RACIAL DIFFERENCES IN BRAIN HEALTH AT MIDLIFE AND THE POTENTIAL MEDIATING ROLE OF CARDIORESPIRATORY FITNESS AND CARDIOMETABOLIC RISK

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ABSTRACT

Blacks are at a higher risk for adverse brain-related outcomes, including stroke and dementia. Due to associations of vascular risk factors with brain health, differences in brain health may result from a greater burden of vascular risk factors in blacks, especially in midlife. However, relationships between vascular risk factors and midlife racial disparities in brain health have been underexplored. The overall objective of this dissertation is to improve our understanding of racial disparities in brain health outcomes and test for potential mediators of any observed racial differences. This objective was addressed through three studies. Since cerebral small vessel disease is a major cause of both stroke and dementia, our first study aimed to examine the current literature to determine if blacks exhibit more subclinical markers of cerebral small vessel disease than whites. We found that blacks appear to be at a greater risk for developing white matter hyperintensities, but relationships with other markers of cerebral small vessel disease remain unclear. Major limitations in the current literature include: 1) a lack of representation by younger age groups, 2) limited geographic representation, 3) few study samples, and 4) the lack of reporting diverse markers for brain health. The second study investigated racial differences in brain health among a middle-aged population. After adjustment for demographics, blacks exhibited

significantly lower gray matter volume, smaller hippocampus, less cortical surface area, and a thinner cerebral cortex than whites ($p<0.05$ for all). No differences in cerebral blood flow were found. The third study evaluated whether cardiorespiratory fitness (CRF) and/or cardiometabolic risk (CMR) mediate the relationship between race and brain health found in the second study. We found that CRF and CMR partially mediated the association of race with cortical surface area and gray matter volume. Overall, the findings from these three complementary studies are of public health relevance by revealing that brain health disparities exist in an otherwise healthy midlife population and by illuminating potential mediators for these disparities. Future work is needed to better understand these disparities. Researchers should investigate other potential pathways, examine younger populations and observe changes in brain health overtime.

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PREFACE

Four years ago, I set out on an adventure driven by my passion to preserve brain health. On July 31st of 2014, I packed up my life in the back of a U-Haul and moved from Boulder to Pittsburgh. Since then, a lot has happened. I have learned about the brain and heart from leading experts. I have traveled across the country presenting the research I am passionate about. I have grown as a person, a scientist, and even a sports fan. Our brains are key to who we are as people, personality, thought, consciousness. As the population grows older, we are challenged not only to preserve the health of the physical body, but also the consciousness that lies within them.

I would like to thank my committee members, each of whom has provided patient advice and guidance throughout the research process. Thank you all for your unwavering support. Also, I would like to thank the training grant which has allowed me to pursue the research I am passionate about. Akira, Emma, and Trevor: thank you for teaching me so much, providing structure, feedback, and for supporting me in my research endeavors.

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1.0 INTRODUCTION

This dissertation topic stemmed from observations of epidemiologic trends with regard to racial disparities in rates of stroke and subclinical brain disease. It appears that blacks are at greater risk of cerebral small vessel disease and brain related sequelae (stroke, dementia, and vascular cognitive impairment). If these trends continue unabated, their public health burden will increase as the population becomes older and more demographically diverse (Ortman, Velkoff, & Hogan, 2014; Pantoni, 2010). Current work attempting to identify potential sources of racial health disparities in cerebrovascular and brain health are limited. Most of the literature is derived from a few samples of limited geographic areas. Also, the majority of studies focus on distal markers of disease and include populations older than 65. Problematic from this perspective is that racial differences in stroke risk are greatest in populations younger than 65. Each chapter of this dissertation contributes to an improved understanding of the epidemiology of racial differences in cerebrovascular and brain health. The following introductory sections provide necessary context for each dissertation chapter. First, general information about cerebral small vessel disease (cSVD), the disease pathology, and documented disparities in brain health are presented. Second, we present findings from a review of the literature on racial disparities in subclinical brain health. Third, we investigate relationships between race and brain health in a healthy middle-aged community sample. Fourth, we will explore potential mediators of relationships between race and

brain health. Finally, we will discuss the comprehensive findings of these studies and potential directions of future research.

1.1 CEREBRAL SMALL VESSEL DISEASE

Small vessels in the brain undergo remodeling and exhibit signs of damage that accumulate with older age. Common findings on histopathological examination of postmortem brains of older individuals (i.e., those 60 years and older) include tortuosity of venules and arterioles, capillary rarefaction, small infarcts, microhemorrhages and enlarged perivascular spaces. These features are taken as manifestations of aging microcirculation. With the advent of magnetic resonance imaging (MRI), a wider range of cerebral age-related changes have been identified. These include parenchymal changes, such as infarcts, lacunes, periventricular spaces and also abnormalities of cerebral blood flow (CBF), white matter hyperintensities (WMH) and reduced fiber alignment (via diffusion tensor imaging). Although studies relating MRI and histopathological features of age-related cerebral microcirculation are sparse, the above MRI measures are nonetheless considered lesions of presumed vascular origin and are grouped together and referred to as “neuroradiological markers of cSVD”(Joanna M. Wardlaw et al.).

The neuroradiological features of cSVD have become the focus of intense study. Numerous reports, reviews and meta-analyses have been published on the relationships between the radiological markers of cSVD and negative health outcomes, including stroke, dementia, disability and mortality. Although major goals in this field encompass developing a precise understanding of cSVD pathogenesis and identifying potential prevention and treatment targets, many pressing

barriers to these goals remain unaddressed. Racial differences in markers of cSVD have been observed but the reasons behind these disparities remain unknown.

1.2 RACIAL DISPAIRITIES IN BRAIN HEALTH

Racial disparities in dementia and stroke are evident (F Gottesman, Fornage, S Knopman, & H Mosley, 2015; Husaini et al., 2003; Mozaffarian et al., 2015). Blacks are at a higher risk of stroke and developing dementia than whites (G. Howard et al., 2016; Mayeda, Glymour, Quesenberry, & Whitmer, 2016). If these trends continue unabated, the public health burden of disparities in dementia and stroke will increase as the population becomes older and more ethnically and racially diverse (Ortman et al., 2014; Pantoni, 2010). The clearest racial differences in stroke risk are seen in those under age 65 (Ayala et al., 2001; Heyman et al., 1971; V. J. Howard, 2013; V. J. Howard et al., 2011; Rosamond et al., 1999). Blacks under the age of 65 are estimated to be between 2.2-4.0 times more likely to suffer from a stroke than whites and twice as likely to die from a stroke (Ayala et al., 2001; Heyman et al., 1971; G. Howard et al., 2016; V. J. Howard, 2013; V. J. Howard et al., 2011; Rosamond et al., 1999). Additionally, dementia incidence is consistently found to be highest among blacks, with modest estimates predicting that blacks are at 40% higher (ranges from 14% to 100%) dementia risk compared with whites (D. Barnes et al., 2009; Katz et al., 2012; Mayeda et al., 2016; Miles, Froehlich, Bogardus, & Inouye, 2001). Finally, vascular dementia accounts for a larger proportion of cases in blacks than whites (Mayeda et al., 2016; Miles et al., 2001). The reasons behind these persistent racial disparities are not fully understood, but it has been suggested that there may be differential exposures or susceptibilities to the pathogenic effects

of known etiological factors for dementia and stroke among blacks and whites, including cSVD (F Gottesman et al., 2015; Gulli et al., 2016; Mayeda et al., 2016; Miles et al., 2001).

Even prior to the onset of later clinical events and outcomes noted above, blacks appear to be at a higher risk for detrimental subclinical brain changes that presage stroke, cognitive impairment, and dementia (F Gottesman et al., 2015). For example, studies have found associations between black race and reduced cerebral vascular reactivity (Hurr, Kim, Harrison, & Brothers, 2015), increased burden of WMH (B Zahodne et al., 2015; Brickman et al., 2008; Hannah Gardener et al., 2012; R. F. Gottesman et al., 2010; Nyquist et al., 2014), increased WMH progression (F Gottesman et al., 2015; R. F. Gottesman et al., 2010), a higher prevalence of subclinical brain infarcts (Bryan et al., 1999; F Gottesman et al., 2015; G. Howard et al., 1998) and increased cerebral atrophy (B Zahodne et al., 2015; F Gottesman et al., 2015). Indeed, only a few studies have found no racial differences in indicators of brain health (Aggarwal et al., 2010; B Zahodne et al., 2015; Bryan et al., 1999; Jennings et al., 2013; Liu et al., 2015), including those reporting no racial differences in WMH (Aggarwal et al., 2010; Liu et al., 2015), subclinical brain infarcts (B Zahodne et al., 2015; Bryan et al., 1999), and global cerebral blood flow (Jennings et al., 2013). However, little is known about racial differences in brain health during midlife., all of the above research has been conducted on populations over the age of 65 years. For example, with the exception of two of the above studies (Hurr et al., 2015; Jennings et al., 2013), all of the above research has been conducted on populations over the age of 65 years.

1.3 THE POTENTIAL ROLE OF VASCULAR RISK FACTORS

Vascular risk factors have been consistently associated with an increased risk of cognitive decline, cSVD, and subclinical brain damage (Jorgensen, 2018; Khan, Porteous, Hassan, & Markus, 2007; S.-A. Kim & Park, 2015; Qiu & Fratiglioni, 2015; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). The integrity of the vascular system is essential for maintaining proper brain function and disturbing the circulatory system of the brain increases susceptibility to damage and degeneration (Kalaria, 2010; O'Rourke & Safar, 2005). In the following section we will briefly summarize the evidence linking cardiovascular risk factors to brain health and known racial disparities in cardiovascular disease.

In a recent review, we examined potential risk factors for cSVD within healthy aging populations (Jorgensen). When examining traditional cardiovascular risk factors, we found that association of risk factors with both WMH and SBI/lacunes appears most consistent for hypertension and blood pressure parameters. However, descriptive studies examining the associations of antihypertensive medications with WMH or SBI/lacunes yield mixed findings. We did not find antihypertensive intervention trials in older adults without prior stroke. Measures of large vessel disease (stiffness, distensibility, intima media thickness, plaque and heart disease) appeared more strongly related to SBI/lacunes than to WMH. This is consistent with a prior report(Khan et al., 2007) suggesting different risk profile patterns for WMH as compared to SBI/lacunes. However, a recent study of the Lothian Birth Cohort found that a combined vascular stiffness score, although being a significant predictor, accounted for less than 2% of the variation in the prevalence of WMH (J. M. Wardlaw et al., 2014). This finding is limited in that it was conducted in a primarily white sample. Lifestyle factors such as smoking(Debette et al., 2011; Dickie et al., 2016; Gons et al., 2011; Knopman, Mosley, Catellier, & Sharrett, 2005; Nyquist et

al., 2014; E. J. van Dijk et al., 2008) and sedentary behavior(Sexton et al., 2016) have consistently been implicated in higher probability of having WMH and more recently with reduced CVR in periventricular white matter.(Gauthier et al., 2015) Among the newer measures of cSVD, Jennings, et al. found reduced CBF was associated with increased cardiometabolic risk and worse intima media thickness.(Jennings et al., 2013)

Associations of cSVD with inflammation, dyslipidemia, or obesity were not consistent across studies. The state of the evidence is strongest for a positive association of inflammatory factors with WMH. Both CRP and IL-6 have been found to be related to WMH, (Nadkarni et al., 2016); Satizabal, Zhu, Mazoyer, Dufouil, and Tzourio (2012) but overall study results are mixed. (Aribisala et al., 2014; Markus et al., 2005; Nadkarni et al., 2016; Satizabal et al.; Schmidt et al., 1997; Schmidt et al., 2006; E. Van Dijk et al., 2005) Cumulative exposure, longer duration of exposure and variability over time in the levels of these factors all appear to be important, but few studies examined these characteristics concurrently. We found no strong evidence to support an association between inflammatory factors and SBI/lacunes. No studies evaluated inflammatory factors in relation to CBF or CVR, and no studies evaluated these associations in those <60 years of age. Future studies should focus on those areas and attempt to account for cumulative exposure to inflammatory factors.

Overall, the evidence does not support a strong link between diabetes and cSVD.(Dearborn et al., 2015; Debette et al., 2011; G. Howard et al., 1998; Knopman et al., 2005; Knopman et al., 2011; J. E. Lee et al., 2016; Longstreth et al., 1998; Nyquist et al., 2014; Ramos et al., 2014; Schmidt et al., 1997; E. J. van Dijk et al., 2008; Vermeer, Koudstaal, Oudkerk, Hofman, & Breteler, 2002) Diabetes may interact with other risk factors such as sleep duration(Ramos et al., 2014) and SBP,(Knopman et al., 2011) and these interactions should be evaluated in future studies.

It has been suggested insulin resistance may be a more sensitive risk factor for SBI/lacunes than diabetes, as both cross-sectional (J. E. Lee et al., 2016) and longitudinal associations(Dearborn et al., 2015) have been reported.

Due to the strong associations between vascular risk factors with brain health and function (Khan et al., 2007; S.-A. Kim & Park, 2015; Qiu & Fratiglioni, 2015; Whitmer et al., 2005), it is possible that racial differences in brain health result from a greater burden of vascular risk factors in blacks (F Gottesman et al., 2015; Heyman et al., 1991; V. J. Howard et al., 2011; Mayeda et al., 2016; Miles et al., 2001; Sacco et al., 2001). However, vascular risk factors have not been fully tested as explanatory factors that partly account for racial differences in brain health outcomes (F Gottesman et al., 2015).

Nevertheless, racial differences in cardiovascular health have been documented extensively (Havranek et al., 2015). Blacks have been consistently found to have increased cardiovascular disease risk and a higher prevalence of cardiovascular disease risk factors, including: diabetes, hypertension, physical inactivity, obesity, and smoking (Benjamin et al., 2017). Additionally, blacks are more likely to have clustering of cardiovascular disease risk factors than whites (Sharma, Malarcher, Giles, & Myers, 2003). Blacks have been found to be twice as likely as the other racial groups to have 4 or more cardiovascular risk factors and had lowest percent of people with no risk factors (Sharma et al., 2003). It appears that there may also be differences in the age of onset for many of subclinical cardiovascular disease processes, whereby blacks may have earlier onset of hypertension (L. L. Barnes et al., 2016; Heffernan, Jae, Wilund, Woods, & Fernhall, 2008; Montagne et al., 2015; Shen et al., 2017) thicker IMT and higher PWV at younger ages (Benjamin et al., 2017; Budoff et al., 2006; D'Agostino et al., 1996; T. C. Lee, O'Malley, Feuerstein, & Taylor, 2003; Lefferts et al., 2017; Manolio et al., 2008; Orakzai et al.,

2006; Thurston & Matthews, 2009; Wassel et al., 2009; Wendell, Waldstein, Evans, & Zonderman, 2017). Blacks in general have been found to have less CAC but increased carotid intima thickness than whites and, more recently, that some of these differences may be explained by a genetic difference (Benjamin et al., 2017; Budoff et al., 2006; D'Agostino et al., 1996; T. C. Lee et al., 2003; Manolio et al., 2008; Orakzai et al., 2006; Wassel et al., 2009). Finally, it is important to note that SES factors are found to interact with many of these relationships (Thurston & Matthews, 2009; Wendell et al., 2017).

Despite evidence the mounting evidence on all sides, studies examining relationships between subclinical cardiovascular disease, race, and brain health are rare. How these racial differences in the subclinical cardiovascular disease pathology impact brain health is unknown, and research in this area could help to elucidate why blacks are at a greater risk of stroke and stroke death than other populations(Sharma et al., 2003).

1.4 CONCEPTUAL MODEL

The conceptual model reflects much of the preceding thoughts that have driven the hypotheses tested within this dissertation. It reflects our understanding of the many potential mediators between race and brain health. The model consists of 3 hypothesized relationships between race subclinical CVD markers/ mediators and structural brain health. The model also reflects that these relationships are not occurring in isolation. Instead we recognize the many possible confounding factors including social, demographic, genetic, environmental, health behaviors, and the presence of co-morbid conditions. These potential confounding factors are often associated with brain changes, either protective or detrimental, and also differ by race.

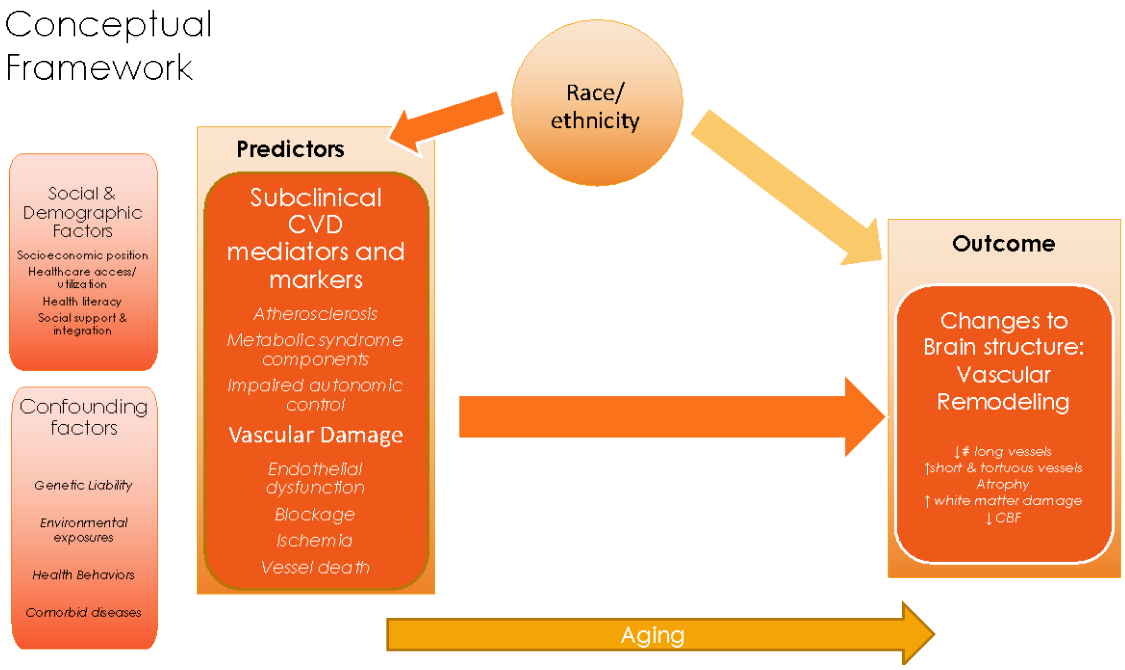

Figure 1.1 Conceptual Model

2.0 RACIAL DIFFERENCES IN BRAIN HEALTH: A REVIEW OF THE LITERATURE

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2.1 ABSTRACT

Background: Blacks are at a higher risk than whites for several adverse brain-related outcomes, such as stroke and dementia. Since cerebral small vessel disease (cSVD) is a major cause of both stroke and dementia, we aimed to examine whether blacks exhibit more subclinical markers of cSVD than whites.

Methods: We carried out a literature search following PRISMA guidelines to examine the estimates of prevalence and risk for markers of cSVD and race in otherwise healthy individuals. This review adopts the STRIVE definition of cSVD.

Results: We found 33 publications which met our search criteria. The average age across publications was 65 years, studies samples came from similar geographic locations, a limited number of study samples, and most studies examined white matter hyperintensities as a marker of subclinical brain health. Blacks appear to be at a greater risk for developing white matter hyperintensities. Relationships between race with other markers of brain health remain unclear.

Conclusion: Future work needs to be done in younger populations with more geographic variation in order to determine whether differences in brain health are due to true differences in risk.

2.2 INTRODUCTION

Racial differences in stroke and dementia are evident but the reasons behind these disparities remain poorly understood (F Gottesman et al., 2015; Husaini et al., 2003; Mozaffarian et al., 2015). If these trends continue unabated, the public health burden of disparities in dementia and stroke will increase as the population becomes older and more ethnically and racially diverse (Ortman et al., 2014; Pantoni, 2010). Stroke and cerebral small vessel disease (cSVD) share risk factors and pathophysiology (J. M. Wardlaw et al., 2014; J. M. Wardlaw, C. Smith, & M. Dichgans, 2013); therefore, it would be expected that racial disparities in stroke risk should confer to higher risk for subclinical brain changes in blacks before a clinical event (Smith et al., 2017). At the present time, advancements in neuroimaging, increased understanding of the underlying neuropathology, and changing clinical guidelines and recommendations have begun to shift the focus of research from overt stroke events to subclinical brain changes that may be related to stroke pathophysiologically, but do not present clinically as stroke (R. Gottesman, Fornage, S Knopman, & H Mosley, 2015; Sacco et al., 2013; Joanna M. Wardlaw et al.). These changes present a unique opportunity to explore whether racial differences in subclinical brain health are evident in the literature. To this date, we are aware of only one review examining racial differences in subclinical brain health and it was limited to only ARIC publications(R. Gottesman et al., 2015). In an effort to better understand the racial differences in subclinical brain health we completed a review of the literature with the focus being on subclinical brain changes. This review will further current understanding

of racial disparities in brain health by summarizing findings across several studies, examining novel and earlier stage markers of cerebrovascular disease, and by identifying important gaps in the current literature.

2.3 METHODS

We carried out a literature search to examine the state of research and knowledge surrounding markers of cSVD and race in otherwise healthy individuals. This review adopts the STRIVE definition of neuroradiological markers of cSVD (Joanna M Wardlaw, Eric E Smith, et al., 2013). By this definition, cSVD is thought to comprise a syndrome of radiological manifestations affecting brain areas with predominantly poor collateral vascularization (e.g. watershed areas, fronto-subcortical regions, etc.). Radiological markers of cSVD include features seen on neuroimaging include recent small subcortical infarcts, lacunes, white matter hyperintensities, perivascular spaces, and brain atrophy (Joanna M Wardlaw, Eric E Smith, et al., 2013). To account for the most recent methodological developments to characterize brain circulation, we include more novel markers of cSVD, which appear to be more direct measures of vasculature integrity. For example, endothelial dysfunction, an early stage marker of cSVD, can be measured by CBF at rest and changes in response to specific challenges (e.g. breath-holding or hypercapnia) (Joanna M Wardlaw, Eric E Smith, et al., 2013) We also searched for morphological measures (e.g. tortuosity, density) of arterioles via time-of-flight MRI and of small veins via ultrahigh field susceptibility-weighted MRI.

COMMONLY USED NEURORADIOLOGICAL MARKERS OF cSVD

- White matter hyperintensities: WMH
- Silent brain infarcts: SBI
- Lacunes: Small sharply defined regions of tissue loss most frequently associated with deep gray and white matter
- Brain atrophy: A lower brain volume that is not related to a specific macroscopic focal injury such as trauma or infarction.

