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Imaging, Cognitive, and Functional Correlates of Vascular Depression in Older Black Adults

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by

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ABSTRACT

Black older adults have a higher prevalence of vascular conditions (e.g., heart disease) and greater cerebrovascular disease burden compared to Whites. Decreased brain white matter integrity as a result of vascular burden is associated with a form of late-life depression, known as vascular depression (VaDep), which is marked by chronic vascular risk, executive dysfunction, poor treatment response, and high levels of functional disability. Older Black adults may be particularly vulnerable to developing VaDep; however, the literature examining VaDep in Black older adults is sparse. The present study used publicly available data from the Healthy Brain Project, a substudy of the Health, Aging, and Body Composition Study that includes imaging, cognitive, and gait speed data, to test the VaDep hypothesis in a community sample of Black older adults followed for four years.

Multiple regression analyses revealed that total and uncinate fasciculus white matter hyperintensity (WMH) volume, but not clinically-defined vascular burden, predicted depressive symptoms (as measured by the Center for Epidemiologic Studies Depression Scale) both cross-sectionally and longitudinally. Mixed effects regressions compared cognitive performance (Digit Symbol Substitution Test [DSST] and 15-Item Executive Interview [EXIT-15]) and gait speed over four years between vascular depression, non-vascular depression, vascular-only, and healthy groups. The VaDep group had the slowest performance on the DSST at baseline and over time. The non-vascular depression group's EXIT-15 performance improved over time while other groups (including VaDep) remained stable. Both the VaDep and non-vascular depression groups' gait speed declined over time. Exploratory analyses revealed a stronger association between depression and uncinate fasciculus WMH in Black compared to White individuals, and showed that the Black VaDep group had the slowest DSST performance at baseline compared to

all other race and vascular/depression groups. This research supports the validity of the VaDep framework in older Black adults, highlights WMH in the uncinate fasciculus as particularly relevant in identifying Black older adults who are at risk for developing depressive symptoms, and identifies cognitive risks associated with VaDep in older Black adults. It also addresses an important gap in the VaDep literature by examining a group that has historically been underserved.

INDEX WORDS: Vascular depression, Black, African American, Aging, Subthreshold depression, Cognition, White matter hyperintensity

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DEDICATION

This work is dedicated to my husband Paul, who made my dream into his dream too, and who has been my biggest champion since we met ten years ago. Paul: you uprooted your life in Connecticut to build a new one with me in Georgia, and the foundation of your love and support has carried me through this training program. I am deeply grateful for your steadiness, your unwavering support, your patience, and your knack for making me laugh no matter what kind of day I have had. Our relationship has continuously been a source of strength and calm for me, and I could not have asked for a better partner with whom to weather the peaks and valleys of the past five years in this program. I hope to pay you back in kind over many more decades together.

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LIST OF ABBREVIATIONS

Vascular Depression (VaDep)

White Matter Hyperintensities (WMH)

Center for Epidemiological Studies Depression Scale (CES-D)

Digit Symbol Substitution Test (DSST)

Executive Interview (EXIT-15)

1 INTRODUCTION

The impact of vascular disease burden on cognition, physical function, and brain health in late life is well-known (Cipollini et al., 2019; Du & Xu, 2019; Su et al., 2018). Vascular burden also insidiously erodes brain integrity across frontolimbic circuits that are important for both mood and executive functions, and can frequently underlie or exacerbate late-life depression (Aizenstein et al., 2016). In general, late-life depression is associated with accelerated brain aging, dementia, and all-cause and cardiovascular-related mortality (Alexopoulos, 2019; Wei et al., 2019), but vascular depression (VaDep) represents a major sub-group of late-life depression that is tied to even worse cognitive outcomes (Johnson et al., 2019) and is especially treatment resistant (Bella et al., 2010; Gunning-Dixon et al., 2010). Black older adults have elevated rates of vascular disease compared to other racial and ethnic groups in the U.S., and thus may represent a group particularly vulnerable to VaDep (Persaud et al., 2012). However, VaDep in this population is rarely studied and thus is not well characterized (Bogoian & Dotson, 2021). The current study seeks to fill important gaps in the literature by 1) examining the association between clinical and imaging markers of vascular burden and depressive symptoms in a large sample of Black older adults, and 2) determining whether VaDep is related to cognition and gait speed in Black older adults, similar to what has been shown in the literature based on primarily non-Hispanic White samples.

1.1 Vascular Health in Black Older Adults

Black adults have some of the highest rates of vascular disease (e.g., stroke, heart failure, and coronary artery disease) and vascular risk factors (e.g., obesity, high blood pressure, and diabetes) in the U.S., and are less likely to receive sufficient treatment for these vascular conditions compared to other racial and ethnic groups (Gutierrez & Williams, 2014; Mozaffarian

et al., 2016). In fact, Black adults tend to develop cardiovascular diseases at an earlier age than Whites (Ferdinand & Townsend, 2012) and have almost twice the rate of obesity and diabetes, as well as higher odds of hypertension, heart attack, stroke, and cardiovascular-related mortality (Tabaei et al., 2019; Zhang & Rodriguez-Monguio, 2012).

Cardiovascular burden over time is known to negatively impact white matter tracts in the brain, which are made up of myelinated axons responsible for communication between neurons. White matter lesions, seen as white matter hyperintensities (WMH) on MRI scans, are indicative of vascular damage to white matter tracts and are associated with cerebrovascular disease in late life (Rensma et al., 2018). In comparison to other racial groups, Black older adults with vascular-related conditions have increased risk of WMH and brain atrophy (Brickman et al., 2008), at least partially due to racial disparities in healthcare access (Divers et al., 2013) and lifetime burden of racial discrimination (Beatty Moody et al., 2019). Black adults are also more likely to have severe WMH in subcortical regions (Nyquist et al., 2014), greater prevalence of silent lacunar strokes (Prabhakaran et al., 2008), less overall white matter, and greater overall white matter lesion volume (Hsu et al., 2018). Other studies have also shown that larger WMH volume predicts worse language, speed, and executive functioning in Black, but not White, older adults (Zahodne et al., 2015). Taken together, this research suggests that vascular diseases may disproportionately impact white matter integrity in older Black adults, and that white matter changes have a disproportionate impact on cognitive functioning in Black older adults.

1.2 Overview of Late-life Depression

While the prevalence of major depressive disorder among older adults (aged ≥ 65) ranges from 1-5% in most large-scale epidemiological studies (e.g., Hasin et al., 2005; Hasin et al., 2018), up to 23% experience subclinical symptoms of depression in late life (Meeks et al., 2011).

There is evidence that up to 79% of older adults with late-life depression do not receive treatment from available mental health services (Horackova et al., 2019). Additionally, half of all older adults with depression do not respond to first-time pharmacotherapy (Joel et al., 2014), and these individuals with persistent depression are more likely to experience cognitive deficits as they age (Singh-Manoux et al., 2010; Weisenbach et al., 2012). Older adults who experience depression utilize greater outpatient services compared to non-depressed older adults (Huang et al., 2014), have higher rates of falls (Stubbs et al., 2016), and have higher rates of both vascular dementia and Alzheimer's disease (Diniz et al., 2013; Geerlings & Heijer, 2008). Older adults with depressive symptoms that do not meet criteria for major depressive disorder, often referred to as subthreshold depressive symptoms, have greater functional impairment (i.e., impairment in activities of daily living;Karsten et al., 2013) and increased risk of mortality compared to their healthy, same-aged peers (Cuijpers et al., 2013).

Late-life depression is associated with a host of brain abnormalities older adults including neuroimaging evidence of altered structural and functional connectivity in frontal-executive and corticolimbic pathways (Rashidi-Ranjbar et al., 2020). In particular, dysregulation of the frontolimbic network is a hallmark of depression (Tadayonnejad & Ajilore, 2014). This network includes regions such as the amygdala, subgenual anterior cingulate cortex, hypothalamus, orbitofrontal cortex, and nucleus accumbens which, together, function to process emotion and maintain emotional stability (Palazidou, 2012). In late-life depression, however, this entire system is marked by disrupted functional connectivity between regions (Alexopoulos et al., 2013; Fujimoto et al., 2008) as well as volume reduction (Tadayonnejad & Ajilore, 2014) and alterations in cortical thickness (Kim & Han, 2021).

Subthreshold depressive symptoms are related to similar frontolimbic abnormalities in older individuals, even without meeting the clinical criteria for a major depressive episode. Compromised frontal lobe integrity was observed in a longitudinal study of older adults in which the severity of subthreshold depression was associated with more rapid white matter volume loss in the left frontal region (Dotson, Davatzikos, et al., 2009), and with gray matter volume reductions in the frontal and temporal lobes (Dotson, Davatzikos, et al., 2009; Kumar et al., 1998; Kumar et al., 1997). Changes in white matter microstructure (Allan et al., 2016), resting-state connectivity in the anterior cingulate cortex, (Li et al., 2014), and decreased cerebral blood flow in frontal regions of the brain (Dotson, Beason-Held, et al., 2009; McLaren et al., 2016) have also been identified in older adults with subthreshold depression in patterns similar to brain changes seen in late-life major depressive disorder. Overall, subthreshold depressive symptoms are related to both structural and functional abnormalities in the brain quite similar to the deficits observed in major depression among older adults, highlighting the significance of subthreshold symptoms.

1.3 The Vascular Depression Hypothesis

One of the mechanisms impacting these frontolimbic networks is white matter damage, often seen as WMH on MRI scans. When reduced white matter integrity disrupts communication, particularly along these frontolimbic circuits, a “disconnection” between cortical and subcortical brain regions occurs (Liao et al., 2013), thereby yielding mood dysregulation. These white matter changes in late-life depression are also associated with slower processing speed and executive dysfunction (Respino et al., 2019; Ye et al., 2017). Executive dysfunction even without depression puts older adults at risk of functional impairment and mortality (Johnson et al., 2007; Kearney et al., 2013), and in the presence of depression is

additionally associated with impaired gait speed, which is a major risk factor for falls and functional impairment (Patience et al., 2019). Not only are frontolimbic WMH involved in depressed mood and executive dysfunction, but older depressed adults with executive dysfunction have disproportionate functional impairment in performing daily activities, respond poorly to antidepressant treatment, and are more likely to experience a persistent course of depression (Manning et al., 2015; Potter et al., 2004; Sheline et al., 2010).

The mood and cognitive disruption related to white matter damage in late-life depression has long been thought to have a vascular basis. Specifically, the VaDep hypothesis put forth by Alexopoulos et al. (1997) posits that vascular disease may "predispose, precipitate, or perpetuate" (p. 915) some forms of late-life depression. Clinically, VaDep accounts for as many as 50% of all older adults with major depressive disorder (Park et al., 2015) and is described by co-occurrence of depressive symptoms and cardiac illness burden, including vascular risk factors such as hypertension and diabetes (Aizenstein et al., 2016; Taylor et al., 2013). In the U.S. alone, approximately 2.64 million Americans aged 50 and older have been estimated to meet criteria for vascular depression (González et al., 2012). An MRI-based definition has also been proposed for VaDep using the presence of deep (i.e., subcortical) WMH as evidence of cerebrovascular disease (K. R. R. Krishnan et al., 1997), since WMH are imaging indicators of white matter damage and are associated with cerebrovascular disease in late life (Rensma et al., 2018).

Across both clinical and MRI-defined VaDep, mood symptoms are thought to originate from microstructural insults to the cerebrovascular system, specifically to frontolimbic white matter tracts that underlie both cognitive and emotional functions (Dalby et al., 2010; Sheline et al., 2008). This has led to the disconnection hypothesis of VaDep, which proposes that ischemia and white matter lesions interrupt neural pathways important for mood and cognition (Taylor et

al., 2013). Not all older adults with vascular disease develop depression or cognitive changes, however, thus Taylor et al. (2013) have suggested a threshold model for VaDep such that one must accumulate and surpass an initial level of vascular damage to these neural circuits before frontolimbic compromise is seen in the form of depressive, and often cognitive, symptoms.

Given the insidious disintegration of white matter pathways over time, individuals who develop VaDep tend to develop first-time depressive symptoms after age 65 (Krishnan et al., 2004) and experience greater chronicity than non-vascular depression (Barch et al., 2012). Other common features of VaDep include anhedonia, absence of family history of depression, and functional disability (Chang et al., 2016; Krishnan et al., 2004), as well as poor treatment response (Naarding & Beekman, 2011). Executive dysfunction and psychomotor slowing in particular are core clinical features of VaDep (Alexopoulos, 2019) that are linked to more severe WMH and worse treatment response (Culang-Reinlieb et al., 2011; Pimontel et al., 2016). Additionally, the presence of WMH in frontolimbic regions is related to reduced activation of brain regions important for executive function (Venkatraman et al., 2010). Aside from executive dysfunction, there have been mixed results regarding the cognitive profile of VaDep (Naarding et al., 2009), however neuropsychological deficits and neurocognitive sequelae are common (Johnson et al., 2019). VaDep puts older adults at greater risk of developing mild cognitive impairment (Kim et al., 2016), Alzheimer's disease, and vascular dementia (Diniz et al., 2013). VaDep, therefore, occurs within the context of widespread brain vulnerability.

1.4 Vascular Depression in Black Older Adults

There is little research to date that examines the VaDep construct among Black adults despite their vulnerability to vascular conditions. A recent systematic review by Bogoian and Dotson (2021) found just 30 studies that examined the impact of vascular conditions on

depression in middle aged to older (mean age ≥ 50) Black adults, and only 11 studies explicitly addressed the VaDep framework in their research (Azar et al., 2005; Carmasin et al., 2014; González & Tarraf, 2013; Heard et al., 2011; Mast, MacNeill, et al., 2004; Mast, Neufeld, et al., 2004; Mast, Yochim, et al., 2004; Reinlieb et al., 2014; Yochim et al., 2003; Yochim, Kerkar, et al., 2006; Yochim, MacNeill, et al., 2006). Despite study heterogeneity, there was converging evidence for the validity of the VaDep hypothesis in older Black samples. The review also provided preliminary support for cognitive deficits and poor physical outcomes (including slow gait speed and impairment in activities of daily living) associated with co-occurring depression and vascular conditions in this demographic group. Key findings from the review are briefly summarized here.

1.4.1 Prevalence of Vascular Depression in Black Older Adults

Previous studies suggest Black adults with vascular conditions, including cardiovascular disease (González & Tarraf, 2013), coronary artery disease (Boutin-Foste, 2008), diabetes (Cummings et al., 2016), and aortic calcification (Lewis et al., 2009), are more likely to have co-occurring depression compared to other racial groups (Hajjar et al., 2009; Reinlieb et al., 2014). However, other studies found no racial differences in prevalence of depression among vascular samples (e.g., congestive heart failure) (Azar et al., 2005; Freedland et al., 1991; Rohyans & Pressler, 2009; Waldman et al., 2009) and no association of depression with vascular risk factors (e.g., visceral fat). Lack of standardized matching procedures between racial groups and use of primarily self-report depression measures may account for the lack of consistent findings. In addition, in studies that use clinical markers of vascular disease, we cannot guarantee that the vascular conditions have progressed enough to impact the brain (i.e., to cause WMHs in

frontolimbic networks, thus leading to depression). Thus, further evidence is needed to accurately evaluate the presence of racial differences in VaDep prevalence.

1.4.2 Relationship with Cognitive Functioning

Although executive dysfunction is a major feature of VaDep in the larger literature, there is limited research examining cognitive function in Black older adults with VaDep. In a study with an 83% Black sample, self-reported vascular burden was associated with higher depressive symptoms, which in turn were associated with lower verbal fluency over six months (Yochim, MacNeill, et al., 2006). In another study, Black adults were more likely than White adults to have comorbid elevated depressive symptoms and executive dysfunction as measured by Trail Making Test B. (Hajjar et al., 2009). Relatedly, an interaction between vascular risk and executive functioning deficits was found to predict depressive symptoms, such that depressive symptoms increased for the high-risk vascular group only when low performance was demonstrated on the Initiation/Perseveration (I/P) subscale of the Mattis Dementia Rating Scale (Mast, Neufeld, et al., 2004). Moreover, Reinlieb et al. (2014) provided limited support that those with MRI-defined VaDep may perform worse on the I/P subscale and Stroop Color/Word Test compared to a non-vascular depression group, as well as had slower reaction times. Overall, studies using both self-report (Carmasin et al., 2014; Yochim, MacNeill, et al., 2006) and objective measures of vascular conditions (Hajjar et al., 2009; Mast, Yochim, et al., 2004; Reinlieb et al., 2014) provide preliminary support that VaDep in Black older adults may be associated with cognitive deficits, particularly deficits in executive functioning. Longitudinal research with more extensive cognitive data is required to fully examine the cognitive profile of VaDep in Black adults.

1.4.3 Relationship with Functional Status

Gait speed is a common measure used to estimate functional status. It has been designated as a "sixth vital sign" due to its extensive value in predicting functional dependence, frailty, falls, hospitalization, institutionalization, cognitive decline, presence of depressive symptoms, cardiovascular-related events, and all-cause mortality (Middleton et al., 2015). Consistent with this close relationship between vascular disease, cognitive decline, depression, and gait speed, the review by Bogoian and Dotson (2021) found evidence that VaDep is associated with slowed gait speed among Black older adults. In a large community sample of older adults, Hajjar et al. (2009) identified a "vascular aging" phenotype characterized by executive dysfunction, higher depressive symptoms, and slow gait speed. Participants with this vascular aging phenotype had higher rates of cardiovascular conditions, were more likely to be Black compared to other racial groups, were more impaired in instrumental activities of daily living, and were more likely to perform poorly on other physical performance measures.

Studies that examined functional status in other ways found that Black older adults with depression reported high rates of functional impairment and significantly worse quality of life compared to those with low depression scores (Sharma et al., 2009). Black older adults with acute decompensated heart failure and depression were also found to have significantly longer hospital stays, more health comorbidities, and a greater likelihood of having more severe and physically limiting heart failure symptoms than those without depression (Sharma et al., 2009). Some evidence for racial differences was also identified: Compared to White adults, Black adults with co-occurring cardiovascular disease and depression reported more days of functional impairment (González & Tarraf, 2013). Additionally, baseline depressive symptoms and worsening of symptoms over three months were associated with increased all-cause mortality

and hospitalization in Black but not White participants (Mentz et al., 2015). VaDep, therefore, may be associated with slowed gait speed and decline in functional status among older Black adults.

1.5 Objective

Since Black adults have a higher prevalence of vascular disease (Tabaei et al., 2019) and greater WMH burden (Hsu et al., 2018) compared to other racial groups, this population may be at high risk of developing VaDep. However, there is little research to date that examines the VaDep framework in Black older adults, and even less research exploring the role of WMH burden in this population. In the systematic review by Bogoian and Dotson (2021), only one study (Reinlieb et al., 2014) classified VaDep based on severity of WMH, a more proximal measure of vascular burden in the brain compared to clinical criteria. This is a key gap in the literature, given the importance of WMH in the development of mood changes, cognitive decline, and reduced physical function via damage to frontolimbic circuits (Salo et al., 2019). VaDep is associated with treatment resistance, cognitive deficits, and functional disability (Aizenstein et al., 2016), therefore examining VaDep in Black adults is vital for informing successful depression treatment for a vulnerable and underserved population.

Using data from the Health, Aging and Body Composition study (Health ABC) and Healthy Brain Project sub-study (Venkatraman et al., 2011), the present study addresses important gaps in the literature by examining the relationships of vascular health and WMH with depressive symptoms in a Black sample followed for four years, and determining whether operationally-defined VaDep is associated with cognitive outcomes and gait speed.

1.6 Specific Aims and Hypotheses

1.6.1 Aim 1. Test the vascular depression hypothesis in a community sample of Black older adults by examining cross-sectional and longitudinal associations of vascular burden (Aim 1A) and WMH severity (Aim 1B) with depressive symptoms.

Vascular burden was calculated as the number of self-reported and objective measures of vascular conditions, and WMH measures were available for the total brain and for specific tracts in the brain. Depressive symptoms were assessed by self-report questionnaire. Based on the VaDep literature among non-Black samples and findings of the review by Bogoian and Dotson (2021), I hypothesized that participants with greater vascular burden (Hypothesis 1A) and greater WMH severity (Hypothesis 1B) would have more depressive symptoms at baseline and over four years of follow-up.

1.6.2. Aim 2. Examine whether VaDep in Black older adults is associated with cognitive deficits at baseline or cognitive decline over four-year follow-up.

Participants were divided into four groups according to vascular and depressive symptom burden: low vascular burden/low depressive symptoms, high vascular burden/low depressive symptoms, low vascular burden/high depressive symptoms (non-vascular depression), and high vascular burden/high depressive symptoms (VaDep). Consistent with the VaDep hypothesis, it was expected that Black older adults with VaDep would have worse processing speed and executive functioning and experience more cognitive decline over time compared to the other groups.

