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Multimodal Characterization of Vascular Subthreshold Depression During the Menopausal Transition and Beyond

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Multimodal Characterization of Vascular Subthreshold Depression During the Menopausal
Transition and Beyond

by

Alexandria Kaye Bartlett

Under the Direction of Vonetta M. Dotson, PhD

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Arts

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ABSTRACT

This study tested the vascular depression hypothesis in a diverse sample of women, explored the impact of menopause on the vascular–depressive symptoms relationship, and examined associations of vascular subthreshold depression with executive functioning. Data were analyzed from 69 women between ages 45 to 77 years. Principle components analysis was used to generate composite scores representing vascular burden and executive functioning. Results from linear regression analyses found no significant associations between vascular burden and depressive symptoms, no interactions of race or menopause symptoms with vascular burden on depressive symptoms, and no associations between vascular burden by subthreshold depression subgroups and executive functioning. Exploratory analyses revealed poor sleep, high stress, and discrimination predicted greater depressive symptoms. This suggests in healthy women in late middle adulthood, sleep and stress-related mechanisms may be predictive of mood. Future studies should study these relationships with objective measures, using longitudinal methods, and within equally diverse populations.

INDEX WORDS: vascular depression, menopause, vascular burden, depressive symptoms, health disparities, aging

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DEDICATION

To my Peepa, for insisting I phrased my sentences just right and editing my papers until they were filled with red ink: I will forever be a better writer because of you. To my Nana, whose wisdom and joy have always made her my favorite person to get advice from. To my brother, whose calm nature makes for a surprisingly great roommate to a busy grad student. To my dad, who has always been my landing place when the world seemed too large. And to my mom, who endlessly fights for me and lifts me up even when I forget to myself. I would not be here without you.

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1 INTRODUCTION

1.1 Rise in Population Aging

Older adults—persons aged 65 years or more—are the fastest growing segment of the global populace, surpassing children five years and younger for the first time in 2018 and tripling in size between 1980 and 2022 (Gaigbe-Togbe et al., 2022). Projections from the United Nations predict that by 2050, older adults will grow to 1.6 billion and comprise over 16% of the world population (2022). This percentage is expected to be even higher in the United States, where one in every four Americans are projected to be 65 years old or older by 2050 (2021 Profile of Older Americans, 2022). Older adults are invaluable members of our community, providing experience and wisdom that have great impact in our growing world. Despite this, an aging population directly results in a reciprocal rise in several aging-related disorders, leading to broad social, economic, and health challenges.

Biological women are especially vulnerable given that they live nearly six years longer than men on average, share an overrepresented 55% of the older adult population, and undergo unique sex-specific changes throughout their lifespans (2021 Profile of Older Americans, 2022; Arias et al., 2022). Consequently, they are of special public health concern as the world rapidly ages. Physiological changes during the menopausal transition underlie many of the vulnerabilities seen in biological women. For the purpose of this study, “women” refers to biological women since this study focuses on biological vulnerabilities that may not generalize to trans women or other groups.

1.2 Menopause and Aging-Related Vulnerabilities in Biological Women

Compared to men, women carry a unique array of sex-specific cognitive, psychological, and biological vulnerabilities as they age. A large part of this difference is

likely related to the cascade of dimorphic developmental changes that occur under the influence of sex hormones. Estrogen and progesterone are the primary sex hormones expressed in women, and during the natural aging process, circulating levels of estrogen rapidly decrease through a process called menopause. Natural menopause is defined as a twelve-month period without menstruation not due to another cause and typically occurs between the ages of 45 to 54, with the average age at menopause onset being around 51 years of age (Barron & Pike, 2012; Minkin, 2019; Namazi et al., 2019). The years leading up to a woman's final menstrual period are known as the menopausal transition (Maki & Thurston, 2020). Estrogen levels remain relatively stable until approximately two years prior to menopausal onset, when women then experiences a precipitous 67% drop and continual regression in the years following (Barron & Pike, 2012; Horstman et al., 2012; Sowers et al., 2008). By the first year of menopause, women retain only about 20% of their circulating estrogens compared to the 80% preserved testosterone in same-aged men (Horstman et al., 2012). This striking difference in the rate and concentration of available sex hormones appears to have significant implications for aging women (Barron & Pike, 2012; Vest & Pike, 2013).

For example, women experience greater cognitive decline and more frequently report subjective cognitive complaints than men as they progress through menopause from middle to late adulthood (Conde et al., 2021). In two recent large-scale longitudinal studies of sex differences in cognitive functioning (D. A. Levine et al., 2021; Nooyens et al., 2022), findings demonstrated that while women typically had better baseline performance across many cognitive measures in midlife (e.g., memory, processing speed, executive function), they experienced significantly steeper age-related declines in these cognitive domains

relative to their male counterparts between ages 50 to 80 years old (see Figure 1). This pattern aligns with the difference in the rate of decline of circulating sex hormone levels between men and women over this period. Executive functioning is particularly vulnerable in aging women given its dependence on the prefrontal cortices, a brain region directly modulated by estrogen (Page et al., 2023). Relatedly, biological women aged 65 and older are nearly twice as likely to develop Alzheimer’s disease than men (Barron & Pike, 2012; Podcasy & Epperson, 2016) and, once diagnosed, female dementia patients have greater disability and quicker disease progression relative to men (Podcasy & Epperson, 2016; Sinforiani et al., 2010). Given that estrogen supports synaptogenesis and the clearance of beta amyloid, a plaque well known as a hallmark indicator of Alzheimer’s disease (Barron & Pike, 2012; Mosconi et al., 2021), the loss of estrogen’s protective effects through menopause likely explains this finding as well. Taken together, this underscores the increased cognitive risk women face with advancing age.

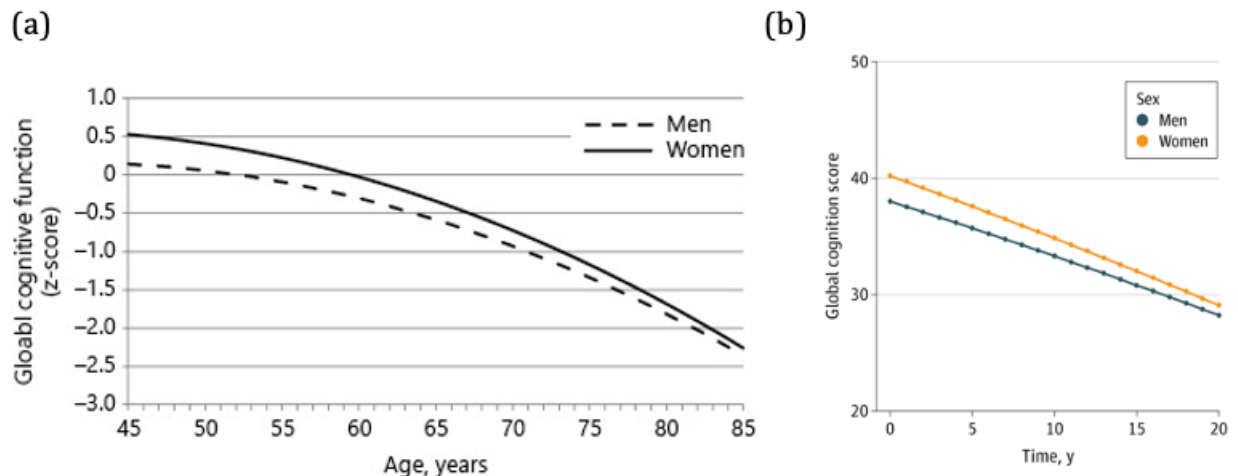


Figure 1: Global cognitive functioning transitioning from midlife to older adulthood.

Adapted from (a) Nooyens et al. (2022) and (b) Levine et al. (2021). Both outcome variables are composite scores based on participant performance across several cognitive measures including a letter digit substitution task, an animal fluency task, and a list learning task, among others. Note that in (b), the average age at baseline (i.e., time “0”) was 58 years old.

Middle-aged and older adult women also experience disproportionate psychological vulnerabilities compared to men. Although this sex difference may in part be accounted for by differences in reporting styles and perceptions of mental health, there is strong evidence to suggest biological mechanisms such as menopause impact this susceptibility (Alblooshi et al., 2023; Kuehner, 2017; Sialino et al., 2021; Slavich & Sacher, 2019). For instance, a recent systematic review evaluating the relationships between menopause and depression/ anxiety (Alblooshi et al., 2023) consistently found associations between the menopausal transition and negative mood, even among women with no prior history of a depressive disorder. Other studies have demonstrated that women in the menopausal transition were more than twice as likely to have elevated depressive symptoms (Freeman et al., 2006; Hildreth et al., 2018; Korthauer et al., 2022) and carried a greater risk for developing new onset depression compared to pre-menopause (Ji et al., 2021). Further, a recent large population-based longitudinal study of persons aged 55-65 years—prime age for the menopausal transition—found that on average, women reported 10% worse general mental health, 30% higher depressive symptoms, and 30% higher anxiety levels than men (Sialino et al., 2021). Moreover, among community-living adults in the United States, 16-18% of women between the ages of 55 to 64 reported clinically significant depressive symptoms compared to only 11-14% in same-aged men (Older Americans 2020: Key Indicators of Well-Being, 2020), and the prevalence of subthreshold depression is estimated to be two to three times higher (Meeks et al., 2011).