NOVEL MARKERS OF cSVD

- Cerebral blood flow (CBF) measured at rest
- Cerebrovascular reactivity (CVR): changes in CBF after stimulation
- Morphology of small arteries and veins (e.g. tortuosity, density)

Figure 2.1. Abbreviation

The search method to examine associations with risk factors is summarized in Figure 1, and it follows the PRISMA guidelines (http://www.prisma-statement.org/). We searched PubMed for review and original articles examining neuroradiological markers of cSVD (see boxed text for definitions). Studies that were cited by the articles thus included were further reviewed and included if appropriate. Vessel morphology articles were not found using these search terms, and therefore a hand search was carried out. We included studies examining community-dwelling, neurologically healthy individuals. Exclusion criteria were: a) hospitalized populations or disease state only population without a white comparison group, b) if no race specific estimates were given (in text, figures, or supplement), c) narrative reviews. For example, if a study dealt with recent stroke patients, that study was excluded. If a study was carried out only in individuals with diabetes and no controls, that study was excluded.

2.4 RESULTS

2.4.1 Characteristics of the Publications

In this search we identified 293 articles, screened 93 articles, and included 33 studies in this review. The mean age across publications was 65.4 years old, with the youngest samples mean age of 23 years old and the oldest sample mean age of 84.5 years old (Figure 2). The mean age weighted by sample size was older by two years at 67.4 years old. One study had a large difference in age between the black and white participants, where the average age for the black participants was 35.6 years and for white participants it was 46.4 years (Isamah et al., 2010). The proportion of publications by study in this review can be seen in Figure 3. The two study samples contributing the most publications were ARIC at 25% and NOMAS at 16%. We observed geographic trends in the sample populations (Figure 4). 31% of the publications were from study populations that the black participants were recruited from Jackson, Mississippi and another 28% were from Northern Manhattan communities, while all other geographic areas had limited coverage and contributed less then 50% to the total. Finally, we found 11 of the 33 articles included in this review had white controls from different geographic locations than the blacks (Bryan et al., 1999; Fornage et al., 2007; R. F. Gottesman et al., 2010; G. Howard et al., 1998; Knopman et al., 2008; Knopman et al., 2005; Knopman et al., 2011; Liao et al., 1997; D. Liao et al., 1996; Michos et al., 2014; Windham et al., 2017). In GENOA samples whites were recruited from Rochester, MN and blacks from Jackson, MS. In ARIC, black participants were primarily recruited from Jackson, MS and Forsyth County, NC; while whites were recruited from Minneapolis, MN and Forsyth County, NC. However, it is important to note that the proportion of blacks recruited from the Forsyth County,

NC site in the ARIC study is very low at around 12% of the sample from Forsyth County, NC (R. Jackson et al., 1996).

2.4.2 Subclinical markers of brain health

The associations between races with subclinical measures of brain health is presented in table 1 and reviewed below.

2.4.2.1 Small vessel characteristics

We did not find any studies examining racial differences in small vessel characteristics.

2.4.2.2 Cerebral Blood Flow

Three cross-sectional studies examined CBF and found no significant differences in CBF (Hurr et al., 2015; Jennings et al., 2013; Selim, Jones, Novak, Zhao, & Novak, 2008). CBF was measured using transcranial Doppler in two of the studies (Hurr et al., 2015; Selim et al., 2008) and by Arterial Spin Labeled MRI in the other (Jennings et al., 2013). Mean ages for the studies were 23 (Selim et al., 2008), 43 (Jennings et al., 2013), and 60 (Selim et al., 2008). Two of the studies were unadjusted (Hurr et al., 2015; Selim et al., 2008), while one the models controlled for age, current smoking status, sex, total brain volume, and Cardiometabolic risk measure or the Framingham index (Jennings et al., 2013).

2.4.2.3 Cerebral Vascular reactivity

One small study (N=42) among college aged adults (aged 23 +/- 4) found that CVR is lower in blacks as compared to age and sex matched whites(Hurr et al., 2015). However, this association

was unadjusted for BMI, blood pressure, and other relevant confounders. Although, BMI was not significantly different between the two groups, blacks tended to have a higher BMI (p=0.07).

2.4.2.4 White Matter Hyperintensities

We found nineteen studies that reported measures of brain health and race, of these three studies solely reported interactions and will be discussed at the end of this section. Of the nineteen studies, five came from ARIC (R. F. Gottesman et al., 2010; Knopman et al., 2011; Liao et al., 1997; D. Liao et al., 1996; Michos et al., 2014), three from NOMAS (Hannah Gardener et al., 2012; J. Marcus et al., 2011) (Hudson et al., 2011), two from WHICAP (B Zahodne et al., 2015; Brickman et al., 2008), two from Genetic Epidemiology Network of Arteriopathy (Knopman et al., 2008; Windham et al., 2017), two are from health ABC samples (Liu et al., 2015; Rosano et al., 2013), and the remaining five from other samples. Twelve of sixteen studies found associations with black race and WMH (B Zahodne et al., 2015; Brickman et al., 2008; H. Gardener et al., 2012; R. F. Gottesman et al., 2010; Knopman et al., 2008; Knopman et al., 2011; Liao et al., 1997; D. Liao et al., 1996; Michos et al., 2014; Nyquist et al., 2014; Windham et al., 2017; Yue et al., 1997). Three studies found no significant association with black race and WMH (Aggarwal et al., 2010; Liu et al., 2015; Prabhakaran et al., 2008; Waldstein et al., 2017), with Liu, Allen et al. 2015 finding the relationship with race borderline insignificant (p=0.062), and Waldstien et al. finding no main effect but a significant interaction with SES (Waldstein et al., 2017). Three studies examined progression of WMH (R. F. Gottesman et al., 2010; Knopman et al., 2011; Michos et al., 2014), while most looked at prevalence in cross-sectional analyses (Aggarwal et al., 2010; B Zahodne et al., 2015; Brickman et al., 2008; Hannah Gardener et al., 2012; Knopman et al., 2008; Liao et al., 1997; D. Liao et al., 1996; Liu et al., 2015; Nyquist et al., 2014; Prabhakaran et al., 2008; Waldstein et al., 2017; Windham et al., 2017; Yue et al., 1997), and only two examined the relationships in

those under age 60 (Nyquist et al., 2014) (Waldstein et al., 2017). The findings from the three longitudinal papers are particularly interesting as it they were the only studies which examined progression of WMH, all finding that substantial progression of WMH occurred in blacks over the roughly 10-year period, compared to whites.

Few studies reported potential risk factor interactions with race(J. Marcus et al., 2011; Waldstein et al., 2017). After stratifying by quartiles of DBP, Marcus et al. found blacks had more WMH than whites only if their DBP was above the lowest quartile of DBP, suggesting an interaction with DBP(J. Marcus et al., 2011). Waldstein et al. found a significant interaction between a measure of SES and WMH, where blacks with low SES has significantly greater lesion volume than whites, but there was no racial differences among high SES groups(Waldstein et al., 2017). Furthermore, these studies varied in how potential confounders were adjusted for three were unadjusted (Aggarwal et al., 2010; B Zahodne et al., 2015; H. Gardener et al., 2012) and two were minimally adjusted (age and sex)(Brickman et al., 2008; J. Marcus et al., 2011).

The two studies that did not find any significant associations (Aggarwal et al., 2010; Liu et al., 2015) were both cross-sectional studies in populations with mean ages ~80 years old and above, however, the null findings cannot be due to age alone as (B Zahodne et al., 2015; Brickman et al., 2008) also in populations over 80. The overall prevalence of hypertension in the Liu et al. study was very high in both whites and blacks (80% and 86% respectively (p=0.20)) which is unusual given that blacks tend to have a higher prevalence of hypertension, and other studies have observed this even in older age groups (B Zahodne et al., 2015; Brickman et al., 2008) suggesting that the comparison population may have been sicker than participants in other studies. Thus, diminishing the difference in WMH between the two groups. Estimates from the Aggarwal et al.

publication were unadjusted and did not report prevalence of CVD risk factors, making it difficult to identify what study population characteristics may have contributed to this difference.

2.4.2.5 SBI / Lacunes

Six of seven the studies examining SBI and race were cross-sectional analysis (Aggarwal et al., 2010; B Zahodne et al., 2015; Bryan et al., 1999; Bryan et al., 1997; G. Howard et al., 1998; Prabhakaran et al., 2008; Yue et al., 1997) one was longitudinal (Knopman et al., 2011). Two studies found an association between SBI/lacunes and black race (Bryan et al., 1999; G. Howard et al., 1998; Prabhakaran et al., 2008) and both happen to be from ARIC samples. Four studies found no significant associations (Aggarwal et al., 2010; B Zahodne et al., 2015; Bryan et al., 1997; Prabhakaran et al., 2008; Yue et al., 1997). However, the estimates from three of these studies (B Zahodne et al., 2015; Bryan et al., 1999; Bryan et al., 1997; Yue et al., 1997) were unadjusted and therefore these findings could be confounded by differences in the populations. The Prabhakaran et al. and Howard et al. studies made appropriate adjustment for covariates and came up with seemingly different results. Prabhakan et al. initially found differences in prevalence of SBI among different racial groups, but after adjustment these were attenuated and became non-significant. Notably, Prabhakaran et al. found a significant interaction between race and age, where younger blacks had the highest odds of SBI. This could potentially explain the difference in findings, given the younger age distribution of the Howard et al. sample population. It could be that the difference in SBI is only seen at younger ages and may disappear with age either due to survival bias or other factors. Hudson et al. only reported findings of an interaction with where higher levels of soluble Receptor for Advanced Glycation End-products were protective against SBI (Hudson et al., 2011).

2.4.2.6 Atrophy / Total Brain Volume

We found ten cross-sectional studies originating from 9 samples that evaluated brain atrophy or examined brain volumes(Aggarwal et al., 2010; B Zahodne et al., 2015; Brickman et al., 2008; Fornage et al., 2007; Knopman et al., 2008; Knopman et al., 2005; Liu et al., 2015; Longstreth Jr et al., 2000; Prabhakaran et al., 2008; Waldstein et al., 2017; Yue et al., 1997) and one longitudinal study (Knopman et al., 2011). Of these studies, three found more brain atrophy or reduced total brain volume in blacks compared to whites (Fornage et al., 2007; Knopman et al., 2008; Waldstein et al., 2017), four found no difference (Aggarwal et al., 2010; Knopman et al., 2005; Liu et al., 2015; Prabhakaran et al., 2008; Yue et al., 1997), and two found greater total brain volume in blacks compared to whites (Brickman et al., 2008; Longstreth Jr et al., 2000).

2.4.2.7 Hippocampal Volume

Four studies reported hippocampal volumes, two found reduced hippocampal size among blacks (Isamah et al., 2010; Prabhakaran et al., 2008), one found no difference (Brickman et al., 2008) and one found greater hippocampal size compared to whites (B Zahodne et al., 2015). Both the study finding no difference and the other finding a larger hippocampal size in blacks came from the WHICAP sample. Only one of the studies was in a sample less than 60 years old (Isamah et al., 2010). Although, Zahodne et. al reported somewhat contradictory findings, where black participants had greater hippocampal than whites but reduced cortical thickness (B Zahodne et al., 2015).

2.4.2.8 Ventricular Size

Seven studies reported ventricular size (Brickman et al., 2008; Isamah et al., 2010; Knopman et al., 2008; Knopman et al., 2005; Knopman et al., 2011; Longstreth Jr et al., 2000; Yue et al., 1997).

Three found no difference in ventricular size (Isamah et al., 2010; Knopman et al., 2005; Knopman et al., 2011) and four found better ventricular size (Brickman et al., 2008; Knopman et al., 2008; Longstreth Jr et al., 2000; Yue et al., 1997). The Knopman et al. paper reported that while there were no differences in ventricle size at baseline, black males had significantly higher ventricular worsening compared to white males (Knopman et al., 2011); there were no significant racial differences between females.

2.4.2.9 Sulcal Size

Four studies reported differences in sulcal size (Knopman et al., 2005; Knopman et al., 2011; Longstreth Jr et al., 2000; Yue et al., 1997). One reported no difference (Knopman et al., 2005) and two reported better sulcal grades among blacks (Longstreth Jr et al., 2000; Yue et al., 1997). In a longitudinal analysis Knopman et al. found worse sulcal grades among black males compared to white males but no racial differences among females, conversely at follow-up fewer blacks than whites and sulci grade worsening (Knopman et al., 2011).

Only two of these studies reported interactions with race (Brickman et al., 2008; Waldstein et al., 2017). Brickman et al. found that vascular disease was associated with smaller relative brain volume, particularly among blacks (Brickman et al., 2008). Waldstein et al. found significant interactions with SES and race for all outcomes (Waldstein et al., 2017).

2.5 DISCUSSION

In summary, few prospective studies have examined the relationships between race and the development of cSVD markers. Most of the research has focused on cross-sectional examinations

(prevalence or odds ratios) without examining if race impacts the risk of development of this disease pathology. The Knopman et al. and Gottesman et al. papers were the only two found to examine progression of subclinical disease markers and both were from ARIC study samples (R. F. Gottesman et al., 2010; Knopman et al., 2011). Gottesman et al. found that blacks were more likely to have significant WMH disease progression(R. F. Gottesman et al., 2010). Knopman et al. found that while significantly more blacks had SBI at baseline when compared to whites, there was no difference in the rate of progression between races (Knopman et al., 2011). The vast majority of the evidence examines WMH, SBI, and total brain volumes, with only a few studies looking at CBF and one examining CVR.

The mean age across publications included in this review is 65.4 years old. Given that blacks are known to have a higher risk of stroke and stroke death, particularly under the age of 65 years, the findings from studies in older populations may be subject to survival bias. Where the blacks participating in these MRI studies may be particularly resilient and the true population differences in brain health may be underestimated. Given there is such a disparity in stroke risk by age, it is imperative that future work examines younger populations, earlier markers, and uses advanced statistical methods to account for survival bias.

Over 50% of studies are derivative from black populations in Jackson, MS and northern Manhattan communities which is problematic given that there are documented geographic trends in stroke risk, whereby in regions known as the “stroke-belt” the risk of stroke and exposure to risk factors is much higher (Borhani, 1965). Additionally, it has been previously found that the stroke mortality ratio, comparing blacks to whites, varies among states (G. Howard, Howard, Katholi, Oli, & Huston, 2001). For example, it was found that blacks in Florida have 92% higher risk of dying from stroke than whites, while blacks in New York are only at a 6% higher risk (G.

Howard et al., 2001). In a further analysis, Howard et al. found that the age adjusted black-to-white stroke mortality ratio was consistently higher for southern states compared to non-southern states and that this difference is larger than what is expected from accounting for the increased risk in the "Stroke Belt" (V. J. Howard, 2007). Therefore, the studies sampling southern blacks and northern whites, (Bryan et al., 1999; Fornage et al., 2007; R. F. Gottesman et al., 2010; G. Howard et al., 1998; Knopman et al., 2008; Knopman et al., 2005; Knopman et al., 2011; Liao et al., 1997; D. Liao et al., 1996; Michos et al., 2014; Windham et al., 2017) may see differences in risk that are due to geography alone, but since they are unable to properly adjust for geographic confounds, it may be difficult to determine whether the racial differences in brain health are due to geography or other factors.

Overwhelmingly, most studies reported measures of WMH and most of these studies found a relationship between increased WMH in blacks as compared to whites (B Zahodne et al., 2015; Brickman et al., 2008; Hannah Gardener et al., 2012; R. F. Gottesman et al., 2010; Knopman et al., 2008; Knopman et al., 2011; Liao et al., 1997; Duanping Liao et al., 1996; Michos et al., 2014; Nyquist et al., 2014; Windham et al., 2017; Yue et al., 1997). Evidence was unclear for SBI, atrophy, hippocampal volumes, and sucal grades. The evidence above appears to suggest that there is no difference in CBF between blacks and whites and no difference or potentially better ventricular grades among blacks. These unexpected findings could be the result of survivor bias, as the ages of subjects in these studies are over 65 and may potentially reflect mechanisms of resilience. There were no studies reporting racial differences in small vessel characteristics and only one study reporting impaired CVR among blacks. Future work should be done to assess novel markers of cSVD including CVR and small vessel characteristics in younger populations to reduce survival bias.

It has been theorized that such seemingly premature appearance of cSVD among blacks could be due to the higher burden of cardiovascular risk factors and diseases in blacks as compared to whites. However, substantial evidence in support of this theory is lacking. Only two publications included in this review had comprehensive measures of vascular-related characteristics.(R. F. Gottesman et al., 2010; Prabhakaran et al., 2008) Furthermore, the role of cardiovascular risk factors remains unclear as the findings of these two publications came to somewhat opposing conclusions. One found that adjustment for cardiovascular risk factors (smoking, hypertension, diabetes, hypercholesterolemia, and cardiac disease)(Prabhakaran et al., 2008) attenuated racial differences, whereas the other did not (R. Gottesman et al., 2015; R. F. Gottesman et al., 2010). It is important to note that time of exposure and of measurement of the outcomes, as well as duration of exposure all need to be taken into account. We noticed that cardiovascular risk factors were often measured at an older age in studies where cardiovascular risk factors failed attenuate racial differences in cSVD.(R. F. Gottesman et al., 2010; Nyquist et al., 2014) Perhaps the explanatory effect of cardiovascular risk factors is stronger earlier in age, as compared to later in life, when the process of cSVD accumulation has already been unfolding for a long time. Another possibility is that the older subgroups of blacks who are participating in MRI studies are exceptionally resilient. Blacks are known to have a higher risk of death and morbidity as compared to whites; hence, studies with older subgroups of blacks may be vulnerable to survival bias.

In summary, more work needs to be done in order to determine the reasons underlying racial health disparities in stroke and dementia risk. In order to reduce confounding that may be due to geography, future studies to include multiple geographic sites and ensure both white and black participants are recruited from each site. Also, we would suggest that future studies should begin to focus on younger age groups, without clinical disease, and early stage markers of the

disease process. Expansion of this research is key in resolving these health disparities by determining risk factors and developing a clearer understanding of the underlying pathologic mechanisms prevention or delay of stroke and dementia is possible.