1.6.3 Aim 3. Examine whether VaDep in Black older adults is associated with slower gait speed at baseline or decline in gait speed over four-year follow-up.

It was expected that Black older adults with VaDep at baseline would have the slowest baseline gait speed and greatest decline in gait speed over time, compared to all other groups.

1.6.4 Exploratory Aim. Examine the impact of race on the relationships between depressive symptoms and vascular health, as well as cognitive and functional outcomes in VaDep.

The analyses from Aims 1-3 were repeated with the inclusion of non-Hispanic White participants from the Healthy Brain Project, who were similar in age to the Black sample, to determine whether effects differ by race. These analyses were exploratory given the little research available that has examined race differences in Black compared to White individuals with VaDep.

2 METHODS

2.1 Participants

Data came from Health ABC, a prospective study of older adults that began in 1997-1998 (Simonsick et al., 2001). Data from this study are available to the public (https://healthabc.nia.nih.gov/). Health ABC was designed to assess how weight-related health conditions and behavioral factors affect functional decline and independence in older adults. Participants in the study were required to be aged 70-79 at baseline (1997-1998) and to live in either Memphis, TN or Pittsburgh, PA. Participants were recruited from a random sample of Medicare-eligible adults living within designated zip codes and were considered eligible for the study if they reported no difficulty performing activities of daily living, walking a quarter mile, or climbing 10 steps without resting. Participants were also required to be free of life-threatening cancers and plan to participate in the study for at least three years. This study was approved by the institutional review boards of the University of Pittsburgh, the University of Tennessee, Memphis, and of the Coordinating Center, the University of California San Francisco. All

participants gave written informed consent. The original longitudinal cohort consisted of 3,075 men and women, aged 70-79 at baseline. Almost half of the women (45%) and one third of the men (33%) in the baseline sample are Black.

The present analyses used the ancillary Healthy Brain Project conducted at the University of Pittsburgh data collection site from 2006-2011. A total of 325 participants were seen annually during that time with 314 receiving at least one 3-Tesla MRI scan. To be eligible for the Healthy Brain Project, participants had to meet the following additional criteria: had not been hospitalized for major clinic events in the previous 3 months (e.g., fracture or psychiatric problem), had not received lithium within the preceding week, and had no contraindication for 3-Tesla MRI (i.e., questionable history of metallic fragments, cardiac pacemaker, aneurism clip, cochlear implants, shrapnel, history of metal fragments in eyes or other body parts, neurostimulators, weight of 250lb or more, or claustrophobia). The Healthy Brain Project was approved by the Institutional Review Board and all participants provided informed consent. All participants with a Teng Mini-Mental State Exam (3MS; Teng & Chui, 1987) score of 78 or lower at the Healthy Brain Project baseline were excluded from the present analyses, since that cutoff is highly sensitive to screening for dementia with 88% sensitivity and 90% specificity (Bland & Newman, 2001). Other studies have found that older Black adults have lower unadjusted scores on the 3MS compared to Whites (Mehta et al., 2004) and that scores are more strongly affected by years of education in Black compared to White older adults (Ryan et al., 2019). An alternative 3MS cut-off score for dementia has not been proposed, however, so the cut-off score of 78 or lower was used in the current study to screen for dementia. After removing participants with suspected dementia and with missing demographic information, the total sample of participants was 292 (113 Black; 179 White). Since the sample size varied somewhat

for each analysis based on the availability of data for the variables of interest, demographic characteristics are summarized for each analysis in Tables 2 through 9.

2.2 Measures

2.2.1 Depressive Symptoms

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D), a commonly used, 20-item self-report measure of depressive symptoms with high internal consistency among the general population (Cronbach's alpha = 0.85; Carleton et al., 2013; Haringsma et al., 2004; Radloff, 1977). This scale has well-documented validity in an older adult population (Gellis, 2010; Gomez & McLaren, 2015; Lewinsohn et al., 1997) as well as in Black adults (Adams et al., 2019; Kim et al., 2011). The CES-D was collected yearly for study participants, thus longitudinal CES-D data is available for baseline and up to four additional timepoints in the Healthy Brain Project. The CES-D total score ranges from 0 to 60, with higher scores indicating higher depressive severity. This score was used as a continuous measure for Aim 1A and 1B, whereas the highest tertile of scores was used to form "high" and "low" depressive symptom groups for Aim 2 and 3 analyses. Typically, a score of 16 is the cut-off for clinical depression (Lewinsohn et al., 1997). However, since the Healthy Brain Project sample (and Health ABC parent study) was not recruited for depression, the highest tertile was used to create high and low depressive symptoms groups.

2.2.2 Vascular Burden

A number of subjective and objective variables related to cardiovascular/cerebrovascular health are available in the dataset (see Table 1). Variables from the original Health ABC baseline that assessed participants' previous history of vascular conditions during their lifetime were summed along with objective vascular measurements collected at the Healthy Brain Project

baseline to form a cumulative vascular burden score (1 point per condition). The cumulative vascular burden score (possible range of 0 to 6) was used in the statistical analyses for this project.

2.2.3 Cognitive Function

A battery of neuropsychological tests was administered to Healthy Brain Project participants at baseline and subsequent follow-up visits; however, there is a high amount of missing neuropsychological data in the dataset. The present analyses focused on the Digit Symbol Substitution Test (DSST) and 15-Item Executive Interview (EXIT-15) since the literature shows processing speed and executive function deficits in VaDep, and the available data for these tests was nearly complete.

The DSST is a paper-and-pencil measure of information processing speed and psychomotor performance. It consists of nine digit-symbol pairs, and participants are required to fill in as many corresponding symbols for the given digits within 90 seconds (Wechsler, 1981). The score for this measure is the total number of symbols correctly coded, and a higher score indicates better processing speed. This test has high test-retest reliability (Matarazzo & Herman, 1984).

The EXIT-15 is a shortened form of the original 25-item Executive Interview (Royall et al., 1992) that was developed for the Health ABC study. This measure assesses executive functions including inhibition of automatic responses and intrusions, word and design fluency, and sequencing tasks. Each item is scored as 0 (intact performance), 1 (partial error or equivocal response), or 2 (incorrect response or failure to perform the task) for a total score ranging from 0 to 30, with a lower score indicating better performance. Scores were used as a continuous measure for Aim 2.

2.2.4 Gait Speed

Gait speed was measured as the time needed to walk a 20-meter straight course setup along a hallway (Cesari et al., 2009). Timing was recorded with a stopwatch and began with the first footfall over the starting line and ended with the first footfall over the finishing line (Watson et al., 2010). Height-normalized gait speed was used in the analyses for Aim 3 and was calculated by dividing gait speed (in meters) by each participant's height (in millimeters) and multiplying by 1,000.

2.2.5 Covariates

Baseline age, sex, and years of education (< 12 years, 12 years, or > 12 years) were included as covariates. Additional variables of interest related to social determinants of health (e.g., financial need, race-related stress, socioeconomic status) were not available in this dataset.

2.3 Imaging

MRI scanning was performed at the MR Research Center of the University of Pittsburgh using a 3-Tesla Siemens Tim Trio MR scanner. An iterative algorithm automatically selected "seeds" of possible WMH lesions and then used fuzzy connectedness to segment WMH lesions around the seeds (Wu et al., 2006). The segmented WMH voxels were then localized to the different white matter tracts using the automated method described in the Johns Hopkins University White Matter Atlas. The current analyses used volumes based on this process for total WMHs and for WMHs in regions of interest in the uncinate fasciculus, superior longitudinal fasciculus, and upper and lower cingulum, based on previous literature suggesting these specific tracts are altered in depression (Tadayonnejad & Ajilore, 2014). WMH variables have been normalized to total brain volume in the Healthy Brain Project dataset.

2.4 Data Analysis

A series of regression analyses were performed in SAS to address the three aims. Any CES-D scores, WMH volumes, gait speed, or cognitive test scores ≥ 3 standard deviations from the mean were removed from the respective data analysis. This was to prevent exceptionally high scores from skewing the data or driving the results of the analyses.

2.4.1 Aim 1: Vascular Burden and Depression

Multiple regression analyses were performed to examine cross-sectional and longitudinal associations of clinical vascular burden (Aim 1A) and WMH severity (Aim 1B) with depressive symptoms, as a test of the vascular depression hypothesis. Since the VaDep hypothesis posits that vascular disease predicts depression rather than vice versa, clinical vascular burden (calculated as the summed value of all subjective and objectively-measured vascular conditions; see Table 1) or WMH severity served as the independent variables in following analyses.

Cross-sectional analyses used clinical vascular burden (Aim 1A) and WMH volumes (Aim 1B) to predict baseline CES-D scores when controlling for baseline age, sex, and education level. Separate regression analyses examined cumulative vascular burden, total WMH volume, as well as uncinate fasciculus, superior longitudinal fasciculus, and upper and lower cingulum WMH volume. All WMH volumes were normalized for total brain volume prior to being entered in the analyses, therefore total brain volume was not entered into the Aim 1B statistical models as a separate covariate.

Longitudinal analyses used separate multiple regression models to examine baseline clinical vascular burden and WMH volumes as predictors of depressive symptom burden over the four follow-up visits. Depressive symptom burden was calculated as the average total CES-D score across all annual follow-up visits for each participant. This average score was chosen as the

outcome variable because it captures the chronicity of depressive symptoms over time. The longitudinal models also controlled for baseline age, sex, and education level.

2.4.2 Aim 2: Vascular Depression and Cognitive Function

Mixed effects regression analyses were performed in SAS using the PROC MIXED procedure to analyze the longitudinal relationship between baseline VaDep status and cognitive deficits at baseline or cognitive decline over four-year follow-up. Vascular burden by depression groups were formed based on cutoff scores for the CES-D and the vascular burden variable. As is common with other community samples that do not select participants based on having a diagnosis of major depression, there were low numbers of participants who met the CES-D cutoff score for clinical levels of depression (CES-D ≥ 16) in the Healthy Brain Project sample. In order to better balance participants across groups, therefore, the highest tertile of CES-D score in the sample (CES-D ≥ 7) was used to delineate "depressed" and "non-depressed" groups. Thus, depression refers to subthreshold depression. A cutoff of two on the vascular burden variable delineated high and low vascular burden based on findings from the Bogoian and Dotson (2021) systematic review which showed that having two or more vascular diseases or vascular risk factors in conjunction with depression was consistently linked to negative outcomes (Azar et al., 2005; Carmasin et al., 2014; Hamm et al., 1993; Lamar et al., 2015; Mast, MacNeill, et al., 2004; Mast, Neufeld, et al., 2004; Mast, Yochim, et al., 2004; Yochim et al., 2003; Yochim, Kerkar, et al., 2006; Yochim, MacNeill, et al., 2006).

The VaDep group was then operationally defined as having ≥ 2 vascular conditions and having a score of 7 or more on the CES-D. Using mixed-effects regression analyses, DSST and EXIT-15 performance of the VaDep group was compared to the cognitive performance of the following groups: non-vascular depression (CES-D ≥ 7, < 2 vascular conditions), vascular-only

(CES-D < 7, ≥ 2 vascular conditions), and healthy (CES-D < 7, < 2 vascular conditions). Mixed-effects regression analyses yield information on the unique effects of each predictor, including fixed and random effects, adjusting for all other terms in the model. Mixed-effects models account for correlations among repeated measurements on the same participant, are unaffected by unequal numbers of visits among participants, and account for differences in the interval between visits. Thus, mixed-effects analyses are ideal for examining VaDep effects on longitudinal changes in cognitive functioning.

VaDep group, interval, and interval^2 were entered as independent variables with DSST and EXIT-15 scores as dependent variables in separate models. Interval represents the number of years since baseline testing and therefore captured longitudinal changes. Interval^2 was included to capture nonlinear longitudinal changes. Baseline age, sex, and education were entered as covariates. Independent variables and their interactions were modeled as fixed effects, while intercept and interval were modeled as random effects. All two- and three-way interactions were included in the models. A backward elimination procedure was used: All main effects remained in the model while non-significant interaction terms ($p > 0.05$) were eliminated from the model in stages until a final solution was reached (Morrell et al., 1997).

2.4.3 Aim 3: Vascular Depression and Gait Speed

Mixed effects regression models were also used to examine whether vascular burden by depression group was associated with gait speed at baseline or gait speed decline over four years of follow-up. Models paralleled the analyses for Aim 2, with height-adjusted gait speed as the dependent variable in place of the cognitive test scores.

2.4.4 Exploratory Aim

Since it is unclear, based on the larger literature, whether VaDep is associated with worse outcomes in Black compared to White older adults, exploratory analyses were conducted to examine the impact of race on the relationship between depressive symptoms and vascular health, and on VaDep-related cognitive and physical function. The Black sample did not significantly differ in age from the non-Hispanic White participants (N = 179) from the Healthy Brain substudy. Therefore, analyses for Aims 1-3 were repeated on the total Healthy Brain sample with the addition of race as a predictor.

2.4.5 Power Analyses

Post-hoc power analyses were conducted using G*Power 3.1.9.2 (Erdfelder et al., 1996) in order to identify the current study's ability to detect effects assuming four predictors, including covariates, for all Aim 1 analyses and cross-sectional analyses for Aims 2 and 3, and assuming eight predictors, including covariates, for Aims 2 and 3 longitudinal analyses. All analyses were adequately powered to detect medium effects at the .05 alpha level, including main and exploratory aims (see Table 22).

3 RESULTS

3.1 Aim 1A: Clinical Vascular Burden and Depression

Neither cross-sectional ($F(1, 107) = 1.76$, $p = .169$) nor longitudinal ($F(1, 107) = 1.92$, $p = .061$) relationships between cumulative vascular burden and depressive symptoms were observed in this community sample of older Black adults (Table 10), although the longitudinal analysis trended towards significance. To better understand these findings, we performed post-hoc analyses stratified by sex and age. No interactions of sex or age with cumulative vascular burden were significant.

3.2 Aim 1B: WMH Burden and Depression

As hypothesized, a cross-sectional relationship between WMH volume and depressive symptoms was observed. Analyses revealed that greater total WMH volume ($F(1, 106) = 7.63$, $p < .001$; Table 11, Fig. 1) and greater WMH volume in the uncinate fasciculus ($F(1, 106) = 4.67$, $p < .001$; Table 12, Fig. 3) were associated with higher depressive symptoms at baseline. Longitudinal analyses revealed a positive relationship of total WMH volume ($F(1, 106) = 6.77$, $p < .001$; Table 11, Fig. 2) and WMH volume in the uncinate fasciculus ($F(1, 106) = 3.96$, $p < .001$; Table 12, Fig. 4) with CES-D scores over the follow-up period, such that greater WMH volume at baseline predicted higher average depressive symptoms over four years of follow-up. WMH volume in the superior longitudinal fasciculus and upper and lower cingulum were not associated with depressive symptoms at baseline or with average depressive symptoms over the follow-up period (see Tables 13-15).

3.3 Aim 2: Vascular Depression and Cognitive Function

Cross-sectional analysis of cognitive performance revealed an effect of vascular burden by depression group on processing speed (DSST: $F(3, 104) = 4.59$, $p < .01$; Table 16), but not executive functioning (EXIT-15: $F(3, 104) = 2.86$, $p = .123$; Table 18). Of the four groups, the VaDep group had the slowest DSST performance (Fig. 5). Similarly, the VaDep group had the slowest DSST performance in the longitudinal analysis (Group $F(3, 104) = 4.10$, $p < .01$; Table 17), but their rate of decline over four years did not differ from other groups (Group × Interval: $F(3, 236) = 0.11$, $p < .956$; Fig. 6). In the longitudinal analysis, there was a significant interval by group interaction for the EXIT-15 ($F(3, 164) = 3.43$, $p < .05$; Table 19) such that the non-vascular depression group's executive functioning performance improved over time, the VaDep group improved slightly over time, and the healthy and vascular-only groups' performance

stayed relatively stable (Fig. 7). Although the effect did not reach significance, the VaDep group had the worst EXIT-15 performance across all timepoints (Fig. 7).

3.3.1 Post-hoc Analysis

Based on the findings from Aim 1, in which WMH but not vascular burden was associated with depressive symptoms, post-hoc analyses were performed in which the four vascular burden by depression groups were defined using WMH burden instead of clinical vascular burden. A median split of total WMH volume was performed and individuals with total WMH volume in the 50th percentile or higher were considered to have "high" vascular burden, instead of using two or more clinical vascular conditions to form the "high" vascular burden groups.

Results mirrored the findings when using clinical vascular burden to define vascular/depression groups: There were no cross-sectional effects of group on DSST or EXIT-15 scores (DSST $F(3, 103) = 3.31$, $p = 0.134$; EXIT-15 $F(3, 103) = 3.12$, $p = .073$); however, group significantly predicted DSST longitudinally ($F(3, 104) = 4.74$, $p < 0.01$) and a nearly significant trend was observed for EXIT-15 ($F(3, 104) = 2.57$, $p = 0.058$). The VaDep group had the slowest performance on the DSST compared to all other groups, and the non-vascular depression group again improved over time on the EXIT-15, in contrast to the other groups ($F(3, 162) = 4.44$, $p < 0.01$).

3.4 Aim 3: Vascular Depression and Gait Speed

Cross-sectional analyses revealed that gait speed did not differ among vascular burden by depression groups ($F(3, 100) = 2.29$, $p = .120$; Table 20). When examining group differences over time, there was a significant interval by group interaction ($F(3, 144) = 2.78$, $p < .05$) and a significant interval^2 by group interaction ($F(3, 144) = 2.77$, $p < .05$; see Table 21). Gait speed for

both the VaDep and non-vascular depression groups worsened over time, while the non-depressed groups initially declined but then improved in the last visit (Fig. 8).

3.4.1 Post-hoc Analysis

Similar to the primary analyses, there were no significant vascular burden by depression group differences in baseline gait speed when defining high vascular risk by WMH volume. Longitudinally, there was a significant interval by group interaction ($F(1, 148) = 7.39$, $p < .01$) and interval^2 by group interaction ($F(1, 148) = 3.97$, $p < .05$), such that both depression group's gait speed declined over time whereas the non-depressed groups' gait speed initially declined and then improved.

3.5 Exploratory Analyses

When data from Black and White individuals were combined, the association of greater WMHs in the uncinate fasciculus with higher baseline CES-D scores was greater in Black than in White participants ($F(1, 280) = 3.49$, $p < .05$; Fig. 9), as was the association of WMHs in the uncinate fasciculus with average CES-D across four years ($F(1, 281) = 2.65$, $p < .01$; Fig. 10). The Black VaDep group had the lowest DSST scores compared to all other Black and White groups (race × group: $F(3, 273 = 5.52$, $p < .05$; Fig. 11). There were no other significant interactions between race and vascular burden by depression group.

4 DISCUSSION

To my knowledge, this study is the first to examine the predictive value of both clinical and imaging markers of vascular burden on depressive symptoms, longitudinally, in an older Black sample. This study provides further support for the validity of the VaDep hypothesis among older Black adults. Findings suggest that total WMH burden is more closely related to

concurrent depressive symptoms and to depressive symptom burden over four years compared to clinical measures of vascular burden (e.g., presence of self-reported and objectively-measured diabetes, hypertension, peripheral artery disease, etc.). The hypothesis that participants with VaDep at baseline would perform more poorly on cognitive tasks compared to other vascular/depression groups was also supported, as was the hypothesis regarding gait speed decline.

4.1 Imaging and Clinical Predictors of Vascular Depression

White matter lesions, seen as WMH on neuroimaging, are known to underlie VaDep (K. R. Krishnan et al., 1997) and are important indicators of vascular damage to the brain. It is logical, therefore, that WMH burden would predict greater depressive symptoms when clinically-measured vascular burden did not. WMH volume is a marker of true vascular insult to the brain, whereas clinical diagnoses of vascular conditions, such as diabetes and hypertension, are risk factors for cerebrovascular damage, especially with prolonged exposure. My findings suggest that WMH burden is sensitive to predicting even subthreshold depression among older Black adults.

It is striking that the VaDep relationship between cerebrovascular disease and depressive symptoms is present at the level of subthreshold depression. This result is consistent with findings from the broader literature indicating that individuals with subthreshold depression experience white matter microstructural changes similar to those observed in major depressive disorder (Allan et al., 2016). Severity of subthreshold depressive symptoms are also associated with more rapid white matter volume loss in the left frontal region (Dotson, Davatzikos, et al., 2009) and with gray matter volume reductions in the frontal and temporal lobes among older adults (Dotson, Davatzikos, et al., 2009; Kumar et al., 1998; Kumar et al., 1997). Subthreshold

depressive symptoms have also recently been linked to the presence of clinical vascular conditions in mid-to-late life, including elevated blood pressure variability (Sible et al., 2022) and an overall cardiovascular health score that includes a number of modifiable vascular risk factors such as body weight, blood glucose, total cholesterol, blood pressure, and frequency of physical activity (Carroll et al., 2020). Together, these findings highlight the significance of depressive symptoms that are considered "non-clinical" and thus might be overlooked by health professionals.

