ability that when impaired, leads to significant disruption to daily life (e.g., the ability to recall past events and experiences, information about future plans/obligations, etc.; Hering, Kliegel, Rendell, Craik, & Rose, 2018). Memory ability is also known to decline within the process of normal aging, and to a greater extent in certain disease processes (Salthouse, 2011; Nyberg et al., 2012). While certain forms of memory can be generally resilient to the aging process (e.g.,

procedural memory, semantic memory; Bäckman, Small, Wahlin, & Larsson, 2000; Nyberg et al., 2003), episodic memory, or recollection of specific events and experiences, tends to show the largest degree of age-related decline (Nyberg et al., 2012; Gorbach et al., 2017). Progressive memory impairment with an "amnestic" pattern (i.e., *rapid* forgetting of learned information) is a hallmark pattern of cognitive decline seen in AD, and its presumed diagnostic precursor, amnestic MCI (Graham, Emery, & Hodges, 2004). Operationally, memory function is assessed by presenting patients or participants with verbal or visual information to be learned (e.g., lists of words, stories, geometric figures), and after a delay period, asking them to spontaneously recall or reproduce the information, with the degree of loss of information over time representative of the degree of memory impairment (Morris & Copeland, 2018). Deficits in both memory and executive functioning are thought to be highly related to functional changes in aging, given their importance for independence in activities of daily living (Hering, Kliegel, Rendell, Craik, & Rose, 2018; Cahn-Weiner, Boyle, & Malloy, 2002). Due to their relevance to functional independence and sensitivity to the cognitive changes seen in aging, these domains will be the focus of cognitive performance in the proposed analysis.

Racial Differences in Cognitive Aging and Disease

Studies evaluating cognitive changes in late life find that Black/African Americans display greater cognitive impairment and poorer cognitive performance in late life compared to White Americans (Schwartz et al., 2004; Moody-Ayers, Mehta, Lindquist, Sands, & Covinsky, 2005; Lee et al., 2012; Gupta et al., 2016; Diaz-Venegas, Downer, Langa, &Wong, 2016; Weuve et al., 2018). Despite criticisms of cognitive tools, which posit that racial differences in test performance are due largely to psychometric/measurement issues (e.g., biased test development, inappropriate test norms for racial minority examinees), evidence suggests that these racial

differences exist beyond what would be expected due to methodological limitations in measurement tools (Schwartz et al., 2004). Furthermore, there is evidence of these differences in both normal age-related decline, and in risk of disease, with studies showing Black/African Americans are at greater risk for MCI and AD (Tang et al., 2001; Gupta et al., 2016; Weuve et al., 2018). This finding is supported by recent meta-analytic data from population-based studies, which reported African Americans' incidence rates of AD as 64% higher than that of White Americans (Steenland, Goldstein, Levey & Wharton, 2016). Across longitudinal studies, there is also evidence of steeper, more rapid cognitive decline among Black/African Americans when compared with trajectories of decline across aging, for both healthy and demented samples (Lee et al., 2012; Weuve et al., 2018). In review of this evidence, and with a better understanding of the risk factors for cognitive decline, it seems prudent to evaluate the extent to which differences in important risk variables may explain such racial differences in cognitive outcomes.

Disparities in Risk and Protective Factors for Cognitive Aging

Education and Occupational Attainment

In an effort to understand potential interventions in the course of cognitive aging, research points to a number of health and lifestyle factors that represent either greater risk, or protection/buffering of cognitive decline, including educational and occupational attainment, social engagement, and physical activity across the lifespan (Scarmeas, Albert, Manly, & Stern, 2006; Hall et al., 2007; Wang, MacDonald, Dekhtyar, & Fragtilioni, 2017; Chan et al., 2018;). Among these, educational and occupational attainment are critical, as they are directly related to cognitive reserve and represent early life course achievements that are important for later cognitive outcomes.

The cognitive reserve hypothesis posits that certain individuals maintain clinically intact cognitive performance in the face of brain changes or pathology associated with aging or disease (Stern, Alexander, Prohovnik, Mayeux, 1992). Distinct from brain reserve, which suggests that individuals with greater brain volume require greater pathology to reach the threshold for which clinical consequences become apparent, cognitive reserve refers to efficiency and ability to compensate for pathology (Barulli & Stern, 2013; Stern, Barnes, Grady, Jones, & Raz, 2019). Cognitive reserve is frequently operationalized by proxy measures; educational attainment and pre-morbid intellectual ability most commonly, as well as occupational intensity, and engagement in social and leisure activities (Scarmeas, Albert, Manly, & Stern, 2006; Smart, Gow & Deary, 2014; Lane, Windsor, Andel & Luszcz, 2017; Opdebeeck, Martyr, & Clare, 2016). It is believed that higher intellectual ability (IQ) and factors that contribute to higher IQ, such as more advanced educational attainment and more cognitively engaging occupational involvement, support the use of efficient executive and processing skills, cognitive flexibility, and compensatory neural strategies (Siedlecki et al., 2009; Darby, Brickhouse, Wolk, & Dickerson, 2017). There is support for the hypothesized compensation strategy in task related fMRI and EEG research. High cognitive reserve in young and older adult participants (indicated by education and pre-morbid IQ estimates) is associated with differential task-related brain activation (Steffener, Brickman, Rakitin, Gazes, & Stern, 2009; Gu et al., 2018; Anthony & Lin, 2018). Given their apparent representativeness of cognitive reserve factors, education and occupational attainment are sometimes considered to be protective in their ability to buffer cognitive decline in both aging and even early stages of AD (Stern et al., 1994; Stern, Albert, Tang & Tssai, 1999). Disparities in these critical factors are especially important given their influence on cognitive trajectories.

Racial group membership in the United states has historically represented a point of disparity for a number of circumstances, with differences in socioeconomic status (SES) falling along racial lines (LaVeist, 2005). Education is an early determinant of several downstream consequences and is one of the early areas of disparity seen across racial groups, known as the educational achievement gap (Norman, Ault, Bentz, & Meskimen, 2001; Sullivan, Meschede, Dietrich, & Shapiro, 2015). Historic educational policies including prohibition of African Americans from educational institutions, and later segregated school systems, promoted suboptimal educational quality among minority communities (Sullivan et al., 2015). These disparities have persisted in part due to strong intergenerational effects of parents' educational level, and associated occupational and income level, on children's educational success (Dubow, E. F., Boxer, P., & Huesmann, 2009). Disparities are further maintained by policies which tend to disadvantage minority and low-income groups, and shape educational and career opportunities for minority youth (e.g., declining affordability of quality and higher education, residential segregation, and property-tax based school districts leading to unequal educational quality) (Ahmad & Hamm, 2013; Orfield, Frankenberg, Ee, & Kuscera, 2014; Rothstein, 2015). At the collegiate level, due to differences in family SES, African American students have historically shown lower graduation/completion rates at four-year institutions, which in turn influences disparities seen in occupational attainment (Cross & Slater, 2001; Nguyen, Bibo, & Engle, 2012). Furthermore, labor statistics provide evidence for disparities in the hiring of racial minorities which further divide racial groups at the level of occupational attainment (Masel, Raji, & Peek, 2010; Quillian, Pager, Hexel, & Midtbøen, 2017).

A growing literature exists that evaluates the influence of education on racial differences in late life cognitive outcomes. In their three-year study of cognitive decline in a bi-racial

sample, Sachs-Ericsson and Blazer (2005) found that African American participants had fewer years of education on average and had higher rates of cognitive decline compared to White participants. Additionally, education and literacy significantly mediated the relationship between race and cognitive decline. Recent studies with samples from across the United States report a similar mediating role of education and related factors in the relationship between race/ethnicity and cognitive outcomes (e.g., education and literacy, education and health literacy, education, and physical activity; Masel, Raji & Peek, 2010; Sisco et al., 2014; Gupta et al., 2016). In each case, education plays at least a partial role in explaining racial differences in cognitive performance. Education and SES generally are known to also have consequences for health outcomes, particularly cardiovascular risk and disease, and these potential effects should also be included in these types of evaluations.

Cardiovascular risk

Cardiovascular disease (CVD) is known to be a risk factor for cognitive decline and neurodegenerative disease. Evidence for the relationship between cardiovascular health and cognitive function shows that adults with elevated cardiovascular risk (CVR; e.g., high blood pressure, diabetes, smoking) and disease (e.g., heart attack, heart failure) show lower cognitive performance and are at greater risk of cognitive decline (including dementia) later in life (Knopman et al., 2001; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995; Vicario et al., 2005; Oveisgharan & Hachinski, 2010; Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011). Cross-sectional studies show that among older adult samples, individuals with cardiovascular disease, higher blood pressure, and greater arterial stiffness display greater cognitive dysfunction, particularly in executive function, memory and attentional domains (DeRight, Jorgensen, & Cabral, 2015; Hajjar, Goldstein, Martin, & Quyyumi, 2016; Liebel et al., 2017).

Risk calculators, such as the Framingham risk score, designed to quantify a person's risk for cardiovascular disease (e.g., stroke, coronary artery disease), using indicators such as diabetes, blood pressure, and smoking habits, have also been shown to predict later cognitive functioning and later progression of dementia (Elias et al., 2004; Viticchi et al, 2017).

The proposed mechanisms for the relationship between cardiovascular risk/disease and cognitive decline remain under investigation and are thought to be somewhat unique to the type of CVD/CVR in question, but with some overlapping mechanistic properties (Liebel & Sweet, 2019). Some include metabolic dysfunction, atherosclerosis and arteriosclerosis, dysregulation of the blood-brain barrier, and compromised cerebral blood flow/perfusion resulting in cerebrovascular disease (e.g., hemorrhagic and ischemic brain changes, cerebral small vessel disease), particular impacts to white matter integrity, and subsequent cognitive impairment including vascular dementia (Jefferson et al., 2007; Bangen et al., 2009; Iadecola, 2013; Iadecola et al., 2016; Moroni et al., 2018; Liebel & Sweet 2019).

Race-based health disparities are also present in cardiovascular risk and disease. Again, African Americans tend to display higher rates of risk factors for cardiovascular disease, as well as higher incidence of the severe negative consequences of vascular disease including stroke (Kurian & Cardarelli, 2007; Magnani et al., 2016). Furthermore, cardiovascular and other health disparities are also highly associated with socioeconomic disparities such as those seen in educational, occupational and income inequality. There is consistent evidence of a link between education, SES and disease, as they often embody access to important resources critical for positive health outcomes (Link & Phelan, 1995; Winkleby et al., 1992; Silventoinen, Pankow, Jousilahti, Hu, & Tuomilehto, 2005; Kanjilal et al., 2006; Veronesi et al., 2016; Mirowsky, 2017). Thus, the role of socioeconomic factors as they relate to both cognitive reserve and

cardiovascular risk is important to consider when evaluating the racial differences in cognitive outcomes. Given this literature, there is evidence to suggest a sequential relationship between SES/cognitive reserve factors and cardiovascular risk in their mediating role of the relationship between racial group membership and cognitive performance.

While there appears to be a concrete understanding in the public health domain about social and socioeconomic determinants of health outcomes, particularly cardiovascular health, these concepts have narrowly been applied to aging research where the concrete link between physical health problems (cardiovascular health in particular) and cognitive functional impairment is also well understood. The goal of the proposed analyses is to evaluate each of these risk factors as playing a sequential role in mediating the relationship between racial group membership and cognitive outcomes.

Neuroimaging Correlates of Cognitive Aging

In addition to cognitive performance measures, the literature suggests age-related cognitive changes and cardiovascular disease burden have effects on neuronal integrity. With the availability of neuroimaging analysis in aging research, there is a wealth of evidence for structural and functional brain changes associated with cognitive decline in late life and their associations with the identified mediators in the proposed analysis.

Magnetic resonance imaging (MRI) allows for imaging of the structure of the brain by producing a strong magnetic field which aligns protons in the water nuclei of tissue corresponding with that magnetic field. Application of radiofrequency (RF) pulses stimulates protons in the body to spin out of this equilibrium, and when the radiofrequency pulse is removed, protons realign with the magnetic field (Hashemi, Bradley, & Lisanti, 2012). The timing of this realignment, or relaxation, as well as the energy released by protons as they realign

with the magnetic field, is dependent on the environment of the molecules, and is thus different for different tissues of the body (e.g., bone, blood, fat, etc.). Tissues are characterized by tissue specific time constants, or relaxation times.

Images collected from MRI rely primarily on two time constants. Longitudinal relaxation time, or T_1, is the time for spinning protons to realign with the magnetic field. Transverse relaxation time, or T_2, is the time for excited protons to lose phase coherence, go out of phase with each other following removal of the RF pulse (Hashemi, Bradley, & Lisanti, 2012). By detecting these properties during the realignment of proton spin back to equilibrium, MRI allows for the imaging of different tissues, (e.g., grey matter, white matter, and cerebrospinal fluid in the brain). The type of image collected from MRI scans differ based on these time properties, and one may be preferred for viewing certain types of tissue abnormalities. In T_1-weighted images, the contrast and brightness of the resulting image is determined by the T_1 properties of the tissues. In these images, white matter and gray matter appear light or gray, while cerebrospinal fluid (CSF) and potential abnormalities (e.g., areas of demyelination) appear dark. In contrast, in T_2 weighted images, the image contrast and brightness is dependent on tissue T_2 properties. In these images, gray matter appears light grey, white matter appears dark, while CSF and lesions appear bright white (or hyperintense), making this sequence preferred for visualizing lesions. These techniques allow for differentiation of tissue types and thus structures within the brain to help quantify brain volume and the volume of specific brain regions.

Regional Volumetric Evidence

Evidence of structural changes in cognitive aging primarily focus on the association between decreased brain volume and cognitive decline (Hedden & Gabrieli, 2004, Salthouse, 2011). There is a general decrease in brain volume as we age, independent of the more extensive

brain atrophy seen in neuropathology such as dementia (Courchesne et al., 2000; Fotenos, Snyder, Girton, Morris & Buckner, 2005; Fjell & Walhovd, 2010). Although there is variability in regions implicated in these volumetric changes, there is consistent evidence of structural changes in the anterior structures of the brain associated with age, including the frontal lobes (Abe et al., 2008; Carne, Vogrin, Litewka & Cook, 2006; Kalpouzos et al., 2009; Allen, Bruss, Brown & Damasio, 2005). Age related volumetric changes are thought to mediate the relationship between age and cognitive changes, as volumetric changes in the prefrontal cortex and temporal lobes are associated with decline in executive functions and episodic memory (Brickman et al., 2006; Head, Rodrigue, Kennedy & Raz; 2008; Head, Kennedy, Rodrigue, & Raz; 2009; Gorbach et al., 2017). There is some criticism regarding the true magnitude of this mediating effect, as well as issues regarding replication of findings (Salthouse, 2011; Van Petten, 2004; Raz & Rodrigue, 2006). Furthermore, the proposed mechanism for volumetric decreases may not be representative of the true neuronal and glial cell changes that occur with age (Salthouse, 2011). While there is a wealth of research suggesting volumetric analyses convey information about gross brain integrity, it is considered to be a somewhat crude measure, with limited association to cognitive function.

White Matter Structure

Another way researchers approach evaluating brain and cognitive changes associated with aging is by focusing specifically on the degradation of white matter. White matter is comprised of the myelinated axonal projections of neurons, and is responsible for communication, and coordination of neural activity of different brain regions. Myelination of axons is responsible for the efficiency of communication across brain regions, as it allows for faster propagation of electrical impulses down the axon. Researchers have evaluated the presence

of white matter structural abnormalities as sources of cognitive impairment through reduction of efficient communication between brain regions (Ylikoski et al., 1993; O'Sullival et al., 2001; Bennet, Madden, Vaidya, Howard & Howard, 2010; de Groot et al., 2001).

White matter hyperintensities (WMH) are a type of structural abnormality seen on neuroimaging thought to result from chronic ischemia associated with cerebral small vessel disease and have been implicated as a source of cognitive dysfunction among older adults (Ylikoski et al., 1993; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009). WMHs are non-specific areas of hyperintense signal appearing on the T2-weighted or FLAIR image and are thought to indicate rarefication of myelin and white matter damage (Mayda, Yoshita & DeCarli, 2010). These white matter abnormalities appear commonly on MRI scans of normally aging older adults as well as in MCI and AD samples, and appear to increase in quantity and volume with age (DeCarli et al., 1995; Gunning-Dixon & Raz, 2003; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Van DenBerg, Geerlings, Biessels, Nederkoorn & Kloppenborg, 2018).