2.6 TABLES AND FIGURES

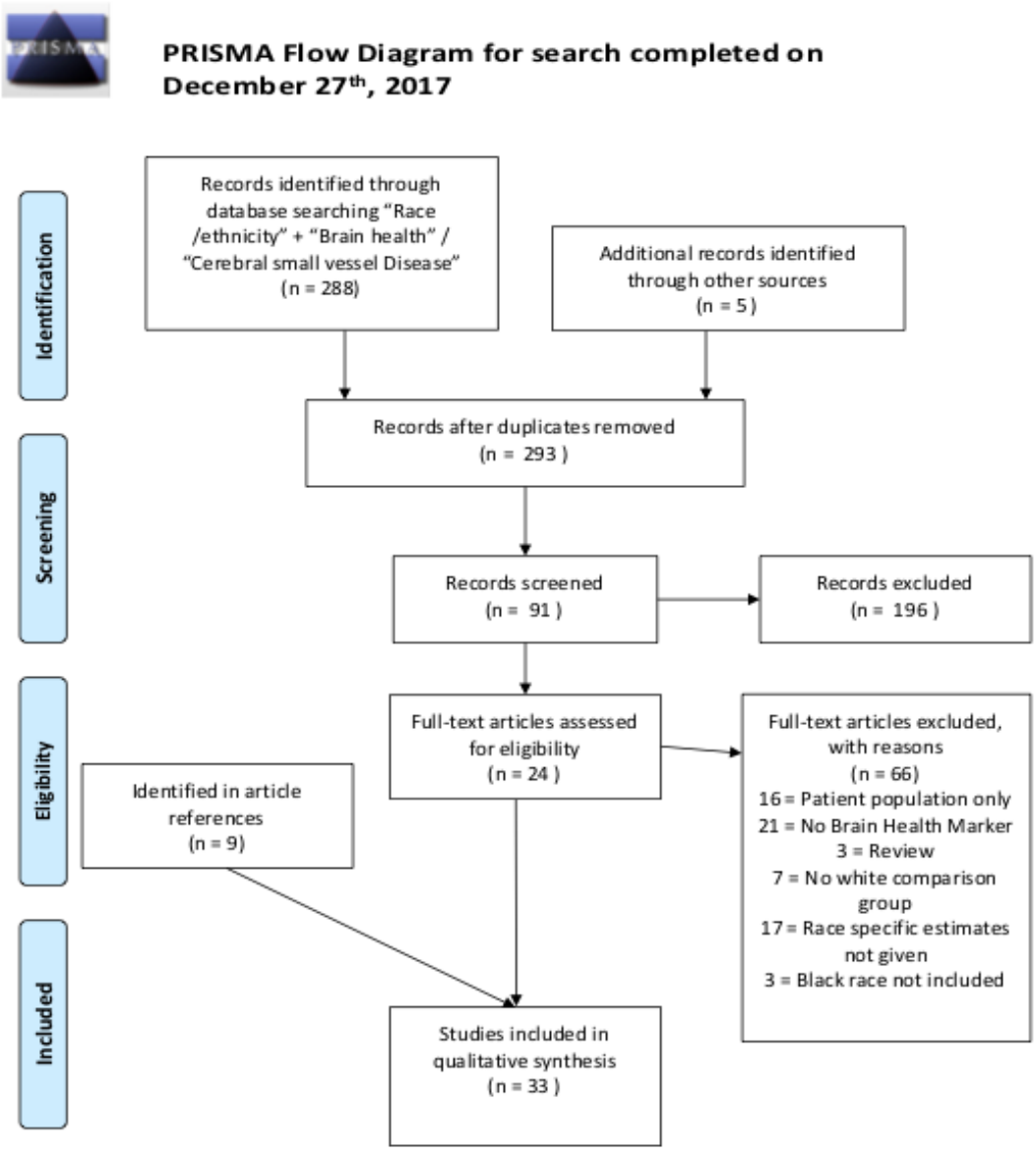

Figure 2.2 PRISMA guideline summary of articles included in review

Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

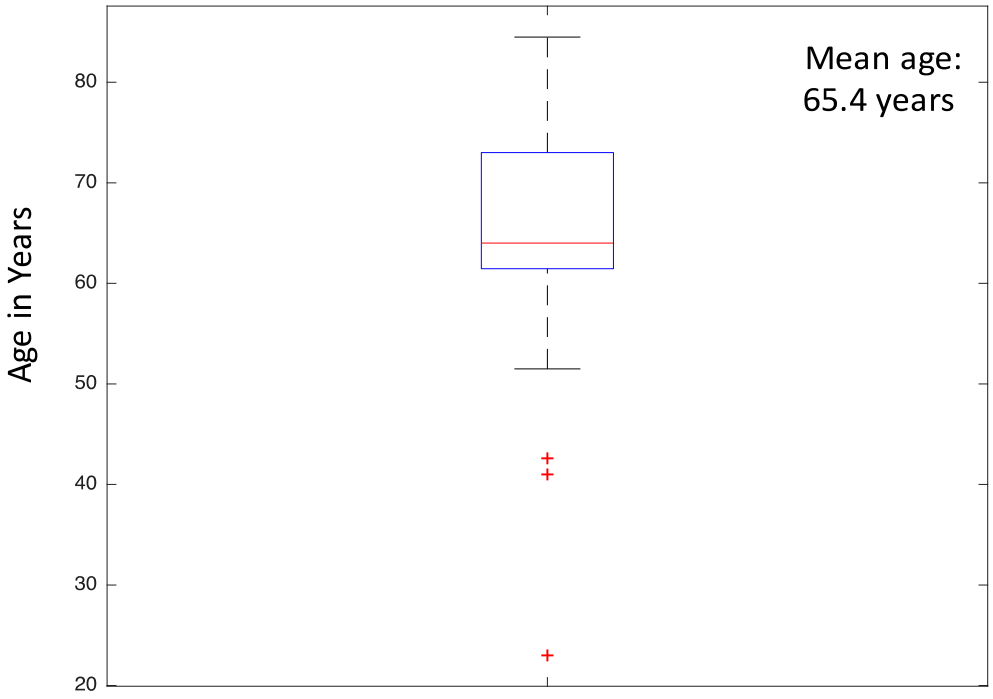

Figure 2.3 Distribution of mean ages across publications

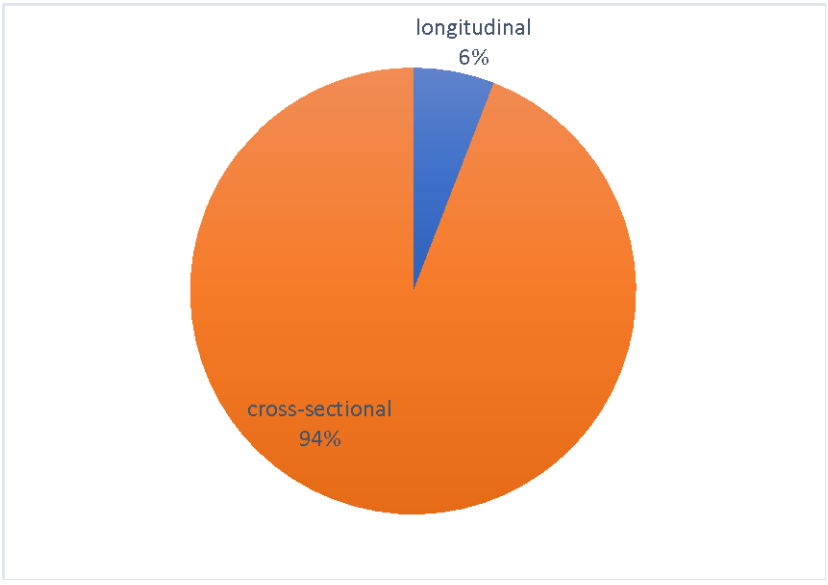

Figure 2.4 Neuroimaging measurement by publication

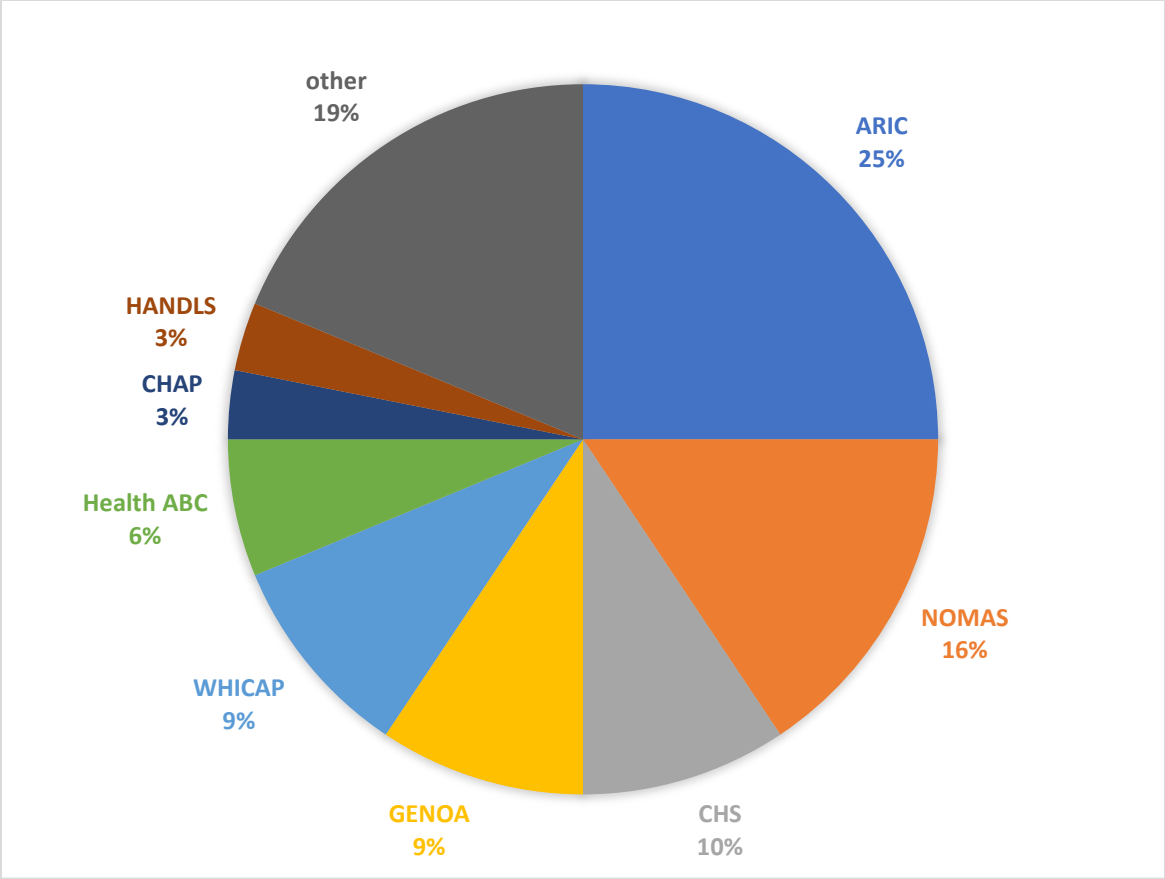

Figure 2.5 Publications by study samples

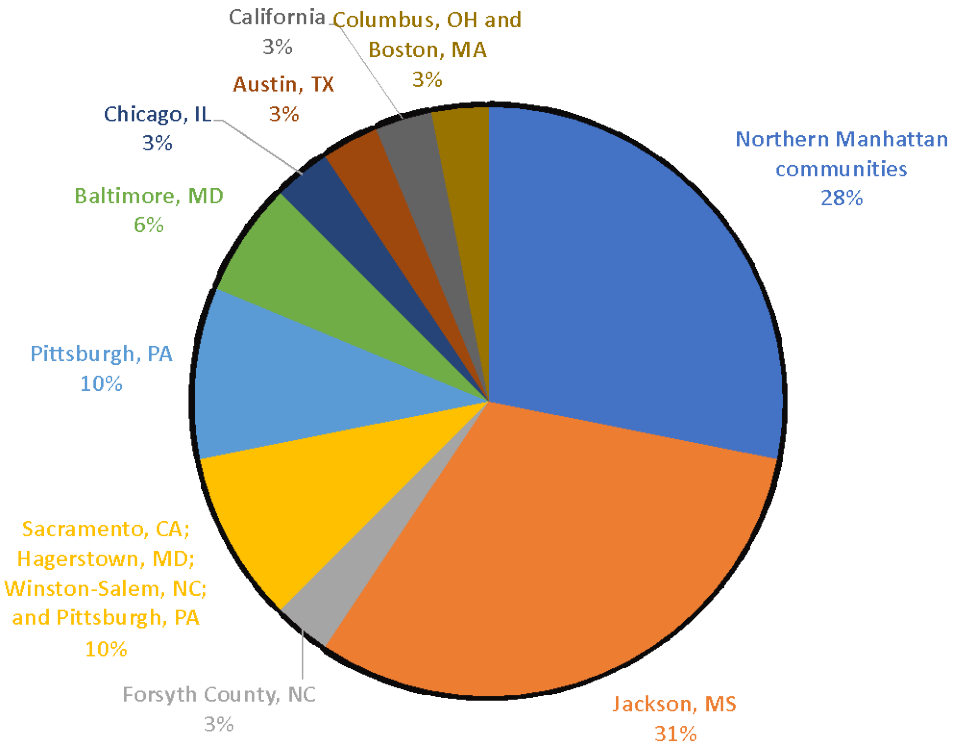

Figure 2.6 Publications by geographic location of black participants

Table 2.1 Reported Association of Subclinical Brain health with Black Race compared to White Race

Measure of Brain health	Positive	Negative	No Significant Differences
CBF			Selim et al., 2008; Jennings et al., 2013; Hurr et al., 2015
CVR		Hurr et al., 2015	
WMH	Liao et al., 1996; Liao et al., 1997; Yue et al., 1997; Brickman et al., 2008; Knopman et al., 2008; Gottesman et al., 2010; Knopman et al., 2011; Gardener et al., 2012; Michos et al., 2014; Nyquist et al., 2014; B Zahodne et al., 2015; Windham et al., 2017		Prabhakaran et al., 2008; Aggarwal et al., 2010; Liu et al., 2015; Waldstein et al., 2017
SBI	Howard et al., 1998; Bryan et al., 1999		Bryan et al., 1997; Prabhakaran et al., 2008; Aggarwal et al., 2010; B Zahodne et al., 2015
Atrophy	Fornage et al., 2007; Knopman et al., 2008; Waldstein et al., 2017	Longstreth et al. 2000; Brickman et al., 2008	Knopman et al., 2005; Prabhakaran et al., 2008; Aggarwal et al., 2010; Liu et al., 2015
Hippocampal volumes	B Zahodne et al., 2015	Isamah et al., 2010; Prabhakaran et al., 2008	Brickman et al., 2008

Table 2.1 Continued

Ventricular Size		Yue et al., 1997; Longstreth et al., 2000; Brickman et al., 2008; Knopman et al., 2008	Knopman et al., 2005; Isamah et al., 2010; Knopman et al., 2011
Sulcal Grade	Knopman et al., 2011	Yue et al., 1997; Longstreth et al., 2000	Knopman et al., 2005

Table 2.2 Summary of studies included in this review

Author [Reference]	Study Design	Sample Characteristics	Dependent Variable	Independent Variable	Covariates	Major results regarding race
(Duanping Liao et al., 1996)	Cross-sectional	Atherosclerosis Risk in Communities Study; N=1920; aged 62; 62% female; 49% black	WMH	Race, htn, blood pressure	age, ethnicity and sex	1. Blacks with htn had ↑ odds of having WMH grade >3 compared to whites. 2. Adjustment for SBP and DBP attenuated the relationship but it remained significant.
(Bryan et al., 1997)	Cross-sectional	Cardiovascular Health Study; N= 3658; aged 72.2; 58% female; 15.36% black	SBI	Age. Sex, race	unadjusted	1. SBI prevalence was not differ between blacks and non-blacks.
(Liao et al., 1997)	Cross-sectional	Atherosclerosis Risk in Communities Study; N=1920; aged 62; 62% female; 49% black	WMH	hypertension, blood pressure, race	age, ethnicity and sex	1. Blacks had ↓ prevalence in WMH overall. 2. Blacks had a ↑ prevalence of severe WMH (>= grade 3) than in whites. 3. Associations between risk factors for the development of WMH in the study (smoking, alcohol intake, systolic and

Table 2.2 Continued

						diastolic blood pressure, pulse pressure, and hypertension were all stronger for the AAs than for the whites ($p<0.15$ for the interaction).
(Yue et al., 1997)	Cross-sectional	Cardiovascular Health Study; N=3660; aged >65 yrs; % female not given. 15% black Also, a separate analysis of healthier individuals of CHS N = 1,488; 15% black	brain atrophy (Ventricular size and sulcal size) and WMH	age, sex, and race.	age, sex, and race	1. Black race was ↔ with: ↑ White matter grade, ↓ ventricular and ↓ sulcal grades 2. Healthy subgroup: race was n/s with ventricular or sulcal grade.
(G. Howard et al., 1998)	Cross-sectional	Atherosclerosis Risk in Communities Study; N=1737; aged 63; 62% female; 48% black	SBI/Lacunes	smoking, race	smoking, age, race, sex, htn, diabetes, HDL, TG, alcohol use, BMI, leisure-time activity, dietary fat intake (indexed as a Keys score)	1. black race ↔ ↑ SBI
(Bryan et al., 1999)	Cross-sectional	Atherosclerosis Risk in Communities Study; N= 1890;	SBI/Lacunes	race	unadjusted	1. black race↔↑SBI prevalence

Table 2.2 Continued

		aged 62.6 yrs; 59.6% female; 49.0% black				
(Longstreth Jr et al., 2000)	Cross-sectional	Cardiovascular health study; N=3,255, aged >65 yrs;	brain atrophy: ventricular grade and sulcal grade	Age, race, sex	Sex stratified: male models controlled for: Age, years of school, CHF, pack years of smoking, alcohol, insulin use, abnormal electrocardiogram, IMT, white matter grade. Female models controlled for age, smoking, diabetic medication, estrogen use, albumin, and white matter grade.	Black race was ↔ with: 1. ↓ ventricular grade 2. ↓ sulcal grade regardless of sex.
(Knopman et al., 2005)	Cross-sectional	Atherosclerosis Risk in Communities Study; N= 1812; aged 62 yrs; 59.6% female; 50% black	brain atrophy: ventricular size and sulcal size	CVD risk factors	age, race, and sex	Race n/s ↔ with ventricular size or sulci size scores after age and sex adjustments
(Fornage et al., 2007)	Cross-sectional	Genetic epidemiology network of arteriopathy (GENOA); N= 756; blacks aged 64 yrs and whites aged 62 yrs;	WMHV, total brain volume	variation in the genes encoding MMP3 and MMP9	unadjusted	Black race was ↔ with: 1. ↑WMH volume (2.2 cm^3 diff) 2. ↓brain volume (86.5 cm^3 diff)

Table 2.2 Continued

		blacks 68% female and whites 60% female; 47% black				
(Brickman et al., 2008)	Cross-sectional	Washington Heights-Hamilton Heights-Inwood Community Aging Project; N= 769; aged 80.1 yrs; 67.1% female; 34.6% black	WMHV, total brain volume, lateral ventricle volume, hippocampus volume, and entorhinal cortex volume	race and vascular disease score range, 0-4 1 point for each: diabetes, htn, heart disease, and clinical stroke)	age, sex	1. black race ↔↑more severe WMH burden 2. associations with age were similar across racial-ethnic groups. 3. vascular disease ↔ ↑WMH burden, particularly in blacks 4. no sig diff in hippocampal volume or entorhinal cortex volume 5. black race ↔↑total brain volume 6. black race ↔ ↓ ventricles 7. interaction: black race by vascular disease hx
(DeCarli et al., 2008)	Cross-sectional	University of California at Davis Alzheimer's Disease Center; N= 184 controls; aged 73.5 yrs;	Brain volume, hippocampal volume, log of WMH	Race and cognitive status	age, gender, education, racial or ethnic status	Blacks had a ↓ hippocampal volume, but no p-value reported comparing to white.

Table 2.2 Continued

		62.8% female; 32% black				Main effect of race and TBV appears to be driven by Hispanics not blacks. n/s: TBV and log WMH
(Knopman et al., 2008)	Cross-sectional	A subset of Genetic Epidemiology Network of Arteriopathy; N= 1253; aged 63.8; 64.8% female; 48.7% black	brain atrophy (calculated by total intracranial volume - brain volume), ventricular volume, and WMH	urine albumin/creatinine ratio, race and sex	age at time of MR exam, gender, race, and total intracranial volume (for BA and VV) or brain volume (for WMH)	Black race was ↔ with: 1. ↑ brain atrophy 2. ↓ ventricular volume 3. ↑ WMH volume
(Prabhakaran et al., 2008)	Cross-sectional	Northern Manhattan Study; N= 892; aged 71.3; 59.0% female; 19.2% black	SBI/Lacunes	race	age, sex, race-ethnicity, education level, current smoking, HTN, diabetes, hypercholesterolemia, cardiac disease	1. Black race (ns after adjustment) ↔ ↑SBI 2. Significant interaction of race and age such that younger blacks had ↑odds of having SBI.
(Selim et al., 2008)	Cross-sectional	N=212; aged 56.82 yrs; 53.33% female; 6% of controls black;	CBF – measured by transcranial dopplar	cerebral blood flow regulation in patients with type-2 diabetes mellitus, hypertension, and stroke compared to control	Unadjusted	Flow velocities in the middle cerebral arteries were reduced in blacks but this was not significant.

Table 2.2 Continued

(Aggarwal et al., 2010)	Cross-sectional	Chicago Health and Aging Project; N= 575; aged 79.8 yrs; 57.0% female; 58.3% black	WMHV (natural log (WMHV/ TCV) SBI/Lacunes	race	unadjusted	Black race was: 1. n/s ↔ with WMHV 2. n/s ↔ infarcts 3. n/s ↔ having >1 infarct 4. n/s ↔ with WMHV 5. n/s ↔ with TBV
(R. F. Gottesman et al., 2010)	Longitudinal 6 yrs between predictor and outcome (mean follow-up not provided)	Atherosclerosis Risk in Communities Study; N=983; aged 72 yrs; 61.6% female, 49.3% black	WMH measured twice, 9 yrs apart	race, SBP, cumulative average SBP SBP 5 times (1st 4 visits ~3 yrs apart and 5th visit about 7 yrs after 4th visit)	age, sex, education, prevalent CHD at visit 3, diabetes at visit 3, BMI at visit 3, race, smoking status at visit 3	1. black race ↔substantial WMH progression 2. no significant interaction with 20 mm-hg increase in cumulative mean SBP by race
(Isamah et al., 2010)	Cross-sectional	N=69; whites aged 46.4 yrs, blacks aged 35.6 yrs; 36.23% black	Amygdala, hippocampus, the orbitofrontal cortex, the caudate nucleus, the lateral ventricles, and total cerebral volume		age, sex, total cerebral volume and education level in years as independent variables.	Black race was ↔ with: 1. ↓ total brain volume 2. ↑ left/ right orbitofrontal cortex volumes 3. ↓ Right amygdala 3. ↓ Left amygdala but n/s (p=0.06) 4. n/s differences in total white matter, total gray matter, left/right Caudate, or ventricular volumes.

Table 2.2 Continued

(Hudson et al., 2011)	Cross-sectional	Northern Manhattan Study; N=1102; aged 70.7 yrs; 59.7% female, 20.0% black	SBI and WHV	soluble Receptor for Advanced Glycation End-products (sRAGE) and race	age, sex, race-ethnicity, education, insurance status, current smoking, HDL, LDL, diabetes, Estimated Glomerular Filtration Rate, systolic and diastolic blood pressure	Interactions were observed by race-ethnicity between sRAGE levels and MRI measurements Among blacks, those in the upper quartile of sRAGE had a similarly ↓ risk of SBI and ↓ WMHV.
(Knopman et al., 2011)	longitudinal 10 year change in MRI	Atherosclerosis Risk in Communities Study; N=1112; aged 61.7 yrs; xx% female, 34.6% black	Infarcts, ventricular size, sulcal widening, and WMH	Diabetes	unadjusted	At baseline Black race was ↔ with: 1. ↑ sulci grade in males 2. n/s sulci grade in females 3. n/s ventricular grade 4. ↑ WMH grade progression of WMH of >=1 grade 5. ↑ infarcts at baseline At follow-up: 1. ↑ ventricular worsening in black men 2. n/s in females

Table 2.2 Continued

						3. ↓ sulci grade worsening 4. ↑ WMH grade progression of WMH of >=1 grade 5. n/s incident infarcts
(Justin Marcus et al., 2011)	Longitudinal 7.2 yrs follow-up single Neuro-timepoint	Northern Manhattan Study; N= 1,281; aged 64 yrs; 59.3% female; 64.6% Hispanic, 15.6% white, and 17.5% Black	WMHV Measured at the end of follow-up	Blood pressure	Race, TCV	1. Blacks with DBP in Q2, Q3, or Q4 had ↑WMH than whites of the same quartile of BP. 2. n/s difference between whites and blacks in Q1 of DBP. 3. ↔ b/t DBP and WMH greatest in blacks *(Reported in supplement)*
(Hannah Gardener et al., 2012)	Longitudinal 7.2 yrs follow-up	Northern Manhattan Study; N= 966; aged 72 yrs; 60% female; 66% Hispanic, 15% white, and 17% Black	WMHV Measured at the end of follow-up	Mediterranean-style diet (MeDi) Measured at baseline	age at MRI, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, caloric intake, smoking, LDL, HDL, SBP, DBP, interaction between DBP and antihypertensive medication use,	1.Black race ↔↑WMHV than whites

Table 2.2 Continued

					diabetes, cardiac disease hx, BMI	
(Rosano et al., 2013)	Longitudinal 10 yrs follow-up	Healthy Brain Project; N=303; aged 82.9 yrs, 59% female, 41% black	WMH measured at end of 10yrs follow-up only	PWV measured at baseline only	age, race, sex, education, incident stroke, incident myocardial infarction, incident cardiovascular events, slope of change in SBP, DBP, PP, and BMI	1. ↑ PWV ↔ with ↑ WMHV roughly 10 years later within left superior longitudinal fasciculus, 2. associations stronger in blacks than whites
(Jennings et al., 2013)	Cross-sectional	N=576; aged 42.6 yrs; 53% female; 83% white	CBF	vascular risk factors	age, race, current smoking status, sex, total brain volume, cardiometabolic risk measure, MetS, or the Framingham Index	1. ↑ cardiometabolic risk indices ↔ ↓ CBF 2. ↑Framingham risk and ↑ cIMT↔↓CBF 3. ns: race with CBF
(Michos et al., 2014)	Cross-sectional	Atherosclerosis Risk in Communities Study; N=888; aged 61.2 yrs; 59.7% female, 49.6% black	WMH score	Vitamin D	Unadjusted	In those with clinically normal vitamin D, black race was ↔ with: 1. ↑ prevalence of white matter score>3 2. ↑ white matter progression 3. ↑ prevalence of SBI
(Nyquist et al., 2014)	Cross-sectional	593 healthy asymptomatic individuals from families with an early-onset CAD	WMH (CHS score)	race and other known vascular risk factors	age, sex, htn, diabetes, current smoking, obesity	Black race was ↔ with: 1. extreme WMH CHS scores 2. extreme DWMHV

Table 2.2 Continued

		index case; aged 51.5 yrs; 58.3% female;36% black				3. in race-stratified analysis: ↑age and female sex ↔extreme DWMH in blacks; ↑age and obesity ↔extreme DWMH in whites
(Wiegman et al., 2014)	Cross-sectional	Washington Heights-Hamilton Heights-Inwood Community Aging Project; N=243; aged 84.5; XX% female; 35.4% black	CMB		Unadjusted	No racial differences in prevalence or location of CMB.
(Hurr et al., 2015)	Cross-sectional	N=42; aged 23; 52% female; 50% black	CBF – measured by TCD; Cerebral vascular reactivity	Race	unadjusted	Blacks race was ↔ with: 1. attenuated cerebral vascular capacity to respond to hypercapnia 2. n/s diff in resting CBF
(B Zahodne et al., 2015)	Cross-sectional	Washington Heights-Hamilton Heights-Inwood Community Aging Project; N=638; aged 80.0; 68%	WMHV SBI/Lacunes Hippocampal volume Cortical thickness	race	unadjusted	Black race ↔ with: 1. ↑ WMHV 2. ↓ Cortical thickness 3. ↑ Hippocampal volume 4. ns: race with SBI

Table 2.2 Continued

		female; 36% black				
(Liu et al., 2015)	Cross-sectional	Health, Aging, and Body Composition Study; N=283 aged 83 yrs; 42.0% female; 40.6% black	WMH, MD, Grey matter atrophy	race	sex, income, literacy, BMI, diabetes and drinking habits	1. Black race was ↔ with ↓ mean diffusivity (e.g. ↑ gray matter micro-structural integrity, p=0.032), independent of sex, income, literacy, body mass index, diabetes and drinking habits. 2. Racial differences were not significant for WMH or Grey matter atrophy.
(Caunca et al., 2016)	Cross-sectional	NOMAS; N=935 aged 70 yrs; xx% female; 15% black	CMB	race	age, cerebral parenchymal fraction, DBP, SBI, subclinical infarcts; WMH volume, SBI, hypertensive medication use, Triglycerides	The difference in CMB distribution was not statistically significant across race/ethnic group or APOE genotype
(Waldstein et al., 2017)	Cross-sectional	Healthy Aging in Neighborhoods of Diversity across the Life Span; N=147, aged 52.1 yrs; 56% female; 43% black	WM lesion volume, total brain volume, grey matter volume, and white matter volume	Race, SES	Age, sex, SES	Black race was ↔ with: 1. ↓ TBV (B=−83.95 cc, p<.001), 2. ↓ grey matter volume (B=−47.47cc, p<.001)

Table 2.2 Continued

						3. ↓ white matter volume (B=−34.38cc, p<.001) 4. ns: race with WMHv 5. significant race x SES interactions for all outcomes.
(Windham et al., 2017)	Longitudinal 5.2 years between risk factor and MRI	Genetic Epidemiology Network of Arteriopathy study; N=1702, aged 61 yrs; 64% female; 48% black	Total Brain Volume and WMH	Waist circumference, BMI and Race	age, sex, diabetes, systolic and diastolic blood pressure, antihypertension medication use, smoking, high density lipoprotein cholesterol, and total intracranial volume. Models for WC included height.	Black race was ↔ with: 1. ↑ WMHv 2. more variable WMH 3. n/s: atrophy and TBV

3.0 RACIAL DIFFERENCES IN BRAIN HEALTH AT MIDLIFE

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3.1 ABSTRACT

Background: Blacks are at a higher risk than whites for several adverse brain-related outcomes, such as stroke and dementia. Further, much of what is known about racial differences in brain health is nearly exclusive to those >65 years old. It thus remains unclear whether relationships between race and brain health are apparent in midlife.