Studies examining the relationship between WMH burden and depressive symptoms are usually cross-sectional and usually focus on total WMH volume. Thus, the current study was novel in its demonstration that uncinate fasciculus WMH volume was associated with the severity of depressive symptoms at baseline and also with the chronicity of depressive symptoms over four years among older Black adults. The uncinate fasciculus, an important white matter tract that connects limbic structures such as the amygdala and hippocampus to the prefrontal cortex, is often disrupted in late-life depression (Steffens et al., 2011). Individuals with late-life depression have greater WMH burden (Sheline et al., 2008; Wen et al., 2014) and poorer white matter integrity (Charlton et al., 2014; Harada et al., 2016; Wen et al., 2014) in the uncinate fasciculus compared to non-depressed elders. Reduced white matter integrity in the uncinate fasciculus has also been associated with apathy, as opposed to depression, in older adults (Hollocks et al., 2015). Given that apathy is a hallmark feature of VaDep (Aizenstein et al., 2016), the role of the uncinate fasciculus is an interesting area for future exploration within the VaDep hypothesis, particularly in older Black samples.

4.2 Vascular Depression and Cognitive Performance

The VaDep group had a similar trajectory of processing speed performance over time compared to the other vascular/depression groups; however, individuals with VaDep had the slowest performance on the DSST both at baseline and longitudinally. This was true when VaDep was defined based on clinical measures and when it was based on WMH volume. It is unsurprising that processing speed performance was significantly impacted by subthreshold VaDep symptoms given that processing speed is highly affected by changes in brain health. A large, population-based study found that low psychomotor speed as measured by the DSST was associated with increased risk of all-cause dementia, Alzheimer's disease, Parkinson's disease, disability, and depressive symptoms (Amieva et al., 2019). Another study using longitudinal data from the Health ABC study found that being in the lowest compared to the highest quartile of DSST performance was associated with nearly twice the odds of developing one or more disorders of global cognition, gait speed, and depression (Rosano et al., 2016). Moreover, in that study, those who developed disorders of cognition, mobility, or mood were more likely to be older, Black, and less educated, and to have vascular risk factors including hypertension, diabetes, and markers of peripheral artery disease.

In the present study, the non-vascular depression group's executive functioning improved over time compared to the VaDep group, which had slight improvement, and health and vascular-only groups, which had relatively stable trajectories. Although the effect was not significant, the VaDep group had the poorest EXIT15 performance across both WMH and clinical definitions of VaDep. This finding of improved executive function for the non-vascular depression group could reflect the more transient nature of cognitive impairment in non-vascular depression, in contrast to the more stable executive dysfunction when cognitive impairment is

present in those with VaDep (Aizenstein et al., 2016). This suggestion is strictly speculatory, however, given that there is no information about whether individuals with non-vascular depression or VaDep received depression treatment over the course of the study. The larger VaDep literature has consistently identified a relationship between VaDep and executive dysfunction (Alexopoulos, 2019) and there is some limited evidence to suggest that VaDep in Black individuals is also associated with executive dysfunction (Reinlieb et al., 2014; Yochim, MacNeill, et al., 2006). Therefore, the lack of relationship of VaDep with executive functioning in this sample was unexpected. It is possible that, given the subthreshold nature of the depressive symptoms experienced by this study sample, the VaDep symptoms were not severe enough to affect executive functioning. Additionally, the EXIT-15 is a measure that combines a number of executive functions into one assessment. More subtle relationships between subthreshold VaDep and executive functions might be uncovered if measures are used to assess individual aspects of executive functioning separately, such as verbal fluency, set-switching, and frontal motor programming.

4.3 Vascular Depression and Gait Speed

When vascular burden by depression group was based on a clinical definition, the VaDep group did not have slower gait speed at baseline. However, both the VaDep and non-vascular depression groups had gait speed trajectories that worsened over time when compared to the vascular-only and healthy groups. Additionally, when high vascular risk was defined as WMH burden instead of clinically-defined vascular burden, the VaDep group's gait speed declined over time while all other groups' gait speed performance improved.

The literature regarding gait speed and VaDep is mixed. The triad of slow gait speed, executive dysfunction, and depression was related to high cardiovascular burden in one

community sample (Hajjar et al., 2009), and older adults with trajectories of high inflammation, slow gait, and depressive symptoms formed a high-mortality risk phenotype in another longitudinal study (Brown et al., 2016). Additionally, in an older, 41% Black sample, chronic inflammation—a known correlate of vascular disease—over 10 years was associated with slowed gait speed and higher WMH (Nadkarni et al., 2016). These data suggest that vascular risk (broadly including inflammation and WMH) and slow gait are related in the context of late-life depression.

Frailty, which by definition includes slow gait speed (Fried et al., 2001), is also highly comorbid with late-life depression (Soysal et al., 2017), while WMH burden has been linked to both the progression (Siejka et al., 2020) and severity (Maltais et al., 2019) of frailty symptoms. Interestingly, one study found that while greater frailty was not associated with greater WMH burden or cognitive impairment, slow gait speed alone was associated with poorer performance on tests of episodic memory, processing speed, and executive functioning (Brown et al., 2020). In light of the current study findings, which identify a decline in gait speed over time for individuals with subthreshold VaDep, the relationship between gait speed and VaDep is worth further exploration given their shared etiology of WMH and inflammation.

4.4 Race Differences in VaDep and its Correlates

In this study sample, total and uncinate fasciculus WMH burden were predictive of depressive symptoms in a way that clinical indicators of vascular disease were not. Additionally, exploratory analyses revealed that the relationship between uncinate fasciculus WMH burden and depressive symptoms was stronger in Black than in White individuals. These findings suggest the importance of neuroimaging in the diagnosis of VaDep for older Black individuals and suggests that WMH in the uncinate fasciculus may play a particularly important role in the

onset and trajectory of VaDep in this demographic group. Future work should examine the role of the uncinate fasciculus among Black older adults, perhaps as a more specific marker of VaDep.

There is a body of research supporting the differential impact of WMH on brain health among older Black adults. The association of regional WMH and cortical thinning, which is another sign of pathological aging and brain vulnerability, has been found to be stronger among Black compared to White Americans (Rizvi et al., 2021). Additionally, a combination of higher peripheral inflammation and lower executive function was associated with decreased white matter integrity for Black participants only in another study (Boots et al., 2020). Regarding cognition, larger WMH volume was associated with deficits in speed/executive functioning among Black but not White adults (Zahodne et al., 2015). WMH may also have a unique relationship with other vascular risk factors in predicting cognitive outcomes among Black individuals. A recent study found that, in the presence of greater WMH burden, higher diastolic blood pressure was associated with faster rates of episodic memory decline in an older Black sample (Lamar et al., 2022). This finding suggests that high blood pressure alongside already-present WMH burden puts older Black adults at risk for accelerated cognitive aging. Overall, WMH may differentially impact the development of neuropsychiatric disorders among aging Black adults compared to other racial/ethnic groups, and the present relationship found between WMH in the uncinate fasciculus and depression adds to our understanding of this phenomenon.

Similar to previous studies suggesting a disproportionate impact of depression on Black compared to White adults (Vyas et al., 2020), the Black VaDep group had the slowest processing speed performance on the DSST in the cross-sectional analysis for this study. Greater levels of depression have been associated with worse episodic memory in Black but not White adults

(Dixon et al., 2021). Additionally, in a nationally representative sample, Black older adults had the highest disease burden of depression, were the most likely to have comorbid cardiovascular disease and depression compared to all other racial/ethnic groups, and had significantly more days of functional impairment compared to Whites (González & Tarraf, 2013). On a clinical level, the cognitive consequences of subthreshold VaDep for this older Black sample point to the importance of screening for depression among older Black adults with vascular conditions.

There are shared cultural experiences of racial discrimination that, at least in part, may account for these race differences. For racial and ethnic minorities in the U.S., experiences of racism are associated with poorer general health, physical health, and mental health, including depression, anxiety, and psychological stress (Paradies et al., 2015). Recent research into the impact of racism on brain health indicates that Black adults may be specifically at risk for neuropsychiatric disorders. For example, greater perceived discrimination was directly associated with faster memory decline in an older Black sample, whereas Hispanic ethnicity was not linked to memory decline in one study (Zahodne et al., 2019). Chronic inflammation has been linked to faster global cognitive decline in an older Black sample (Boots et al., 2022), and greater lifetime racial discrimination has been associated with greater white matter lesion burden (Beatty Moody et al., 2019). Additionally, Zahodne et al. (2022) found that lifetime racial discrimination (e.g., discrimination in the labor or housing market) was associated with lower hippocampal volume in an older Black sample, whereas more frequent, everyday discrimination was associated with faster WMH accumulation over four years. Racism and discrimination, therefore, negatively affect brain health and cognitive aging among Black individuals in a way that creates and perpetuates racial disparities.

Inequalities in health care access, unemployment, and poverty, also play a major role in race-related vascular health disparities (Maraboto & Ferdinand, 2020; Mensah, 2018). Low socioeconomic status (Waldstein et al., 2017) and lifetime racial discrimination (Beatty Moody et al., 2019) have both been linked to greater white matter lesion volume in Black adults. Racial discrimination also may have a unique interaction with mood and cognitive function: In a large community sample of older adults, greater perceived discrimination among Black adults with depression led to faster memory decline compared to Hispanic participants (Zahodne et al., 2019). Racial discrimination has also been associated with greater odds of multimorbidity in a dose-dependent fashion, such that the more experiences of everyday racial discrimination, the greater likelihood that Black adults will have multiple chronic diseases, many of which are vascular in nature (Oh et al., 2021). Therefore, Black older adults may be particularly vulnerable to VaDep in light of the negative impact that racial discrimination and other psychosocial and socioeconomic factors have on white matter integrity and vascular health.

These findings regarding discrimination, brain integrity, and vascular health are particularly relevant for the present study's sample, which consists entirely of Black individuals in their eighth decade of life. It must be taken into account that these individuals, born primarily in the 1940s, were raised into adulthood within a racially-segregated society that had wide-ranging negative consequences for socio-economic wellbeing, health, and educational quality (Dotson & Stringer, 2022). Particularly given that experience of discrimination is linked to higher vascular and inflammatory markers (Cuevas et al., 2020; Moody et al., 2019; Ong et al., 2017), the impact of lifetime experiences of racism, including experiences of discrimination in housing, the workforce, educational opportunities, and the legal and criminal justice systems,

cannot be overlooked as important factors that may be impacting brain health in this aging Black sample.

4.5 Implications

This study provides support for the validity of the VaDep hypothesis and suggests that WMH burden, particularly in the uncinate fasciculus, is linked to subthreshold VaDep in older Black adults. From a broader perspective, this study fills an important gap in the literature by shedding light on a vulnerable and under-studied group of individuals who are at risk for developing VaDep. Black Americans are far less likely than other racial/ethnic groups in the U.S. to have optimal cardiovascular health (Brown et al., 2018), are more likely to have an earlier age of onset for chronic cardiovascular diseases, and are more likely to develop multimorbidity (i.e., the presence of two or more coexisting chronic conditions) at an earlier age than their White peers (Quiñones et al., 2019). Multimorbidity increases aging individuals' risk of disability, functional decline, poor quality of life, and high healthcare costs (Marengoni et al., 2011), and the number of medical conditions developed by Black adults increases in a dose-dependent fashion based on their experience of everyday discrimination (Oh et al., 2021). Racial health disparities are present in the diagnosis and treatment of depression for Black adults as well. Black individuals with late-life depression are less likely to have been treated with antidepressants (Hall et al., 2015; Mansour et al., 2020) and are up to 61% less likely to report treatment with medication or counseling compared to their older White peers (Vyas et al., 2020) The present study, therefore, draws attention to the negative cognitive and functional impacts of subthreshold VaDep in a group of older adults that is in great need of culturally-informed depression diagnosis and intervention.

Based on the above-mentioned racial health disparities that make aging Black adults more vulnerable to negative health outcomes in late life, it is essential to assess for VaDep in this population in order to prevent a host of additional negative cognitive and functional consequences. The findings from this study suggest that cognitive and gait slowing may accompany subthreshold depressive symptoms and high vascular risk. Therefore, clinicians should assess and implement treatments for vascular disease and mood symptoms, even if DSM-5 criteria for major depression have not been met. Non-pharmacologic strategies for maintaining heart health and mental health should be implemented early, since maintaining heart health may prevent or delay the onset of depressive symptoms (Willis et al., 2018). For example, exercise has been shown to support white matter integrity (Mendez Colmenares et al., 2021; Sexton et al., 2016) and to reduce depressive symptoms among older adults (Klil-Drori et al., 2020), on par with the success of treatment with psychological or pharmacological therapies (Cooney et al., 2013). Therefore, management of vascular conditions in mid-life through use of exercise and use of both pharmacologic and non-pharmacologic solutions should be considered as long-term strategies for promoting healthy mood in later life.

4.6 Future Directions

In light of the paucity of research examining VaDep in Black older adults, there are a number of important future directions for this line of work. First and foremost, future work should investigate the efficacy of accessible non-pharmacologic interventions such as exercise in the prevention and treatment of VaDep in racially diverse groups. Exercise interventions should be evaluated for their ability to prevent and treat clinical depressive symptoms, as well as their ability to improve (or mitigate damage to) brain white matter health in the context of VaDep.

To reduce the risk of VaDep in this vulnerable group, future research should also examine protective factors for aging Black adults with high vascular burden. The present study sample was quite old (*M*= 82.49 years) and had high chronic vascular burden, yet overall was experiencing low levels of clinically-significant depression. This indicates that there are yet-to-be studied features of resilience that will be important to identify for the health and wellness of future generations. Psychosocial resilience in Black adults has been associated with better cardiovascular health (Kim et al., 2020) and increased social support is associated with better depression medication adherence in older Black females (Gerlach et al., 2017); therefore, identifying ways to promote resilience among older Black adults may directly reduce this vulnerable population's risk of VaDep.

Exploration of gender-based coping strategies may also yield profiles of both vulnerability and resilience for older Black adults. A population-based study examining age and gender differences in psychological stress found that older Black men experienced less life interference from psychological stress compared to other Black gender/age groups (Watkins & Johnson, 2018). In contrast, Black men, especially those with low socioeconomic status, may be at high risk for poor health due to gendered coping responses to stress, economic marginality, and adverse working conditions (Williams, 2003).

Culturally-specific coping strategies must also be explored. John Henryism, which is a high-effort, active coping style often used by Black Americans, has been shown to be simultaneously related to less depression/psychological distress (Bronder et al., 2013), worse cardiovascular health (Sherman A., 2019), and higher allostatic load (Robinson & Thomas Tobin, 2021). These results are mixed, however; some studies have found that John Henryism is linked to higher, rather than lower, levels of depression (Hudson et al., 2016) and is not

consistently linked to cardiovascular health in Black women (Felix et al., 2019). Given that VaDep is a direct consequence of high vascular burden in late life, understanding the role of John Henryism (and other culturally-relevant coping strategies) as a risk or protective factor for VaDep may be beneficial towards identifying future culturally-informed treatment strategies for aging Black adults.

4.7 Limitations

Primary limitations of this study include the inability to control for more extensive psychosocial factors such as socioeconomic status, marital status, retirement status, and experience of discrimination and adversity, which are all known to play a role in depression, vascular disease, and cognitive impairment in late life. Since the community sample did not allow for an analysis of clinical depression, there are additional limitations in the extent that findings can be generalized to the broader VaDep literature. However, as noted earlier, subthreshold depression is even more common in older adults than major depression, thus, examination of subthreshold VaDep is relevant and significant. The data also did not allow past history of anxiety, trauma, substance abuse, and other psychiatric disorders that often co-occur with depression to be taken into account.

4.8 Conclusion

The limited inclusion of Black older adults in the existing VaDep literature is a glaring gap that perpetuates racial disparities in age-related neuropsychiatric disorders. This study is an initial step to begin addressing this important gap in the literature. Broadly, the present study supports the validity of the VaDep framework in an older Black sample, and identifies WMH in the uncinate fasciculus as particularly relevant for the onset and course of VaDep in Black older adults. The presence of subthreshold VaDep, when defined using WMH burden, resulted in

cognitive and gait slowing across four years of follow-up. Based on these findings, it is imperative that healthcare providers 1) screen for depression in older Black adults with high vascular burden, even if depressive symptoms are not frankly endorsed, and 2) monitor for both cognitive and functional impairment when vascular risk and depressive symptoms, even at a low level, are present. Older Black adults are an understudied, under-treated, and particularly vulnerable group of older adults. Given its etiological basis in chronic, treatable vascular risk factors, VaDep is a potentially preventable and modifiable form of depression. Continued research into VaDep, particularly interventions and methods for preventing the onset of VaDep through management of mid-life vascular disease, has the potential to have a wide-ranging positive impact on a population particularly vulnerable to negative aging outcomes.

Table 1. Variables Included in the Cumulative Vascular Burden Score

Hypertension	Baseline diagnosis of hypertension by self-report & medication use
	History of hypertension by self-report & medication use
	History of hypertension based on systolic/diastolic blood pressure measurements
Diabetes	Baseline diagnosis of diabetes based on fasting glucose or oral glucose tolerance test criteria
	History of diabetes by self-report or medication use
Peripheral artery disease	Baseline diagnosis of peripheral artery disease based on ankle-arm index measurement < 0.90
	History of peripheral artery disease diagnosis based on self-report
Metabolic Syndrome	History of metabolic syndrome based on abdominal circumference, blood pressure, high density lipoprotein, fasting glucose, and fasting triglyceride criteria
Obesity	Baseline body mass index > 30
Previous Cardiovascular disease	Self-report, medication, or hospital records indicating a history transient ischemic attack, stroke, angina, or myocardial infarction
Note. One point was added for the presence of each condition and summed to form the Cumulative Vascular Burden score (range of 0-6).	

Table 2. Aim 1A Cross-Sectional Sample Characteristics

	Black (n = 113)		**White (n = 179)**		**Total (n = 292)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline Age (years)	82.49	2.51	82.88	2.87	82.73	2.74
Education (years)**	13.38	2.34	14.61	2.20	14.14	2.33
Sex (% female) **	66.37%	--	50.84%	--	56.85%	--
Baseline CES-D (0-60)	6.04	5.89	7.22	6.18	6.76	6.09
Baseline 3MS (0-100) **	91.90	5.61	95.23	4.49	93.95	5.20
Medical Comorbidities						
Obesity (%)	34.51%	--	17.88%	--	24.32%	--
Hypertension (%)	77.88%	--	70.39%	--	73.29%	--
Diabetes (%)	38.94%	--	22.91%	--	29.11%	--
Metabolic Syndrome (%)	31.53%	--	33.15%	--	32.53%	--
Peripheral Artery Disease (%)	23.89%	--	12.85%	--	17.12%	--
Previous CVD (%) †	18.58%	--	11.73%	--	14.38%	--
Total Vascular Burden**	2.25	1.28	1.69	1.19	1.90	1.25

Note. CES-D = Center for Epidemiologic Studies Depression Scale, 3MS = Teng Mini-Mental State Exam, CVD = cardiovascular disease.