In addition to cognitive and psychological vulnerabilities, gender-based vascular differences are also observed across middle to late life. Research suggests that the pattern of vascular changes across the female lifespan mirrors that of hormonal and cognitive

changes: Women generally evidence better cardiovascular health than men through early and middle adulthood, then sex differences equalize during the sixth decade, and afterward women's cardiovascular health more rapidly declines to at or below that of men through older adulthood (El Khoudary, 2020; Merz & Cheng, 2016; Muka et al., 2016). This pattern was also demonstrated by a large community based study that compared longitudinal changes in pulse wave velocity (PWV) values between men and women (van Hout et al., 2021). PWV is a noninvasive ultrasound technique used to measure arterial stiffness, and it is quickly emerging as the gold standard for assessing cardiovascular risk (Marshall et al., 2024; Pereira et al., 2015). Results found that women overtake men in mean PWV between 60 to 65 years old, indicative of worsening age-related arterial stiffness. Relatedly, more older adult women than men live with hypertension (Merz & Cheng, 2016), which is a major risk factor for stroke, heart disease, and dementia, among other conditions (Tsao et al., 2023). Further, while white matter hyperintensity (WMH) volumes—areas of macrostructural brain damage of presumed vascular origin observed on neuroimaging as hyperintense regions (Wardlaw et al., 2015)—are prevalent among both older men and women (Debette & Markus, 2010; Wardlaw et al., 2015), a recent study (Lohner et al., 2022) found that WMH burden accelerated at a faster rate in menopausal women than in same-aged men. This is consistent with the broader literature noting the increased susceptibility to vascular deterioration during the menopausal transition (El Khoudary et al., 2020; Muka et al., 2016).

In summary, physiological changes during menopause may predispose aging women to worse cognitive, psychological, and biological vulnerabilities compared to their

male counterparts. Vascular and hormonal processes likely synergistically combine to contribute to these increased risks observed in biological women.

1.3 Interplay of Vascular Health, Menopause, and Mood

There may be important interrelationships between hormonal changes, vascular risk, and depression. As previously established, the steep loss of estrogen during the menopausal transition marks a period of increased vascular risk and accelerated vascular decline for aging women. Since estrogen is involved in reducing cholesterol levels (Shumaker et al., 2003), directly supports vasodilation and, subsequently, promotes blood flow (Muka et al., 2016; Zhu et al., 2019), the absence of estrogen's protective effects through menopause appears to underpin this finding. Declining vascular health may have important consequences on mood. For instance, a recent analysis found that increasing vascular age was associated with a 1.10 to 1.38 increased odds of depression (Feng et al., 2024). In addition, studies consistently show connections between high vascular burden and depression, including increased risk of depression and greater depressive symptom severity (Pozo et al., 2023; Salo et al., 2019; Zhang et al., 2023). The relationship between vascular function and mood symptoms also appears to be reciprocal, as depression itself almost doubles the risk of developing cardiovascular disease (Hildreth et al., 2018), is associated with endothelial dysfunction and increased arterial stiffness (Fiedorowicz, 2014), and represents an independent predictor of death and all-cause mortality due to vascular disease (El Khoudary et al., 2020).

Moreover, it is possible that the menopause symptoms themselves may adversely impact mood through probable vascular pathways. For instance vascular and endocrine dysfunction are thought to give rise to vasomotor symptoms, cardinal signals of

menopause that include hot flashes, night sweats (Maki & Thurston, 2020), and other sudden, acute episodes of intense warmth often accompanied by sweating and flushing (Thurston & Joffe, 2011). A recent metanalytic study found that vasomotor symptoms were highly associated with new onset depressive symptoms (Alblooshi et al., 2023), which supports that vascular processes may be involved. Taken together, menopause-related vascular decline may increase women's susceptibility for depressive symptoms.

1.4 Vascular Depression and Menopause

Given the vascular and mood-related vulnerabilities tied to menopause, it is possible that women in the menopausal transition may be at increased risk for a particularly debilitating form of depression known as vascular depression. Coined by Alexopoulos and colleagues (1997), they—along with others who have since extended the idea (Aizenstein et al., 2016; Jellinger, 2021; Taylor et al., 2013)—propose that cumulative vascular brain lesions can disrupt mood-relevant white matter pathways in the brain, which ultimately leads to a greater predisposition for depression. The hypothesis is supported not only by findings of higher prevalence of depression in adults with comorbid vascular conditions (Blöchl et al., 2023; El Khoudary, 2020; Hildreth et al., 2018) but also by evidence from neuroimaging (Jellinger, 2021; Krishnan et al., 1997; Rushia et al., 2020) and clinical studies (Barch et al., 2012; Rapp et al., 2005; Sheline et al., 2010; Wei et al., 2018) showing that vascular depression likely represents its own unique form of depression.

Vascular depression is believed to have a characteristically different presentation than other types of depression. Compared to non-vascular depression that often recurs chronically throughout the lifespan and evidences strong heritability, vascular depression first appears much later in life and frequently occurs spontaneously in individuals with no

family history of depression (Aizenstein et al., 2016; Jellinger, 2021, 2023; Krishnan et al., 1997; Taylor et al., 2013). Moreover, vascular depression is associated with pronounced attentional and executive deficits and disproportionate functional disability, likely a result of the damaged frontosubcortical networks from chronic vascular disturbances (Aizenstein et al., 2016; Jellinger, 2021). This is further substantiated by evidence from neuroimaging that shows greater WMH loads in persons with vascular depression than those with non-vascular depression (Aizenstein et al., 2016; Krishnan et al., 1997), particularly in frontal and temporal brain regions (Taylor et al., 2013) that are known to be involved in executive functioning, attentional control, and emotion regulation. Similar findings have also been demonstrated in studies with overrepresented multiethnic cohorts, including those within our lab (Bogoian et al., 2024; Bogoian & Dotson, 2022; Levy et al., 2024). Menopausal women may be at increased risk for this type of depression. In support of this, preliminary work in our lab using data from the Health, Aging, and Body Composition (Health ABC) study found that older adult women were over 40% more likely to have vascular subthreshold depression (i.e., elevated levels of depressive symptoms that do not meet criteria for clinical depression) than same-aged men (Bartlett et al., 2025).

Figure 2 provides a flow chart of possible mechanisms linking menopause with vascular depression. This model shows how the menopausal transition may start a cascade of physiological changes that can disproportionately predispose women to vascular depression. More specifically, lower circulating estrogen concentrations initiated by the onset of menopause create a vulnerability for subsequent arterial stiffening due to the rapid loss of estrogen's support in vasodilation (Muka et al., 2016). This reduced vascular responsiveness and arterial flexibility decreases the body's ability to accommodate changes

in blood flow, which in turn increases susceptibility of developing various cardiovascular conditions over time. The resulting higher vascular disease burden increases vulnerability for neurovascular events such as stroke (Tsao et al., 2023; Zhu et al., 2019) and causes microvascular lesions that are observable on neuroimaging as WMHs (Blöchl et al., 2023; Taylor et al., 2013). As WMHs begin to accumulate in frontal and temporal regions, they start to disrupt frontostriatal white matter connections (Aizenstein et al., 2016; Blöchl et al., 2023; Taylor et al., 2013), altering structural and functional brain regions that are integral to regulating cognitive and emotional functioning. These changes can eventually lead to significant mood disturbances, as well as executive dysfunction.

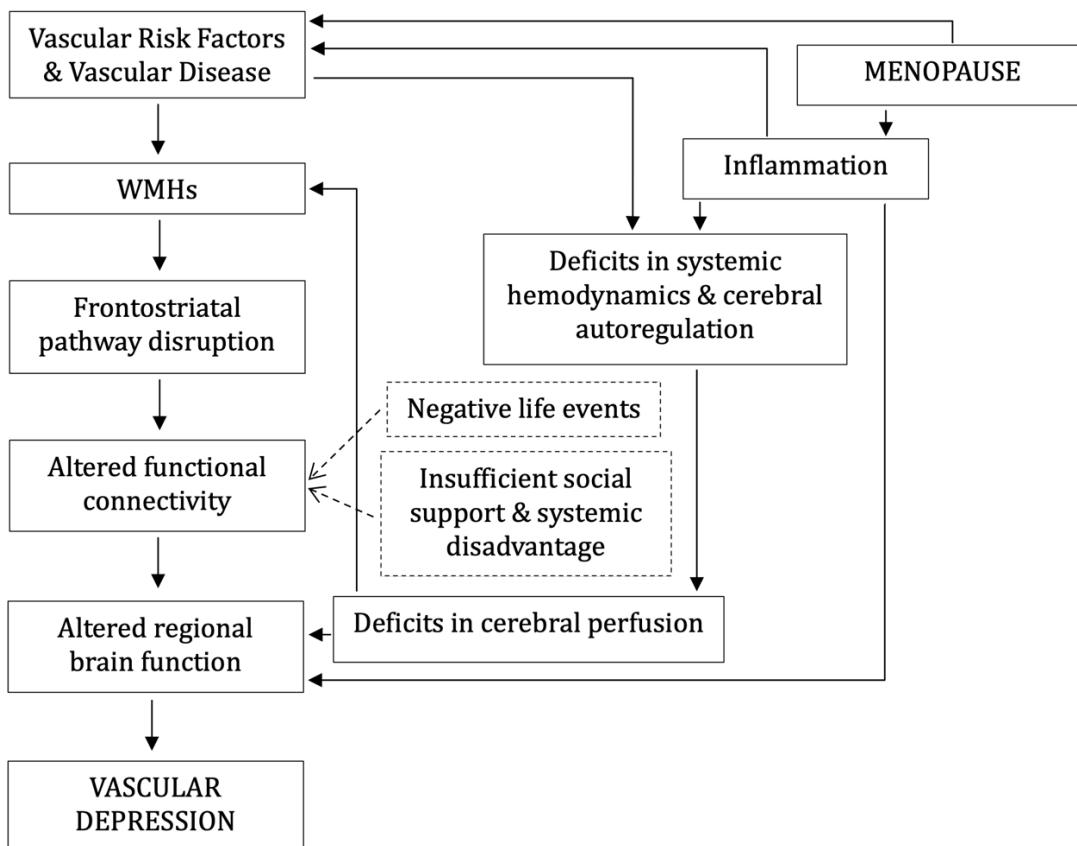


Figure 2: Flow chart of a possible mechanism through which menopausal status could contribute to vascular depression risk.

