DEMENTIA, BRAIN STRUCTURE, AND VASCULAR RISK FACTORS IN VERY OLD BLACKS AND WHITES

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ABSTRACT

Dementia is a disease of old age, and a major cause of disability and mortality in the elderly. African American or blacks have higher dementia prevalence and incidence than Caucasians or whites, and such racial disparities tend to be largest in the oldest old (≥ 85 years of age). Moreover, the oldest old is the fastest growing segment of the elderly population in US. Therefore, reducing racial disparities in dementia in the oldest old is of high **public health relevance**.

Racial differences in dementia should have neurological correlates on racial differences in brain structure. However, among previous studies examining racial differences in brain structure, most applied neuroimaging methods with low resolution, and detected only brain macro-structural characteristics in cohorts of young old adults. Moreover, the sample sizes of oldest old blacks in previous works were too small to draw final conclusions.

In this dissertation, a review of dementia, brain structure, and vascular risk factors is conducted first (Section 2), followed by an overview of their racial differences between elderly blacks and whites (Section 3). Gaps in knowledge and a proposal to address these gaps are presented in Section 4 and Section 5. The proposal involves leveraging an existing cohort of community-dwelling black and white adults (≥ 79 years of age) into an evaluation of brain

structure and dementia. In this cohort, cutting-edge and high resolution neuroimaging modalities have been applied to obtain measures of brain structure at baseline and three years after, and data on vascular risk factors have been recorded at regular intervals in the previous decade.

This dissertation work will not only provide estimates of dementia prevalence rates in very old blacks and whites in the context of other important determinants of dementia, but also offer new evidence for the pathophysiology of the association between race and dementia. The primary hypothesis is that racial differences in dementia or cognition is related to racial differences in vascular risk factors, and this is explained by racial differences in brain structural abnormalities.

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1.0 INTRODUCTION

African Americans or blacks are the largest minority among the adults ≥ 65 years of age in the United States (US) [1]. From 2010 to 2030, elderly blacks in the US are projected to increase by 114%, as compared to an increase of 59% in their white counterparts [2]. Older age is one of the strongest risk factors for dementia, and dementia risk increases exponentially with age in the elderly. Another strong risk factor for dementia is race. Compared to whites of similar age, elderly blacks have lower cognitive functions and higher dementia risk, and such racial disparities are largest in the oldest old (≥ 85 years of age) [3,4]. This racial disparity is of very high public health relevance, because the oldest old is the fastest growing segment of the US elderly population [5], and because medical care of patients with dementia has imposed huge economic and psychological burdens on our society and caregivers [6].

What can explain the racial differences in dementia and cognitive function between elderly blacks and whites? Previous brain imaging studies show that both macro- and micro-brain structural characteristics predict cognitive decline [7-10]. Compared to brain macro-structural measures, such as brain atrophy and white matter hyperintensities (WMHs), brain micro-structural measures are even stronger predictors of memory, executive function, information processing speed, and global cognition [9-13]. Therefore, racial differences in cognitive impairments may be explained by racial differences in brain structure.

Previous studies suggest a vascular pathogenesis for both structural brain impairment and dementia development. A higher burden of vascular risk factors, such as hypertension and diabetes, is associated with greater brain atrophy [14,15], a higher grade of WMHs [16,17], worse brain micro-structural integrity [18-21], and consequentially higher dementia risk (Dickstein, 2010). Moreover, previous literature has shown a greater burden of vascular risk factors in blacks compared to whites of similar age [22-25]. Therefore, racial differences in vascular risk factors may contribute to racial differences in cognitive impairment through their impact on brain structure.

Another important domain of factors contributing to higher dementia risk is lower socioeconomic status, such as education and family income, which have been reported to be lower in blacks than in whites [23,24], and which are also related to brain structure and dementia risk [26-28]. Therefore, studies of racial differences in dementia also need to account for racial differences in socioeconomic status.

The central goal of this dissertation is to test the hypothesis that racial differences in brain MRI measures explain the associations between racial differences in vascular risk factors and dementia, and to explore to what extent these relationships are independent of socioeconomic status. First, I conducted a review of the literature pertaining racial differences in dementia, cognitive function, brain structure and vascular risk factors with a specific focus on blacks and whites. Interrelationships among vascular risk factors, brain structure, and cognitive function were also reviewed. Since racial differences in dementia are largest in the oldest old, results in adults older than 85 were given special attention. Based on this literature review, several gaps in knowledge were identified, and a conceptual model (Figure 1) is proposed to generate hypotheses for further studies. On the basis of this conceptual model, new studies are proposed to address the major gaps in knowledge. These studies focus on a cohort of very old (≥ 79 years of age) subjects

of two races (white and black), which was examined at baseline and three years later to identify important brain structural risk factors for dementia by race. Results of these studies, discussion, and directions for further research are outlined in detail in later sections of this document.

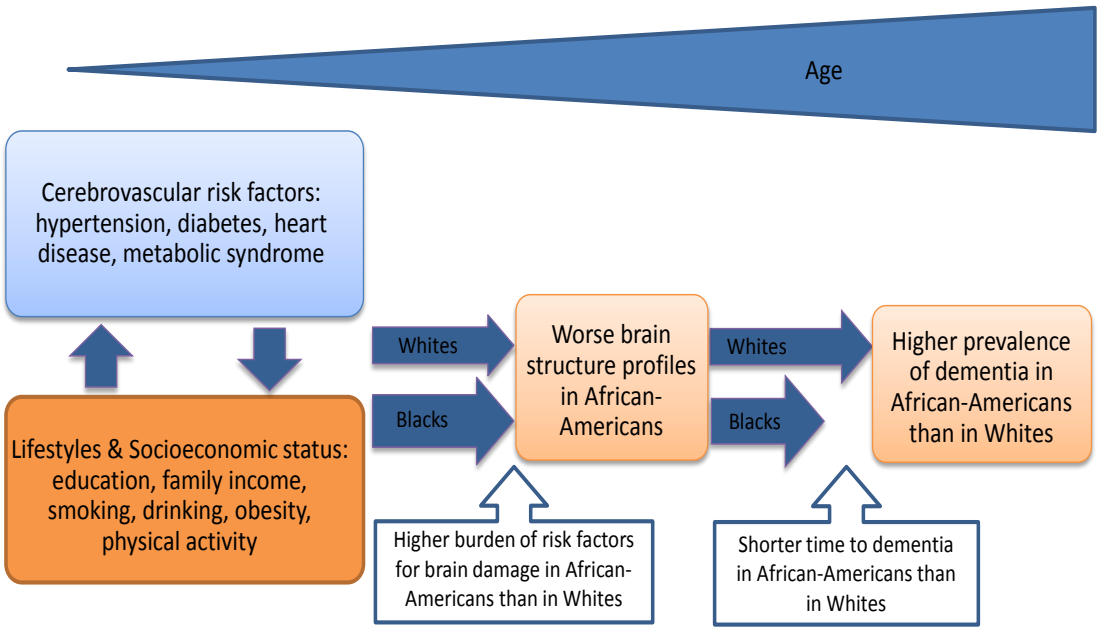

Figure 1 Conceptual model of racial differences in dementia

2.0 DEMENTIA, BRAIN STRUCTURE, AND VASCULAR RISK FACTORS

2.1 EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF DEMENTIA

In the elderly, dementia is one of the most common diseases and a major cause of disability and mortality [29]. It is characterized by memory loss and impairments of other cognitive functions, which interfere significantly with social activities or relationships with others [30]. The prevalence of dementia is 0.7% to 1.8% among those aged 60-64, starts to increase exponentially with older age [29], and is 29% to 64% among those aged above 90 across global burden of disease regions [31]. In addition to geographic variation, the range of values is in part related to differences in classification criteria. Moreover, such an increase with older age is more striking in elderly blacks than in whites [3,32]. For example, in Northern Manhattan residents, the prevalence of dementia in blacks increased from 9.1% (age: 65-74) to 19.9% (age: 75-84) and to 58.6% (age: ≥ 85), whereas, in the same age ranges of whites, it increased from 2.9% to 10.9% and to 30.2% [3]. Therefore, the oldest old, especially the oldest old blacks, bear the highest burden of dementia in the U.S. population.

The most common subtypes of dementia are Alzheimer's disease (AD) and vascular dementia (VaD), which account for 50-80% and 10-30% of prevalent dementia cases respectively [29]. Compared to whites, blacks are more likely to have VaD [33]. The age-adjusted incidence of VaD was almost two times higher in blacks than in whites (2.72% vs. 1.46%) in the Cardiovascular Health Study [32]. It is estimated that there were 35.6 million dementia cases worldwide in 2010, with numbers expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 [31].

Clinically, AD is associated with more memory impairments, whereas VaD patients have milder impairment of memory and stronger impairments in executive function such as judgment. [34]. However, the clinical classification of VaD and AD is still controversial, and can mask common vascular pathological mechanisms underlying the two main subtypes of dementia [35]. The emerging concept of mixed dementia refers to a broad spectrum of conditions in which cognitive declines may be attributable to the presence of both AD and vascular-related alterations [36] . However, generally accepted and validated neuropathological criteria for the diagnosis of mixed dementia AD are not available, and its true prevalence is not known [37]. Brain autopsy is necessary to determine the coexistence of Alzheimer's and vascular pathologies. According to a review of autopsy studies, the prevalence of mixed dementia varied from 2% to 58% [37], depending on the diagnostic criteria, autopsy sample size, and population characteristics.

Post-mortem studies of AD-related pathology have been very helpful to clarify some of the main factors in the pathogenesis of AD. Amyloid plaques of amyloid-β (Aβ) and neurofibrillary tangles (NFTs) of hyperphosphorylated tau, are two hallmarks of the AD brain [38]. The conventional hypothesis for the etiology of AD is the amyloid cascade hypothesis [39], which states that the accumulation of brain Aβ deposition triggers the production of NFTs, cell death, and ultimately the clinical symptoms of AD. However, controversies have arisen regarding this hypothesis because there is a lack of associations between amounts of Aβ deposition and AD severity, and Aβ deposition has never been found to be neurotoxic in vivo [40].

Neurofibrillary tangles (NFTs) of hyperphosphorylated tau are the second pathological hallmark of the AD brain. When tau is abnormally hyperphosphorylated, it loses its biological activity, becomes resistant to degradation, and may go through conformational changes that render its aggregation into paired helical filaments (PHFs) [41]. Studies on correlation between pathological

hallmarks and clinical symptoms of AD have demonstrated that neurofibrillary pathology and not Aβ plaques correlate with the presence of dementia in humans [42]. Nonetheless, the pathogenetic relationship between Aβ and tau hyperphosphorylation is still unclear [43].

Apolipoprotein E (ApoE) expression in the brain is only secondary to liver. Astrocytes, and to some extent microglia, are the major cell types that express ApoE in the brain [44]. In humans the ApoE gene shows polymorphism which results in three different alleles ε2, ε3 and ε4. ApoE may facilitate the clearance of Aβ (ε2 > ε3 > ε4) and mediate tau hyperphosphorylation (ε2 < ε3 < ε4) in an isoform-dependent manner [45,46]. The presence of at least one ε4 allele on the ApoE genotype is considered the main genetic risk factor for sporadic AD [47], and those homozygous for the ApoE ε4 allele have a 12-fold increase in the risk for AD [48].

Recent evidence from epidemiological, pathological, and neuroimaging studies implicates neurovascular dysfunction as an integral part of AD, and has given rise to the vascular hypothesis [36]. These studies revealed distinct associations between AD and various vascular risk factors, such as hypertension, total cholesterol, type II diabetes mellitus, hypotension, and smoking [36]. A number of vascular lesions have also been found in AD brains, such as blood-brain barrier dysfunction, small vessel diseases, atherosclerotic plaques, and cerebral amyloid angiopathy (CAA) [49]. CAA is defined as the deposition of Aβ peptide within the walls of the leptomeninges and parenchymal arteries, arterioles, and capillaries with a concomitant thickening of arteriole walls and formation of microaneurysms [50]. Actually, a very high percentage (70%-90%) of AD patients shows amyloid pathology in their brain vessels, which narrows the vessels and produces hypoperfusion [51].

Pathologically, brain infarction and cerebral hemorrhage, especially multiple silent infarcts, are major characteristics of VaD [34]. However, “pure” VaD is rare, and common vessel disorders and lesions are shared by AD and VaD. VaD is most frequently caused by degenerative

vessel disorders, such as atherosclerosis and small vessel disease (including small vessel arteriosclerosis, arteriolosclerosis, lipohyalinosis, and CAA) [52]. Meanwhile, atherosclerosis, silent infarcts, small vessel disease and CAA are prevalent in the AD brain too [52]. Previous brain imaging studies showed that brain small vessel diseases, measured by WMHs, silent infarcts and lacunar infarcts, are more prevalent in blacks than in whites [53-57].

Why is it important to examine this problem in the context of older age? As described above, dementia is a disease of old age. The dementia prevalence is very low before age 60, and increases exponentially thereafter [31]. Macro- and micro-structural integrity of brain white matter and gray matter decline with advanced age [58]. Moreover, the prevalence of key risk factors for dementia, such as hypertension and diabetes, also increases with older age. [59] [60], and these also contribute to the increase of dementia risk with older age. Therefore, older age is a major precipitating factor of dementia epidemic in the population.

Recent reviews [40,61] have proposed that aging, amyloid deposition, and vascular risk factors may play synergistic roles in the pathogenesis of dementia. Distinguishing these roles in the possible etiology of dementia is very important because these vascular factors are more prevalent in blacks than in whites, which may explain the racial differences in dementia prevalence and incidence. The conceptual model for dementia pathophysiology is illustrated in Figure 2.

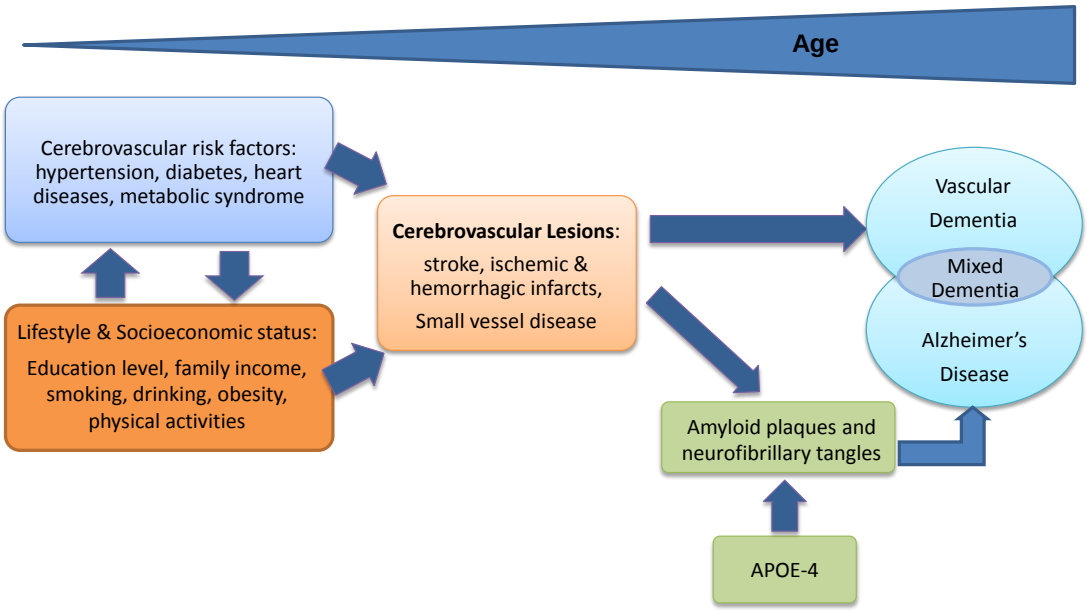

Figure 2 Pathophysiology of dementia

2.2 CLASSIFICATION AND FUNCTIONAL NEUROANATOMYG OF DEMENTIA

The diagnosis of dementia is complex and usually based on a comprehensive evaluation of neuropsychological and neurological information, and brain MRI exams. The diagnosis of dementia requires impairments in at least two cognitive domains, including memory, language, visual-spatial abilities, semantic knowledge and executive functions. Moreover, cognitive deficits must be severe enough to interfere with the individual's activities of daily living (ADLs) [62]. Dementia can be further classified according to type (AD, VaD, Parkinson's disease, or other) using standardized criteria and MRI. There are a number of classification criteria, such as those found in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and those defined by National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease Related Disorders Association (NINDS-ADRDA). Table 1 lists

sample tests for each of those cognitive domains that are typically examined in the neuropsychological battery for dementia diagnosis.

In typical AD patients, the entorhinal cortex is the earliest site of atrophy, closely followed by the hippocampus, amygdala, and parahippocampus, and then the temporal neocortex and all neocortical association areas, usually in a symmetrical fashion [63]. Hippocampal atrophy is associated with the early symptoms of memory loss [64]. Previous brain MRI studies showed that hippocampal and medial temporal lobe atrophies were the most consistent predictors of future dementia [65,66]. In addition to the temporal lobe, the frontal lobe is another brain region predicting dementia development [66]. In particular, the prefrontal cortex is critical for the performance of executive functions [67]. One longitudinal study found that prefrontal cortex atrophy was better than medial temporal lobe atrophy in distinguishing those with cognitive decline from those with incident dementia [68]. Nonetheless, atypical AD cases with language difficulties may have left temporal atrophy, and those with visual-spatial dysfunctions may have posterior cortical atrophy [63].

Table 1 Typical tests of cognitive domains in dementia diagnosis

Domain	**Sample Test**
Global Cognition	Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR)
Verbal Memory	California Verbal Learning Test; CERAD Word List Learning; WMS-R Logical Memory
Visual Memory	Rey Osterrieth Figure; WMS-R Visual Reproduction
Language	Boston Naming Test; verbal fluency (category and initial letter); Token Test
Visual-Spatial Skills	Rey Osterrieth Figure Copy; Benton Line Orientation; Block Design
Executive Functions	Digit Span backward; Trail Making Test B; Stroop Color-Word Test; Clock Drawing

Neuroimaging Correlates of Cognitive Function: Studies of Brain Macro-Structure Brain atrophy and white matter hyperintensities (WMHs) are common features observed on brain images by Magnetic Resonance Imaging (MRI) of the elderly [69]. MRI scans weighted by T1 relaxation properties of protons (^{1}H nuclei) in water molecules (T1-weighted MRI) of brain tissue are used to estimate brain atrophy because they provide appreciable contrast of brain gray matter, white matter, and cerebrospinal fluid (CSF). T2-weighted and fluid attenuated inversion recovery (FLAIR) scans can suppress CSF so as to bring out hyperintense lesions in white matter, which may reflect demyelination and gliosis [70].

In the cross-sectional analysis of brain MRI data, brain atrophy can be measured by brain parenchymal fraction (BPF), gray matter fraction (GMF), ventricular enlargement, and sulcal width [53,57,71,72]. BPF, an indicator of total brain atrophy, represents the percentage of the intracranial volume (ICV) that is occupied by brain tissue. Ventricular enlargement, an indicator of subcortical brain atrophy, can be assessed with the ventricular fraction (VF) as the percentage ventricular volume of the total ICV, or be assessed with the visual grading of ventricular size by neuroradiologists. Cortical atrophy can be assessed with the cortical gray matter fraction (GMF) as the percentage cortical gray matter volume of the total ICV, or be assessed with the visual grading of sulcal width by neuroradiologists. Lower BPF indicates more total brain atrophy, higher VF or larger ventricular size indicates more subcortical brain atrophy, and lower GMF or wider sulcus indicates more cortical brain atrophy.

Cross-sectional measures of brain atrophy are valid only when their normal values were the same among different study subjects. However, such assumption may not hold in the real world, especially in populations of high heterogeneity. Therefore, it is methodologically superior to measure brain atrophy in longitudinal settings. With longitudinal brain MRI data, brain atrophy

can be measured by the absolute change or the percentage change of brain volume, such as brain parenchymal volume, gray matter volume, or the volume of a specific brain region [73-75]. Compared to the cross-sectional measure, the longitudinal measure of brain atrophy does not rely on the assumption of same normal value, and therefore should have higher measurement validity. On the other hand, the variation of brain MRI measurements over time may reduce the reliability of the longitudinal measure of brain atrophy [76].

Previous brain MRI studies have shown that brain atrophy and WMHs are associated with impairments of various cognitive functions. Atrophy in different brain regions is associated with the decline of different cognitive functions. For instance, hippocampal atrophy is an independent predictor of memory decline [7], and prefrontal cortex atrophy is associated with executive function decline [77]. White matter hyperintensities are usually considered as a marker of cerebral small vessel diseases [70]. In a meta-analysis of 17 pertinent studies [8], the presence of WMHs increased the overall risk of dementia by 90% (Hazard Ratio=1.9, CI: 1.3 to 2.8) and was also consistently associated with declines in executive function and information processing speed across studies.

