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Identifying and Characterizing Cognitive Profiles in Midlife Females: A Latent Profile Analysis

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IDENTIFYING AND CHARACTERIZING COGNITIVE PROFILES IN MIDLIFE FEMALES: A LATENT PROFILE ANALYSIS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Females are at two-thirds greater risk of developing Alzheimer's disease (AD) than males. Due to this notable sex difference in cognitive aging and disease burden, there has been an increased focus on understanding the critical role of the menopausal transition (decline in fertility during midlife) as it relates to cognitive functioning across midlife. Thus, the present cross-sectional study used a sample of midlife females at different stages in the menopausal transition (*N*=202; Age 40-60 years) as part of a larger, multimodal design study, to elucidate distinct cognitive profiles while accounting for education, which were then characterized by other demographic factors, cardiovascular and metabolic health indicators, and medication use. Using latent profile analyses, four distinct cognitive profiles were identified which differed only based on race. Depressive symptoms significantly differed between the profiles marked by a strength or weakness in verbal learning and memory, with those in the worse performing profile reporting higher levels of depressive symptoms. In the sub-sample of participants with confirmed staging (*n*=139), menopause stage did not moderate this association. This study confirms prior research findings that suggest negative mood states, particularly sadness and anxiety, are prevalent during the menopausal transition and are related to verbal learning and memory. Further research is necessary to establish causal relations between depressive symptoms, menopause stage, and specific cognitive outcomes to develop effective interventions for improving cognitive functioning during and beyond, particularly for those from marginalized

backgrounds. The findings from this study indicate that depressive symptoms are critical to identify and treat, and likely influence cognitive functioning during the menopausal transition.

CHAPTER ONE

INTRODUCTION

Despite human development being a cumulative, lifelong process, much of the existing research focuses on developmental transitions between infancy, early childhood, adolescence, and young adulthood as well as the late life stage (ages 65+). However, less is known about midlife (approximately ages 40-64), a period marked by unique challenges regarding physical and mental health as well as shifting social roles and responsibilities (Hughes et al., 2018; Infurna et al., 2020). Though research is scant, existing evidence suggests that midlife is marked by decline in several cognitive domains, including working memory, processing speed, and executive functioning. The decline in cognitive functioning may depend on lifestyle factors such as physical activity and fitness and allostatic load (Dahl, 2004; Narbutas et al., 2019), which may be a precursor to neurodegenerative-related decline for some individuals. Importantly, those assigned female at birth (referred to as female hereafter) are at greater risk of developing Alzheimer's disease (AD) than those assigned male at birth, a disease with high societal costs as demonstrated by unpaid dementia care valued at $271.6 billion dollars in 2021 alone. With AD on the rise, by 2060 it is expected that as many as 13.8 million Americans will carry a diagnosis ("2022 Alzheimer's Disease Facts and Figures," 2022). One key contributor to sex differences in AD is the menopausal transition during midlife, which involves a sharp change in sex-hormones (Barha & Liu-Ambrose, 2020; Morgan et al., 2018). Given the changes that midlife presents, especially among females, research that identifies patterns of cognitive function and related physical and psychological factors may provide a critical window of opportunity for

identification of decline and introduction of early interventions. The overarching aim of the current cross-sectional study was to identify and characterize cognitive profiles within a sample of middle-aged females in terms of behavioral and psychological factors and to investigate whether these factors are more impactful during specific phases of the menopause transition.

The menopause transition broadly occurs in three phases: perimenopause (extreme fluctuation in estradiol or E2), menopause (12 consecutive months without menses), and post-menopause (years after menopause is reached). Multiple estrogen-regulated neurophysiological systems (i.e., circadian rhythms, sensory processing, and thermoregulation) are disrupted during the menopause transition resulting in a constellation of symptoms such as vasomotor symptoms, sleep disturbance, and mood changes which likely affect cognitive functioning (Barha & Liu-Ambrose, 2020; Brinton et al., 2015; Gava et al., 2019). Because of this, many view the menopause transition as not only a reproductive transition, but also a neuroendocrinological transition which may play a key role in cognitive functioning. For example, E2 and other female-sex hormones heavily influence structural and functional brain development across the lifespan and serve as regulators of many neural processes (Pike et al., 2009). Menopause stage, after accounting for age, hormone therapy, hysterectomy, and genetic factors, was associated with the brain's connectivity, structure, amyloid plaque formation, and glucose metabolism, with effects most notable in brain regions that support higher-order cognitive functioning (Mosconi et al., 2021; Weber & Mapstone, 2009).