Adapted and modified from Krishnan & McDonald (1995), Taylor et al. (2013), and Aizenstein et al. (2016).

Figure 2 also highlights the importance of considering other potential factors that may influence vascular depression risk including sociodemographic and environmental elements. This subject will be detailed in the sections below.

1.5 Role of Racial Disparities

A wealth of evidence supports the existence of significant health disparities between Black and non-Hispanic White (NHW) groups. These disparities are shaped in part by differences in structural inequities in the social context and environmental exposures encountered by these two subpopulations. In a landmark paper discussing contextual influences on cognitive aging, Glymour and Manly (2008) eloquently explain how distal racially patterned social exposures and environmental features manifest as disparities in behavior, physical health, psychological functioning, and cognitive outcomes in older adults (see Figure 3 for an illustration of this concept). Although race is a social construct and not an inherent biologic feature, it serves as an important proxy of these unmeasured social determinants of health (Glymour & Manly, 2008; Mays et al., 2003). Further, the United States population continues to diversify with each passing year (Vespa et al., 2020), highlighting a need for researchers to consider ethnorracial factors in their study design.

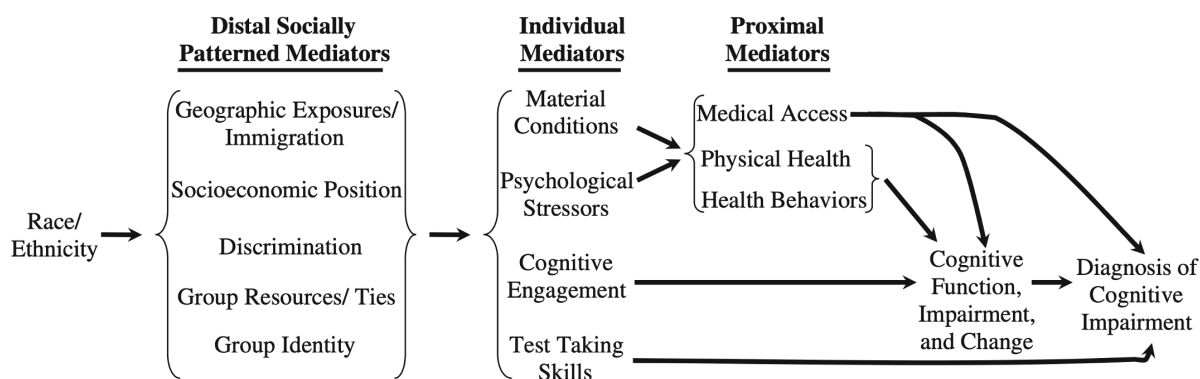


Figure 3: Influence of life course experience on cognitive aging. Adapted from Glymour & Manly (2008).

Studies consistently demonstrate that Black Americans evidence greater incidence and prevalence of several vascular risk factors and vascular diseases than NHWs, including disproportionately higher frequencies of high cholesterol, diabetes, hypertension, and obesity (Carnethon et al., 2017; Tsao et al., 2023). In fact, Black Americans have been found to have higher rates of hypertension than any other group in the world (Tsao et al., 2023). Consequently, Black Americans have also been shown to have greater WMH burden than NHWs, which are tied to many deleterious health outcomes including stroke, dementia risk, and all-cause mortality (Brickman et al., 2008; Levy et al., 2024).

In addition to differences in vascular risk, evidence suggests that depressive symptoms may also differ between racial groups, although the research literature is somewhat mixed. For instance, some studies indicate that Black adults endorse fewer depressive symptoms than NHW adults despite enduring disproportionately less favorable contextual factors that appear to contradict expectations for this group (Glymour & Manly, 2008; Jackson et al., 2010; Jang et al., 2014). In contrast, other works demonstrate much higher rates of depression in Black adults than NHWs (Bogoian & Dotson, 2022; Hooker et al., 2019; Vyas et al., 2020) as well as increased chronicity of depressive symptomatology and greater disease burden (Bailey et al., 2019; Williams et al., 2007).

The research literature additionally suggests that experiences of menopause may differ by racial group. Evidence from the Study of Women's Health Across the Nation (SWAN)—the largest and longest study of the menopausal transition to date—suggests Black women undergo menopause up to 12 months sooner than NHW women, with the average age at onset being 49.3 years for Black women (El Khoudary, 2020). Moreover, while the average length of the menopausal transition is typically seven years, Black

women evidenced significantly longer menopausal transition periods that could last up to 14 years, though certain health behaviors such as smoking may be more predictive of this finding than race alone (El Khoudary et al., 2019). Nonetheless, results such as these are critical given that earlier age at menopause has been associated with accelerated cognitive aging (M. E. Levine et al., 2016). Experiences of menopausal symptomology also appear to differ by race, as reports of vasomotor symptoms are highest among Black and Hispanic women (Avis et al., 2001; Bromberger et al., 2004; El Khoudary, 2020; Minkin, 2019), while NHW women typically report more psychosomatic symptoms (Avis et al., 2001).

Taken together, investigating the interplay of vascular health, depressive symptoms, and menopause in different racial and ethnic groups can help us better understand how existing literature on vascular depression risk may generalize to the broader population.

1.6 Knowledge Gaps and Rationale for Current Study

In sum, many studies have demonstrated that women are particularly vulnerable to vascular dysfunction during the menopausal transition. It is also well established that increased vascular burden adversely affects mood and cognition. Despite these connections, however, very few studies have investigated the interplay between vascular changes, depressive symptoms, and the menopausal transition concurrently. Studies also rarely incorporate newer assessments of vascular health, such as PWV measures. Further, to date, vascular depression has not been studied as a function of menopause, representing a large gap in the literature considering how women are susceptible to vascular and neuroendocrine decline through midlife that may make them especially vulnerable to vascular depression. In addition, the interrelationships between menopause, vascular health, and depressive symptoms may vary between women from different ethnoracial

backgrounds due, in part, to racially patterned social determinates of health. Considering that racial and ethnic minorities are underrepresented in research yet hold disproportionately elevated rates of cardiovascular disease risk and burden, this leaves another significant research gap in identifying a group that may be especially vulnerable to vascular depression in middle to late adulthood.

To address these knowledge gaps, the current study examined whether vascular burden interacts with menopausal symptoms to influence depressive symptom severity in middle-aged to older adult women. This study additionally examined whether potential effects differed between Black and White women, as well as other potential moderators such as perceived racial discrimination that may account for any possible differences. By using principal components analysis (PCA), this study combined traditional measures of vascular health (e.g., self-reported vascular conditions) with modern tools like PWV to create a comprehensive vascular composite metric that may better capture cardiovascular risk. This study also included an overrepresentation of Black women, highlighting a potentially vulnerable group who are not typically the focus in vascular depression research. Lastly, to test the vascular depression hypothesis's implication that vascular depression is associated worse frontally-mediated cognitive functioning than non-vascular depression, this study investigated whether vascular subthreshold depression was associated with worse executive functioning.

1.7 Specific Aims and Hypotheses

1.7.1 Aim 1: To examine the association of multimodal vascular markers with depressive symptoms in a diverse sample of middle-aged to older women.

Middle-aged to older adult women may represent a group vulnerable to vascular depression due to heightened incidence of depression during perimenopause (Freeman et al., 2006; Hildreth et al., 2018; Korthauer et al., 2022) along with hormonal changes that increase the risk for vascular disease (El Khoudary et al., 2020; Muka et al., 2016; Zhu et al., 2019). This aim not only examined the relationships between vascular health and depressive symptoms in at-risk women, but it did so in a more comprehensive manner than previous vascular depression studies by including multiple self-report and peripheral measures of vascular health. It was expected that vascular burden, quantified as a composite of this study's multimodal assessment, would be positively associated with depressive symptoms.

1.7.2 Aim 2: To examine potential moderators of the relationship between vascular burden and depressive symptoms, including (a) race and (b) total menopausal symptoms.

Several factors could moderate the relationships between depression and vascular disease. For example, previous works demonstrate that vascular burden is more strongly associated with depressive symptoms in Black compared to NHW older adults (Bogoian & Dotson, 2022), and that the combination of higher WMH burden and depression synergistically impacts dementia risk in Black, but not NHW, older adults (Levy et al., 2024). In addition, total menopause symptoms may be tied to vascular and mood-related

outcomes through the menopausal transition (El Khoudary et al., 2020; M. E. Levine et al., 2016). It was hypothesized that the association between depressive symptoms and vascular burden would be greater in Black compared to NHW women (aim 2a) and as a function of experiencing more menopausal symptoms (aim 2b). Exploratory analyses examined other potential moderators, including physical activity, perceived discrimination and stress, and sleep quality that differ across race and have known links to vascular health and depressive symptoms (Jellinger, 2021; Noetel et al., 2024). We hypothesized that greater aerobic activity engagement, higher stress and discrimination, and poor sleep would be associated with a stronger vascular burden–depressive symptoms link.