2.3 NEUROIMAGING CORRELATES OF COGNITIVE FUNCTION: STUDIES OF BRAIN MACRO-STRUCTURE

Brain atrophy and white matter hyperintensities (WMHs) are common features observed on brain images by Magnetic Resonance Imaging (MRI) of the elderly [69]. MRI scans weighted by T1 relaxation properties of protons (^{1}H nuclei) in water molecules (T1-weighted MRI) of brain tissue are used to estimate brain atrophy because they provide appreciable contrast of brain gray matter, white matter, and cerebrospinal fluid (CSF). T2-weighted and fluid attenuated inversion recovery

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2.4 NEUROIMAGING CORRELATES OF COGNITIVE FUNCTION: STUDIES OF BRAIN MICRO-STRUCTURE

Compared to the brain macro-structural measures generated by MRI, Diffusion Tensor Imaging (DTI) can identify markers of brain micro-structure for normal-appearing tissue. Water diffusion in brain tissue is not random, but interacts with many obstacles, such as cell membranes, myelin sheaths and white matter fiber tracts [78]. Therefore, the diffusion pattern of water molecules can reveal microscopic details of brain structural architecture [78]. DTI models the diffusion of water molecules in each voxel using a single ellipsoid, and three eigenvalues can be calculated for diffusivity along the three primary axes of the ellipsoid [79]. The average of these three eigenvalues is denoted as mean diffusivity (MD). Specifically, MD is an estimate of the average magnitude of water diffusion and in grey matter and it represents the density of the molecular structure. Greater structural density results in greater restriction of water diffusion and a lower MD value. By contrast, fractional anisotropy (FA) is a composite measure of pairwise differences of the three

eigenvalues, and is particularly useful to depict directionality of water diffusion in anisotropic tissues, such as white matter tracts. Lower FA values in white matter may indicate a loss of myelin sheaths, axons, and oligodendrocytes [80].

Overall, MD is considered a marker of abnormalities of the brain parenchyma that precede measurable changes to grey matter macrostructure [81,82]. The pathological correlates of mean diffusivity of gray matter include neuronal degeneration, amyloid plaque deposition, cerebral amyloid angiopathy, and perivascular space enlargement. Higher MD in the grey matter is also related to cortical thinning and lower tissue density [82,83]. Most of the evidence of histological correlates of MD is, however, from animal studies. For example, one study of an APP/PS1 mouse model of Alzheimer's disease [84] found higher mean diffusivity values in bilateral neocortext in APP/PS1 mice than in controls. MD has also been studied in few human neurologic diseases, and it is found to increase in multiple sclerosis [85] and Parkinson's disease [86].

Previous studies in older adults have shown that higher mean diffusivity of gray matter is associated with older age and greater brain atrophy [87,88], and hippocampal MD explains higher percentage of age variability than hippocampal volume or fractional anisotropy in healthy adults [9]. Mean diffusivity of hippocampus associates almost linearly with higher memory test scores, whereas hippocampal volume and fractional anisotropy do not associate with memory in the elderly [9,89]. Moreover, mean diffusivities of total gray matter and hippocampus increase progressively across normal controls, MCI patients, and AD patients [80,90], while such changes are not found in fractional anisotropy of hippocampus[90].

Previous studies have also shown that mean diffusivities of total gray matter and hippocampus are better discriminators of MCI to AD converters versus non-converters than volumetric measures [80]. Therefore, compared to volumetric measures or factional anisotropy, mean

diffusivity of gray matter, especially of hippocampus, is a better marker of aging, memory, and dementia. However, most previous studies are cross-sectional, and longitudinal studies are needed to further verify the superiority of gray matter mean diffusivity in predicting memory decline and dementia risk than volumetric measures or fractional anisotropy. Furthermore, hippocampal mean diffusivity starts to increase exponentially after age 60 [9], and the associations between hippocampal mean diffusivity and memory test scores seem to be greatest in the oldest old group [89], therefore study of gray matter mean diffusivity in the oldest old might be of the most value.

In addition to DTI indices of gray matter, DTI indices of white matter also have stronger associations with cognitive functions, as compared to the MRI measures. Compared to WMHs, DTI indices of white matter had stronger correlations with global cognition, executive function, memory, and information processing speed [10-13]. One study in healthy older adults showed that the FA of white matter alone explained 25%, 33% and 45% of the variances in executive function, in episodic memory, and in information processing speed, respectively [10].

2.5 VASCULAR RISK FACTORS AND DEMENTIA

Vascular risk factors, such as hypertension, smoking, hyperlipidemia, and diabetes mellitus, are also risk factors for dementia [36]. Hypertension is the biggest risk factor of stroke and hence a cause of VaD [91]. Moreover, hypertension is also associated with increased risk for AD in the elderly [92]. Hypertension is involved in the pathogenesis of dementia through a variety of mechanisms, including atherosclerosis, small vessel disease, cerebrovascular dysfunction, silent infarcts, and microbleeds [91]. Nonetheless, the relationship between blood pressure and cognitive function might be age dependent [93,94]. Hypertension in mid-life is a risk factor of cognitive impairment in late-life

in various longitudinal studies [93], however the association between late-life blood pressure and cognitive function seem to be opposite in the older old (age ≥ 75), especially in the oldest old [94]. The positive association between low blood pressure and cognitive impairment in the oldest old is reported in both cross sectional and prospective studies [95-98]. There is a need to verify such associations through study of hypertension and brain structure in the oldest old.

Type 2 Diabetes is another important risk factor for dementia. Two recent reviews have suggested that the risk of VaD is increased by 2- to 3-fold in people with type 2 diabetes, and with a 1.5- to 2.0-fold increased risk of AD [99,100]. The etiology of dementia in patients with type 2 diabetes is probably multifactorial, including hyperglycemia, hypoglycemia, cerebrovascular disease, inflammation, and dysregulation of hypo-thalamic-pituitary-adrenal axis [101].

2.6 VASCULAR RISK FACTORS AND BRAIN STRUCTURE

Previous brain MRI studies found associations between vascular risk factors and brain macro-structural lesions, such as brain atrophy and WMHs. Hypertension and stroke are associated with increased burden of WMHs [16,17], and brain ischemia is probably the intermediate pathway [70,102]. However, associations between hypertension and brain atrophy are more complicated. Some studies show that high midlife blood pressure is related to brain atrophy in later life [103,104], while others show that in older adults, low blood pressure levels lead to an increased risk for brain atrophy [96,105]. These inconsistencies may be related to the crossover of blood pressure in the elderly population, i.e. mean systolic and diastolic blood pressure increases up to age 75 years but decreases thereafter [106], because studies suggested that a certain level of blood pressure is necessary to maintain adequate cerebral perfusion in the oldest old [94,95]. In addition to

hypertension, diabetes is another important risk factor for brain atrophy and WMHs. Compared to non-diabetic controls, diabetic patients have greater progressions in both brain atrophy and WMHs in longitudinal studies [14,107].

Likewise, previous brain DTI studies have shown associations between vascular risk factors and micro-structural integrity in normal-appearing brain parenchyma (see Appendix C). For instance, hypertension is associated with lower micro-structural integrity in corpus callosum, frontal lobe, temporal lobe, and total white matter [18,19,108,109]. Type 2 diabetes is associated with lower micro-structural integrity in hippocampus, cingulate cortex, prefrontal cortex, superior longitudinal fasciculus, uncinate fasciculus, and inferior longitudinal fasciculus [20,21,110]. Metabolic syndrome tends to impair the micro-structural integrity of white matter more in anterior regions than in posterior regions, especially in the prefrontal lobe [111-113].

In sum, previous studies strongly suggest a vascular pathogenesis for both brain macro- and micro-structural changes. Therefore, if there were any racial differences in brain structure, racial differences in vascular risk factors may be important contributors.

3.0 RACIAL DIFFERENCES IN DEMENTIA, BRAIN STRUCTURE, AND VASCULAR RISK FACTORS

3.1 RACIAL DIFFERENCES IN DEMENTIA PREVALENCE AND INCIDENCE IN THE ELDERLY

A synopsis of previous studies on racial differences in dementia is included in Appendix A. A summary of this synopsis is provided here, and highlights the frequency of dementia in blacks. In the North Manhattan Aging Project (NMAP) and the Washington Heights and Inwood Study (WHI), the prevalence of dementia and incidence of AD were two to three times higher in elderly blacks than in whites of similar age [3,4]. According to the NMAP, the prevalence of dementia in three age strata (65-74, 75-84, 85+) was 9.1%, 19.9% and 58.6% in blacks, and was 2.9%, 10.9% and 30.2% in whites.

Among 4 US communities (Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pennsylvania), in the Cardiovascular Health Study (CHS), a nearly 1.5-times higher dementia incidence in elderly blacks than in elderly whites [32]. Specifically, the age-adjusted incidence (per 100 person-years) was 5.88% in black women versus 3.47% in white women, and was 5.30% in black men versus 3.53% in white men. However, in the Established Populations for Epidemiologic Studies of the Elderly (EPESE) conducted in one urban and four rural counties of North Carolina, neither dementia prevalence nor 3-year incidence significantly differed between elderly blacks and whites [33]. Likewise, the Einstein Aging Study (EAS) conducted in Bronx County of New York also failed to find overall significant racial differences in dementia incidence during 4 years of follow-up [114].

A possible explanation for discrepancies in these study results is that the dementia ascertainment methods varied across these studies. In the EPESE study, the determination of dementia was done retrospectively by interviewing survivors or proxies. By contrast, the NMAP and CHS ascertained dementia based on prospectively collected data, and therefore their dementia diagnosis would be more reliable than that of the EPESE study. In the EAS study, memory loss was a required criterion to make diagnosis of dementia, while there was no such requirement in the CHS study.

Another explanation for the discrepancy in study results may be the differences in study sampling and hence in characteristics of the respective study populations. For example, institutionalized subjects were excluded from both the EPESE and the EAS studies. The EPESE study was conducted largely in rural counties as compared to urban counties in other studies, and the EAS study pre-screened willing-to-participate subjects by phone. Exclusion of institutionalized subjects and multiple screening procedures might be reasons for the much lower dementia incidence in the EAS study than that in other studies. Moreover, the adjustment of education in the analysis of the EAS study might also contribute to its non-significant test result of racial differences in dementia.

The frequency of dementia appears to be most pronounced among blacks over age 85 years. Dementia prevalence was 58.6% vs. 30.2% and AD incidence (per 100 person-years) was 11.4% vs. 4.2% for blacks and whites in the oldest old northern Manhattan residents (NMAP and WHI studies). Although the EAS study did not find significant racial differences in dementia incidence in all age groups, it did detect a 1.5 times higher incidence in oldest old blacks than in whites (black: 8.34% vs. white: 5.85% per 100 person-years).

In the oldest old, sex may be a modifier for racial differences in dementia. Although the EPESE study did not find racial differences in overall dementia incidence, it did find that blacks were nearly 5 times more likely to develop dementia in men (black: 23% vs. white:4.7% per 100 person-years), while racial differences of inverse direction were found in women (black; 4.4 % vs. white: 12.8% per 100 person-years). Similar results were also found in the oldest old of the CHS study: Black men had a five times higher dementia incidence than white men (black: 40.4% vs. white: 8.4% per 100 person-years), but black women had lower dementia incidence than white women (black: 8.7% vs. white: 10.8% per 100 person-years).

In summary, compared to the younger old, racial differences in dementia tend to be larger in the oldest old, especially in the oldest old men. In the oldest old women, the two studies with data stratified by sex (EPESE and CHS) observed lower dementia risk in blacks than in whites. However, none of above results in the oldest old formally tested racial differences in dementia rates, and sample sizes of this age group were usually small, especially for blacks (person years for oldest old blacks: 54 in CHS, 216 in EAS and 149 in WHI; person years for oldest old whites: 532 in CHS, 820 in EAS and 166 in WHI). Therefore, further studies in the oldest old with larger sample sizes of blacks and with inferential statistical tests are warranted.

3.2 RACIAL DIFFERENCES IN MORTALITY RATE IN THE ELDERLY

Although racial differences in dementia tend to be largest among the oldest old, racial differences in all-cause mortality reverse around age 80 [115-118]. Specifically, the black-white mortality crossover refers to the elevated mortality rate in blacks relative to whites up to age 78 with an inversion of this pattern after age 78 [119]. This crossover effect is usually thought to be a product of

selective mortality, in which high mortality rates among young, disadvantaged blacks, results in a more robust group of survivors which compose the oldest old population, thus contributing to phenomenon of survival bias [120,121].

Among those aged 80 or older in the North Carolina EPESE study, blacks had significantly lower risk of all-cause mortality (HR=0.75) and of CHD mortality (HR=0.44) than whites [119]. Further analyses of elderly subjects in 4 waves showed that the adjustment of income-related terms (including income, income*race, and income*age) altered the black-white mortality crossover in men but not in women [120]. However, analyses in the Americans Changing Lives study showed that family income did not alter the black-white mortality crossover [121]. Therefore, further studies are still needed to clarify the black-white mortality crossover around oldest ages, and potential contributors with differential effects on the mortality crossover by sex should also be considered.

Although studies have repeatedly shown associations between brain structural abnormalities and mortality [122,123], previous studies on racial crossover of mortality did not account for brain structural measures. It is possible that very old blacks would have healthier brains compared to the whites of similar age, and that these differences may either explain the racial mortality crossover or be one of the results of survivor bias among very old blacks. Therefore, it is worthwhile to study whether racial differences in brain structure and function contribute to the mortality crossover in the oldest old.

What about racial differences in survival after AD or dementia diagnosis? Results of previous studies are mixed. Studies regarding survival after AD diagnosis found longer or similar survival time in elderly blacks than in whites [124,125]. Regarding racial differences in survival after dementia diagnosis, the CHS cognition study [126] suggested a shorter survival time in blacks than in whites, because demented blacks had a higher proportion of VaD than demented whites and the

median survival time for patients with VaD (3.9 years) was shorter compared to those with AD (7.1 years). However, another study conducted at Baylor Alzheimer's Disease Center [127] did not find racial differences in survival time after dementia diagnosis, which was probably due to the similar proportions of VaD among dementia patients of the two races in its sample. Therefore, racial differences in AD prevalence might be overestimated or not affected by racial differences in AD survival, while racial differences in dementia prevalence might be underestimated by shorter dementia survival in blacks than in whites.

3.3 RACIAL DIFFERENCES IN COGNITIVE FUNCTION IN THE ELDERLY

A synopsis of previous studies on racial differences in cognitive functions is included in Appendix B. Previous cross-sectional analyses consistently reported worse cognitive functions in elderly blacks than in their white counterparts [128-133]. Compared to whites of similar age, elderly blacks had lower performances in memory [128-130], in information processing speed [128,129,133], and in global cognition [128-133]. In the Chicago Health and Aging Project (CHAP), the Mini-mental State Exam (MMSE) mean score and the Symbol Digit Modalities Test (SDMT) mean score were 2.6 points (24.4 in blacks vs. 27 in whites) and 13 points (21 in blacks vs. 34 in whites) lower respectively in elderly blacks than in whites [129]. Likewise, in the Health, Aging and Body Composition Study (Health ABC), the Modified Mini-mental State Exam (3MS) mean score and the Digital Symbol Substitution Test (DSST) score were 7 points (86 in blacks vs. 93 in whites) and 14 points (28 in blacks vs. 42 in whites) lower respectively in elderly blacks than in whites [133]. Therefore, compared to racial differences in global cognition (measured by the MMSE or the 3MS), racial differences in information processing speed (measured by the SDMT or the DSST) seem to be more striking.

What about racial differences in rates of cognitive decline over time in the elderly? My literature review of longitudinal studies revealed mixed results (see Appendix B). The Texas study [131] found a much higher risk of cognitive impairment in elderly blacks than in whites (Odds Ratio=3.52, significant after multivariate adjustment). Both the Health Retirement Study (HRS) and the EPESE study observed greater declines in global cognition in blacks than in whites, but these differences were not significant [128,132]. Results of non-significant racial differences may be due to a relatively young population (mean age=60) in the HRS study, or due to the exclusion of institutionalized subjects in the EPESE study. In contrast, during four consecutive interview waves in 8 years, the study of Asset and Health Dynamics Among the Oldest Old (AHEAD) showed significantly lower rates of memory and global cognition decline in elderly blacks than in whites. Cognition in the HRS and AHEAD studies were both measured by the Telephone Interview of Cognitive Status (TICS), which has a lower reliability than cognitive tests done by face-to-face interview [134]. Moreover, institutionalized subjects were also excluded from the AHEAD study, and its attrition rate was unneglectable (about 17% between two consecutive waves) and higher in blacks than in whites. Therefore, the atypical results in the AHEAD study may arise from multiple study limitations: low reliability of the telephone cognitive test, exclusion of institutionalized subjects, and differential loss-to-follow-up bias.

Nevertheless, no studies have analyzed racial differences in the cognitive functions in the oldest old. Since racial differences in cognitive functions may be much larger in the oldest old, further studies in older populations and with more reliable and highly discriminative tests of racial differences in cognition are warranted.

3.4 RACIAL DIFFERENCES IN BRAIN STRUCTURE IN THE ELDERLY

Since cognitive functions are correlated with brain structure, racial differences in cognitive impairments may be attributable to racial differences in brain structure. A literature review (see below) of racial differences in brain structure between older blacks and whites was conducted.

In sum, older blacks seem to have lower total brain atrophy (higher brain parenchymal volume/ICV) than whites; however, the racial differences are only significant in one study in non-demented subjects [55] and not in other two studies that included demented subjects [135,136]. In addition, both relative ventricular size and sulcal width, markers of subcortical and cortical atrophy respectively, tend to be smaller in older blacks than in whites [53,55,57]. Results regarding the indicator of cerebral small vessel diseases-WMHs are quite consistent across studies. Significantly a greater relative volume of WMHs (volume of WMHs/ICV) or grade of WMHs is found in older blacks than in whites [53,55,137].

Another marker of brain ischemic lesions-infarct tends to be more prevalent in older blacks than in whites; however, the racial differences are only significant in one out of six pertinent studies [54,56,57,135,136,138]. Therefore, previous studies have shown a higher burden of WMHs and a trend of lower brain atrophy and higher infarcts prevalence in older blacks than in whites. The majority non-significant results of racial differences in brain infarcts might be due to its semi-quantitative method of infarct counting or due to the adjustment of vascular risk factors in analysis.

What about racial differences in brain structure in the oldest old? Unfortunately, It is not possible to draw any conclusions in this regard because the majority participants in previous MRI studies were young old. In the two studies with the oldest populations (mean age=80 in both studies), one found less brain atrophy and higher WMHs in blacks than in whites [55], while the other found no significant racial differences in brain atrophy, WMHs, or brain infarcts [136].

There are a number of limitations in these studies. Firstly, comparing brain MRI measures between blacks and whites was not a main objective in most studies, and hence only a few studies conducted formal statistical tests for racial differences in brain structure and very few examined these differences adjusting for other determinants of brain structure (e.g., socioeconomic and vascular risk factors). Secondly, since young old subjects have much lower dementia risk than the oldest old, racial differences in brain structure might be underestimated in previous studies because the majority of their participants were young old. Thirdly, all previous studies used 1.5-Tesla MRI scans, which have lower resolution than 3.0-Tesla MRI scans and cannot detect brain micro-structural characteristics as can DTI scans. Of note, only one study had longitudinal brain MRI data [57], but there were no formal tests of racial differences in longitudinal brain structural changes. Therefore, neuroimaging studies with MRI scans of greater resolution and DTI scans in populations older than 75 years of age are needed to clarify controversies in the literature.

3.5 LITERATURE REVIEW: RACIAL DIFFERENCES IN BRAIN STRUCTURE BETWEEN OLDER BLACKS AND WHITES

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3.5.1 Abstract

Background: The population of elderly blacks in US is projected to increase at a double rate of their white counterparts from 2010 to 2030, and they are also at a much higher risk of dementia. Racial differences in brain structure might contribute to racial differences in dementia.

Methods: Direct key words were used to search all relevant articles in "Ovid MEDLINE(R)". The algorithm to combine different key words was: 'brain' and ('MRI' or 'Magnetic Resonance' or 'DTI' or 'Diffusion Tensor') and ('white$' or 'Caucasian$') and ('black$' or 'African American$'), and the limitation 'Human' was applied. 227 articles yielded from the search algorithm, and 9 of them were chosen as the most relevant for review.