†Includes TIA, stroke, angina, and myocardial infarction

**$p < 0.01$

Table 3. Aim 1A Longitudinal Sample Characteristics

	Black (n = 113)		**White (n = 179)**		**Total (n = 292)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline Age (years)	82.49	2.51	82.88	2.87	82.73	2.74
Education (years) **	13.38	2.35	14.61	2.20	14.14	2.33
Sex (% female) **	66.37%	--	50.84%	--	56.85%	--
Total Follow-Up Interval (years)	3.13	1.72	3.27	1.58	3.22	1.63
Baseline CES-D (0-60)	6.04	5.89	7.22	6.19	6.76	6.09
Average CES-D over Follow-Up	7.10	5.69	7.62	6.14	7.42	5.97
Baseline 3MS (0-100) **	91.90	1.28	95.23	4.49	93.95	5.20
Total Vascular Burden **	2.25	1.28	1.69	1.19	1.90	1.25

Note. CES-D = Center for Epidemiologic Studies Depression Scale, 3MS = Teng Mini-Mental State Exam

**$p < 0.01$

Table 4. Aim 1B Cross-Sectional Sample Characteristics

	Black (n = 112)		**White (n = 177)**		**Total (n = 289)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline MRI Age (years)	82.50	2.50	82.85	2.87	82.71	2.73
Education (years) **	13.34	2.34	14.65	2.14	14.14	2.31
Sex (% female) *	66.67%	--	52.33%	--	57.95%	--
WMH Volume (mm^3)						
Total**	0.008	0.009	0.005	0.006	0.006	0.007
Uncinate Fasciculus	0.0003	0.0004	0.0004	0.0004	0.0003	0.0004
Superior Longitudinal Fasciculus*	0.0006	0.001	0.0004	0.0007	0.0005	0.001
Upper Cingulum	0.0003	0.0007	0.0002	0.0005	0.0002	0.0006
Lower Cingulum	0.0000	0.0000	8.83xE-6	0.0000	0.0000	0.0000
Baseline CES-D (0-60)	6.02	5.94	7.13	6.09	6.69	6.04
Baseline 3MS (0-100) **	91.82	5.62	95.26	4.45	93.91	5.21
Medical Comorbidities						
Obesity (%)	34.23%	--	18.02%	--	24.38%	--
Hypertension (%)	77.48%	--	72.09%	--	74.20%	--
Diabetes (%)	38.74%	--	21.51%	--	28.27%	--
Metabolic Syndrome (%)	31.19%	--	32.75%	--	32.14%	--
Peripheral Artery Disease (%)	24.32%	--	13.37%	--	17.67%	--
Previous CVD[†] (%)	18.92%	--	11.63%	--	14.49%	--
Total Vascular Burden**	2.21	1.27	1.69	1.21	1.91	1.26

Note. CES-D = Center for Epidemiologic Studies Depression Scale, 3MS = Teng Mini-Mental State Exam, CVD = cardiovascular disease.

[†]Includes TIA, stroke, angina, and myocardial infarction

* $p < 0.05$, ** $p < 0.01$

Table 5. Aim 1B Longitudinal Sample Characteristics

	Black (n = 112)		**White (n = 177)**		**Total (n = 289)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline MRI Age (years)	83.02	2.83	82.63	2.62	82.87	2.76
Education (years) **	13.34	2.34	14.65	2.14	14.14	2.31
Sex (% female) *	66.67%	--	52.33%		57.95%	--
Total Follow-Up Interval (years)	3.12	1.72	3.27	1.58	3.21	1.64
WMH Volume (mm^3)						
Total**	0.008	0.009	0.005	0.006	0.0061	0.008
Uncinate Fasciculus	0.0004	0.0004	0.0003	0.0004	0.0004	0 .0004
Superior Longitudinal Fasciculus*	0.0006	0.0015	0.0003	0.0007	0.0005	0.001
Upper Cingulum	0.0003	0.0007	0.0002	0.0005	0.0002	0.0006
Lower Cingulum	0.0000	0.0001	8.83 E-6	0.0000	0.0000	0.0001
Baseline CES-D (0-60)	6.02	5.94	7.13	6.09	6.69	6.05
Average CES-D over Follow-Up	7.12	5.74	7.49	6.06	7.35	5.93
Baseline 3MS (0-100) **	91.82	5.62	95.26	4.45	93.91	5.21
Total Vascular Burden **	2.24	1.27	1.69	1.21	1.91	1.26

Note. CES-D = Center for Epidemiologic Studies Depression Scale, 3MS = Teng Mini-Mental State Exam

*$p < 0.05$, **$p < 0.01$

Table 6. Aim 2 Baseline Sample Characteristics

	Black (n = 112)		**White (n = 173)**		**Total (n = 285)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline Age (years)	82.48	2.52	82.93	2.89	82.76	2.75
Education (years) **	13.39	2.35	14.67	2.18	14.17	2.33
Sex (% female) **	66.07%	--	50.57%	--	56.64%	--
Baseline CES-D (0-60)	6.03	5.92	7.20	6.19	6.74	6.10
Baseline 3MS (0-100) **	91.88	5.63	95.18	4.53	93.89	5.23
Baseline DSS (0-90) **	33.95	12.70	40.39	12.17	37.86	12.76
Baseline EXIT-15 (0-30) **	6.32	3.30	4.73	3.13	5.36	3.29
Group (%)						
Healthy (Low Dep/Low Vasc)	23.21%	--	30.46%	--	27.62%	--
Vascular Only (Low Dep/High Vasc)	41.07%	--	28.16%	--	33.22%	--
Non-vascular Depression (High Dep/Low Vasc)	11.61%	--	21.84%	--	17.83%	--
Vascular Depression (High Dep/High Vasc)	24.11%	--	19.54%	--	21.33%	--
Medical Comorbidities						
Obesity (%)	34.82%	--	17.82%	--	24.48%	--
Hypertension (%)	77.68%	--	70.11%	--	73.08%	--
Diabetes (%)	39.29%	--	21.84%	--	28.67%	--
Metabolic Syndrome (%)	31.82%	--	32.95%	--	32.51%	--
Peripheral Artery Disease (%)	23.21%	--	12.07%	--	16.43%	--
Previous Cardiovascular Disease† (%)	18.75%	--	12.07%	--	14.69%	--
Total Vascular Burden**	2.25	1.28	1.67	1.18	1.90	1.25

Note. CES-D = Center for Epidemiologic Studies Depression Scale, 3MS = Teng Mini-Mental State Exam, DSST = Digit Symbol Substitution Test (higher score = better performance), EXIT-15= 15-Item Executive Interview

†Includes TIA, stroke, angina, and myocardial infarction

**$p < 0.01$

Table 7. Aim 2 Longitudinal Sample Characteristics

	Black (n = 112)		**White (n = 174)**		**Total (n = 286)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline Age (years)	82.48	2.52	82.93	2.89	82.76	2.75
Education (years) **	13.39	2.35	14.67	2.18	14.17	2.33
Sex (% female) *	66.07%	--	50.57%	--	56.64%	--
Total Follow-up Interval	3.14	1.73	3.27	1.56	3.22	1.63
Baseline CES-D (0-60)	6.03	5.92	7.20	6.19	6.74	6.10
Baseline DSST (0-90) **	33.95	12.70	40.39	12.17	37.86	12.76
Baseline EXIT-15 (0-30) **	6.32	3.30	4.73	3.13	5.36	3.29
Baseline 3MS (0-100) **	91.88	5.63	95.18	4.53	93.89	5.23
Group (%)						
Healthy (Low Dep/Low Vasc)	23.21%	--	30.46%	--	27.62%	--
Vascular Only (Low Dep/High Vasc)	41.07%	--	28.16%	--	33.22%	--
Non-vascular Depression (High Dep/Low Vasc)	11.61%	--	21.84%	--	17.83%	--
Vascular Depression (High Dep/High Vasc)	24.11%	--	19.54%	--	21.33%	--
Total Vascular Burden **	2.25	1.28	1.67	1.18	1.90	1.25

Note. CES-D = Center for Epidemiologic Studies Depression Scale, 3MS = Teng Mini-Mental State Exam, DSST = Digit Symbol Substitution Test (higher score = better performance), EXIT-15= 15-Item Executive Interview

*$p < 0.05$. **$p < 0.01$

Table 8. Aim 3 Baseline Sample Characteristics

	Black (n= 108)		**White (n= 170)**		**Total (n= 278)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline Age (years)	82.43	2.45	82.82	2.87	82.67	2.72
Education (years) **	13.41	2.33	14.59	2.20	14.13	2.32
Sex (% female) *	65.14%	--	50.88%	--	56.43%	--
Baseline CES-D (0-60)	5.99	5.95	7.22	6.06	6.74	6.04
Baseline Gait Speed (m/s)	0.89	0.19	0.91	0.19	0.90	0.19
Baseline 3MS Score (0-100) **	91.74	5.62	95.12	4.55	93.81	5.25
Group (%)						
Healthy (Low Dep/Low Vasc)	23.85%	--	30.41%	--	27.86%	--
Vascular Only (Low Dep/High Vasc)	41.28%	--	27.49%	--	32.86%	--
Non-vascular Depression (High Dep/Low Vasc)	11.93%	--	20.47%	--	17.14%	--
Vascular Depression (High Dep/High Vasc)	22.94%	--	21.64%	--	22.14%	--
Medical Comorbidities						
Obesity (%)	32.11%	--	18.13%	--	23.57%	--
Hypertension (%)	80.73%	--	69.59%	--	73.93%	--
Diabetes (%)	36.70%	--	23.39%	--	28.57%	--
Metabolic Syndrome (%)	28.97%	--	33.53%	--	31.77%	--
Peripheral Artery Disease (%)	23.85%	--	13.45%	--	17.50%	--
Previous Cardiovascular Disease (%)	18.35%	--	12.28%	--	14.64%	--
Total Vascular Burden**	2.20	1.28	1.7	1.21	1.89	1.26

Note. CES-D = Center for Epidemiologic Studies Depression Scale, 3MS = Teng Mini-Mental State Exam, DSST = Digit Symbol Substitution Test (higher score = better performance), EXIT-15= 15-Item Executive Interview

*$p < 0.05$, **$p < 0.01$

Table 9. Aim 3 Longitudinal Sample Characteristics

	Black (n= 108)		**White (n= 170)**		**Total (n= 278)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline Age (years)	82.43	2.45	82.82	2.87	82.67	2.72
Education (years) **	13.37	2.30	14.59	2.21	14.12	2.32
Sex (% female) *	65.74%	--	51.18%	--	56.83%	--
Total Follow-Up Interval (years)	3.13	1.72	3.27	1.58	3.21	1.63
Baseline CES-D (0-60)	6.03	5.96	7.20	6.08	6.74	6.05
Baseline Gait Speed (m/s)	0.89	0.19	0.91	0.19	0.90	0.19
Baseline 3MS (0-100) **	91.75	5.64	95.15	4.55	93.83	5.26
Group (%)						
Healthy (Low Dep/Low Vasc)	24.07%		30.59%		28.06%	
Vascular Only (Low Dep/High Vasc)	40.74%		27.65%		32.73%	
Non-vascular Depression (High Dep/Low Vasc)	12.03%		20.59%		17.27%	
Vascular Depression (High Dep/High Vasc)	23.15%		21.18%		21.94%	
Total Vascular Burden **	2.20	1.28	1.7	1.21	1.90	1.26

Note. CES-D = Center for Epidemiologic Studies Depression Scale, 3MS = Teng Mini-Mental State Exam

*$p < 0.05$, **$p < 0.01$

Table 10. Results of Aim 1A Regression Analyses: Clinical Vascular Burden Predicting CES-D Score

	Cross-sectional			**Longitudinal**		
	df	*b*	*SE*	df	*b*	*SE*
Age	1	0.001	0.22	1	-0.003	0.214
Sex: Male	1	0.006	1.17	1	-0.077	1.126
Sex: Female	0	0	--	0	0	--
Education: < 12 years	1	0.197	0.012	1	0.0983	1.561
Education: 12 years	1	0.230*	1.23	1	0.203*	1.179
Education: > 12 years	0	0	--	0	0	--
Clinical Vascular Burden	1	0.130	0.043	1	0.177	0.417

Note. CES-D = Center for Epidemiologic Studies Depression Scale

*$p < 0.05$

Table 11. Results of Aim 1B Regression Analyses: Total WMH Volume Predicting CES-D Score

	Cross-sectional			**Longitudinal**		
	df	*b*	*SE*	df	*b*	*SE*
Age	1	-0.076	0.194	1	-0.079	0.190
Sex: Male	1	-0.349	1.058	1	-0.102	1.038
Sex: Female	0	0	--	0	0	--
Education: < 12 years	1	0.008	1.455	1	0.095	1.427
Education: 12 years	1	0.167	1.112	1	0.147	1.091
Education: > 12 years	0	0	--	0	0	--
Total WMH	1	0.467***	52.314	1	0.40***	51.317

Note. CES-D = Center for Epidemiologic Studies Depression Scale, WMH = white matter hyperintensity

***$p < 0.001$

Table 12. Results of Aim 1B Regression Analyses: Uncinate Fasciculus WMH Burden Predicting CES-D Score

	Cross-sectional			Longitudinal		
	df	*b*	*SE*	df	*b*	*SE*
Age	1	-0.047	0.204	1	-0.051	0.199
Sex: Male	1	0.038	1.117	1	-0.039	1.094
Sex: Female	0	0	--	0	0	--
Education: < 12 years	1	0.004	1.537	1	0.093	1.505
Education: 12 years	1	0.221*	1.160	1	0.200*	1.136
Education: > 12 years	0	0	--	0	0	--
Uncinate Fasciculus WMH	1	0.350***	1274.690	1	0.327***	1248.866

Note. CES-D = Center for Epidemiologic Studies Depression Scale, WMH = white matter hyperintensity volume

* $p < 0.05$, *** $p < 0.001$

Table 13. Results of Aim 1B Regression Analyses: Superior Longitudinal Fasciculus WMH Burden Predicting CES-D Score

	Cross-sectional			Longitudinal		
	df	*b*	*SE*	df	*b*	*SE*
Age	1	-0.038	0.216	1	-0.039	0.211
Sex: Male	1	0.005	1.175	1	-0.070	1.147
Sex: Female	0	0	--	0	0	--
Education: < 12 years	1	-0.002	1.631	1	0.090	1.593
Education: 12 years	1	0.223*	1.237	1	0.207*	1.208
Education: > 12 years	0	0	--	0	0	--
Superior Longitudinal Fasciculus WMH	1	0.168	391.610	1	0.131	382.306

Note. CES-D = Center for Epidemiologic Studies Depression Scale, WMH = white matter hyperintensity volume

* $p < 0.05$

Table 14. Results of Aim 1B Regression Analyses: Upper Cingulum WMH Burden Predicting CES-D Score

	Cross-sectional			Longitudinal		
	df	*b*	*SE*	df	*b*	*SE*
Age	1	-0.034	0.184	1	-0.042	0.176
Sex: Male	1	-0.068	1.018	1	-0.161	0.976
Sex: Female	0	0	--	0	0	--
Education: < 12 years	1	0.013	1.460	1	0.113	1.399
Education: 12 years	1	0.225*	1.054	1	0.194*	1.010
Education: > 12 years	0	0	--	0	0	--
Upper Cingulum WMH	1	-0.006	699.973	1	0.007	670.669

Note. CES-D = Center for Epidemiologic Studies Depression Scale, WMH = white matter hyperintensity volume

* $p < 0.05$

Table 15. Results of Aim 1B Regression Analyses: Lower Cingulum WMH Burden Predicting CES-D Score

	Cross-sectional			Longitudinal		
	df	*b*	*SE*	df	*b*	*SE*
Age	1	-0.034	0.184	1	-0.040	0.176
Sex: Male	1	-0.069	1.016	1	-0.162	0.972
Sex: Female	0	0	--	0	0	--
Education: < 12 years	1	0.014	1.434	1	0.127	1.373
Education: 12 years	1	0.225*	1.053	1	0.198*	1.008
Education: > 12 years	0	0	--	0	0	--
Lower Cingulum WMH	1	-0.013	6134.868	1	-0.048	5871.793

Note. CES-D = Center for Epidemiologic Studies Depression Scale, WMH = white matter hyperintensity volume

* $p < 0.05$, *** $p < 0.001$

Table 16. Aim 2: Regression Coefficients in the Final Mixed Effects Regression Model with Vasc/Dep Group Predicting DSST Score at Baseline

	df	***b***	***SE***
Age	1	-0.083	0.444
Sex: Male	1	-0.223**	2.336
Sex: Female	0	0	--
Education: < 12	1	-0.308***	3.224
Education: 12	1	-0.245**	2.575
Education: > 12	0	0	--
Healthy (Low Dep/Low Vasc)	1	0.020	3.246
Vascular Only (Low Dep/High Vasc)	1	0.337**	2.790
Non-vascular Depression (High Dep/Low Vasc)	1	0.198*	3.950
Vascular Depression (High Dep/High Vasc)	0	0	--

Note. DSST = Digit Symbol Substitution Test

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

Table 17. Aim 2: Regression Coefficients in the Final Mixed Effects Regression Model with Vasc/Dep Group Predicting DSST Score Over Time

	df	***b***	***SE***
Baseline age	1	-0.563	0.397
Sex: Male	1	-7.067***	2.083
Sex: Female	0	0	--
Education: < 12 years	1	-10.726***	2.871
Education: 12 years	1	-4.745*	2.306
Education: > 12 years	0	0	--
Healthy (Low Dep/Low Vasc)	1	1.856	2.921
Vascular Only (Low Dep/High Vasc)	1	7.681*	2.514
Non-vascular Depression (High Dep/Low Vasc)	1	7.903*	3.580
Vascular Depression (High Dep/High Vasc)	0	0	--
Interval	1	-0.375	0.767

Note. DSST = Digit Symbol Substitution Test

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

Table 18. Aim 2: Regression Coefficients in the Final Mixed Effects Regression Model with Vasc/Dep Group Predicting EXIT-15 Score at Baseline

	df	***b***	***SE***
Age	1	0.076	0.121
Sex: Male	1	0.187*	0.637
Sex: Female	0	0	--
Education: <12 years	1	0.249**	0.879
Education: 12 years	1	0.198**	0.702
Education: >12 years	0	0	--
Healthy (Low Dep/Low Vasc)	1	-0.114	0.885
Vascular Only (Low Dep/High Vasc)	1	-0.220	0.760
Non-vascular Depression (High Dep/Low Vasc)	1	0.048	1.077
Vascular Depression (High Dep/High Vasc)	0	0	--

Note. EXIT-15 = 15-Item Executive Interview

*$p < 0.05$, **$p < 0.01$

Table 19. Aim 2: Regression Coefficients in the Final Mixed Effects Regression Model with Vasc/Dep Group Predicting EXIT-15 Score Over Time

	df	***b***	***SE***
Baseline age	1	0.127	0.110
Sex: Male	1	1.555**	0.575
Sex: Female	0	0	--
Education: < 12 years	1	2.667***	0.793
Education: 12 years	1	1.443*	0.638
Education: > 12 years	0	0	--
Healthy (Low Dep/Low Vasc)	1	-0.8814	0.8969
Vascular Only (Low Dep/High Vasc)	1	-1.5278*	0.7742
Non-vascular Depression (High Dep/Low Vasc)	1	0.466	1.093
Vascular Depression (High Dep/High Vasc)	0	0	--
Interval	1	0.041	1.064
Interval^2	1	-0.706	0.858
Interval x Healthy	1	0.573	0.684
Interval x Vascular Only	1	1.185	0.619
Interval x Non-vascular Depression	1	-1.247*	0.887
Interval x Vascular Depression	0	0	--

Note. EXIT-15= 15-Item Executive Interview

*$p < 0.05$, ***$p < 0.001$

Table 20. Aim 3: Regression Coefficients in the Final Mixed Effects Regression Model with Vasc/Dep Group Predicting Height-adjusted Gait Speed at Baseline

	df	***b***	***SE***
Age	1	-0.040	0.005
Sex: Male	1	-0.296**	0.025
Sex: Female	0	0	--
Education: < 12 years	1	-0.046	0.034
Education: 12 years	1	-0.023	0.027
Education: > 12 years	0	0	--
Healthy (Low Dep/Low Vasc)	1	0.009	0.035
Vascular Only (Low Dep/High Vasc)	1	-0.152	0.030
Non-vascular Depression (High Dep/Low Vasc)	1	-0.227*	0.041
Vascular Depression (High Dep/High Vasc)	0	0	--

*$p < 0.05$, **$p < 0.01$

Table 21. Aim 3: Regression Coefficients in the Final Mixed Effects Regression Model with Vasc/Dep Group Predicting Height-adjusted Gait Speed Over Time

	df	***b***	***SE***
Baseline age	1	-0.001	0.005
Sex: Male	1	-0.081***	0.024
Sex: Female	0	0	--
Education: < 12 years	1	-0.012	0.034
Education: 12 years	1	-0.008	0.027
Education: > 12 years	0	0	--
Healthy (Low Dep/Low Vasc)	1	0.002	0.035
Vascular Only (Low Dep/High Vasc)	1	-0.038	0.030
Non-vascular Depression (High Dep/Low Vasc)	1	-0.086*	0.042
Vascular Depression (High Dep/High Vasc)	0	0	--
Interval	1	-0.064	0.068
Interval^2	1	0.017	0.050
Interval x Healthy	1	-0.217	0.113
Interval x Vascular Only	1	-0.027	0.097
Interval x Non-vascular Depression	1	0.307	0.184
Interval x Vascular Depression	0	0	--
Interval^2 x Healthy	1	0.194*	0.090
Interval^2 x Vascular Only	1	0.025	0.074
Interval^2 x Non-vascular Depression	1	-0.239	0.159
Interval^2 x Vascular Depression	0	0	--