While considered nonspecific in their pathophysiology WMHs are largely thought to be result and indicator of small vessel vascular disease, with a large body of evidence linking WMH volume with cardiovascular risk and disease (de Leeuw, et al., 2000; de Leeuw et al., 2002). In their recent review, Maroni and colleagues (2018) reported consistent evidence from both cross-sectional and longitudinal studies linking various indicators of cardiovascular disease with greater WMH burden, including smoking, hypertension, atrial fibrillation, carotid atherosclerosis, heart failure, diabetes, and congenital heart disease. Some research also points to differential associations between cardiovascular risk factors and location of WMH. Evidence suggests that periventricular white matter hyperintensities (PVWMH, lesions adjacent to the lateral ventricles), more so than deep white matter hyperintensities (DWMH, located in

subcortical white matter, distinct from ventricles), show stronger association with age and vascular risk factors, although this evidence is mixed (Delando-Wood et al., 2008; deGroot et al., 2001; DeCarli, Fletcher, Ramey, Harvey, & Jagust; 2005).

WMHs are also associated with cognitive function in aging populations, as well as other neurologic populations who display significant white matter disease, with studies demonstrating that individuals with greater volume of WMH display poorer cognitive performance on various tasks. The pathology of multiple sclerosis (MS), which involves diffuse white matter demyelination, demonstrates how white matter lesions may result in cognitive impairment, as cognitive impairment, particularly in attention, processing speed, executive function and memory, appears in 40-70% of MS patients, and is shown to be related to white matter lesion burden (Rogers & Paynegyres, 2007). A similar pattern is seen in high WMH burden in certain neurodegenerative disease like vascular dementia, as WMH burden along with cerebral microhemorrhages and lacunar infarcts are considered the primary pathology in vascular dementia (Gorelick et al., 2011; Prins & Scheltens, 2015). Independent of these pathological processes where white matter disease is a primary feature, the association between WMH burden and cognition is still present. An early study conducted by DeCarli et al. (1995) found that in otherwise healthy adults, greater WMH volume was associated with poorer performance on immediate and delayed memory, processing speed, and other frontal-lobe mediated neuropsychological tests. Similarly, recent reviews and meta-analytic data of the relations between WMH and cognitive performance report consistent negative associations between WMH and executive performance and information processing speed (Aggarwal et al., 2010; Prins & Scheltens, 2015; Kloppenborg at al., 2014; Van DenBerg, et al. 2018). Processing speed and executive performance are thought to be particularly affected by WM lesions due to

disruption of the efficient subcortical connections between brain regions which are required for these tasks (Delano-Wood et al., 2008). Memory has also been implicated in the progression of WMH, with one study finding that the progression of WMH volume over a span of 4 years, was associated with corresponding decline in both executive functioning and memory (Maillard et al., 2012). It is also increasingly recognized that vascular disease and resulting white matter changes in the form of WMH are involved in AD pathology, in addition to amyloid burden (O'Brien & Markus, 2014; Love & Miners, 2015; Love & Miners, 2016; Alosco et al., 2018).

Generally, there is strong evidence that these lesions which are associated with age and appear to be partially a consequence of vascular disease have consequences for cognitive performance in both normal aging and in neurodegenerative disease. WMH are an ideal measure in an analysis of cardiovascular risk and cognitive outcomes, particularly as they may demonstrate how populations susceptible to greater cardiovascular health risks may in turn be at greater risk for specific neuropathology leading to poorer cognitive outcomes.

Many studies conducted thus far on WMH in aging include largely White samples, and there are very few studies that evaluate the potentially variable relations between these WM lesions and elevated cardiovascular risk factors among racial minority groups. One study conducted in a sample of older African Americans found that WMH volume, particularly in the frontal lobes, was associated with poorer delayed memory performance (Meier et al., 2012). However, this study did not evaluate the potential influence of cardiovascular disease and other variables relevant to cognitive aging that might differ based on racial group membership.

Diffusion Tensor Imaging

Another method for quantifying the degradation of white matter is diffusion tensor imaging (DTI), a neuroimaging technique that evaluates white matter structure through the

diffusion of water in WM tracts (Basser, Mattiello, & LeBihan, 1994). DTI is perhaps even more sensitive a measure of white matter degradation, as it may detect microstructural changes which precede actual lesion formation (Salthouse, 2011).

Water molecules typically diffuse down WM tracts in a parallel direction to the axon and myelin sheath. Molecular water diffusion perpendicular to the axon is restricted due to the axonal cell membrane, microfilaments, and the presence of the myelin sheath (Pierpaoli, & Basser, 1996). Thus, the movement of water within fibrous tissues like WM is considered anisotropic, or primarily unidirectional. As fibers begin to degrade and structural integrity is compromised, diffusion becomes increasingly isotropic, and more directionally heterogeneous. DTI captures the degree of anisotropic and isotropic molecular water movement based on the measurement of the DTI-based eigenvalues $\lambda 1$, $\lambda 2$, and $\lambda 3$, which denote the rate of diffusion corresponding to the three principal axes of the diffusion ellipsoid within a diffusion tensor (see Figure 1; Alexander, Lee, Lazar & Field, 2007). Using these values, metrics for determining the degree of isotropic and anisotropic molecular water diffusion in WM can be derived.

The two common DTI derived metrics include mean diffusivity (MD) and fractional anisotropy (FA). MD refers to the average amount of water diffusion, based on the average diffusivity across the three eigenvalues (three directional axes) with higher values indicated greater diffusivity, and greater isotropy (Pierpaoli & Basser, 1996; Bennet et al., 2010). Conversely, FA represents the diffusion of water along the primary axis (parallel to the axon) relative to the other two axes (Pierpaoli & Basser; Bennet et al., 2010). Higher FA values represent greater diffusivity in the direction parallel to the axon as opposed to perpendicular to the axon and is an indicator of greater anisotropy. Using these two values descriptively, more "intact" white matter tracts will display greater anisotropic movement, reflecting greater

coherence of orientation of water diffusion, and thus greater FA and/or lower MD. Lower FA and/or greater MD, indicating greater isotropic diffusion, would represent the breakdown of white matter. These profiles correspond with the age-related DTI changes noted in the literature, which pervasively demonstrate age- related increases in MD and decreases in FA (O'Sullivan et al., 2001; Hsu et al., 2008; Lebel, Caverhill-Godkewitsch, & Beaulieu, 2010; Carmichael & Lockhart, 2011; Madden et al., 2012). Additionally, there appears to be worsening of WM degradation based on these metrics in pathological aging. MCI and AD samples show decreased FA, and increased MD relative to healthy controls (Bartzokis et al., 2014; Alves et al., 2012; Bosch et al., 2012; Gyebnar et al., 2018).

Other metrics including radial diffusivity (RD) and axial diffusivity (AD) have also been used in relation to the more frequently used MD and FA to better understand the etiology of white matter structural changes. AD represents diffusivity only in the primary direction, where RD refers to diffusivity in the perpendicular axes (Pierpaoli & Basser, 1996; Bennet et al., 2010). There is more consistent evidence for an increase in RD associated with aging which is also associated with decreases in FA (Bhagat and Beaulieu, 2004; Davis et al., 2009; Bennet et al., 2010). There is less of a consistent directionality of AD change associated with aging, with studies finding evidence of both increases and decreases in AD with advanced age (Bennet et al., 2010; Burzynska et al., 2010).

Like regional volumetric changes, DTI derived, age-associated WM changes appear to follow an anterior-posterior progression, with age-related changes in MD and FA seen most prominently in anterior projections. Regional differences in FA seen in initial DTI studies were common in the genu of the corpus callosum, and pericallosal WM compared to in more posterior regions (Pfefferbaum et al., 2000; Sullivan & Pfefferbaum, 2003). These findings have been

replicated with work showing greatest WM change in tracts which transverse frontal and parietal lobe structures, where more advanced pathological processes in MCI and AD see more posterior and temporal changes (Burzynska et al., 2010; Michielse et al., 2010; Davis et al., 2009; Head et al., 2004; Lebel et al., 2010). These findings support the white matter retrogenesis hypothesis, where areas that myelinate later in development become the first to experience degradation (Brickman et al., 2012). Additionally, recent evidence suggests that as well as an anterior-posterior gradient for WM changes, there is also a superior-inferior gradient, with greater degradation seen in cortico-cortical WM connections (e.g., superior longitudinal fasciculus) compared to tracts connecting cortical and subcortical regions (e.g., corticospinal) (Stadlbauer, Salomonowitz, Strunk, Hammen, Ganslandt, 2008).

Age associated changes in DTI derived WM structure are also known to be related to cognitive performance in older adulthood, and similar to the pattern of WM lesions, are thought to mediate the relationship between age and cognitive decline (Grieve, Williams, Paul., Clark & Gordon, 2007; Raz & Kennedy, 2009; Gold., Powell, Xuan, Jicha, & Smith, 2010). WM degradation is implicated in the "disconnection" theory of cognitive decline, which posits that the disruptions in white matter tracts that occur with age are the structural basis for executive dysfunction and processing speed inefficiencies that underlie cognitive difficulties in aging and neurodegenerative disease (O'Sullivan et al., 2001; Bartokis et al., 2004; Bartokis, 2004; Bennet & Madden, 2014). Many studies report findings of decreased executive function, working memory, and processing speed associated with decreased FA and higher MD in aging (Grieve et al., 2007; Charlton et al., 2006; Kennedy & Raz, 2009; Kerchner et al., 2012; Mayo et al., 2018; Hinault, Larcher, Bherer, Courtney & Dagher, 2019). In these studies, there is consistent evidence of superior and anterior transversing tracts involved in age related changes and

cognitive performance, namely the genu of the corpus callosum, the corona radiata, and the superior longitudinal fasciculus. These were the focus of the planned DTI analyses in the present study.

Although not considered as strongly an indicator of vascular disease in the way WMHs are (diffusion changes in WM are attributed to multiple etiologies), there is sufficient evidence for a vascular influence of WM microstructure (Delano-Wood et al., 2010; Kennedy & Raz, 2009). Kennedy and Raz (2009) found that among diagnosed hypertensive adults there was reduced WM anisotropy and increased diffusivity beyond what was due to age. Also, in the non-hypertensive adults, higher arterial pressure was associated with deleterious WM changes in frontal regions.

Again, evidence of reported differences in DTI WM metrics based on race-based socioeconomic and vascular risk factors is limited. One study evaluated vascular risk factors alone in an African American sample and found that untreated elevated mean arterial blood pressure was related to lower FA in the genu of the corpus callosum but not to neuropsychological test performance (Leritz et al., 2010). This study provides some support for the need for the proposed analysis, as differences in cardiovascular risk indicators among African Americans may explain outcome differences seen in disease prevalence and cognitive performance across racial groups.

Current Aims

The aim of the present analysis was to explicate the racial differences observed in cognitive outcomes through a trajectory of socioeconomic and environmental risk factors that appear to incur disproportionate cardiovascular and WM disease burden. Specifically, we hypothesized that racial differences in cognitive performance would also be observed in white

matter structure as indicated by WMH volume and DTI diffusivity metrics in anterior transversing tracts, as these are sensitive neuroanatomical correlates of age-related cognitive decline. Additionally, we hypothesized that the relationships between racial group membership and cognitive/WM outcomes would be mediated by indicators of cardiovascular risk, as Black/African Americans tend to display higher levels of CV risk which represent risk for both cognitive decline and white matter degradation. Furthermore, we hypothesized that racial differences seen in cardiovascular risk would itself be mediated by the various socio-economic and environmental risk factors which are disparate between racial groups, including education and occupational intensity. Finally, we hypothesized a sequential mediating role of socioeconomic factors and cardiovascular risk on the relationship between racial group membership and cognitive/WM outcomes (Figure 2), and such an analysis might expand upon research suggesting that attainment or absence of important lifestyle factors may place members of certain demographics at greater risk of negative health trajectories and may explain racial differences seen in cognitive health outcomes.

CHAPTER 2

METHODS

Sample and Participants

The participants and data in the current analysis were obtained from the public data base provided by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://www.loni.usc.edu/). ADNI is a multi-site, longitudinal study which was developed to support early detection and tracking of the course of AD through clinical, genetic, neuroimaging, and biomedical markers of healthy, MCI, and AD subjects. The ADNI participant data was collected across four cohorts, corresponding to four waves of data collection, ADNI1, ADNI GO, ADNI2, and ADNI3. Written informed consent was obtained and approved by the Institutional Review Board at each participating center, and participants took part in baseline clinical, neuropsychological, and MRI assessments, and additional subsequent assessment depending upon the diagnostic group and study cohort.

The number of participants included in the final analysis was dependent on availability of data within the ADNI data set within cohorts. Due to small proportion of Black participants with completed data for the variables of interest (n=111), a matched selection of White participants was chosen to make statistical comparisons between racial groups of equivalent group size. Based on the proportion of males and females, and cognitive status among the Black sample, a matched selection of white participants with equal representation of gender and AD status was selected using SPSS to ensure an equal distribution of males and females, as well as disease status across both groups. Analyses based on cognitive performance included participant data

from all cohorts where available (ADNI1, Go, 2 and 3), with a total sample size of n=221 (See **Chapter 3**). Analyses including imaging WMH data included only participants from the ADNI1, ADNI GO, and ADNI 2 cohorts (n=153), while DTI data was only available for ADNI GO and ADNI2 (n=22; See **Chapter 4**).

Variables and Measures

Racial Group Membership and Socio-environmental Factors

Racial group membership was reported by each ADNI participant at the initial screening visit. Participants reported race and ethnicity (i.e., Hispanic/non-Hispanic origin). For the purposes of the proposed analysis, individuals who identify as White or Black/African American and self-identified as non-Hispanic were included in the analysis.

Educational attainment was determined by self-reported years of education. Self-reported longest lifetime occupation was also collected from the ADNI data database. Occupational intensity was determined using the US Department of Labor O*NET resource, a data collection project used and source of standardized information on job characteristics and worker attributes for numerous career positions. Modeled after a previous study using this network (Pool et al., 2016), ratings of importance for 10 cognitive processes required for each occupation were averaged to create a summary score to represent occupational cognitive intensity ranging from 0 to 100 for each participant's named occupation.

Cardiovascular Risk

Cardiovascular risk was determined using the Framingham Risk Score to calculate 10-year hard coronary artery disease (Wilson et al., 1998). This score calculates risk based on gender, age, systolic blood pressure, treatment for hypertension, smoking history, diabetes

history, and body mass index (BMI). The information used to calculate this score was gathered from vital signs and medical history collected from available ADNI records.

Cognitive Assessments

Cognitive performance was measured using the psychometrically validated ADNI-Executive Function (EF) and ADNI-Memory (Mem) composite scores (Gibbons et al., 2012; Crane et al., 2012). The tasks included for the ADNI-EF composite scores included the Digit Symbol Substitution and Digit Span Backwards from the WAIS-R, Trails A and B, Category Fluency, and Clock Drawing subtests. The tasks included for the ADNI-MEM composite scores included longitudinal Rey Auditory Verbal Learning Test (RAVLT), AD Assessment Schedule - Cognition (ADAS-Cog), Mini-Mental State Examination (MMSE), and Logical Memory subtest. The methods and description of IRT analysis for these scores, including accounting for missing data from subtests across ADNI waves are described in the above manuscripts, and in the publicly available ADNI methods documents (Gibbons et al., 2012; Crane et al., 2012).

MRI Acquisition

Imaging data was collected from ADNI baseline data for precalculated WMH volumes and DTI metrics. Participant data was collected from several sites, equipped with a 1.5 Tesla scanner for part of the ADNI1 cohort, and a 3-Tesla MRI scanner for the remaining ADNI1, ADNI2, and ADNI GO cohorts. The 3D Magnetization Prepared - Rapid Gradient Echo (MPRAGE) T_1-weighted sequence was acquired using the following parameters: repetition time (TR) =2300 ms; echo time (TE) = 2.98 ms; inversion time (TI) =900 ms; 170 sagittal slices; within plane FOV = 256 × 240 mm; voxel size = 1.1 × 1.1 × 1.2 mm; flip angle = 9 °; bandwidth = 240 Hz/pix. The T_2 FLAIR scans were obtained using an echo-planar imaging sequence with the following parameters: TR = 9000 ms, TE = 90 ms, and TI = 2500 ms, number

of slices = 42 axial, slice thickness = 5 mm. The axial DTI sequences were obtained using the following parameters: T1-weighted SPGR sequences (256 × 256 matrix; voxel size = 1.2 × 1.0 × 1.0 mm^3; TI = 400 ms; TR = 6.98 ms; TE = 2.85 ms; flip angle = 11°), and diffusion-weighted images (DWI; 256 × 256 matrix; voxel size: 2.7 × 2.7 × 2.7 mm^3; TR = 9000 ms; scan time = 9 min) were collected. 46 separate images were acquired for each DTI scan. Five T2-weighted images with no diffusion sensitization (b_0 images) and 41 diffusion-weighted images (b = 1000 s/mm^2).