Results: In older adults, relative brain volume (brain parenchymal volume/intracranial volume) is significantly higher in blacks than in whites (1.6% higher) in only one out of three pertinent studies. Relative ventricular size or grade is significantly smaller in blacks than in whites, while sulcal width tends to be larger in blacks than in whites in the younger old (mean age < 70) but smaller in blacks than in whites in the older old (mean age ≥ 70). The relative volume or grade of white matter hyperintensities (WMHs) is significantly higher in blacks than in whites in three out of six studies, while racial differences in brain infarcts prevalence is significant (about 10% higher in blacks than in whites) in only one out of six pertinent studies.

Conclusions: Among brain macro-structural measures, only the results of racial differences in WMHs were consistent with the higher burden of vascular risks in blacks than in whites. Both brain atrophy and infarcts in older blacks show resilience to their higher burden of vascular risks compared to whites, especially in the older old.

3.5.2 Introduction

Mild cognitive impairment and dementia are two major mental health problems in the elderly (age ≥ 65). Compared to their white counterparts, blacks are at higher risks of cognitive impairment and dementia [139,140]. According to the Washington Heights-Inwood Columbia Aging Project, prevalence of dementia in the three age strata (65-74, 75-84, 85+) was 2.9%, 10.9% and 30.2% in whites, while was 9.1%, 19.9% and 58.6% in blacks [6]. Blacks were the largest minority (8.4% of 40.4 million) in the US elderly in 2010, and the population of elderly blacks was projected to increase by 114% from 2010 to 2030, as compared to an increase of 59% of their white counterpart [2].

Higher risk of cognitive impairments in blacks compared to whites should have its corresponding worse profiles in brain structure in blacks than in whites, because brain structural measures generated by Magnetic Resonance Imaging (MRI), like volumetric atrophy and white matter hyperientensities (WMHs), are associated with various cognitive functions [7,8,77]. However, up to date, racial differences between blacks and whites on brain structure are still inconclusive. Among seven studies with comparison of brain volumetric atrophy between blacks and whites, four of them did not find any significant racial differences [26,135,136,141], while other three studies [55,57,142] reported significant results. Volume of WMHs seemed to be greater in blacks than in whites in some studies [55,57,142-145], but not in others [26,135,141]. Reasons for these inconsistent results are not clear, and therefore an insightful review of these publications is necessary to clarify their seemingly inconsistent results and resolve the controversy.

This review examined racial differences between blacks and whites in brain structural measures in the elderly with or without dementia. Except for brain MRI studies, studies using Diffusion Tensor Imaging (DTI) were also searched. Results in similar populations and of similar

structural measures (brain atrophy, WMHs, and brain infarcts) were compared, and reasons for inconsistency if any were discussed. Finally, this review summarized the limitations of previous studies and provided directions for further research.

3.5.3 Methods

The database ‘Ovid MEDLINE(R) 1946 to June Week 2 2013’ was used for the literature search. Instead of mapping the key words to subheadings, the direct key words search was used to obtain all relevant articles. The first key word ‘brain’ was used, and there were 972,173 hits. The second set of key words was ’MRI’ or ‘Magnetic Resonance’ or ‘DTI’ or ‘Diffusion Tensor’, and there were 498,599 hits in total. The third set of key words was ‘black$’ or ‘African American$’, there were 158,067 hits. The fourth set of key words was ‘white$’ or ‘Caucasian$’, and there were 255,408 hits. The algorithm to combine all these results was: ‘brain’ and (‘MRI’ or ‘Magnetic Resonance’ or ‘DTI’ or ‘Diffusion Tensor’) and (‘white$’ or ‘Caucasian$’) and (‘black$’ or ‘African American$’), and the limitation ‘Human’ was applied. This ended up yielding 227 articles. Limiting publications to the last 20 years did not change the search results. We chose not to limit the age group of search as “65 years or older”, otherwise nearly half of the targeted articles would be lost. The title and abstract of each article among the 227 was read, and 9 most relevant with samples of community-dwelling older adults were chosen for review. The flow diagram for the literature search can be found in Figure 3.

3.5.4 Results

3.5.4.1 Racial Differences in Brain Atrophy

Relative brain volume (brain parenchymal volume/intracranial volume) in all three relevant studies [55,135,136] was reported slightly higher in blacks than in whites, with a racial difference ranging from 0.9% to 1.6% (Appendix D). However, racial differences were significant in only one of the three studies, and this study was done in the non-demented elderly [55]. All three studies [53,55,57] with ventricular size data reported smaller relative ventricular size or grade in blacks than in whites (two of them were significant, and one had no statistical test). There is only one relevant longitudinal study [57], and no statistical tests were performed to compare longitudinal changes in brain structure between the two races. Longitudinally, proportion of subjects with ventricular grade worsening was reported lower in black females than in white females (74% vs. 79%) but higher in black males than in white males (80% vs. 75%) during ten years of follow-up from their 60s to 70s [57]. Sulcal width was reported larger in blacks in the younger old [57] (no statistical test and mean age=62), and significantly smaller in blacks in the older old [53] (mean age=72). In ten years of follow-up of the longitudinal study [57], proportion of subjects with sulcal grade worsening was reported higher in whites (77% in females and 79% in males) than in blacks (64% in females and 63% in males).

Only two studies [55,135] have examined racial differences in volume of brain sub-regions, i.e. in hippocampus and entorhinal cortex, and none of them found significant racial differences.

3.5.4.2 Racial Differences in WMHs

Among six studies with WMHs data (Appendix D)., three studies in the older old (mean age≥72) [53,55,137] found significantly greater relative WMHs volume or higher WMHs grade in blacks than

in whites with [55,137] or without [53] adjustment of vascular risk factors. However, in other two studies [135,136] in the older old, racial differences of WMHs were not significant with [135] or without [136] multivariate adjustment. The single longitudinal study [57] found that WMHs grade was lower in black females than in white females but higher in black males than in white males at the baseline (mean age=62), whereas the proportion of subjects with WMHs grade worsening during 10 years post baseline was higher in blacks (70.0% in both females and males) than whites (56.4% in females and 50.9% in males) in both sexes. However, there was no statistical test for the racial differences in longitudinal WMHs changes.

3.5.4.3 Racial Differences in Brain Infarcts

Among six studies with brain infarcts data (Appendix D), two studies [54,57] were done in younger old cohorts (mean age=62). One found significantly higher prevalence of both brain infarcts (21% vs. 10%) and lacune (17% vs. 9%) in blacks than in whites. The other [57] reported similar infarcts incidence rates between the two races in females (21% in both races) and slightly higher incidence rate in black males than in white males (20% vs 18%); however, there were no statistical tests of racial differences in this study. All three studies [135,136,138] in the older old (mean age ≥ 72) did not find significant racial differences in prevalence of brain infarcts (25% to 31% in blacks and 30% to 31% in whites). The last study [56] in subjects of wider age range (age>55) and without stoke found that higher subclinical infarcts prevalence in blacks than in whites was more prominent in the younger (age: 55-75) than in the older (age >75) age group, i.e. significant interaction between age and race, however the main effect of race was not significant after multivariate adjustment.

3.5.5 Discussion

There is a weak trend of less brain atrophy in blacks compared to whites in the older adults, but such racial differences are only significant in some studies using different brain atrophy indices. Volume of WMHs is significantly higher in older blacks than in older whites in general, while racial differences in prevalence of brain infarcts seem to be only significant (higher in blacks) in the younger old populations (mean age < 70) and not in the older old populations (mean age ≥ 70).

Among different indices of brain atrophy, ventricular size is usually considered as a measure of subcortical brain atrophy, while sucal width is a measure of cortical atrophy. Subcortical brain atrophy is lower in blacks than in whites in the younger old [57], in the older old [53], and in the non-demented [55]. Longitudinally, there might be a qualitative interaction between sex and race in ventricular enlargement [57], however such interaction effect was not tested and hence need further study. With regard to cortical atrophy, its racial difference was reversed from the younger old [57] (higher in blacks) to the older old [53] (higher in whites), and higher rate of cortical atrophy in whites than in blacks from their 60s to 70s might account for the reversion [57]. However, such racial differences in cortical atrophy rate are not adequately studied, and the apparently higher rate of cortical atrophy in whites needs further examination.

Since both cortical and subcortical brain atrophy are lower in blacks than whites in the older old, total brain atrophy in the older old should have similar racial differences. However, only a weak trend of lower total brain atrophy in blacks was observed in the older old, suggesting the complexity of brain atrophy measured from different perspectives. Moreover, relative brain volume (brain parenchymal volume/intracranial volume), relative ventricular size, or sucal width may not be valid measures of brain atrophy, because they are all cross-sectional and are assumed

to have the same normal values in blacks and whites. In contrast, the longitudinal change in brain volume should be a better measure reflecting the "real" atrophy rate of the brain. To better assess racial differences in brain atrophy, further longitudinal data of brain MRI in biracial populations are needed.

In the older adults, blacks tend to have greater relative WMHs volume (WMHs/ICV) or higher WMHs grade than whites. WMHs is usually considered as a neuroimaging marker for small vessel diseases in white matter, and is related to vascular risk factors, like hypertension, diabetes, and stroke. Consistent with the higher burden of vascular risks in older blacks than older whites [22-25], most studies in the older old found significantly higher relative WMHs volume or grade in blacks than in whites. Moreover, such racial differences were significant even after adjustment of vascular risk factors [55,137]. Even though directions of racial differences in the 10-years rate of white matter grade are opposite between males and females in the younger old, they are higher in blacks than whites in both sexes [57]. Therefore, like the interaction between sex and race in the longitudinal ventricular enlargement, similar qualitative interaction seems to exist for WMHs in the younger old [57]. In both interactions, brain structural profiles were more favorable in blacks than in whites in females but less favorable in blacks than in whites in males, and hence older black females might be more resilient than older black males to their higher burden of vascular risks compared to older whites.

Racial differences in prevalence of brain infarcts between blacks and whites are not yet conclusive. Brain infarcts are actually brain ischemic lesions, which can be atherothrombotic or embolic, and therefore higher vascular risks in older blacks should cause higher prevalence of brain infarcts among them. However, there are no significant racial differences in the older old [135,136,138], and the over adjustment of vascular risk factors may only account for part of the reasons

[136]. Actually, significant racial differences in brain infarcts prevalence (higher in blacks) are only found in one younger old study cohort [57], and there are similar infarcts incidence in the two races longitudinally. Therefore, non-significant racial differences in brain infarcts in the older old are not consistent with the higher vascular risk burdens in blacks compared to whites, which may be due to the selection bias in MRI studies in the older old. The older old with severer brain infarcts may be less likely to participate or more likely to die before ancillary MRI studies, and therefore only those without severe brain infarcts or with mild brain infarcts were enrolled in ancillary MRI studies.

3.5.6 Conclusions

In sum, among the three major brain macro-structural measures, only the results of racial differences in WMHs are consistent with the higher vascular risk burden in blacks than in whites in older adults. Both brain atrophy and infarcts in older blacks show resilience to their higher burden of vascular risks, especially in the older old. Therefore, vascular pathogenesis should not be the only mechanism considered for the racial differences in brain structure, and other mechanisms of brain structural impairments should also be examined in further studies. For example, there might be different aging physiology and neurological degeneration processes between blacks and whites. Moreover, racial differences of brain structure characteristics need to be explored with higher resolution methodologies to capture more subtle differences in micro-structure and also to explore the spatial distribution of such differences. Comparison of brain MRI measures between blacks and whites was not a main objective of most studies, and only some of the studies had statistical tests of racial differences in brain MRI measures, and did not formally test for confounding of socioeconomic status and vascular risk factors. Another limitation of

previous studies is that for the most part they were cross-sectional analyses. Longitudinal brain structural changes are more preferable than cross-sectional measures to study the underlying mechanisms of racial differences.

Therefore, racial differences in brain structure between older blacks and whites are not conclusive to a great extent, and further studies, especially longitudinal studies, to systematically compare brain structure measures between the two races are needed. Moreover, in addition to vascular pathogenesis, further studies should also explore other pathophysiological mechanisms to explain the racial differences in brain structure.

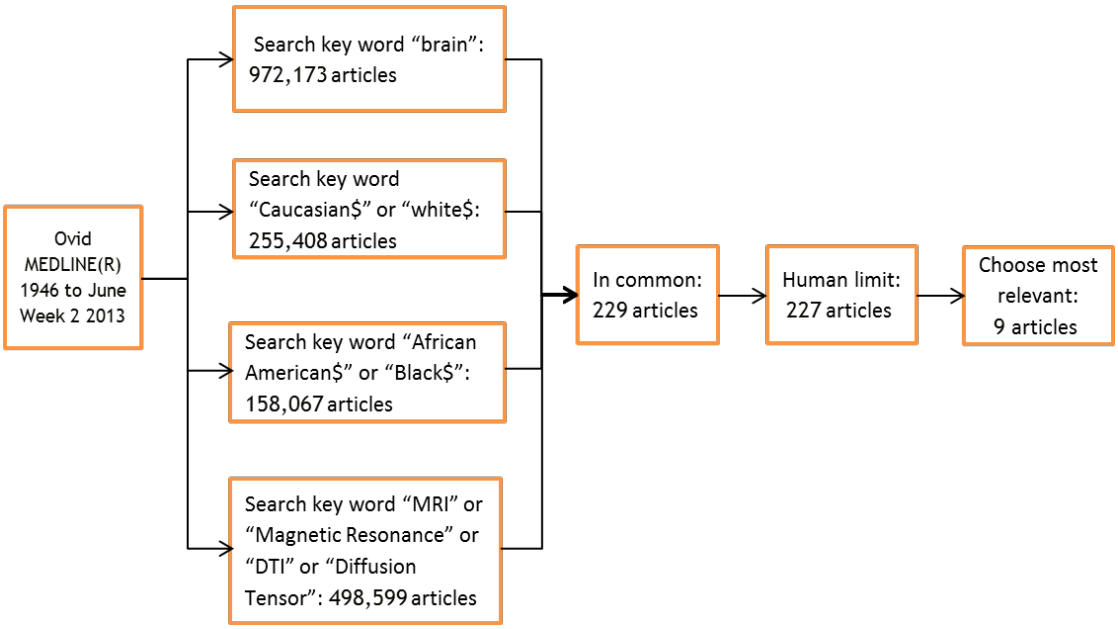

Figure 3 Flow chart of literature search in Ovid MEDLINE

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3.6 RACIAL DIFFERENCES IN VASCULAR RISK FACTORS IN THE ELDERLY

Previous studies have consistently found higher hypertension rates or blood pressure, higher diabetes rates or glucose levels, higher high-density lipoprotein cholesterol (HDL-C), lower triglyceride levels, and lower levels of physical activity in blacks than in whites [22-25]. Moreover, such racial differences exist in both young and older populations. However, conclusions about racial differences in smoking, drinking, body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), and total cholesterol have been less consistent. This may be because of a higher heterogeneity in behavioral and dietary habits across study populations.

Overall, hypertension and diabetes are among the most important vascular risk factors for brain structural and cognitive impairments. According to the National Health and Nutrition Examination Survey (NHANES) during 1999-2004 [146], prevalence of hypertension in those aged 60-69 was 18% (74.2% vs. 56.0%) higher in black wen than in white men, and was 26% (84.1% vs. 58.4%) higher in black women than in white women; prevalence of hypertension in those aged ≥ 70 was 20% (83.4% vs. 63.3%) higher in black men than in white men, and was 4% (83.1% vs. 78.8%) higher in black women than in white women (Figure 4). According to the National Health Interview Survey (NHIS) in 2011 [147], prevalence of diabetes in those aged 65-74 was 8% (30.7 % vs. 22.8 %) higher in black men than in white men, and was 13% (31.2% vs. 18.4%) higher in black women than in white women; prevalence of diabetes in those aged ≥ 75 was 16% (38.1 % vs. 21.7 %) higher in black men than in white men, and was 9% (25.9% vs. 16.6%) higher in black women than in white women (Figure 4).

Therefore, racial differences in hypertension and diabetes exist in both young old and older old populations, although they become less evident for women. In regard to racial differences in vascular risk factors in the oldest old, there is a paucity of data and statistical reporting. Therefore,

it remains to be studied whether a higher prevalence of diabetes and hypertension still exists in the oldest old blacks than in whites.

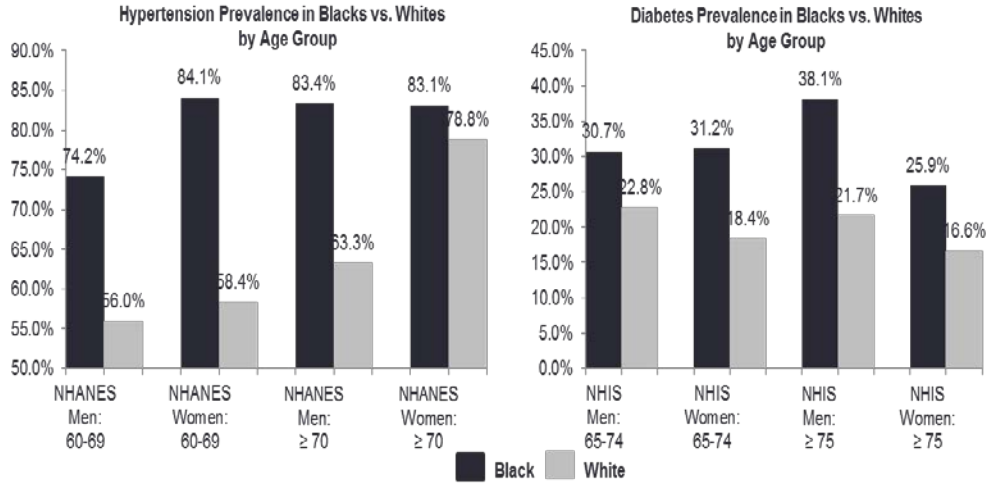

Figure 4 Prevalence of hypertension and diabetes by race and age group in the NHANES and NHIS studies

4.0 SUMMARY OF LITERATURE REVIEW AND GAPS IN KNOWLEDGE

The key results of this literature review on racial differences in dementia, cognition, hypertension and diabetes are summarized in Table 2. In general, elderly blacks have a higher burden of dementia and cognitive impairments than their white counterparts. However, available data on racial differences in dementia incidence and/or cognitive decline may be affected by methodological differences in the studies, including relatively young study populations, exclusion of institutionalized subjects, less reliable ascertainment of dementia or cognition, and differential loss-to-follow-up bias.

Racial differences in dementia prevalence and incidence in the oldest old tend to be larger than in the younger old; however, racial differences in dementia incidence in the oldest old might be modified by sex, because some studies observed lower dementia incidence in oldest old black women than in white women. **Due to the small sample sizes of oldest old blacks (N<60), it is still premature to draw any conclusions for this age group.** Since the oldest old, especially the oldest old blacks, bear the highest burden of cognitive impairments in the population, **further studies with larger sample sizes of oldest old blacks and more reliable assessment of dementia and cognition are warranted.**

What can explain the higher burden of cognitive impairments in elderly blacks than in whites? Previous MRI and DTI studies have shown consistent associations between brain macro- or micro- structural measures and cognitive functions. However, results regarding racial differences in brain structure are still inconclusive. Even though elderly blacks have a higher burden of WMHs than their white counterparts in various studies, racial differences in brain atrophy and infarcts seem to be non-significant. Non-significant findings in previous MRI studies

may be due to their young old study populations and low resolution brain images. **Therefore, further brain MRI studies with older subjects from both races and high-resolution images are needed.** Even though brain micro-structural integrity measures generated by DTI are better predictors of cognitive functions than brain MRI measures, no studies have employed DTI scans to detect racial differences in brain micro-structural integrity. **Racial differences in brain micro-structural characteristics need to be explored with higher resolution methodologies to capture more subtle differences in micro-structure and also to explore the spatial distribution of such differences.**

Previous studies have also suggested a vascular pathogenesis for both brain macro- and micro-structural impairments. Elderly blacks have a higher burden of vascular risk factors, like hypertension and diabetes, than elderly whites. Therefore, the higher burden of vascular risk factors might contribute to the higher burden of WMHs and other brain structural impairments in elderly blacks than in whites, and finally lead to their higher dementia risk and worse cognitive functions. Nonetheless, previous studies have also shown the resilience of brain atrophy in older blacks to their higher burden of vascular risk factors because there is a trend of higher relative total brain volume, smaller relative ventricular size, and narrower sulcus in older blacks than in whites. **Therefore, vascular pathogenesis may not be the only mechanistic pathway for the racial differences in brain structure, so other mechanisms of brain structural impairment should also be examined to explain racial differences in brain structure.** For example, brain aging pathology and neurological degeneration process might be different in elderly blacks and whites.