*$p < 0.05$, ***$p < 0.001$

Table 22 Post-hoc Power Analyses

Analysis	Sample Size	Number of Predictors	Power (1-β)
Main Aims			
Aim 1A	N = 113	4	**Medium Effect: 0.95** Small Effect: 0.43
Aim 1B	N = 112	4	**Medium Effect: 0.91** Small Effect: 0.18
Aim 2A Cross-Sectional	N = 112	4	**Medium Effect: 0.91** Small Effect: 0.18
Aim 2B Longitudinal	N = 112	8	**Medium Effect: 0.82** Small Effect: 0.14
Aim 3A Cross-Sectional	N = 108	4	**Medium Effect: 0.90** Small Effect: 0.18
Aim 3B Longitudinal	N = 108	8	**Medium Effect: 0.80** **Large Effect: 0.997**
Exploratory Aims			
Exploratory Aim 1A	N = 292	6	**Medium Effect: 0.999** Small Effect: 0.38
Exploratory Aim 1B	N = 289	6	**Medium Effect: 0.999** Small Effect: 0.38
Exploratory Aim 2	N = 285	11	**Medium Effect: 0.998** Small Effect: 0.28
Exploratory Aim 3	N = 278	11	**Medium Effect: 0.998** Small Effect: 0.28

Note. ***Bolded effect value*** *= adequate power*

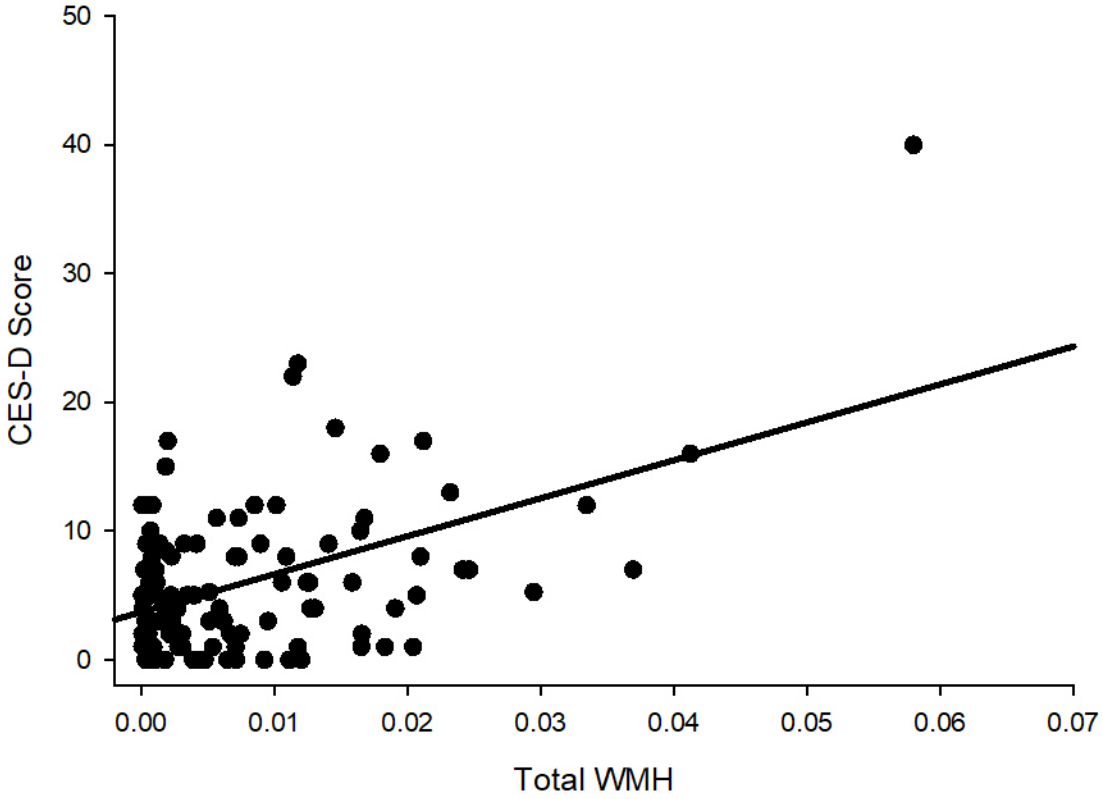

Figure 1. Association of Total WMH and CES-D Score at Baseline

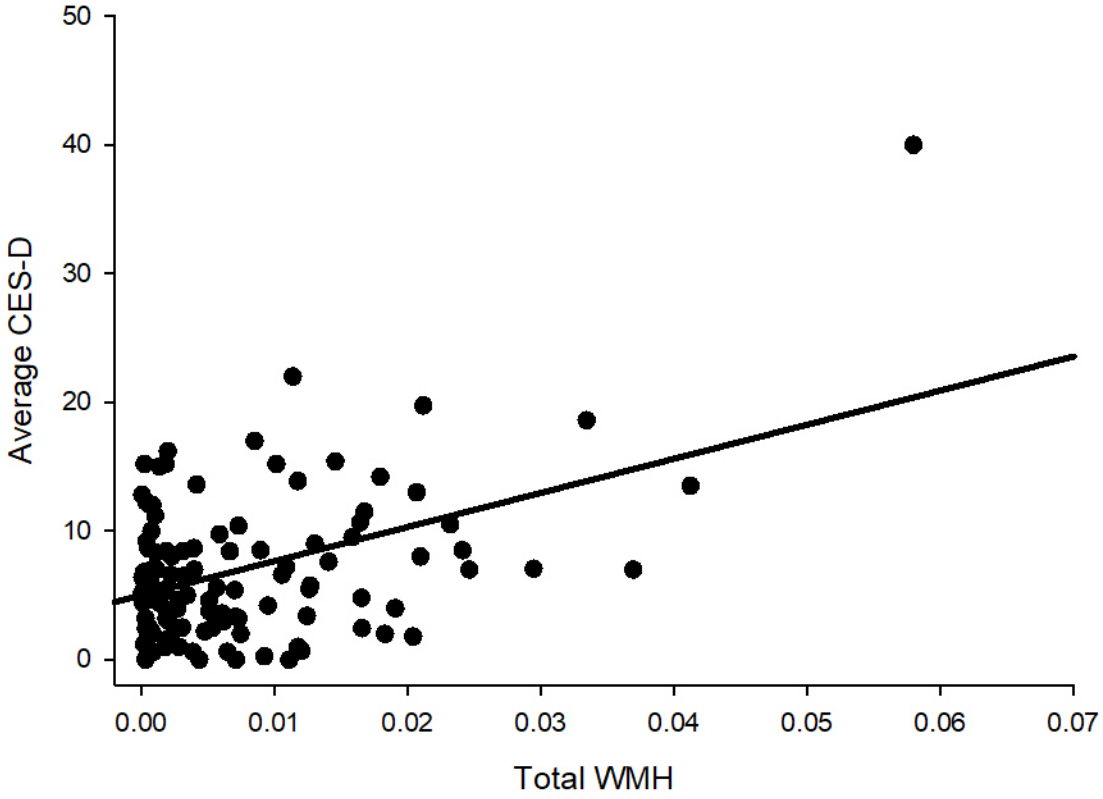

Figure 2. Total WMH Predicting CES-D Score Over Follow-Up

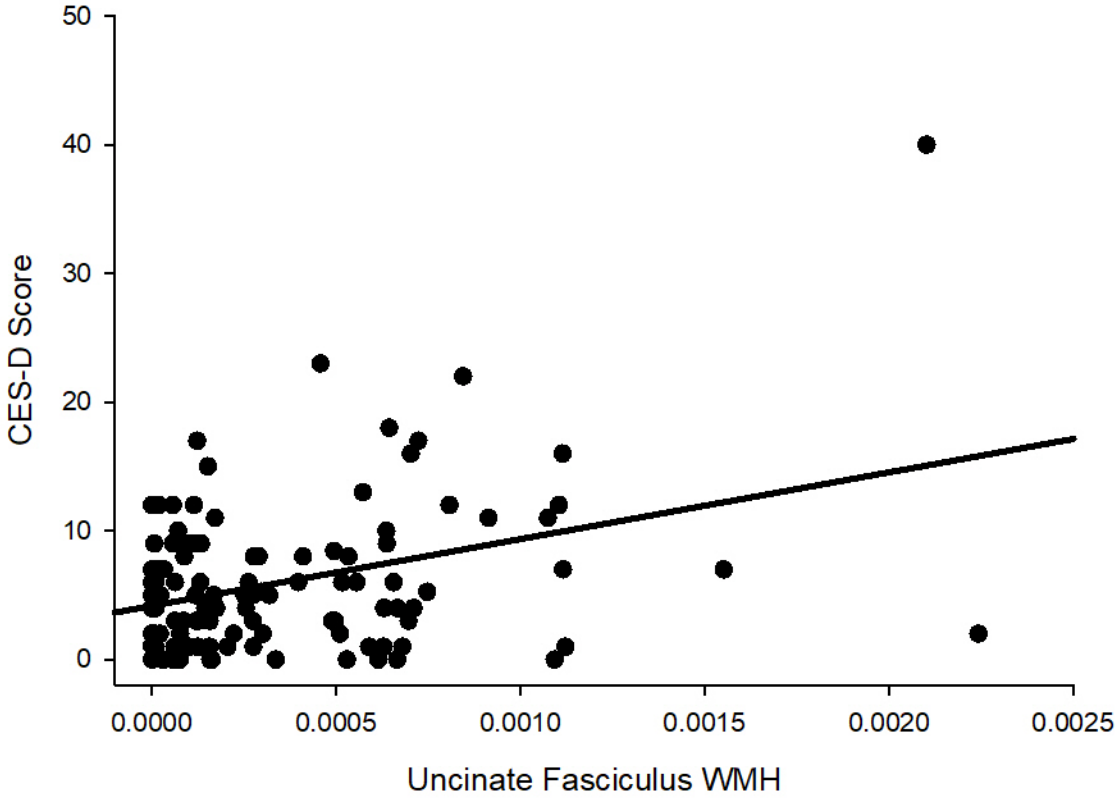

Figure 3. Association of Uncinate Fasciculus WMH and CES-D Score at Baseline

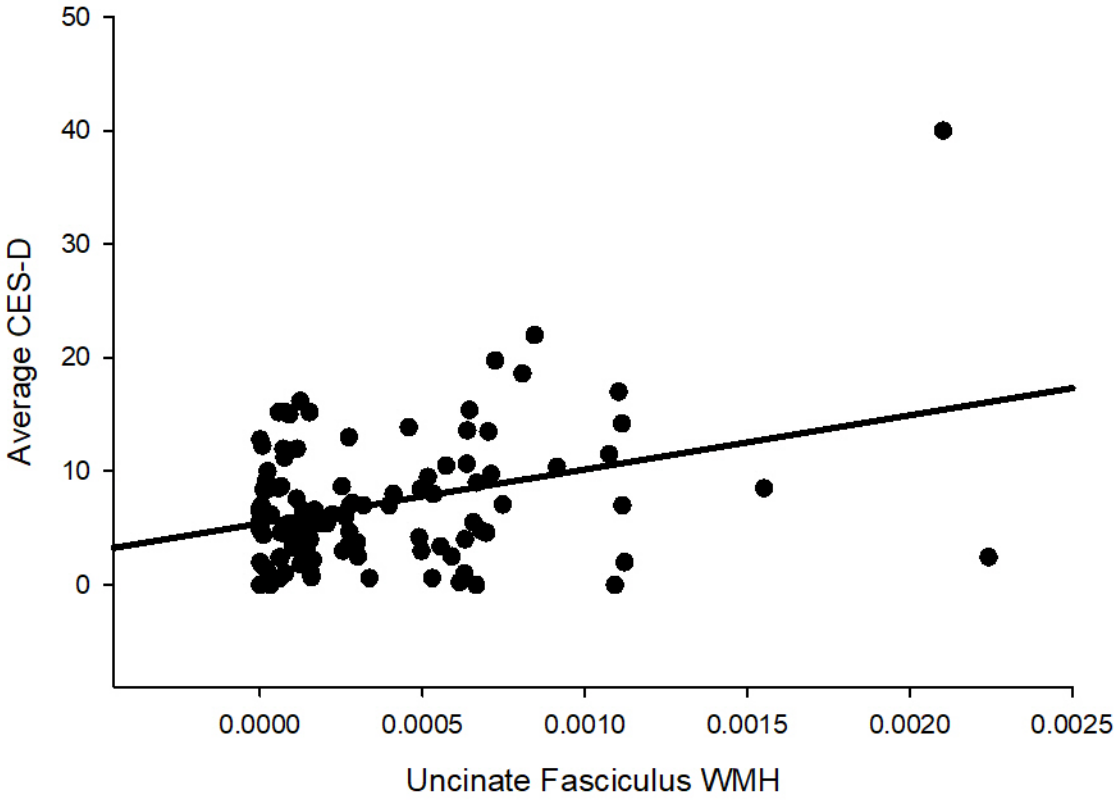

Figure 4. Uncinate Fasciculus WMH Predicting CES-D Score Over Follow-Up

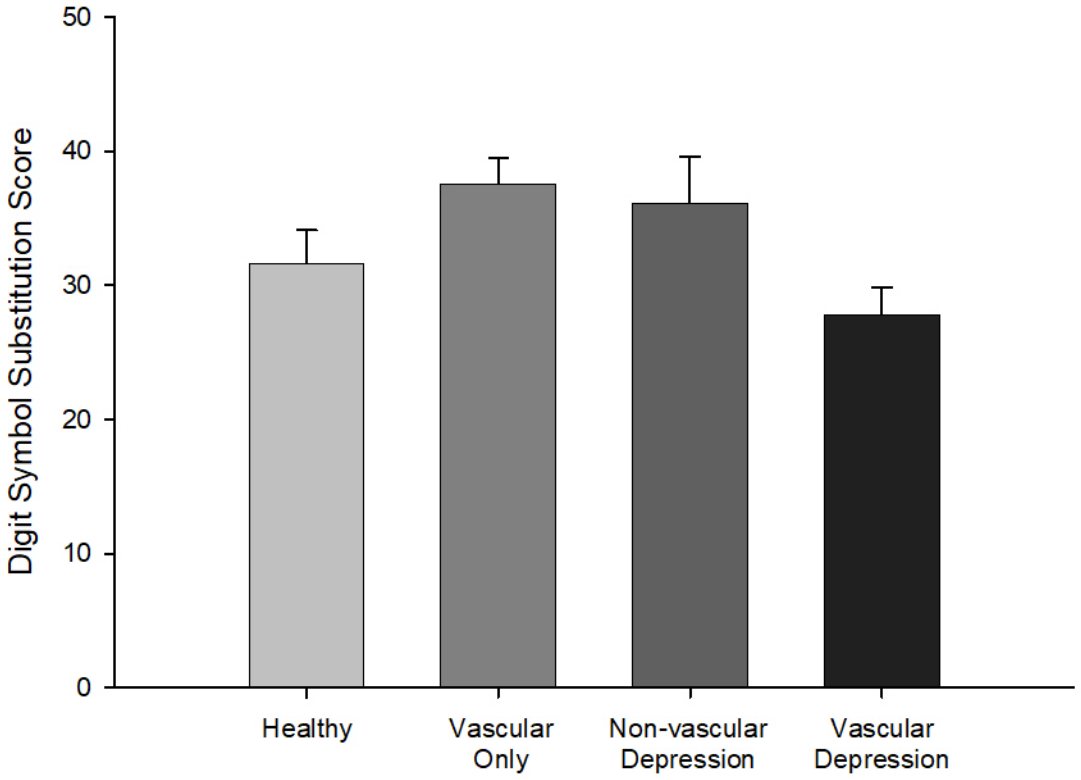

Figure 5. Association of Vasc/Dep Group and Digit Symbol Substitution Score

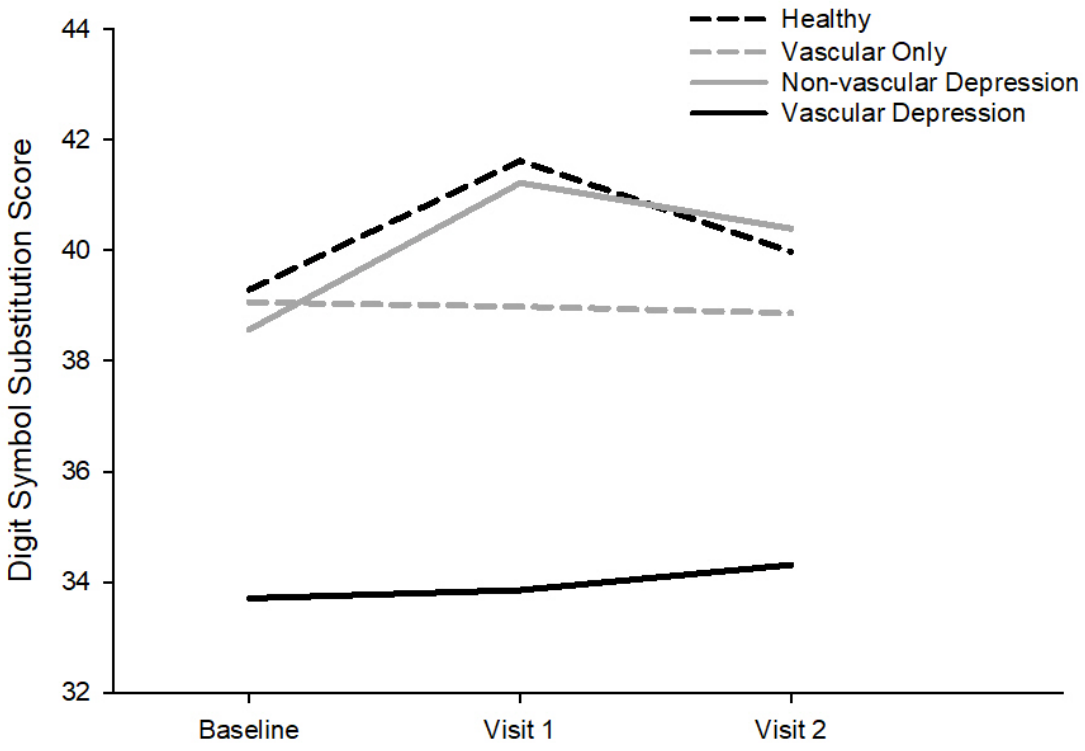

Figure 6. Vasc/Dep Vascular/depression group membership Predicting Digit Symbol Substitution Test Performance Over Follow-Up

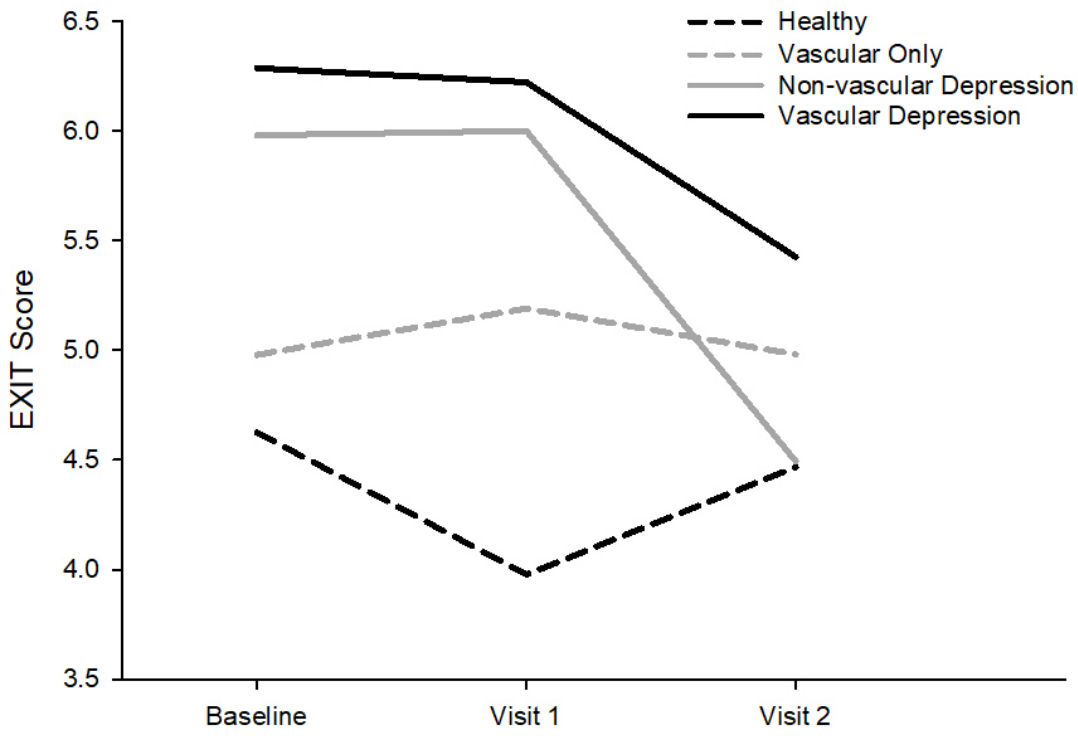

Figure 7. Vasc/Dep Vascular/depression group membership x Interval Interaction Predicting EXIT-15 Performance Over Follow-Up