These neurophysiological changes (i.e., increase in pro-inflammatory cytokines and reduction in brain glucose metabolism and growth hormones, amyloid plaque formation) often begin before declines are observed in cognitive performance that are indicative of neurodegenerative disease (ND) (Betthauser et al., 2022; Hampel et al., 2021). Researchers

propose that certain neuropsychological changes during menopause may place females at an increased risk for mid-to-late-life decline in cognitive functioning and increased lifetime risk for dementia (Barha & Liu-Ambrose, 2020; Morgan et al., 2018). Importantly, Mosconi and colleagues (2021) found that brain biomarkers (i.e., cerebral glucose metabolism, white/grey matter, connectivity, etc.) stabilized, and sometimes even recovered, in post-menopause as demonstrated by longitudinal imaging (Mosconi et al., 2021). This suggests that there are compensatory responses across the natural menopause transition which may allow for brain adaptation to a hypo-estrogenic post-menopausal state. Perimenopause, a transition stage characterized by extreme fluctuations in sex-hormones, is marked by notable neuroendocrine symptoms (vasomotor, sleep disturbances). Therefore, it is a particular area of interest in determining who might be at risk for poor neuroendocrine adaptation thus compromised neuropsychological functioning. Understanding behavioral and psychological factors implicated in the menopausal transition, particularly as they relate to cognitive functioning, is also crucial. The current study aims to explore cognitive profiles during midlife as well as characterize these profiles, along with menopause staging, in terms of behavioral and psychological functioning.

Menopause and Cognitive Functioning

The relevance of the menopausal transition to cognitive functioning remains an area of debate (Cave, 2022; Conde et al., 2021; Henderson, 2011). Premature menopause, whether surgical or due to ovarian failure, is marked by faster cognitive decline, including worse verbal fluency and executive functioning (Georgakis et al., 2019; Orprayoon et al., 2021; Ryan et al., 2014). Verbal learning and memory decline are most consistently documented in the natural menopausal transition (Weber et al., 2014), though research also indicates processing speed, attention/working memory, and verbal fluency as other cognitive domains may be impacted

(Maki & Weber, 2021). Research aimed at understanding the menopausal transition via performance based cognitive tasks has led to variable outcomes (Maki & Weber, 2021). Outcome variability may be due to a few factors including test selection, timing, population, location, staging techniques, and inclusion (or exclusion) of menopause symptoms. There are several longitudinal studies underway aimed at delineating the menstrual transition and associated symptoms. One such study, the Study of Women's Health Across the Nation (SWAN), has focused on cognitive performance across the menopausal transition. The first four years of data collection showed temporary decline in verbal memory and processing speed during perimenopause, but resolution of these problems in postmenopausal stages aligns well with neuropsychological evidence that there underlying brain adaptation occurring across natural menopause (El Khoudary et al., 2020a; Mosconi et al., 2021). Decline in verbal memory and processing in perimenopause remained significant after controlling for sleep disturbances, vasomotor, depressive, anxiety symptoms. Interestingly, the cognitive domains most often documented as being affected by the menopause transition are those in which females typically demonstrate an advantage compared to males, namely verbal learning and memory (Asperholm et al., 2019; Halpern, 2011) and those that fluctuate across the menstrual cycle (Hampson, 1990; Phillips & Sherwin, 1992).

Verbal learning and memory deficits are prognostic indicators of mild cognitive impairment (MCI) and AD. Clinically, cognitive functioning is often evaluated using a person-centered cognitive profile to aid in identifying patterns of strengths and weaknesses which can help clinicians identify whether a cognitive pattern aligns with emerging ND processes or other disease population (e.g., depression, ischemic disease, multiple sclerosis, etc.). For instance, there are distinct cognitive profiles documented in AD (characterized by memory and language