Since the oldest old tend to have the largest racial differences in cognitive impairments, it is worthwhile to investigate any racial differences in brain structure in this age group. However, most previous studies were done in the young old, and there is a lack of data about racial

differences in vascular risk factors, brain structure, and cognition in the oldest old. Moreover, only some studies had statistical tests of racial differences in brain MRI measures, or formally tested for confounding of socioeconomic status and vascular risk factors. **Therefore, studies integrating state of the art neuroimaging, with extensive characterization of vascular risk factors and the socio-economic status of oldest old blacks and whites are warranted.** Also, considering that dementia incidence tends to be lower in the oldest old black women than in white women, the oldest old black women may be a particularly resilient group to be investigated.

Another limitation of previous MRI studies is that for the most part they were cross-sectional and did not examine each of the three main contributors to dementia, which was outlined in Figure 2, including brain structural abnormalities, vascular risk factors, and socioeconomic status. **Further longitudinal MRI studies that examine each of these components are more preferable than cross-sectional studies to reveal the underlying mechanisms of racial differences in dementia.**

Table 2 Summary of racial differences in dementia, cognition, hypertension, and diabetes

Race/Sex	Dementia prevalence	Dementia incidence (per 100 PYs)	Global cognition and processing speed	Rate of cognitive decline	Prevalence of hypertension	Prevalence of diabetes
Black:	NMAP: 9.1% in 65-74, 19.9% in 75-84, 58.6% in ≥ 85;	WHI (4-year AD incidence): 1.7% in 65-74, 4.4% in 75-84, 11.4% in ≥ 85; EAS (4-year): 0.50% in 70-74, 2.53% in 75-84, 8.34% in ≥ 85;	TICS score in HRS: 8.7 TICS score in AHEAD: 3.5 points lower than whites SPMSQ score in EPES: one point lower than whites MMSE score in CHAP: 24.4 SDMT score in CHAP: 21.09 3MS score in HABC: 86.0 DSST score in HABC: 27.9	TICS score in HRS: declined 0.04 more in blacks every 2 year, but not significant*. TICS score in AHEAD: declined 0.06 less in blacks each year than in whites (p-value*<0.05). SPMSQ score in EPES: declined one point more than whites over 3 years, but not significant. Cognitive decline (SPMSQ decline ≥ 2) in Texas study: higher odds of cognitive decline in blacks (OR*=3.52, CI:2.85-4.35)	NOMAS (mean age=69): 78%	NOMAS (mean age=69):22%
White:	NMAP: 2.9% in 65-74, 10.9% in 75-84, 30.2% in ≥ 85;	WHI (4-year AD incidence): 0.4% in 65-74, 2.6% in 75-84, 4.2% in ≥ 85; EAS (4-year): 0.53% in 70-74, 1.89% in 75-84, 5.86% in ≥ 85;	TICS score in HRS: 9.5 MMSE score in CHAP: 27.0 SDMT score in CHAP: 34.08 3MS score in HABC: 93.0 DSST score in HABC: 41.5		NOMAS (mean age=69): 63%	NOMAS (mean age=69):12%
Black Men:	EPESE: 5.0% in 65-74, 10.5% in 75-84, 11.5% in ≥ 85;	EPESE (3-year): 4.4% in 65-74, 8.1% in 75-84, 23% in ≥ 85;			NHANES 1999-2004 (aged 60-69): 74.2% NHANES 1999-2004 (aged ≥ 70): 83.4%	NHIS 2001 (aged 65-74): 30.7 % NHIS 2001 (aged ≥ 75): 38.1 %

Table 2 Continued

Race/Sex	Dementia prevalence	Dementia incidence (per 100 PYs)	Global cognition and processing speed	Rate of cognitive decline	Prevalence of hypertension	Prevalence of diabetes
		CHS (5.4-year): 2.11% in 65-74, 5.64% in 75-84, 40.39% in ≥ 85;				
White Men:	EPESE: 3.5% in 65-74, 5.1% in 75-84, 7.2% in ≥ 85;	EPESE (3-year): 0.1% in 65-74, 6.0% in 75-84, 4.7% in ≥ 85; CHS (5.4-year): 1.37% in 65-74, 3.57% in 75-84, 8.43% in ≥ 85;			NHANES 1999-2004 (aged 60-69): 56.0%) NHANES 1999-2004 (aged ≥ 70): 63.3%	NHIS 2001 (aged 65-74): 22.8 % NHIS 2001 (aged ≥ 75): 21.7 %
Black Women	EPESE: 2.8% in 65-74, 13.5% in 75-84, 10.8% in ≥ 85;	EPESE (3-year): 2.4% in 65-74, 8.3% in 75-84, 4.4% in ≥ 85; CHS (5.4-year): 1.82% in 65-74, 5.08% in 75-84, 8.66% in ≥ 85;			NHANES 1999-2004 (aged 60-69): 84.1% NHANES 1999-2004 (aged ≥ 70): 83.1%	NHIS 2001 (aged 65-74): 31.2% NHIS 2001 (aged ≥ 75): 25.9%
White Women:	EPESE: 1.7% in 65-74, 10.1% in 75-84, 11.9% in ≥ 85;	EPESE (3-year):: 7.9% in 65-74, 11.2% in 75-84, 12.8% in ≥ 85; CHS (5.4-year): 1.04% in 65-74, 4.24% in 75-84, 10.82% in ≥ 85;			NHANES 1999-2004 (aged 60-69): 58.4% NHANES 1999-2004 (aged ≥ 70): 78.8%	NHIS 2001 (aged 65-74): 18.4% NHIS 2001 (aged ≥ 75): 16.6%
*Adjusted by socioeconomic status and health-related conditions. NOMAS=North Manhattan Study						

5.0 PROPOSAL OF NEW STUDIES

5.1 STUDY OBJECTIVES AND HYPOTHESES

This proposal aimed to address these limitations, and would test for racial differences using neuroimaging data obtained with a very high resolution methodology in a cohort of very old (age ≥ 80 years) blacks and whites, for whom extensive characterizations of socioeconomic status, cardiovascular diseases, cognitive functions, and other health-related conditions were obtained ten years prior to and four years post the baseline brain MRI scans. Moreover, follow-up brain MRI and dementia adjudication data are also available for these very old participants 3 years after the baseline MRI visit. This approach would allow for a systematic comparison of brain structural characteristics between very old blacks and whites in a longitudinal setting, and also to explore other mechanisms beyond the vascular pathway that may explain the racial differences in brain structural changes.

The overall study hypotheses are as follows:

1. Compared to very old whites, very old blacks have lower cognitive functions and worse brain structural profiles; lower cognitive functions in very old blacks can be explained by their worse brain structural profiles.

2. Compared to very old whites, very old blacks have higher burden of vascular risk factors; worse brain structural profiles in very old blacks can be explained by their higher burden of vascular risk factors.

5.2 STUDY POPULATION

The Health ABC study is a prospective observational study of older adults aimed at characterizing body composition and its relationship to physical changes with age. 3075 well-functioning black and white community-dwelling older adults were recruited from a sample of white Medicare beneficiaries selected at random and all age-eligible black residents in designated ZIP code areas in and around Memphis, Tennessee and Pittsburgh, Pennsylvania between March 1997 and July 1998. The inclusion criteria were: 70-79 years old, not having any self-reported difficulty in walking one quarter mile, walking up 10 steps, or performing basic activities of daily living. Persons with a life-threatening cancer or plans to move out of the area within 3 years were excluded. Therefore, subjects in the Health ABC study were healthier than the general population of similar ages, in terms of physical functioning and mobility.

During 2006-2007, 819 Health ABC study subjects were seen at the Pittsburgh site, and among them 339 were eligible and willing to participate in the HBP study (Figure **5**). The inclusion criteria of the HBP study were: able to walk without assistance, completed the 6-meter walking test, and eligible for a MRI. In the end, 314 underwent 3-T brain MRI exams, and 283 had complete DTI data. Therefore, compared to the general population of similar ages, subjects in the HBP study should be healthier in terms of walking performance.

Compared to the 1.5-Tesla MRI, the 3.0-Tesla sequence enables a higher signal-to-noise ratio, which provides a more accurate volumetric quantification. Mean diffusivity of gray matter and fractional anisotropy of white matter measure the micro-structural integrity of normal appearing brain tissues respectively. Moreover, extensive data were also collected for cognitive functions and vascular risk factors in this study. Since about 40% of the 314 subjects scanned with 3.0-Tesla brain MRI are blacks, this sample provides a unique chance of detecting racial differences in brain macro- and micro-structural characteristics, cognitive impairments, and vascular risk factors between very old blacks and whites.

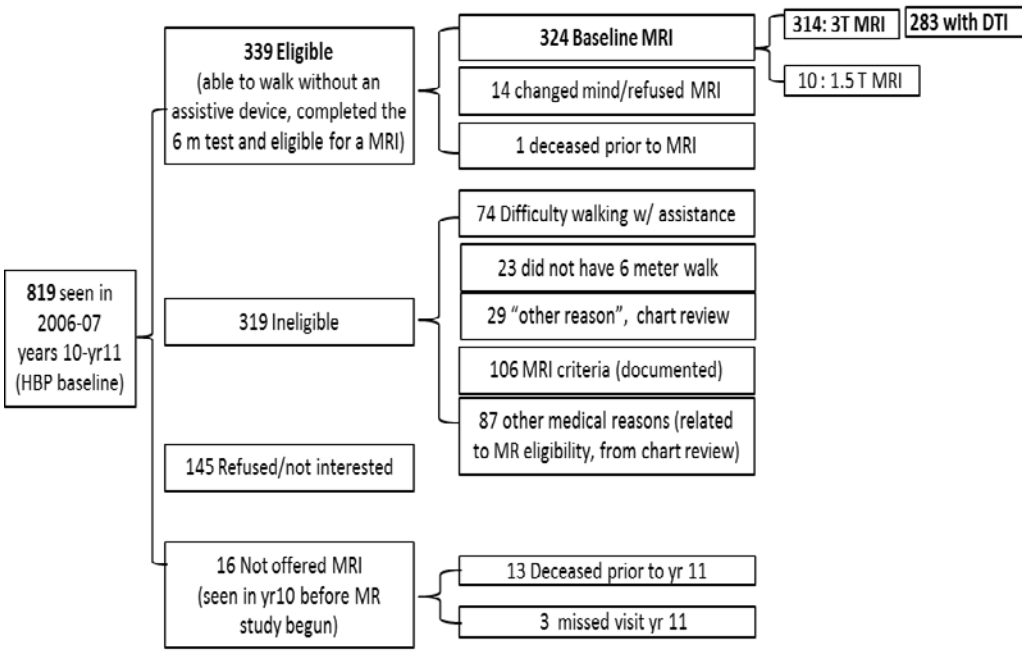

Figure 5 Flow chart of subject enrollment in the Healthy Brain Project

5.3 MEASURES OF COGNITIVE FUNCTIONS

The Modified Mini-Mental State Exam (3MS) is a revised version of the Mini-Mental State Exam (MMSE) [148], and is recognized as a valid tool for dementia screening in the general population [149].

Teng reported its test-retest reliability ranging from 0.91 to 0.93, and with a cutting score of 79/80 it had a sensitivity of 91% and a specificity of 97% for dementia [150]. Moreover, the 3MS test has better reliability and validity for dementia or cognitive impairment compared to the MMSE test [149]. The scoring range of the 3MS test (0 to 100 points) is much wider than the MMSE test (0 to 30 points), and meanwhile both have strongly skewed distribution. A study in Canada [151] reported a median score of 85 in the overall elderly (age ≥ 65 years) and of 72 in the oldest old (age ≥ 85 years) respectively, and also found less ceiling effect in the 3MS test than in the MMSE test.

Digit Symbol Substitution Test (DSST) is a pencil-and-paper test of psychomotor performance in which participants are given a key grid of number and matching symbols and a test section with numbers and empty boxes. The completion time is 90 seconds, and the score is the number of correct number-symbol matches, which can range from 0 to 100. DSST is very simple to administer and has high test-retest reliability [152]. It measures not only information processing speed, but also executive function, working memory, and visuo-spatial attention [153]. Moreover, the adjustment of DSST can explain aging-related cognitive declines in memory and executive function [153,154], both of which are commonly impaired in dementia. Lower DSST scores predicted higher incidence of dementia in 6.5 years after baseline in the elderly [155].

5.4 NEW STUDY: WHITE MATTER HYPERINTENSITIES, GRAY MATTER INTEGRITY AND COGNITION IN OCTOGENARIAN BLACKS AND WHITES

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5.4.1 Abstract

Objective: To quantify racial differences in brain macro-and micro-structure in a cohort of octogenarians, and to examine whether these differences would contribute to racial differences in cognition.

Methods: A cross-sectional study of 283 adults 79-89 years old (59.4% white; 42.0% women) with data on white matter hyperintensities (WMH), gray matter atrophy (GMA) and diffusion tensor imaging of normal appearing white and gray matter (fractional anisotropy and mean diffusivity). Standardized betas (sβ) of race predicting cognition (digit symbol substitution test (DSST), modified mini-mental state test (3MS)) and neuroimaging markers were computed in multivariable regression models adjusted for age, sex, literacy, smoking, drinking, income, hypertension and diabetes. Bootstrapping was applied to test the hypothesis that neuroimaging markers would mediate racial differences in cognition.

Results: In multivariable models, black race was associated with lower DSST (sβ=-.18, p=.01), lower 3MS (sβ=-.15, p=.004) and higher WMH (sβ=.15, p=.045), but also with lower mean diffusivity (i.e. higher gray matter micro-structural integrity, sβ=-.14, p=.047). WMH and mean diffusivity were each inversely associated with DSST (sβ=-.17, p=.008, sβ=-.20 p=.003) and 3MS (sβ=-.17, p=.004, sβ=-.16, p=.011); however, only mean diffusivity significantly changed the racial differences in DSST and 3MS, while WMH did not.

Conclusions: Among adults who survive to very old age, higher microstructural integrity of gray matter in blacks may contribute to reduce racial differences in cognition. Future studies should examine whether higher microstructural integrity of gray matter is a characteristic of blacks

surviving to very old age, and whether maintaining their microstructural integrity would reduce racial disparities in cognition.

5.4.2 Introduction

Racial differences in dementia represent an urgent public health problem, though the underlying neural correlates are poorly understood. Neuroimaging studies have yielded inconsistent or indirect evidence for these neural correlates. Several studies have found no significant racial differences in gray matter volume or white matter hyperintensities [56,135,136,138,156]. Other studies report that blacks are more likely to have severe white matter lesions and greater subclinical brain infarcts as compared to whites,[53,54] but one study reported lower brain atrophy in blacks compared to whites.[55]

Lower cardiometabolic health and socioeconomic status in blacks than in whites have been suggested as explanatory factors of racial disparities in cognition, but this evidence is also inconsistent. A recent longitudinal study of cognitively normal adults aged ≥ 65 years concluded that reducing ethnic disparities in diabetes could reduce racial differences in incident dementia by 17%.[157] Conversely, in another study of community-dwelling adults aged ≥ 70 years,[158] racial differences in cognition were not explained by stroke, hypertension, or diabetes. Furthermore, studies of racial disparities in dementia have seldom applied objective neuroimaging measures. Many studies have relied on crude visual ratings of neuroimaging markers of macro-structural brain integrity, not accounting for micro-structural abnormalities in the brain's parenchyma.

In the current investigation, we integrate neuroimaging markers of micro- and macro-structure in elderly blacks and whites aged 79 to 89, who have been extensively characterized as part of the Health, Aging and Body Composition study over the ten years preceding brain imaging. The goal is to identify potential contributing factors to racial differences in cognition. Specifically, we quantify the relative contribution of neuroimaging markers to performance on the mini-mental state examination test, which has been previously used as a marker of dementia in this cohort [159]

and on the digit symbol substitution test, a well-established indicator of dementia, disability and mortality.[155,160,161]

5.4.3 Methods

5.4.3.1 Subjects

Participants of the Health, ABC study have been seen at regular intervals at the Pittsburgh site from 1997-98 to 2011-12. Of the 1,527 participants enrolled in the study in 1997-98 at the Pittsburgh site, 819 were alive and 586 of these were invited in 2006-07 to participate in the Healthy Brain Project (HBP), a neuroimaging study of cognition and mobility, whereas the other 233 were not invited because they were walking with a cane and/or did not have mobility performance measures and/or they had been hospitalized for major clinic events in the previous 3 months (fracture, psychiatric problem). Among the 586 invited to the study, 99 were ineligible for a brain MRI, 145 were not interested or refused and 342 were eligible and interested. Of these, 283 were included in this study who had complete data on Diffusion Tensor Imaging (DTI) obtained via 3 Tesla magnet. This study was approved by the institutional review boards of the University of Pittsburgh and the University of Tennessee, Memphis, and that of the Coordinating Center, the University of California San Francisco. All participants signed a written informed consent.

5.4.3.2 Demographic, Cardiometabolic Conditions, and Behavioral Risk Factors

Prevalent disease variables were computed at the time of MRI for coronary heart disease (CHD), hypertension, myocardial infarction, stroke and diabetes using data collected since study entry in 1997-98. CHD was determined through self-report or *Health Care Financing Administration (HCFA)* data of myocardial infarction, angina, bypass or angioplasty. Determination of

cardiovascular disease included self-reported CHD, cerebrovascular disease or HCFA report of stroke. Study participants with average sitting systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg concurrently or before the year of MRI were classified as hypertensive.

Myocardial infarction was determined through coronary heart disease history and myocardial event during Health ABC follow-up. Stroke was determined through self-reported stroke, transient ischemia attack, or carotid endarterectomy. Diabetes mellitus status was determined through self-report, use of hypoglycemia medication, a fasting glucose of ≥126 mg/dl, or a 2-hour glucose tolerance test ≥ 200mg/dl, in accordance with the American Diabetes Association criteria in 2002.

Age was calculated as number of years from date of birth to the MRI date. Body mass index was calculated as weight (kg)/height^2(m) at the HBP baseline. Education and family income were collected in the Health ABC study 1997-98, and were dichotomized at >high school education and at ≥ 25,000 dollars annually. Health literacy was quantified in 2006 using the score from the Rapid Estimate of Adult Literacy in Medicine, and was dichotomized at literacy level ≥ 9th grade. Serum creatinine, smoking status, drinking status, and physical activities (kcal/kg/week, including walking and stairs climbing) were collected in the Health ABC study in 2006 or 2007, whichever was concurrent with year of MRI scanning.

5.4.3.3 Cognitive Assessment

The DSST was administered to all participants at regular intervals from study entry to time of MRI in 2006-07 according to a protocol previously described.[161] The DSST is a pencil-and-paper test of psychomotor performance[162], in which the subject is given a key-grid of numbers and matching symbols and a test section with numbers and empty boxes. The test consists of filling in as many empty boxes as possible with a symbol matching each number. The testing time is 90 seconds. The score is the number of correct number-symbol matches. The strategy to solve the DSST consists of sequential encoding and retrieval of numbers and matching symbols. Short-term memory, perceptual organization, visuomotor coordination, and selective attention are important factors that determine performance. The DSST has high test-retest reliability.[163]

The modified mini-mental state examination (3MS) was administered to all participants at regular intervals from study entry to time of MRI. The 3MS is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory.[148] Possible scores range from 0 to 100, with higher scores indicating better cognitive function.

5.4.3.4 Magnetic Resonance Imaging Protocol and Summary Measures

Participants were scanned with a Siemens 12-channel head coil on a 3-T Siemens Tim Trio MR scanner at the Magnetic Resonance Research Center of the University of Pittsburgh, using a previously published protocol [164-166]. Details on measurements of white matter hyperintensities (WMH), gray matter volume, intracranial volume (ICV) and diffusion tensor (mean diffusivity and fractional anisotropy) have been previously published [165].

WMH volume was obtained from T2-weighted FLAIR image using an automated method. Total WMH volume was estimated by summing all voxels classified as WMH and normalized for

total brain volume. WMH was highly skewed (skewness = 2.4), thus, log transformed values were used (skewness = -.49).

Gray matter volume was calculated by segmenting the skull-stripped T1-weighted image in native anatomical space using the FAST-FMRIB's Automated Segmentation Tool [167]. The total gray matter volume was estimated in cubic millimeters by summing all gray matter voxels. Total ICV was computed as the volume contained within the 'inner skull' using the brain extraction tool [168]. Brain atrophy index was computed as: (ICV - total gray matter volume) / ICV.