1.7.3 Aim 3: To determine whether vascular subthreshold depression in middle-aged to older adult women is associated with cognitive deficits.

Previous studies underscore the impact of vascular depression on cognitive functioning, particularly in executive functioning (Aizenstein et al., 2016; Beltran-Najera et al., 2023; Taylor et al., 2013). Studies from our lab document similar relationships in samples with higher vascular burden and subthreshold levels of depressive symptoms (Bogoian et al., 2024). The current study compared performance on tests of executive functioning in women with vascular subthreshold depression to healthy, vascular only, and depression only subgroups. It was predicted that the vascular subthreshold depression group would demonstrate worse executive functioning performance.

2 METHODS

A secondary data analysis was performed using data from the E2: Sex Hormones and Alzheimer's Disease Prevention study (R01, Whitney Wharton, PI), an ongoing project at the Emory University School of Nursing.

2.1 Participants

Participants were 45 to 85 years old and were recruited from previous cohorts from the E2 PI's lab as well as from the Emory Goizueta Alzheimer's Disease Research Center, ResearchMatch.org, the Emory Alzheimer's Disease Research Center Minority Engagement Core, and metro Atlanta communities. Participants were eligible if they demonstrated capacity to consent, scored at least a 15 on telephone Mini-Mental Status Exam, did not have contraindications for lumbar puncture or MRI, were not pregnant or planning to become pregnant, had no history of substance use disorders, were free from significant neurological impairment, and did not have any psychiatric disorder or unstable medical condition. All participants provided written consent to participate in the study consistent with the guidelines of Emory University's Institutional Review Board. As of July 24th, 2024, data from 152 participants were collected, 99 of whom were assigned female at birth.

After removing entries with missing data points, data from 69 participants were available. A sensitivity power analysis in G*Power software (Faul et al., 2009) suggested that a sample size of 55 would provide 80% power to detect medium-sized effects ($f^2 = .16$ with α set to .05 and two predictors). Participants were 62.6 years old with 16.3 years of education on average, and the sample had an over-representative 46.4% Black participants. Detailed sample characteristics are summarized in Table 2.1.

Table 2.1: Sample Characteristics

	Total Sample	Black Only	NHW Only
N	69	32	37
Age (years)	62.6 ± 8.6	61.4 ± 8.1	63.7 ± 8.9
Education (years)	16.3 ± 2.4	16.0 ± 2.4	16.6 ± 2.4
Annual Income [N, (% of sample)]	--	--	--
<\$19,000	7 (10.1%)	3 (9.4%)	4 (10.8%)
\$20,000–\$39,000	15 (21.7%)	12 (37.5%)	3 (8.1%)
\$40,000–\$59,000	11 (15.9%)	4 (12.5%)	7 (18.9%)
\$60,000–\$79,000	6 (8.7%)	4 (12.5%)	2 (5.4%)
>\$80,000	30 (43.5%)	9 (28.1%)	21 (56.8%)
Vascular Burden Composite	0.0 ± 1.0	-0.1 ± 0.8	0.1 ± 1.2
Pulse Wave Velocity (m/s)	5.8 ± 2.2	5.5 ± 1.8	6.1 ± 2.5
Vascular Risk Sum Score	1.4 ± 1.0	1.1 ± 1.1	1.6 ± 1.0
BMI (kg/m ²)	27.1 ± 4.7	28.0 ± 4.3	26.4 ± 4.8
Systolic Blood Pressure (mm Hg)	126.6 ± 16.6	125.2 ± 13.6	127.8 ± 18.9
Depressive Symptoms (CES-D Score)	10.3 ± 9.1	12.0 ± 10.0	8.8 ± 8.1
Somatic Symptoms	4.0 ± 3.6	4.5 ± 3.9	3.6 ± 3.2
Negative Affect	2.1 ± 2.5	2.4 ± 2.8	1.8 ± 2.3
Anhedonia	2.4 ± 2.7	2.6 ± 2.9	2.2 ± 2.6
Total Menopause Symptoms	3.4 ± 2.0	3.5 ± 2.3	3.3 ± 1.8
Executive Functioning Composite	0.0 ± 1.0	-0.2 ± 0.9	0.2 ± 1.0
Digit Span Backwards Score	4.8 ± 1.5	4.4 ± 1.6	5.2 ± 1.4
Trails B Time	85.7 ± 47.3	100.1 ± 62.0	73.2 ± 23.9
FAS Score	43.9 ± 11.9	44.4 ± 8.5	43.5 ± 13.4
Perceived Stress Scale	11.9 ± 6.9	13.3 ± 6.9	10.8 ± 6.8
Perceived Discrimination Sum Score	15.7 ± 13.9	20.3 ± 16.5	11.7 ± 9.8
High Sleep Quality (% yes)	63.8	62.5	64.9
Aerobic Activity in Last 4 Months (% yes)	79.7	81.3	78.4
Weekly Exercise (% yes)	66.7	81.3	62.2

NHW = Non-Hispanic White; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale

2.2 Measures

2.2.1 Vascular Burden Measures

The E2 study includes a rich characterization of vascular health that allowed the current study to test the vascular depression hypothesis using more comprehensive assessments of vascular burden than has been used in previous research. To take advantage of the comprehensive vascular assessments available, PCA was used to create a vascular burden composite that incorporated each of the self-report and peripheral measures of vascular health listed in Table 2.2. This newly derived “vascular burden” composite variable served as the predictor in aims 1 and 2.

Self-reported history of or treatment for vascular conditions and risk factors (hypertension, hyperlipidemia, diabetes, heart attack, bypass surgery, stroke, history of smoking) were summed to create a vascular risk sum score, with one point for each condition. Total scores ranged from 0 to 7. This sum score along with the peripheral markers listed in Table 2.2 comprise the vascular burden composite.

Peripheral markers were acquired during participants’ physical examination at their baseline study visit, which included height and weight, which were used to calculate body mass index (kg/m^2), as well as measures of their blood pressure. Assessment also included PWV measures to quantitatively assess arterial stiffness and, indirectly, cardiovascular risk (Pereira et al., 2015).

Table 2.2: *Vascular markers comprising the vascular burden composite*

Self-report Vascular Risk Sum Score
Sum of vascular conditions and risk factors: hypertension, hyperlipidemia, diabetes, heart attack, bypass surgery, stroke, history of smoking

Measured Peripheral Markers

Body mass index

Heart rate

Systolic blood pressure

Pulse wave velocity value

2.2.2 Depressive Symptom Measures

Symptoms of depression were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), which measures the frequency and severity of depressive symptoms experienced in the previous week (Radloff, 1977). Scores range between 0 to 60, with higher scores representing more severe depressive symptoms. The total score on the CES-D served as the dependent variable for aims 1 and 2. Based on previous work showing the importance of symptom dimensions of depression in predicting vascular disease and WMH (Carleton et al., 2013; Kirton et al., 2014), exploratory analyses also examined scores on the three CES-D subscales identified by previous factor analysis (Carleton et al., 2013): negative affect, anhedonia, and somatic symptoms.

2.2.3 Cognitive Measures

Participants received a comprehensive battery of cognitive tests during the E2 study. Based on literature highlighting deficits in “frontal” functions in vascular depression including executive function (Aizenstein et al., 2016; Jellinger, 2021; Taylor et al., 2013), analyses for aim 3 specifically focused on performance on tests that assess this domain. To minimize Type I error, a composite score representing executive functioning based on PCA was used as the dependent variable for aim 3.

Digit Span Backward provided a measure of working memory (Wechsler, 1991), which is often described to be a function of executive function (McCabe et al., 2010). This

test requires the participant to briefly remember increasingly longer series of numbers and repeat the sequence in either forward or reverse order, depending on the task. The total scores on the backward subtest served as the outcome measure.

Controlled Oral Word Association Test (COWAT/FAS) is a measure of letter verbal fluency that requires respondents to retrieve words that correspond to a particular letter, a frontally-mediated skill (Spreen & Benton, 1977). During this task, the participant is asked to orally produce as many words as they can think of within 60 seconds that begin with the letter F, A, or S. Total scores for FAS (all letters combined) were used in the analyses.

Trail Making Test (TMT) Part B is a test of cognitive switching (Reitan, 1992) that requires visual scanning, speeded motor dexterity, and dual processing. Participants are asked to not only quickly draw a line connecting an array of labeled circles, but to also switch between connecting numbers and letters in sequential order. Completion time of Trails B in seconds—corrected for directionality (since longer completion times represented worse performance in this case)—were used in the analyses.

2.2.4 Menopausal Symptoms

We initially proposed to use menopausal status as a moderator in aim 2; however, coding of menopausal status was discontinued in the E2 study. Instead, participant's self-report of menopausal symptoms was collected. Considering that menopausal status would have been based on experiences with menopausal symptoms and the reciprocal influence of menopausal symptoms on symptoms of depression (Strauss, 2011), total menopausal symptoms was an appropriate alternative to use for the current study. Symptoms of menopause (yes/no variable) were summed to create a total menopause symptoms

variable, with one point for each condition. Total scores ranged from 0 to 7. Table 2.3 summarizes the symptoms.