Each MPRAGE image provided is linked with related files which have undergone specific pre-processing correction steps provided by the Mayo Clinic including the following (replicated and available from http://adni.loni.usc.edu/methods/mri-tool/mri-analysis/#mri-pre-processing-container).

1. Gradwarp: gradwarp is a system-specific correction of image geometry distortion due to gradient non-linearity. The degree to which images are distorted due to gradient non-linearity varies with each specific gradient model. We anticipate that most users will prefer to use images which have been corrected for gradient non-linearity distortion in analyses.

2. B1 non-uniformity: this correction procedure employs the B1 calibration scans noted in the protocol above to correct the image intensity non-uniformity that results when RF transmission is performed with a more uniform body coil while reception is performed with a less uniform head coil.

3. N3: N3 is a histogram peak sharpening algorithm that is applied to all images. It is applied after grad warp and after B1 correction for systems on which these two correction steps are performed. N3 will reduce intensity non-uniformity due to the wave or the

dielectric effect at 3T. 1.5T scans also undergo N3 processing to reduce residual intensity non-uniformity.

White Matter Hyperintensities

WMHs were segmented using different approaches in ADNI1 (Schwarz et al., 2009) and ADNI GO and ADNI2 (DeCarli et al., 2005). The method used in ADNI1 employed proton density (PD), T1, and T2 magnetic resonance images. A Bayesian Markov random field approach was adopted, where the joint posterior probability of the presence of WMH at each voxel is maximized. The posterior probability consists of likelihood computed from image intensities, spatial prior that regularizes the location of WMHs, and contextual prior that encourages neighbor voxels to have the same labels. The method used in ADNI GO and ADNI2 employed fluid-attenuated inversion recovery (FLAIR) and T1 images. FLAIR are first coregistered to the T1 image, then an inhomogeneity correction is applied. The binary WMH mask is then estimated based on histogram fitting and thresholding at 3.5 standard deviations above the mean signal in brain matter distribution. The spatial prior and tissue class constraints are incorporated with the WMH mask in a Bayesian approach for the final segmentation. Because these methodologies resulted in significant difference in WMH volumes across waves, this was controlled for in the analysis by standardizing volumes within each phase, thus WMH volumes were represented by z-scores.

Diffusion Tensor Imaging

DTI values were obtained through the processing steps described in ADNI procedures, and consistent with work published using the ADNI 3T MR available data (Nir et al., 2013). Briefly, raw DWI volumes were aligned to the average b0 image to correct for head motion and eddy current distortions using Functional MRI of the Brain (FMRIB) Software Library (FSL)

(www.fmrib.ox.ac.uk/fsl). Extra-cerebral tissue was removed from the T_1-weighted anatomical scans using ROBEX and FreeSurfer (Iglesias et al., 2011; Fischl et al., 2004). Anatomical scans were corrected for intensity inhomogeneity using the MNI *nu_correct* tool (www.bic.mni.mcgill.ca/software/). Non-brain tissue was also removed from the diffusion-weighted images using the Brain Extraction Tool (BET) from FSL (Smith, 2002). Data from different subjects was aligned into the same 3D coordinate space with each T_1-weighted anatomical image linearly aligned to a standard template using FSL *flirt* (Jenkinson, Bannister Brady & Smith, 2002). Echo-planar imaging (EPI) correction for EPI-induced susceptibility artifacts was also completed using (FSL *flirt*). The resulting 3D deformation fields were then applied to the remaining 41 DWI volumes prior to estimating diffusion parameters. A single diffusion tensor (ellipsoid) was modeled for each voxel of the brain eddy- and EPI-corrected DWI scans using FSL *dtifit*, and scalar anisotropy and diffusivity maps were obtained from the resulting diffusion tensor eigenvalues (we employ only FA and MD in the current analysis).

FA images from The Johns Hopkins University (JHU) ICBM-DTI-81 White Matter Atlas (Hua et al., 2008; Mori et al., 2008) were elastically registered to each subject's corrected FA images, and these images were applied to the stereotaxic JHU "Eve" atlas WM labels (http://cmrm.med.jhmi.edu/cmrm/atlas/human_data/file/AtlasExplanation2.htm). The atlas ROIs were superimposed into the same coordinate space as subject results, and the average FA and MD were calculated within each of the ROIs for each subject.

Tract-based spatial statistics (TBSS) (Smith et al., 2006), provided in the FSL software package (http://www.fmrib.ox.ac.uk/fsl/), was also performed according to protocols outlined by the ENIGMA-DTI group: http://enigma.loni.ucla.edu/ongoing/dti-working-group/. All subjects' corrected FA maps were linearly, then elastically registered (Leow et al., 2007) to the ENIGMA-

DTI template in ICBM space. The resulting 3D deformation fields were then applied to the three diffusivity maps. All subjects' spatially normalized FA and MD data were projected onto the skeletonized ENIGMA-DTI template. Mean anisotropy and diffusivity measures were calculated along the skeleton in the ROIs. The ROIs included in this analysis were global white matter, genu of the corpus callosum, anterior cingulum, and superior longitudinal fasciculus, based on previous literature that points to these anterior and cortico-cortical tracts implicated in both aging and in association with vascular risk (Stadlbauer, Salomonowitz, Strunk, Hammen, Ganslandt, 2008).

Statistical Plan and Power Analysis

A standardized composite score for SES measures was calculated based on education and occupational intensity to represent a cognitive reserve composite.

Despite theoretical justification for temporal precedence, the current data are cross-sectional. To address the primary aims, a series of sequential, mediated regression models using the Hayes PROCESS Macro in SPSS (Hayes, 2012) were conducted. Specifically, these models probed the direct and indirect effects of racial group membership on cognitive performance, WMH, and DTI metrics (MD and FA for each region of interest). Cognitive reserve and cardiovascular risk were included sequentially as mediators of the association between racial group membership and each outcome. These models assume several hypotheses: 1) Racial group membership predicts the primary outcome (i.e., cognitive performance, WMH, DTI metrics, for each model respectively), 2) The relationship between racial group membership and the primary outcomes is mediated by socioeconomic status, 3) The relationship between racial group membership and the primary outcomes is mediated by cardiovascular risk, 4) The relationship between racial group membership and the primary outcomes is mediated sequentially by

socioeconomic status and cardiovascular risk, such that inclusion of both mediators in the model explains greater variability in the X on Y relationship above and beyond what is explained by either of these mediators alone.

The series of conceptual models is presented in Figure 2.1. The corresponding statistical model is presented in Figure 2.2. Each model output provided by Hayes process includes the direct effect of X on Y, the indirect effect of X on Y through M_1, the indirect effect of X on Y through M_2, and the indirect effect of X on Y through M_1 and M_2 (where X = race, Y = cognition/WMH/DTI, M_1 = cognitive reserve, and M_2 = CVR). At each of these levels, the change in variance in the relationship between X and Y accounted for by inclusion of each mediator in the model is reported in the form of the R^2 statistic.

An *a priori* power analysis was conducted to determine the necessary sample size needed to detect a significant effect using G*Power software (Faul, Erdfelder, Buchner, & Lang, 2009). This analysis was based on an expected medium effect size, and alpha level of .05 was corrected to .016 account for repeated analyses for three primary outcomes (cognitive performance, WMH, and DTI). To achieve power of 0.8 with five predictor variables and included in each mediation analysis, the total sample size required was estimated at 124 participants. Based on this power analysis, it was determined that the limited sample available for the DTI analysis was underpowered to detect the hypothesized effect, and this analysis was modified and carried out in an exploratory fashion (See **Chapter 4**).

CHAPTER 3

CARDIOVASCULAR RISK PARTIALLY EXPLAINS RACIAL DIFFERENCES IN EXECUTIVE PERFORMANCE [1]

[1] Robinson, T.L., and L.S. Miller. To be submitted to *The Clinical Neuropsychologist*.

Abstract

While cognitive decline is known to occur universally in aging, there is evidence of disparity in cognitive decline and risk of disease across racial groups. There are also known disparities in risk and protective factors for cognitive decline, with Black/African Americans displaying a greater degree of cardiovascular risk (CVR) and disease, while historically demonstrating lesser access and attainment of certain protective factors, like educational and occupational attainment. The current analysis sought to evaluate differences in cognitive outcomes across racial groups as a consequence of differential attainment of these risk and protective factors. Using a mediated regression model, we evaluated if the association between racial group membership and performance on executive and memory tasks was mediated sequentially by cognitive reserve (CR) factors and CVR as measured by Framingham Risk Score (FRS) in a matched sample of Black (n=111) and White (n=110) older adults. Results showed that Black participants displayed greater CVR compared to White participants, but there were no differences in education or occupational intensity. Black participants also displayed lower mean executive performance scores, but there was no significant difference in memory performance. In the regression analysis, racial group membership significantly predicted executive performance, and this relationship was partially mediated by CVR, but not by education and occupational attainment. These results suggest that differences in CVR across racial groups partially explain differences in executive function performance, despite similar attainment of cognitive reserve factors. Findings suggest that CVR may be a target for prevention of cognitive decline among Black older adults, while there remain unexplained contributors to racial disparities in cognitive performance.

Introduction

Numerous efforts and resources are directed to understanding, preventing, and intervening in the course of cognitive and functional decline in older adults. Research on risk and protective factors for cognitive decline in both normal and pathological aging identifies risk based on genetic, physical health, and socio-environmental/lifestyle factors. Protective factors, including cognitive reserve (e.g., educational attainment, occupational complexity) and health factors like cardiovascular disease and risk, have been discussed as potential modifiable risk factors to affect cognitive and functional changes in aging (Stern, Alexander, Prohovnik, & Mayeux, 1992; Yaffe et al., 2020). However, there is evidence of differences in late life cognitive performance across racial groups, including evidence of greater risk of dementia (e.g., Alzheimer's dementia) among Black/African American older adults (Weuve et al., 2018). Given the breadth of evidence suggesting racial/ethnic disparities in important risk and protective factors for cognitive health in aging, there is reason to evaluate the relation between racial group membership and cognitive outcomes in late life as a result of a trajectory of differential socioeconomic and physical health risk factors which also impact cognitive health. The purpose of the current analysis was to evaluate if observed differences in cognitive performance of Black and White older adults are explained by differential attainment of socioeconomically based cognitive reserve factors, and subsequent disparity in cardiovascular risk.

There is an expected degree of cognitive change that occurs with aging and this age-related cognitive decline (ARCD) exists independently of a pathological neurodegenerative process (Boyle et al., 2013; Carlo et al., 2000; Ebly, Hogan & Parhad, 1995). Cognitive change in aging can impact multiple domains including attention, processing speed, memory, spatial processing, and executive function (Glisky, 2007; Meijer, van Boxtel, van Gerven, van Hooren,

& Jolles, 2009; Tucker-Drob, Johnson, & Jones, 2009). In this analysis, we focus on the domains of memory and executive function, as there is evidence of executive functioning (e.g., inhibitory control, working memory, and cognitive flexibility) being highly sensitive to early decline in the aging process (Raz, 2000; Gonoi et al., 2010; Diamond, 2013; Brickman et al., 2012). Memory is also a domain commonly implicated in aging, particularly in the pattern of memory decline seen in AD, and its presumed diagnostic precursor, amnestic MCI (Graham, Emery, & Hodges, 2004; Nyberg et al., 2012; Gorbach et al., 2017). Deficits in both memory and executive functioning are thought to be highly related to functional changes in aging, given their importance for independence in activities of daily living (Hering, Kliegel, Rendell, Craik, & Rose, 2018; Cahn-Weiner, Boyle, & Malloy, 2002).

In identifying risk and protective factors for cognitive aging, cognitive reserve and cardiovascular disease are commonly discussed, and it is important to consider how racial disparities among these variables may contribute to cognitive outcomes among historically marginalized populations. The cognitive reserve hypothesis posits that some individuals demonstrate less clinical expression of brain changes associated with aging or disease (Stern, Alexander, Prohovnik, & Mayeux, 1992). Cognitive reserve is frequently operationalized using proxy measures such as pre-morbid IQ, educational attainment, or occupational complexity, as it is theorized that these contribute to and support the use of efficient executive and processing skills, cognitive flexibility, and thus compensatory neural strategies in the face oof brain change (Scarmeas, Albert, Manly, & Stern, 2006; Siedlecki et al., 2009). In the United States, disparities in educational access, educational attainment, and education quality have historically fallen along racial lines, with education being both an early point of disparity between Black and White Americans, and an early determinant of a number of downstream health and economic

consequences (Norman, Ault, Bentz, & Meskimen, 2001; Sullivan, Meschede, Dietrich, & Shapiro, 2015). Furthermore, labor statistics provide evidence for disparities in the hiring of racial minorities which further divide racial groups at the level of occupational attainment (Masel, Raji, & Peek, 2010; Quillian, Pager, Hexel, & Midtbøen, 2017). Literature which has addressed the effects of educational disparities in Black and White Americans has demonstrated that African American samples tend to have lower average educational attainment, and higher rates of cognitive decline compared to White samples (Sachs-Ericsson & Blazer, 2005). Education and related factors have been shown to mediate the relationship between race and cognitive decline and other cognitive outcomes in some samples (e.g., education and literacy, education and health literacy, education and physical activity; Sachs-Ericsson & Blazer, 2005; Masel, Raji & Peek, 2010; Sisco et al., 2014; Gupta et al., 2016; Jean et al., 2019).

The downstream effects of disparities in education and occupation on health outcomes are also important to consider in their relation to cognitive and brain health. Cardiovascular disease is shown to be related to cognitive decline, and more evidence has revealed that risk factors for cardiovascular disease are related to cognition (Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011). Adults with hypertension, diabetes, higher BMI, and other risk factors for cardiovascular disease demonstrate greater evidence of cognitive decline later in life (Knopman et al., 2001; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995; Oveisgharan & Hachinski, 2010; Yaffe et al., 2020). Cross-sectional studies show that among older adult samples, individuals with cardiovascular disease, higher blood pressure, and greater arterial stiffness display greater cognitive dysfunction, particularly in executive function, memory, and attentional domains (Elias, Wolf, D'Agostino, Cobb & White, 1993; Hajjar, Goldstein, Martin, & Quyyumi, 2016; Leibel et al., 2017). There are various proposed mechanisms for this

relationship, including metabolic dysfunction, dysregulation of the blood-brain barrier, and compromised perfusion associated with cardiovascular risk and disease which in turn lead to cerebrovascular changes and thus cognitive impairment (Jefferson et al., 2007; Bangen et al., 2009; Iadecola, 2013; Iadecola et al., 2016; Moroni et al., 2018; Liebel & Sweet 2019). Risk calculators, such as the Framingham risk score, designed to quantify a person's risk for cardiovascular disease (e.g., stroke, coronary artery disease), using indicators such as diabetes, blood pressure, and smoking habits, have also been shown to predict cognitive functioning and later progression of dementia (Elias et al., 2004; Viticchi et al, 2017).

Race-based disparities are also present in cardiovascular risk and disease. Again, African Americans tend to display higher rates of risk factors for cardiovascular disease, as well as higher incidence of severe negative consequences of cardiovascular disease including stroke (Kurian & Cardarelli, 2007; Magnani et al., 2016). These disparities are also highly associated with socioeconomic disparities such as those seen in educational and occupational attainment, and income. There is consistent evidence of a link between education, SES, and health or disease, as they often embody access to important recourses critical for positive health outcomes (Link & Phelan, 1995; Winkleby et al., 1992; Silventoinen, Pankow, Jousilahti, Hu, & Tuomilehto, 2005; Kanjilal et al., 2006; Veronesi et al., 2016; Mirowsky, 2017). Thus, the role of socioeconomic factors as they relate to both cognitive reserve and cardiovascular risk is important to consider when evaluating the racial differences in cognitive outcomes. Given this literature, there is evidence to suggest a sequential relationship between cognitive reserve factors and cardiovascular risk in their mediating role of the relationship between racial group membership and cognitive performance. The goal of the proposed analyses is to evaluate each of these risk factors as playing a sequential role in mediating the relationship between racial group

membership and cognitive outcomes. We hypothesized: 1) Racial group membership predicts cognitive performance, 2) The relationship between racial group membership and cognition is mediated by socioeconomic status, 3) The relationship between racial group membership and cognition is mediated by cardiovascular risk, 4) The relationship between racial group membership and cognition is mediated sequentially by socioeconomic status and cardiovascular risk, such that inclusion of both mediators in the model explains greater variability in the X on Y relationship above and beyond what is explained by either of these mediators alone.