Mean diffusivity was obtained from the diffusion weighted images as an average magnitude of molecular motion or measure of cell structure damage [169]. DTI data was pre-processed using the FMRIB's Diffusion Toolbox [170] to remove eddy current distortions, and the tensors were computed and diagonalized to determine the eigenvalues from which mean diffusivity (MD) maps were computed. Following automated segmentation of white matter, gray matter, and cerebrospinal fluid obtained from the T1-weighted images, MD maps were restricted to normal appearing gray matter. Voxels with an MD > 1.3×10^{-3} mm^2/s were removed from the MD maps to reduce any confounding partial volume effect induced from cerebrospinal fluid.

5.4.4 Statistical Analysis

All sample characteristics were tested for racial differences using chi-squared tests for dichotomous and t-tests for continuous variables. Due to the skewed distribution of 3MS, WMH, physical activity, and serum creatinine, medians and inter-quartile ranges were calculated, and median tests were used to test for racial differences. Analyses with 3MS were conducted with both raw 3MS and transformed 3MS (square root of (100-3MS)). Log transformed WMH was used in all analyses.

Slopes of DSST and 3MS were computed for blacks and whites separately, using data obtained at all available time points in 1997-98 (study entry), 1999-2000, 2001-2002, 2004-2005, and 2006-2007 (time at which the MRI was obtained). Racial differences in rate of decline were tested using the interaction term between visit year and race in mixed effects models.

To test for racial differences in cognitive tests scores at time of MRI and in neuroimaging markers, linear regression models were constructed with race as the main independent variable, adjusted for variables that are known to be related to race, cognition and neuroimaging: age, sex, literacy, smoking, drinking, income, hypertension and diabetes. To quantify the contribution of the neuroimaging markers in explaining the racial difference in cognition, ANCOVA models with cognitive test scores as the dependent variables, race as the main independent variable, and age, sex, literacy, smoking, drinking, income, hypertension, and diabetes as covariates were constructed. Then a neuroimaging marker differing by race was added to the ANCOVA model, and the race coefficient and its significance were compared before and after the adjustment of the neuroimaging marker. The mediation effects of neuroimaging markers on racial differences in cognition were further tested using the method proposed by Preacher and Hayes (2008).

To appreciate the potential clinical relevance of the neuroimaging markers differing by race, multivariable linear regression models with DSST or 3MS as the dependent variable and a neuroimaging marker as the main independent variable were examined separately for blacks and whites. The association between the neuroimaging marker and the cognitive test score was tested after adjusting for age, sex, literacy, smoking, drinking, income, hypertension and diabetes.

Rate of cognitive decline were computed for blacks and whites in HBP separately, using 3MS and DSST data obtained at all available time points in 1997-98 (study entry), in 1999-2000, in 2001-2002, in 2004-2005 and in 2006-07 (time at which the MRI was offered). Racial

differences in rate of decline were tested using the interaction term of time by race in mixed effect models.

Exploratory analyses to address selection bias included all participants who returned for the clinic visit in 2006-07 at the Pittsburgh site, and compared population characteristics in those included in the HBP to those not included. Linear regression models were built with population characteristics as dependent variable, and race, cohort (e.g. included in HBP or not), and the interaction of race by cohort as covariates. A significant interaction between race and cohort would be interpreted as an indication that racial differences in cognitive function among those included in the HBP were different from racial differences among those not included in the HBP.

5.4.5 Results

Compared to whites, blacks consisted of more women, reported fewer years of education, lower health literacy and lower family income, but were of similar age (Table 3). Racial differences in cardiometabolic conditions indicated a higher cardiometabolic burden in blacks compared to whites; however, these differences were only significant ($p<0.05$) for diabetes and body mass index, not for other measures (Table 3).

In multivariable models adjusted for age, sex, literacy, smoking, drinking, income, hypertension and diabetes (Table 4), black race was associated with significantly lower DSST, lower 3MS and higher WMH but also with lower MD, indicating higher gray matter integrity. Racial differences in gray matter atrophy or fractional anisotropy were not significant ($p>0.05$ for both).

The associations between black race with lower DSST and 3MS were robust to adjustment for WMH and MD (Table **5**), and were also independent of other covariates. In HBP subjects,

racial differences in DSST were similar at study entry and at time of MRI (Figure 6), and cognitive declines over time were also similar in blacks compared to whites (p=0.1933 for time by race interaction in the mixed effect model). However, racial differences in 3MS were smaller at study entry than at time of MRI (Figure **7**), and cognitive declines over time were faster in blacks compared to whites (p=0.002 for time by race interaction in the mixed effect model).

Mediation models testing the explanatory role of neuroimaging measures on racial differences in cognition indicated that MD significantly suppressed the racial differences in 3MS (indirect effect=0.5119; 95% CI=0.1469, 1.1390) and DSST (indirect effect=1.3880; 95% CI=0.4502, 2.6882). By contrast, WMH did not significantly mediate or suppress the racial differences in 3MS (indirect effect=-0.1397; 95% CI=-0.5014, 0.0501) or DSST (indirect effect=-0.3489; 95% CI=-1.2398, 0.1269).

Further study of the association between neuroimaging measures and cognitive tests stratified by race revealed that the associations of higher MD and higher WMH with lower DSST and lower 3MS were stronger for blacks than for whites (Table **6**) after adjustment for age, sex, literacy, smoking, drinking, income, hypertension and diabetes.

Exploratory analyses to address selection bias showed that participants included in this study were more likely to be white, male, and have higher DSST and 3MS scores compared to the entire group of participants alive at time of the study (Table **7**). Moreover, racial differences in DSST and 3MS in HBP subjects were similar to those observed in the parent cohort at time of MRI (interaction terms of race by cohort for DSST and 3MS: p=0.47 and 0.84, respectively).

5.4.6 Discussion

In this study of very old adults living in the community, blacks who survived to a very old age had greater micro-structural gray matter integrity compared to whites of similar age, and such greater microstructural integrity appeared to explain at least some of the racial differences in cognition. Moreover, greater micro-structural gray matter integrity was related to higher cognitive scores in blacks but not in whites, even after accounting for other risk factors for lower cognition. If confirmed, these results would suggest that gray matter microstructure may be protective against cognitive decline for blacks displaying exceptional survival. Longitudinal studies are warranted to determine whether gray matter micro-structure buffers the negative impact of macro-structural brain characteristics on dementia risk.

Diffusion tensor imaging of gray matter has been used to uncover micro-structural abnormalities, otherwise undetectable on conventional imaging. Specifically, mean diffusivity of gray matter increases with old age,[87,88] development of Alzheimer's, and mild cognitive impairment.[80,171] Higher mean diffusivity of gray matter may indicate loss of neurons, dendrites, and enlargement of extracellular space[84] in normal appearing gray matter. Given that the progression of structural brain abnormalities can be delayed by interventions on cardiometabolic risk factors late in life,[172-175] addressing micro-structural abnormalities prior to macro-structural damage may substantially impact the development of dementia in blacks, especially for those who survive to a very old age.

While the determinants of gray matter micro-structural integrity are largely unknown, some evidence suggests that diabetes[20,176] is related to lower gray matter micro-structural integrity. Exploratory analyses of the factors potentially contributing to mean diffusivity in this sample

confirm these associations (Figure **8**). Given the higher prevalence of cardiometabolic conditions in blacks compared to white, blacks would be expected to have lower micro-structural integrity. However, in our sample, the higher micro-structural integrity in blacks compared to white (e.g. lower mean diffusivity) was robust to adjustment to cardiometabolic conditions. Micro-structural abnormalities may accumulate over a long period time, whereas our measurements of cardiometabolic factors mostly extended to ten years prior to the neuroimaging measurements. It is possible that measurement of risk factors in mid-life would be more helpful to explain the racial differences in mean diffusivity hereby observed. Higher gray matter micro-structural integrity in blacks may also be a result of survival bias. The black participants of this sample appear to have survived to an exceptionally old age compared to 75 years of life expectancy at birth according to the national vital status reports 2010. Although we cannot completely rule out this possibility, survival bias existed in both very old blacks and very old whites, and there is no evidence of greater survival bias in HBP blacks than in HBP whites (results not shown).

Our finding of racial disparities in DSST and 3MS is congruent with previous research.[136] Severity of cognitive decline in our sample was also similar to those observed of the parent cohort[165] However, contrary to prior reports of accelerated cognitive decline in blacks compared to whites[131], we found no racial differences in cognitive decline as measured via DSST (Figure 6). One possibility is that higher micro-structural integrity in blacks offsets an otherwise accelerated decline. Recently, higher DSST has been shown to be a marker of longevity among a predominantly white cohort ($\geq$ 65 years old) with a high burden of WMH.[160] Therefore, the implications of preserved microstructural integrity for exceptional longevity should also be explored.

Together, this study provides novel findings regarding racial differences in cognition and neuroimaging markers. However, the cross-sectional nature of this study limited our ability to determine whether longitudinal changes in gray matter integrity are paralleled by improved or stabilized cognitive performance. In addition, DSST provides a narrow index of cognitive function. Future work should include a more comprehensive neuropsychological assessment. In sum, these findings support future work with multi-ethnic samples which examine longitudinal change in gray matter micro-structural integrity with multiple assessments cognitive performance.

Table 3 Population characteristics stratified by race. N (%) is reported unless noted otherwise

Population characteristics	White (n =168)	Black (n =115)	p--Value[b]
Demographic factors			
Age (year), mean (SD)	83.2 (2.84)	82.7 (2.68)	0.20
Gender, female	84 (50)	79 (69)	0.001
Psychosocial factors			
Health literacy: ≥ 9th grade	150 (94)	72 (67)[d]	<.001
Education: >high school	101 (60)[d]	44 (38)	<.001[c]
Family income: ≥ 25K annual	99 (69)	36 (34)[d]	<.001[c]
Cardiometabolic conditions			
Diabetes[a]	35 (20)	41 (35)[d]	0.005[c]
Cardiovascular diseases[a]	47 (28)[d]	36 (31)	0.60[c]
Hypertension[a]	134 (80)	98 (86)	0.20
Coronary heart disease[a]	38 (22)[d]	29 (25)	0.60[c]
Myocardial infarction[a]	25 (15)[d]	20 (17)	0.60[c]
Stroke[a]	14 (8)	11 (9)	0.70
Body mass index (kg/m^2), mean (SD)	26.7 (4.02)[d]	28.6 (4.77)	<.001
Serum creatinine (mg/dL), median (IQR)	0.98 (0.84, 1.16)[d]	1.03 (0.87, 1.17)[d]	0.10[c]
Lifestyle and other factors			
Smoker, ever	77 (46)[d]	57 (50)[d]	0.60[c]
Drinker, current	106 (66)	34 (31)[d]	<.001[c]
Physical activity (kcal/kg/week), median (IQR)	2.7 (0.8, 7.4)	1.7 (0.4, 4.8)	0.10
ApoE, presence of allele 4	32 (29)	36 (23)[d]	0.20[c]

Abbreviations: IQR=inter--quartile range; SD=standard deviation

[a]*Prevalence at time of MRI.*

[b]*p--Values were calculated from median test for 3MS, physical activities and serum creatinine, from student's t--test for other continuous variables, and from Chi--squared test for categorical variables*

[c]*Statistically significant (p<0.05) differences between males and females in the whole sample.*

[d]*Statistically significant (p<0.05) differences between males and females within each race.*

Table 4 Brain structural measures and cognitive test scores stratified by race

	White (n =168)	Black (n =115)	P Value[c]
Brain structural measures:			
White matter hyperintensities [a], median (IQR)	0.0032 (0.0010, 0.0067)[e]	0.0041 (0.0011, 0.0124)	0.045
Gray matter atrophy [b], mean (SD)	0.72 (0.021)	0.72 (0.025)	0.5
Mean diffusivity, mm^2s^{-1}, mean (SD)	1.32 (0.106)	1.28 (0.114)	0.047
Fractional anisotropy, mean (SD)	0.36 (0.013)	0.36 (0.015)	0.26
Cognitive tests:			
Digit symbol substitution test (DSST), points, mean (SD)	40 (12.56)	32 (13.49)	0.01
Modified mini--mental state score (3MS), median (IQR), points	96 (93, 98)	91.5 (86, 96)	0.004

Abbreviations: IQR=inter--quartile range; SD=standard deviation

[a]*White matter hyperintensities: total volume of white matter hyperintensities/total brain volume.*

[b]*Gray matter atrophy: (intracranial volume--gray matter volume)/ intracranial volume.*

[c]*p-Values were calculated from linear regression models adjusted for age, sex, literacy, smoking, drinking, income, hypertension and diabetes.*

Table 5 Linear regression models with race as the main independent variable and digit symbol substitution test (DDST) score and modified mini-mental state exam (3MS) score as dependent variables

Model	Independent variable	Standardized coefficient (unstandardized coefficient, standard error), p value	
		DSST	3MS*
1	Race	-.18 (-4.97, 1.90), p=.01	-.15 (-2.11,.87), p=.017 (0.004)
2	Race	-.16 (-4.28, 1.89), p=.03	-.13 (-1.76,.87),p=.044 (0.011)
	White matter hyperintensities	-.17(-3.55, 1.33), p=.008	-.17 (-1.78,.61), p=.004 (0.033)
3	Race	-.21 (-5.74, 1.89), p=.003	-.18 (-2.41,.87), p=.006 (0.001)
	Mean diffusivity	-.20 (-23.60, 7.84), p=.003	-.16 (-9.32,3.63), p=.011 (0.028)

All models were adjusted for age, sex, literacy, smoking, drinking, income, hypertension, and diabetes.
** p values in parentheses are from models using root square of (100-3MS) as dependent variables*

Table 6 Linear regression models stratified by race with neuroimaging markers as the main independent variables and digit symbol substitution test (DDST) score and modified mini-mental state exam (3MS) score as dependent variables

Model	Independent variable	Standardized coefficient (unstandardized coefficient , standard error), p value for DSST		Standardized coefficient (unstandardized coefficient , standard error), p value* for 3MS	
		Blacks	Whites	Blacks	Whites
1	Mean diffusivity	-.20 (-21.68,12.43), p=.09	-.20 (-24.08,10.92), p=.03	-.19 (-11.84, 6.18), p= .27 (.06)	-.14 (-7.18,4.71), p= .13 (.10)
2	White matter hyperintensities	-24 (-4.07,1.74), p=.02	-.10 (-2.49,2.15), p=.30	-.22 (-2.20,.86), p=.01 (.01)	-.10 (-1.03,.92), p= .27 (.20)

All models were adjusted for age, sex, literacy, smoking, drinking, income, hypertension and diabetes.

** p-values in parentheses are from models using root square of (100-3MS) as main independent variables*

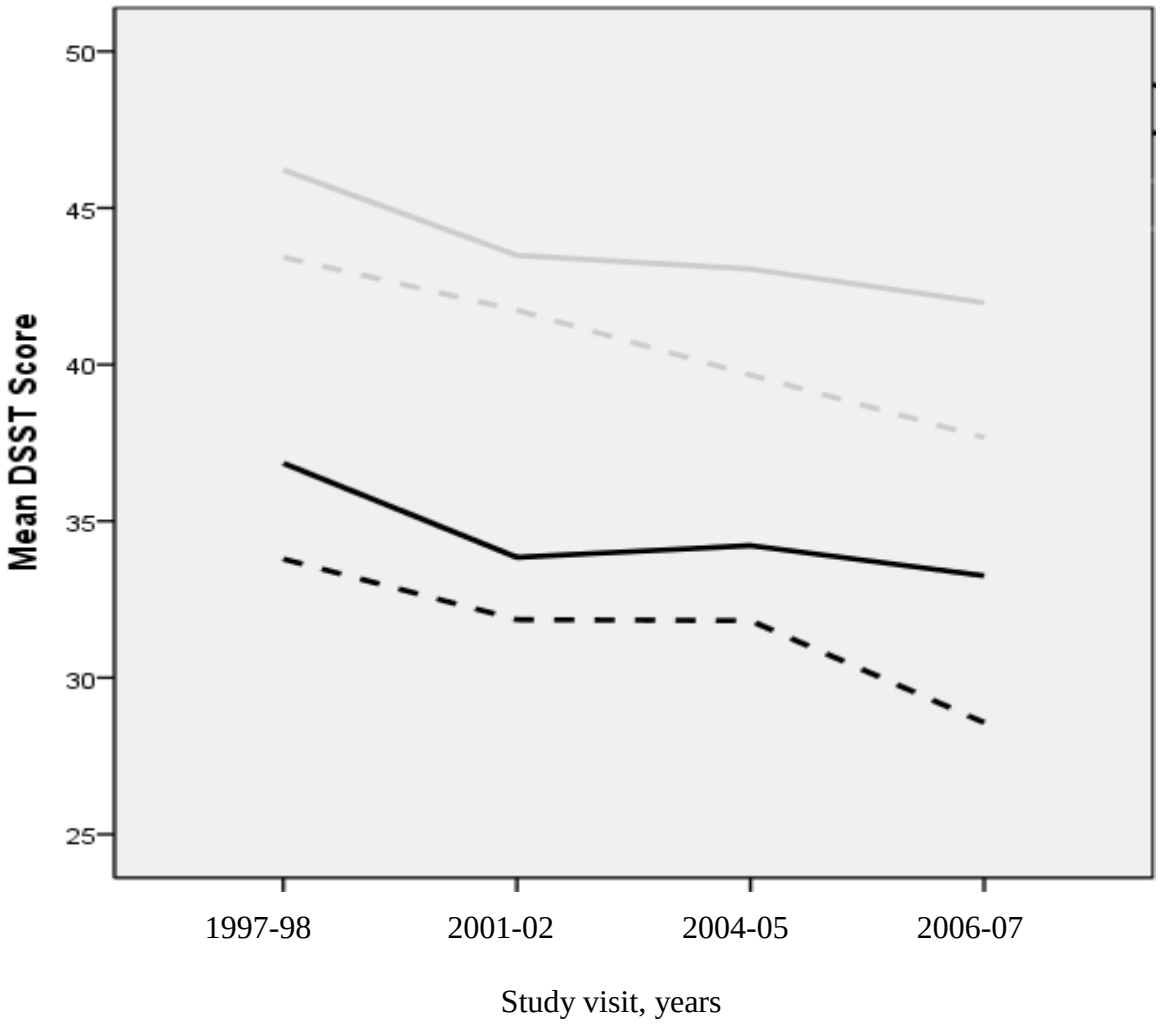

Figure Legend: Black lines represent black participants and gray lines represent white participants. The solid lines represent participants in the Healthy Brian Projects (HBP); the dashed lines represent Health, Aging, and Body Composition Study (HABC) participants who were seen during 2006-07 at the Pittsburgh site but were not enrolled in the HBP study.

Figure 6 Mean scores of Digit Symbol Substitution Test (DSST) by study subgroup over time

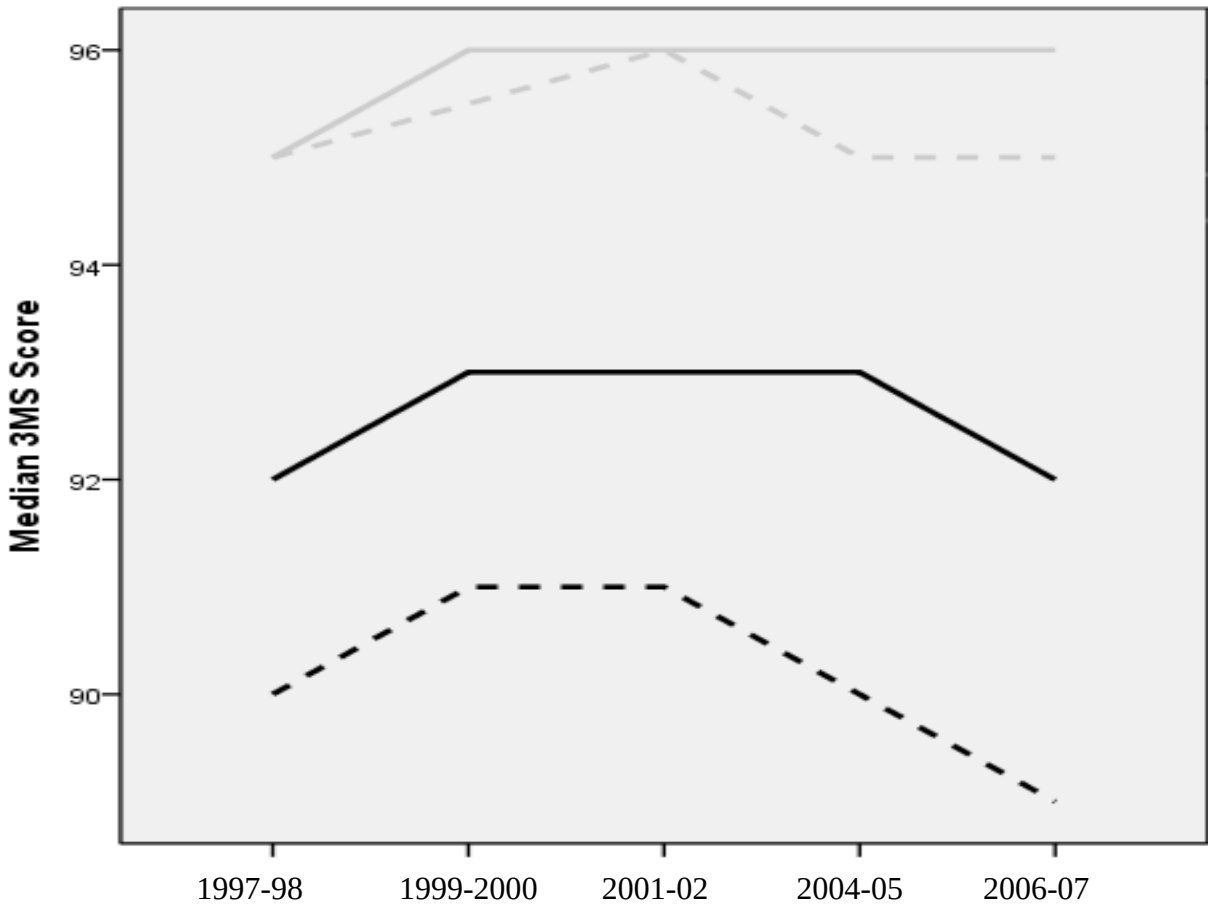

Figure Legend: Black lines represent black participants and gray lines represent white participants. The solid lines represent participants in the Healthy Brian Projects (HBP); the dashed lines represent Health, Aging, and Body Composition Study (HABC) participants who were seen during 2006-07 at the Pittsburgh site, but were not enrolled in the HBP study.