Methods: 747 community volunteers (20.6% black) aged 30–54 years old, underwent neuroimaging to assess brain morphology and cerebral blood flow (CBF). Linear regression was used to examine relationships between race and brain health after controlling for potential differences in demographic factors (age, sex, years of schooling, family income, and current smoking).

Results: After adjustment for demographics, blacks exhibited significantly lower gray matter volume, smaller hippocampus, less cortical surface area, and a thinner cerebral cortex than whites (all p's<0.05). We observed no significant differences in CBF by race. Similar but attenuated effects were seen in sex stratified models. There remained a significant and unexplained effect of race on hippocampal volume, cortical surface area, mean cortical thickness, cortex volume, and gray matter volume equivalent to: 29.04, 9.47, 10.66, 9.20 and 13.96 years of aging, respectively. **Conclusion:** Race differences in brain health are evident in midlife. These results have implications for understanding the pathways by which race may impact brain health prior to the onset of stroke and other clinical outcomes later in life.

3.2 INTRODUCTION

Racial disparities in dementia and stroke are evident (F Gottesman et al., 2015; Husaini et al., 2003; Mozaffarian et al., 2015). Blacks are at a higher risk of stroke and developing dementia than whites (G. Howard et al., 2016; Mayeda et al., 2016 & Whitmer, 2016). If these trends continue unabated, the public health burden of disparities in dementia and stroke will increase as the population becomes older and more ethnically and racially diverse (Ortman et al., 2014; Pantoni, 2010). The clearest racial differences in stroke risk are seen in those under age 65 (Ayala et al., 2001; Heyman et al., 1971; V. J. Howard, 2013; V. J. Howard et al., 2011; Rosamond et al., 1999). Blacks under the age of 65 are estimated to be between 2.2-4.0 times more likely to suffer from a stroke than whites and twice as likely to die from a stroke (Ayala et al., 2001; Heyman et al., 1971; G. Howard et al., 2016; V. J. Howard, 2013; V. J. Howard et al., 2011; Rosamond et al., 1999). Additionally, dementia incidence is consistently found to be highest among blacks, with modest

estimates predicting that blacks are at 40% higher (ranges from 14% to 100%) dementia risk compared with whites (D. Barnes et al., 2009; Katz et al., 2012; Mayeda et al., 2016; Miles et al., 2001). Finally, vascular dementia accounts for a larger proportion of cases in blacks than whites (Mayeda et al., 2016; Miles et al., 2001). The reasons behind these persistent racial disparities are not fully understood, but it has been suggested that there may be differential exposures or susceptibilities to the pathogenic effects of known etiological factors for dementia and stroke among blacks and whites, including cerebral small vessel disease (CSVD) (F Gottesman et al., 2015; Gulli et al., 2016; Mayeda et al., 2016; Miles et al., 2001).

Even prior to the onset of later clinical events and outcomes noted above, blacks appear to be at a higher risk for detrimental subclinical brain changes that presage stroke, cognitive impairment, and dementia (F Gottesman et al., 2015). For example, studies have found associations between black race and reduced cerebral vascular reactivity (Hurr et al., 2015), increased burden of white matter hyperintensities (WMH) (B Zahodne et al., 2015; Brickman et al., 2008; Hannah Gardener et al., 2012; R. F. Gottesman et al., 2010; Nyquist et al., 2014), increased WMH progression (F Gottesman et al., 2015; R. F. Gottesman et al., 2010), a higher prevalence of subclinical brain infarcts (Bryan et al., 1999; F Gottesman et al., 2015; G. Howard et al., 1998) and increased cerebral atrophy (B Zahodne et al., 2015; F Gottesman et al., 2015). Indeed, only a few studies have found no racial differences in indicators of brain health (Liu, Allen et al. 2015)(Aggarwal, Wilson et al. 2010)(B Zahodne et al., 2015)(Bryan, Cai et al. 1999)(Jennings et al., 2013), including those reporting no racial differences in WMH (Liu, Allen et al. 2015)(Aggarwal, Wilson et al. 2010), subclinical brain infarcts (B Zahodne et al., 2015)(Bryan, Cai et al. 1999), and global cerebral blood flow (Jennings et al., 2013). However, little is known about racial differences in brain health during midlife. For example, with the

exception of two of the above studies (Hurr et al., 2015; Jennings et al., 2013), all of the above research has been conducted on populations over the age of 65 years.

In view of the above, cumulative evidence thus suggests that among older adults, there appear to be racial differences in some but not all suspected indicators of subclinical brain health (B Zahodne et al., 2015; Brickman et al., 2008; Bryan et al., 1999; F Gottesman et al., 2015; Hannah Gardener et al., 2012; R. F. Gottesman et al., 2010; G. Howard et al., 1998; Nyquist et al., 2014). However, current research on indicators of brain health is limited in that most studies have focused on older populations (i.e., over 65-years-old) and have primarily measured only WMH. The age groups studied previously and the measurement of only WMH are problematic for several reasons. First, examining only older populations raises the problem of survival bias, and further limits our understanding of the early disease process. This is particularly important to consider when examining racial differences because blacks are at higher risk of disease morbidity and mortality than whites (J. Xu, Kochanek, Murphy, & Tejada-Vera, 2016). The blacks who are surviving into old age are likely to be relatively healthier than blacks who do not survive into old age. As a result, when studies of brain health outcomes are completed in older adult populations, the risk profiles of those most vulnerable to pathogenic disease processes are not fully captured. The findings from studies in older populations may also not be generalize to all blacks, and they may omit a portion of the population that may benefit the most from preclinical prevention and intervention strategies. Moreover, in our previous review, we found that there appeared to be an age dependent relationship between female sex and markers of cSVD (Jorgensen, 2018; Lisabeth & Bushnell, 2012). The interactions between race, sex, and markers of brain health are not well studied in younger populations. Yet, we had found consistent evidence among adults > 60 years of age for an association between female sex and having higher more markers of cSVD (Longstreth

et al., 1998; E. J. van Dijk et al., 2008; Vermeer et al., 2002) but in studies with younger mean ages female sex was not associated with cSVD. . Second, WMH are a marker of late-stage CSVD, and they are most prevalent after age 65 (Pantoni, 2010). Examining only WMH may be biasing the literature to reflect pathology for those who survive long enough to develop WMH, adding to the possibility of survivor bias. Additionally, WMH take many years to develop and reflect largely irreversible disease processes (Pantoni, 2010). When WMH develop, there is already advanced parenchymal damage, reduced cerebral blood flow, and abnormalities of the small penetrating vessels (arteriolar thickening, tortuous vessels, and venular collagenosis) (Pantoni, 2010). Therefore, WMH are not ideal to target for treatment because the underlying pathology may be irreversible or difficult to halt.

Besides WMH, there are many other markers of brain health that are thought to indicate early damage and are related to aging, cognitive decline, dementia risk, stroke risk, and CSVD processes (Appelman et al., 2009; Pantoni, 2010; Peres, De Guio, Chabriat, & Jouvent, 2016; Smith et al., 2015; Walhovd et al., 2005; Joanna M Wardlaw, Colin Smith, & Martin Dichgans, 2013). Some of these markers include cortical white matter volume (A.-T. Du et al., 2005; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Guttmann et al., 1998; Smith et al., 2015; Walhovd et al., 2005), hippocampal volume (Cuénod et al., 1993; Jack, Petersen, O'brien, & Tangalos, 1992; Schuff et al., 2009; Y. Xu et al., 2000), amygdala volume (Cuénod et al., 1993; Jack et al., 1992; Y. Xu et al., 2000), cortical thickness (Lemaitre et al., 2012; Smith et al., 2015; Storsve et al., 2014), cortical surface area (Lemaitre et al., 2012; Storsve et al., 2014) and cerebral blood flow (CBF) (Girouard & Iadecola, 2006; Jennings et al., 2013; Shaw et al., 1984). Racial differences in the above brain health markers have not been thoroughly examined. Examining whether racial differences in brain health markers are evident at midlife will help to identify

potential starting points for the disparities in stroke and dementia seen later in life. Furthermore, these early markers of brain health potentially reflect a more reversible disease state where intervention may lead to prevention or delay of progression to dementia or stroke events.

Accordingly, this study tested cross-sectional relationships between race and preclinical brain health metrics that are associated with early risk and that often appear prior to the onset of WMH and late stage outcomes (e.g. stroke and dementia) in a middle-aged population. We expected that middle-aged blacks (aged 30-54 years) would have comparatively worse brain health (e.g. reduced cerebral blood flow, lower brain volumes) than same-aged whites. Second, we tested whether these differences could in part be explained by demographic factors. Finally, we explored whether racial differences in brain health differed by sex. If so, this could help to identify people at risk for early detrimental brain changes.

3.3 METHODS

3.3.1 Sample selection

The sample for the present study derived from a combination of two parent samples of midlife and community dwelling adults who were recruited by mass-mail solicitations to residents of Western Pennsylvania, USA (see Figure 3.1). The parent studies were the Adult Health and Behavior project, phase-II (AHAB-II; February 2008 to August 2011)(Gianaros et al., 2014) and the Pittsburgh Imaging Project (PIP; August 2008 to October 2014)(Lockwood, Marsland, Cohen, & Gianaros, 2016). The total AHAB-II sample consisted of 490 adults. The total sample for PIP consisted of 331 adults. There were 44 adults who participated in both PIP and AHAB-II, and

these participants' data were only included in the AHAB-II sample for this analysis. The total combined sample was 777 adults. Race was coded as black and white, with people of other races and ethnicities not included in the analysis (n=30).

Adults with any of the following conditions were excluded from participating in either study: (1) History of clinical CVD or a CVD event, including Stage II hypertension, stroke, myocardial infarction, congestive heart failure, or arrhythmia. (2) Chronic kidney disease, a liver condition, or a chronic lung disease. (3) Type I or II diabetes in PIP or insulin-dependent diabetes/fasting glucose > 126mg/dL in AHAB II. (4) Any neurological or cerebrovascular disorder. (4) Pregnancy or lactation. (5) Claustrophobia. (6) Presence of medical devices, implants, or other metal objects in or on the body that could not be removed, tattooed eyeliners, or a body habitus prohibiting MR scanning. (7) Any current use of psychotropic prescriptions, or medications for insulin, glucocorticoids, arrhythmias, hypertension, lipids, and weight-loss. Additionally, PIP had the following additional exclusionary criteria that did not overlap with AHAB-II: prior cardiovascular surgery, cancer, cerebrovascular trauma, neurosurgery, and color-blindness. AHAB-II participants had to be working at least 25 h/week outside of the home. AHAB-II participants also had the following exclusionary criteria that did not overlap with PIP: (1) alcohol consumption > 5 portions 3 times or more/week; (2) use of fish-oil supplements (fish-oil, algae, algal oil, or docosahexaenoic acid supplements); and (3) shift work.

3.3.2 Magnetic Resonance Imaging (MRI)

High resolution T1-weighted structural MRI data were collected in both PIP and AHAB-II using the same magnetization-prepared rapid gradient echo sequence (MPRAGE) on a 3T Trio TIM scanner (Siemens, Erlangen, Germany), which was equipped with a 12-channel head coil. MRI

data were preprocessed and analyzed with methods published previously (Marsland, 2015). The FreeSurfer 5.3.0 software package (http://surfer.nmr.mgh.harvard.edu) was used to measure cortical surface area, cortical thickness, and volumetric data (Fischl and Dale, 2000). Cortical thickness is a measure of the combined thickness of the layers of the cerebral cortex. Cortical thickness is influenced by the number and the size of cells within a column, packing density, as well as by the number of synaptic connections and the extent of axonal myelination (Rakic 1988; Eickhoff et al. 2005). Cortical surface area is a measure corresponding to the number of folds in the cortex. There is evidence to suggest that cortical thickness and cortical surface area are differentially affected in normal aging (Lemaitre et al., 2012) and dementia (Dickerson et al., 2009). Brain regions were chosen a priori because of known relationships with aging, cognitive decline, and dementia risk.

Resting cerebral blood flow (CBF) images were acquired with a pulsed arterial spin-labeling (PASL) sequence using a flow-sensitive alternating inversion recovery method (S. G. Kim, 1995), specifically applying a saturation pulse 700ms after an inversion pulse. To reduce transit artifact, a 1000ms delay separated the end of the labeling pulse and the time of image acquisition. Resting CBF image acquisition parameters were: field of view (FOV)=240×240mm, matrix size=64×64, repetition time (TR)=4sec, echo time (TE)=18ms, and flip angle (FA)=90°. Twenty-one slices (5mm thick, 1mm gap) were acquired sequentially in an inferior-to-superior direction, yielding 80 total CBF images (40 labeled, 40 unlabeled; 2 initial discarded images allowing for magnetic equilibration).

3.3.3 Covariates

Several variables were considered that might contribute to associations between black race, brain structure. These included age (years), sex, years of education, and income adjusted for household size.

3.3.4 Statistical Analysis

Descriptive statistics comparing demographics, brain health measures, and cardiovascular risk factors by “blacks” to “white” groups were completed first. Linear regression was used to assess whether the association between brain health and race could be accounted for demographic differences. All regression models were adjusted for study (AHAB-II or PIP). Regression models with volume and surface area were adjusted for intracranial volume (ICV). Model 1 was adjusted for study and ICV or global CBF where appropriate. Model 2 included additional adjustment for age and sex. Model 3 included all adjustments in model 2, along with years of education and income adjusted for the number of people in the household (family adjusted income). Model 4 included all of the adjustments made in model three and added an adjustment for current smoking (yes/ no). All assumptions of normality and independence were met. Finally, a sex stratified analysis was completed to examine whether differences in brain health by race were similar of different across sex groups. All analyses were conducted with SAS, version 9.4 (SAS Institute Inc., Cary, NC).

3.3.5 Supplemental Analyses

In a post hoc analyses we examined entorhinal cortex volume as an additional outcome due to role in memory and hypothesized relationship with dementia (Braak & Braak, 1995; A. Du et al., 2004). For completeness, we also examined whether traditional risk factors for stroke (hypertension, hyperlipidemia, diabetes mellitus and obesity)(Romero, Morris, & Pikula, 2008) would attenuate any of the observed differences between blacks and whites. Systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), total cholesterol (mg/dL), blood glucose (mg/dL), and BMI (kg/m^2) were added to the fully adjusted model. As described previously (Jennings et al.), components were assessed in the morning after a 12 hour, overnight fast. Prior to analysis: cholesterol and glucose were winsorized at the 1st and 99th percentiles. All values were standardized, and z-scores were used in the modeling.

3.4 RESULTS

3.4.1 Population Characteristics

There were many differences in the baseline characteristics between the blacks and whites in the sample (table 1). Black participants were less likely to be male, were older, had fewer years of schooling, a lower family adjusted income and more likely to smoke (all p's <0.05).

3.4.2 Brain health outcomes

In unadjusted bivariate relationships, blacks had significantly lower mean cortical white matter volume, hippocampal volume, amygdala volume, cortical surface area, cortical thickness, gray matter volume, and cortex volume ($p<0.001$ for all). However, global CBF was not significantly different by race ($p=0.71$). Also, blacks on average had significantly smaller intracranial volumes ($p<0.0001$).

The results from the linear regression analysis show that in fully adjusted models, differences by race in several brain areas were statistically significant. On average, black participants have 0.40 cm^3 smaller hippocampus, 42.16 cm^2 less surface area, 0.04 mm thinner cortex, 21.17 cm^3 smaller cortex, and 24.71 cm^3 less gray matter volume (all p's <0.001) than whites after adjusting for study, intracranial volume, sex, age, years of schooling, family income, and current smoking. Significant differences in cortical white matter volume and amygdala volume were attenuated and became non-significant after adjustment for education and family income ($p=0.11$ and $p=0.127$, respectively); suggesting that socioeconomic status (SES) partly accounts for race differences in cortical white matter and amygdala volumes. The additional adjustment for current smoking had minimal impact on the estimates. Cerebral blood flow measures were not found to be significantly related to race in any models.

3.4.3 Sex stratified analysis

Demographic differences were similar to what was found in the total population, both male and female black participants had fewer years of schooling, a lower family adjusted income and were more likely to smoke (all p's <0.001). Black men had an older mean age than white men, but this

difference was not statistically significant. Although, both black males and black females had older mean ages than their white counterparts, the age differences was not significant either sex strata (both p's<0.05).

In examining associations with markers of brain health in sex stratified, minimally adjusted models, we found similar trends from the total population in each sex. Black men, on average, had significantly less cortical white matter volume, amygdala volume, hippocampal volumes, cortical surface area, cortical thickness, gray matter volume, and cortex volume (all p's<0.05). Global CBF was not significantly different (p=0.39). We found similar trends but smaller effect sizes in females. However, there were no significant differences in cortical white matter volume (p<0.12) or amygdala volume (p<0.28) found between black and white women. Global CBF was not significantly different from whites in males or females. On average, the racial difference in brain health markers was greater in males compared to females; the only exception being cortical thickness where the racial difference in cortical thickness was greater in females. There were minimal differences (less than 10%) in the betas for cortical white matter volume.

3.4.4 Supplemental Analyses

In a supplemental analysis we examined entorhinal cortex volume as an additional outcome. Entorhinal cortex was added because the entorhinal cortex and the hippocampus are essential parts of the medial temporal lobe system that supports declarative memory (Braak & Braak, 1995). It has been hypothesized that AD starts in the entorhinal cortex before spreading to the hippocampus and eventually to the cortex (Braak & Braak, 1995). Also the entorhinal cortex has been found in some studies to have a higher rate of atrophy than the hippocampus(A. Du et al., 2004). We found that black participants on average had significantly lower mean entorhinal cortex volume at 3.45

cm^3 (95% CI: 3.35, 3.54) compared to 4.00 cm^3 (95% CI: 3.95, 4.06) in white participants. In fully adjusted models, the difference in mean entorhinal cortex volume between blacks and whites was attenuated but remained significant at -0.35 cm^3 (95% CI: -0.47, -0.23). Furthermore, black males compared to white males had a smaller mean entorhinal cortex volume -0.47 cm^3 (95% CI: -0.67, -0.28); this trend was similar but slightly lower in females -0.29 cm^3 (p =0.171 for race by sex interaction term). Age was not found to be a significant predictor of entorhinal cortex volume in fully adjusted models (p=0.16), so race differences in years of aging was not calculated.

Additionally, we examined whether the addition of traditional stroke risk factors (hypertension, hyperlipidemia, diabetes mellitus, and obesity) to the model would further attenuate any of the observed differences in brain health markers. We found that the addition of blood pressure, total cholesterol, blood glucose and BMI had minimal effect on the beta for race in models of cortical surface area, gray matter volume, and cortical volume (table 3.iv). The addition of these variables also slightly increased the difference in the beta for race in models of hippocampal volume and entorhinal cortex. The beta for black race was attenuated by 25% in models of cortical thickness after the addition of stroke risk factors. A more in-depth investigation of potential mediating factors is presented in chapter 4 of this dissertation.

3.5 DISCUSSION

In this cross-sectional study of midlife adults, race was significantly related to several brain health markers, except for CBF measures. Relationships between race and both cortical white matter volume and amygdala volumes were attenuated and became non-significant after adjustment for socioeconomic status measures (education and income). The latter finding indicates that social

factors, such as education and income, may contribute to racial differences in brain health. Furthermore, in sex stratified models, we found similar trends in both sexes, but differences between black and white men tended to be greater than those among women. Together, these findings agree with other epidemiological evidence regarding relationships of race and subclinical brain health (B Zahodne et al., 2015; Brickman et al., 2008; Bryan et al., 1999; F Gottesman et al., 2015; Hannah Gardener et al., 2012; R. F. Gottesman et al., 2010; G. Howard et al., 1998; Nyquist et al., 2014). This work also adds to the current literature by focusing on midlife individuals and markers of early brain health prior to late stage disease seen in older populations.