Methods

Sample and Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

A total of 111 participants with available medical health and cognitive test data at screening/baseline identified as Black/African American. Given the disproportionate representation of Black participants relative to White participants in the ADNI cohorts, a matched sample of 110 White participants was selected. Based on the proportion of males and females, and cognitive status among the Black sample, a matched selection of white participants with equal representation of gender and AD status was selected using SPSS to ensure equal

distribution across racial groups. The final sample consisted of 221 participants, (138 women and 83 men) with a mean age of 72.54 years (*SD* = 7.34). Descriptive statistics for the total sample and racial groups included in the sample are presented in Table 3.1.

Variables and Measures

Racial Group Membership, Education and Occupation

Individuals from the sample who identified as White or Black/African American and self-identified as non-Hispanic were included in the analysis. Educational attainment was also self-reported years of education provided in ADNI. Self-reported longest lifetime occupation was also collected from ADNI. Occupational intensity was calculated for each participant's reported occupation using the US Department of Labor Occupational Information Network (O*NET) resource, a data source of standardized information on job characteristics and worker attributes for numerous career positions. Modeled after a previous study using this network (Pool et al., 2016), ratings (0-7) available on O*NET of the importance of 10 cognitively related work variables for each participant's occupation were averaged to create occupational cognitive requirements summary scores for each participant. The 10 cognitively related tasks are presented in Table 3.2.

Cardiovascular Risk

Cardiovascular risk was determined using the Framingham Risk Score to calculate 10-year hard coronary artery disease (Wilson et al., 1998). This score calculates risk based on gender, age, systolic blood pressure, treatment for hypertension, smoking history, diabetes history, and body mass index (BMI). The information used to calculate this score was gathered from vital signs and medical history collected from available ADNI records.

Cognitive Performance

Cognitive performance was measured using the psychometrically validated ADNI-Executive Function (EF) and ADNI-Memory (Mem) composite scores (Gibbons et al., 2012; Crane et al., 2012). The tasks included for the ADNI-EF composite scores included the Digit Symbol Substitution and Digit Span Backwards from the WAIS-R, Trail Making Test Part A and B, Category Fluency, and Clock Drawing subtests. The tasks included for the ADNI-MEM composite scores included longitudinal Rey Auditory Verbal Learning Test (RAVLT), AD Assessment Schedule - Cognition (ADAS-Cog,), Mini-Mental State Examination (MMSE), and Logical Memory subtest. The methods and description of IRT analysis for these scores, including accounting for missing data from subtests across ADNI waves are described in the above manuscripts, and are also described in the ADNI methods documents.

Statistical Plan

Bivariate correlations were conducted to assess the relationships between variables of interest. A standardized composite score for the socioeconomically based cognitive reserve variables was calculated using a combined z-score of education and average scores for cognitive work activities for each participant.

To address the primary aim, a serial mediated regression analysis using Hayes' PROCESS Macro for SPSS (Hayes, 2012) was applied to assess the direct effect of racial group membership on cognitive performance, and the individual and sequential mediating effects of cognitive reserve composite and cardiovascular risk scores. This model probed 1) the direct effect of racial group membership on cognitive performance, 2) the indirect/mediating effect of cognitive reserve on the relationship between racial group membership and cognitive performance 3) the indirect/mediating effect of CVR on the relationship between racial group

membership and cognitive performance, and 4) The sequential mediating effect of cognitive reserve and CVR on the relationship between racial group membership and cognitive performance. The conceptual model is presented in Figure 2.1.

An *a priori* power analysis indicated that based on an expected medium effect size and corrected alpha level for repeated analysis (executive function and memory), a total sample of 124 participants was needed to achieve power of 0.8 in our model.

Results

Sample Characteristics

There was no significant difference in mean years of education between racial groups, (M=15.52 years, SD = 2.84; $t(219) = -1.73$, $p = .09$). There was also no significant difference in occupational cognitive requirements scores, ($t(219) = -1.15$, $p = .25$), and the cognitive reserve composite did not differ by racial groups, ($t(219) = -1.70$, $p = 0.09$).

The average Framingham risk score (FRS) for the overall sample was 18.36 (SD = 3.94), and the Black/African American participants had a higher mean score compared to the White participants (M = 17.79, SD = 3.88; $t(219) = 2.15$, $p < .05$).

The total sample had a mean memory composite score of 0.43 (SD = 0.86), with z-scores ranging from -1.89 to 2.43. The mean executive function composite score was 0.21 (SD = 1.11), with z-scores ranges from -3.02 to 2.73. Black and White participants in this sample did not differ in memory performance, ($t(219) = 0.14$, $p = .89$), however, Black sample participants displayed a lower mean composite score in the executive functioning domain compared to the White sample ($t(219) = -3.36$, $p < .01$).

Bivariate Correlations

Bivariate correlational analysis of the variables of interest are displayed in Table 3.3. These analyses revealed significant relationships between the cognitive reserve composite score and ADNI-EF (r = .19, p < .01), CR composite score and ADNI-Mem (r = .21, p < .01), FRS and ADNI-EF (r = -28, p < .001), and FRS and ADNI-Mem (r = -.15, p < .05). Age was also significantly related to cognitive reserve composite, FRS, and both cognitive composite scores, and so it was controlled for in the primary analysis.

Sequential Mediation Model

The results of the regression analysis and statistical model are presented in Figure 3.1. When evaluating executive functioning performance as the primary outcome variable, while controlling for age, the overall model was significant (R^2 =16.54, p <.001). The analysis of the total effect of racial group membership on executive performance was significant (β = 0.56, SE = 0.14, p <0.0001). This effect was mediated by M2, as the indirect pathway of the effect of race on executive performance through FRS was significant (β = 0.052, SE = 0.027, p <0.01). While there was a significant effect of the cognitive reserve composite score on executive performance, (β = 0.21, SE = 0.078, p <0.01), the indirect pathway through M1, the cognitive reserve composite score, was not significant. The overall indirect pathway through both mediators was not significant, and serial mediation of race on executive performance through cognitive reserve composite and FRS score was not detected. The significant mediation through M2 only partially accounted for the overall variance, as the direct effect after inclusion on the mediators remained significant (β = 0.47, SE = 0.14, p <0.001).

In the model evaluating memory performance score as the primary outcome (Figure 3.2), when controlling for age, there was no significant direct effect of racial group membership on memory performance. There was a significant effect of race on FRS score (β = -1.52, SE = 0.49, p <0.01), and of cognitive reserve composite score on memory performance (β = 0.21, SE = 0.065, p <0.01). However, there were no significant indirect effects indicating mediation by either cognitive reserve or FRS score.

Discussion

The results of this analysis revealed that in our sample, there were significant differences in executive performance between racial groups. This difference was explained, in part, by the higher relative cardiovascular risk among Black members of the sample, while education and cognitive intensity of work activities did not explain significant variance in this main effect. Memory performance did not differ based on racial group membership, and there were no significant mediating effects of cognitive reserve or of cardiovascular risk when evaluating memory as the primary outcome. Importantly, while there was a partial mediating effect of FRS on the differences seen in executive performance, there remained a significant amount of unexplained variance in the model, indicating that race continues to represent a source of disparity in performance on cognitive measures, beyond what is accounted for by the commonly considered cognitive reserve and health factors that contribute to differential cognitive outcomes.

The results of this analysis are somewhat consistent with literature in cognitive aging that suggests there is differential performance on cognitive tasks between racial groups, and it appears that some of these differences are explained disparities in cardiovascular risk. Other work has demonstrated a significant relationship between cardiovascular risk or disease and cognitive functioning in African Americans, or in other historically underserved populations

(Pugh, Kiely, Milberg & Lipsitz, 2003; Stickel, McKinnon, Ruiz, Grilli, & Ryan, 2019). We expected to see that this relationship would also be influenced by cognitive reserve factors, as education has frequently been shown to represent another disparity which falls along racial lines, and mediates racial differences in cognitive outcomes (Wilson, Barnes, Weuve & Evans, 2016; Masel, Raji & Peek, 2010; Sisco et al., 2014; Gupta et al., 2016). However, the absence of this finding may be a product of the sample, in that the Black and White participants did not differ in educational attainment or occupational complexity. While there was evidence of group differences trending in a direction such that the mean education in years was higher among the White relative to Black members of the sample, this difference did not reach statistical significance. This finding of no significant differences in education is somewhat inconsistent with the larger trends in education among the population of Black older adults (American Council on Education, 2021), and may be a consequence of the smaller representation of Black participants in ADNI. In fact, a criticism of many large AD cohort studies, including ADNI, is the small proportion of Black and other minority participants which may make these samples less representative of the larger Black older adult population (Shin & Doraiswamy, 2016). This discrepancy in representativeness of Black participants may have affected our results in education and occupation, and also possibly the degree to which other variables in our analyses were related to our primary outcomes.

Despite this, our findings demonstrate that when significant differences in educational attainment are not present, cardiovascular risk remains a point of disparity between Black and White older adults, and accounts for significant variability in the relationship between race and executive performance above and beyond what is explained by education and occupational complexity. This finding may prompt further study of what other factors continue to place

African Americans at greater risk of developing cardiovascular disease which may in turn contribute to differential cognitive outcomes in late life (e.g., quality of education, direct measures of socioeconomic status/income, psychosocial factors).

Our sample demonstrated a difference in performance and mediation by FRS solely in the executive functioning domain. The lack of significant findings in the memory domain may suggest that performance on measures of executive functioning is more sensitive to the effects of race via cardiovascular disease. This is particularly relevant to consider given the hypothesized etiology of cognitive change associated with cerebrovascular disease. Research suggests that executive domains may be more greatly implicated in vascular disease, as is it is shown to impact white matter integrity, and thus the subcortical pathways involved in coordinating frontostriatal connections, which is distinct from the memory impairment seen in AD pathology (Pugh, Kiely, Milberg & Lipsitz, 2003; Reed et al., 2007; Nishalta, et al., 2014). Further studies in this area may seek to evaluate this more directly by looking at potential differences in markers of cerebrovascular disease among Black and White participants (e.g., white matter hyperintensity burden), to assess if racial disparities in cardiovascular risk and cognitive performance are related to differential white matter disease burden.

Some limitations and possible improvements to the current study may also contribute to further research in this area. Firstly, a primary limitation to the current analysis was the relatively low number of Black/African Americans present in the data set available for analysis. This was addressed in our study by using a matched sample, however, ideally more equal representation of racial and ethnic groups in large cohort-based research samples would improve the ability to investigate racial and ethnic differences across research disciplines. Furthermore, as noted previously, the limited number of African Americans present in this sample increases the

likelihood that the sample of African Americans are not as representative of the larger population of older adult African Americans, and thus reduces the generalizability of these findings. Other methodological limitations include the use of composite scores which reduces variability in our cognitive outcome measures. Specifically, the inclusion of certain measures within the ADNI EF and ADNI Memory composite scores may have influenced the degree to which effects in these cognitive domains were detected. Particularly given that many significant results were found in the executive functioning but not memory domain, this may raise questions about the degree to which certain memory measures are more sensitive to racial or other demographic differences, (e.g., use of the RAVLT in rather than the California Verbal Learning test or Hopkins Verbal Learning Test). However, use of composite scores allowed for evaluation of cognitive performance within domains without the loss of power from repeated analysis based on individual test scores. We also employed the Framingham risk score based on BMI rather than the lipids-based score which includes objective measures of hyperlipidemia. This was due to the lack of availability of lipid data for all included participants. Future work may consider other possible measures of cardiovascular risk and disease (e.g., lipids, other biomarker data) that may also contribute to differential cognitive outcomes. Finally, the sample employed healthy, MCI, and AD subjects, and there was not sufficient power to assess the primary aims within these diagnostic categories. However, future study may evaluate these relationships within diagnostic groups, to assess the generalizability of these findings across the spectrum of older adults' cognitive status.

Overall, the results of this analysis reveal the racial differences in executive performance appear to be partially mediated by differential cardiovascular risk among Black and White participants of the ADNI sample. Many researchers evaluating racial disparities in cognitive and

other health outcomes, posit that race represents a proxy for numerous other lifestyle, health, psychosocial, and socioeconomic factors that lead to differential outcomes. Our analysis suggests that for cognitive outcomes, cardiovascular risk is *one* of those factors. There remained a significant amount of unexplained variance in our model suggesting that a number of factors which are unaccounted for likely also contribute to differential cognitive outcomes across racial groups. Further research should be conducted to understand what these may be, including other health, psychosocial, and potential methodological factors (e.g., cognitive tools, appropriateness of normative data for cognitive measures) which contribute to apparent racial differences in cognitive performance. In addition to these implications for research, these results may also provide insight into clinical or lifestyle considerations for cognitive aging. As physical health and cardiovascular risk are considered a key, modifiable risk factor for cognitive aging and dementia, this study suggests that given the disparities in outcomes, there should be an even greater focus of prevention and intervention among African Americans displaying these risk factors. There is broad research suggesting that physical activity interventions can buffer the progression of cognitive decline in aging and disease as well as have positive effects for cardiovascular health, (Meyers, 2003; Brasure et al., 2018; Yang et al., 2020), making these a promising intervention among at-risk groups, both for physical health and prevention of cognitive and functional consequences.

CHAPTER 4

RACIAL DIFFERENCES IN CARDIOVASCULAR RISK ARE NOT ASSOCIATED WITH DIFFERENCES IN WHITE MATTER IN A SAMPLE OF BLACK AND WHITE OLDER ADULTS[2]

[2] Robinson, T.L., and L.S. Miller. To be submitted to *The Clinical Neuropsychologist*.

Abstract

Research suggests there are racial disparities in cognitive performance and risk of neurodegenerative disease, as well as disparities in risk factors for cognitive decline in aging. Black/African Americans display higher rates of cardiovascular risk (CVR), while historically displaying lesser access to and attainment of protective factors like education and occupational attainment. Given greater burden of CVR among Black older adults, it is prudent to assess if these disparities incur greater burden of brain changes associated with CVR. This work evaluated if racial differences in cognitive reserve and cardiovascular risk are associated with differences in white matter structure as determined by hyperintensity burden (WMH) and diffusion tensor imaging (DTI). Using regression analysis, we evaluated racial differences in WMH and DTI metrics, and assessed if this relationship was explained by differences in cognitive reserve and cardiovascular risk in Black and White older adults. Results did not reveal difference in WMH burden across racial groups. While racial group membership predicted CVR, and higher CVR was associated with greater WMH burden, there was no mediating effect of CVR on the relationship between racial group membership and WMH. In a smaller subsample of participants, education and CVR were related to DTI measures in some anterior white matter tracts, however, there were no racial differences in white matter structure as measured by DTI. Exploratory analyses showed that WMH was associated with worse executive performance. WMH partially mediated the relationship between CVR and executive function, but there was a differential relationship such that CVR appeared to significantly predict executive performance among Black, but not White members of the sample. Taken together, these results suggest that although there are disparities in CVR that partially explain racial differences in executive performance, these differences do not seem to occur solely by way of pathological white matter changes.

Exploratory analyses suggest that CVR may be a more critical predictor executive performance in Black compared to White older adults.

Introduction

Research on cognitive aging and dementia suggests differences in late life cognitive performance and outcomes across racial groups, including evidence of greater risk of dementia (e.g., Alzheimer's dementia) among Black/African Americans compared to White older adults (Weuve et al., 2018). Research on risk and protective factors for cognitive decline in aging identifies positive factors, like cognitive reserve (e.g., educational attainment occupational complexity), and negative risk factors, like cardiovascular disease, as modifiable risk factors to cognitive decline in aging (Stern, Alexander, Prohovnik, & Mayeux, 1992; Yaffe et al., 2020). Furthermore, there is evidence of a significant relationship between cardiovascular disease and neuroimaging evidence of white matter structural changes which may partially explain cognitive changes associated with cardiovascular risk (de Leeuw et al., 2002; Maroni et al., 2018). Given the proposed relationship between cardiovascular risk/disease and white matter structural changes and known racial disparities in both cardiovascular risk and cognitive outcomes, there is reason to evaluate if racial group membership is associated with greater white matter disease burden as a consequence of greater cardiovascular risk. The purpose of the current analysis was to evaluate if differential cardiovascular risk among Black and White older adults contributes to greater pathological brain changes between these groups, which in turn contribute to differential cognitive performance.