deficits) versus other NDs. Therefore, research that characterizes person-centered cognitive profiles during the menopausal transition may be more impactful and relevant to how clinicians understand and work with females across this crucial transition. Most studies to date have investigated cognitive data cross-sectionally or longitudinally, while only one known study has used a cognitive profiling approach. Focusing on the perimenopause stage, Weber et al. (2021) assessed longitudinal latent trajectories of performance-based cognitive measures, yielding four distinct profiles (cognitively normal, weakness in verbal learning and memory, strength in verbal learning and memory, and strength in attention and executive function). Interestingly, the weakness in verbal learning and memory profile demonstrated less hormonal variability and more sleep problems than the cognitively normal group, and the strength in verbal learning and memory group had fewer vasomotor and depressive symptoms than the cognitively normal group, while the strength in attention and executive function group had fewer sleep problems than the cognitively normal group (Weber et al., 2021). Though Weber and colleagues were able to delineate longitudinal cognitive profiles across the perimenopause stage and examine menopause symptoms and hormone levels, research investigating the full range of the reproductive transition (late reproductive stage through post menopause) via a person-centered approach to understand cognitive functioning is needed.

Determining menopause stage is an important and complex process. Research suggests that females can experience menopausal symptoms (vasomotor, mood and sleep disruptions) during early perimenopause, sometimes spanning up to a decade, and is impacted by ethnicity and other characteristics like the age of onset of menopausal transition and smoking. (Anklesaria, 2013; Macêdo et al., 2023). For example, the SWAN study has documented racial disparities in reproductive aging, finding that Black females in the study entered midlife with

more adverse cardiovascular and metabolic profiles and physical limitations than their white counterparts and were 50% more likely to experience hot flashes than white participants (Harlow et al., 2022). Additionally, longer duration of the menopausal transition has been documented in Black females as compared to white females (Paramsothy et al., 2017). Because age, pathology, and symptom type cannot be used to characterize where someone is in the menopausal transition and considerable variability across ethnic groups, researchers and clinicians must take a multifactorial approach (El Khoudary et al., 2020a). Urinary hormonal assays, menstrual calendars, and buccal cell smears can all be used to determine the stages of menopause transition (Woods & Mitchell, 2016). Studies of cognitive functioning rely on a variety of methods to characterize menopause staging including self-reported bleeding patterns, and estradiol and other sex hormone levels. However, the Stages of Reproductive Aging Workshop (STRAW_ 10+) staging criteria is currently considered the gold standard for assessing menopause staging (Harlow et al., 2012).

The STRAW 10+ staging system utilizes principal criteria (menstrual cycle), supportive biometric criteria (endocrine, antral follicle count), and descriptive characteristics. However ideal, it is not always feasible to collect biometric data to confirm menopausal status. Therefore, the STRAW 10+ guidelines establish that the menstrual cycle criteria (bleeding patterns; considered principal) are the most important criteria due to lack of standardized and available biometric analytics (Harlow et al., 2012). Using the STRAW 10+ criteria, this study will employ questionnaires to evaluate menstrual cycle and bleeding patterns and provide an estimate of staging. This approach sometimes leads to staging errors, however, especially for those who do not have regular cycles due to reasons beyond perimenopause, such as history of partial oophorectomy, conditions such as polycystic ovarian syndrome (PCOS), or the use hormonal

contraceptives. There is a need to understand the full range of cognitive functioning influenced by menopause stage and factors that influence the magnitude of cognitive changes. Important individual factors, especially behavioral and psychological, may be key indicators and could potentially provide areas for tailored intervention.

Behavioral Factors

Due to a myriad of reasons, several behavioral shifts take place during midlife. Time required to engage in health promoting behaviors such as quality sleep and ample physical activity are often illusive in midlife due to the burden of juggling multiple roles such as caregiver to both children and elderly parents, peak career obligations, and increases in other social demands (Infurna et al., 2020). Current research supports a well-established association between cognitive functioning and various behavioral factors including sleep and physical activity during young adulthood and late life. However, less is known about sleep and physical activity and the role they play in predicting cognitive profiles in middle-aged females who are experiencing the menopause transition. Thus, the present study will examine sleep and physical activity as behavioral factors that may predict cognitive profiles during the critical midlife transition, as well as whether the potential benefits vary based on where an individual is within the menopause transition.