Very few studies have examined relationships with brain health markers and race in middle-aged populations. Assuming a linear decline with age, we found that mean racial differences in hippocampal volume remained in fully adjusted models and were equivalent to 29.04 years of aging (see table 3.7). Similarly, we found that mean differences in cortical surface area, cortical thickness, cortex volume, and gray matter volume that were equivalent to 9.47, 10.66, 9.20, and 13.96 years of aging, respectively which were not accounted for by age, sex, ICV, study, education, family adjusted income, or current smoking. These are large effect sizes for an otherwise healthy middle-aged population. For example, these estimates exceed the racial difference in life expectancy, where blacks born in the 1970's are expected to have a ~6.5 year short lifespan than whites (NHCS, 2017). Additionally, we found no racial differences in CBF measures which is consistent with findings from other studies (Hurr et al., 2015; Jennings et al., 2013; Selim et al., 2008). These patterns of findings suggest that indicators of morphology, such as volume, may be independent of CBF or may be more susceptible to risk factors in midlife, while markers such as CBF may be more resilient to change. In support of this, a recent study illustrated that CBF values were independent of concurrent age-related tissue volume reduction, finding that

perfusion can remain unaltered in regions of significant tissue atrophy (Chen, Rosas, & Salat, 2011).

Currently, there are many studies supporting a relationship between CSVD and measures of brain atrophy (Joanna M Wardlaw, Eric E Smith, et al., 2013). Relatedly, both hippocampal and amygdala volumes are known to decrease with normal aging (Blatter et al., 1995; Mueller et al., 1998; Walhovd et al., 2005). In examining the Pearson correlations with age, we found all brain health markers to be significantly correlated with age (table 3.ii, appendix). The strongest correlations with age were cortical thickness and surface area (-0.24 and -0.21, respectively). The correlations with age and cortical white matter volume, amygdala volume, hippocampal volumes, and CBF measures were similar (appendix table 3.ii). We observed that age was significantly and inversely related to all of the brain health markers (appendix table 3.i). Each year in aging was associated with a 0.77 cm^3, 0.007 cm^3, 0.014 cm^3 reduction in cortical white matter, amygdala volume, and hippocampal volume, respectively (Table 3.7). We also observed a 4.45 cm^2 reduction in cortical surface area, a 0.003 mm reduction in cortical thickness, a 1.77 cm^3, reduction in cortex volume, a 2.3 cm^3 reduction in grey matter volume, and a 0.2 ml per min per 100g reduction in global blood flow per each year of aging (Table 3.7). The reduction is cortical thickness found here is similar to what was found in the Smith et al. paper (mean age 58 years +/- 8), where for every additional 10 years of age, the cerebral cortex was 0.026mm thinner (95% CI = 0.019–0.033) (Smith et al., 2015).

Interestingly, smaller hippocampal and amygdala volumes are found in people with dementia (Cuénod et al., 1993; Jack et al., 1992; Y. Xu et al., 2000), as well as in those with mild cognitive impairment who are at a higher risk of developing dementia (A. Du et al., 2001; Frankó, Joly, & Initiative, 2013; Y. Xu et al., 2000). Moreover, longitudinal studies of the brain have found

that lower hippocampal and amygdala volume increase the risk of developing dementia in cognitively normal adults (den Heijer et al., 2006; A. Du et al., 2001; Kaye et al., 1997). For example, Den Heijer et al. found that compared with those remaining free of dementia, baseline hippocampal and amygdala volumes were 17% smaller in persons who received a clinical diagnosis of dementia within 2 to 3 years after MRI and still 5% smaller in those whose conditions were diagnosed 6 years after MRI. Similarly, increasing hippocampal volume has been related to improvements cognitive functioning (Maass et al., 2015). The relationship between amygdala and hippocampal size in the literature, along with our findings that blacks have smaller hippocampi, may indicate that there is a higher risk for dementia in this group that is present even at middle age. Finally, the cross-sectional nature of this study prevents us from measuring brain atrophy per se; however, brain volumes adjusted for ICV are commonly used as a surrogate marker for brain atrophy.

The specific morphologic findings of this study are different than the four previous studies that have examined relationships between race and differences in brain volumes in healthy older populations (B Zahodne et al., 2015; Brickman et al., 2008; Knopman et al., 2005; Liu et al., 2015). Knoppman et. al found that race was not significantly associated with ventricular size or sulci size scores after age, race, and sex adjustments in the ARIC study (Knopman et al., 2005). Liu et al. found no racial differences in grey matter atrophy ($p=0.4$) (Liu et al., 2015). Both Brickman et al. and Zahdone et al. examined relationships in the Washington Heights-Inwood Columbia Aging Project (WHICAP) study (mean age >80 years old). Zahodne et al. reported that blacks had greater hippocampal volumes and lower cortical thickness (B Zahodne et al., 2015). Similarly, Brickman et al. found that black participants had larger relative brain volumes ($p<0.001$), smaller ventricles ($p=0.046$), and more severe WMH burden ($p < 0.001$) than whites (Brickman et al., 2008).

Brickman also found no significant differences in hippocampal volume (p=0.482). All of these studies used quantitative methods except for Knoppman et al. which used a 10-point scale categorized by two raters (Knopman et al., 2005). A major difference is that these studies were carried out in much older populations and therefore could be the result of survival bias where blacks surviving into older age may be more resilient to the disease process. This bias could diminish the differences in brain health between blacks and whites. Our study, with a mean age that is 25 to 40 years younger than the other studies found that blacks had smaller hippocampal brain volumes, less surface area, and lower cortical thickness when compared to whites independent of study, ICV, age, sex, years of schooling, and family income. However, longitudinal studies starting in midlife are needed to examine whether the rate of atrophy is different by racial group or whether the smaller volumes observed are a result of developmental processes. Despite not knowing the cause of this difference, the smaller the size of the hippocampus confers a higher risk of developing dementia (den Heijer et al., 2006) and should not be overlooked.

In this analysis we found that the black white differences in brain health seemed to be attenuated in the female sex group. This is interesting and may indicate a potential protective effect of female sex on brain health. There are known sex differences in stroke, dementia risk, markers of cSVD and brain structure(Cosgrove, Mazure, & Staley, 2007; Jorgensen, 2018). In our previous review, we found that there appeared to be an age dependent relationship between female sex and markers of cSVD (Jorgensen, 2018; Lisabeth & Bushnell, 2012). We had found consistent evidence among adults > 60 years of age for an association between female sex and having higher more markers of cSVD (Longstreth et al., 1998; E. J. van Dijk et al., 2008; Vermeer et al., 2002). However, in the Jorgensen et al. review, we also found results in studies with a younger mean age that female sex was not associated with cSVD markers.(Jorgensen, 2018) This raises the possibility

that relationships between cSVD disease markers and sex may differ by age, with sex-related effects on SBI stronger for older as compared to younger subgroups. These findings mirror age and sex interactions found in stroke incidence, whereby younger women are at lower risk of stroke than men, but older post-menopausal women are at greater risk of stroke than men.(Lisabeth & Bushnell, 2012) The reasons for such sex-related differences and the interaction with age are not clear, but they could be due to differences in hormonal profiles and their changes over time, and/or in overall disease burden in vascular districts outside the brain.

Determining what factors contribute to differences in brain health is important to understanding the disease etiology and determining the best ways to help prevent the progression and decrease racial disparities in brain health. Here we found that socioeconomic factors such as education and income attenuated the relationship of race and both cortical white matter volume and amygdala volume. These findings agree with other work linking SES to brain structure and function (Gianaros et al., 2017) and should be investigated further.

In conclusion, our study found that there are racial differences in morphologic markers of brain health but not in CBF in a middle age population. Additionally, that socioeconomic status may attenuate some of these differences. These findings were consistent but attenuated in sex stratified analyses. Our study had several strengths, including a large sample size, relatively healthy population, and the examination of many markers of brain health. However, our study is limited by a cross-sectional design and future longitudinal studies should be completed to confirm these findings.

3.6 TABLES AND FIGURES

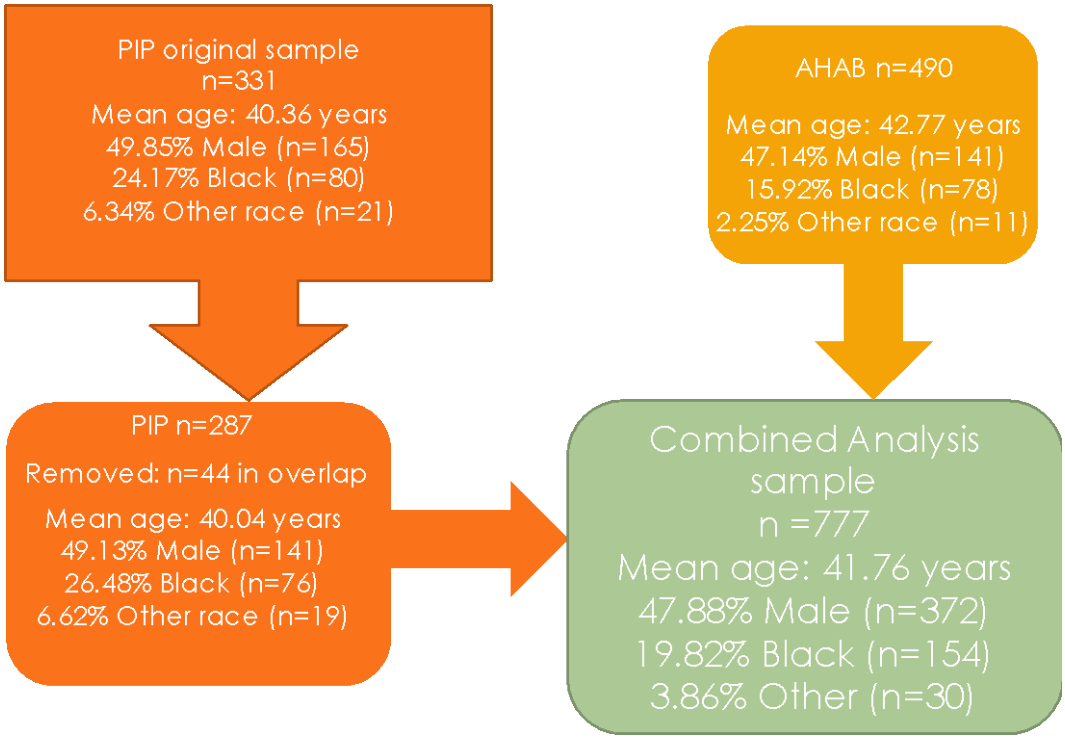


Figure 3.1 Sample selection

Table 3.1 Population Characteristics by Race

		Black (n=154)	White (n=593)	P VALUE
Male	(%)	38.31	49.58	0.0126
Age in years	(mean) (min, max)	42.99 (30, 54)	41.55 (30, 54)	0.0239
Years of School	(mean) (min, max)	15.05 (9, 24)	17.06 (9, 24)	<.0001
Family Income Adjusted for household number	(mean)	28.73	34.77	<.0001
	(min, max)	(14.52, 51.11)	(13.84, 57.74)	
Current Smoker	(%)	32.47	17.74	0.0003

Table 3.2 Brain Health Markers by Race

		Black	White	P VALUE
Cortical White Matter Vol, cm^3	(n) mean 95% CI	142 460.2 (450.4, 470.0)	572 492.2 (487.4, 496.9)	<.0001
Hippocampal Vol, cm^3	(n) mean 95% CI	142 7.8 (7.6, 7.9)	572 8.4 (8.4, 8.5)	<.0001
Amygdala Vol, cm^3	(n) mean 95% CI	142 3.1 (3.0, 3.1)	572 3.2 (3.2, 3.3)	<.0001
Cortical Surface Area, cm^2	(n) mean 95% CI	143 1606.44 (1579.0, 1633.8)	562 1718.51 (1704.8, 1732.2)	<.0001
Cortical thickness, mm	(n) mean 95% CI	143 2.46 (2.43, 2.47)	572 2.51 (2.50, 2.52)	<.0001
Cortex volume, cm^3	(n) mean 95% CI	142 431.5 (423.8, 439.2)	572 476.3 (472.1, 480.4)	<.0001
Gray matter volume, cm^3	(n) (mean) 95% CI	142 608.4 (598.0, 618.8)	572 665.5 (659.9, 671.0)	<.0001
Global CBF (ml /min/100g)	(n) mean 95% CI	139 59.3 (57.3, 61.28)	562 58.4 (57.6, 59.3)	0.709
Intracranial volume, cm^3	(n) mean 95% CI	142 1242.7 (1203.1, 1282.3)	572 1363.1 (1342.1, 1384.1)	<.0001

Table 3.3 Linear regression models for brain health measure by race

Brain Health Measure	Model 1		Model 2		Model 3		Model 4	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Cortical White Matter Vol, cm^3	**-11.11****	**(-18.74, -3.48)**	**-10.10****	**(-17.74, -2.47)**	-6.56	(-14.64, 1.51)	-5.68	(-14.32, 2.96)
Amygdala Vol, cm^3	**-0.067***	**(-0.13, -0.004)**	**-0.07***	**(-0.13, -0.002)**	-0.05	(-0.12, 0.02)	-0.05	(-0.12, 0.02)
Hippocampal Vol, cm^3	**-0.43*****	**(-0.56, -0.29)**	**-0.41*****	**(-0.55, -0.28)**	**-0.40*****	**(-0.55, -0.25)**	**-0.40*****	**(-0.56, -0.25)**
Cortical Surface area cm^2	**-56.11*****	**(-79.01, -33.20)**	**-50.92*****	**(-73.04, -28.79)**	**-42.77*****	**(-66.19, -19.35)**	**-42.16****	**(-67.28, -17.03)**
Cortical Thickness, mm	**-0.06*****	**(-0.074, -0.038)**	**-0.05*****	**(-0.06, -0.029)**	**-0.04*****	**(-0.06, -0.02)**	**-0.04*****	**(-0.062, -0.023)**
Cortex Vol, cm^3	**-26.85*****	**(-33.14, -20.57)**	**-24.32*****	**(-30.13, -18.50)**	**-21.17*****	**(-27.32, -15.02)**	**-21.17*****	**(-27.67, -14.68)**
Gray Matter Vol, cm^3	**-32.10*****	**(-40.00, -24.21)**	**-29.24*****	**(-36.38, -22.10)**	**-25.16*****	**(-32.72, -17.60)**	**-24.71*****	**(-32.69, -16.72)**
Global CBF (ml/min/100g)	0.48	(-1.54, 2.49)	0.14	(-1.72, 1.99)	0.4	(0.01, -1.57)	0.77	(-1.33, 2.87)

*B reported for African American race , * p<0.05, **p<0.01, ***p<0.001*

Model 1 adjusted for study, ICV if volume or surface area measure is outcome, global CBF if frontal CBF is outcome.

Model 2 = Model 1 + sex and age.

Model 3 = Model 2 + years of schooling and family income.

Model 4 = Model 3 + current smoking.

Table 3.4 Population Characteristics by Sex and Race

		Men			Women		
		Black (n=59)	White (n=294)	p value	Black (n=95)	White (n=299)	p value
Age in years	mean (std) (min, max)	42.17 (6.06) (30, 54)	40.68 (7.26 (31, 54)	0.141	43.51 (7.07) (30, 54)	42.41 (6.90) (30, 54)	0.1806
Years of School	mean (std) (min, max)	**14.64 (2.61)** (9, 24)	**17.42 (2.93)** (10, 24)	**<.0001**	**15.31 (2.58)** (9, 21)	**16.71 (2.75)** (10, 24)	**<.0001**
Family Income Adj for household number	mean (std) (min, max)	**29.75 (8.01)** (14.97, 47.07)	**35.20 (7.30)** (13.84, 57.74)	**<.0001**	**28.11 (6.75)** (14.52, 51.11)	**34.35 (7.31)** (15.54, 51.44)	**<.0001**
Current Smoker	%	**39.22**	**17.36**	**0.0004**	**36.14**	**21.69**	**0.0078**

Table 3.5 Race differences in Brain Health Measures by Sex (minimally adjusted)

Brain Health Measure	Total Sample		Males		Females	
	B	95% CI	B	95% CI	B	95% CI
Cortical White Matter Vol, cm^3	**-11.11****	**(-18.74, -3.48)**	**-16.41****	**(-28.28, -4.54)**	-8.00	(-18.00. 2.00)
Amygdala Vol, cm^3	**-0.067***	**(-0.13, -0.004)**	**-0.12***	**(-0.22, -0.03)**	-0.04	(-0.13, 0.04)
Hippocampal Vol, cm^3	**-0.43*****	**(-0.56, -0.29)**	**-0.69*****	**(-0.92, -0.46)**	**-0.26****	**(-0.43, -0.10)**
Cortical Surface area cm^2	**-56.11*****	**(-79.01, -33.20)**	**-68.3*****	**(-103.79, -32.81)**	**-52.95*****	**(-82.35, -23.54)**
Cortical Thickness, mm	**-0.06*****	**(-0.074, -0.038)**	**-0.05****	**(-0.07, -0.02)**	**-0.06*****	**(-0.08, -0.03)**
Cortex Vol, cm^3	**-26.85*****	**(-33.14, -20.57)**	**-31.01*****	**(-40.94, -21.09)**	**-25.67*****	**(-33.60, -17.73)**
Gray Matter Vol, cm^3	**-32.10*****	**(-40.00, -24.21)**	**-38.34*****	**(-50.78, -25.91)**	**-30.70*****	**(-40.39, -21.00)**
Global CBF (ml/min/100g)	0.48	(-1.54, 2.49)	-0.92	(-3.68, 1.84)	0.08	(-2.48, 2.63)

*B reported for African American race , * p<0.05, **p<0.01, ***p<0.001*

Model is adjusted for study, ICV if volume or surface area measure is outcome.

Table 3.6 Race differences in Brain Health Measures by Sex in fully adjusted models

Brain Health Measure	Males		Females		Percent Difference in Beta (male to female)	p-value for sex*race interaction term
	B	95% CI	B	95% CI		
Cortical White Matter Vol, cm^3	-11.47	(-25.09, 2.14)	-1.12	(-12.60, 10.36)	90.22	0.15
Amygdala Vol, cm^3	-0.09	(-0.20, 0.02)	-0.02	(-0.11, 0.07)	75.97	0.221
Hippocampus Vol, cm^3	**-0.57****	**(-0.83, -0.31)**	**-0.30****	**(-0.49, -0.10)**	48.16	**0.012**
Cortical Surface area cm^2	**-57.25****	**(-97.15, -17.35)**	-32.48	(-65.55, 0.59)	43.27	0.461
Cortical Thickness, mm	-0.03	(-0.06, 0.00)	**-0.05*****	**(-0.07, -0.02)**	-62.57	0.655
Gray matter Vol, cm^3	**-29.08*****	**(-42.42, -15.74)**	**-21.71*****	**(-31.76, -11.66)**	25.34	0.417
Cortex Vol, cm^3	**-24.23*****	**(-34.94, -13.52)**	**-19.06*****	**(-27.37, -10.75)**	21.34	0.469
Global CBF (ml/min/100g)	0.04	(-3.18, 3.27)	0.78	(-2.07, 3.64)	-	0.601

*B reported for black race, * p<0.05, **p<0.01, ***p<0.001*

Model is adjusted for study, ICV if volume or surface area measure is outcome, years of schooling, family income, and current smoking.

Table 3.7 Racial difference in brain health converted to difference in aging (years) in fully adjusted model

Brain health measure	B (SE) for black race	p-value	B (SE) for age (years)	p-value	black: white difference equivalent to years of aging
Cortical White Matter Vol, cm^3	-5.67 (4.40)	0.197	-0.77 (0.24)	0.0013	n/s
Amygdala Vol, cm^3	-0.05 (0.04)	0.1491	-0.007 (0.002)	0.0002	n/s
Hippocampal Vol, cm^3	**-0.40 (0.08)**	**<.0001**	-0.014 (0.004)	0.0013	29.04
Cortical Surface area cm^2	**-42.16 (12.80)**	0.001	-4.45 (0.69)	<.0001	9.47
Cortical Thickness, mm	**-0.042 (0.01)**	<.0001	-0.003 (0.0005)	<.0001	13.92
Cortex Vol, cm^3	**-21.17 (3.30)**	**<.0001**	-1.77 (0.18)	<.0001	11.96
Gray Matter Vol, cm^3	-24.71 (4.07)	**<.0001**	-2.30 (0.22)	<.0001	10.73
Global CBF (ml/min/100g)	0.77 (1.07)	0.4726	-0.20 (0.06)	0.0007	n/s

*B reported for black race, * p<0.05, **p<0.01, ***p<0.001*

Model adjusted for study, ICV if volume or surface area measure is outcome, sex, age, years of schooling, family income, and current smoking.

3.7 SUPPLEMENTAL TABLES AND FIGURES

Table 3.i. Correlations between brain health measures and covariates

Covariate	**Cortical White Matter Vol, cm^3**	**Amygdala Vol, cm^3**	**Hippocampus Vol, cm^3**	**ERC**	**Cortical Surface Area, cm^2**	**Cortical Thickness, mm**	**Gray matter Vol, cm^3**	**Cortex Vol, cm^3**	**Global CBF (ml/min/ 100g)**
Age (yrs)	-0.1	-0.14	-0.12	-0.07	-0.21	-0.24	-0.26	-0.26	-0.12
	0.0069	0.0001	0.0014	0.048	<.0001	<.0001	<.0001	<.0001	0.0022
Years of school	0.15	0.08	0.13	0.16	0.15	0.13	0.2	0.2	-0.02
	<.0001	0.0302	0.0004	<.0001	<.0001	0.0004	<.0001	<.0001	0.5287
Family Income	0.19	0.14	0.16	0.21	0.17	0.10	0.19	0.19	-0.08
	<.0001	0.0003	<.0001	<.0001	<.0001	0.01	<.0001	<.0001	0.0373
Intracranial Volume	0.73	0.55	0.60	0.53	0.70	0.27	0.79	0.75	-0.34
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

Prob > |r| under H0: Rho=0.

Table 3.ii Correlations between brain health measures

	Cortical White Matter Vol	Amygdala Vol	Hippocampal Vol	Cortical Surface Area	Cortical Thickness	Gray Matter vol	Cortex vol	Total Brain vol	Global CBF	Entorhinal Cortex vol
Cortical White Matter Vol	1	0.65 <.0001	0.65 <.0001	0.90 <.0001	0.08 0.0399	0.83 <.0001	0.82 <.0001	0.95 <.0001	-0.17 <.0001	0.56 <.0001
Amygdala Vol		1	0.71 <.0001	0.64 <.0001	0.30 <.0001	0.71 <.0001	0.69 <.0001	0.71 <.0001	-0.16 <.0001	0.51 <.0001
Hippocampal Vol			1	0.65 <.0001	0.27 <.0001	0.73 <.0001	0.70 <.0001	0.73 <.0001	-0.16 <.0001	0.51 <.0001
Cortical Surface Area				1	0.05 0.1581	0.89 <.0001	0.90 <.0001	0.94 <.0001	-0.14 0.0002	0.59 <.0001
Cortical Thickness					1	0.45 <.0001	0.48 <.0001	0.29 <.0001	-0.12 0.0011	0.29 <.0001
Gray Matter vol						1	0.98 <.0001	0.96 <.0001	-0.21 <.0001	0.65 <.0001
Cortex vol							1	0.95 <.0001	-0.19 <.0001	0.65 <.0001
Total Brain vol								1	-0.20 <.0001	0.64 <.0001
Global CBF									1	-0.20 <.0001
Entorhinal Cortex vol										1

Table 3.iii Race differences in Brain Health Measures by study in fully adjusted models

Brain Health Measure	PIP			AHAB-II			Percent Difference in Beta (PIP to AHAB)
	B	SE	p-value	B	SE	p-value	
Cortical White Matter Vol, cm^3	-7.74	6.14	0.21	-2.03	6.42	0.752	-
Amygdala Vol, cm^3	-0.04	0.05	0.42	-0.04	0.05	0.449	-
Hippocampal Vol, cm^3	-0.52	0.11	<.0001	-0.26	0.12	0.027	51%
Entorhinal Cortex vol, cm^3	-0.36	0.09	<.0001	-0.35	0.09	<.0001	3%
Cortical Surface area cm^2	-54.43	18.96	0.0044	-27.02	17.88	0.073	50%
Cortical Thickness, mm	-0.04	0.01	0.0098	-0.03	0.01	0.003	33%
Cortex Vol, cm^3	-24.50	4.83	<.0001	-16.28	4.67	0.001	34%
Gray Matter Vol, cm^3	-28.12	5.86	<.0001	-19.03	5.80	0.001	32%
Global CBF (ml/min/100g)	-0.05	1.56	0.7383	1.01	1.51	0.619	-

B reported for black race.