With the availability of neuroimaging in aging research, many studies present evidence of structural and functional brain changes associated with cognitive decline in late life and their associations with cardiovascular risk factors. Evaluating the integrity of white matter in the brain

is one way to assess subtle brain changes associated with cognitive aging, and research suggests that white matter disease may also have a strong association with cardiovascular risk and disease (Pantoni, 2002; Moroni et al., 2018). White matter, which is comprised of the myelinated axonal projections of neurons, is responsible for the efficient communication and coordination of neural activity between brain regions. Damage to or compromising of brain white matter structure is shown to be related to cognitive impairment through reduction of efficient connectivity between brain regions (Ylikoski et al., 1993; O'Sullival et al., 2001; Bennet, Madden, Vaidya, Howard & Howard, 2010; deGroot et al., 2001).

White matter hyperintensities (WMH) are a type of structural abnormality seen on neuroimaging thought to result from chronic ischemia associated with cerebral small vessel disease and have been implicated as a source of cognitive dysfunction among older adults (Ylikoski et al., 1993; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009). WMH are patchy areas of signal hyperintensity distributed throughout the deep or periventricular white matter evident on magnetic resonance imaging (MRI), T2-weighted or FLAIR series. They are rather common in healthy/normally aging brains, as well as in MCI and AD samples, and are known to increase with age (DeCarli et al., 1995; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Van DenBerg, Geerlings, Biessels, Nederkoorn & Kloppenborg, 2018). While they are quite common in the aging brain, a higher volume of WMHs is shown to be associated with worse cognitive function, with studies finding that individuals with greater WMH volume display poorer cognitive performance on executive functioning, immediate and delayed memory, and processing speed tasks (DeCarli et al., 1995; Aggarwal et al., 2010; Prins & Scheltens, 2015; Van DenBerg, et al. 2018; Langen et al., 2018). While the pathophysiology of age-related WMH is not certain, there is a large body of evidence linking these lesions to CV

risk factors and disease (e.g., hypertension, diabetes, smoking, atrial fibrillation, carotid atherosclerosis, heart failure) in both cross sectional and longitudinal studies (de Leeuw, et al., 2000; de Leeuw et al., 2002, Maroni et al. 2018).

Diffusion tensor imaging (DTI) is another a neuroimaging technique that evaluates white matter structure through the diffusion of water in WM tracts (Basser, Mattiello, & LeBihan, 1994). The movement of water within fibrous tissues like WM is considered anisotropic, or primarily unidirectional. As fibers begin to degrade and structural integrity is compromised, diffusion becomes increasingly isotropic, and more directionally heterogeneous. Two common DTI derived metrics include mean diffusivity (MD)—the average amount of total water diffusion across all directional axes of the tract; and fractional anisotropy (FA)—the diffusion of water along the primary axis (parallel to the tract) relative to the other axes (Pierpaoli & Basser; Bennet et al., 2010). Using these two values descriptively, more "intact" white matter tracts will display greater anisotropic movement, thus greater FA and/or lower MD, whereas lower FA and/or greater MD would represent greater isotropic diffusion, and thus more compromised white matter. These patterns are related to DTI changes in aging and disease, with modestly decreased FA and increased MD associated with age, and to a greater extent, MCI and AD (Lebel, Caverhill-Godkewitsch, & Beaulieu, 2010; Carmichael & Lockhart, 2011; Madden et al., 2012; Bartzokis et al., 2014; Alves et al., 2012; Bosch et al., 2012; Gyebnar et al., 2018). These WM changes appear to follow an anterior-posterior progression, with age-related changes in MD and FA seen in anterior projections (e.g., genu of the corpus callosum, and pericallosal WM; Pfefferbaum et al., 2000; Sullivan & Pfefferbaum, 2003), as well as more superior cortico-cortical WM connections (e.g., superior longitudinal fasciculus) compared to tracts connecting subcortical regions (Stadlbauer, Salomonowitz, Strunk, Hammen, Ganslandt, 2008).

Age associated changes in DTI derived WM structure are also shown to be related to cognitive performance, and similar to the pattern of WMHs, are thought to mediate the relationship between age and cognitive decline (Grieve, Williams, Paul., Clark & Gordon, 2007; Raz & Kennedy, 2009; Gold., Powell, Xuan, Jicha, & Smith, 2010). Many studies demonstrate evidence of decreased executive function, working memory, and processing speed associated with decreased FA and higher MD in aging (Grieve et al., 2007; Charlton et al., 2006; Kennedy & Raz, 2009; Kerchner et al., 2012; Mayo et al., 2018; Hinault, Larcher, Bherer, Courtney & Dagher, 2019). In these studies, there is consistent evidence of superior and anterior transversing tracts involved in age related changes and cognitive performance, namely the genu of the corpus callosum, the corona radiata, and the superior longitudinal fasciculus. Furthermore, although not considered as strongly an indicator of vascular disease in the way WMHs are (diffusion changes in WM are attributed to multiple etiologies), there is some evidence for a vascular influence of DTI derived WM microstructure (Delano-Wood et al., 2010; Kennedy & Raz, 2009).

Given fairly consistent literature drawing associations between white matter structure, cardiovascular risk, and also cognitive performance, these metrics are ideal for evaluating possible neural mechanisms of cardiovascular risk and cognitive outcomes. Furthermore, they may contribute to understanding how populations susceptible to greater cardiovascular health risks may in turn be at greater risk for specific neuropathology leading to poorer cognitive outcomes. Many studies conducted with WM metrics include largely White samples. There are some studies of DTI and WMH conducted in samples of racial minorities, which show meaningful relationships between WMH, cognition, CVD risk, and DTI (Meier et al., 2012; Leritz et al., 2010). There is also some literature showing generally greater WMH volume among Black and Hispanic older adults, and evidence that cardiovascular disease, socioeconomic status,

and education significantly influence this disparity (Waldstein et al., 2017; Hsu et al., 2018; Brickman et al., 2008). We propose an analysis of these variables in the context of differential cognitive reserve (e.g., education and occupational complexity) and CVD risk among Black and White older adults. Specifically, we hypothesized that racial differences would be observed in white matter structure as indicated by WMH volume/DTI diffusivity metrics, and the relationship between racial group membership and WM outcomes would be mediated by cognitive reserve and indicators of cardiovascular risk, as Black/African Americans tend to display lower reserve and higher levels of CV risk which represent risk for both cognitive decline and white matter degradation. Specifically we hypothesized the 1) Racial group membership would be associated with less cognitive reserve factors, greater CVR, and greater WM pathology, 2) The relationship between racial group membership and WM pathology would be mediated by cognitive reserve factors, 3) The relationship between racial group membership and WM pathology would be mediated by CVR, 4) The relationship between racial group membership and WM pathology would be mediated, sequentially by cognitive reserve and CVR risk.

Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

Our sample included 153 participants (76 Black, 77 White), with a mean age of 73.27 (*SD* = 7.08), from the ADNI1, ADNI GO and ADNI2 waves. Participants were selected based on the available sample of Black/African American participants with available medical history and imaging data, with a matched sample of White participants selected to ensure equal distribution of age, gender, and cognitive status (e.g., AD, MCI, normal controls) across racial groups. Descriptive statistics for the total sample and racial groups included in the sample are presented in Table 4.1. A smaller subsample of participants within this sample had available DTI data.

Variables and Measures

Racial Group Membership, Education and Occupation

Individuals from the sample who identified as White or Black/African American and self-identified as non-Hispanic were included in the analysis. Educational attainment was self-reported years of education provided in ADNI. Self-reported longest lifetime occupation was also collected from ADNI. Occupational intensity was calculated for each participant's reported occupation using the US Department of Labor Occupational Information Network (O*NET) resource, a data collection project used and source of standardized information on job characteristics and worker attributes for numerous career positions. Modeled after a previous study using this network (Pool et al., 2016), ratings (0-7) available on O*NET of the importance of 10 cognitively related work variables for each participant's occupation were averaged to create occupational cognitive requirements summary scores for each participant. The 10 cognitively related tasks are presented in Table 3.2.

Cardiovascular Risk

Cardiovascular risk was determined using the Framingham Risk Score to calculate 10-year hard coronary artery disease (Wilson et al., 1998). This score calculates risk based on gender, age, systolic blood pressure, treatment for hypertension, smoking, diabetes, and body mass index (BMI). The information used to calculate this score was gathered from vital signs and medical history collected from available ADNI records.

Cognitive Performance

Cognitive performance was measured using the psychometrically validated ADNI-Executive Function (EF) and ADNI-Memory (Mem) composite scores (Gibbons et al., 2012; Crane et al., 2012). The tasks included for the ADNI-EF composite scores included the Digit Symbol Substitution and Digit Span Backwards from the WAIS-R, Trails A and B, Category Fluency, and Clock Drawing subtests. The tasks included for the ADNI-MEM composite scores included longitudinal Rey Auditory Verbal Learning Test (RAVLT), AD Assessment Schedule - Cognition (ADAS-Cog), Mini-Mental State Examination (MMSE), and Logical Memory subtest. The methods and description of IRT analysis for these scores, including accounting for missing data from subtests across ADNI waves are described in the above manuscripts, and in the publicly available ADNI methods documents (Gibbons et al., 2012; Crane et al., 2012).

MRI Acquisition

Imaging data was collected from ADNI1, ADNI GO and ADNI2 baseline data where available. Images were collected using 1.5 Tesla scanner for part of the ADNI1 cohort, and a 3 Tesla MRI scanner for remaining ADNI1, and all ADNI2 and ADNI GO cohorts. The 3D Magnetization Prepared - Rapid Gradient Echo (MPRAGE) T_1-weighted sequence was acquired using the following parameters: repetition time (TR) =2300 ms; echo time (TE) = 2.98 ms;

inversion time (TI) =900 ms; 170 sagittal slices; within plane FOV = 256 × 240 mm; voxel size = 1.1 × 1.1 × 1.2 mm; flip angle = 9 °; bandwidth = 240 Hz/pix. The T_2 FLAIR scans were obtained using an echo-planar imaging sequence with the following parameters: T1-weighted SPGR sequences (256 × 256 matrix; voxel size = 1.2 × 1.0 × 1.0 mm^3; TI = 400 ms; TR = 6.98 ms; TE = 2.85 ms; flip angle = 11°), and diffusion-weighted images (DWI; 256 × 256 matrix; voxel size: 2.7 × 2.7 × 2.7 mm^3; TR = 9000 ms; scan time = 9 min) were collected. 46 separate images were acquired for each DTI scan. Five T2-weighted images with no diffusion sensitization (b_0 images) and 41 diffusion-weighted images (b = 1000 s/mm^2).

Each MPRAGE image provided is linked with related files which have undergone specific pre-processing correction steps provided by the Mayo Clinic including the following (replicated and available from http://adni.loni.usc.edu/methods/mri-tool/mri-analysis/#mri-pre-processing-container).

1. Gradwarp: gradwarp is a system-specific correction of image geometry distortion due to gradient non-linearity. The degree to which images are distorted due to gradient non-linearity varies with each specific gradient model. We anticipate that most users will prefer to use images which have been corrected for gradient non-linearity distortion in analyses.

2. B1 non-uniformity: this correction procedure employs the B1 calibration scans noted in the protocol above to correct the image intensity non-uniformity that results when RF transmission is performed with a more uniform body coil while reception is performed with a less uniform head coil.

3. N3: N3 is a histogram peak sharpening algorithm that is applied to all images. It is applied after grad warp and after B1 correction for systems on which these two correction

steps are performed. N3 will reduce intensity non-uniformity due to the wave or the dielectric effect at 3T. 1.5T scans also undergo N3 processing to reduce residual intensity non-uniformity.

White Matter Hyperintensities

WMHs were segmented using different approaches in ADNI1 (Schwarz et al., 2009) and ADNI GO and ADNI2 (DeCarli et al., 2005). The method used in ADNI1 employed proton density (PD), T1, and T2 magnetic resonance images. A Bayesian Markov random field approach was adopted, where the joint posterior probability of the presence of WMH at each voxel is maximized. The posterior probability consists of likelihood computed from image intensities, spatial prior that regularizes the location of WMHs, and contextual prior that encourages neighbor voxels to have the same labels. The method used in ADNI GO and ADNI2 employed fluid-attenuated inversion recovery (FLAIR) and T1 images. FLAIR are first coregistered to the T1 image, then an inhomogeneity correction is applied. The binary WMH mask is then estimated based on histogram fitting and thresholding at 3.5 standard deviations above the mean signal in brain matter distribution. The spatial prior and tissue class constraints are incorporated with the WMH mask in a Bayesian approach for the final segmentation. Because these methodologies resulted in significant difference in WMH volumes across waves, this was controlled for in the analysis by standardizing volumes within each phase, thus WMH volumes were represented by z-scores.

Diffusion Tensor Imaging

DTI images and values were obtained through the processing steps described in ADNI procedures, and consistent with work published using the ADNI 3T MR available data (Nir et al., 2013). Briefly, raw DWI volumes were aligned to the average b0 image to correct for head

motion and eddy current distortions using Functional MRI of the Brain (FMRIB) Software Library (FSL) (www.fmrib.ox.ac.uk/fsl). Extra-cerebral tissue was removed from the T_1-weighted anatomical scans using ROBEX and FreeSurfer (Iglesias et al., 2011; Fischl et al., 2004). Anatomical scans were corrected for intensity inhomogeneity using the MNI *nu_correct* tool (www.bic.mni.mcgill.ca/software/). Non-brain tissue was also removed from the diffusion-weighted images using the Brain Extraction Tool (BET) from FSL (Smith, 2002). Data from different subjects was aligned into the same 3D coordinate space with each T_1-weighted anatomical image linearly aligned to a standard template using FSL *flirt* (Jenkinson, Bannister Brady & Smith, 2002). Echo-planar imaging (EPI) correction for EPI-induced susceptibility artifacts was also completed using (FSL *flirt*). The resulting 3D deformation fields were then applied to the remaining 41 DWI volumes prior to estimating diffusion parameters. A single diffusion tensor (ellipsoid) was modeled for each voxel of the brain eddy- and EPI-corrected DWI scans using FSL *dtifit,* and scalar anisotropy and diffusivity maps were obtained from the resulting diffusion tensor eigenvalues (we employ only FA and MD in the current analysis).

FA images from The Johns Hopkins University (JHU) ICBM-DTI-81 White Matter Atlas (Hua et al., 2008; Mori et al., 2008) were elastically registered to each subjects' corrected FA images, and these images were applied to the stereotaxic JHU "Eve" atlas WM labels (http://cmrm.med.jhmi.edu/cmrm/atlas/human_data/file/AtlasExplanation2.htm). The atlas ROIs were superimposed into the same coordinate space as subject results, and the average FA and MD were calculated within each of the ROIs for each subject.

Tract-based spatial statistics (TBSS) (Smith et al., 2006), provided in the FSL software package (http://www.fmrib.ox.ac.uk/fsl/), was also performed according to protocols outlined by the ENIGMA-DTI group: http://enigma.loni.ucla.edu/ongoing/dti-working-group/. All subjects'

corrected FA maps were linearly, then elastically registered (Leow et al., 2007) to the ENIGMA-DTI template in ICBM space. The resulting 3D deformation fields were then applied to the three diffusivity maps. All subjects' spatially normalized FA and MD data were projected onto the skeletonized ENIGMA-DTI template. Mean anisotropy and diffusivity measures were calculated along the skeleton in the ROIs. The ROIs included in this analysis were global white matter, genu of the corpus callosum, anterior cingulum, and superior longitudinal fasciculus.

Statistical Plan

Bivariate correlations were conducted to assess the relationships between variables of interest. A standardized composite score for the socioeconomically based cognitive reserve variables was calculated using a combined z-score of age, education, and average scores for cognitive work activities for each participant.

To address the aim assessing WMH as the primary outcome, a serial mediated regression analysis using Hayes' PROCESS Macro for SPSS (Hayes, 2012) was applied to assess the direct effect of racial group membership on WMH volume, and the individual and sequential mediating effects of cognitive reserve composite and cardiovascular risk scores. This model assumes the following hypotheses: 1) Racial group membership predicts WMH volume (i.e., differences in WMH volume by race), 2) The relationship between racial group membership and WMHs is mediated by cognitive reserve factors, 3) The relationship between racial group membership and WMH is mediated by cardiovascular risk, 4) The relationship between racial group membership and WMHs is mediated sequentially by cognitive reserve measures and cardiovascular risk, such that inclusion of both mediators in the model explains greater variability in the X on Y relationship above and beyond what is explained by either of these mediators alone. The

conceptual model is presented in Figure 4.1. Due to the limited sample with available DTI data, this model was not applied in assessment of DTI as the primary outcome, and these analyses were conducted in an exploratory fashion (see **DTI Analysis** below).