Table 2.3: *Menopausal symptoms comprising total menopause symptoms*

Mood swings
Hot flashes
Sleep disturbances
Vaginal dryness
Pain during sex
Memory problems
Night sweats

2.2.5 Exploratory Moderators

For aim 2, exploratory analyses examined potential moderators of the vascular burden-depressive symptom relationship in addition to the primary analyses focusing on ethnoracial group and menopause. Specifically, moderators included the following:

1. aerobic activity engagement, based on response to the question, “Have you engaged in cardiovascular exercise during the past 4 months?” (response options: yes, no)
2. sleep quality, evaluated using participants’ response to the question, “Over the past month, how would you rate your sleep quality overall?” on the Pittsburgh Sleep Quality Index (response options: excellent, very good, good, fair, poor) (Buysse et al., 1989)
3. perceived discrimination, as measured using the Major Experiences of Discrimination Scale (Williams et al., 1997) that asks participants to rate how many times in their life they had been discriminated against in eleven specific

- ways (e.g., denied a promotion, hassled by the police, etc.) on a scale of 0 to 9, with higher scores representing more experiences with lifetime discrimination (response options: N/A, 0, 1, 2-3, 4-6, 7-10, 11-20, 20-40, 41-100, over 100)
4. perceived stress, as measured by the Perceived Stress Scale (Cohen et al., 1994) that asks participants to rate how often in the last month they felt or thought about ten specific questions (e.g., “How often have you felt nervous and stressed?” “How often have you been able to control irritations in your life?”) on a scale of 0 to 4, with higher scores suggesting greater stress (response options: never, almost never, sometimes, fairly often, very often)

2.3 Data Analyses

Analyses were performed using IBM SPSS software, Version 29.0. Alpha level was set to .05 for all analyses.

2.3.1 Determining Model Covariates:

A data-driven approach (Vander Weele & Shpitser, 2011) was used to determine covariates in which any socioeconomic variable (i.e., age, race, education level, income level) that significantly and independently related to the independent and dependent variable was included as a covariate. These associations were determined by a series of analyses of variance, chi-square analyses, and correlations depending on the nature of the independent and dependent variables.

Among potential covariates of age, education level, income range, and race, only older age was significantly related to both vascular burden ($p = .007$) and depressive symptoms ($p = .030$); therefore, age was included as a covariate for all analyses in aims 1 and 2. While older age was also significantly related to the vascular depression subgroups

($p = .011$), it was *not* significantly related to the executive functioning composite ($p = .100$); thus, age was not included as a covariate in the model for aim 3. Higher education level was significantly related both to better executive functioning ($p = .041$) and the vascular depression subgroups ($p = .036$), and as a result, education was included as a covariate for the aim 3 analyses.

2.3.2 Aim 1: To examine the associations of multimodal vascular markers with depressive symptoms

To test the hypothesis that a multimodal measure of vascular burden is positively associated with depressive symptoms (aim 1), PCA was first performed using the Dimension Reduction procedure in SPSS to create a composite variable that represents the robust vascular data available within the E2 study. PCA is a technique used to reduce the dimensionality of data (Wold et al., 1987), producing standardized linear composite scores that represent the overall entries from which the composite was derived. This procedure requires that the initial variables be standardized to ensure that each contributes equally to the analyses, and thus all scores were transformed into z-scores and corrected for directionality (e.g., lower scores always equal worse outcome). The PCA used varimax rotation and applied Kaiser's criterion (eigenvalue > 1) to create the composite (DiStefano et al., 2009). This new composite variable representing "vascular burden" was derived using the variables included in Table 2.2.

Multiple regression analyses were then performed with the vascular burden composite predicting total CES-D scores for the primary analysis and predicting CES-D subscale scores for the exploratory analyses, controlling for age.

2.3.3 Aim 2: To examine potential moderators of the vascular burden-depressive symptoms relationship, including (a) race and (b) total menopause symptoms.

To determine whether the relationship between vascular burden and depressive symptoms differed by race or total menopausal symptoms, variables representing the potential moderators and their interaction with vascular burden were added as independent variables to the regression model performed for aim 1. Separate analyses were performed for each potential moderator, and the models included both the main effect as well as an interaction term between the potential moderator and vascular burden.

Exploratory analyses for aim 2 examined other potential moderators, namely aerobic activity engagement, sleep quality, perceived discrimination, and perceived stress. Analyses mirrored those performed for the primary variables of interest.

2.3.4 Aim 3: To determine whether vascular subthreshold depression in middle-aged to older women is associated with cognitive deficits.

We categorized participants into one of four subgroups based on a median split of the vascular burden composite and a cutoff based on the upper tertile of CES-D scores as follows: 1) lower depressive symptoms/lower vascular burden (“healthy”); 2) lower depressive symptoms/higher vascular burden (“vascular only”); 3) higher depressive symptoms/lower vascular burden (“depressive symptoms only”); and 4) higher depressive symptoms/higher vascular burden (“vascular subthreshold depression”). The upper tertile cutoff on the CES-D was chosen to better capture the higher end of the CES-D score range in this non-clinical community sample. Analyses of covariance determined whether groups significantly differed in executive functioning performance, controlling for education.

3 RESULTS

Results are summarized in Tables 3.1–3.5 and Figures 4–6.

3.1 PCA Results

3.1.1 Vascular Burden Composite

For the vascular burden composite, the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was .66, indicating that the data were appropriate for factor analysis. Bartlett's test of sphericity was also significant ($\chi^2 = 39.52, p < .001$), suggesting suitable correlations among the variables for PCA.

The initial eigenvalues indicated that the first component explained 35.7% of the variance, while the second component explained an additional 27.2% of the variance. Given that our goal was to create a single composite, each variable's factor loadings were assessed to determine whether to retain it in the final analyses. Upon examination, heart rate weakly and negatively loaded onto the first component (-.023), suggesting that it did not strongly associate with our intended latent construct of vascular burden in this sample; therefore, heart rate was removed and a new PCA was conducted.

Upon second attempt, all variables loaded positively onto a single component as intended, with this new composite accounting for 50.1% of the total variance. Factor loadings were comparably robust across all four indicators: systolic blood pressure (.794), body mass index (.698), vascular risk sum score (.652), and pulse wave velocity value (.680). Therefore, this new component comprised of these four vascular indicators was used in all analyses.

3.1.2 Executive Functioning Composite

For the executive functioning composite, the KMO measure of sampling adequacy was .57, indicating that the data were fair for factor analysis. Bartlett's test of sphericity was also significant ($\chi^2 = 13.19, p = .004$), suggesting sufficient correlations among the variables for PCA.

Analyses revealed a single component as desired, which explained 50.2% of the variance. Factor loadings were adequate across all three variables: FAS total score (.768), Digit Span Backwards (.772), and Trails B time (.568).

3.2 Results for Aim 1

There were no significant main effects of vascular burden on total depressive symptoms ($\beta = .040, p = .751$) or any of the three CES-D subscales including negative affect ($\beta = .124, p = .334$), anhedonia ($\beta = .016, p = .903$), and somatic symptoms ($\beta = .066, p = .593$) (see Table 3.1).

Table 3.1: Aim 1: Results of Regression Analyses of Vascular Burden Predicting CES-D Scores

	CES-D: Total Score			CES-D: Somatic			CES-D: Anhedonia			CES-D: Negative Affect		
	β	<i>SE</i>	<i>p</i>	β	<i>SE</i>	<i>p</i>	β	<i>SE</i>	<i>p</i>	β	<i>SE</i>	<i>p</i>
Age	-.274	.133	.032*	-.339	.051	.008*	-.169	.041	.192	-.221	.037	.086
VB	.040	1.141	.751	.066	.440	.593	.016	.347	.903	.124	.319	.334

Note: VB = Vascular burden composite; CES-D = Center for Epidemiologic Studies Depression Scale

3.3 Results for Aim 2

There were no significant interactions between race and vascular burden on total depressive symptoms ($\beta = .752, p = .208$). There was also no main effect of race on depressive symptoms ($\beta = -.139, p = .246$) (see Table 3.2). Similarly, no significant total menopausal symptom by vascular burden interactions were found on depressive symptoms ($\beta = -.293, p = .154$), nor were there any significant main effects of total menopausal symptoms on total CES-D scores ($\beta = .195, p = .105$) (see Table 3.3).

Table 3.2: Aim 2: Results of Regression Analyses of Race Moderating the Vascular–CES-D Relationship

	df	β	SE	p
Age	4,64	-.270	.133	.035*
VB	4,64	-.686	5.368	.249
Race	4,64	-.139	1.078	.246
VB x Race	4,64	.752	1.192	.208

Note: VB = Vascular burden composite; CES-D = Center for Epidemiologic Studies Depression Scale

Table 3.3: Aim 2: Results of Regression Analyses of Total Menopause Symptoms Moderating the Vascular–CES-D Relationship

	df	β	SE	p
Age	4,64	-.278	.131	.028*
VB	4,64	.312	1.913	.143
MS	4,64	.195	.528	.105
VB x MS	4,64	-.293	.493	.154

Note: VB = Vascular burden composite; MS = Total menopause symptoms; CES-D = Center for Epidemiologic Studies Depression Scale