Model is adjusted for ICV, years of schooling, family income, and current smoking.

Table 3.iv Linear regression models for brain health measure by race adjusted for stroke risk factors

Brain Health Measure	Fully adjusted model		Model + stroke risk factors		% change in beta for race
	B	95% CI	B	95% CI	
Cortical White Matter Vol, cm^3	-5.68	(-14.32, 2.96)	-5.22	(-14.16 , 3.69)	-
Amygdala Vol, cm^3	-0.05	(-0.12, 0.02)	-0.07	(-0.14, 0.01)	-
Hippocampal Vol, cm^3	**-0.40*** **	**(-0.56, -0.25)**	-0.44***	**(-0.60, -0.28)**	-10%
Entorhinal Cortex vol, cm3	**-0.35*** **	**(-0.47, -0.23**	**-0.38*** **	**(-0.50, -0.26)**	-9%
Cortical Surface area cm^2	**-42.16** **	**(-67.28, -17.03)**	**-41.28** **	**(-67.33, -15.23)**	2%
Cortical Thickness, mm	**-0.04*** **	**(-0.062, -0.023)**	**-0.03** **	**(-0.05, -0.01)**	25%
Cortex Vol, cm^3	**-21.17*** **	**(-27.67, -14.68)**	**-20.44*** **	**(-27.19, -13.69)**	6%
Gray Matter Vol, cm^3	**-24.71*** **	**(-32.69, -16.72)**	**-23.96*** **	**(-32.25, -15.67)**	3%
Global CBF (ml/min/100g)	0.77	(-1.33, 2.87)	1.00	**(-1.17, 3.18)**	-

*B reported for black race, * p<0.05, **p<0.01, ***p<0.001*
Model is adjusted for study, ICV if volume or surface area measure is outcome, years of schooling, family income, and current smoking.

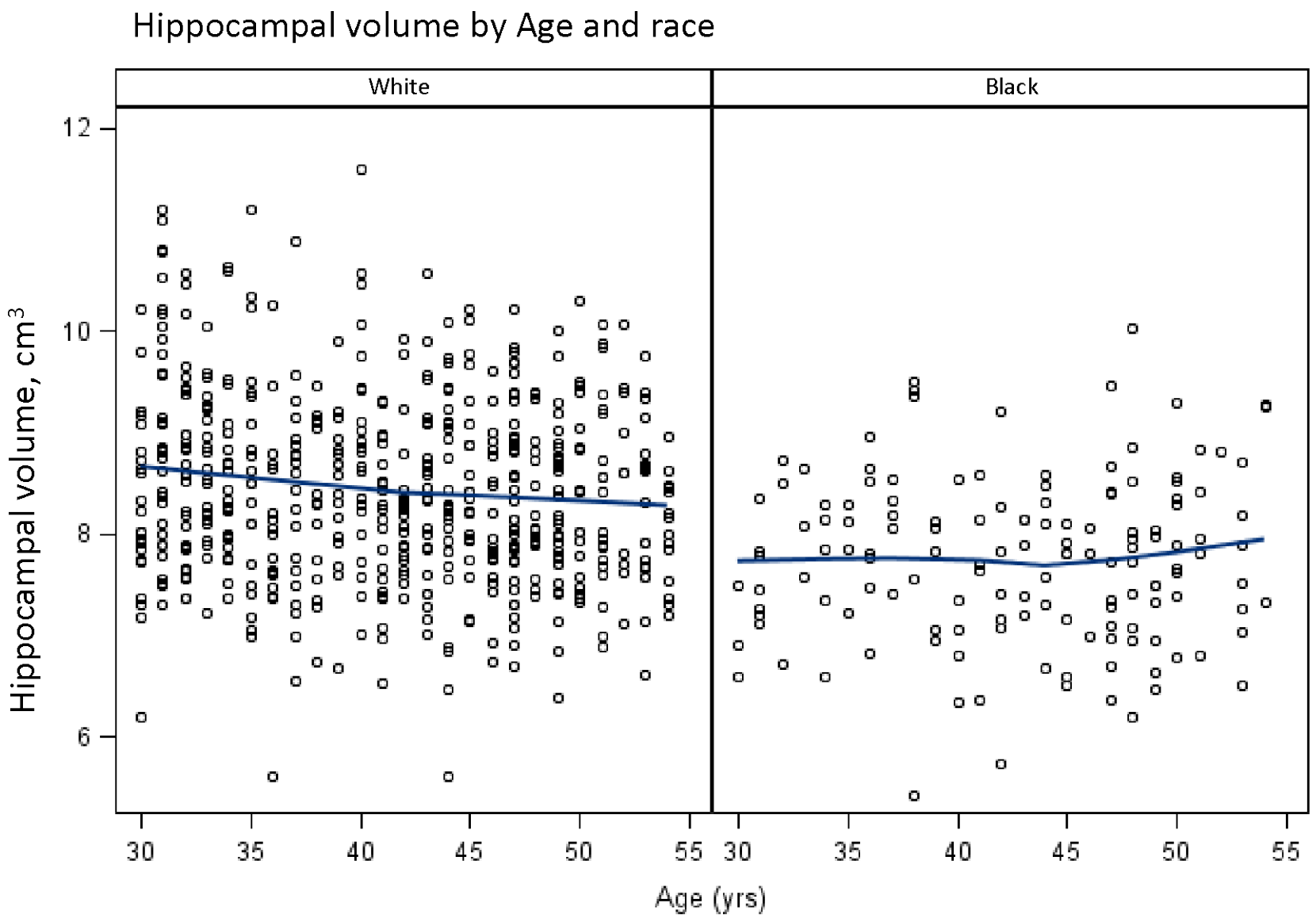


Figure 3.i Loess curve examining race and hippocampal volume by age

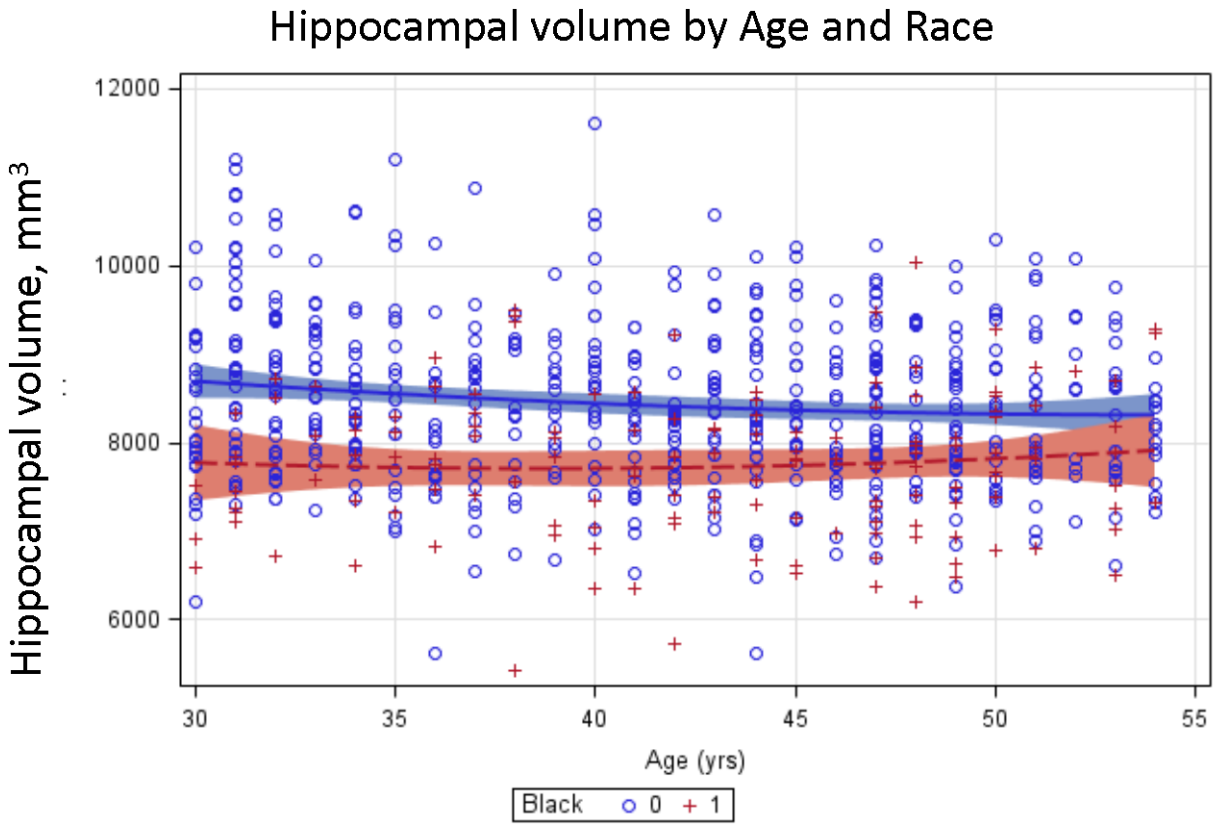


Figure 3.ii Linear regression with 95% CI of hippocampal volume by age (years) and race.

The mean hippocampal volume for black race (red) is lower than for white race (blue), but this difference narrows in older age groups.

Effect decreases overtime. P value for interaction of age * race (p=0.0567) in fully adjusted model.

4.0 RACIAL DIFFERENCES IN BRAIN HEALTH AT MIDLIFE: THE POTENTIAL MEDIATING ROLE OF CARDIORESPIRATORY FITNESS AND CARDIOMETABOLIC RISK

4.1 ABSTRACT

Background: Blacks are at a higher risk than whites for several adverse brain-related outcomes, such as stroke and dementia. Due to associations of vascular risk factors with brain health and function, racial differences in brain health may result from a greater burden of vascular risk factors in blacks. However, vascular risk factors have not been fully tested as possible explanatory factors of racial differences in brain health. Further, much of what is known about racial differences in brain health is nearly exclusive to those >65 years old.

Methods: 747 community volunteers (20.6% black) aged 30–54 years old, underwent neuroimaging to assess brain morphology. Components of composite cardiometabolic risk score (CMR) included: body mass index, waist circumference, high-density lipoproteins, triglycerides, glucose, insulin, SBP, and DBP. Cardiorespiratory Fitness (CRF) was calculated from an equation derived by (Jurca et al., 2005) based on age, sex, body mass index, resting heart rate, and self-reported physical activity level. To test mediation, we used a structural equation model and bootstrapping procedures from the PROCESS v2.14 macro. All models were adjusted for age, sex, household income, education, current smoking, study and intracranial volume.

Results: On average, black partipants had lower CRF and higher CMR compared to white participants. CMR partially mediated the association of race with cortical surface area and gray matter volume by 22.79% and 5.98%, respectively. Independent of CRF, there was an indirect effect of CMR on cortical surface area, cortex volume and gray matter volume. No indirect effects of CRF independent of CMR were found. There remained a significant direct and unexplained effect of race on hippocampal volume, cortical surface area, cortex volume, mean cortical thickness, and gray matter volume.

Conclusion: CRF and CMR factors may partly explain some of the racial differences in brain health and should be investigated further as potential targets for intervention. These results have implications for understanding vascular contributions to disparities in brain health prior to the onset of stroke and other clinical outcomes.

4.2 INTRODUCTION

Our previous findings and the cumulative literature evidence suggests that there appear to be racial differences in subclinical brain disease markers (B Zahodne et al., 2015; Brickman et al., 2008; Bryan et al., 1999; F Gottesman et al., 2015; Hannah Gardener et al., 2012; R. F. Gottesman et al., 2010; G. Howard et al., 1998; Nyquist et al., 2014). Due to the strong associations between vascular risk factors with brain health and function (Khan et al., 2007; S.-A. Kim & Park, 2015; Qiu & Fratiglioni, 2015; Whitmer et al., 2005), it is possible that racial differences in brain health result from a greater burden of vascular risk factors in blacks (F Gottesman et al., 2015; Heyman et al., 1991; V. J. Howard et al., 2011; Mayeda et al., 2016; Miles et al., 2001; Sacco et al., 2001).

However, vascular risk factors have not been fully tested as explanatory factors that partly account for racial differences in brain health outcomes (F Gottesman et al., 2015).

Cardiorespiratory fitness (CRF) and cardiometabolic risk (CMR) are both modifiable factors that are linked to vascular disease and brain health throughout the lifespan. Furthermore, CRF and CMR are related to each other. Longitudinal and cross-sectional studies have found that increases in CRF are associated with decreases in CMR components (Artero et al., 2011; Shuval et al., 2014). CMR score is predictive of incident diabetes, cardiovascular disease, cerebrovascular disease, and stroke (Gami et al., 2007). Independent of race, components of CMR have been associated with lower brain volumes(Gunstad et al., 2008) and reduced cortical thickness (Krishnadas et al., 2013). Additionally, CMR score has been associated with lower CBF (Jennings et al., 2013) and was found to be a significant mediator of relationships between SES and brain health (Gianaros et al., 2017). While CMR may be detrimental to brain health, physical activity may confer a protection against deteriorating brain health, cognitive decline, and dementia.(Hamer & Chida, 2009) Cardiorespiratory fitness (CRF) is a sensitive and reliable measure of habitual physical activity ("American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults," 1998; Church, Earnest, Skinner, & Blair, 2007; A. S. Jackson, Sui, Hébert, Church, & Blair, 2009; Jurca et al., 2005; Wang et al., 2010). Cross-sectional and longitudinal associations are consistently found between higher CRF and greater gray matter volume, specifically in the prefrontal cortex and hippocampus (Colcombe et al., 2006; Erickson, Leckie, & Weinstein, 2014; Erickson et al., 2011; Hayes, Hayes, Cadden, & Verfaellie, 2013; Maass et al., 2015; Ruscheweyh et al., 2011; Weinstein et al., 2012). These links suggest the possibility of CRF as a predictor of brain volumes. CRF shows further promise as a potential way

to intervene on declining brain volumes. Randomized exercise interventions in middle-aged populations have shown the potential of increasing the volume of the hippocampus and prefrontal cortex in relatively short periods of time such as 6 months(Colcombe et al., 2006; Ruscheweyh et al., 2011) or 1 year(Erickson et al., 2011). Compared to white participants, low CRF has been found to be more prevalent among black or African American participants in many epidemiologic samples (Swift et al., 2017; Swift et al., 2013). Additionally, studies in individuals with low CRF have found independent relationships between race and CMR components, where black race remains associated with a greater prevalence of CMR components, seemingly independent of low CRF(Swift et al., 2013). But relationships between CRF and CVD mortality appear to be similar in both black and white populations (Swift et al., 2013). In all, the above findings suggest that CRF and CMR are related to each other and race, but that independent or synergistic relationships may remain. While many studies have examined CMR and CRF independently, it is important to determine how these factors may work independently or synergistically to impact brain health.

Accordingly, this study tested cross-sectional relationships between race, CRF, CMR score and subclinical brain abnormalities metrics that are associated with early risk and that often appear prior to the onset of WMH and late stage outcomes (e.g. stroke and dementia) in a middle-aged population. We examined whether CRF or a composite metric of vascular risk, a CMR score, would attenuate any observed race differences in brain health. If so, then this would provide initial evidence for the partial contribution of vascular risk to disparities in preclinical brain health outcomes. The latter was formally tested using a sequential mediation analysis following a structural equation model with nonparametric bootstrapping with 95% confidence intervals for indirect mediation effects generated by the bias-corrected method (Shrout & Bolger,

2002)(Preacher & Hayes, 2008). This mediation model also allows us to examine the independent effects and shared effects of the potential mediators (CRF and CMR).

4.3 METHODS

The population sample, covariates, and imaging methods are the same as presented above (section 3.3 methods). Only brain health measures that were identified as statistically significantly different between blacks and whites after adjustment for demographic variables and current smoking (hippocampal volume, cortical surface area, cortical thickness, cortex volume, and gray matter volume) were evaluated for potential mediation.

4.3.1 Cardiorespiratory fitness (CRF)

CRF was calculated from an equation derived by (Jurca et al., 2005) that has been shown to significantly correlate with VO_2 max ($r = .71$, $p < .001$)(Boots et al., 2015). This measure is based on age, sex, body mass index, resting heart rate, and self-reported physical activity level, i.e., CRF = 18.07+ Male(2.77) – Age in years (.10) – BMI (.17) – Resting Heart Rate (.03) + Self-Reported Physical Activity. In AHAB-II only, CRF was derived by averaging the inter-beat interval from an un-paced respiration protocol involving EKG monitoring (i.e. HR = 60000/mean IBI) over three visits. In PIP, heart rate was measured using Dinamap. The CRF score was converted to a z-score and the inverse of this score (e.g. poor CRF) was used in the mediation analysis.

4.3.2 Cardiometabolic risk (CMR) score

As described previously (Jennings et al.), components of the CMR score were assessed in the morning after a 12 hour, overnight fast. A composite index of CMR was computed from the following variables, as based on prior work (Marsland, McCaffery, Muldoon, & Manuck, 2010): body mass index (BMI), waist circumference, high-density lipoproteins (reverse-coded), triglycerides, glucose, insulin, SBP, and DBP (mean of 2 consecutive readings obtained in a seated position). Prior to analysis: glucose and insulin were winsorized at the 1st and 99th percentiles, and logarithm (base 10) transformations were applied to triglyceride and insulin values to correct for skewed distributions. A composite CMR index was then derived by averaging the standardized (z-score) values of the above variables. A higher CMR index score reflects higher vascular risk, comprising higher average values for BMI, waist circumference, high-density lipoproteins, triglycerides, glucose, insulin, SBP, and DBP.

4.3.3 Statistical Analysis

Descriptive statistics for cardiovascular risk factors and potential mediators CRF and CMR were compared by race (blacks versus white) groups were completed first. computed. A series of linear regression models were created for each brain health variable. All regression models were adjusted for study (AHAB-II or PIP). Regression models with volume and surface area were adjusted for intracranial volume (ICV). Models were also adjusted for age, sex, years of education, income adjusted for the number of people in the household (family adjusted income), and current smoking. All assumptions of normality and independence were tested and met.

4.3.3.1 Mediation testing

Prior to the mediation analysis, we tested for interaction effects of race on the relationship between the potential mediators (CRF and CMR) and brain health to determine if the association of each mediator is similar across racial groups. The effects were determined to be similar if the interaction term (Mediator *black race predicting the brain outcome) was not statistically significant ($p>0.1$). Structural equation modeling was used to test the hypothesis that CRF score (M_1) and CMR (M_2) statistically mediates the cross-sectional relationship between race (X) and brain health measures (Y) found to be statistically different in adjusted models. Associations of race with CRF were tested as the effect of X on M_1 ($X\rightarrow M_1$), corresponding to the "a Path." Associations of race with CMR were tested as the effect of X on M_2 ($X\rightarrow M_2$), corresponding to the "b Path." Associations of CRF with brain health measures were tested as the effect of M_1 on Y ($M_1\rightarrow Y$), corresponding to the "d Path." Associations of CMR with brain health measures were tested as the effect of M_2 on Y ($M_2\rightarrow Y$), corresponding to the "e Path." Associations of CRF with CMR were tested as the effect of M_1 on M_2 ($M_1\rightarrow M_2$), corresponding to the "f Path." Associations reflecting the total effects of race on brain health measures without controlling for CMR score were tested as the unadjusted effects of X on Y ($X\rightarrow Y$) or "c Path." Associations reflecting the direct effects of race on brain health measures while controlling for CRF and CMR score were tested as the adjusted effects of X on Y ($X\rightarrow Y$) or "c' Path." Indirect path effects reflecting the association of race and brain health measures—as mediated by CRF ($X\rightarrow M_1\rightarrow Y$), CMR ($X\rightarrow M_2\rightarrow Y$), and sequentially through CRF and CMR ($X\rightarrow M_1\rightarrow M_2\rightarrow Y$)—were tested as the product of the paths (Preacher & Hayes, 2008). Statistical testing of mediation was done by nonparametric bootstrapping (5000 iterations), with 95% confidence intervals (CIs) for indirect mediation effects generated by the bias-corrected method (Shrout & Bolger, 2002). We tested the significance of this indirect effect

using bootstrapping procedures from the PROCESS v2.14 macro (Hayes, 2012). All mediation models were adjusted for age, sex, family income, education, ICV, and study. All analyses were conducted with SAS, version 9.4 (SAS Institute Inc., Cary, NC).

4.4 RESULTS

4.4.1 Relationships between Race and Cardiovascular disease risk factors and potential mediators

Several differences in cardio-metabolic measures between blacks and whites were observed. Blacks had significantly higher SBP, DBP, fasting insulin, and BMI ($p<0.05$ for all) than whites. Blacks also had significantly lower fasting triglycerides and waist circumference when compared to whites (both p's<0.05). There was no difference in fasting HDL or fasting cholesterol (both p's>0.05) (see table 4.1). Blacks also had higher CMR scores and lower CRF (both p's$<.001$) (see table 4.1).

4.4.2 Relationships between potential mediators and markers of brain health

We found that the two potential mediators, poor CRF and CMR score, were significantly positively with correlated with each other (rho $=0.21$, $p<.0001$).

In examining relationships between the potential mediators and brain health markers we found that poor CRF and CMR score were significantly negatively correlated with all measures of

brain health; with the exception of CMR score and cortical thickness (p=0.059) and CMR score with hippocampal and entorhinal cortex volume (both p's>0.05) (see table 4.2).

4.4.3 Linear regression models of CRF and CMRs

In linear regression analyses, we found on average, black participants have 0.40 cm^3 smaller hippocampus, 0.35 cm^3 less entorhinal cortex volume, 42.16 cm^2 less surface area, 0.03 mm thinner cortex, 21.17 cm^3 smaller cortex, and 24.71 cm^3 less gray matter volume ($p<0.001$ for all) than whites after adjusting for study, intracranial volume, sex, age, years of schooling, family income, and current smoking.