Figure 7 Median scores of Modified Mini-mental State Exam (3MS) by study subgroup over time

Table 7 Characteristics of 2006-07 cohort (n=819), MRI cohort (n=314), and those not enrolled (n=505)

	N=819	N=314	N=505 (819-314)	P-value[a]: N=314 vs. N=505
Age, year, mean (SD)	82.4 (2.81)	82.0 (2.75)	82.6 (2.82)	0.0017
Male, n (%)	385 (47.01)	133 (42.36)	252 (49.9)	0.0354
White race, n (%)	530 (64.71)	187 (59.55)	343 (67.92)	0.0148
Education: > high school, n (%)	424 (51.83)	161 (51.44)	263 (52.08)	0.8584
Modified Mini-mental Score (3MS), median (IQR)	91.4 (7.94)	92.4 (7.41)	90.8 (8.21)	0.0235
Digit Symbol Substitution test (DSST),, mean (SD)	35.9 (13.31)	38.3 (12.63)	34.4 (13.52)	<.0001
Diabetes, n (%)	207 (25.31)	78 (24.84)	129 (25.6)	0.8093
Hypertension, n (%)	580 (70.82)	213 (67.83)	367 (72.67)	0.1386
Systolic blood pressure, mmHg , mean (SD)	134.3 (20.41)	134.6 (18.4)	134.1 (21.59)	0.7258
Diastolic blood pressure, mmHg , mean (SD)	69.1 (10.41)	69.4 (9.8)	68.9 (10.78)	0.4687
Body mass index, kg/m^2, mean (SD)	27.7 (4.7)	27.4 (4.5)	27.9 (4.81)	0.1509

Abbreviations: IQR=inter-quartile range, SD=standard deviation

[a] p-Values were calculated from median test for 3MS, from student's t-test for other continuous variables, and from Chi-squared test for categorical variables

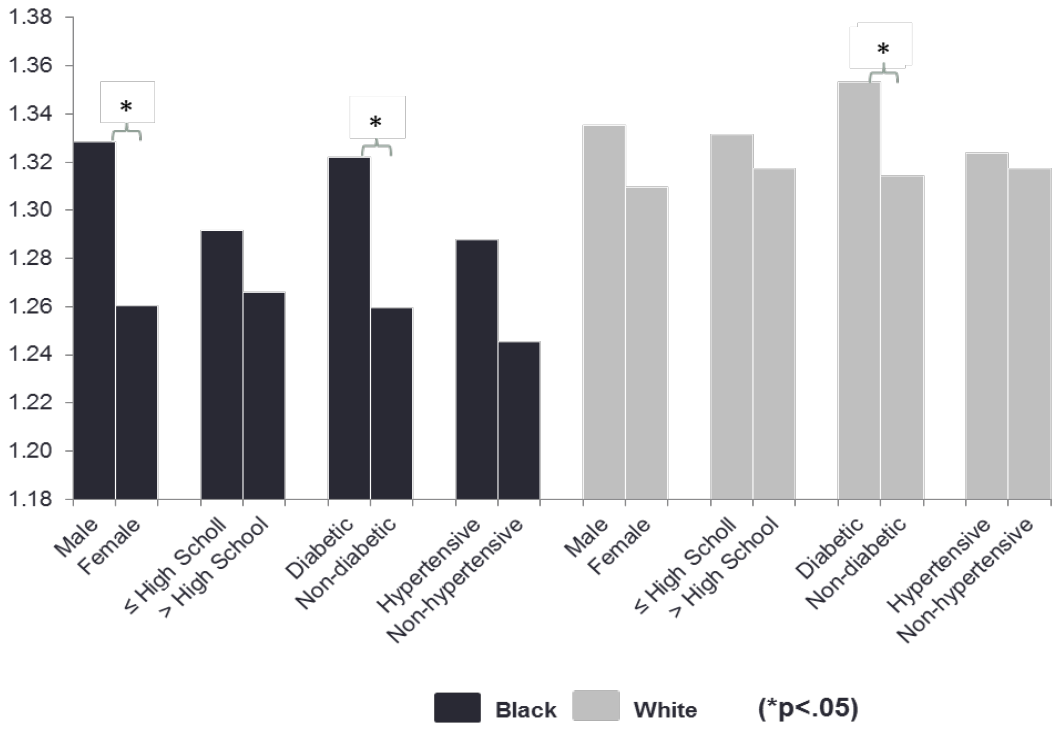

Figure 8 Mean diffusivity stratified by population characteristics and race, and significant associations indicated by asterisks

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6.0 FURTHER ANALYSES AND DISCUSSION

6.1 FURTHER ANALYSES STRATIFIED BY SEX

To explore whether racial differences in brain structure differ by sex, Table 8 described age-adjusted racial differences in brain imaging markers stratified by sex. Racial differences in gray matter atrophy and fractional anisotropy were still non-significant within either sex. However, white matter hyperintensities were significantly greater in black men than in white men, and racial differences in mean diffusivity were only significant in women but not in men. Therefore, previous results of lower mean diffusivity in blacks than in whites were actually driven by lower mean diffusivity in black women than in white women.

To study potential reasons for better gray matter integrity in the black woman of the HBP study as compared to the white women, Table 9 compared a variety of health-related conditions between black and white women in the HBP study at the Health ABC study baseline and at the HBP study baseline respectively.

As shown in Table 9, black women had lower level of health literacy, higher prevalence of hypertension and diabetes, higher prevalence of cardiovascular disease (CVD) and coronary heart disease (CHD), higher BMI, lower 3MS and DSST scores, and higher percentage of ApoE allele 4 carriers. All these racial differences indicated worse health conditions in black women than in white women. The only possible factors that might explain the results of racial differences in gray matter integrity in women are the current drinking rate and the triglyceride level, which are both lower in black women than in white women. However, the correlations between mean diffusivity and triglyceride level or current drinking status were not significant ($p>0.2$) in the HBP women.

Therefore, none of the health-related conditions examined in Table 9 explained the racial differences in gray matter microstructural integrity in women.

Table 8 Age-adjusted racial differences in brain imaging markers stratified by sex

	Men					Women				
	White (n =84)		Black (n =36)		p-value	White (n =84)		Black (n =79)		p-value
	LSmean*	SE	LSmean*	SE		LSmean*	SE	LSmean*	SE	
Mean diffusivity	0.00133	0.000011	0.00134	0.000016	0.887	0.00131	0.000011	0.00126	0.000012	0.006
Fractional anisotropy	0.362	0.0015	0.359	0.0024	0.307	0.356	0.0014	0.355	0.0015	0.894
Gray matter volume/ intracranial volume	0.278	0.0026	0.273	0.0040	0.368	0.282	0.0024	0.285	0.0024	0.376
ln(white matter hyperintensities)	-6.56 (0.00142)^	0.137	-6.02 (0.00243)^	0.208	0.033	-6.01 (0.00245)^	0.138	-6.32 (0.00180)^	0.142	0.115

*LSmeans are age adjusted least square means of outcome variable in the two races in ANCOVA models constructed for each gender
^Retransformed value of the LSmean to its raw scale.

Table 9 Characteristics of HBP women subjects by race at the Health ABC study baseline and at the HBP baseline

	HABC Baseline			HBP Baseline		
Sample Characteristics	White (n =96)	Black (n =85)	p-Value*	White (n =96)	Black (n =85)	p-Value*
Age (year), mean (SD)	72.8 (2.63)	72.8 (2.69)	0.9803	82.8 (2.67)	82.8 (2.74)	0.9235
Education: >high school, n (%)	46 (47.92)	33 (38.82)	0.2183	46 (47.92)	33 (38.82)	0.2183
Health Literacy: ≥ 9th grade, n (%)	87 (93.55)	61 (76.25)	**0.0013**	87 (93.55)	61 (76.25)	**0.0013**
Prevalent hypertension, n (%)	40 (42.11)	49 (57.65)	**0.0373**	70 (72.92)	67 (79.76)	0.2826
Prevalent diabetes, n (%)	5 (5.21)	11 (12.94)	0.0674	15 (15.63)	24 (28.24)^	**0.0395**
Prevalent CVD, n (%)	9 (9.47)	19 (22.89)	**0.0142**	18 (18.75)	27 (31.76)	**0.0432**
Prevalent CHD, n (%)	5 (5.26)	12 (14.46)	**0.0373**	11 (11.46)	21 (24.71)	**0.0197**
Smoker, n (%)	33 (34.38)	35 (41.18)	0.3457	33 (34.38)	35 (41.18)	0.3457
Current Drinker, n (%)	61 (63.54)	29 (34.12)	**<.0001**	54 (61.36)	20 (25.32)	**<.0001**
Body mass index (kg/m2), mean (SD)	25.7 (4.04)	29.1 (5.4)	**<.0001**	26 (4.21)	28.8 (5.09)	**<.0001**
SBP (mmHg), mean (SD)	135.6 (21.37)	139.7 (19.73)	0.1796	138.6 (20.76)	132.9 (16.52)	**0.0475**
DBP (mmHg), mean (SD)	71.2 (9.65)	74.6 (10.25)	**0.0241**	70.4 (10.69)	68.4 (10.06)	0.2006
Fasting TC (mg/dL), mean (SD)	216.7 (36.04)	221.2 (41.26)	0.4518	208.1 (40.16)	203.4 (46.09)	0.4845
Fasting TG (mg/dL), median (IQR)	122 (96, 152)	106 (79, 138)	**0.0100**	109.5 (81, 153)	92 (74.5, 142)	0.0646
Fasting LDL (mg/dL), mean (SD)	126.7 (33.13)	133.4 (37.01)	0.2090	120.5 (33.7)	120.8 (41.84)	0.9685
Fasting HDL (mg/dL), mean (SD)	62.5 (16.34)	63.6 (16.99)	0.6803	61.3 (17.53)	61.4 (14.01)	0.9739
IL-6, (mg/dL), median (IQR)	1.4 (0.9, 1.9)	1.5 (1, 2.4)	0.4456	2.0 (1.4, 3.6)	2.5 (1.7, 4.8)	**0.0372**
ApoE, presence of allele 4, n (%)	21 (22.11)	32 (39.51)	**0.0121**	21 (22.11)	32 (39.51)	**0.0121**
3MS, points, median (IQR)	95 (91, 97)	92 (88, 96)	**0.0207**	96 (93, 98)	93 (88, 97)	**0.0031**
DSST, points, mean (SD)	46.2 (10.2)	38.3 (12.81)	**<.0001**	39.9 (12.78)	33.8 (13.76)	**0.0028**

*p-Values were calculated from t-test for continuous variables, from Chi-squared test for categorical variables, and from median test for 3MS and IL-6

6.2 SELECTION BIAS IN THE HBP STUDY

As shown in Figure **5**, only 41% (339 out of 819) of those who were seen at the Pittsburgh site of the Health ABC study in 2006-07 were recruited by the HBP study. It is possible that subjects enrolled in the HBP study were healthier than those not enrolled, and hence the results of racial differences in brain structure in the HBP study were biased. To examine potential selection bias in the HBP study, we compared characteristics of the HBP subjects with those not enrolled in the HBP study and who were seen in 2006-07 (Table **10**) at the Pittsburgh site. Compared to those not enrolled, HBP subjects were 0.6 years younger, 7.5% more likely to be women, 8.4% more likely to be blacks, had 2 points higher median 3MS score and 3.9 points higher mean DSST score. However, there were no significant differences in education, hypertension, diabetes, BMI, or walking speed. Compared to the inter-quartile range or standard deviation, selection bias in 3MS or DSST was relatively small. Therefore, we did not find substantial selection bias in the recruitment of the HBP study from the Health ABC study. It seems unlikely that differences in health characteristics between those included and those excluded would have impacted the results of racial difference in brain structure in the HBP study.

In addition, Table **11** and Table **12** illustrate results of similar analyses of selection bias in blacks and in whites separately. HBP black subjects had higher cognitive function test scores and faster walking speed than black subjects not enrolled, and HBP white subjects had better cognitive functions and younger age than white subjects not enrolled. Further analyses showed that selection bias in 3MS or DSST did not differ by race ($p>0.50$ for the interaction term of race by HBP inclusion). Therefore, we did not find differential selection bias by race in the HBP study.

Table 10 Characteristics of Health ABC subjects seen at the Pittsburgh site during 2006-07 (n=819), those enrolled in the MRI study (n=314), and those not enrolled (n=505)

	Subjects seen at the Pittsburgh site during 2006-07	Subjects enrolled in the HBP study	Subjects not enrolled in the HBP study	P-value: N=314 vs. N=505
	N=819	N=314	N=505	
Age, year, mean (SD)	82.4 (2.81)	82.0 (2.75)	82.6 (2.82)	**0.0017**
Male, n (%)	385 (47.01)	133 (42.36)	252 (49.9)	**0.0354**
White Race, n (%)	530 (64.71)	187 (59.55)	343 (67.92)	**0.0148**
Education: > high school, n (%)	424 (51.83)	161 (51.44)	263 (52.08)	0.8584
3MS, median (IQR)	94 (88, 97)	95 (89, 97)	93 (87, 97)	**0.0235***
DSST, mean (SD)	35.9 (13.31)	38.3 (12.63)	34.4 (13.52)	**<.0001**
Diabetes, n (%)	207 (25.31)	78 (24.84)	129 (25.6)	0.8093
Hypertension, n (%)	580 (70.82)	213 (67.83)	367 (72.67)	0.1386
SBP, mmHg , mean (SD)	134.3 (20.41)	134.6 (18.4)	134.1 (21.59)	0.7258
DBP, mmHg , mean (SD)	69.1 (10.41)	69.4 (9.8)	68.9 (10.78)	0.4687
BMI, kg/m^2, mean (SD)	27.7 (4.7)	27.4 (4.5)	27.9 (4.81)	0.1509
Walking speed, m/sec, mean (SD)	1.39 (0.341)	1.41 (0.342)	1.36 (0.339)	0.0561

*p-value was obtained from the median test.

Table 11 Characteristics of Health ABC black subjects seen at the Pittsburgh site during 2006-07 (n=289), those enrolled in the MRI study (n=127), and those not enrolled (n=162)

	Black subjects seen at the Pittsburgh site during 2006-07	Black subjects enrolled in the HBP study	Black subjects not enrolled in the HBP study	P-value: N=127 vs. N=162
	N=289	N=127	N=162 (289-127)	
Age, year, mean (SD)	82 (2.74)	81.8 (2.61)	82.2 (2.83)	0.1902
Male, n (%)	109 (37.72)	42 (33.07)	67 (41.36)	0.1491
Education: > high school, n (%)	106 (36.68)	50 (39.37)	56 (34.57)	0.4005
3MS, median (IQR)	90 (84, 95)	92 (86, 95)	89 (82, 94)	**0.0381***
DSST, mean (SD)	30.5 (13.4)	33.3 (12.83)	28.2 (13.47)	**0.0014**
Diabetes, n (%)	101 (34.95)	43 (33.86)	58 (35.8)	0.7308
Hypertension, n (%)	230 (79.58)	97 (76.38)	133 (82.1)	0.2311
SBP, mmHg , mean (SD)	135 (20.6)	134.5 (18.64)	135.4 (22.06)	0.7306
DBP, mmHg , mean (SD)	70 (10.88)	69.5 (10.3)	70.3 (11.33)	0.5189
BMI, kg/m^2, mean (SD)	28.9 (5.21)	28.5 (4.7)	29.3 (5.57)	0.2288
Walking speed, m/sec, mean (SD)	1.3 (0.33)	1.3 (0.32)	1.2 (0.33)	**0.0341**

*p-value was obtained from the median test.

Table 12 Characteristics of Health ABC white subjects seen at the Pittsburgh site during 2006-07 (n=530), those enrolled in the MRI study (n=187), and those not enrolled (n=343)

	White subjects seen at the Pittsburgh site during 2006-07	White subjects enrolled in the HBP study	White subjects not enrolled in the HBP study	P-value: N=187 vs. N=343
	N=530	N=187	N=343 (530-187)	
Age, year, mean (SD)	82.5 (2.83)	82.1 (2.84)	82.8 (2.81)	**0.0072**
Male, n (%)	276 (52.08)	91 (48.66)	185 (53.94)	0.2456
Education: > high school, n (%)	318 (60.11)	111 (59.68)	207 (60.35)	0.8801
3MS, median (IQR)	95 (91, 98)	96 (92, 98)	95 (90, 97)	**0.0378***
DSST, mean (SD)	38.8 (12.32)	41.7 (11.32)	37.2 (12.58)	**<.0001**
Diabetes, n (%)	106 (20.04)	35 (18.72)	71 (20.76)	0.5745
Hypertension, n (%)	350 (66.04)	116 (62.03)	234 (68.22)	0.1505
SBP, mmHg , mean (SD)	133.9 (20.32)	134.6 (18.28)	133.4 (21.36)	0.5282
DBP, mmHg , mean (SD)	68.6 (10.12)	69.4 (9.47)	68.2 (10.45)	0.2009
BMI, kg/m^2, mean (SD)	27 (4.25)	26.7 (4.21)	27.3 (4.27)	0.1276
Walking speed, m/sec, mean (SD)	1.4 (0.33)	1.5 (0.34)	1.4 (0.33)	0.0727
*p-value was obtained from the median test.				

Is it possible that the higher gray matter integrity in blacks than in whites in the HBP study was due to a higher proportion of "healthy" subjects among blacks? We calculated the proportion of "healthy" subjects stratified by race, based on different definitions of "healthy" (absence of cerebrovascular risk factors, including hypertension, diabetes, cardiovascular disease, stroke, smoking, and drinking) in Table 13. The white subjects in the HBP study consistently had significantly higher proportions of "healthy" subjects than the black subjects. Therefore, racial differences in the proportion of "healthy" subjects do not explain racial differences in gray matter integrity hereby observed.

Table 13 Comparisons of proportion of "healthy' subjects between blacks and whites in the HBP study

Healthy Status	White (n =187)	Black (n =127)	p-Value
Without hypertension or diabetes	55 (29.41)	20 (15.87)	0.0059
Without hypertension, diabetes, cardiovascular disease, and stroke	43 (22.99)	14 (11.11)	0.0075
Without hypertension, diabetes, cardiovascular disease, and stroke, and non-smoker and not current drinker	21 (11.23)	6 (4.72)	0.0436

There remains the possibility that the Health ABC subjects represent a unique population, because of the inclusion criteria of the parent study. To address this question, we compared these participants to very old survivors in the CHS study. The CHS cohort was a sample of individuals aged 65 years or olders from Medicare eligibility lists of four communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. We compared health-related conditions between HBP subjects and 79-89 years old survivors in 1999-2000 (10 years after the baseline visit in 1989-1990) of the CHS study, and stratified the results by race (Table 14). Compared to very old Year 10 survivors of the CHS study, HBP subjects had higher cognitive test scores, higher education level, and higher hypertension or diabetes prevalence. According to the national survey data (NHANES 1999-2004 and NHIS 2001) in Table 2, prevalence of hypertension was about 84% and 71% in blacks and in whites older than 70, and prevalence of diabetes was about 32% and 19% in blacks and in whites older than 75. Therefore, prevalence of hypertension or diabetes in the HBP study was close to the national survey data, while prevalence in the CHS study might be underestimated by only using self-reported data in the analyses. Actually, the 3MS scores in the HBP study were close to older subjects without dementia in the Cardiovascular Health Study Cognition Study [177]. Therefore, the

HBP subjects may represent very old subjects with high levels of education and cognitive function. Therefore, caution should be paid when generalizing the results of racial differences in brain structure to other study populations.