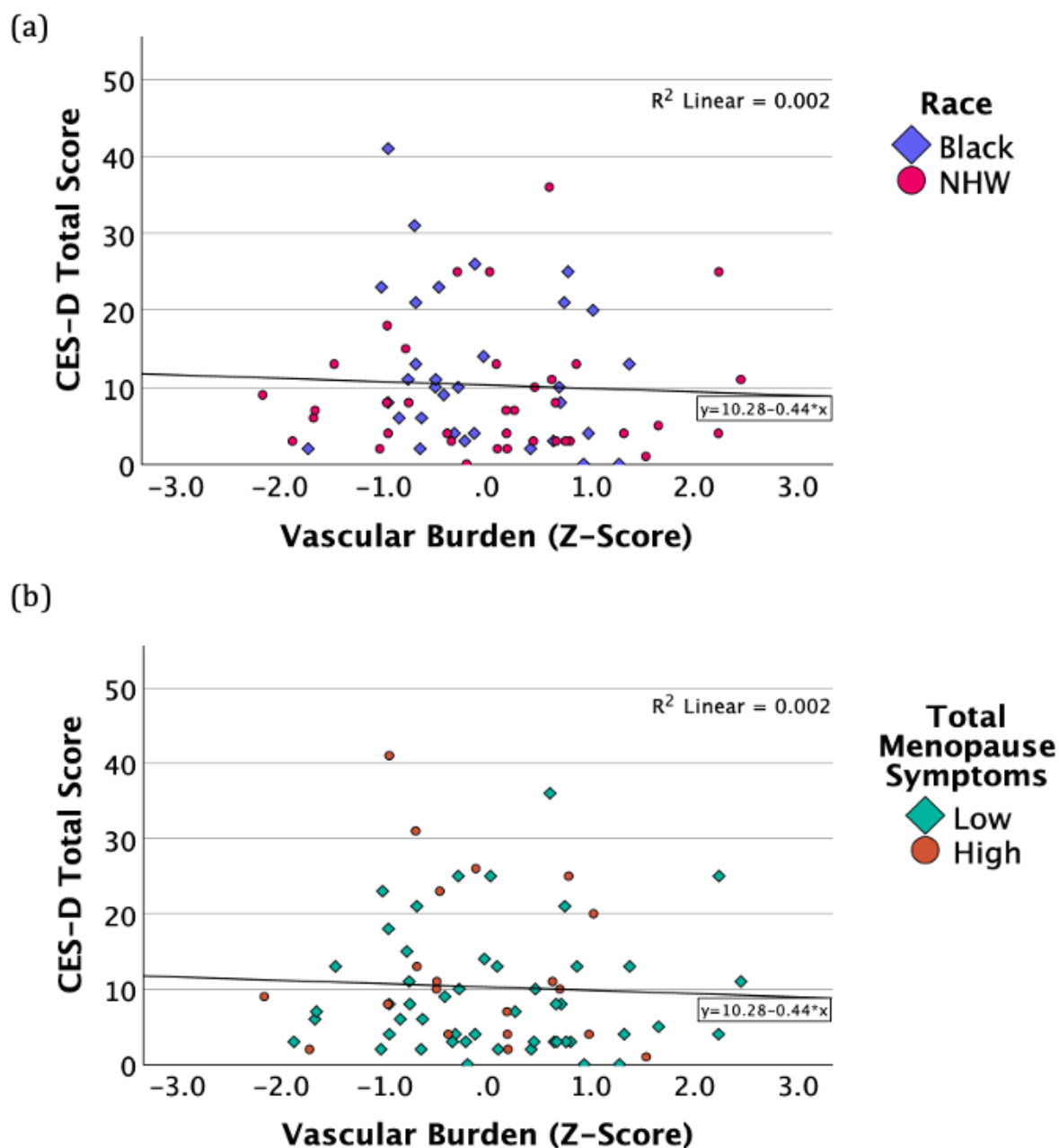


Figure 4: Scatter plots of the Vascular Burden Composite by CES-D Total Scores.

Stratified by race (a) and total menopause symptoms (b) in the total sample. Note that the above relationships are not significant, and the fit lines represent the overall relationship between vascular burden and CES-D score. High menopause symptoms were coded as the upper tertile of endorsed symptoms (5 or more). CES-D = Center for Epidemiologic Studies Depression Scale.

Exploratory analyses revealed there were no significant moderating effects of sleep quality ($\beta = .062, p = .830$), aerobic exercise engagement ($\beta = -.423, p = .150$), perceived discrimination ($\beta = .026, p = .886$), or perceived stress ($\beta = -.138, p = .364$) on the relationship between vascular burden and CES-D scores (see Table 3.4). However, a significant main effect of sleep quality on total depressive symptoms ($\beta = .445, p < .001$) indicated that better sleep quality was associated with lower CES-D scores. Significant main effects of perceived stress ($\beta = .797, p < .001$) and perceived discrimination ($\beta = .300, p = .013$) on total depressive symptoms were also observed, such that higher stress and discrimination predicted greater depressive symptoms. There was no significant main effect of aerobic exercise engagement on depressive symptoms ($\beta = .105, p = .379$).

Table 3.4: Aim 2: Results of Regression Analyses of Exploratory Predictors Moderating the Vascular–CES-D Relationship

	df	β	SE	p
<i>Sleep Quality</i>				
Age	4,64	-.248	.121	.033*
VB	4,64	-.086	2.666	.773
SQ	4,64	.445	.993	<.001*
VB x SQ	4,64	.062	.822	.830
<i>Exercise</i>				
Age	4,64	-.328	.137	.013*
VB	4,64	.435	2.744	.154
AA	4,64	.105	2.664	.379
VB x AA	4,64	-.423	2.917	.150
<i>Discrimination</i>				
Age	4,64	-.209	.132	.096
VB	4,64	.002	1.671	.990
PD	4,64	.300	.077	.013*
VB x PD	4,64	.026	.080	.886
<i>Stress</i>				
Age	4,64	-.012	.091	.893
VB	4,64	-.013	1.389	.931
PS	4,64	.797	.108	<.001*
VB x PS	4,64	-.138	.098	.364

Note: VB = Vascular burden composite; SQ = Sleep quality; AA = Any aerobic activity in the last 4 months; PD = Perceived discrimination; PS = Perceived stress; CES-D = Center for Epidemiologic Studies Depression Scale

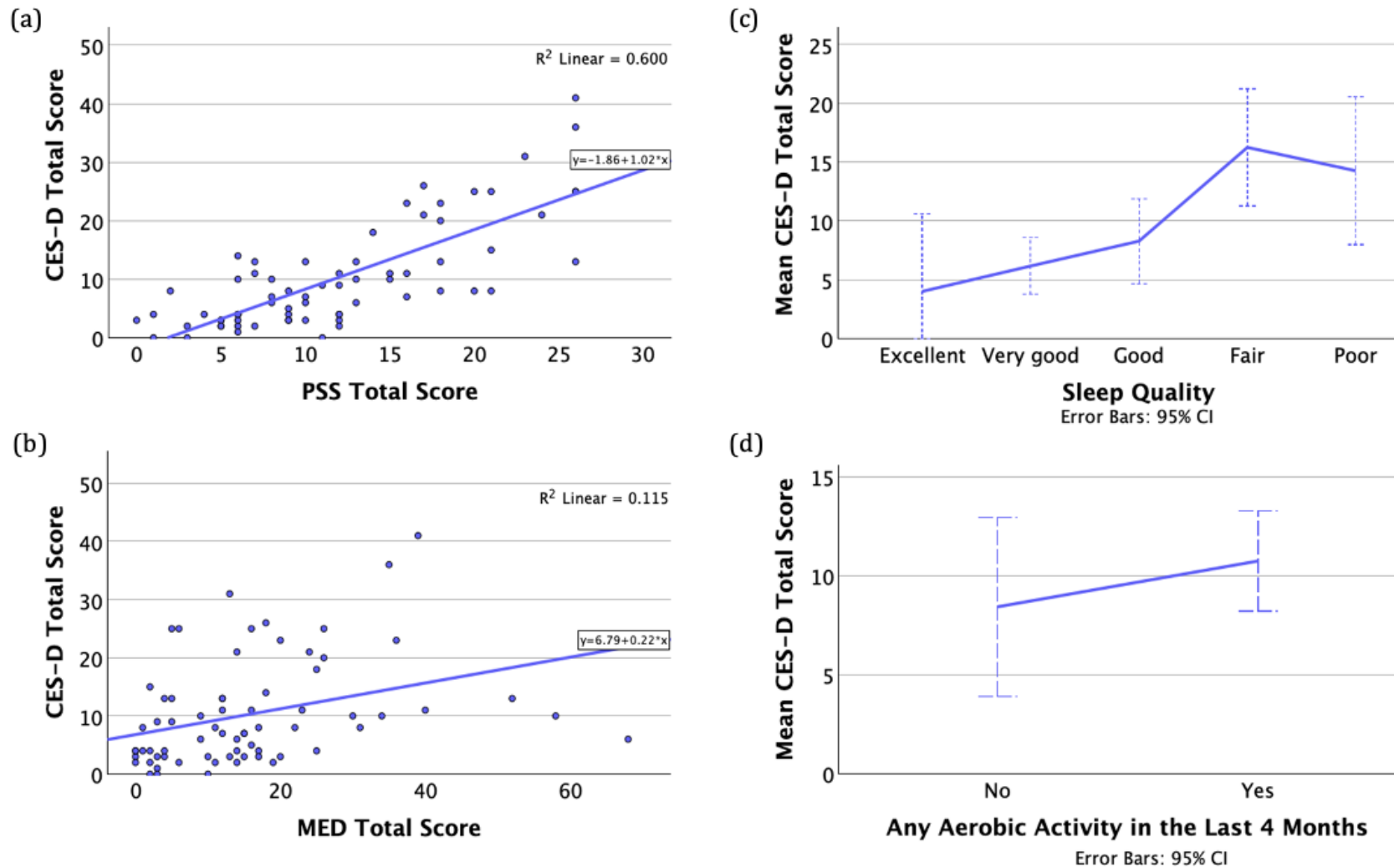


Figure 5: Results of main effects for exploratory moderators, including (a) perceived stress, (b) perceived discrimination, (c) sleep quality, and (d) aerobic activity.