Sleep

The menopause transition is marked by significant disruptions in sleep. Both subjective and objective measures of sleep have been used to examine associations between menopause staging and sleep disturbances. Objective and subjective measures of sleep offer slightly different measures of sleep that do not always highly correspond, possibly due to the variability in measurement and instrument use (Otte et al., 2015). Self-reported sleep disturbances during

the menopause transition are common (Tom et al., 2010). Objective and subjective accounts of poor sleep quality, insufficient sleep duration, and nocturnal awakenings among females experiencing the menopausal transition have been noted (Gava et al., 2019; Shea et al., 2021). Cross-sectional and longitudinal research on menopause-related sleep disturbances among females report worse sleep quality and greater severity of symptoms related to menopause (i.e., vasomotor symptoms/hot flashes) (Ameratunga et al., 2012; Santos et al., 2021). Kravitz and Joffe (2011) found that objective measures of sleep (via wrist-worn actigraphy) documented that females who experience elevated vasomotor symptoms had more sleep fragmentation than those who did not experience vasomotor symptoms. Research comparing perimenopausal (ages 45-51), postmenopausal (ages 59-71) and young (ages 20-26) females found similar patterns of sleep efficiency and duration as measured by polysomnography for the peri-and post-menopausal groups and that they had lower efficiency scores and shorter sleep duration than the young group. Interestingly, self-reported sleepiness and mood were similar across all groups, while insomnia was reported more in the postmenopausal group (Kalleinen et al., 2008). Additional research on gonadotropin-releasing hormone agonist models show that nighttime vasomotor symptoms, a prominent symptom in the menopause transition and especially the perimenopause stage, interrupt sleep (Joffe et al., 2013). In the SWAN study, vasomotor symptoms in both late perimenopausal and postmenopausal women were associated with more sleep difficulties than the premenopausal group. Additional sleep analyses in the SWAN study documented associations between hormone levels and sleep disturbances, which suggests that changes in hormone levels, but not baseline levels, were associated with sleep disturbances, and further suggesting that menopausal staging may be an important factor to evaluate (Kravitz & Joffe, 2011). Kravitz and Joffe also documented that those vasomotor symptoms significantly impacted

sleep such that females who experiences vasomotor symptoms had more sleep fragmentation than those who did not experience vasomotor symptoms as measured by actigraphy. Finally, data from the SWAN study demonstrates differences between African American and white midlife female's objectively measured sleep via actigraphy. Specifically, African American females had shorter sleep duration and more interrupted sleep than their white counterparts (Harlow et al., 2022). Overall, research suggests that self-reported and objectively measured sleep disturbances are experienced across the menopausal transition (El Khoudary et al., 2020b) and poor sleep may have an adverse impact on both cognitive and cardiovascular health.

Sleep and cognitive functioning are robustly related across the lifespan. However, the strength of this well documented association may depend on menopause staging, all of which have clear links to cognitive functioning (Benitez & Gunstad, 2012; Kronholm et al., 2009). Sleep, cognitive functioning, and menopause transition research has primarily focused on the impact of sleep duration and sleep quality on cognitive functioning. Perimenopause is particularly associated with declines in attention, working memory and verbal memory (Weber et al., 2021), and research suggests sleep disturbance may predict future cognitive decline in these specific domains. Subjective measures of sleep quality are significantly positively associated with performance-based measures of executive functioning/attention and memory domains during midlife (Rana et al., 2018). However, mixed findings are prevalent when comparing objective and subjective sleep measures in relation to cognitive functioning. For example one study in an adult population (N= 489, $Mage$ = 45.5) that evaluated subjective versus objective measures of sleep as it relates to cognitive functioning found that greater objective sleep quality and longer sleep latency onset were associated with improved performance on conceptual flexibility tasks while subjective sleep was not associated with any cognitive domain

performance (Bernstein et al., 2019). One longitudinal study found that midlife extreme sleep durations and extreme changes in sleep duration over time were associated with worse global cognitive functioning in females aged 70 or older (Devore et al., 2014), however distinct cognitive domains could not be differentiated. Virta and colleagues (2013) documented that sleep quality is significantly associated with visual-spatial recall, updating in working memory, and set shifting, supporting the notion that sleep quality could be a critical factor in cognitive integrity during midlife, though the study is limited by the use of a phone-based measure of cognitive functioning (Virta et al., 2013).