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Table 14 Comparisons of racial differences in health-related conditions between HBP subjects and those 79-89 years of age at Year 10 of the CHS study

Sample Characteristics	HBP White (n =187)	CHS White (n =1258)	p-Value*	HBP Black (n =127)	CHS Black (n =196)	p-Value*
Age (year), mean (SD)	83.1 (2.86)	82.6 (2.85)	**0.0275**	82.8 (2.73)	82.8 (2.87)	0.8836
Male, n (%)	91 (48.66)	529 (42.1)	0.0883	42 (33.07)	59 (30.1)	0.5740
3MS, median (IQR)	96 (93, 98)	93 (84, 97)	**<.0001**	92 (87, 96)	83 (71, 93)	**<.0001**
DSST, mean (SD)	39.7 (12.51)	35.9 (12.88)	**0.0002**	32.5 (13.28)	24.8 (11.74)	**<.0001**
College education, n (%)	111 (59.68)	500 (39.7)	**<.0001**	50 (39.37)	46 (23.5)	**0.0023**
Prevalent hypertension, n (%)	150 (80.65)	586 (47.2)	**<.0001**	105 (84)	118 (60.8)	**0.0026**
Prevalent diabetes, n (%)	41 (21.93)	145 (11.7)	**<.0001**	46 (36.22)	50 (25.9)	**0.0489**
Body mass index (kg/m^2), mean (SD)	26.7 (4.03)	25.4 (4.09)	**<.0001**	28.5 (4.78)	27.6 (5.56)	0.1177
Former or Current Smoker, n (%)	85 (45.5)	591 (48.3)	0.4706	64 (50.4)	88 (47.6)	0.6237

*p-Values were calculated for the differences between HBP subjects and CHS subjects within each race, using t-test (continuous variables), median test (3MS), or chi-squared test (categorical variables).

6.3 SURVIVAL BIAS IN THE HEALTH ABC STUDY

Since all HBP subjects were older than 79, it is possible that higher gray matter integrity in blacks than in whites was due to greater survival bias (as measured by differences between survivors and non-survivors at baseline) in blacks than in whites. To study potential survival bias between those who came back to the Health ABC visits during 2006-07 and those who did not, and to study whether such survival bias was similar between blacks and whites, Table 15 and Table 16 compare baseline characteristics of Health ABC subjects who were seen and those who were lost to follow-up during 2006-07 by race and sex. Linear regression or logistic regression models were constructed for continuous or categorical health related conditions respectively, with health-related condition as outcome, race (black vs white), survival (survivor vs. non-survivor), and race*survival interaction as covariates. P-values of the race*survival interaction term in the models were shown in the last column of the two tables, which indicate whether the survival bias in health-related conditions significantly differed by race.

In men of both races (Table 15), survivors had younger mean age (difference in white: 1 year; in black: 0.7 year), higher rate of college education (difference in white: 8.2%; in black: 14.2%), higher 3MS median score (difference in white: 1 point; in black: 3 points), higher DSST mean score (difference in white: 5.0 points; in black: 5.2 points), lower rate of smoker (difference in white: 9.5%; in black: 8.0%), lower rate of pulmonary disease (difference in white: 5.0%; in black: 6.0%), and faster walking speed (difference in white: 0.1 m/sec; in black: 0.1 m/sec), as compared to those who were lost to follow-up. In addition, in whites, survivors had lower rate of diabetes (difference: 6.1%) and higher mean BMI (difference: 0.5 kg/m2), and in blacks, survivors

had lower rate of cardiovascular disease (difference: 11.3%). However, in the regression models for all these health-related conditions, none of the race*survival interaction terms was significant. Therefore, there is no evidence that survival bias differ by race in the Healthy ABC men during 2006-07.

In women of both races (Table 16), survivors had younger mean age (difference in white: 0.8 year; in black: 1.1 year), higher rate of college education (difference in white: 7.2%; in black: 11.1%), higher 3MS median score (difference in white: 2 points; in black: 4 points), higher DSST mean score (difference in white: 4.3 points; in black: 6.0 points), lower rate of cardiovascular disease (difference in white: 6.3%; in black: 10.0%), lower mean systolic blood pressure (difference in white: 2.9 mmHg; in black: 5.1 mmHg), and faster walking speed (difference in white: 0.1 m/sec; in black: 0.1 m/sec), as compared to those who lost to follow-up. In addition, in whites, survivors had lower rate of smoker (difference: 10.0%), higher rate of current drinker (difference: 9.3%), higher mean BMI (difference: 0.7 kg/m2), and in blacks, survivors had lower rate of diabetes (difference: 10.2%), lower rate of hypertension (difference: 8.6%), and lower rate of pulmonary disease (difference: 6.6%). However, except for 3MS, the race*survival interaction terms in regression models of other health-related conditions were not significant. Therefore, survival bias in 3MS was significantly greater in black women (4 points difference) than in white women (2 points difference), but there is no evidence that survival bias differ by race in other health-related conditions in the Healthy ABC women during 2006-07.

Therefore, there is no strong evidence that very old blacks had greater survival bias than very old whites in the Health ABC study. On the contrary, very old black survivors had worse profiles of health-related conditions than very old white survivors. Therefore, the results of higher

gray matter microstructural integrity in the HBP study cannot be explained by racial differences in survival bias.

Table 15 Characteristics of Health ABC men at baseline in those who were still seen during 2006-07 and those who were lost-to-follow-up

	White survivor	White non-survivor	Survivor vs. non-survivor in whites	Black survivor	Black non-survivor	Survivor vs. non-survivor in blacks	Survival bias in whites vs. in blacks
	N=528	N=411	P-value*	N=220	N=332	P-value*	P-value^
Age, year, mean (SD)	73.5 (2.82)	74.5 (2.94)	**<.0001**	73.1 (2.69)	73.8 (2.81)	**0.0063**	0.2683
Education: > high school, n (%)	334 (63.38)	227 (55.23)	**0.0116**	75 (34.09)	66 (19.94)	**0.0002**	0.1008
3MS, median (IQR)	94 (90, 97)	93 (88, 96)	**<.0001**	88 (82, 93.5)	85 (76, 91)	**0.0035**	0.3071
DSST, mean (SD)	41.4 (11.83)	36.4 (11.42)	**<.0001**	27.2 (13.33)	22.0 (13.18)	**<.0001**	0.9137
Smoker, n (%)	352 (66.92)	314 (76.4)	**0.0015**	142 (64.55)	240 (72.51)	**0.0471**	0.6777
Current Drinker, n(%)	342 (65.14)	255 (62.35)	0.3774	105 (47.73)	148 (45.26)	0.5704	0.9218
Diabetes, n (%)	59 (11.17)	71 (17.27)	**0.0072**	45 (20.45)	75 (22.59)	0.5514	0.1822
Hypertension, n (%)	217 (41.41)	181 (44.36)	0.3663	113 (51.6)	193 (58.84)	0.0945	0.4330
Cardiovascular Disease, n (%)	171 (32.63)	146 (36.14)	0.2643	53 (24.77)	117 (36.11)	**0.0056**	0.1096
Pulmonary Disease, n (%)	44 (8.33)	58 (14.15)	**0.0046**	21 (9.55)	51 (15.5)	**0.0428**	0.9044
SBP, mmHg , mean (SD)	132.8 (19.88)	133.4 (19.75)	0.6456	138.6 (20.36)	139.1 (23.09)	0.7929	0.9658
DBP, mmHg , mean (SD)	71.1 (10.64)	71.2 (10.83)	0.8531	74.9 (11.86)	75.7 (12.34)	0.4602	0.4258
BMI, kg/m^2, mean (SD)	27.2 (3.61)	26.7 (3.76)	**0.0310**	27.5 (4.35)	27 (4.43)	0.2395	0.8671
Walking speed, m/sec, mean (SD)	1.5 (0.25)	1.4 (0.23)	**<.0001**	1.4 (0.22)	1.3 (0.21)	**<.0001**	0.3841

Table 15 Continued

*p-Values were calculated from median test for 3MS, from student's t-test for other continuous variables, and from Chi-squared test for categorical variables.

^p-Values were calculated for the race*survivor interaction term in the linear regression or logistic regression models. For 3MS, the transformed value as square root (100-3MS) was used as the outcome in the model.

Table 16 Characteristics of Health ABC women at baseline in those who were still seen during 2006-07 and those who were lost to follow-up

	White survivor	White non-survivor	Survivor vs. non-survivor in whites	Black survivor	Black non-survivor	Survivor vs. non-survivor in blacks	Survival bias in whites vs. in blacks
	N=538	N=317	P-value*	N=353	N=376	P-value*	P-value^
Age, year, mean (SD)	73.3 (2.79)	74.1 (2.73)	**<.0001**	72.8 (2.75)	73.9 (3.05)	**<.0001**	0.4667
Education: > high school, n (%)	267 (49.63)	134 (42.41)	**0.0411**	112 (31.82)	77 (20.7)	**0.0007**	0.1945
3MS, median (IQR)	96 (92, 98)	94 (90, 96)	**<.0001**	91 (85, 95)	87 (81, 92)	**<.0001**	**0.0197**
DSST, mean (SD)	44.7 (11.44)	40.4 (11.56)	**<.0001**	32.9 (14.73)	26.9 (13.57)	**<.0001**	0.2093
Smoker, n (%)	201 (37.36)	150 (47.32)	**0.0043**	146 (41.48)	177 (47.2)	0.1207	0.3926
Current Drinker, n(%)	299 (55.78)	147 (46.52)	**0.0089**	109 (30.97)	112 (29.79)	0.7296	0.1416
Diabetes, n (%)	33 (6.15)	31 (9.78)	0.0513	56 (15.91)	98 (26.13)	**0.0007**	0.7035
Hypertension, n (%)	225 (41.98)	153 (48.57)	0.0616	218 (62.29)	263 (70.89)	**0.0143**	0.5684
Cardiovascular Disease, n (%)	87 (16.48)	71 (22.76)	**0.0244**	74 (21.7)	116 (31.78)	**0.0025**	0.6344
Pulmonary Disease, n (%)	58 (10.86)	37 (11.71)	0.7047	31 (8.81)	57 (15.41)	**0.0067**	0.0915
SBP, mmHg , mean (SD)	133.0 (19.37)	135.9 (20.21)	**0.0421**	136.6 (20.46)	141.7 (24.09)	**0.0025**	0.3071
DBP, mmHg , mean (SD)	68.6 (10.83)	68.6 (11.76)	0.9784	71.7 (11.58)	72.4 (13.11)	0.4369	0.5653
BMI, kg/m^2, mean (SD)	26.3 (4.49)	25.6 (4.59)	**0.0340**	29.9 (5.96)	29.5 (5.76)	0.3600	0.5946
Walking speed, m/sec, mean (SD)	1.4 (0.21)	1.3 (0.21)	**<.0001**	1.2 (0.22)	1.1 (0.22)	**<.0001**	0.5448

Table 16 Continued

*p-Values were calculated from median test for 3MS, from student's t-test for other continuous variables, and from Chi-squared test for categorical variables.

^p-Values were calculated for the race*survivor interaction term in the linear regression or logistic regression models. For 3MS, the transformed value as square root (100-3MS) was used as the outcome in the model.

7.0 PUBLIC HEALTH IMPLICATION AND DIRECTION OF FURTHER RESEARCH

7.1 PUBLIC HEALTH IMPLICATION

The oldest old is the fastest growing segment of the elderly population, and also has the largest racial disparities in dementia between blacks and whites. This dissertation has shown that very old blacks have worse profiles in vascular risk factors and cognition, but higher gray matter microstructural integrity than very old whites. Further analyses comparing the HBP subjects and very old survivors of the CHS study indicated that the HBP subjects might represent very old subjects with high levels of education and cognitive function. Therefore, one should be cautious when generalizing results of HBP to other populations.

Previous studies have also shown that mean diffusivity of gray matter is a stronger marker of aging and cognitive impairment, as compared to other markers of gray matter integrity [80]. As shown in a paper of Dr. Carlesimo, et al.[9], the hippocampal mean diffusivity increased steeply in those older than 80 years of age, but the changes of hippocampal volume or fractional anisotropy were less striking. The mediation analyses showed that higher mean diffusivity in blacks partially attenuated racial differences in cognition. Therefore, maintaining gray matter microstructural integrity in blacks would help to reduce racial differences in cognition or dementia.

Among the candidate factors to improve mean diffusivity, diabetes seems to play an important role. Moreover, our analyses showed that very old blacks had higher prevalence of diabetes than very old whites. Therefore, reducing racial differences in diabetes may further improve gray matter integrity in blacks, and thus reducing racial differences in cognitive function and/or dementia.

7.2 DIRECTION OF FURTHER RESEARCH

I have identified two potential directions for future research to further our understanding of the mechanisms underlying racial differences in dementia.

First, studies may be conducted in South Africa, which has the highest proportion of older population in southern Africa, and a population of diverse ethnic composition [178]. As the ethnic and demographic distributions are changing in the world, Africa will have the largest population growth from now to 2050 [179]. Now, Africa is passing through both the demographic transition (population aging) and epidemiological transition (non-infectious disease becoming leading cause of death) in just a few decades [180]. It is estimated that elderly could account for 4.5% of the population by 2030 and nearly 10% of the population by 2050 [181] . In most African countries, cardiovascular disease is now the second most common cause of death [180]. It is also estimated that about 2.76 million people were living with dementia in Africa in 2010 [182]. However, the research of racial differences in dementia in Africa is still limited. Therefore, South Africa provides a unique opportunity of studying the dynamic between cardiovascular disease and population aging on brain structure and dementia, as well as their racial differences.

A second line of research could focus on racial differences in brain structure between blacks and whites in the Europe. However, only one relevant study was conducted in older adults (mean age=70) in London [183]. The study found greater proportions of subjects with multiple brain infarcts or with severe WMH in African Caribbeans than in Caucasian Europeans, but did not find racial differences in proportions of subjects with any brain infarct or with mild to moderate WMH. Nonetheless, there were no DTI measures in this study, and therefore racial differences in brain microstructural integrity could not be explored.

Therefore, both Africa and Europe can provide opportunities to study racial differences in brain structure and dementia, in diverse contexts other than the US. Future studies in these regions will be able to provide new perspectives and inputs to this research question.

APPENDIX A: SYNOPSIS OF RACIAL DIFFERENCES IN DEMENTIA

First Author, Year	Study and Design	Sampling	Sample size and mean age	Outcome Diagnosis	Prevalence or Incidence	Test of Racial Differences
Tang, 2001	Washington Heights and Inwood Study (WHI), prospective study (about 4 years)	Probability sample of Medicare beneficiaries residents	610 blacks (mean age=75.8) and 418 whites (mean age=76.9), not demented at baseline	Clinical diagnosis of probable and possible AD	Incident rate per 100 person-years: 65-74: 1.7% in blacks and 0.4 in whites 75-84: 4.4% in blacks and 2.6% in whites ≥85: 11.4% in blacks and 4.2% in whites	Significant higher risk of AD in blacks: HR (black vs. white)=2.4, adjusted for education, stroke, diabetes, heart disease and hypertension.
Gurland, 1998	North Manhattan Aging Project (NMAP), prospective study (18 months on average)	Random sample of Medicare beneficiaries (≥ 65 years old), including nursing home residents	729 blacks and 432 whites at baseline; 454 blacks and 267 whites at follow-up	Cognitive screen and then clinical diagnosis of dementia	Prevalence of dementia: 65-74: 9.1% in blacks and 2.9 in whites 75-84: 19.9% in blacks and 10.9% in whites ≥85: 58.6% in blacks and 30.2% in whites Incidence of dementia during 18 months: 8.2% in blacks and 3.1% in whites	blacks had significantly higher prevalence of dementia in all age groups, and had significantly higher incidence in all ages combined.
Fillenbaum, 1998	Duke Established Populations for Epidemiologic Studies of the Elderly (EPES), prevalence study (as of Jan 1990)	Multistage probability sample of community residents aged 65 and older (1 urban and 4 rural	188 blacks and 175 whites for prevalence study; 622 blacks and 471 whites for incidence study	Cognitive screen and then clinical diagnosis of dementia	Prevalence of dementia in men: 65-74: 5.0% in blacks and 3.5% in whites 75-84: 10.5% in blacks and 5.1% in whites ≥85: 11.5% in blacks and 7.2% in whites Prevalence of dementia in women:	There were no racial differences in dementia prevalence or incidence

First Author, Year	Study and Design	Sampling	Sample size and mean age	Outcome Diagnosis	Prevalence or Incidence	Test of Racial Differences
	and 3-year retrospective incidence study.(1987-1989)	counties in North Carolina). Prevalence study: 10% of original cohort were random selected by 12 strata (n=363). Incidence study: All screened positive (n=1117) were interviewed and 10% of screened negative (n=294) were interviewed			65-74: 2.8% in blacks and 1.7% in whites 75-84: 13.5% in blacks and 10.1% in whites ≥85: 10.8% in blacks and 11.9% in whites 3-year Incidence of dementia in men: 65-74: 4.4% in blacks and 0.1% in whites 75-84: 8.1% in blacks and 6.0% in whites ≥85: 23% in blacks and 4.7% in whites 3-year Incidence of dementia in women: 65-74: 2.4% in blacks and 7.9% in whites 75-84: 8.3% in blacks and 11.2% in whites ≥85: 4.4% in blacks and 12.8% in whites	
Katz, 2012	Einstein Aging Study (EAS), prospective study (3.9 years of follow-up on average)	Systematically recruited community-based cohort of 1944 adults (1168 dementia free) aged 70 or older in Bronx County (urban), NY.	300 blacks and 818 whites Mean age=78.8 years at baseline for the whole cohort	Clinical diagnosis of dementia and AD	Dementia incidence per 100 person-years: 70-74: 0.50% in blacks and 0.53% in whites 75-79: 1.75% in blacks and 1.22% in whites 80-84: 3.41% in blacks and 2.47 in whites 85-89: 7.41% in blacks and 4.55% in whites 90+: 12.35% in blacks and 11.17% in whites	Race is not a significant risk factor for dementia, AD or aMCI in the COX proportional hazard model. Blacks are twice as likely as whites (HR=2.04) to develop naMCI.
Fitzpatrick, 2004	Cardiovascular Health Study (CHS), prospective study (5.4 years of follow-up on average)	5201 whites and 687 blacks randomly recruited from Medicare eligibility lists in four US communities	492 blacks and 2865 whites free of dementia between 1992 and 1994	All blacks were evaluated for dementia, while 51% whites were screened as high risk and then further evaluated.	Dementia incidence per 100 person-years in men: <75: 2.11% in blacks and 1.37% in whites 75-79: 4.23% in blacks and 2.67% in whites 80-84: 7.81% in blacks and 5.84% in whites	Age-adjusted incidence of dementia scaled to age 80 was significantly higher in blacks: 5.88% in blacks woman and 5.30% in blacks men; 3.47% in white women and 3.53% in white men.