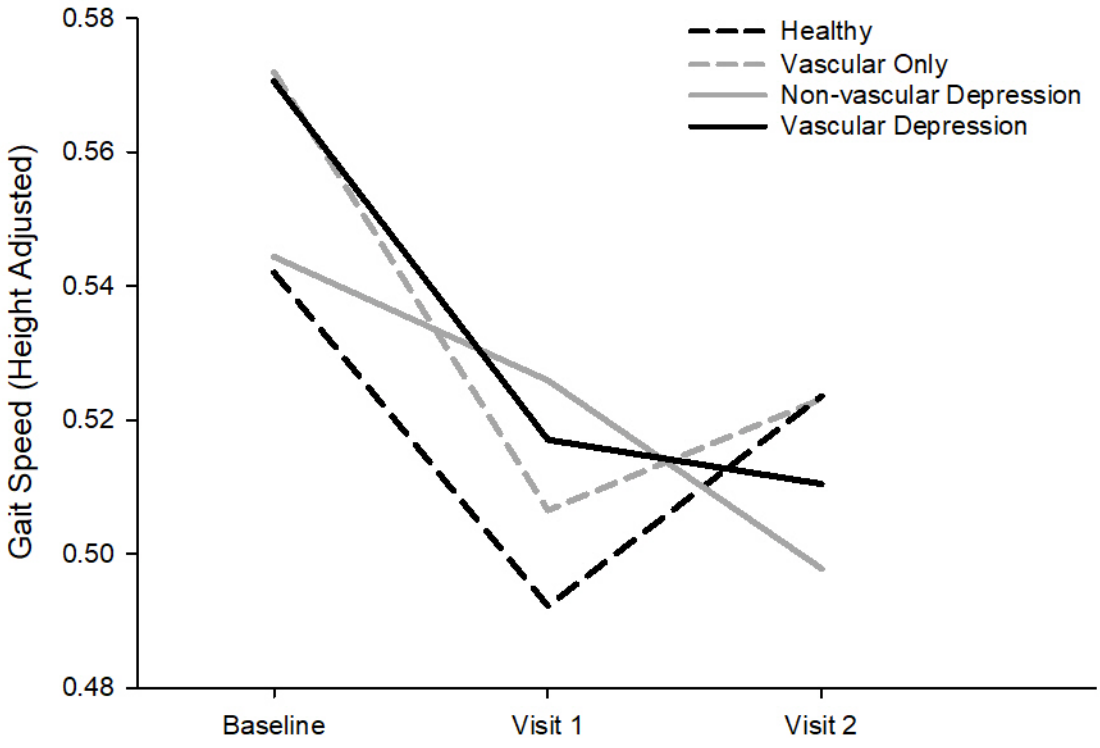

Figure 8. Vasc/Dep Vascular/depression group membership Predicting Gait Speed Performance Over Follow-Up

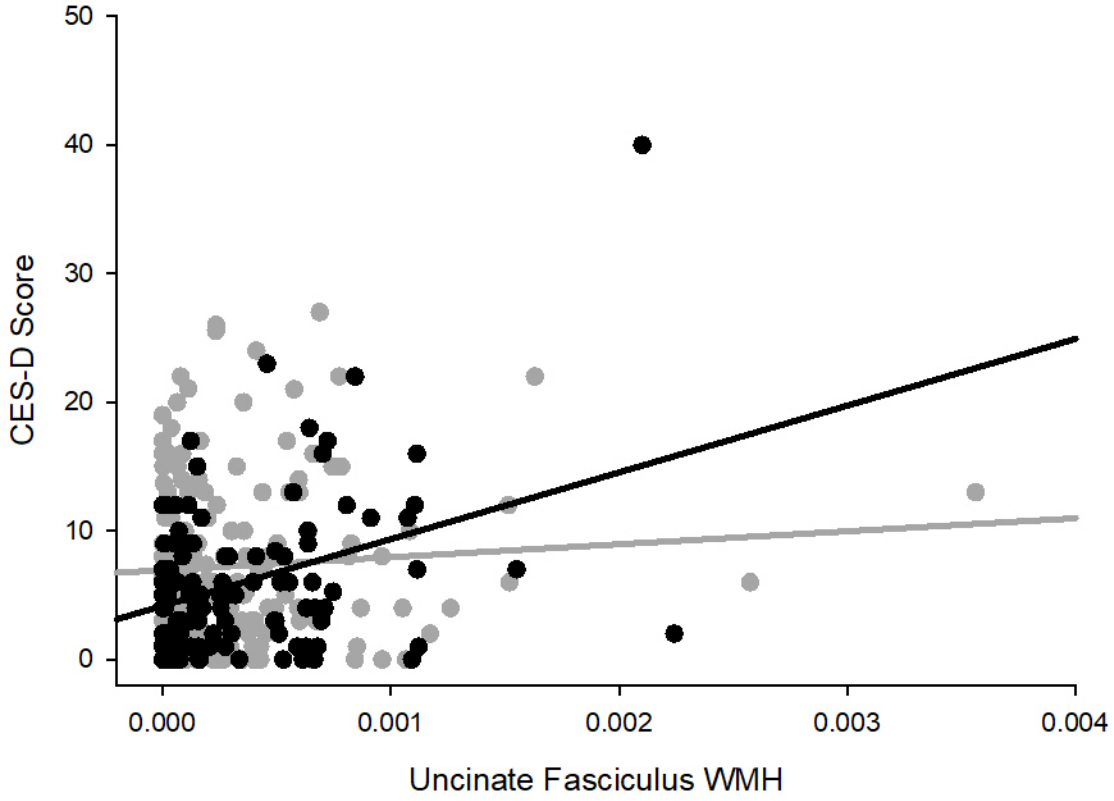

Figure 9. Race differences in association between uncinate fasciculus WMH burden and CES-D score at baseline

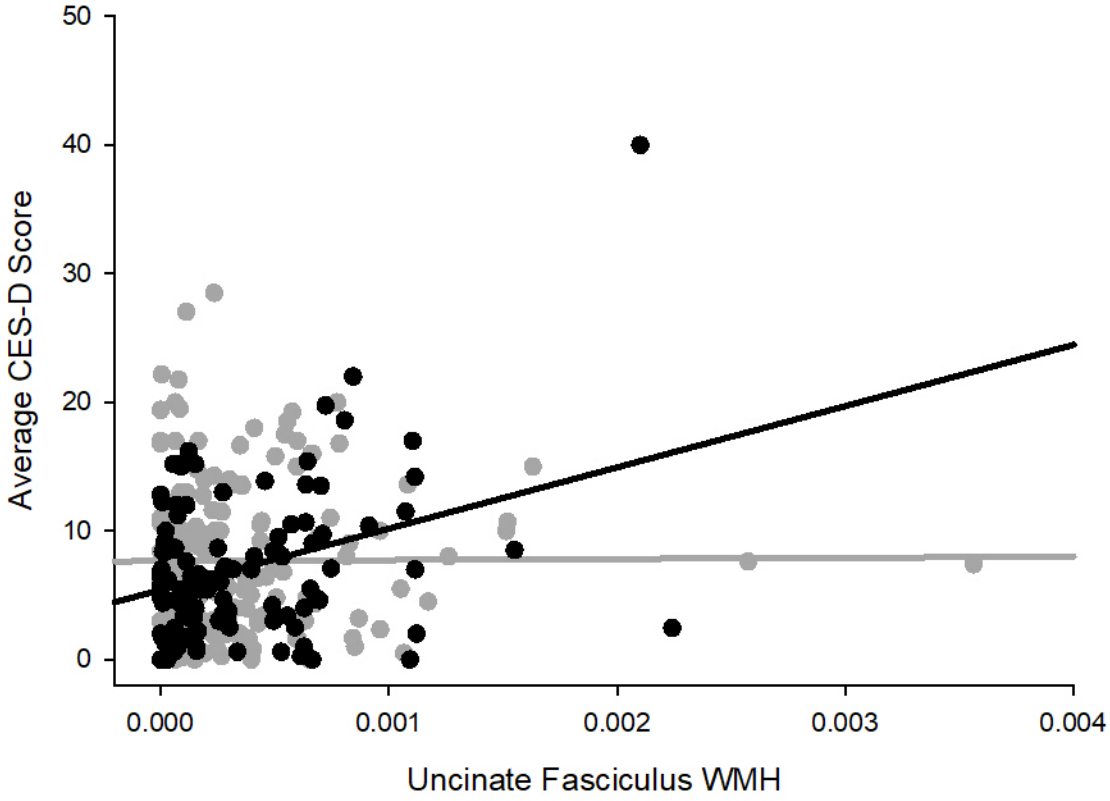

Figure 10. Race differences in association between uncinate fasciculus WMH burden and average CES-D score over time

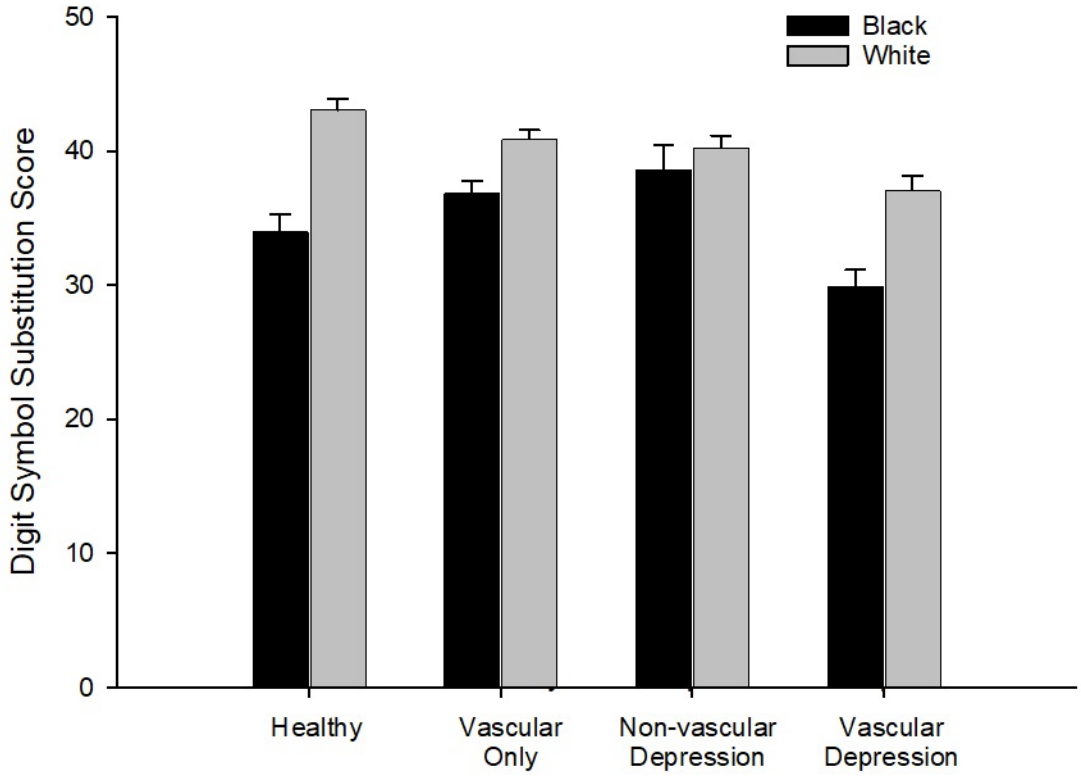

Figure 11. Race differences in VaDep group and baseline DSST

5 REFERENCES

Adams, L. B., Gottfredson, N., Lightfoot, A. F., Corbie-Smith, G., Golin, C., & Powell, W. (2019). Factor Analysis of the CES-D 12 among a Community Sample of Black Men. *Am J Mens Health*, *13*(2), 1557988319834105. https://doi.org/10.1177/1557988319834105

Aizenstein, H. J., Baskys, A., Boldrini, M., Butters, M. A., Diniz, B. S., Jaiswal, M. K., . . . Tene, O. (2016). Vascular depression consensus report - a critical update. *BMC Medicine*, *14*(1), 161. https://doi.org/10.1186/s12916-016-0720-5

Alexopoulos, G. S. (2019). Mechanisms and treatment of late-life depression. *Translational Psychiatry*, *9*(1), 188. https://doi.org/10.1038/s41398-019-0514-6

Alexopoulos, G. S., Hoptman, M. J., Yuen, G., Kanellopoulos, D., Seirup, J., Lim, K. O., & Gunning, F. M. (2013). Functional connectivity in apathy of late-life depression: a preliminary study. *J Affect Disord*, *149*(0), 398-405. https://doi.org/10.1089/pho.2008.2318

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular depression' hypothesis. *Archives of General Psychiatry*, *54*, 915-922. https://doi.org/10.1001/archpsyc.1997.01830220033006

Allan, C. L., Sexton, C. E., Filippini, N., Topiwala, A., Mahmood, A., Zsoldos, E., . . . Ebmeier, K. P. (2016). Sub-threshold depressive symptoms and brain structure: A magnetic resonance imaging study within the Whitehall II cohort. *J Affect Disord*, *204*, 219-225. https://doi.org/10.1016/j.jad.2016.06.049

Amieva, H., Meillon, C., Proust-Lima, C., & Dartigues, J. F. (2019). Is Low Psychomotor Speed a Marker of Brain Vulnerability in Late Life? Digit Symbol Substitution Test in the

Prediction of Alzheimer, Parkinson, Stroke, Disability, and Depression. *Dement Geriatr Cogn Disord*, *47*(4-6), 297-305. https://doi.org/10.1159/000500597

Azar, A. R., Murrell, S. A., & Mast, B. T. (2005). Race and vascular depression risk in community-dwelling older adults. *The American Journal of Geriatric Psychiatry*, *13*(4), 329-332. https://doi.org/10.1176/appi.ajgp.13.4.329

Barch, D. M., D'Angelo, G., Pieper, C., Wilkins, C. H., Welsh-Bohmer, K., Taylor, W., . . . Sheline, Y. I. (2012). Cognitive improvement following treatment in late-life depression: relationship to vascular risk and age of onset. *Am J Geriatr Psychiatry*, *20*(8), 682-690. https://doi.org/10.1097/JGP.0b013e318246b6cb

Beatty Moody, D. L., Taylor, A. D., Leibel, D. K., Al-Najjar, E., Katzel, L. I., Davatzikos, C., . . . Waldstein, S. R. (2019). Lifetime discrimination burden, racial discrimination, and subclinical cerebrovascular disease among African Americans. *Health Psychology*, *38*(1), 63-74. https://doi.org/10.1037/hea0000638

Bella, R., Pennisi, G., Cantone, M., Palermo, F., Pennisi, M., Lanza, G., . . . Paolucci, S. (2010). Clinical presentation and outcome of geriatric depression in subcortical ischemic vascular disease. *Gerontology*, *56*(3), 298-302. https://doi.org/10.1159/000272003

Bland, R. C., & Newman, S. C. (2001). Mild dementia or cognitive impairment: the Modified Mini-Mental State examination (3MS) as a screen for dementia. *Can J Psychiatry*, *46*(6), 506-510. https://doi.org/10.1177/070674370104600604

Bogoian, H. R., & Dotson, V. M. (2021). Vascular depression in Black Americans: a systematic review of the construct and its cognitive, functional, and psychosocial correlates. *Clin Neuropsychol*, 1-31. https://doi.org/10.1080/13854046.2021.1933188

Boots, E. A., Castellanos, K. J., Zhan, L., Barnes, L. L., Tussing-Humphreys, L., Deoni, S. C. L., & Lamar, M. (2020). Inflammation, Cognition, and White Matter in Older Adults: An Examination by Race. *Front Aging Neurosci*, *12*, 553998. https://doi.org/10.3389/fnagi.2020.553998

Boots, E. A., Feinstein, D. L., Leurgans, S., Aiken-Morgan, A. T., Fleischman, D. A., Lamar, M., & Barnes, L. L. (2022). Acute versus chronic inflammatory markers and cognition in older black adults: Results from the Minority Aging Research Study. *Brain Behav Immun*, *103*, 163-170. https://doi.org/10.1016/j.bbi.2022.04.014

Brickman, A. M., Schupf, N., Manly, J. J., Luchsinger, J. A., Andrews, H., Tang, M. X., . . . Brown, T. R. (2008). Brain morphology in older African Americans, Caribbean Hispanics, and Whites from northern Manhattan. *Archives of Neurology*, *65*(8), 1053-1061. https://doi.org/10.1001/archneur.65.8.1053

Bronder, E. C., Speight, S. L., Witherspoon, K. M., & Thomas, A. J. (2013). John Henryism, Depression, and Perceived Social Support in Black Women. *Journal of Black Psychology*, *40*(2), 115-137. https://doi.org/10.1177/0095798412474466

Brown, A. F., Liang, L. J., Vassar, S. D., Escarce, J. J., Merkin, S. S., Cheng, E., . . . Longstreth, W. T., Jr. (2018). Trends in Racial/Ethnic and Nativity Disparities in Cardiovascular Health Among Adults Without Prevalent Cardiovascular Disease in the United States, 1988 to 2014. *Ann Intern Med*, *168*(8), 541-549. https://doi.org/10.7326/m17-0996

Brown, P. J., Roose, S. P., O'Boyle, K. R., Ciarleglio, A., Maas, B., Igwe, K. C., . . . Rutherford, B. R. (2020). Frailty and Its Correlates in Adults With Late Life Depression. *Am J Geriatr Psychiatry*, *28*(2), 145-154. https://doi.org/10.1016/j.jagp.2019.10.005

Brown, P. J., Roose, S. P., Zhang, J., Wall, M., Rutherford, B. R., Ayonayon, H. N., . . . Yaffe, K. (2016). Inflammation, Depression, and Slow Gait: A High Mortality Phenotype in Later Life. *J Gerontol A Biol Sci Med Sci*, *71*(2), 221-227. https://doi.org/10.1093/gerona/glv156

Carleton, R. N., Thibodeau, M. A., Teale, M. J., Welch, P. G., Abrams, M. P., Robinson, T., & Asmundson, G. J. (2013). The center for epidemiologic studies depression scale: a review with a theoretical and empirical examination of item content and factor structure. *PLoS One*, *8*(3), e58067. https://doi.org/10.1371/journal.pone.0058067

Carmasin, J. S., Mast, B. T., Allaire, J. C., & Whitfield, K. E. (2014). Vascular risk factors, depression, and cognitive change among African American older adults. *International Journal of Geriatric Psychiatry*, *29*(3), 291-298. https://doi.org/10.1002/gps.4007

Carroll, A. J., Huffman, M. D., Zhao, L., Jacobs, D. R., Stewart, J. C., Kiefe, C. I., . . . Hitsman, B. (2020). Associations between depressive symptoms, cigarette smoking, and cardiovascular health: Longitudinal results from CARDIA. *J Affect Disord*, *260*, 583-591. https://doi.org/10.1016/j.jad.2019.09.049

Cesari, M., Kritchevsky, S. B., Newman, A. B., Simonsick, E. M., Harris, T. B., Penninx, B. W., . . . Pahor, M. (2009). Added value of physical performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. *J Am Geriatr Soc*, *57*(2), 251-259. https://doi.org/10.1111/j.1532-5415.2008.02126.x

Chang, K. J., Hong, C. H., Kim, S. H., Lee, K. S., Roh, H. W., Kang, D. R., . . . Son, S. J. (2016). MRI-defined versus clinically-defined vascular depression; comparison of prediction of

functional disability in the elderly. *Archives of Gerontology and Geriatrics*, *66*, 7-12. https://doi.org/10.1016/j.archger.2016.04.010

Charlton, R. A., Lamar, M., Zhang, A., Yang, S., Ajilore, O., & Kumar, A. (2014). White-matter tract integrity in late-life depression: associations with severity and cognition. *Psychol Med*, *44*(7), 1427-1437. https://doi.org/10.1017/s0033291713001980

Cipollini, V., Troili, F., & Giubilei, F. (2019). Emerging Biomarkers in Vascular Cognitive Impairment and Dementia: From Pathophysiological Pathways to Clinical Application. *Int J Mol Sci*, *20*(11). https://doi.org/10.3390/ijms20112812

Cooney, G. M., Dwan, K., Greig, C. A., Lawlor, D. A., Rimer, J., Waugh, F. R., . . . Mead, G. E. (2013). Exercise for depression. *Cochrane Database Syst Rev*(9), Cd004366. https://doi.org/10.1002/14651858.CD004366.pub6

Cuevas, A. G., Ong, A. D., Carvalho, K., Ho, T., Chan, S. W. C., Allen, J. D., . . . Williams, D. R. (2020). Discrimination and systemic inflammation: A critical review and synthesis. *Brain Behav Immun*, *89*, 465-479. https://doi.org/10.1016/j.bbi.2020.07.017

Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., & Penninx, B. W. (2013). Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. *Br J Psychiatry*, *202*(1), 22-27. https://doi.org/10.1192/bjp.bp.112.112169

Culang-Reinlieb, M. E., Johnert, L. C., Brickman, A. M., Steffens, D. C., Garcon, E., & Sneed, J. R. (2011). MRI-defined vascular depression: a review of the construct. *International Journal of Geriatric Psychiatry*, *26*(11), 1101-1108. https://doi.org/10.1002/gps.2668

Dalby, R. B., Frandsen, J., Chakravarty, M. M., Ahdidan, J., Sørensen, L., Rosenberg, R., . . . Ostergaard, L. (2010). Depression severity is correlated to the integrity of white matter

fiber tracts in late-onset major depression. *Psychiatry Research*, *184*(1), 38-48. https://doi.org/10.1016/j.pscychresns.2010.06.008

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F., 3rd. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry*, *202*(5), 329-335. https://doi.org/10.1192/bjp.bp.112.118307

Divers, J., Hugenschmidt, C., Sink, K. M., Williamson, J. D., Ge, Y., Smith, S. C., . . . Freedman, B. I. (2013). Cerebral white matter hyperintensity in African Americans and European Americans with type 2 diabetes. *Journal of Stroke and Cerebrovascular Diseases*, *22*(7), e46-52. https://doi.org/10.1016/j.jstrokecerebrovasdis.2012.03.019

Dixon, J. S., Coyne, A. E., Duff, K., & Ready, R. E. (2021). Predictors of cognitive decline in a multi-racial sample of midlife women: A longitudinal study. *Neuropsychology*, *35*(5), 514-528. https://doi.org/10.1037/neu0000743

Dotson, V. M., Beason-Held, L., Kraut, M. A., & Resnick, S. M. (2009). Longitudinal study of chronic depressive symptoms and regional cerebral blood flow in older men and women. *Int J Geriatr Psychiatry*, *24*(8), 809-819. https://doi.org/10.1002/gps.2298

Dotson, V. M., Davatzikos, C., Kraut, M. A., & Resnick, S. M. (2009). Depressive symptoms and brain volumes in older adults: a longitudinal magnetic resonance imaging study. *J Psychiatry Neurosci*, *34*(5), 367-375. http://www.ncbi.nlm.nih.gov/pubmed/19721847

Dotson, V. M., & Stringer, A. Y. (2022). Culturally sensitive neuropsychological assessment in Black Americans. In F. Irani & D. Byrd (Eds.), *Cultural diversity in neuropsychological assessment*. Routledge.