Overall, these findings indicate that sleep plays a crucial role in cognitive functioning, particularly during midlife, and especially for females experiencing fluctuations in hormones and variations in sex hormones, which differ by menopause stage. This emphasizes the significance of sleep as a target for intervention in the prevention of cognitive decline and dementia. Though we know that sleep related factors can influence optimal cognitive functioning in multiple domains across the lifespan, no study has utilized a person-centered approach to consider how sleep relates to cognitive profiles in the context of the menopause transition.

Physical Activity

Physical activity (PA) and fitness levels often decline across midlife and are influenced by factors such as age, sex, health-related behaviors, attitudes, appraisals, and social participation (Holahan et al., 2017). Benefits of PA during midlife are noteworthy as demonstrated by Patel and colleagues (2006) research that found that PA in midlife is associated with reduced risk for morbidities that might affect mobility in late life, such as coronary heart disease, diabetes, and certain cancers. PA has also been linked to various health benefits, including improved physical function, delayed onset of chronic diseases, and increased quality of life Moreover, PA is related

to greater life satisfaction across all ages (Maher et al., 2015), and lower levels of depression in midlife (Cooper-Patrick et al., 1997). PA and cognitive functioning also demonstrate a robust positive association, with research documenting cognitive benefits from regular PA across the lifespan (Gaertner et al., 2018).

Short- and long-term benefits of PA for females during midlife have been examined and overall has a positive effect on memory domains (Henderson, 2011). The SWAN group found that PA trajectories during midlife are related to physical function decline during late midlife for females (Pettee Gabriel et al., 2017). Additionally, female's PA patterns in midlife differ from male's PA patterns in terms of the determinants, including reproductive factors unique to females, such as menopause and childbearing (Laakkonen et al., 2017). Females also experience greater cognitive gains from exercise in late life than their male counterparts, yet less is known about midlife (Barha & Liu-Ambrose, 2020). Research suggests that changes in cognitive functioning during the menopause transition may be influenced by PA, though it does not account for all cognitive differences between stages. For instance, a cross-sectional study reported that physically active pre- and early post-menopausal females demonstrated a significant difference in working memory such that post-menopausal females had poorer working memory performance and this was not explained by physiological phenomena (such as arterial stiffness). However, no differences between physically active pre -and early post-menopausal females were observed in episodic memory, processing speed, and inhibition/switching tasks (Debray et al., 2022). Additionally, regular leisure-time PA has been shown to improve body composition and neurotrophic factors while alleviating menopausal symptoms, an important area in need of intervention to improve quality of life (Arsani et al., 2020; Kim & Kang, 2020).

Though we know that PA can influence optimal cognitive functioning in multiple domains across the lifespan, no study has utilized a person-centered approach to consider how PA relates to cognitive profiles in the context of midlife for females, and more specifically, whether the association is moderated by menopausal staging. Considering the extreme fluctuation in sex hormones during perimenopause and then the overall decline of sex hormones post menopause, it is important to consider how different stages of menopause confer differing cognitive outcomes in the context of individual factors. Thus, while there is no clear consensus on the effects of menopause staging on cognitive functioning, both sleep and PA appears not only to promote cognitive functioning but also to alleviate menopausal symptoms and improve quality of life in middle-aged females.

Psychological Factors

The menopause transition and accompanying hormonal fluctuations that occur, especially during the perimenopause stage, are suggested to increase sensitivity to psychosocial stress, and heightened risk for anxiety and depressive symptoms (Gordon et al., 2016, 2019; Joffe et al., 2020; Soares & Cohen, 2001). Psychological wellbeing and experiences of stress influences cognitive functioning. As evidenced through research on neuropsychological sequalae of psychiatric and mood disorders, deficits in multiple cognitive domains are implicated in various mood states (i.e., depressed, manic) such as attention, executive functioning, memory, and processing speed, with evidence of deficits increasing with symptom severity (Culpepper et al., 2017; Marvel & Paradiso, 2004; Richardson & Adams, 2018). Importantly, both objective (performance-based) and subjective (patient reported) cognitive dysfunction characterize mood disorders, for example attentional biases towards sad or happy stimuli as evidenced through research on depressed or manic populations. Furthermore, individuals with a history of mood

disorders often demonstrate residual cognitive deficits, even while in full recovery (Chamberlain & Sahakian, 2006). This association may be particularly salient during life transitions characterized by both chronological aging and hormonal changes that place an individual at heighted risk for experiencing variable cognitive functioning in the context of impaired mood. Although many aspects of psychological functioning may be affected across the menopause transition, two aspects that may be particularly relevant to cognitive functioning are psychological stress and depressive symptoms.