Given prior results (See **Chapter 3**), which revealed that cognitive reserve factors did not differ between racial group and that in the current sample these variables did not explain significant variance in CVD risk or in cognitive performance, an additional, exploratory model was adopted to evaluate racial differences in cognitive performance as a consequence of the sequential role of cardiovascular risk and white matter burden. This model assumes the following hypotheses: 1) Racial group membership predicts cognitive performance specifically executive function, 2) The relationship between racial group membership and cognitive performance is mediated by cardiovascular risk, 3) The relationship between racial group membership and cognitive performance is mediated by WMH burden, 4) The relationship between racial group membership and WMHs is mediated sequentially by both CVD risk and WMH burden. The conceptual model is presented in Figure 4.2. Additional exploratory analyses were also conducted, and results are discussed below.

Results

Sample Characteristics

There was no significant difference in mean years of education, (M=15.97 years, SD = 2.97; $t(151) = -1.52$, $p = .13$), or in occupational intensity, ($t(151) = -1.15$, $p = .25$) across racial groups. The average Framingham risk score (FRS) for the overall sample was 18.93 (SD = 3.86), and while Black/African American participants had a higher mean score compared to the White participants (M=19.49 (3.98) M=18.38 (3.68), respectively) this difference in mean FRS was not

statistically significant (p = .075). The mean executive function composite score was 0.062 (*SD* = 1.07), and Black sample participants displayed a lower mean composite score in the executive functioning domain compared to the White sample ($t(151) = -3.16$, $p < .01$). There was no significant difference between memory composite scores (p = .31). There was also no difference in standardized WMH volumes between racial groups (p = .68) or DTI derived values (see **DTI Analysis** below).

Cardiovascular Risk, White Matter Hyperintensities, and Cognitive Performance

Bivariate correlations among the variables of interest are displayed in Table 4.2. Cardiovascular risk score was negatively associated with executive performance (r = -.23, p < .01) and positively associated WMH burden (r = .24, p < .01). WMH burden was negatively associated with executive performance (r = -.33, p < .01). Education was positively associated with EF (r = -.31, p <. 01), as was occupational complexity (r = .19, p < .05), but neither education, occupational complexity, nor the cognitive reserve composite score were related to WMH burden. Memory performance was positively related to occupational complexity and education but was not associated with WMHs or cardiovascular risk score. As anticipated, age was significantly related to cardiovascular risk, and WMH burden, and so it was controlled for in the primary analysis.

Results of the primary regression analysis are presented in Figure 4.3. When evaluating WMH burden as the primary outcome variable, while controlling for age, the direct effect of racial group membership on WMH burden was not significant (β = -.12, SE = 0.15, p =.43). While there were no significant indirect pathways through either M1, cognitive reserve composite, or M2, FRS, there was a significant relationship between racial group membership and FRS. There were no other significant pathways in this model.

A secondary model was conducted to evaluate the role of FRS and WMH burden on ADNI-EF score among the racial groups within the sample (Figure 4.4). When evaluating ADNI-EF score as the primary outcome, of the total effect of racial group membership on ADNI-EF score was significant (β = .56, SE = 0.1, p <.001). Again, there were no significant indirect pathways through M1, FRS, or M2, WMH burden, but there was a significant effect of racial group membership on FRS score (β = -1.37, SE = 0.56, p <.05), and a significant effect of WMH burden on ADNI-EF score (β = -.25, SE = 0.08, p <.001). In the absence of significant mediating pathways, the total effect of racial group membership on ADNI-EF score remained significant when controlling for the mediators (β = .51, SE = 0.56, p <.001). A statistical model of these results is presented in Figure 5d. When this model was replicated using memory performance score as the primary outcome, there was no significant direct effect of racial group membership on memory performance, nor were there any significant mediating/indirect effects in this model.

Additional exploratory models were conducted to evaluate the simple mediating effect of WMH on the relationship between FRS and executive performance measured using the ADNI-EF composite score. This was conducted both in the complete sample and within racial groups. In the total sample (Figure 4.5), the direct effect of FRS on ADNI EF was significant (β = .23, SE = 0.02, p <.01). This relationship was mediated by WMH volume, as there was a significant relationship between FRS and WMH burden (β = .061, SE = 0.02, p <.01), and a significant relationship between WMH burden and ADNI-EF score (β = -.31, SE = 0.084, p <.01). The indirect effect was also significant (β = -.018, SE = 0.006). The total direct effect of X on Y remained significant after controlling for the mediator, indicating a partial mediation effect. In the subsample of White participants, (n=77; Figure 4.6), there was no significant direct effect of

FRS on EF functioning, although the indirect effect through WMH burden was significant (β = -.038, SE = 0.014). In the Black/African American subsample (n=76; Figure 4.7), there was a significant direct effect of FRS on ADNI-EF (β = -.077, SE = 0.029 p < .01), however, the indirect effect through WMH burden, was not significant, and mediation was not detected.

Diffusion Tensor Imaging Analysis

The available DTI data for the sample of Black/African American participants was limited within ADNI, which resulted in a significantly underpowered sample size to complete the proposed analysis (n=22), including Black and matched White participants. As such, the proposed analyses were assessed in an exploratory fashion. In the DTI subsample, there were no significant differences in mean years of age (M=73.4, SD = 8.30; t(20) = -1.92, p = .07), education, (M=15.5 years, SD = 2.36; t(20) = -.096, p = .92), occupational intensity scores, (t(20) = -0.54, p = .59), Framingham risk sore (M=19.76, SD = 4.3; t(20) = -1.92, p = .07), or cognitive composite scores between racial groups (EF t(20) = -1.11, p = .28; Memory t(20) = 1.58, p = .13). There were also no differences in DTI derived values (i.e., FA, or MD) in either the genu of the corpus callosum, anterior corona radiata, or superior longitudinal fasciculus between racial groups.

Bivariate correlation analysis revealed that age was associated lower FA (Left r = -.55, p < .01, Right r = -.57, p <.01), and greater MD (Left r = .58, p < .01, Right r = .55, p <.01) in the bilateral anterior corona and greater MD in the left superior longitudinal fasciculus (r = .51, p < .05). Education was associated with greater FA in the left but not right superior longitudinal fasciculus (r = .43, p < .05), and lower MD in the bilateral anterior corona radiata, (Left r = -.49, p < .05, Right r = -.47, p <.01), and genu of the corpus callosum (Left r = -.42, p < .05, Right r = -.47, p <.05). Framingham risk score was associated with lower FA in the bilateral, anterior

corona radiata (Left r = -.45, p < .05, Right r = -.47, p <.05), and the left but not right superior longitudinal fasciculus (r = -.53, p <.05). Framingham risk score was also associated with lower MD in these regions, including the bilateral anterior corona radiata (Left r = .46, p < .05, Right r = .45, p < .05), an in the bilateral superior longitudinal fasciculus (Left r = .61, p < .01, Right r = .53, p < .05). Framingham risk score was not related to FA or MD values in the genu of the corpus callosum.

Higher memory composite score was related to greater FA in the bilateral anterior corona radiata (Left r = .47, p < .05, Right r = .51, p <.05), but not to FA values in the longitudinal fasciculus or genu of the corpus callosum. There were no associations between memory performance and MD values in any regions of interest. Higher EF composite score was related to higher FA (Left r = .54, p < .05, Right r = .53, p <.01), and lower MD (Left r = -.56, p < .01, Right r = -.71, p <.01) in the bilateral corona radiata. Higher EF was also associated greater FA the left superior longitudinal fasciculus (r = .46, p <.05), and lower MD in the bilateral SLF (Left r = .56, p < .01, Right r = .56, p <.01) but not to the genu of the corpus callosum.

In a series of exploratory regression analyses, a mediating effect of Framingham risk score on the relationship between executive performance and DTI values was not detected in this subsample.

Discussion

Overall, the results of the current analysis and the exploratory aims demonstrated findings in partial support of trends in the literature regarding cardiovascular risk, WM integrity, and executive function. Preliminary analyses showed that in the total sample, burden of WMH increased with increasing cardiovascular risk score. However cognitive reserve factors were not

associated with WMH. In the primary proposed analysis, the hypothesis that a sequence of differential attainment of these protective and risk factors across racial groups would lead to greater white matter disease burden in the form of WMH was not supported, as there were no differences in WMH across racial groups. This was despite the finding that race predicted cardiovascular risk in this model. This is inconsistent with the few studies showing greater WMH burden among Black or Hispanic relative to White older adults, particularly when they display greater cardiovascular risk (Brickman et al., 2008; Hsu et al., 2018). However, it may suggest that WMH are not as direct a measure of cardiovascular disease as some literature suggests, and thus may not be the only mechanism by which cardiovascular risk contributes to cognitive changes.

Given the relationships observed between cardiovascular risk, WMHs, and executive performance, with Black participants displaying lower executive performance, and both high cardiovascular risk and WMH burden, further analyses were conducted to assess if racial differences in executive performance could be explained by these variables. In our sample, racial group predicted executive performance, and although racial group membership was associated with cardiovascular risk, and WMHs were associated with executive function, there was no significant mediating effect. Taken together, these findings suggest Black/African Americans in our sample show worse performance on executive measures, however, this relationship is not explained by greater white matter disease burden. This is true in spite of the relationship observed between racial group membership and cardiovascular risk, with Black participants displaying higher risk scores. Probing these relationships further, simple mediation analyses show that in our subsample of White participants, there is no direct effect of cardiovascular risk on executive function, although in this group we see the expected cardiovascular disease →

white matter disease → cognition indirect effect. Conversely, in the subsample of Black participants, we do see a significant effect of cardiovascular risk on executive performance, however, this relationship is not explained by white matter disease. These findings suggest not only that there is possibly a differential effect of cardiovascular risk on executive performance across racial groups, but that for the Black older adults in our sample, WMH do not explain the association between cardiovascular risk and cognitive performance. This raises questions about how we conceptualize cardiovascular risk as it relates to racial differences in cognitive outcomes.

It is important to understand that conditions like hypertension, diabetes, hyperlipidemia, etc., are *risk factors* for cognitive decline, meaning they increase the likelihood of adverse cognitive outcomes, while the exact mechanism remains undefined (Johansen, M, Langton-Frost, & Gottesman, 2020). Our findings suggest that other factors or potential mechanisms besides white matter changes may contribute to the relationship between race, CVD risk, and cognition. Some other mechanisms that can be investigated include biomarker data, congruent with hypotheses that CVD risk factors may directly affect production or degradation of pathological brain markers such as beta amyloid (Stampfer, 2006). Other potential mechanisms to explore are the role of gray matter. While there is significant research focusing on WMH in cognition and cardiovascular risk, given that one hypothesized mechanism of CVR and cognition is decreased cerebral perfusion, cerebral gray matter may be an area of further investigation given it is also susceptible to negative effects of hypoperfusion associated with CVD (Ciacciarelli, Sette, Giubilei & Orzi, 2020). Some work evaluating cardiovascular risk and cognition have found changes to gray matter volume and structural networks associated with cardiovascular risk (Kharabian Masouleh et al., 2018; Song et al., 2020). Furthermore, given that our exploratory findings suggest that the relationship between cardiovascular risk and cognition may be different

for Black and White older adults, researchers should also consider how other aspects of racial group membership and identity may incur greater cognitive consequences associated with cardiovascular disease through shared mechanisms. For example, there is evidence that experiences of sociopolitical and socioeconomic disparities among historically underserved minority groups represents significant risk to overall physical wellbeing through increasing allostatic load, and thus may impact both cardiovascular health and mental/cognitive wellbeing (Karlamangla et al., 2002; Rodriquez et al., 2019; D'Amico, Amestoy & Fiocco, 2020). Other potential shared mechanisms could be related to health literacy, and other aspects of education. While education and work complexity did not explain significant variance in our model, measures of education quality, health literacy, and other socioeconomic factors may relate to a person's access to or engagement with health care, and in turn affect both cardiovascular and brain health. Generally, these findings suggest a pattern that far more appears to explain the observed differences we see in cognitive outcomes beyond the known risk factors typically proposed, and further work is needed to identify what these variables may be.

Some limitations and possible improvements to the current study may also contribute to further research in this area. A primary limitation to the current analysis was the relatively low number of Black/African Americans present in the data set available for analysis. This was addressed in our study by using a matched sample, however, ideally more equal representation of racial and ethnic groups in large cohort-based research samples would improve the ability to investigate racial and ethnic differences across research disciplines. Furthermore, as noted previously, the limited number of African Americans present in this sample increases the likelihood that the sample of African Americans included in the analysis are not as representative of the larger population of older adult African Americans, and thus reduces the generalizability

of these findings. We also employed the Framingham risk score based on BMI rather than the lipids-based score which includes objective measures of hyperlipidemia. This was due to the lack of availability of lipid data for all included participants. Future work may consider other possible more direct measures of cardiovascular risk and disease (e.g., lipids, other biomarker data) that may also contribute to differential cognitive outcomes. Regarding cognitive status, the sample employed healthy, MCI, and AD subjects, and there was not sufficient power to assess the primary aims within these diagnostic categories. However, future study may evaluate these relationships within diagnostic groups, to assess the generalizability of these findings across the spectrum of older adults' cognitive status. Finally, the relatively small sample with available DTI data limits our interpretations and generalizability of the exploratory analyses, however, the existing patterns between cardiovascular risk and DTI values suggest this may be an area of further study.

Despite these limitations, the current results provide meaningful insights into the relationships between cardiovascular risk, white matter changes, and executive functioning in the context of racial differences in older adult cognitive performance. These findings suggest that the poorer cognitive performance associated with greater cardiovascular disease risk in Black older adults is not explained by WMH burden, and that there is, possibly, differential association between cardiovascular risk and cognition in Black and White samples. These findings point us toward future research which may further elucidate the multifaceted aspects of race, and what experiences and/or mechanisms may explain the changes in both cardiovascular risk and cognition among Black older adults. It also further highlights the importance of prevention and intervention of cardiovascular disease among underrepresented groups, as they may be more strongly associated with cognitive outcomes among these populations.

CHAPTER 5

DISSERTATION DISCUSSION

The results presented in the above analyses point to important trends related to risk factors and outcomes in cognitive aging across racial groups. Firstly, our analyses revealed that in our sample, there were significant differences in executive performance between racial groups. This difference was explained, in part, by the higher relative cardiovascular risk among Black members of the sample, while education and cognitive intensity of work activities did not explain significant variance in this main effect. While the sample did display relative differences in education across racial groups, this difference was not statistically significant. The lack of findings in the memory domain may be related to methodological factors, including which measures were included in the composite score (e.g., MMSE score is not often considered an independent memory measure, other memory measures may be differentially affected by race/demographics), but may also reflect the idea that certain domains, particularly executive functioning, may be more associated with cardiovascular risk. Furthermore, our findings suggests that even when known protective factors like education are generally comparable across a sample of White and Black older adults, cardiovascular risk in the form of higher BMI, hypertension, smoking, and diabetes, still stands out as a partial mediator of differences we see in cognitive functioning across racial groups. This is consistent with trends in research which note that greater CVR is related to worse cognition, and also that populations who are disproportionately affected by these disease processes are consequently at risk of worse cognitive

outcomes. The observation of significant residual or unexplained variance in this relationship suggests that racial group membership continues to represent a source of disparity in performance on cognitive measures, beyond what is accounted for by the commonly considered cardiovascular disparities. This presents the opportunity to investigate what remaining factors contribute to the racial gaps we see across cognitive functioning and other health disparities that fall across racial lines.

The hypothesis that a sequence of differential attainment of these protective and risk factors across racial groups would lead to greater white matter disease burden in the form of WMH was not supported, as there were no differences in WMH across racial groups. DTI analyses were underpowered to detect significant effects, but again, there did not appear to be differences in white matter integrity across racial groups, although there was some evidence that cardiovascular risk was associated with greater isotropic water movement in some anterior WM structures. These findings were interesting in their *lack* of significant relationships, in that although there appears to be greater CVR among African Americans, and CVR was generally related to WMH and DTI metrics (although to a lesser extent and in a small subsample), Black/African Americans did not display greater evidence of white matter disease. This highlights some of the ambiguity in the literature regarding CVR and WM disease, and the idea that these risk factors may not share as direct a connection to WM pathology as some studies have suggested, and there may be other means by which CVR affects brain health.