Adjustment for CRF attenuated the beta estimates for race in the models for hippocampal volume by 2.4%, entorhinal cortex by 8.57%, cortical surface area by 15.5% and gray matter volume by 4.2% but black race remained a significant predictor in each model. The addition of CRF had little impact on the relationship between race and cortex volume but it increased the racial difference in mean cortical thickness by 17.6%. The increase in the racial difference of cortical thickness is inconsistent with the mediation analyses undertaken, and therefore, CRF was not tested as a mediator for the relationship between race and cortical thickness.

After adding the CMR score to the fully adjusted models, the relationship between race and hippocampal volume was attenuated by 7.6% cortical surface area by 13.0%, cortex volume by 5.9% and gray matter volume by 8.5% but black race remained significant in each model. The addition of CMR score had little impact on the relationship between race and cortical thickness but increased the difference in entorhinal cortex volume by 5.71%. The increase in the racial difference of entorhinal cortex is inconsistent with the current mediation analyses, and therefore, CMR was not tested as a mediator for the relationship between race and entorhinal cortex.

4.4.4 Interaction effects

To determine if the effect of each mediator is similar across racial groups we tested for interaction effects of race on the relationship between the potential mediators (CRF and CMR) and brain health markers. No significant interaction effects were found ($p>0.1$ for all interaction estimates). Although not significant, the interaction between race and CRF on hippocampal volume ($F= 2.08$, $p=0.15$) indicated that a one standard deviation decrease in CRF was associated with a steeper for decline in hippocampal volume for blacks than for whites. Overall, these findings suggest that the effect of CRF and CMR on the brain health outcomes does not significantly differ by race, after accounting for ICV, study, age, sex, income, education, and current smoking.

4.4.5 Mediation results

To investigate the potential mediating role of CRF and CMR score, we hypothesized a sequential process to the mediation whereby, poorer CRF would lead to increased CMR score and poorer brain health. Testing this sequential mediation chain considers both the correlation between CRF and CMR (Pearson correlation =0.21) that testing each mediator independently would ignore. The results of the linear regression (table 4.3) only supported testing sequential mediation for hippocampal volume, cortical surface area, cortical surface area and gray matter volume. The addition of CRF or CMR score to the model of black race and cortical thickness or entorhinal cortex volume resulted in a beta larger than the unadjusted beta. This increase in the beta for race suggests an effect inconsistent with the mediation analyses undertaken and therefore, cortical thickness and entorhinal cortex volume was not pursued in the mediation analysis.

A summary of the mediation results in presented in figures 4.1-4.3. Mediation models showed a significant indirect effect, with CRF and CMR score partially mediating the association of race with cortical surface area (-2.11 cm^2 [95% CI: -6.42, -1.08]). CMR score was found to mediate the association independent of CRF (-3.31 cm^2 [95% CI: -10.32, -1.16]). CRF did not independently mediate this association with race and cortical surface area (0.83 cm^2 [95% CI: -2.19, 6.16]). Additionally, we found a similar significant indirect effect, with CRF and CMR score partially mediating the association of race with gray matter volume (-0.66 cm^3 [95% CI: -2.02, -0.04]). Likewise, CMR score was found to mediate the association independent of CRF for gray matter volume (-1.04 cm^3 [95% CI: -3.40, -0.02]). In each of these models, the independent effect of CMR score was larger than that of the shared CRF and CMR score path. Finally, we found no significant mediation effect of CRF or CMR on hippocampal volumes or cortex volume (all 95% CI overlap 0). In sum, CRF and CMR partially mediated the association of race with cortical surface area and gray matter volume by 22.79% and 5.98%, respectively. These findings suggest that race relates to brain health in part through its association with CRF and CMR score, but not through CRF alone.

4.5 DISCUSSION

In this cross-sectional study of middle-aged black and white adults, we found that relationships between race and both cortical white matter volume and cortical surface area were partially mediated through CRF and CMR score. The effect size of CMR score, independent of CRF, was consistently larger than the path leading through both CRF and CMR score. But, we also found that there remained a significant direct effect of race on hippocampal volume, cortical surface area,

cortex volume, gray matter volume and mean cortical thickness that was independent of CRF and CMR score. Additionally, we found the effect of CRF or CMR was not significantly different by race. Together, these findings agree with other epidemiological findings regarding relationships of race, brain health, and vascular disease risk (B Zahodne et al., 2015; Brickman et al., 2008; Bryan et al., 1999; F Gottesman et al., 2015; Hannah Gardener et al., 2012; R. F. Gottesman et al., 2010; G. Howard et al., 1998; Nyquist et al., 2014). This work also adds to the current literature by focusing on midlife individuals and markers of early brain health prior to late stage disease seen in older populations.

Overall, we found several differences in vascular risk factors where blacks tended to have more adverse risk factor profiles. Blacks had higher blood pressure, glucose, insulin, BMI, CMR scores and lower CRF. However, blacks had lower waist circumference and triglycerides than whites. Also, there were no significant differences in HDL or total cholesterol. These findings are consistent with what has been found in previous work (as reviewed in Kurian, 2007)(Mensah, Mokdad, Ford, Greenlund, & Croft, 2005). In a systematic review of racial differences in vascular risk factors, it was found that blacks tend to have more hypertension and diabetes, but differences in lipids or BMI/ waist circumference were not consistently found (Kurian & Cardarelli, 2007). Furthermore, our finding that blacks have a higher CMR score on average is comparable to findings that blacks have an increased clustering of vascular risk factors than whites (Sharma, Malarcher, Giles, & Myers, 2004). In order to determine whether the impact of CRF or CMR is the same on brain health by race, we tested for interaction effects and found no significant interaction effects of race on CRF or CMR (all p's>0.1).

Ultimately, in mediation models, we found that CRF and CMR score partially explained the relationships between race and cortical surface area and gray matter volume but not the other

markers of brain health. Also, there remained a significant direct effect of race on hippocampus volume, cortical surface area, and mean cortical thickness that was independent of CMR scores. This novel finding suggests several possibilities. First, in the context of race, it is possible that CMR may differentially impact brain health in middle age. It is known that cortical thickness and cortical surface area are inversely related (Storsve et al., 2014), thought to be genetically unrelated (Panizzon et al., 2009), and argued to reflect different morphometric features of neurodevelopment, aging, and disease (Storsve et al., 2014)(Dickerson et al., 2009; Ostby et al., 2009; Panizzon et al., 2009; White et al., 2010; Winkler et al., 2010; Eyler et al., 2011; Lemaitre et al., 2012). This may be why CMR mediated the relationship between race and cortical surface area, but not cortical thickness. Therefore, managing CMR may be important for preventing accelerated aging related declines in cortical surface area, cortical volume and gray matter volume. Moreover, it has been shown that improvements in CRF can increase the volume and perfusion of the hippocampus and improve cognitive functioning (Colcombe et al., 2006; Erickson et al., 2011; Ruscheweyh et al., 2011). Despite CRF only accounting for a small amount of the racial disparity in brain health, improving CRF among blacks could be a way of reducing this disparity as it has been linked to increasing and preserving brain volumes, especially the hippocampus.

Second, the impact of race on hippocampal volume, cortical surface area, mean cortical thickness, cortex volume, and grey matter volume remains to be explained. Other factors need to be examined in order to determine other mediators of the relationship between race and brain health. Some factors that should be investigated include subclinical cardiovascular disease measures, health behaviors (Durazzo et al., 2014; Erickson et al., 2011), and social factors (stress, occupation, and discrimination)(Gianaros et al., 2017). Subclinical cardiovascular disease measures (including CAC, IMT, carotid plaque) have been related to poorer cognition and

dementia risk in older populations (Kuller et al., 2016; van Oijen et al., 2007; Wendell et al., 2012) and it would be important to evaluate if differences in subclinical cardiovascular disease mediate the relationship between race and brain health changes.

In conclusion, our study found that CRF and CMR partially mediated the relationships between race and cortical surface area, cortex volume, and grey matter volume but not with other markers of brain health. The effect through CMR, independent of CRF, tended to be larger than that through CRF and CMR. Our study had several strengths, including a large sample size, relatively healthy population, and the examination of many markers of brain health. However, our study is limited by a cross-sectional design and future longitudinal studies should be completed to confirm these findings. Furthermore, we did not have the gold standard for fitness, VO_2 max, measured and instead CRF was calculated from an equation derived by (Jurca et al., 2005). Although, this measure is highly correlated with VO_2 max, future studies interested in race and fitness should consider measuring VO_2 max directly from at least a subset of participants to better determine the impact of fitness on brain health.

4.6 FIGURES AND TABLES

Table 4.1 Cardiovascular measures by Race (unadjusted)

		Black	White	P VALUE
Avg. SBP	(n)	154	589	
	(mean)	122.00	115.80	<.0001
Avg. DBP	(n)	142	572	
	(mean)	74.42	71.84	<.0001
Fasting Glucose (mg/dL)	(n)	150	558	
	(mean)	95.36	94.85	<.0001
Fasting Insulin (uIU/mL)	(n)	135	544	
	(mean)	13.1	11.01	0.0009
	(median)	11	10	0.03*
Fasting Triglycerides (mg/dL)	(n)	150	588	
	(mean)	91.22	107.62	0.0066
	(median)	77	89.00	0.0004*
Fasting HDL (mg/dL)	(n)	150	588	
	(mean)	54.86	54.18	0.6299
Fasting Cholesterol (mg/dL)	(n)	150	588	
	(mean)	191.68	195	0.271
Waist Circumference (cm)	(n)	154	592	
	(mean)	66.44	71.94	0.035
	median	68.26	80.01	0.26*
Body Mass Index (kg/m^2)	(n)	154	593	
	(mean)	29.15	26.40	<.0001
Height (in)	(n)	154	593	
	(mean)	67.06	67.51	0.19
Potential mediators				
CMR score	(n)	135	538	
	(mean)	0.19	0.00	0.0009
CRF	(n)	123	504	
	(mean)	-0.41	0.09	<.0001

* Wilcoxon

Table 4.2 Correlations between potential mediators and markers of brain health (adjusted for ICV)

covariate	**Hippocampus Vol, cm^3**	**Entorhinal Cortex vol, cm^3**	**Cortical Surface Area, cm^2**	**Cortical Thickness, mm**	**Gray Matter vol, cm^3**	**Cortex vol, cm^3**	**Total Brain vol, cm^3**
Poor CRF	-0.18	-0.20	-0.28	-0.14	-0.38	-0.34	-0.32
	<.0001	<.0001	<.0001	0.0008	<.0001	<.0001	<.0001
CMR	-0.05	0.00	-0.10	-0.07	-0.13	-0.14	-0.12
score	0.176	0.973	0.014	0.059	0.001	0.001	0.003

Prob > |r| under H0: Partial Rho=0

Table 4.3 Linear regression models for Brain health measure by Race

Brain Health Measure		Fully adjusted model		Fully adjusted model + poor CRF			Fully adjusted model + CMR		
		B	95% CI	B	95% CI	% change in B for Black race	B	95% CI	% change in B for Black race
Hippocampal Vol, cm^3	Black	-0.4***	(-0.56, -0.25)	-0.40***	(-0.57, -0.22)	2.40%	-0.37***	(-0.54, -0.20)	7.60%
	Mediator			-0.03	(-0.12, 0.07)		-0.01	(-0.12, 0.10)	
	Adj R2		0.42		0.41			0.42	
Entorhinal Cortex vol, cm^3	Black	-0.35***	(-0.47, -0.23)	-0.32***	(-0.45, -0.19)	8.57%	-0.37***	(-0.50, -0.24)	-5.71%
	Mediator			-0.02	(-0.09, 0.06)		-0.01	(-0.09, 0.08)	
	Adj R2		0.37		0.39			0.38	
Cortical Surface area cm^2	Black	-42.16**	(-67.29, -17.03)	-35.64*	(-62.85, -8.43)	15.50%	-36.68**	(-63.91, -9.45)	13.00%
	Mediator			-9.12	(-24.19, 5.95)		-14.45	(-32.24, 3.35)	
	Adj R2		0.56		0.57			0.57	
Mean Cortical Thickness, mm	Black	-0.03***	(-0.05, -0.01)	-0.04***	(-0.06, -0.02)	-17.60%	-0.03***	(-0.06, -0.01)	-1.00%
	Mediator			0.003	(-0.01, 0.02)		-0.003	(-0.02, 0.01)	
	Adj R2		0.15		0.14			0.14	
Cortex Vol, cm^3	Black	-21.17***	(-27.67, -14.68)	-21.28***	(-28.31, -14.25)	-0.50%	-19.93***	(-26.88, -12.98)	5.90%
	Mediator			-1.48	(-5.38, 2.41)		-3.75	(-8.30, 0.79)	
	Adj R2		0.68		0.69			0.69	
Gray Matter Vol, cm^3	Black	-24.71***	(-32.70, -16.72)	-23.67***	(-32.39, -14.94)	4.20%	-22.60***	(-31.18, -14.02)	8.50%
	Mediator			-3.10	(-7.94, 1.73)		-5.45	(-11.06, 0.15)	
	Adj R2		0.73		0.73			0.74	

** p<0.05, **p<0.01, ***p<0.001*

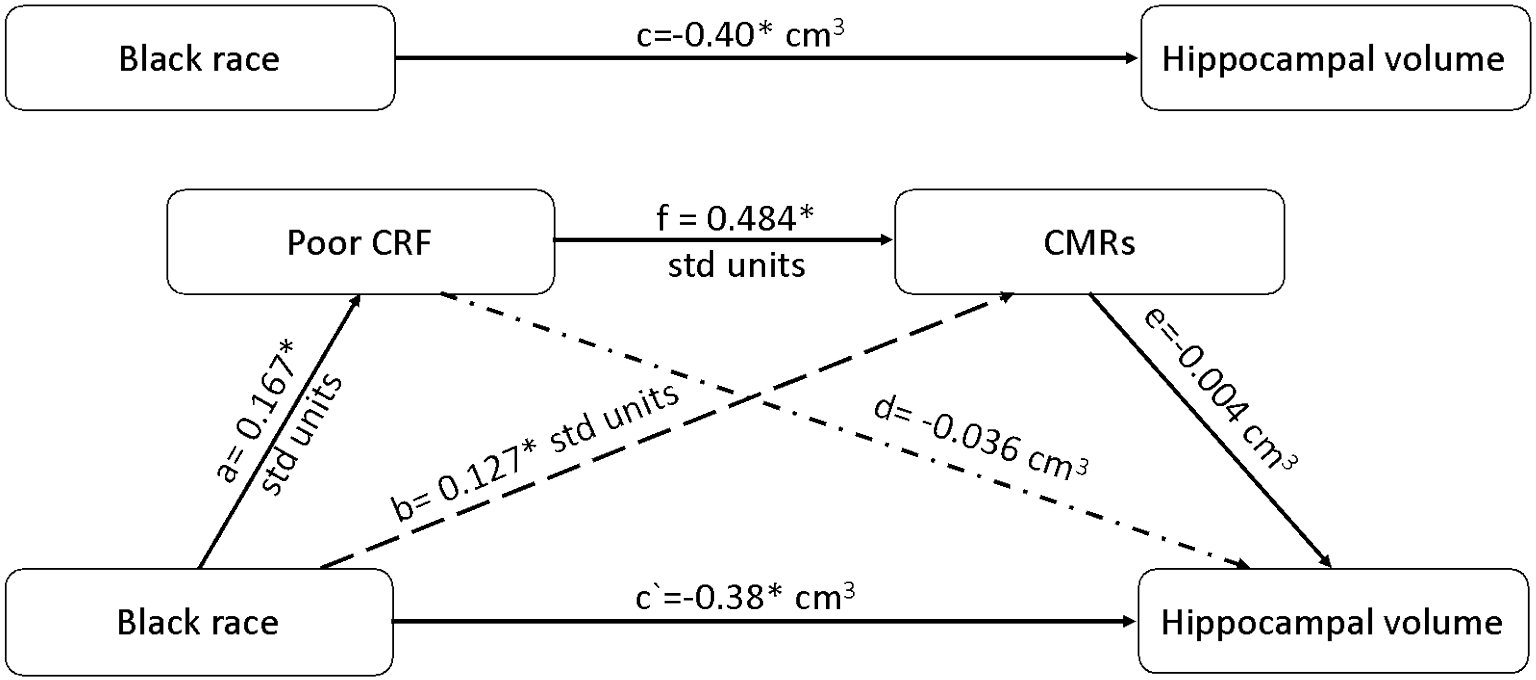
Models are adjusted for study, ICV if volume or surface area measure is outcome, sex, age, years of schooling, family income, and current smoking.

Table 4.4 Test for interaction between race and potential mediator with the brain health markers

Brain Health Measure	Potential mediator	
	CRF	CMR
Hippocampal Vol, cm^3	2.08 (0.15)	0.81 (0.37)
Entorhinal Cortex Vol, cm^3	0.06 (0.81)	0.10 (0.75)
Cortical Surface area cm^2	0.05 (0.82)	0.01 (0.92)
Cortical Thickness, mm	0.38 (0.54)	0.06 (0.81)
Cortex Vol, cm^3	0.33 (0.57)	0.07 (0.80)
Gray Matter Vol, cm^3	0.07 (0.79)	0.004 (0.95)

F-test and (p-value) reported.
Model adjusted for study, ICV if volume or surface area is outcome, age, sex, years of schooling, family adjusted income, and current smoking.

a. Hippocampal Volume

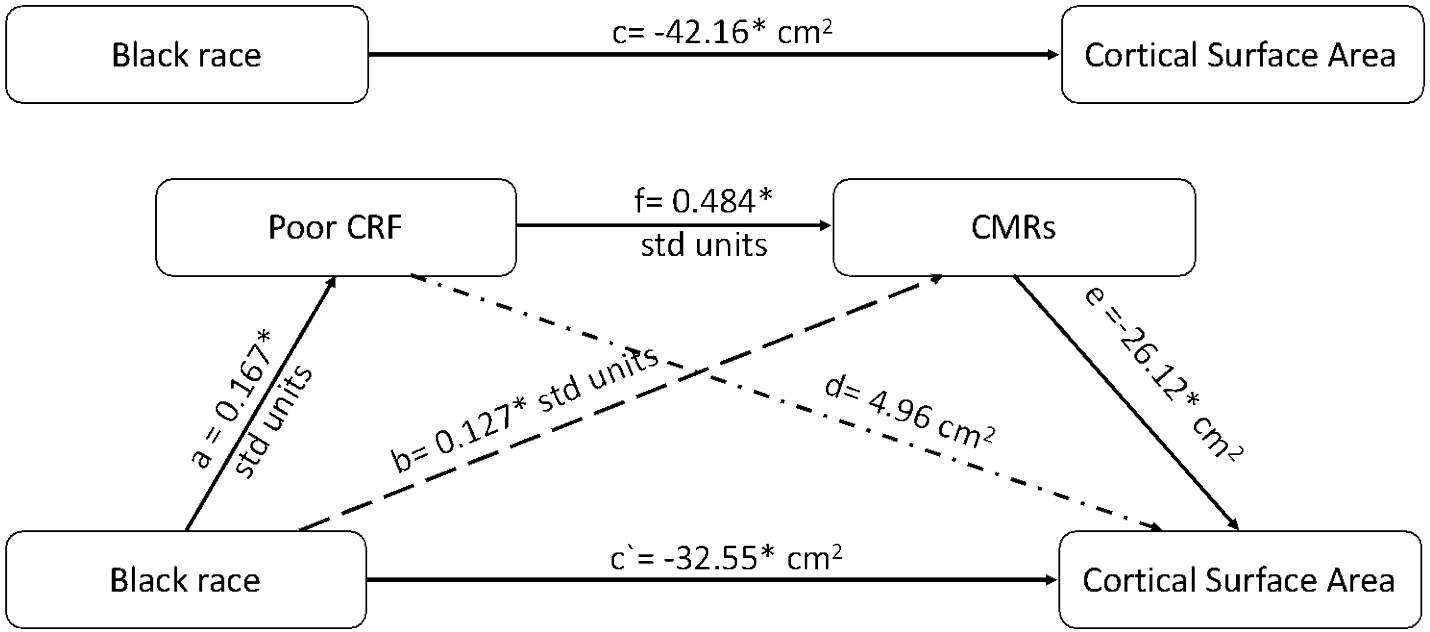


Percent mediation:
n/s
Indirect effects summary:

Black → Poor CRF → Hippocampal volume	= -0.006 [95% CI: -0.035, 0.017]
Black → Poor CRF → CMRs → Hippocampal volume	= -0.0005 [95% CI: -0.027, 0.022]
Black → CMRs → Hippocampal volume	= -0.0003 [95% CI: -0.015, 0.016]

Figure 4.1 Mediation results for Hippocampal volume

b. Cortical Surface Area

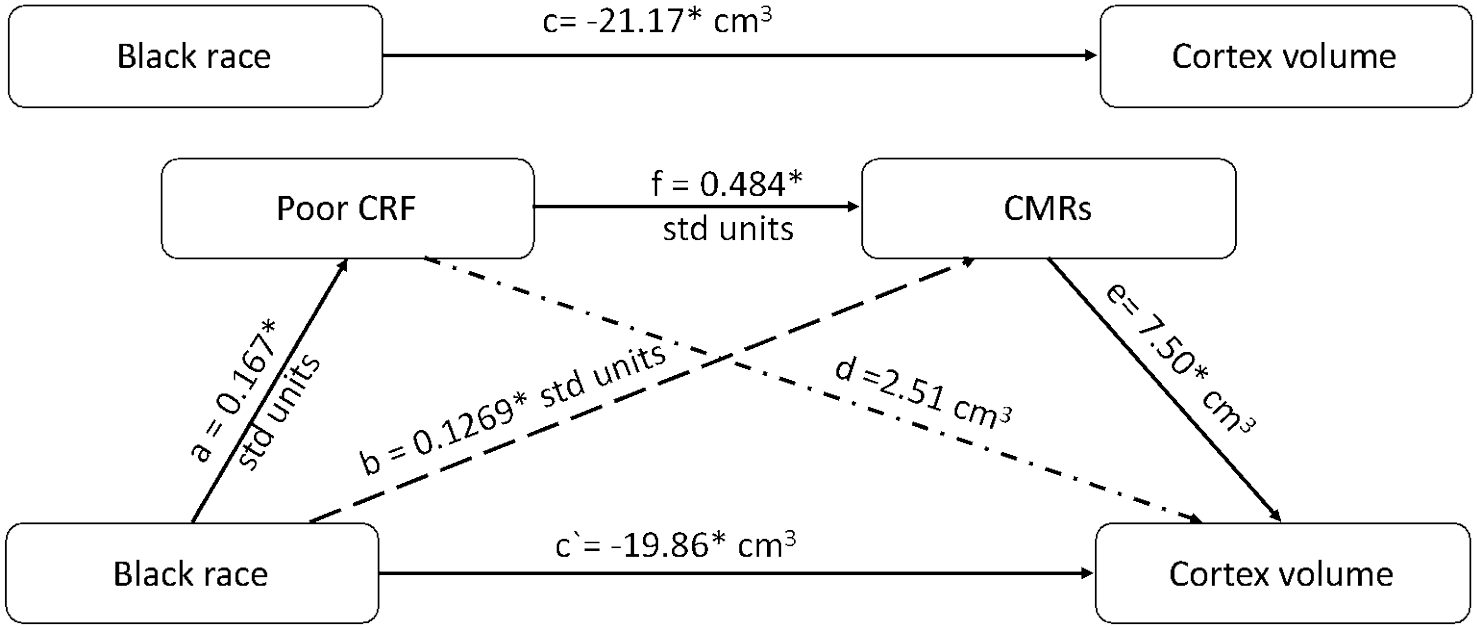


Percent mediation:
22.79%
Indirect effects summary:

Black → Poor CRF → Cortical surface area	= 0.83 [95% CI: -2.19, 6.16]
Black → Poor CRF → CMRs → Cortical surface area	= -2.11 [95% CI: -6.42, -1.08]
Black → CMRs → Cortical surface area	= -3.31 [95% CI: -10.32, -1.16]

Figure 4.2 Mediation Results for Cortical Surface Area

c. Cortex volume

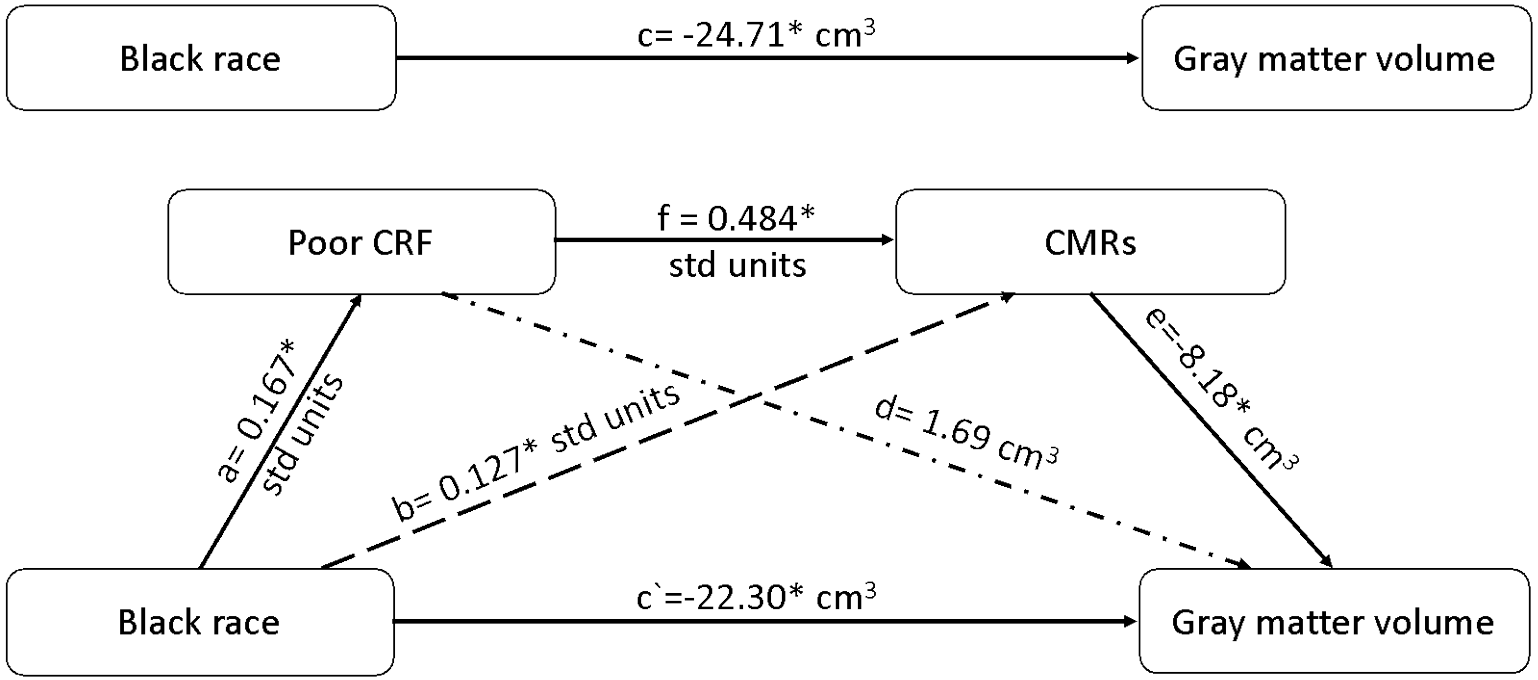


Percent mediation:
n/s
Indirect effects summary:

Black → Poor CRF → Cortex volume	= 0.42 [95% CI: -0.46, 1.60]
Black → Poor CRF → CMRs → Cortex volume	= -0.95 [95% CI: -2.54, 0.006]
Black → CMRs → Cortex volume	= -0.61 [95% CI: -1.52, 0.004]

Figure 4.3 Mediation Results for Cortex Volume

d. Gray Matter Volume



Percent mediation:
5.98%
Indirect effects summary:

Black → Poor CRF → Gray matter volume	= 0.28 [95% CI: -0.66, 2.00]
Black → Poor CRF → CMRs → Gray matter volume	= -0.66 [95% CI: -2.02, -0.04]
Black → CMRs → Gray matter volume	= -1.04 [95% CI: -3.40, -0.02]

Figure 4.4 Mediation Results for Grey Matter Volume

Table 4.5 Racial Difference in Brain Health converted to Difference in Aging (years)

	fully adjusted model				
Brain Health Measure	B for direct effect of black race	p-value	B for age in fully adj model	p-value	black:white difference equivalent to years of aging
Hippocampus Vol, cm^3	-0.38	<.0001	-0.014	0.0079	26.51
Cortical Surface area cm^2	-32.55	0.0264	-4.34	<.0001	7.51
Cortex Vol, cm^3	-19.86	<.0001	-1.77	<.0001	11.25
Gray Matter Vol, cm^3	-22.30	<.0001	-2.29	<.0001	9.75

Model adjusted for study, ICV, sex, age, years of schooling, family income, current smoking and the mediating role of CRF and CMR

5.0 DISSERTATION DISCUSSION

5.1 MAJOR FINDINGS

Contemporary evidence suggests that blacks are at greater risk of cerebral small vessel disease and brain related sequelae (stroke, dementia, and vascular cognitive impairment). However, current work attempting to identify potential sources of racial health disparities in cerebrovascular and brain health are limited. This dissertation aimed to improve our understanding of racial disparities in brain health outcomes through three complementary studies. The first explored existing literature investigating race and markers of brain health, pointed to gaps in knowledge, and suggested directions of future research. The second examined whether there are racial differences in brain health in a midlife population. Finally, the third assessed whether cardiorespiratory fitness and cardiometabolic risk mediate the relationship between race and brain health.

The literature review presented in chapter two of this dissertation highlighted gaps in our understanding of race and brain health. Based on the 33 publications included in the review, blacks appear to be at a greater risk for developing white matter hyperintensities. However, relationships between race with other markers of brain health remain unclear. In this review we identified major limitations in the current research. These include: 1) a lack of representation by younger age groups (specifically <65 years old), 2) limited geographic representation, 3) many publications originating from only a few study samples, and 4) the lack of reporting diverse markers for brain health (most

publications only report white matter hyperintensities). These limitations may lead to major biases that have limited our understanding of the pervasiveness of brain health disparities across the lifespan. In response to these gaps in knowledge, we set out to examine race and brain health in a middle-aged population and test potential mediators of this relationship.

The results from our investigation of racial differences in brain health among a middle-aged population are presented in chapter three. We found that blacks and whites differ in almost every marker of brain health except for global cerebral blood flow. Adjustment for demographics and socioeconomic variables attenuated relationships with race and both cortical white matter volume and amygdala volume. After adjustment for demographics and socioeconomic variables, blacks exhibited significantly lower gray matter volume, smaller hippocampus, less cortical surface area, and a thinner cerebral cortex than whites (all p's<0.05). The magnitude of the effect of race on brain health was similar but somewhat smaller among females compared to males. There remained a significant and unexplained (by demographics and SES variables) effect of race on hippocampal volume, cortical surface area, mean cortical thickness, cortex volume, and gray matter volume equivalent to: 29.04, 9.47, 10.66, 9.20 and 13.96 years of aging, respectively.

Finally, the results of the mediation analysis indicated that CRF and CMR partially mediated the association of race with cortical surface area, cortex volume and gray matter volume. The percent mediation for cortical surface area and gray matter volume was 22.79% and 5.98%, respectively. Additionally, we found that independent of CRF, there was an indirect effect of CMR on cortical surface area and gray matter volume. No indirect effects of CRF independent of CMR were found. There remained a significant direct and unexplained effect of race on hippocampal volume, cortical surface area, cortex volume, mean cortical thickness, and gray matter volume equivalent to 26.51, 7.51, 11.25, and 9.75 respectively. These are considered large and clinically

relevant differences for a middle-aged population, and future studies should investigate other potential mediators for these relationships. Additionally, longitudinal studies will be invaluable in establishing these relationships overtime and determining whether these differences are due to developmental causes, differences in susceptibility, or differences in exposure to risk factors for detrimental brain changes.

In sum, race differences in brain health are evident in midlife. CRF and CMR factors may partly explain some of the racial differences in brain health and should be investigated further as potential targets for intervention. These results have implications for understanding the pathways by which race may impact brain health prior to the onset of stroke and other clinical outcomes later in life.

5.2 PUBLIC HEALTH SIGNIFICANCE

Racial differences in stroke and dementia are evident but the reasons behind these disparities remain poorly understood (F Gottesman et al., 2015; Husaini et al., 2003; Mozaffarian et al., 2015). If these trends continue unabated, the public health burden of disparities in dementia and stroke will increase as the population becomes older and more ethnically and racially diverse (Ortman et al., 2014; Pantoni, 2010). This dissertation is a significant work from a public health perspective for three main reasons. First, they illustrate that disparities in brain health exist in an otherwise healthy midlife population. Second, we investigated whether known risk factors for brain health decline contribute to this disparity. Third, this serves as a call to action for scientists, public health researchers and clinicians to investigate these disparities further. Our findings suggest that efforts to preserve brain health should begin before midlife, because by midlife racial differences in brain

health are already apparent. Research efforts should work to prevent further decline, promote preservation, and delay or prevent dementia and stroke events. Moreover, we need to better understand when these disparities begin, how they progress, and what factors confer resilience and risk.

5.3 FUTURE DIRECTIONS

The cumulative findings from this dissertation illuminates the need for future work. Many questions remain: Are these findings generalizable to other populations? When do these disparities begin? What other factors contribute to these disparities? What can we do to improve outcomes and prevent decline? In order to better understand these disparities, future researchers should consider adopting 1) a life course approach, starting during early life development, 2) a more complete understanding of exposure and race interactions 3) the use of multimodal neuroimaging paired with cognitive evaluation. Each of these three suggestions will be discussed below.

First, to improve our understanding of these disparities future researchers should adopt a life course approach. A life course approach to race and brain health research would allow researchers to observe changes in brain health overtime and determine when disparities begin. A life course approach would also assist with the investigation of potential pathways, establish causal links, and reduce survival bias. Here we found that there were differences in brain health markers that were independent of many factors thought to perpetuate the disparities in stroke and dementia risk (blood pressure, smoking, fitness, metabolic factors, etc.). Particularly, we found differences in hippocampal volume that were not explained by the factors we examined here. As many of these volumes are known to decline with age, these findings may suggest that blacks are experiencing

advanced brain aging. This advanced brain aging may be due to more rapid declines in brain volume with aging, a similar rate in declines but declines starting at an earlier age, or less volume achieved during development. Upon further investigation, it appears that the race differences in hippocampal volume were higher at younger ages than at older ages, whereby declining volumes in the white population lead to a smaller difference between the two groups (P-value for interaction of age * race (p=0.057) in fully adjusted model) (figure 3.i.). Hippocampal volumes among the blacks alone appear to be maintained and the decline in hippocampal volume with aging observed in the whites is not observed in the blacks. Since this study is cross-sectional, it is not possible for us to determine if the rate of change in brain volumes over-time is the same or different between the two groups. We suspect that even in this middle-aged population we are observing survival bias in the black sample. This bias gives the appearance that the gap is closing, when really, studies are not including those persons who are most vulnerable to these brain changes at older ages. We know that minority populations are more likely to suffer from comorbidities that may lead to exclusion from MRI studies and have a higher risk of mortality from stroke especially at ages before 65. This may bias the findings even in our middle-aged sample. Future studies should examine younger populations and follow individuals over time to determine whether they are experiencing more rapid brain aging. Additionally, studies of early development would nicely complement our understanding of these processes by exposing factors that may drive these disparities later in life. Studies or early life would also help us to understand whether differences in brain volumes are due to differences in development or an increased rate of decline later in life.

Second, determining what factors contribute to differences in brain health is important to understanding the disease etiology and determining the best ways to help prevent the progression and decrease racial disparities in brain health. Identification of these factors is just the first step;

implementation of interventions will require a more complete understanding of the barriers and potential risk factor interactions with race. Here we found that fitness, cardiometabolic risk, and socioeconomic factors (such as education and income) attenuated the magnitude of the relationship between race and many markers of brain health. These findings offer insights into possible targets for intervention. Improving education and reducing cardiometabolic risk could be key factors in reducing health disparities. The challenge is developing interventions that are accessible, generalizable and sustainable. Also, we need to be careful in designing interventions that will reduce health disparities and not perpetuate them. Interventions could reduce disparities either by primarily targeting minority groups or choosing interventions that may have an added benefit for blacks over whites. For example, improving fitness has been acknowledged as a way to prevent decline and increase brain volumes. Although CRF was not an independent mediator of race and brain health in this cross-sectional analysis, we found a non-significant trend indicating a possible interaction between race and CRF with hippocampal volume ($p=0.15$). This suggests that the effect of poor CRF may be worse for blacks as compared to whites. It is possible that exercise interventions may have an added benefit among those who are black and could help reduce racial disparities. Future studies should examine the potential of exercise interventions to reduce racial disparities in brain health. Beyond examining these factors, future researchers need to ensure that they are taking a multifaceted approach to understanding these health disparities. Race and disease relationships are unique to the human population. Race is an abstract and socially constructed concept. Race is interwoven with many different aspects of life, including: culture, diet, beliefs, behaviors, social and societal relationships. These complex interactions between race and many aspects of life can easily introduce bias. Studies need to be carefully designed to measure or control

for as many of these biases as possible. Future work examining these relationships requires a holistic approach where the complexity of race is not ignored.

Finally, this dissertation has focused mainly on differences in brain structure, with the exception of CBF, in an effort to understand racial disparities in brain health. However, the role of cognition and brain function will be key to identifying the mechanisms by which these physical differences in brain structure may lead to an increase in risk of dementia. Future research in this area needs to consider not only brain structure, but bridge both structure and function to fully understand brain health resilience and the risk for detrimental brain changes in this population. For example, we observed differences in brain volumes but not global CBF. This finding was somewhat unexpected, as many argue that changes to CBF may contribute to atrophy. In order to better understand the implications of these findings, longitudinal data are needed, along with measures of cognitive performance. Here it is impossible to tell whether the preservation of CBF may help to compensate for the loss of tissue volume, or if volume loss precedes declines in CBF. Furthermore, a decline in CBF may be more detrimental to a person who has already experienced volume loss (e.g. if you have fewer neurons and all of a sudden you are unable to provide enough nutrients to the neurons you have you will be unable to perform the task). Understanding these relationships between structure, function, and performance may help to uncover targets for intervention.

In conclusion, future research would benefit from a life course approach that examines complex interactions with race and integrates multimodal neuroimaging paired with cognitive assessment. An example of conceptual framework that integrates the above points is given in figure 5-a. Cross-disciplinary work is required in order to fully understand exposures, potential barriers, and to design lasting interventions.

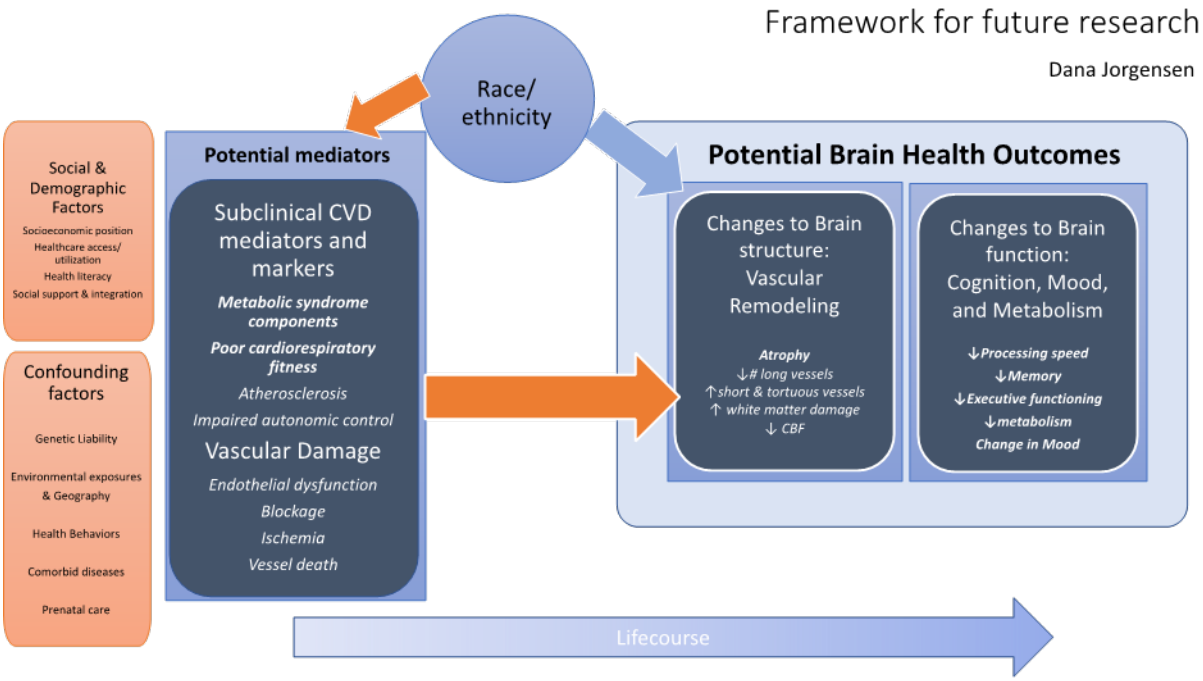


Figure 5.1 Framework for Future Research

5.4 FUTURE CHALLENGES

Advancements in neuroimaging have allowed us to not only visualize brain tissue, but to explore relationships between brain tissue and the vasculature that feeds it. Small penetrating arteries of the white matter and basal ganglia are hard to visualize with most non-invasive techniques such as CT and MRI. However, with ultra-high field time-of-flight MR angiography, we can now begin to characterize these penetrating small arteries in vivo. Small vessels usually manifest as thin, smooth and relatively straight vasculature with moderate branching. As mentioned in a prior review (Jorgensen, 2018), in disease states these penetrating vessels may be recruited as collateral pathways and greatly increase in number, with a more tortuous and aggressively branching pattern,

and are prone to hemorrhage. Time-of-flight MR angiography can be used to visualize small arteries as thin thread-like areas of flow-related contrast. Using this technique, features of cerebrovascular disease, such as reduced vessel number and increases in tortuosity, can be examined. These measures could then be evaluated as potential contributors to disparities in brain health. However, there are no standard approaches to processing these images. This lack of a standard methodology is possibly the greatest challenge when using this type of data. But, it also offers an excellent opportunity for innovation and creation of both an optimal segmentation and quantification method.

Before vessel characteristics can be examined, the vessels need to be extracted from the surrounding brain tissue, a process termed “segmentation”. There are several ways to segment cerebral vasculature. The current “gold standard” method for segmentation would be hand tracing. Whereby trained individuals trace the structure of the vasculature in a MRI visualization software (like HOROS). Typically, this would be done in triplicate and the results of each tracing compared. This methodology is limited and often not an optimal choice for segmentation. Hand tracing is time consuming, requires the tracer to have focus, and the quality and consistency of tracings can be dependent on many extraneous factors. Some of these factors include, the resolution and quality of the image, amount of light in the room, the tracer’s vision, and the amount of coffee the tracer had that day. All of these factors can be minimized or controlled, but the process of hand tracing these vessels is imperfect and unrealistic on a large scale. Automated and semi-automated segmentation show promising results. Several programs exist that can segment vessels in a semi-automated fashion. HOROS and 3D Slicer are two examples of such programs. HOROS is relatively easy to learn and offers a fast segmentation based on either thresholding and/or growing algorithms. Unfortunately, the HOROS segmentation includes vessels outside of the brain which

will need to be removed later. 3D slicer offers similar algorithms and does not include vessels outside of the brain. But, 3D slicer is bulky, not intuitive, and time intensive. The key issue with either software is the segmentation product is difficult to use for quantification purposes. A final approach to segmentation relies on collaboration with computer scientists and neuroimaging specialists. A key advantage to working with time of flight images is that the vasculature is so much whiter than the surrounding brain tissue. This dramatic difference in intensity can be used as an easy way to remove nonvascular tissue. Using a bimodal distribution of voxel intensity, a threshold is set to determine the probability that each voxel was either part of vascular tissue or not. This does an excellent job for an initial segmentation; however, special masks are needed to remove non-cerebral vasculature while preserving the carotids.

After the segmentation step comes quantification. There is no current standard for quantification. But, features of vasculature, including reduced arterial vessel number and increased arterial tortuosity, have been positively associated with aging (Bullitt et al., 2010) and inversely associated with exercise (Bullitt et al., 2009) in healthy individuals. These findings are consistent with previous findings from postmortem studies of small vessel disease where small vessels appear to greatly increase in number, with a more tortuous and aggressively branching pattern in brains with cerebral small vessel disease compared to those without (Fazekas et al., 1993)(see (Jorgensen, 2018) for a review of pathologic correlates). However, the differentiation of small arteries from small veins is challenging in postmortem examination (Black, Gao, & Bilbao, 2009; Brown, 2010; Brown & Thore, 2011; Fazekas et al., 1993; Moody, Brown, Challa, & Anderson, 1995; Moody et al., 2004). Therefore, more studies of in vivo vascular characteristics are needed and could provide valuable information about arteriole vascular characteristics and pathologic responses to risk factors. In future studies quantifying vasculature, is important to keep in mind what that we

are attempting to capture a physiologic process and need to use measures that reflect this process. The methods used to quantify vessels should reflect two things: 1) features of the underlying pathophysiology and 2) an understanding of the strengths and limitations of the segmentation product. Optimizing these two points should result in the best and most physiologic variables for both analysis and interpretation of the findings.

In conclusion, there is ample opportunity to develop techniques to quantify cerebral vasculature. Multidisciplinary collaboration will be required in the development of such techniques. In the end, development of such methods will help improve our understanding of the inter-relationships between the vasculature and the neurons. We hope that a better understanding of these relationships will help us treat, diagnose, and identify vulnerable populations in the future.

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