Note that the main effects of perceived stress, perceived discrimination, and sleep quality on depressive symptoms were significant, but the effect of any aerobic activity engagement was not. CES-D = Center for Epidemiological Studies Depression Scale; PSS = Perceived Stress Scale; MED = Major Experiences of Discrimination.

3.4 Results for Aim 3

The vascular subthreshold depression subgroups were not significantly associated with the executive functioning composite ($F(3,65) = .378, p = .769$) (see Table 3.5).

Table 3.5: Aim 3: Results of ANCOVA of Vascular Burden by Depressive Symptom Subgroup Predicting Executive Function ($R^2 = .077$; Adjusted $R^2 = .020$)

	df	Mean square	F	p
Education	1	4.548	4.639	.035*
Vasc/Dep Subgroup	3	0.371	0.378	.769

Note: Vasc/Dep Subgroup = Vascular burden by depressive symptoms subgroup: "Healthy" N = 22, "Vascular Only" N = 22, "Depressed Only" N = 13, "Vascular Subthreshold Depression" N = 12

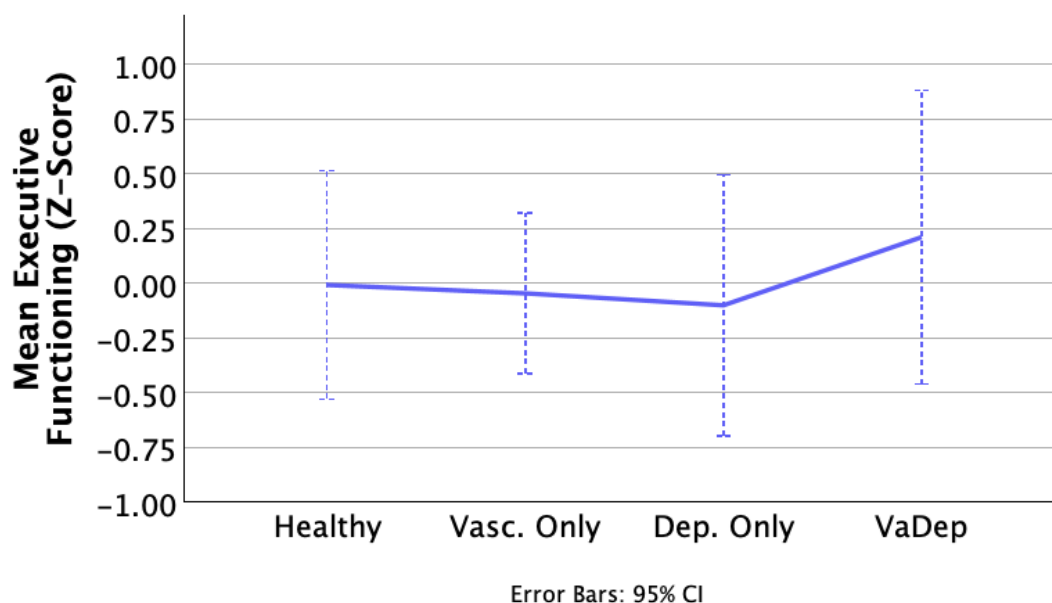


Figure 6: Executive functioning composite in each of the vascular burden by depressive symptoms group.

Note that there are no significant group differences. Healthy = low vascular burden and depressive symptoms; Vasc. Only = high vascular burden only; Dep. Only = high depressive symptoms only; VaDep = vascular subthreshold depression.

4 DISCUSSION

The present study investigated whether vascular burden is related to depressive symptoms in a cohort of ethnoracially diverse middle-aged to older women, and whether ethnoracial group or total menopausal symptoms moderated these relationships. We also investigated whether operationally defined vascular subthreshold depression was differentially associated with executive functioning.

4.1 Associations of Vascular Burden with Depressive Symptoms

Contrary to our first hypothesis, there were no main effects of vascular burden on total depressive symptoms or any of its subscales including negative affect, anhedonia, and somatic symptoms. Upon first glance, these findings appear inconsistent with the bulk of previous works highlighting established connections between vascular health and mood symptoms, particularly through midlife and beyond (Barch et al., 2012; Jellinger, 2023; Krishnan & McDonald, 1995; Taylor et al., 2013). For instance, in a large population-based longitudinal study that similarly examined middle-aged to older participants who were depression- and dementia-free at initial visit (Adams et al., 2017), researchers found that the odds of new onset depression decreased by 10% for every one-point increase in total vascular risk factor burden. Relatedly, another study found that the negative effects of high vascular burden on depressive symptoms were as deleterious in adults younger than 60 as they were in older adults (Lugtenburg et al., 2017). A different longitudinal study in a largely British sample (Blöchl et al., 2022) showed that high vascular risk factor burden during midlife more strongly contributed to elevated depressive symptoms at 10-year follow up than late-life vascular burden. Thus, a large body of evidence suggests that we

should see a relationship between vascular burden and depressive symptoms in our current study.

Importantly, however, the participants in our study had good vascular health relative to other similarly aged community samples. For example, the average PWV value across our total sample was 5.8m/s, with a range of 2.1 to 11.0m/s (lower scores indicate better vascular health). The accepted mean normal PWV value for our sample's age category of 60 to 65 years old is 6.8m/s with a recommended cutoff of 10.0m/s to signal abnormally elevated arterial stiffness (van Hout et al., 2021), speaking to our sample's good vascular health. Adding additional evidence to our sample's relatively good vascular health is the restricted range of the total vascular risk sum score variable, which comprised common vascular indicators such as hypertension, hyperlipidemia, diabetes, and smoking behaviors, yet no participant in our study endorsed more than three vascular conditions. Lastly, our sample demonstrated an average systolic blood pressure of 126.6mm Hg, which is over 10 mm Hg lower than the mean average blood pressure of 139mm Hg observed in women based on data collected by the American Heart Association (Salomon, 2024). In fact, our sample better matches the systolic blood pressure ranges for 40–59-year-olds. In short, it follows that within a sample with such low vascular burden, "higher" vascular burden is still fairly low and therefore might not be associated with depressive symptoms.

Another potential explanation for the lack of association between vascular burden and depressive symptoms in the current study is the sample's relatively young age. The majority of evidence for the vascular depression hypothesis stems from studies within exclusively older adult groups (Aizenstein et al., 2016; Alexopoulos et al., 1997; Bogoian & Dotson, 2022; Jellinger, 2021; Sheline et al., 2010), which suggests that the adverse effects

of cumulative vascular burden may have not yet risen to the threshold needed to significantly impact mood in samples that include middle-aged adults in addition to older adults. However, though vascular depression is typically described as a subtype of late-life depression due to this established literature in older adulthood, our recent work (Beltran-Najera et al., 2023; Levy et al., 2024; Mustafa et al., 2023) showed associations between vascular burden and depressive symptoms as early as midlife in groups that are characterized by accelerated vascular aging (specifically, people living with HIV and Black middle-aged to older adults). Thus, the age of the sample would not fully explain our results. Potentially more relevant are the markers of vascular burden in the current study. Based on our previous work indicating that WMHs in the uncinate fasciculus were associated with higher depressive symptoms when traditional clinical indices were not (Bogoian et al., 2024), it is possible that using WMH load in this brain region in the current study would have yielded different results. However, WMH data was not available for this study, which is a limitation.

It is also possible that the current study did not find an association between vascular burden and depressive symptoms due to its inclusion of only women, though it is unclear why this would contribute to these findings. To our knowledge, previous literature supporting relationships between vascular burden and depressive symptoms has included both men and women (Aizenstein et al., 2016; Jellinger, 2021; Salo et al., 2019), and no study has examined the impact of menopause on these relationships. Thus, it is possible that gender may influence the vascular–depressive symptom relationship. However, it is unclear how gender alone would explain our lack of vascular–depressive symptoms association considering that the broader research literature supports adverse vascular and

mood-related risks for women compared to men (El Khoudary et al., 2019, 2020; Lohner et al., 2022), which might suggest that vascular burden would contribute to depressive symptoms more in women than in same-aged men. Additional studies in larger samples are needed to determine whether the current findings are an anomaly, and studies that include men will be useful to examine potential sex differences.

4.2 Moderating Effects of Menopausal Symptoms and Race

Contrary to expectation, neither race nor total menopause symptoms significantly moderated the relationship between vascular burden and depressive symptoms, which was unexpected given the literature supporting race differences in vascular burden as well as connections between vascular mechanisms and experience with menopausal symptoms. For instance, previous work consistently shows that Black adults evidence higher vascular burden compared to other racial groups (Bogoian & Dotson, 2022; Levy et al., 2024; Thurston & Joffe, 2011), suggesting that Black women may have been particularly vulnerable to worsening mood compared to NHW women. However, in our subsample, the Black women were actually healthier than NHW women on most of the vascular metrics assessed, which is unusual compared to the bulk of previous studies and thus may not be representative of the total population. Relatedly, cardinal symptoms of menopause such as vasomotor symptoms have been associated with increased vascular dysfunction, and these symptoms negatively impact mood (Strauss, 2011). However, in our sample, experiences of menopause were fairly even between the racial subgroups and were not related tied to participants' vascular health.

Main effects of race and total menopausal symptoms on depressive symptoms were also not found, which was similarly unexpected given previous studies showing race

differences in depressive symptoms and in the experience of menopausal symptoms. For instance, research shows that the menopausal transition marks a time of increased vulnerability for mood disturbances (Alblooshi et al., 2023; El Khoudary et al., 2019; Maki & Thurston, 2020), suggesting a connection between experience of menopausal symptoms and worsening mood. Further, a large longitudinal prospective study (Strauss, 2011) found that women who experienced worse menopausal symptoms were more likely to evidence higher depressive symptoms. Presence of vasomotor symptoms in particular elevates the risk for menopause-associated depression, and the literature consistently suggests increased frequencies and severity of vasomotor symptoms in Black women compared to other ethnic groups (Alblooshi et al., 2023; Thurston & Joffe, 2011).