Relatedly, exploratory analyses showed that while Black/African Americans in our sample had worse performance on executive measures, this relationship was not explained by greater WMH burden. This was true in spite of the relationship observed between racial group membership and cardiovascular risk, with Black participants displaying higher risk scores. This

again suggests that these white matter changes may not be the primary mechanism by which cardiovascular risk contributes to cognitive changes in late life. Given that WMH are known to be associated with CVD and cognitive decline, it may be that there is not as direct a relationship between these variables as some literature suggests. Also, as WMH are seen in otherwise healthy aging brains, perhaps there is a critical threshold for the volume of WMH present before cognitive changes are apparent, and this likely differs across individuals and populations. It is also possible that other factors or potential mechanisms besides white matter changes contribute to the relationship between race, CVD risk, and cognition, and should be investigated further. These might include biomarker data, congruent with hypotheses that CVD risk factors may directly affect production or degradation of pathological brain markers such as beta amyloid (Stampfer, 2006). Other potential mechanisms to explore are the role of gray matter. While there is significant research focusing on WMH in cognition and cardiovascular risk, given that one hypothesized mechanism of CVR and cognition is decreased cerebral perfusion, cerebral gray matter may be an area of further investigation given it is also susceptible to negative effects of hypoperfusion associated with CVD (Ciacciarelli, Sette, Giubilei & Orzi, 2020). Some work evaluating cardiovascular risk and cognition have found changes to gray matter volume and structural networks associated with cardiovascular risk (Kharabian Masouleh et al., 2018; Song et al., 2020).

Finally, exploratory analyses also pointed to a potential differential relationship between cardiovascular risk and executive performance across racial groups, in that cardiovascular risk may be a more robust predictor of executive performance in Black/African Americans. Future research should therefore consider how other aspects of racial group membership and identity may incur greater cognitive consequences associated with cardiovascular disease through shared

mechanisms. For example, there is evidence that experiences of sociopolitical and socioeconomic disparities among historically underserved minority groups represent significant and unique risk to overall physical wellbeing through increasing allostatic load, and thus may impact both cardiovascular health and mental/cognitive wellbeing (Karlamangla et al., 2002; Rodriquez et al., 2019; D'Amico, Amestoy & Fiocco, 2020).

Taken together, these analyses demonstrate that important, modifiable risk factors for CVD and for cognitive decline in aging appear to be more prevalent among Black compared to White older adults, and therefore it may be a relevant goal to target treatment and prevention of these risk factors among racial minority groups. While there is mixed evidence on the effectiveness of reversing cognitive changes associated with CVR, (e.g., anti-hypertensive drugs; Iadecola et al., 2016), prevention of cardiovascular disease and risk remains an important goal in the reduction of cognitive decline. This can be accomplished through known prevention and intervention techniques for both CVR and cognitive decline, such as diet and exercise and intervention programs. There is sufficient evidence that exercise interventions have a buffering effect on the progression of cognitive decline (Brasure et al., 2018; Yang et al., 2020), and these may be ideal in addressing CVR and associated cognitive and brain changes. Some work suggests exercise-based cardiovascular rehabilitation has a positive effect on regional volumetric changes seen in cardiovascular disease, (Anazado, Shoemaker, Suskin & Lawrence, 2013), further demonstrating exercise interventions as a potential focus on intervention in this area.

While the focus of this study is not necessarily on the historical factors which contribute to race-based disparities in socioeconomic attainment and health outcomes, this work should be considered in this context. The effects of systemic inequalities on health outcomes appear to be far reaching, including long-term effects on cognitive health and quality of life into late life.

Relatedly, even though cardiovascular risk was determined to partially explain racial differences in cognitive outcomes, the remaining, unexplained variance seen in this study still leaves the question of racial differences in cognitive performance largely unanswered. There remain many considerations that researchers seeking to understand cognitive aging through a sociocultural lens are still trying to understand, including literacy, health related quality of life, and perceptions of discrimination, as the unique psychosocial stressors associated with ethnic and minority identity may incur greater stress-related disease burden (Barnes et al., 2012; Zahodne, Manly, Smith, Seeman & Lachman, 2017). While they are often difficult to quantify and measure clinically, a better understanding of these contributors may help us understand and affect positive change toward disparate cognitive outcomes across racial and ethnic groups.

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Table 3.1

Sample Demographic Characteristics and Key Study Variables: Chapter 3

Variable	Black (n=111)	White (n=110)	Total (n=221)	Sig. difference
Sex %female	63.8%	61.8 %	62.4%	na
Age	71.62 (7.44)	73.46 (7.14)	72.5 (7.34)	na
Education	15.20 (2.98)	15.85 (2.65)	15.52 (2.83)	na
Diagnosis	NC = 49% MCI = 35% AD = 16%	NC = 48% MCI = 36% AD = 16%	NC = 48% MCI = 36% AD =16%	na
ADNI EF	-0.0345 (1.08)	0.458 (1.08)	0.211 (1.11)	$p < .01$
ADNI Mem	0.83(0.07)	0.89 (0.08)	0.432 (0.859)	na
FRS	18.93 (3.94)	17.79 (3.88)	18.36 (3.94)	$p < .05$

Note: NC=Healthy controls, MCI= Mild cognitive impairment, AD=Alzheimer's dementia, ADNI EF= Executive functioning composite score, ADNI Mem= Memory composite score, FRS: Framingham risk score, representing cardiovascular risk.

Table 3.2

*O*NET variables list*

Judging qualities of things, services, people
Evaluating information against standards
Processing information
Analyzing data or information
Making decisions and solving problems
Thinking creatively
Updating and using job-relevant knowledge
Developing objectives and strategies
Scheduling work and activities
Organizing, planning, and prioritizing

Note: Modeled after Poole et al., 2016, each variable score, rated on a scale of 0-7, was averaged for each occupation to create an occupational cognitive requirements score.

Table 3.3

Bivariate correlations among key study variables: Chapter 3

	Age	Education	Work Activities	ADNI-Mem	ADNI-EF	FRS	SEF Score
Age	--	.002	.040	-.185**	-.303**	.370**	.027
Education	.002	--	.512**	.265**	.247**	-.135*	.870**
Work Activities	.040	.512**	--	.101	.089	.024	.869**
ADMI-Mem	-.185**	.265**	.101	--	.601**	-.149*	.207**
ADNI-EF	-.303**	.247**	.089	.601**	--	-.275**	.191**
FRS	.370**	-.135*	.024	-.149*	-.275**	--	-.061
CR Composite	.027	.870**	.869**	.207**	.191**	-.061	--

Note: ADNI EF= Executive functioning composite score, ADNI Mem= Memory composite score, FRS= Framingham risk score, representing cardiovascular risk, CR Composite= cognitive reserve composite score, including education and cognitive complexity of work activities.

* Correlation is significant at the 0.01 level. ** Correlation is significant at the 0.01 level.

Table 4.1

Sample Demographics and Key Study Variables: Chapter 4

Variable	Black (n=76)	White (n=77)	Total (n=153)	Sig. difference
Sex %female			61.4%	na
Age	72.64 (7.45)	73.89 (6.89)	73.27 (7.08)	na
Education	14.91 (3.11)	15.64 (2.81)	15.27 (2.97)	na
Occupation	3.54 (.386)	3.52 (.466)	3.53 (.426)	na
Diagnosis	NC = 43%	NC = 40%	NC = 41%	
	MCI = 39%	MCI = 41%	MCI = 41%	
	AD = 17%	AD = 19%	AD = 18%	
ADNI EF	-0.206 (1.05)	0.328 (1.03)	0.0628 (1.07)	$p < .01$
ADNI Mem	0.38 (0.84)	0.24 (0.89)	0.32 (0.87)	na
FRS	19.49 (3.98)	18.38 (3.68)	18.93 (3.86)	na ($p = .07$)

Note: NC=Healthy controls, MCI= Mild cognitive impairment, AD=Alzheimer's dementia, ADNI EF= Executive functioning composite score, ADNI Mem= Memory composite score, FRS: Framingham risk score, representing cardiovascular risk.

Table 4.2

Bivariate correlations among key study variables: Chapter 4

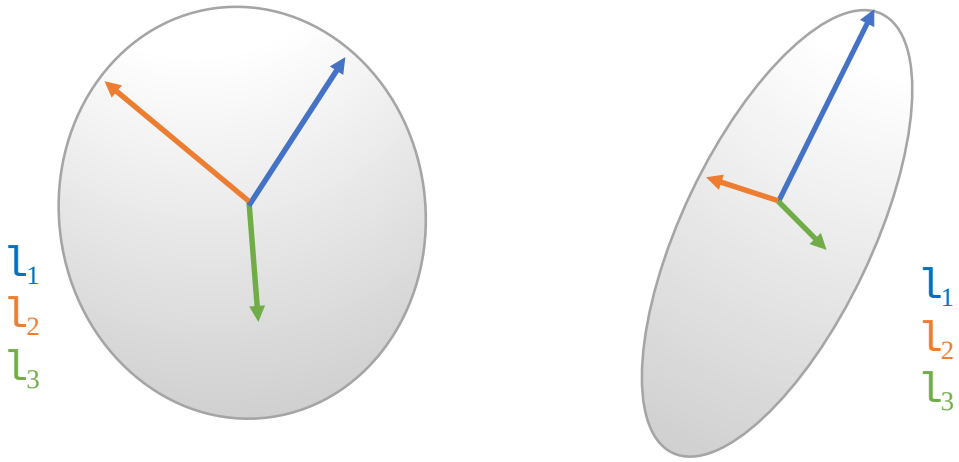
	Age	Education	Work Activities	ADNI-EF	ADNI-Mem	FRS
Age	--					
Education	-0.70	--				
Work Activities	-.048	.566**	--			
ADNI-EF	-.292**	.312**	.189*	--		
ADNI-Mem	-.126	.305**	.207*	.573**	--	
FRS	.378**	-.100*	-.054	-.229**	-.038	--
WMH	.310**	-.090	-.005	-.325**	-.137	.236**

Note: ADNI EF= Executive functioning composite score, ADNI Mem= Memory composite score, FRS= Framingham risk score, representing cardiovascular risk, WMH= White matter hyperintensity volume (standardized).

* Correlation is significant at the 0.01 level. ** Correlation is significant at the 0.01 level (2-tailed).

Figure 1

Diffusion Tensor

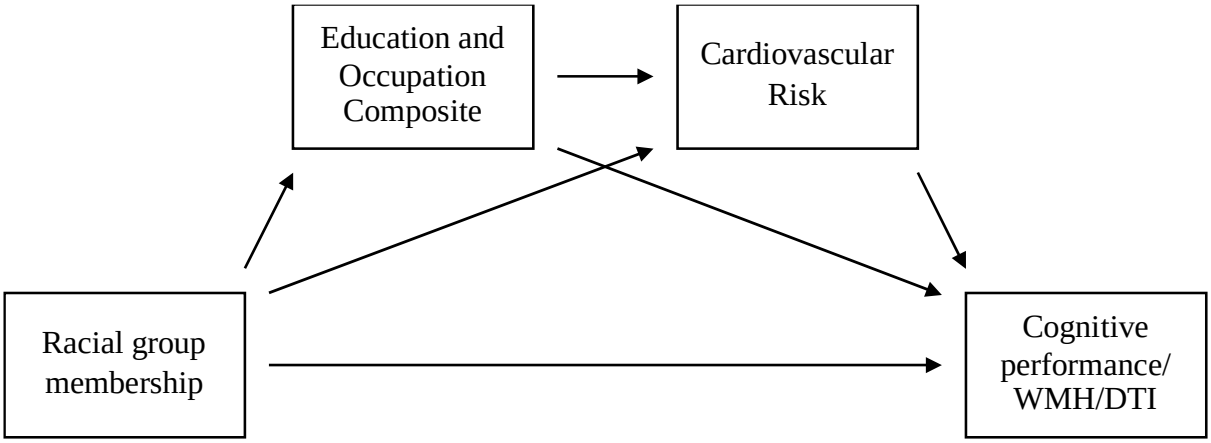


Isotropic Anisotropic

Note: Displays eigenvalues corresponding to diffusion in three primary directions represented in isotropic versus anisotropic movement.

Figure 2.1

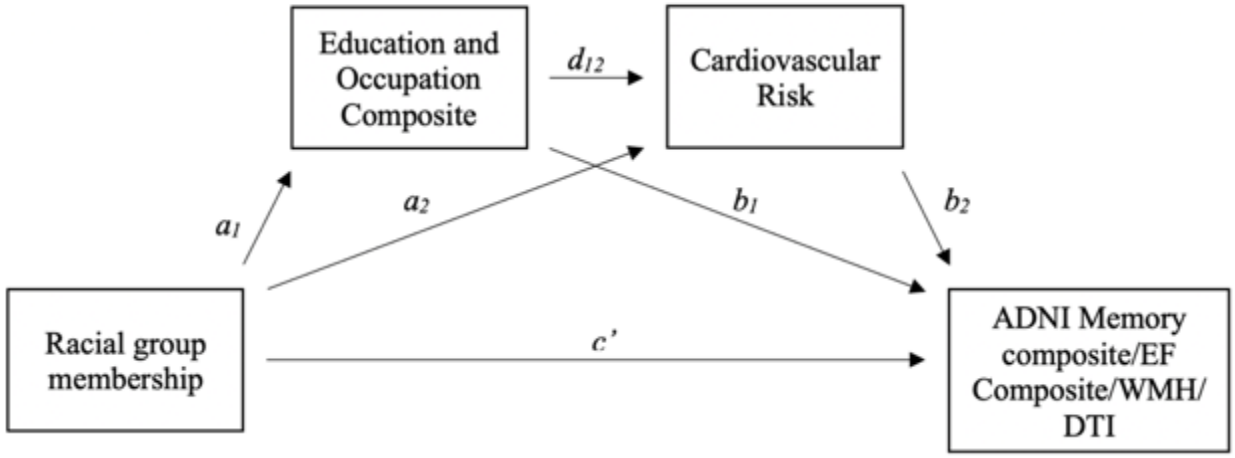
Conceptual Model of the Primary Analyses



Note: Corresponds with Hayes, 2017 Model 6; Mediation with two sequential moderators.

Figure 2.2

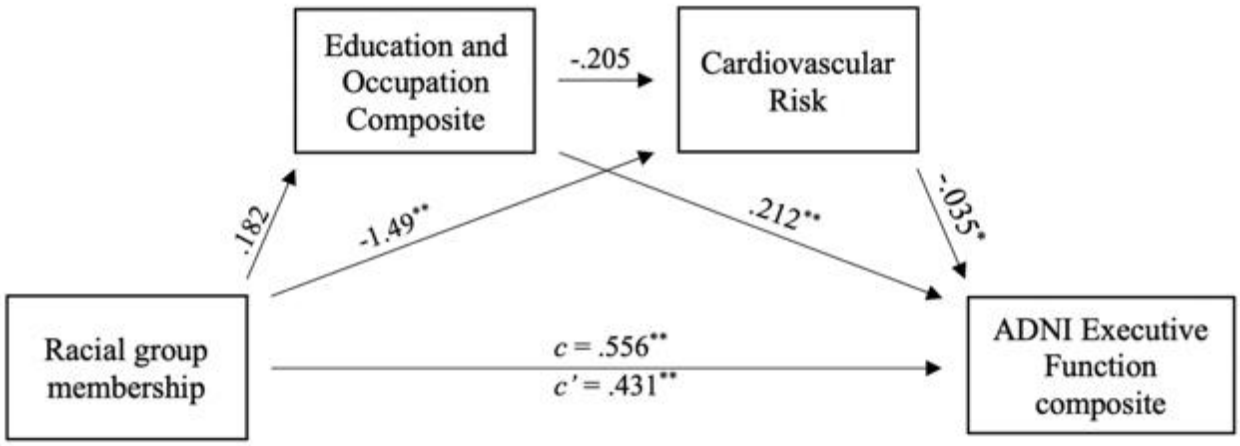
Statistical Model for the Primary Analyses



Note: Results estimate the indirect effect of racial group membership on cognition through SES factors only (= a_1 b_1) the indirect effect of racial group membership on cognition through CV risk only (= a_2 b_2), the indirect effect of racial group membership on cognition through SES and CV in serial a_1 d_{21} b_2 , and the direct effect of racial group membership on cognition (c').