Du, J., & Xu, Q. (2019). Neuroimaging studies on cognitive impairment due to cerebral small vessel disease. *Stroke Vasc Neurol*, *4*(2), 99-101. https://doi.org/10.1136/svn-2018-000209

Erdfelder, E., Faul, F., & Buchner, A. (1996). GPOWER: A general power analysis program. *Behavior Research Methods, Instruments & Computers*, *28*(1), 1-11. https://doi.org/10.3758/BF03203630

Felix, A. S., Shisler, R., Nolan, T. S., Warren, B. J., Rhoades, J., Barnett, K. S., & Williams, K. P. (2019). High-Effort Coping and Cardiovascular Disease among Women: A Systematic Review of the John Henryism Hypothesis. *J Urban Health*, *96*(Suppl 1), 12-22. https://doi.org/10.1007/s11524-018-00333-1

Ferdinand, K. C., & Townsend, R. R. (2012). Hypertension in the US Black population: risk factors, complications, and potential impact of central aortic pressure on effective treatment. *Cardiovasc Drugs Ther*, *26*(2), 157-165. https://doi.org/10.1007/s10557-011-6367-8

Freedland, K. E., Carney, R. M., Rich, M. W., & Caracciolo, A. (1991). Depression in elderly patients with congestive heart failure. *Journal of Geriatric Psychiatry*, *24*(1), 59-71. https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,shib&db=psyh&AN=1991-27822-001&site=ehost-live&scope=site&custid=gsu1

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., . . . McBurnie, M. A. (2001). Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*, *56*(3), M146-156. https://doi.org/10.1093/gerona/56.3.m146

Fujimoto, T., Takeuchi, K., Matsumoto, T., Fujita, S., Honda, K., Higashi, Y., & Kato, N. (2008). Metabolic changes in the brain of patients with late-onset major depression. *Psychiatry Res*, *164*(1), 48-57. https://doi.org/10.1016/j.pscychresns.2007.03.010

Geerlings, M. I., & Heijer, T. D. (2008). History of depression , depressive symptoms , and medial temporal lobe atrophy and the risk of Alzheimer disease.

Gellis, Z. D. (2010). Assessment of a brief CES-D measure for depression in homebound medically ill older adults. *J Gerontol Soc Work*, *53*(4), 289-303. https://doi.org/10.1080/01634371003741417

Gomez, R., & McLaren, S. (2015). The Center for Epidemiological Studies Depression Scale: Measurement and structural invariance across ratings of older adult men and women. *Personality and Individual Differences*, *75*, 130-134. https://doi.org/10.1016/j.paid.2014.11.005

González, H. M., & Tarraf, W. (2013). Comorbid cardiovascular disease and major depression among ethnic and racial groups in the United States. *International Psychogeriatrics*, *25*(5), 833-841. https://doi.org/10.1017/S1041610212002062

González, H. M., Tarraf, W., Whitfield, K., & Gallo, J. J. (2012). Vascular depression prevalence and epidemiology in the United States. *J Psychiatr Res*, *46*(4), 456-461. https://doi.org/10.1016/j.jpsychires.2012.01.011

Gunning-Dixon, F. M., Walton, M., Cheng, J., Acuna, J., Klimstra, S., Zimmerman, M. E., . . . Alexopoulos, G. S. (2010). MRI signal hyperintensities and treatment remission of geriatric depression. *Journal of Affective Disorders*, *126*(3), 395-401. https://doi.org/10.1016/j.jad.2010.04.004

Gutierrez, J., & Williams, O. A. (2014). A decade of racial and ethnic stroke disparities in the United States. *Neurology*, *82*(12), 1080-1082. https://doi.org/10.1212/wnl.0000000000000237

Hajjar, I., Yang, F., Sorond, F., Jones, R. N., Milberg, W., Cupples, L. A., & Lipsitz, L. A. (2009). A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: Relationship to blood pressure and other cardiovascular risks. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences*, *64*(9), 994-1001. https://doi.org/10.1093/gerona/glp075

Hall, C. A., Simon, K. M., Lenze, E. J., Dew, M. A., Begley, A., Butters, M. A., . . . Reynolds, C. F., 3rd. (2015). Depression Remission Rates Among Older Black and White Adults: Analyses From the IRL-GREY Trial. *Psychiatr Serv*, *66*(12), 1303-1311. https://doi.org/10.1176/appi.ps.201400480

Hamm, V. P., Bazargan, M., & Barbre, A. R. (1993). Life-style and cardiovascular health among urban Black elderly. *Journal of Applied Gerontology*, *12*(2), 155-169. https://doi.org/10.1177/073346489301200203

Harada, K., Matsuo, K., Nakashima, M., Hobara, T., Higuchi, N., Higuchi, F., . . . Watanabe, Y. (2016). Disrupted orbitomedial prefrontal limbic network in individuals with later-life depression. *J Affect Disord*, *204*, 112-119. https://doi.org/10.1016/j.jad.2016.06.031

Haringsma, R., Engels, G. I., Beekman, A. T., & Spinhoven, P. (2004). The criterion validity of the Center for Epidemiological Studies Depression Scale (CES-D) in a sample of self-referred elders with depressive symptomatology. *Int J Geriatr Psychiatry*, *19*(6), 558-563. https://doi.org/10.1002/gps.1130

Hasin, D. S., Goodwin, R. D., Stinson, F. S., & Grant, B. F. (2005). Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch Gen Psychiatry*, *62*(10), 1097-1106. https://doi.org/10.1001/archpsyc.62.10.1097

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of adult DSM-5 Major Depressive Disorder and its specifiers in the United States. *JAMA Psychiatry*, *75*(4), 336-346. https://doi.org/10.1001/jamapsychiatry.2017.4602

Heard, E., Whitfield, K. E., Edwards, C. L., Bruce, M. A., & Beech, B. M. (2011). Mediating effects of social support on the relationship among perceived stress, depression, and hypertension in African Americans. *J Natl Med Assoc*, *103*(2), 116-122. https://doi.org/10.1016/s0027-9684(15)30260-1

Hollocks, M. J., Lawrence, A. J., Brookes, R. L., Barrick, T. R., Morris, R. G., Husain, M., & Markus, H. S. (2015). Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Brain*, *138*(Pt 12), 3803-3815. https://doi.org/10.1093/brain/awv304

Horackova, K., Kopecek, M., Machů, V., Kagstrom, A., Aarsland, D., Motlova, L. B., & Cermakova, P. (2019). Prevalence of late-life depression and gap in mental health service use across European regions. *Eur Psychiatry*, *57*, 19-25. https://doi.org/10.1016/j.eurpsy.2018.12.002

Hsu, F. C., Sink, K. M., Hugenschmidt, C. E., Williamson, J. D., Hughes, T. M., Palmer, N. D., . . . Freedman, B. I. (2018). Cerebral structure and cognitive performance in African Americans and European Americans with type 2 diabetes. *The Journals of Gerontology.*

Series A, Biological Sciences and Medical Sciences, *73*(3), 407-414. https://doi.org/10.1093/gerona/glx255

Huang, H., Menezes, P. R., da Silva, S. A., Tabb, K., Barkil-Oteo, A., & Scazufca, M. (2014). The association between depressive disorders and health care utilization: results from the Sao Paulo ageing and health study (SPAH). *Gen Hosp Psychiatry*, *36*(2), 199-202. https://doi.org/10.1016/j.genhosppsych.2013.11.003

Hudson, D. L., Neighbors, H. W., Geronimus, A. T., & Jackson, J. S. (2016). Racial Discrimination, John Henryism, and Depression Among African Americans. *J Black Psychol*, *42*(3), 221-243. https://doi.org/10.1177/0095798414567757

Joel, I., Begley, A. E., Mulsant, B. H., Lenze, E. J., Dew, M. A., Blumberger, D., . . . Team, I. (2014). Dynamic prediction of treatment response in late-life depression. *Am J Geriatr Psychiatry*, *22*(2), 167-176. https://doi.org/10.1016/j.jagp.2012.07.002.DYNAMIC

Johnson, J. K., Lui, L. Y., & Yaffe, K. (2007). Executive function, more than global cognition, predicts functional decline and mortality in elderly women. *J Gerontol A Biol Sci Med Sci*, *62*(10), 1134-1141. https://doi.org/10.1093/gerona/62.10.1134

Johnson, L. A., Large, S. E., Izurieta Munoz, H., Hall, J. R., & O'Bryant, S. E. (2019). Vascular depression and cognition in Mexican Americans. *Dementia and Geriatric Cognitive Disorders*, *47*(1-2), 68-78. https://doi.org/10.1159/000494272

Karsten, J., Penninx, B. W., Verboom, C. E., Nolen, W. A., & Hartman, C. A. (2013). Course and risk factors of functional impairment in subthreshold depression and anxiety. *Depress Anxiety*, *30*(4), 386-394. https://doi.org/10.1002/da.22021

Kearney, F. C., Harwood, R. H., Gladman, J. R., Lincoln, N., & Masud, T. (2013). The relationship between executive function and falls and gait abnormalities in older adults: a

systematic review. *Dement Geriatr Cogn Disord*, *36*(1-2), 20-35. https://doi.org/10.1159/000350031

Kim, G., Decoster, J., Huang, C. H., & Chiriboga, D. A. (2011). Race/ethnicity and the factor structure of the Center for Epidemiologic Studies Depression Scale: a meta-analysis. *Cultur Divers Ethnic Minor Psychol*, *17*(4), 381-396. https://doi.org/10.1037/a0025434

Kim, J. H., Islam, S. J., Topel, M. L., Ko, Y. A., Mujahid, M. S., Vaccarino, V., . . . Lewis, T. T. (2020). Individual Psychosocial Resilience, Neighborhood Context, and Cardiovascular Health in Black Adults: A Multilevel Investigation From the Morehouse-Emory Cardiovascular Center for Health Equity Study. *Circ Cardiovasc Qual Outcomes*, *13*(10), e006638. https://doi.org/10.1161/circoutcomes.120.006638

Kim, S., Woo, S. Y., Kang, H. S., Lim, S. W., Choi, S. H., Myung, W., . . . Kim, D. K. (2016). Factors related to prevalence, persistence, and incidence of depressive symptoms in mild cognitive impairment: vascular depression construct. *International Journal of Geriatric Psychiatry*, *31*(7), 818-826. https://doi.org/10.1002/gps.4400

Kim, Y. K., & Han, K. M. (2021). Neural substrates for late-life depression: A selective review of structural neuroimaging studies. *Prog Neuropsychopharmacol Biol Psychiatry*, *104*, 110010. https://doi.org/10.1016/j.pnpbp.2020.110010

Klil-Drori, S., Klil-Drori, A. J., Pira, S., & Rej, S. (2020). Exercise Intervention for Late-Life Depression: A Meta-Analysis. *J Clin Psychiatry*, *81*(1). https://doi.org/10.4088/JCP.19r12877

Krishnan, K. R., Hays, J. C., & Blazer, D. G. (1997). MRI-defined vascular depression. *Am J Psychiatry*, *154*(4), 497-501. https://doi.org/10.1176/ajp.154.4.497

Krishnan, K. R. R., Hays, J. C., & Blazer, D. G. (1997). MRI-defined vascular depression. *American Journal of Psychiatry*, *154*(4), 497-501. https://doi.org/10.1176/ajp.154.4.497

Krishnan, K. R. R., Taylor, W. D., McQuoid, D. R., MacFall, J. R., Payne, M. E., Provenzale, J. M., & Steffens, D. C. (2004). Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biological Psychiatry*, *55*(4), 390-397. https://doi.org/10.1016/j.biopsych.2003.08.014

Kumar, A., Jin, Z., Bilker, W., Udupa, J., & Gottlieb, G. (1998). Late-onset minor and major depression : early evidence for common neuroanatomical substrates detected by using MRI. *Proc. Natl. Acad. Sci. USA*, *95*(June), 7654-7658.

Kumar, A., Schweizer, E., Zhisong, J., Miller, D., Bilker, W., Swan, L. L., & Gottlieb, G. (1997). Neuroanatonmical Substrates of Late-Life Minor Depression. *Arch Neurol*, *54*, 613-617.

Lamar, M., Fleischman, D. A., Leurgans, S. E., Aggarwal, N., Yu, L., Kim, N., . . . Barnes, L. L. (2022). Relationship of blood pressure and white matter hyperintensity burden with level of and change in cognition in older Black adults. *Psychosom Med*. https://doi.org/10.1097/psy.0000000000001059

Lamar, M., Rubin, L. H., Ajilore, O., Charlton, R., Zhang, A., Yang, S., . . . Kumar, A. (2015). What Metabolic Syndrome Contributes to Brain Outcomes in African American & Caucasian Cohorts. *Curr Alzheimer Res*, *12*(7), 640-647. https://doi.org/10.2174/1567205012666150701102325

Lewinsohn, P. M., Seeley, J. R., Roberts, R. E., & Allen, N. B. (1997). Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging*, *12*(2), 277-287. https://doi.org/10.1037//0882-7974.12.2.277

Li, R., Ma, Z., Yu, J., He, Y., & Li, J. (2014). Altered local activity and functional connectivity of the anterior cingulate cortex in elderly individuals with subthreshold depression. *Psychiatry Res*, *222*(1-2), 29-36. https://doi.org/10.1016/j.pscychresns.2014.02.013

Liao, Y., Huang, X., Wu, Q., Yang, C., Kuang, W., Du, M., . . . Gong, Q. (2013). Is depression a disconnection syndrome? Meta-analysis of diffusion tensor imaging studies in patients with MDD. *Journal of Psychiatry & Neuroscience*, *38*(1), 49-56. https://doi.org/10.1503/jpn.110180

Maltais, M., de Souto Barreto, P., Moon, S. Y., Rolland, Y., & Vellas, B. (2019). Prospective association of white matter hyperintensity volume and frailty in older adults. *Exp Gerontol*, *118*, 51-54. https://doi.org/10.1016/j.exger.2019.01.007

Manning, K. J., Alexopoulos, G. S., Banerjee, S., Morimoto, S. S., Seirup, J. K., Klimstra, S. A., . . . Gunning-Dixon, F. (2015). Executive functioning complaints and escitalopram treatment response in late-life depression. *Am J Geriatr Psychiatry*, *23*(5), 440-445. https://doi.org/10.1016/j.jagp.2013.11.005

Mansour, R., Tsamakis, K., Rizos, E., Perera, G., Das-Munshi, J., Stewart, R., & Mueller, C. (2020). Late-life depression in people from ethnic minority backgrounds: Differences in presentation and management. *J Affect Disord*, *264*, 340-347. https://doi.org/10.1016/j.jad.2019.12.031

Maraboto, C., & Ferdinand, K. C. (2020). Update on hypertension in African-Americans. *Prog Cardiovasc Dis*, *63*(1), 33-39. https://doi.org/10.1016/j.pcad.2019.12.002

Marengoni, A., Angleman, S., Melis, R., Mangialasche, F., Karp, A., Garmen, A., . . . Fratiglioni, L. (2011). Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev*, *10*(4), 430-439. https://doi.org/10.1016/j.arr.2011.03.003

Mast, B. T., MacNeill, S. E., & Lichtenberg, P. A. (2004). Post-stroke and clinically-defined vascular depression in geriatric rehabilitation patients. *Am J Geriatr Psychiatry*, *12*(1), 84-92.

Mast, B. T., Neufeld, S., MacNeill, S. E., & Lichtenberg, P. A. (2004). Longitudinal support for the relationship between vascular risk factors and late-life depressive symptoms. *Am J Geriatr Psychiatry*, *12*(1), 93-101.

Mast, B. T., Yochim, B., MacNeill, S. E., & Lichtenberg, P. A. (2004). Risk factors for geriatric depression: the importance of executive functioning within the vascular depression hypothesis. *J Gerontol A Biol Sci Med Sci*, *59*(12), 1290-1294. https://doi.org/10.1093/gerona/59.12.1290

Matarazzo, J. D., & Herman, D. O. (1984). Base rate data for the WAIS-R: test-retest stability and VIQ-PIQ differences. *J Clin Neuropsychol*, *6*(4), 351-366. https://doi.org/10.1080/01688638408401227

McLaren, M. E., Szymkowicz, S. M., O'Shea, A., Woods, A. J., Anton, S. D., & Dotson, V. M. (2016). Dimensions of depressive symptoms and cingulate volumes in older adults. *Transl Psychiatry*, *6*, e788. https://doi.org/10.1038/tp.2016.49

Meeks, T. W., Vahia, I. V., Lavretsky, H., Kulkarni, G., & Jeste, D. V. (2011). A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *Journal of Affective Disorders*, *129*(1-3), 126-142. https://doi.org/10.1016/j.jad.2010.09.015

Mehta, K. M., Simonsick, E. M., Rooks, R., Newman, A. B., Pope, S. K., Rubin, S. M., & Yaffe, K. (2004). Black and white differences in cognitive function test scores: what explains

the difference? *J Am Geriatr Soc*, *52*(12), 2120-2127. https://doi.org/10.1111/j.1532-5415.2004.52575.x

Mendez Colmenares, A., Voss, M. W., Fanning, J., Salerno, E. A., Gothe, N. P., Thomas, M. L., . . . Burzynska, A. Z. (2021). White matter plasticity in healthy older adults: The effects of aerobic exercise. *Neuroimage*, *239*, 118305. https://doi.org/10.1016/j.neuroimage.2021.118305

Mensah, G. A. (2018). Cardiovascular Diseases in African Americans: Fostering Community Partnerships to Stem the Tide. *Am J Kidney Dis*, *72*(5 Suppl 1), S37-s42. https://doi.org/10.1053/j.ajkd.2018.06.026

Middleton, A., Fritz, S. L., & Lusardi, M. (2015). Walking speed: the functional vital sign. *J Aging Phys Act*, *23*(2), 314-322. https://doi.org/10.1123/japa.2013-0236

Moody, D. L. B., Chang, Y. F., Pantesco, E. J., Darden, T. M., Lewis, T. T., Brown, C., . . . Matthews, K. A. (2019). Everyday Discrimination Prospectively Predicts Blood Pressure Across 10 Years in Racially/Ethnically Diverse Midlife Women: Study of Women's Health Across the Nation. *Ann Behav Med*, *53*(7), 608-620. https://doi.org/10.1093/abm/kay069

Morrell, C. H., Pearson, J. D., & Brant, L. J. (1997). Linear Transformations of Linear Mixed-Effects Models. *The American Statistician*, *51*(4), 338-343. https://doi.org/10.1080/00031305.1997.10474409

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., . . . Turner, M. B. (2016). Executive summary: Heart disease and stroke statistics--2016 update: A report from the American Heart Association. *Circulation*, *133*(4), 447-454. https://doi.org/10.1161/cir.0000000000000366

Naarding, P., & Beekman, A. T. F. (2011). Vascular depression: where do we go from here? *Expert Review of Neurotherapeutics*, *11*(1), 77-83. https://doi.org/10.1586/ern.10.92.