Psychological Stress

Menopause is a significant transition with multiple psychological implications. Females who have significant psychological distress or stress due to menopause may experience more negative symptoms. Females who perceived menopause as a negative experience, or who were highly stressed or distressed, may experience increased negative menopausal symptoms (Bauld & Brown, 2009), and females with negative expectations regarding menopause are prone to experiencing depression, irritability, and vasomotor symptoms, leading to psychological distress (Matthews, 1992). Late onset of menopause has also been associated with psychological stress. Psychosomatic, vasomotor symptoms, low menopausal management, and stress were significantly related to lower psychological well-being in females with late onset menopause (Lee & Lee, 2022).

The impact of psychological stress on cognitive functioning has been documented across various cognitive domains throughout midlife. Specifically, high levels of psychological stress have been linked with lower performance in verbal abilities, processing speed, global cognition, and processing speed (Ihle et al., 2018; Sindi et al., 2017). Further, stress hormone responses [i.e., glucocorticoids (GCs)] are associated with cognitive functioning. Elevated levels of GCs

over time negatively impact the hippocampus, a brain structure implicated in learning and memory. Thus, it is no surprise that this cognitive domain is affected by stress (Marin et al., 2011). Stress has also been shown to be associated with cognitive decline from young adulthood to late midlife, even after controlling for early life circumstances, education, and trait stress (Christensen et al., 2023). Females in midlife demonstrate a positive association between life stress and brain and cognitive reserve further highlighting the negative impact stress has on cognition in this critical period (Schuurmans et al., 2023). For example, research suggests that heightened stress is associated with cognitive deficits in several domains, including working memory, declarative memory, attention, and executive functions (Liston et al., 2009; McIntosh et al., 2022; Popoli et al., 2012; Sokołowski et al., 2019). Additionally, psychological stress and depressive symptoms have been linked to alterations in functional connectivity in the central executive network, which may contribute to deficits in memory and attention (Liston et al., 2014). Taken together, the extant literature suggests that psychological stress has a significant impact on various cognitive domains, particularly working memory, attention, executive function, and declarative memory domains, and that the effects of stress may vary depending on the type, intensity, and duration of stress and the developmental stage of the individual. Though we know that psychological stress can negatively impact optimal cognitive functioning across the lifespan, no study has utilized a person-centered approach to consider psychological stress as it relates to cognitive profiles in the context of the menopause transition.

Depressive Symptoms

Depressive symptoms are common during the menopause transition and in post-menopause. The risk of developing depressive symptoms during perimenopause is higher for females with a prior history of depression and those who experience vasomotor symptoms

(Alblooshi et al., 2023; Augoulea et al., 2019; Azizi et al., 2018; Maki et al., 2018). Importantly, negative mood states encompass depressive symptoms as well as feelings of irritability, fear, anger, and are strongly associated with personality traits such as neuroticism. Researchers have documented that females tend to report higher levels of neuroticism than males and that higher levels of neuroticism are linked to greater severity in depressive symptoms (Ormel et al., 2013; Rodríguez-Ramos et al., 2019). Research suggests that mood disorders during the menopause transition are related to the interactions between estrogen, progesterone, and the serotonergic system (Soares et al., 2003). The perimenopause stage is marked by fluctuations in sex-hormones and may be a window of vulnerability for mood disorders, particularly for those who are susceptible to depressive episodes (Gordon et al., 2015; Joffe et al., 2020; Soares & Cohen, 2001). The psychological symptoms associated with menopause, including mood swings, lack of interest, frustration, irritability, anxiety, and low self-esteem, can overlap with and complicate depressive symptoms. A systematic review and meta-analysis found that females who were perimenopausal or postmenopausal have a higher risk of experiencing depressive symptoms than premenopausal females (Weber et al., 2014). Thus, the menopause transition is a period of increased vulnerability to depressive symptoms, which should be appropriately evaluated and treated accordingly. Depressive symptoms are complex and influenced by various factors, including sex hormones. Animal models and research have documented that sex differences are prevalent in steroid hormone-induced modulation of hippocampus-dependent neuroplasticity, cognition, and depression (Galea et al., 2013). Evidence from community-based studies has also documented clear associations between sex hormones and depressive symptoms (Colangelo et al., 2012; Kische et al., 2017) and that early post-menopause may be a particularly vulnerable period (Colangelo et al., 2012). Further indication of the association between sex hormones and