Figure 3.1

Results Model for the Primary Analyses: Chapter 3

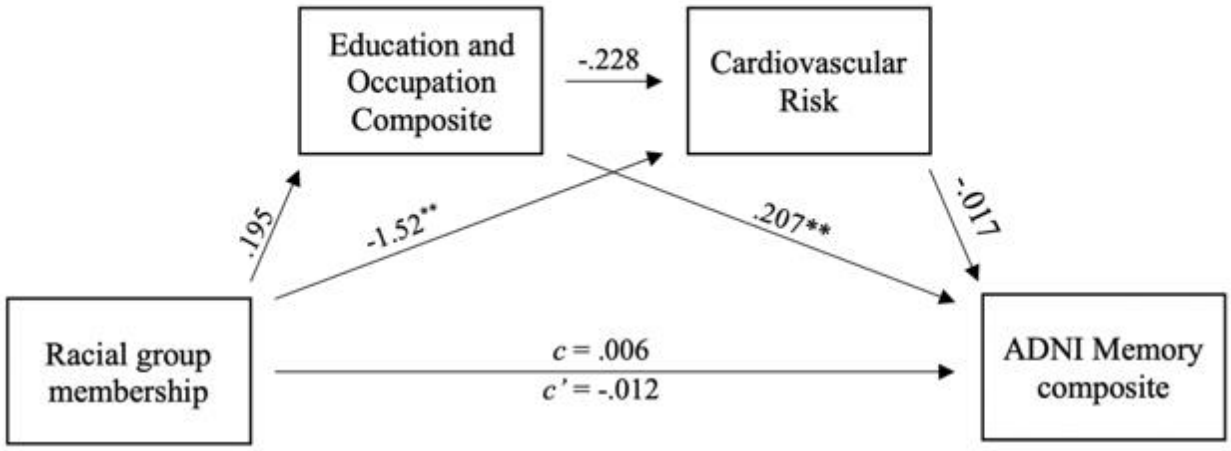


Note: Evaluating executive function as the primary outcome, there was a direct effect of race, and a partial mediating effect of CVR.

* is significant at the 0.01 level. ** is significant at the 0.01 level.

Figure 3.2

Results Model for the Primary Analyses: Chapter 3

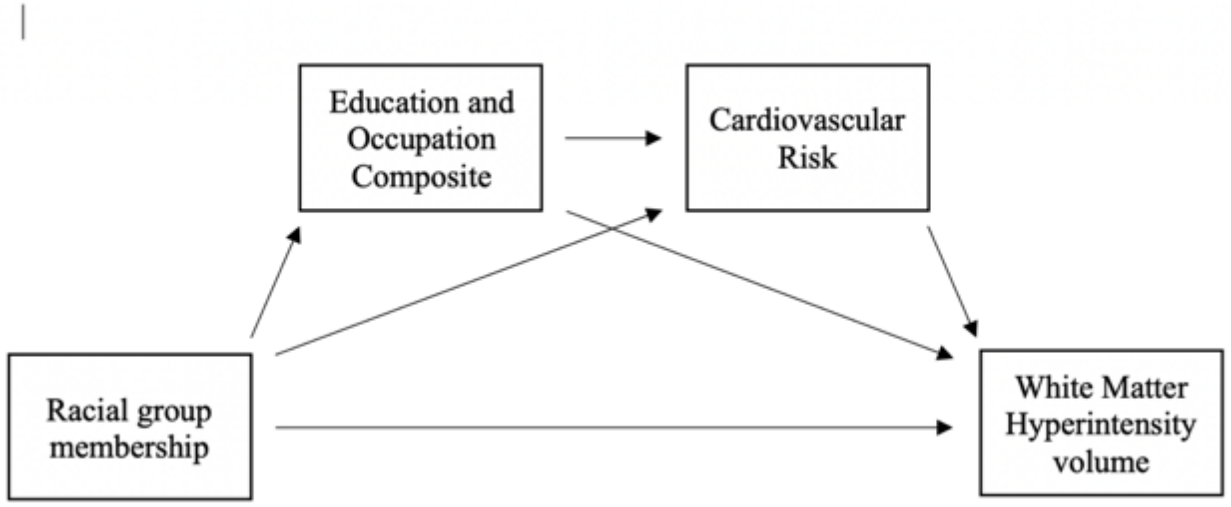


Note: Evaluating memory performance as the primary outcome, there were no significant direct effects of race, and no significant indirect/mediating pathways.

* is significant at the 0.01 level. ** is significant at the 0.01 level.

Figure 4.1

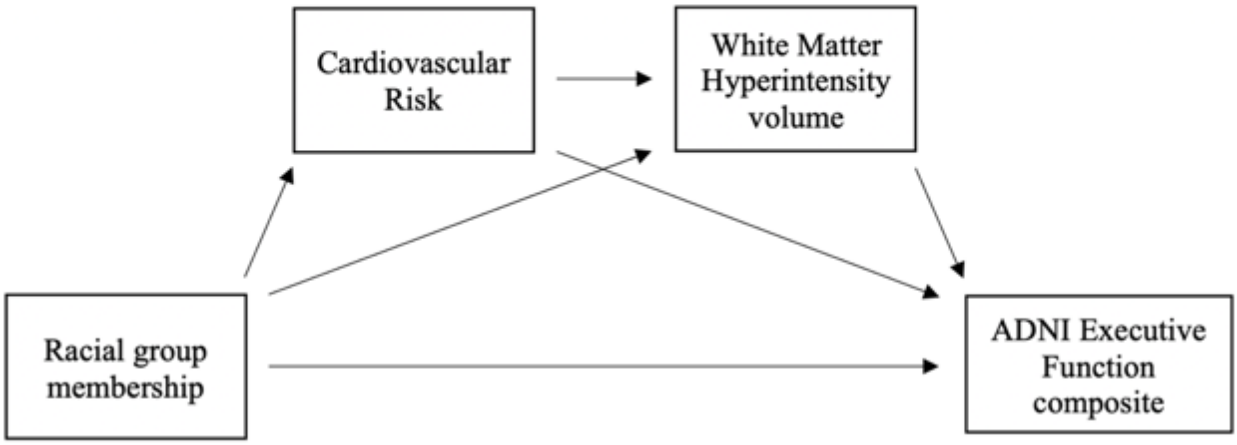
Conceptual Model for Chapter 4 Primary Aim



Note: Model evaluating white matter hyperintensity volume as the primary outcome.

Figure 4.2

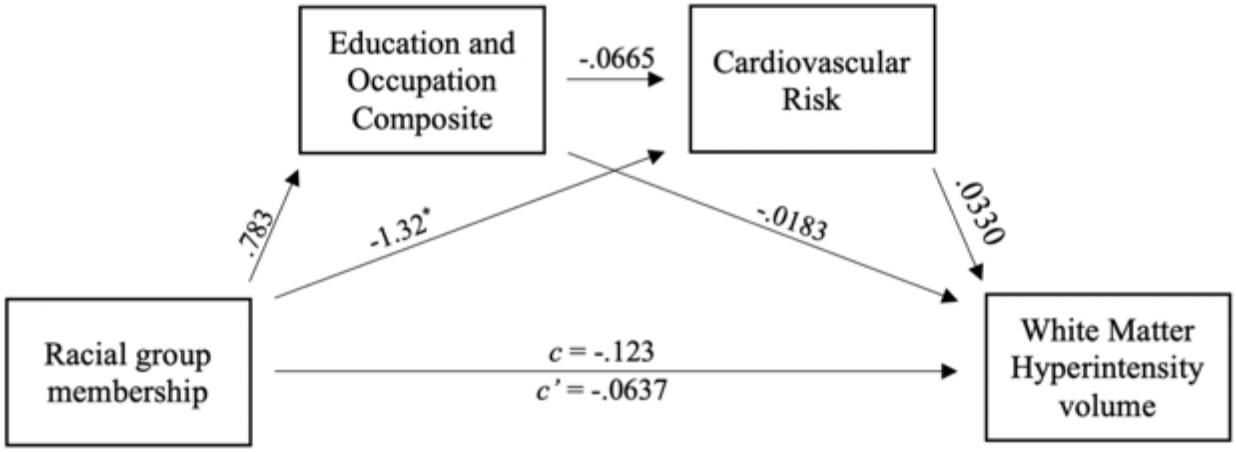
Statistical Model for Exploratory Aim 1: Chapter 4



Note: Model to assess the mediating role of cardiovascular risk and WMH on the relationship between race and executive performance.

Figure 4.3

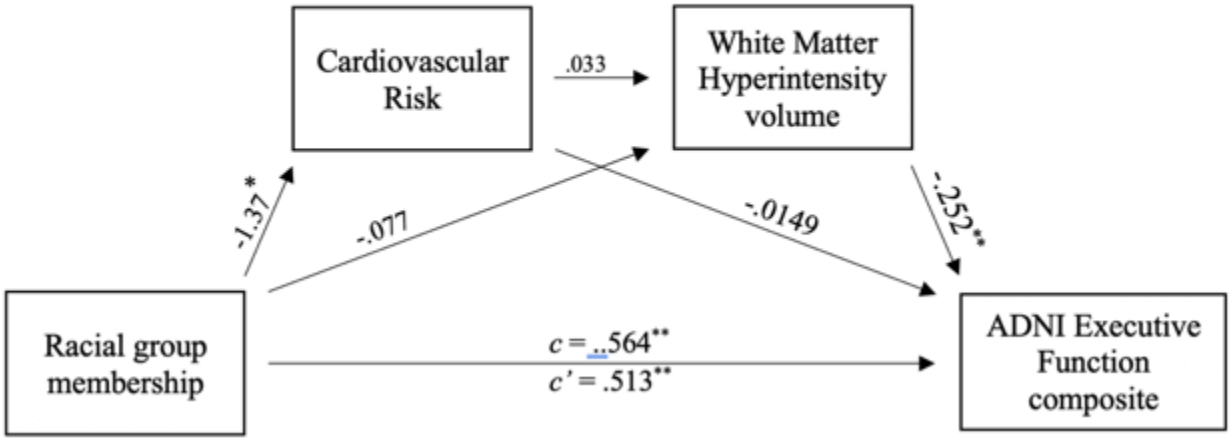
Results Model of Primary Analysis: Chapter 4



Note: There were no differences in WMH volume across racial groups. There was no direct effect on WMH by racial group membership. Despite a significant relationship between racial group membership and cardiovascular risk, there were no significant indirect, mediating effects. * is significant at the 0.01 level. ** is significant at the 0.01 level.

Figure 4.4

Results Model of Exploratory Aim 1: Chapter 4

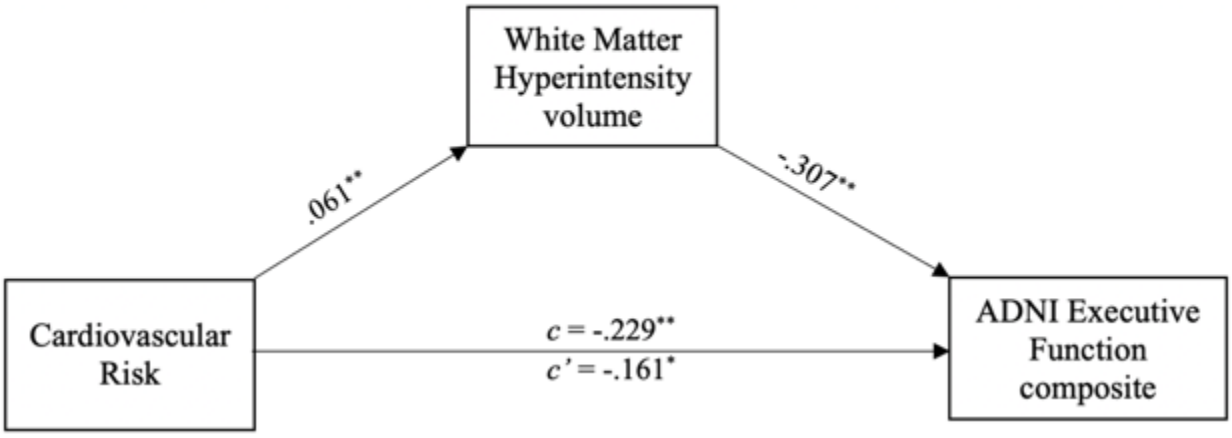


Note: In an exploratory analysis, racial group membership was a significant predictor of execuitve functioning performance and cardiovascular risk. WMH volume was a signifcant predictor of executive performance. However, there were no significant indirect effects through CVR or WMH volume on the relationship between racial group membership and execuitve performance.

* is significant at the 0.01 level. ** is significant at the 0.01 level.

Figure 4.5

Results Model for Exploratory Aim 2: Chapter 4

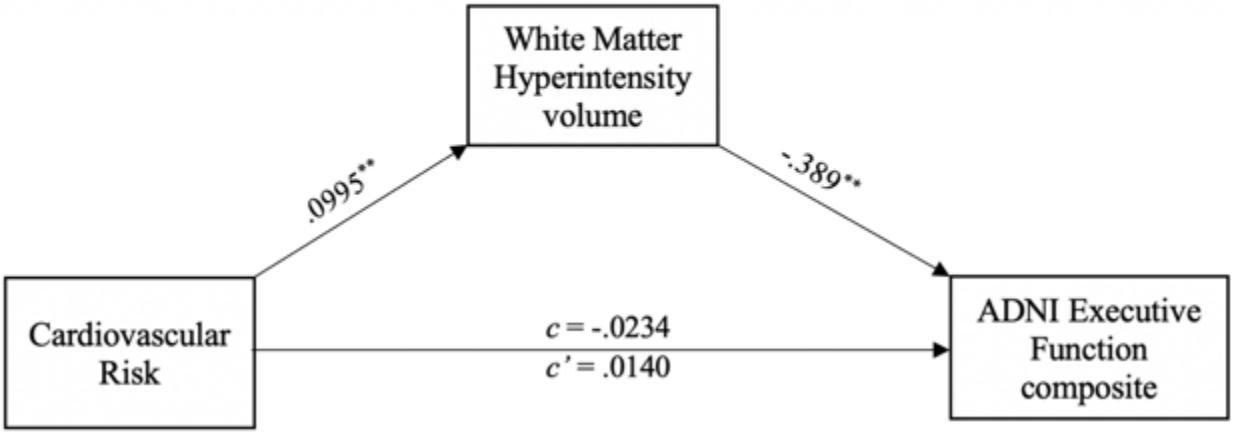


Note: Mediation in the Total Sample (Chapter 4), revealing a partial mediating effect of CVD risk on executive performance through WMH burden.

* is significant at the 0.01 level. ** is significant at the 0.01 level.

Figure 4.6

Results Model for Exploratory Aim 3: Chapter 4

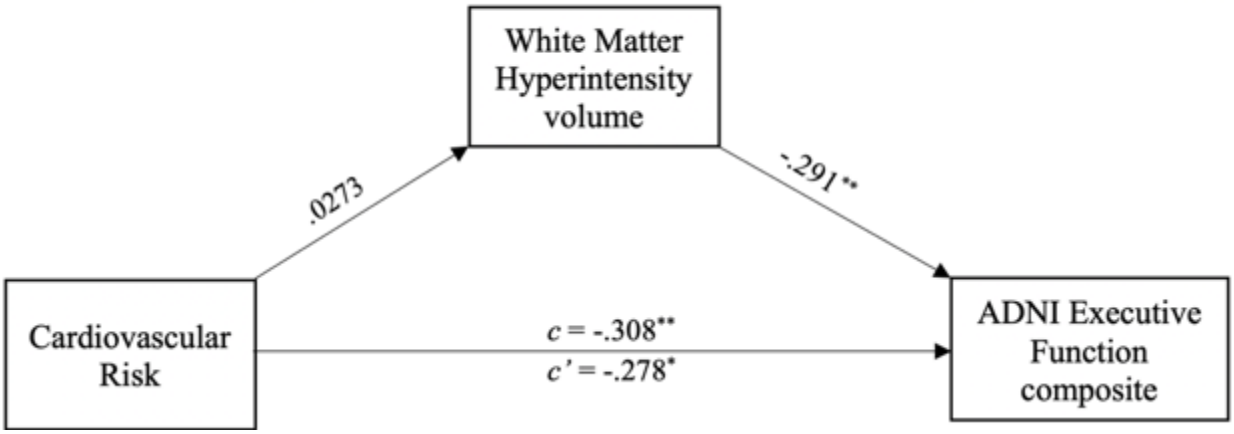


Note: There was no direct effect, but a significant indirect effect of CVD risk on executive performance through WMH burden within the White subsample (Chapter 4).

* is significant at the 0.01 level. ** is significant at the 0.01 level.

Figure 4.7

Results Model for Exploratory Aim 4: Chapter 4



Note: There was a significan direct effect of CVD risk on execuitve performance, but no significant indirect effect through WMH burden within the Black/African American subsample (Chapter 4).

* is significant at the 0.01 level. ** is significant at the 0.01 level.