First Author, Year	Study and Design	Sampling	Sample size and mean age	Outcome Diagnosis	Prevalence or Incidence	Test of Racial Differences
					≥ 85: 40.39% in blacks and 8.43% in whites Dementia incidence per 100 person-years in women: <75: 1.82% in blacks and 1.04% in whites 75-79: 2.89% in blacks and 3.62% in whites 80-84: 9.33% in blacks and 5.70% in whites ≥ 85: 8.66% in blacks and 10.82% in whites	Ascertainment bias and age adjusted incidence of dementia did not differ significantly by race: 5.64% in blacks and 5.88% in whites

APPENDIX B: SYNOPSIS OF RACIAL DIFFERENCES IN COGNITIVE FUNCTION

First Author, Year	Study and Design	Sampling	Sample size and mean age	Outcome Diagnosis	Racial Differences in Cognition at Baseline	Racial Differences in Rate of Cognitive Decline
Masel, 2009	Health and Retirement Study (HRS), prospective study (9 years: 1996-2004)	A nationally representative sample of US adults ≥ 51 years of age	1324 blacks (mean age=60) and 5918 whites (mean age=60)	Mental status and memory measured by Telephone Interview of Cognitive Status	Mental status (0-10) is significantly lower in blacks: 8.7 in blacks and 9.5 in whites Memory (0-20) is significantly lower in blacks: 9.9 in blacks and 11.5 in whites	Mental status: no significant racial differences in the slope of mental status change over time after multivariate adjustment. Memory Score: worsened slightly faster in blacks over time after multivariate adjustment.
Skarupski, 2006	Chicago Health and Aging Project (CHAP), cross-sectional study at baseline	A complete census of three contiguous neighborhoods on the south side of Chicago for Medicare beneficiaries (≥ 65 years old)	3707 blacks (mean age=73.8) and 2279 whites (mean age=76.7)	Four cognitive tests	Blacks had significantly lower performance in all four cognitive tests: East Boston Story: Immediate recall: 7.50 in blacks and 8.75 in whites East Boston Story: 6.81 in blacks and 8.23 in whites. Symbol Digit Modalities Test: 21.09 in blacks and 34.08 in whites Mini-Mental State Exam: 24.41 in blacks and 27.00 in whites	
Sloan, 2005	The study of Asset and Health Dynamics Among the Oldest Old (AHEAD)	A national panel survey of US nonstitutionalized persons aged 70+ years and their	A sample of 7433 at wave 1, and over 10% of respondents typically died	Telephone Interview of Cognitive Status (TICS), Word recall test, 7s subtraction test, and a test of	At wave 1, all cognitive tests were significantly lower in blacks than in whites after multivariate adjustment: TICS: 3.5 points difference	Waves 1-4: TICS score declined at an annual rate of 0.06 less in blacks than in whites ($p<0.05$).

First Author, Year	Study and Design	Sampling	Sample size and mean age	Outcome Diagnosis	Racial Differences in Cognition at Baseline	Racial Differences in Rate of Cognitive Decline
	Prospective study (4 waves)	spouses or partners. Four consecutive interview waves in 1993, 1995, 1998, and 2000.	between two consecutive waves	knowledge, language and orientation	Word recall: 1.3 points difference Subtraction test: 1.11 points difference Knowledge, Language and Orientation: 1.06 points difference	The word recall test score declined at an annual rate of 0.08 less in blacks than in whites ($p<0.001$). There were no significant racial differences in the annual decline the other two tests.
Black, 2002	Prospective study (two years between baseline and follow-up surveys)	A longitudinal survey of community-dwelling residents of Galveston County, Texas, who were aged 75 and older as of 1995	112 blacks (44.1% were aged ≥ 82) and 125 whites (25.6 % were aged ≥ 82)	Cognitive impairment and cognitive decline based on the Short Portable Mental Status Questionnaire and corrected for education and minority status	Blacks had significantly higher percentage of cognitive impairment than whites (25.3% vs. 6.2%) at baseline	Blacks had significantly higher risk of cognitive decline than whites. (OR=3.52) after multivariate adjustment.
Bohannon, 2002	Duke Established Populations for Epidemiologic Studies of the Elderly, prospective study (3 years between the baseline and second in-home interviews)	Multistage probability sample of community residents aged 65 and older (1 urban and 4 rural counties in North Carolina).	1768 blacks (mean age=73.2) and 1434 whites (mean age=72.8)	Short Portable Mental Status Questionnaire (SPMSQ) Score is in terms of errors and can range from 0 to 10.	Blacks made approximately one error more on the SPMSQ than did whites (2.1 vs. 1.2) at baseline	The average increased in errors of SPMSQ in blacks over 3 years was not significantly greater than in whites (0.29 vs. 0.19).
Mehta, 2004	Health ABC study, cross-sectional analysis of baseline data (1997-98)	Random sample of well-functioning Medicare beneficiaries aged 70 to 79 in Pittsburgh, Pennsylvania, and Memphis, Tennessee.	1271 blacks (mean age=73) and 1791 whites (mean age=74)	Modified Mini-Mental State Examination (3MS) and Digital Symbol Substitution Test (DSST)	Blacks had significantly lower unadjusted scores on cognitive function tests than white participants: 3MS scores were 7 points lower in blacks, and DSST scores were 14 points lower in blacks	

APPENDIX C: SYNOPSIS OF VASCULAR RISK FACTORS FOR BRAIN MICRO-STRUCTURAL INTEGRITY

First Author, Year	Study Design	Sample Characteristics	DTI Measures	Risk Factor	Covariates	Major Results
Smoking						
Fuchun Lin, 2013	Cross sectional	Sixty-eight subjects (34 heavy cigarette smokers and 34 healthy non-smoking control subjects, 33–58 years of age). All recruited participants were healthy and had no history of medical or neurological disorders.	FA of whole brain and regions of interest (ROI)	Heavy smoker vs. nonsmoker	Age, gender and education	Compared with non-smokers, heavy smokers had lower FA in the left anterior corpus callosum while exhibiting no areas of higher FA. In the affected region, FA reduction was accompanied by a significantly decreased axial diffusivity and increased radial diffusivity, which suggests that axonal damage and disrupted myelin integrity may be associated with the degraded white matter integrity in heavy smokers.
Xiaochu Zhang, 2011	Cross sectional	48 cigarette smokers and 48 healthy non-smoking controls matched by age, gender and education years	White matter integrity (fractional anisotropy (FA)) and gray matter density (voxel-based morphometry)	High vs. low dependence and high vs. low pack-years smokers	None	Gray matter density was lower in left prefrontal cortex (PFC) in high pack-years smokers and was inversely related to pack-years. In contrast, left insular cortex gray matter density was higher in smokers. Further, the most highly dependent smokers showed lower prefrontal FA.
Rob Gons, 2011	Cross sectional	503 subjects with small-vessel disease, aged between 50 and 85 years	Diffusion tensor imaging parameters in both normal-appearing white matter and white matter lesions	smoking behavior (never, former, current)	Age, sex, alcohol intake, education and cardiovascular risk factors	A history of smoking was associated with significant higher values of mean diffusivity in normal-appearing white matter and white matter lesions and with poorer cognitive functioning compared with those who never smoked. Associations with smoking and loss of structural integrity appeared to be strongest in normal-appearing white matter.

First Author, Year	Study Design	Sample Characteristics	DTI Measures	Risk Factor	Covariates	Major Results
Matthew Hudkins, 2012	Cross sectional	Eighteen smokers (ten male; age=33.7±7.9 years) and 18 nonsmokers (nine male; age=33.3±10.1 years)	FA and apparent diffusion coefficient (ADC, a measure of random diffusion)	smoking	Age and years of education	ADC showed no group difference, but smokers had higher (4.3–21.1%) FA than nonsmokers. The differences were significant in right prefrontal white matter, cingulum, and genu corpus callosum. FA in several regions was negatively correlated with nicotine dependence or cigarettes/day.
Hypertension						
Saartje Burgmans, 2010	Case-control	93 adult volunteers (age 50–77 years; 36 with diagnosis of hypertension or elevated blood pressure)	FA and WMH in seven brain regions: frontal, temporal, parietal and occipital white matter, and the genu, body and splenium of the corpus callosum	Hypertension, age, and age×hypertension	Sex and intracranial volume	Hypertension was associated with decline in fractional anisotropy (frontal lobe, temporal lobe and total FA), and exacerbated age differences in fractional anisotropy more than those in the volume of WMH.
Elizabeth Leritz,, 2010	Case-control	52 middle-older aged African Americans without diagnosed history of CVD	FA in anterior corpus callosum (genu), posterior corpus callosum (splenium), and across the whole brain	mean arterial blood pressure (MABP)	Age	When controlling for age, higher MABP was associated with lower FA in the genu, and there was a trend for this sample relationship with regard to whole brain FA. When the sample was broken into groups based on treatment for BP regulation (medicated / nonmedicated), MABP was related to genu and whole-brain FA only in the non-medicated group.
Rob Gons, 2010	Cross sectional	In 503 patients with small vessel disease, aged between 50 and 85 years	Fractional anisotropy and mean diffusivity in both normal-appearing white matter (NAWM) and WMLs	Blood pressure and hypertension	Age, sex, and cardiovascular risk factors	Increased blood pressure and hypertension were significantly related to lower fractional anisotropy in both NAWM and WMLs and to higher mean diffusivity in WMLs. For hypertensives, odds ratios for the risk of impaired microstructural integrity (fractional anisotropy) were 3.1 (95% CI: 1.8 to 5.7) and 2.1 (95% CI: 1.2 to 3.5) in NAWM and WMLs, respectively, compared with normotensives.
Alasdair MacLullich, 2009	Cross sectional	45 community-dwelling male and normal cognition volunteers aged from 71 to 76	MD and fractional anisotropy were measured in 6 regions of interest in normal-	SBP and DBP	None	Systolic BP was positively and significantly correlated with MD in all 6 regions (r=0.31 to 0.45; P=0.037 to 0.002). (frontal, temporal, parietal, occipital, genu, and splenium). MD was also correlated with diastolic BP in

First Author, Year	Study Design	Sample Characteristics	DTI Measures	Risk Factor	Covariates	Major Results
		without history of stroke, cancer, depression, or dementia.	appearing white matter.			the genu of the corpus callosum (r=0.34, P=0.018). Fractional anisotropy did not correlate significantly with blood pressure.
Kristen Kennedy, 2009	Cross sectional	77 healthy adults (19–84 years old).	Regional FA and ADC	hypertension	Age, sex	Clinically diagnosed and treated arterial hypertension was associated with reduced white matter anisotropy and increased ADC beyond the effects of age. In the normotensive participants, elevation of arterial pulse pressure (a surrogate of arterial stiffness) was linked to deterioration of the white matter integrity in the frontal regions.
Diabetes						
Cherie Falvey, 2013	Cross-sectional	308 elders (mean age 83.3 years; n = 85 with diabetes) from the Health ABC Healthy Brain Substudy	(mean diffusivity [MD] and fractional anisotropy [FA]) measures for the total brain and ROIs	diabetes	Age, race, and sex	On microstructural measures, diabetes was associated with reduced FA for total white matter (P = 0.006) and greater MD for the hippocampus (P = 0.006 left; P = 0.01 right), dorsolateral prefrontal cortex (P = 0.0007, left; P = 0.002, right), left posterior cingulate (P = 0.02), and right putamen (P = 0.02). Further adjustment for stroke, hypertension, and myocardial infarction produced similar results.
Yael Reijmer, 2013	Case control	Thirty-five non-demented older individuals with type 2 diabetes (mean age 71 ± 5 years) and 35 age-, sex-, and education-matched controls.	Fractional anisotropy (FA) and mean diffusivity (MD)	Type 2 diabetes	None	Significant between-group differences in MD values were observed in the SLF, UF, and ILF in both the left and right hemisphere and in the splenium of the CC demonstrating microstructural white matter abnormalities in patients compared with control subjects. A between- group difference in FA was found in the right UF.

First Author, Year	Study Design	Sample Characteristics	DTI Measures	Risk Factor	Covariates	Major Results
Jens Frokjer, 2013	Case-control	Twenty-six patients with DM (21 T1 DM and 5 T2 DM) and gastrointestinal symptoms (mean age=45.8) and 23 healthy control subjects (mean age=43.8)	The apparent diffusion coefficient and fractional anisotropy (FA) were assessed in the "sensory matrix" (cingulate cortex, insula, prefrontal and secondary sensory cortex, amygdala, and corona radiata) and in corpus callosum.	diabetes	None	Patients had decreased FA values compared with control subjects in 1) all areas (P= 0.025); 2) anterior (P<0.001), mid- (P = 0.001), and posterior (P<0.001) cingulate cortex; 3) prefrontal cortex gray matter (P=0.001); 4) corona radiata (P<0.001); 5) secondary sensory cortex (P= 0.008); and 6) anterior white matter (P= 0.045), anterior gray matter (P= 0.002), and posterior gray matter (P= 0.002) insula. No difference was found in corpus callosum (P<0.05). Overall, no difference in ADC values was found between the patients and control subjects.
C-reactive Protein						
Heike Wersching, 2010	Cross-section	321 community-dwelling and stroke-free individuals from the Systematic Evaluation and Alteration of Risk Factors for Cognitive Health Study (mean age 63 years, 248 female).	FA, WMH, brain atrophy	hs-CRP	Full set of risk factors	Higher hs-CRP was related to reduced global fractional anisotropy (β = -0.237, p < 0.001), as well as regional FA scores of the frontal lobes (β= -0.246, p< 0.001), the corona radiata (β= -0.222, p < 0.001), and the corpus callosum (β= -0.141, p= 0.016), in particular the genu (β= -0.174, p= 0.004). We did not observe a significant association of hs-CRP with measures of white matter hyperintensities or brain atrophy.
Julia Miralbell, 2012	Cross sectional	Subjects were 50–65 years old, free from dementia and without history of vascular disease.	Fractional anisotropy (FA); regional gray matter (GM) volumes	CRP	Age, sex and vascular risk factors	Increasing levels of C-reactive protein were associated with white matter (WM) integrity loss in corticosubcortical pathways and association fibers of frontal and temporal lobes, independently of age, sex and vascular risk factors. CRP was not related to gray matter volume changes.
Peter Gianaros, 2012	Cross sectional	155 community-dwelling adults (78 men, 77 women; age=40.7 ± 6.2, range = 30–50 years)	White matter fractional anisotropy and radial diffusivity	CRP and socioeconomic status		Measures of tract integrity followed a socioeconomic gradient: individuals completing more schooling, earning higher incomes, and residing in advantaged neighborhoods exhibited increases in white matter fractional anisotropy and decreases in radial diffusivity, relative to disadvantaged individuals. Moreover,

First Author, Year	Study Design	Sample Characteristics	DTI Measures	Risk Factor	Covariates	Major Results
						analysis of indirect paths showed that adiposity, cigarette smoking, and CRP partially mediated these effects.
Physical Activity						
Alan Gow, 2012	Cross sectional	Lothian Birth Cohort 1936 in their 70s (n= 691)	Fractional anisotropy (FA) and mean diffusivity. atrophy, gray and normal-appearing white matter (NAWM) volumes, and WML load	Physical activities	Age, social class, and health status	A higher level of physical activity was associated with higher FA, larger gray and NAWM volumes, less atrophy, and lower WML load. The physical activity associations with atrophy, gray matter, and WML remained significant after adjustment for covariates, including age, social class, and health status.
Bonita Marks, 2007	Cross sectional	Twenty-eight healthy subjects (13 younger adults, 24±3 years; 15 older adults, 69.6±4.7 years);	Regional FA	Aerobic fitness	Age and gender	After controlling for age and gender, significant ($P<0.05$) positive correlations remained between aerobic fitness and FA in two regions, the uncinate fasciculus (UNC) and the cingulum (CIN). Regression analyses revealed that the unique contribution of aerobic fitness to the FA variance was 15% for the UNC and 13% for the CIN.
Metabolic Syndrome						
Barbara Segura, 2010	Case-control	19 patients with metabolic syndrome aged between 50 and 80 years and 19 age-matched controls without any vascular risk factors for the syndrome	fractional anisotropy (FA) and apparent diffusion coefficient (ADC)	metabolic syndrome		Patients with metabolic syndrome showed an anterior-posterior pattern of deterioration in WM with reduced FA and increased ADC values compared with controls. WM changes were not related to any isolated vascular risk factor.
Keigo Shimoji, 2013	Case-control	Seven Japanese middle-aged men with metabolic syndrome and seven without metabolic syndrome. All subjects are healthy otherwise.	FA	Metabolic syndrome, BMI	none	In the whole-brain analysis, subjects with metabolic syndrome had significantly lower FA values than control subjects in part of the right inferior fronto-occipital fasciculus (IFOF), the entire corpus callosum, and part of the deep white matter of the right frontal lobe. A significant negative correlation was observed between BMI and FA values in the right IFOF ($r= 20.56$, $P = 0.04$).

APPENDIX D: SYNOPSIS OF RACIAL DIFFERENCES IN BRAIN STRUCTURE

First Author, Year	Study Design	Age Group	Sample Size	Sample Characteristics	MRI Measures	Racial Differences in Brain Atrophy Indices	Racial Differences in WMH	Racial Differences in Brain Infarcts	Adjustment
Bryan, 1997	Cross-sectional	65-97, mean= 72	562 B, and 3073 W	Cardiovascular Health Study cohort: (four communities in US)	Infarct-like lesion (ILLs)			Prevalence of ILLs: NS (31% vs 31%) in X^2 test.	None
Yue, 1997	Cross-sectional	≥65	566 B and 3073 W	Cardiovascular Health Study cohort: (four communities in US)	Graded (0-9) sulcal width, ventricular enlargement and WMH	Sucal and ventricular grades: B<W (sig. in without adj.)	White matter grade: B>W (sig. without adj.)		None
Bryan, 1999	Cross-sectional	55-72	926 B and 964 W	A substudy of Atherosclerosis Risk in Communities (probability samples in 4 US communities	Infarct-like lesions (ILLs) and lacune (3-20mm in subcortical regions)			Prevalence of ILLs: B>W (20.7% vs 10.2%, sig. in X^2 test) prevalence of lacune: B>W (16.8% vs 8.6%, sig. in X^2 test)	None
DeCarli, 2008	Cross-sectional	≥60, mean= 75	103 B and 191 W	Convenient sample from AD center and community in California	TCBV=brain parenchymal volume/ICV LWMH=log(WMH/ICV) brain infarcts (cortical or subcortical)	TCBV: NS after adj. (78.5% in B, and 77.6% in W)	LWMH: NS after adj.	Infarcts prevalence: NS after adj.	Age, sex, education, diagnosis (normal, MCI or dementia) and vascular risk factors

First Author, Year	Study Design	Age Group	Sample Size	Sample Characteristics	MRI Measures	Racial Differences in Brain Atrophy Indices	Racial Differences in WMH	Racial Differences in Brain Infarcts	Adjustment
Brickman, 2008	Cross-sectional	≥65, mean= 80	243 B and 203 W	Northern Manhattan residents (not demented)	Total brain parenchymal volume/ICV, lateral ventricular volume/ICV, and WMH/ICV	Total brain parenchymal volume/ICV: B>W (diff=1.6%, sig. after adj.) lateral ventricular volume/ICV: B<W (sig. after adj.)	WMH/ICV: B>W (sig. after adj.)		Age, sex, vascular disease history
Prabhakaran, 2008	Cross-sectional	>55, mean= 71	144 B and 171 W	MRI substudy of Northern Manhattan Study (stroke-free and random sample)	Subclinical brain infarcts (SBI)			SBI prevalence: B>W (24.5% vs 17.6%), but NS after adj.	Age, sex, education and vascular risk factors
Aggarwal, 2010	Cross-sectional	Mean= 80	335 B and 240 W	Chicago Health and Aging Project (community based)	WMHV=natural log [WMH/ICV] relative TBV = total brain parenchymal volume/ICV brain infarcts	Relative TBV: NS in t-test (74.94% in B and 74.00% in W)	WMHV: NS in t-test (−5.16 in B and −5.09 in W)	Brain infarcts: NS in X^2 test	None
Knopman, 2011	Cohort, 10 years between initial and follow-up scans	≥55, ,mean= 62	585 B and 527 W	Substudy of Atherosclerosis Risk in Communities (probability samples in 4 US communities)	Graded (0-9) ventricle size, sulcal width and WMH brain infarcts	Ventricular grade: B < W in both M and F ventricular widening worsening of one grade or more: B F<W F but B M>W M sulcal grade: B M>W M, but similar in B F and W F sucal widening worsening of one grade or more: W>B in both M and F	White matter grade: B F<W F, but B M>W M WMH worsening of one grade or more: B>W in both M and F	Infarcts prevalence: B>W in both M and F. incident infarcts: similar in B F and W F, but B M>W M	No statistical test for racial differences
Gardener, 2012	Cross-sectional	>55, mean =72	169 B and 151 W	MRI substudy of Northern Manhattan Study	WMHV=log(WMH/ICV)		WMHV: B>W (sig. after adj.)		Age, sociodemographic, and

First Author, Year	Study Design	Age Group	Sample Size	Sample Characteristics	MRI Measures	Racial Differences in Brain Atrophy Indices	Racial Differences in WMH	Racial Differences in Brain Infarcts	Adjustment
				(stroke-free and random sample)					vascular risk factors.
B=blacks; W=whites; ; M=male; F=female; NS=not significant (P>0.05) ; sig.=significant (P<0.05) ; adj.=adjustment; WMH=white matter hyperintensities; ICV=intracranial volume; AD=Alzheimer's Disease;									

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