Given the paucity of vascular depression research in women and in Black adults, it will be important for future studies to further examine how the relationship between vascular burden and depressive symptoms could differ throughout the menopausal transition or be moderated by race or social determinants related to race.

4.3 Impacts of Exercise, Sleep Quality, Perceived Stress and Discrimination on Mood

Lower sleep quality as well as higher perceived stress and discrimination were each significantly and independently associated with greater depressive symptoms. However, aerobic activity engagement did not attenuate depressive symptoms in our sample, and there were no interactive effects between vascular burden and any of the exploratory moderators (i.e., physical activity, perceived discrimination, perceived stress, sleep quality) on mood symptoms, contradicting our aim 2 exploratory hypotheses. Again, considering our sample's comparably good vascular health relative to the general population, it is not

surprising that we did not find significant connections between “higher” vascular burden with any exploratory moderator of interest on depressive symptoms.

With respect to sleep, we found that poorer sleep quality adversely impacted mood but did not interact with vascular burden to influence depressive symptoms. Sleep quality has known links with various aspects of health. For example, sleep disturbances correspond to a variety of negative health outcomes including worse vascular health and higher depressive symptoms (Sivertsen et al., 2012; Sun et al., 2018). As it relates to our sample, sleep problems are common in women during the menopausal transition, with up to half of midlife women reporting sleep problems (Kravitz & Joffe, 2011). Vasomotor symptoms appear particularly disruptive to sleep quality (Maki & Thurston, 2020) as women report frequent nighttime awakenings due to night sweats and intense feelings of heat. These menopausal symptoms are already linked to increased vulnerabilities to mood disturbances on their own, thus vasomotor symptoms and their resulting sleep disturbances both contribute to depressive symptoms. In this way, our study’s observed main effect of sleep quality on mood fits with the broader literature.

The current study found significant positive associations of depressive symptoms with perceived stress and discrimination. This result is in keeping with literature documenting higher risks of depression with increasing levels of reported stress and perceived discriminatory events (Hammen et al., 2009; White et al., 2020). Further, meta-analysis has provided strong evidence that experiencing discrimination predicts poor mental health across the lifespan (Schmitt et al., 2014; Yip et al., 2019). As it relates to menopause, fluctuations in ovarian hormone levels (such as that observed in menopausal women) modulate women’s stress response (Slavich & Sacher, 2019), which in turn raises

her predisposition to depressive symptomatology. Considering that depression is often conceptualized as a stress-related disorder (Hammen, 2005), it stands to reason that stressful experiences would be linked to depression.

Aerobic activity engagement was not associated with depressive symptoms in the current sample, and it did not moderate the relationship between vascular burden and depressive symptoms. While increased physical activity has well established effects of reducing depressive symptoms as demonstrated by metaanalysis (Noetel et al., 2024), this positive outcome may in part be mediated through the modification of cardiovascular health (Dotson et al., 2021; Tsao et al., 2023). However, our sample is already very vascularly healthy, which might diminish the benefits physical activity may have had within this cross-sectional study. Of note, this does not suggest that physical activity had *no* advantage in this group. To the contrary, it is possible that the very fact that nearly 80% of the total sample exercised within the last four months of study enrollment and over two-thirds of them endorsed engaging in weekly exercise suggests they remain healthier than analogous community samples, potentially due to their level of physical activity. Supporting this contention, in a large and diverse sample of equally representative Black and NHW adults, Full and colleagues (2021) found that within a seven-day period, replacing only 24 minutes of sedentary time with moderate to vigorous physical activity was related to a striking 15% reduced odds of cardiovascular risk at 10-year follow up. Thus, it is possible that the current sample's better than average vascular health is due to the women having higher levels of aerobic exercise engagement than is typical, which could limit the ability to detect effects usually reported in the literature.

4.4 Vascular Subthreshold Depression and Executive Functioning

Performance on measures of executive functioning did not significantly differ across vascular burden by subthreshold depression subgroups. Although conflicting with our aim 3 hypothesis, this finding adheres to the same pattern observed across rest of our data. Given the minimal impact of vascular burden in our sample, the predictive power of operational definitions of “high” and “low” vascular risk are diminished. Put another way, there is likely to be very little difference between, say, our “healthy” and our “vascular only” subgroups since even those characterized as having “high” vascular burden are still functionally very healthy.

The vascular depression hypothesis suggests that cumulative vascular disturbances drive the declines in cognition and mood within impacted adults (Aizenstein et al., 2016; Alexopoulos et al., 1997; Jellinger, 2021; Taylor et al., 2013). It should be noted that although depressive symptoms themselves have also been linked to cognitive dysfunction independent of vascular burden (Dotson et al., 2021), it has been suggested that vascular factors may play a greater role in depression-related cognitive changes in later decades of life. For example, evidence from metaanalysis suggests that the connections between depression and executive functioning are only found in middle-aged or older adults (Dotson et al., 2020). Since the effect was only observed in midlife or beyond, the authors of that meta-analysis theorized that the association is most likely the result of aging-related neurobiological changes (e.g., rising vascular burden) synergistically combining with depression-related structural and functional brain changes (e.g., alterations to frontolimbic regions) to create a “double jeopardy” of cognitive vulnerability. Thus, based on the

vascular depression hypothesis, we may not expect to find significant differences in executive functioning performance in a vascularly healthy sample.

Lastly, it is important to note that our sample was very well educated, with mean sample characteristics indicating that most have earned their bachelor's degree. Education is often used as a proxy for measuring cognitive reserve, which loosely describes the brain's resistance to functional changes from brain pathology or damage (Yoon et al., 2012). Higher educational attainment has a protective effect on cognitive outcomes (Soldan et al., 2020), which may have additionally contributed to our finding of no group differences in cognitive performance.

4.5 Limitations and Future Directions

There were several limitations to this study. First is the characterization of menopause. In this study, we examined total menopausal symptoms as a moderator of the relationship between vascular burden and depressive symptoms. While menopausal symptoms provide a window into a woman's experience with menopause, it is a narrow indicator that inadequately captures what period in her life course she is currently in, potentially missing important temporal context. Using an indicator such as menopausal status would be more ideal as it follows the Stages of Reproductive Aging Workshop (STRAW) guidelines for categorizing current reproductive age (Soules et al., 2001) and, consequently, may better connect to the menopause-related vascular and cognitive health changes of interest. However, menopausal status was not available for this study. A sample with a broader age range of participants across middle to late adulthood could better capture the present impact of menopause on the vascular health–depression relationships.

Another way to assess the impacts of menopause that we could not investigate in this study was participant age at the onset of menopause. Menopausal onset prior to age 45 is associated with increased vascular events and higher disease burden such as vascular maladies, depression, and neurodegeneration compared to average onset at age 51 (El Khoudary et al., 2020; Muka et al., 2016; Namazi et al., 2019; Sochocka et al., 2023; Zhu et al., 2019). The literature also suggests that Black women may be at particular risk for early menopause onset (El Khoudary et al., 2020). Future studies should explore the impacts of menopause age within diverse samples to better understand its influence on vascular health and depressive symptoms in this group.

As mentioned previously, the sample size is relatively small, which reduces the study's statistical power to reliably detect effects and increases the probability for errors. Small sample sizes can be problematic for PCA, as they can lead to skewed component loadings and produce linear composite scores that may not generalize well to other samples, resulting in findings that are inconsistent with the broader literature. Small samples are also less likely to represent the general population well, which appears to be the case in our study considering our participants' relative vascular health compared to larger community samples of similar age. Future studies should study these relationships in larger cohorts of women to better evaluate the links between vascular burden, menopause, and mood in this group. In addition, this study is cross-sectional, which does not allow us to make causal inferences regarding the effects of menopause or other variables of interest on the relationship between vascular burden and depressive symptoms. A longitudinal study that measures changes in vascular health and menopause-related correlates over time would provide more information on its potential impacts on

mood and cognition. Further, including a comparison group of similarly aged men may boost support for the influence of menopause on the possible findings considering the clear biologically driven contrast.

Finally, while this study incorporated both traditional self-report and novel objective measures of vascular health, WMH data was not available for our analyses and thus could not be included in our robust assessment of vascular burden. Given that WMHs are a more direct measure of vascular brain changes (Aizenstein et al., 2016), it is possible that adding this imaging data would have improved our vascular burden composite to be more sensitive to alterations on various health outcomes. Furthermore, recently published work in our lab (Bogoian et al., 2024) found that greater total WMH volume was positively associated with depressive symptoms in a Black older adult sample, but *not* clinically defined vascular burden (i.e., sum of vascular risk factors), further suggesting that WMHs may have been a stronger predictor to integrate into our composite that would have strengthened our vascular assessment.

4.6 Conclusion

Overall, this study found no significant relationships between vascular burden and depressive symptoms in this healthy sample of middle-aged to older adult women, and did not find any significant moderators to the vascular–depressive symptoms relationships. In the absence of high vascular burden or multiple vascular risk factors, indicators such as poor sleep quality or high perceived stress and discrimination may be predictive of depressive symptoms in women during late middle adulthood. Further studies are needed to fully examine the relationships between menopause, vascular burden, and depressive symptoms in middle-aged to older women in larger, similarly diverse samples.

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