Naarding, P., Veereschild, M., Bremmer, M., Deeg, D., & Beekman, A. T. F. (2009). The symptom profile of vascular depression. *International Journal of Geriatric Psychiatry*, *24*(9), 965-969. https://doi.org/10.1002/gps.2203

Nadkarni, N. K., Boudreau, R. M., Studenski, S. A., Lopez, O. L., Liu, G., Kritchevsky, S., . . . Rosano, C. (2016). Slow gait, white matter characteristics, and prior 10-year interleukin-6 levels in older adults. *Neurology*, *87*(19), 1993-1999. https://doi.org/10.1212/wnl.0000000000003304

Nyquist, P. A., Bilgel, M. S., Gottesman, R., Yanek, L. R., Moy, T. F., Becker, L. C., . . . Vaidya, D. (2014). Extreme deep white matter hyperintensity volumes are associated with African American race. *Cerebrovascular Diseases*, *37*(4), 244-250. https://doi.org/10.1159/000358117

Oh, H., Glass, J., Narita, Z., Koyanagi, A., Sinha, S., & Jacob, L. (2021). Discrimination and Multimorbidity Among Black Americans: Findings from the National Survey of American Life. *J Racial Ethn Health Disparities*, *8*(1), 210-219. https://doi.org/10.1007/s40615-020-00773-z

Ong, A. D., Williams, D. R., Nwizu, U., & Gruenewald, T. L. (2017). Everyday unfair treatment and multisystem biological dysregulation in African American adults. *Cultur Divers Ethnic Minor Psychol*, *23*(1), 27-35. https://doi.org/10.1037/cdp0000087

Palazidou, E. (2012). The neurobiology of depression. *Br Med Bull*, *101*, 127-145. https://doi.org/10.1093/bmb/lds004

Paradies, Y., Ben, J., Denson, N., Elias, A., Priest, N., Pieterse, A., . . . Gee, G. (2015). Racism as a determinant of health: A systematic review and meta-analysis. *PLoS One*, *10*(9), e0138511. https://doi.org/10.1371/journal.pone.0138511

Park, J. H., Lee, S. B., Lee, J. J., Yoon, J. C., Han, J. W., Kim, T. H., . . . Kim, K. W. (2015). Epidemiology of MRI-defined vascular depression: A longitudinal, community-based study in Korean elders. *Journal of Affective Disordors*, *180*, 200-206. https://doi.org/10.1016/j.jad.2015.04.008

Patience, J., Lai, K. S. P., Russell, E., Vasudev, A., Montero-Odasso, M., & Burhan, A. M. (2019). Relationship Between Mood, Thinking, and Walking: A Systematic Review Examining Depressive Symptoms, Executive Function, and Gait. *Am J Geriatr Psychiatry*, *27*(12), 1375-1383. https://doi.org/10.1016/j.jagp.2019.07.007

Persaud, A. D., Singh, D., Whitboume, S. K., & Sneed, J. R. (2012). Vascular depression and African Americans: A population at risk. In J. M. Sullivan & A. M. Esmail (Eds.), *African American identity: Racial and cultural dimensions of the Black experience.* (pp. 221-246). Lexington Books/Rowman & Littlefield. https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,shib&db=psyh&AN=2012-12594-009&site=ehost-live&scope=site&custid=gsu1

Pimontel, M. A., Rindskopf, D., Rutherford, B. R., Brown, P. J., Roose, S. P., & Sneed, J. R. (2016). A meta-analysis of executive dysfunction and antidepressant treatment response in late-life depression. *American Journal of Geriatric Psychiatry*, *24*(1), 31-41. https://doi.org/10.1016/j.jagp.2015.05.010

Potter, G. G., Kittinger, J. D., Wagner, H. R., Steffens, D. C., & Krishnan, K. R. (2004). Prefrontal neuropsychological predictors of treatment remission in late-life depression. *Neuropsychopharmacology*, *29*(12), 2266-2271. https://doi.org/10.1038/sj.npp.1300551

Prabhakaran, S., Wright, C. B., Yoshita, M., Delapaz, R., Brown, T., DeCarli, C., & Sacco, R. L. (2008). Prevalence and determinants of subclinical brain infarction: the Northern Manhattan Study. *Neurology*, *70*(6), 425-430. https://doi.org/10.1212/01.wnl.0000277521.66947.e5

Quiñones, A. R., Botoseneanu, A., Markwardt, S., Nagel, C. L., Newsom, J. T., Dorr, D. A., & Allore, H. G. (2019). Racial/ethnic differences in multimorbidity development and chronic disease accumulation for middle-aged adults. *PLoS One*, *14*(6), e0218462. https://doi.org/10.1371/journal.pone.0218462

Radloff, L. S. (1977). The CES-D Scale:A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement*, *1*(3), 385-401. https://doi.org/10.1177/014662167700100306

Rashidi-Ranjbar, N., Miranda, D., Butters, M. A., Mulsant, B. H., & Voineskos, A. N. (2020). Evidence for structural and functional alterations of frontal-executive and corticolimbic circuits in late-life depression and relationship to mild cognitive impairment and dementia: A systematic review [Systematic Review]. *Frontiers in Neuroscience*, *14*(253). https://doi.org/10.3389/fnins.2020.00253

Reinlieb, M. E., Persaud, A., Singh, D., Garcon, E., Rutherford, B. R., Pelton, G. H., . . . Sneed, J. R. (2014). Vascular depression: Overrepresented among African Americans? *International Journal of Geriatric Psychiatry*, *29*(5), 470-477. https://doi.org/10.1002/gps.4029

Rensma, S. P., van Sloten, T. T., Launer, L. J., & Stehouwer, C. D. A. (2018). Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neurosci Biobehav Rev*, *90*, 164-173. https://doi.org/10.1016/j.neubiorev.2018.04.003

Respino, M., Jaywant, A., Kuceyeski, A., Victoria, L. W., Hoptman, M. J., Scult, M. A., . . . Gunning, F. M. (2019). The impact of white matter hyperintensities on the structural connectome in late-life depression: Relationship to executive functions. *Neuroimage: Clinical*, *23*, 101852. https://doi.org/10.1016/j.nicl.2019.101852

Rizvi, B., Lao, P. J., Chesebro, A. G., Dworkin, J. D., Amarante, E., Beato, J. M., . . . Brickman, A. M. (2021). Association of Regional White Matter Hyperintensities With Longitudinal Alzheimer-Like Pattern of Neurodegeneration in Older Adults. *JAMA Netw Open*, *4*(10), e2125166. https://doi.org/10.1001/jamanetworkopen.2021.25166

Robinson, M. N., & Thomas Tobin, C. S. (2021). Is John Henryism a Health Risk or Resource?: Exploring the Role of Culturally Relevant Coping for Physical and Mental Health among Black Americans. *J Health Soc Behav*, *62*(2), 136-151. https://doi.org/10.1177/00221465211009142

Rohyans, L. M., & Pressler, S. J. (2009). Depressive symptoms and heart failure: examining the sociodemographic variables. *Clin Nurse Spec*, *23*(3), 138-144. https://doi.org/10.1097/NUR.0b013e3181a443b4

Rosano, C., Perera, S., Inzitari, M., Newman, A. B., Longstreth, W. T., & Studenski, S. (2016). Digit Symbol Substitution test and future clinical and subclinical disorders of cognition, mobility and mood in older adults. *Age Ageing*, *45*(5), 688-695. https://doi.org/10.1093/ageing/afw116

Royall, D. R., Mahurin, R. K., & Gray, K. F. (1992). Bedside assessment of executive cognitive impairment: the executive interview. *J Am Geriatr Soc*, *40*(12), 1221-1226. https://doi.org/10.1111/j.1532-5415.1992.tb03646.x

Ryan, J., Woods, R. L., Britt, C., Murray, A. M., Shah, R. C., Reid, C. M., . . . Storey, E. (2019). Normative performance of healthy older individuals on the Modified Mini-Mental State (3MS) examination according to ethno-racial group, gender, age, and education level. *Clin Neuropsychol*, *33*(4), 779-797. https://doi.org/10.1080/13854046.2018.1488996

Salo, K. I., Scharfen, J., Wilden, I. D., Schubotz, R. I., & Holling, H. (2019). Confining the Concept of Vascular Depression to Late-Onset Depression: A Meta-Analysis of MRI-Defined Hyperintensity Burden in Major Depressive Disorder and Bipolar Disorder. *Front Psychol*, *10*, 1241. https://doi.org/10.3389/fpsyg.2019.01241

Sexton, C. E., Betts, J. F., Demnitz, N., Dawes, H., Ebmeier, K. P., & Johansen-Berg, H. (2016). A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. *Neuroimage*, *131*, 81-90. https://doi.org/10.1016/j.neuroimage.2015.09.071

Sheline, Y. I., Pieper, C. F., Barch, D. M., Welsh-Bohmer, K., McKinstry, R. C., MacFall, J. R., . . . Doraiswamy, P. M. (2010). Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry*, *67*(3), 277-285. https://doi.org/10.1001/archgenpsychiatry.2009.204

Sheline, Y. I., Price, J. L., Vaishnavi, S. N., Mintun, M. A., Barch, D. M., Epstein, A. A., . . . McKinstry, R. C. (2008). Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects

matched for vascular risk factors. *American Journal of Psychiatry*, *165*(4), 524-532. https://doi.org/10.1176/appi.ajp.2007.07010175

Sherman A., J. (2019). John Henryism, Structural Racism, and Cardiovascular Health Risks in African Americans. In F. CL, G. DM, B. MA, & G. KL (Eds.), *Racism: Science & Tools for the Public Health Professional* (pp. 171-189). American Public Health Association.

Sible, I. J., Jang, J. Y., Sultzer, D. L., & Nation, D. A. (2022). Visit-To-Visit Blood Pressure Variability and Subthreshold Depressive Symptoms in Older Adults. *Am J Geriatr Psychiatry*. https://doi.org/10.1016/j.jagp.2022.03.006

Siejka, T. P., Srikanth, V. K., Hubbard, R. E., Moran, C., Beare, R., Wood, A., . . . Callisaya, M. L. (2020). White Matter Hyperintensities and the Progression of Frailty-The Tasmanian Study of Cognition and Gait. *J Gerontol A Biol Sci Med Sci*, *75*(8), 1545-1550. https://doi.org/10.1093/gerona/glaa024

Simonsick, E. M., Newman, A. B., Nevitt, M. C., Kritchevsky, S. B., Ferrucci, L., Guralnik, J. M., & Harris, T. (2001). Measuring higher level physical function in well-functioning older adults: expanding familiar approaches in the Health ABC study. *J Gerontol A Biol Sci Med Sci*, *56*(10), M644-649. https://doi.org/10.1093/gerona/56.10.m644

Singh-Manoux, A., Akbaraly, T. N., & Marmot, M. (2010). Persistent depressive symptoms and cognitive function in late midlife: the Whitehall II study. *J Clin Psychiatry*, *71*, 1379-1385.

Soysal, P., Veronese, N., Thompson, T., Kahl, K. G., Fernandes, B. S., Prina, A. M., . . . Stubbs, B. (2017). Relationship between depression and frailty in older adults: A systematic review and meta-analysis. *Ageing Res Rev*, *36*, 78-87. https://doi.org/10.1016/j.arr.2017.03.005

Steffens, D. C., Taylor, W. D., Denny, K. L., Bergman, S. R., & Wang, L. (2011). Structural integrity of the uncinate fasciculus and resting state functional connectivity of the ventral prefrontal cortex in late life depression. *PLoS One*, *6*(7), e22697. https://doi.org/10.1371/journal.pone.0022697

Stubbs, B., Stubbs, J., Gnanaraj, S. D., & Soundy, A. (2016). Falls in older adults with major depressive disorder (MDD): a systematic review and exploratory meta-analysis of prospective studies. *Int Psychogeriatr*, *28*(1), 23-29. https://doi.org/10.1017/s104161021500126x

Su, N., Liang, X., Zhai, F. F., Zhou, L. X., Ni, J., Yao, M., . . . Zhu, Y. C. (2018). The consequence of cerebral small vessel disease: Linking brain atrophy to motor impairment in the elderly. *Hum Brain Mapp*, *39*(11), 4452-4461. https://doi.org/10.1002/hbm.24284

Tabaei, B. P., Chamany, S., Perlman, S., Thorpe, L., Bartley, K., & Wu, W. Y. (2019). Heart age, cardiovascular disease risk, and disparities by sex and race/ethnicity among New York City adults. *Public Health Reports*, *134*(4), 404-416. https://doi.org/10.1177/0033354919849881

Tadayonnejad, R., & Ajilore, O. (2014). Brain network dysfunction in late-life depression: a literature review. *J Geriatr Psychiatry Neurol*, *27*(1), 5-12. https://doi.org/10.1177/0891988713516539

Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular Psychiatry*, *18*(9), 963-974. https://doi.org/10.1038/mp.2013.20

Teng, E. L., & Chui, H. C. (1987). The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*, *48*(8), 314-318.

Venkatraman, V. K., Aizenstein, H., Guralnik, J., Newman, A. B., Glynn, N. W., Taylor, C., . . . Rosano, C. (2010). Executive control function, brain activation and white matter hyperintensities in older adults. *Neuroimage*, *49*(4), 3436-3442. https://doi.org/10.1016/j.neuroimage.2009.11.019

Venkatraman, V. K., Aizenstein, H. J., Newman, A. B., Yaffe, K., Harris, T., Kritchevsky, S., . . . Rosano, C. (2011). Lower Digit Symbol Substitution Score in the Oldest Old is Related to Magnetization Transfer and Diffusion Tensor Imaging of the White Matter. *Front Aging Neurosci*, *3*, 11. https://doi.org/10.3389/fnagi.2011.00011

Vyas, C. M., Donneyong, M., Mischoulon, D., Chang, G., Gibson, H., Cook, N. R., . . . Okereke, O. I. (2020). Association of race and ethnicity with late-life depression severity, symptom burden, and care. *JAMA Network Open*, *3*(3), e201606. https://doi.org/10.1001/jamanetworkopen.2020.1606

Waldman, S. V., Blumenthal, J. A., Babyak, M. A., Sherwood, A., Sketch, M., Davidson, J., & Watkins, L. L. (2009). Ethnic differences in the treatment of depression in patients with ischemic heart disease. *Am Heart J*, *157*(1), 77-83. https://doi.org/10.1016/j.ahj.2008.08.013

Waldstein, S. R., Dore, G. A., Davatzikos, C., Katzel, L. I., Gullapalli, R., Seliger, S. L., . . . Zonderman, A. B. (2017). Differential associations of socioeconomic status with global brain volumes and white matter lesions in African American and White Adults: the HANDLS SCAN Study. *Psychosomatic Medicine*, *79*(3), 327-335. https://doi.org/10.1097/PSY.0000000000000408

Watkins, D. C., & Johnson, N. C. (2018). Age and gender differences in psychological distress among African Americans and Whites: Findings from the 2016 National Health Interview Survey. *Healthcare (Basel)*, *6*(1). https://doi.org/10.3390/healthcare6010006

Watson, N. L., Rosano, C., Boudreau, R. M., Simonsick, E. M., Ferrucci, L., Sutton-Tyrrell, K., . . . Newman, A. B. (2010). Executive function, memory, and gait speed decline in well-functioning older adults. *J Gerontol A Biol Sci Med Sci*, *65*(10), 1093-1100. https://doi.org/10.1093/gerona/glq111

Wechsler, D. (1981). *WAIS-R Manual*. Psychological Corporation.

Wei, J., Hou, R., Zhang, X., Xu, H., Xie, L., Chandrasekar, E. K., . . . Goodman, M. (2019). The association of late-life depression with all-cause and cardiovascular mortality among community-dwelling older adults: systematic review and meta-analysis. *British Journal of Psychiatry*, *215*(2), 449-455. https://doi.org/10.1192/bjp.2019.74

Weisenbach, S. L., Boore, L. A., & Kales, H. C. (2012). Depression and cognitive impairment in older adults. *Curr Psychiatry Rep*, *14*(4), 280-288. https://doi.org/10.1007/s11920-012-0278-7

Wen, M. C., Steffens, D. C., Chen, M. K., & Zainal, N. H. (2014). Diffusion tensor imaging studies in late-life depression: systematic review and meta-analysis. *International Journal of Geriatric Psychiatry*, *29*(12), 1173-1184. https://doi.org/10.1002/gps.4129

Williams, D. R. (2003). The health of men: structured inequalities and opportunities. *Am J Public Health*, *93*(5), 724-731. https://doi.org/10.2105/ajph.93.5.724

Willis, B. L., Leonard, D., Barlow, C. E., Martin, S. B., DeFina, L. F., & Trivedi, M. H. (2018). Association of midlife cardiorespiratory fitness with incident depression and

cardiovascular death after depression in later life. *JAMA Psychiatry*, *75*(9), 911-917. https://doi.org/10.1001/jamapsychiatry.2018.1467

Wu, M., Rosano, C., Butters, M., Whyte, E., Nable, M., Crooks, R., . . . Aizenstein, H. J. (2006). A fully automated method for quantifying and localizing white matter hyperintensities on MR images. *Psychiatry Res*, *148*(2-3), 133-142. https://doi.org/10.1016/j.pscychresns.2006.09.003

Ye, Q., Su, F., Gong, L., Shu, H., Liao, W., Xie, C., . . . Bai, F. (2017). Divergent roles of vascular burden and neurodegeneration in the cognitive decline of geriatric depression patients and Mild Cognitive Impairment patients. *Frontiers in Aging Neuroscience*, *9*, 288. https://doi.org/10.3389/fnagi.2017.00288

Yochim, B., Mast, B. T., & Lichtenberg, P. A. (2003). Cerebrovascular Risk Factors and Depressed Mood in Inner City Older Adults. *Clinical Psychologist*, *7*(1), 11-20. https://doi.org/10.1080/13284200410001707443

Yochim, B. P., Kerkar, S. P., & Lichtenberg, P. A. (2006). Cerebrovascular risk factors, activity limitations, and depressed mood in African American older adults. *Psychol Aging*, *21*(1), 186-189. https://doi.org/10.1037/0882-7974.21.1.186

Yochim, B. P., MacNeill, S. E., & Lichtenberg, P. A. (2006). "Vascular depression" predicts verbal fluency in older adults. *J Clin Exp Neuropsychol*, *28*(4), 495-508. https://doi.org/10.1080/13803390590949322

Zahodne, L. B., Manley, J. J., Narkhede, A., Griffith, E. Y., DeCarli, C., Schupf, N. S., . . . Brickman, A. M. (2015). Structural MRI predictors of late-life cognition differ across African Americans, Hispanics, and Whites. *Current Alzheimer Research*, *12*(7), 632-639. https://doi.org/10.2174/1567205012666150530203214

Zahodne, L. B., Sharifian, N., Kraal, A. Z., Morris, E. P., Sol, K., Zaheed, A. B., . . . Brickman, A. M. (2022). Longitudinal associations between racial discrimination and hippocampal and white matter hyperintensity volumes among older Black adults. *Soc Sci Med*, 114789. https://doi.org/10.1016/j.socscimed.2022.114789

Zahodne, L. B., Sol, K., & Kraal, Z. (2019). Psychosocial Pathways to Racial/Ethnic Inequalities in Late-Life Memory Trajectories. *J Gerontol B Psychol Sci Soc Sci*, *74*(3), 409-418. https://doi.org/10.1093/geronb/gbx113

Zhang, H., & Rodriguez-Monguio, R. (2012). Racial disparities in the risk of developing obesity-related diseases: a cross-sectional study. *Ethnicity and Disease*, *22*(3), 308-316.