depression is evidenced through a study that induced sex hormone fluctuations which found that fluctuating hormones contribute to heightened risk for developing depressive symptoms by affecting intrinsic functional connectivity of key limbic brain structures (Fisher et al., 2017). In conclusion, sex hormones have been implicated in the onset and severity of depressive symptoms. This has been noted during menarche when sex differences in depression begin to emerge. The menopause transition is marked by intense fluctuations in sex hormones, with estradiol dramatically fluctuating until eventually declining when final menstrual period is reached, making this transition period a particularly vulnerable stage for depressive symptoms.

Depressive symptoms are linked to cognitive impairments in several key domains including processing speed, attention, executive function, memory, and language/semantic memory. Impaired cognitive functioning is consistently observed in major depressive disorder, with processing speed, reasoning, and problem-solving showing dysfunction (Mohn & Rund, 2016). For example, one study on community-dwelling older adults noted that initial depressive symptoms affected subsequent processing speed, simple and choice reaction times but cognition did not predict depressive symptoms over time (Bunce et al., 2014). The interplay of cognition and depressive symptoms is evidenced in a longitudinal study using cross-domain latent growth curve analyses that demonstrated a significant association between memory function and depressed affect in older adults. Specifically, the analysis revealed both concurrent associations between somatic symptoms of depression and poor processing speed, but also that poorer delayed recall at baseline predicted a sharper increase in depressed mood over time (Brailean et al., 2017). Extant literature demonstrates strong associations between negative mood states and depression with two large brain networks: the default mode network (DMN) and the fronto-parietal network. Disturbances within these networks are strongly linked to cognitive problems

often observed in depression, particularly executive functions (Brzezicka, 2013). In sum, the adverse effects of depressive symptoms on various cognitive domains are observed across the lifespan and may persist while an individual is in full recovery. However, certain stages in life may confer greater risk for developing depressive symptoms such as hormonal transitions as demonstrated in research during menarche, pregnancy, and menopause (Soares et al., 2003; Steiner et al., 2003).

The Current Study

Although the extant literature demonstrates robust associations between psychological and behavioral functioning and cognitive outcomes, particularly during the menopausal transition, more research is needed to better understand objectively measured cognitive functioning during this crucial hormonal transition and how it relates to individual factors. Utilizing a multimodal (self-report questionnaire and performance-based neuropsychological tests) study design, this cross-sectional study will identify the hidden heterogeneity in cognition in a sample of females in midlife by profiling performance-based cognitive functioning across multiple domains (language, verbal learning and memory, executive functioning, processing speed, attention, etc.) while accounting for educational attainment. Emergent profiles were then characterized via demographic factors (race, ethnicity, socioeconomic status, number of children, marital status), cardiovascular and metabolic health indicators such as blood pressure, body mass index (BMI), cholesterol, etc.), and medications including hormone replacement therapy (HRT). Next, this study examined how individual, and possibly modifiable, factors (i.e., sleep, PA, psychological stress, and depressive symptoms) related to cognitive profiles during this critical window. Finally, given that fluctuating hormones and the accompanying vasomotor symptoms (e.g., hot flashes) and sleep disruptions that occur during perimenopause may be especially

disruptive to cognitive functioning (Weber et al., 2013), this study considered whether associations between individual factors and cognitive profiles are stronger during certain menopausal stages, among a sub-sample of females with confirmed menopause staging via the STRAW 10+ guidelines. The current study aims and hypotheses, depicted in Figure 1, are as follows:

Aim 1: Identify distinct cognitive profiles in a sample of females during midlife while accounting for education and characterize emergent profiles via demographic, cardiovascular and metabolic health indicators, and medication use.

Hypothesis 1a: Three-to-four profiles will emerge (low-functioning, high-functioning, and mixed profiles).

*Hypothe*sis *1b*: There will be demographic and characteristic differences between profiles, though this aim is largely exploratory.

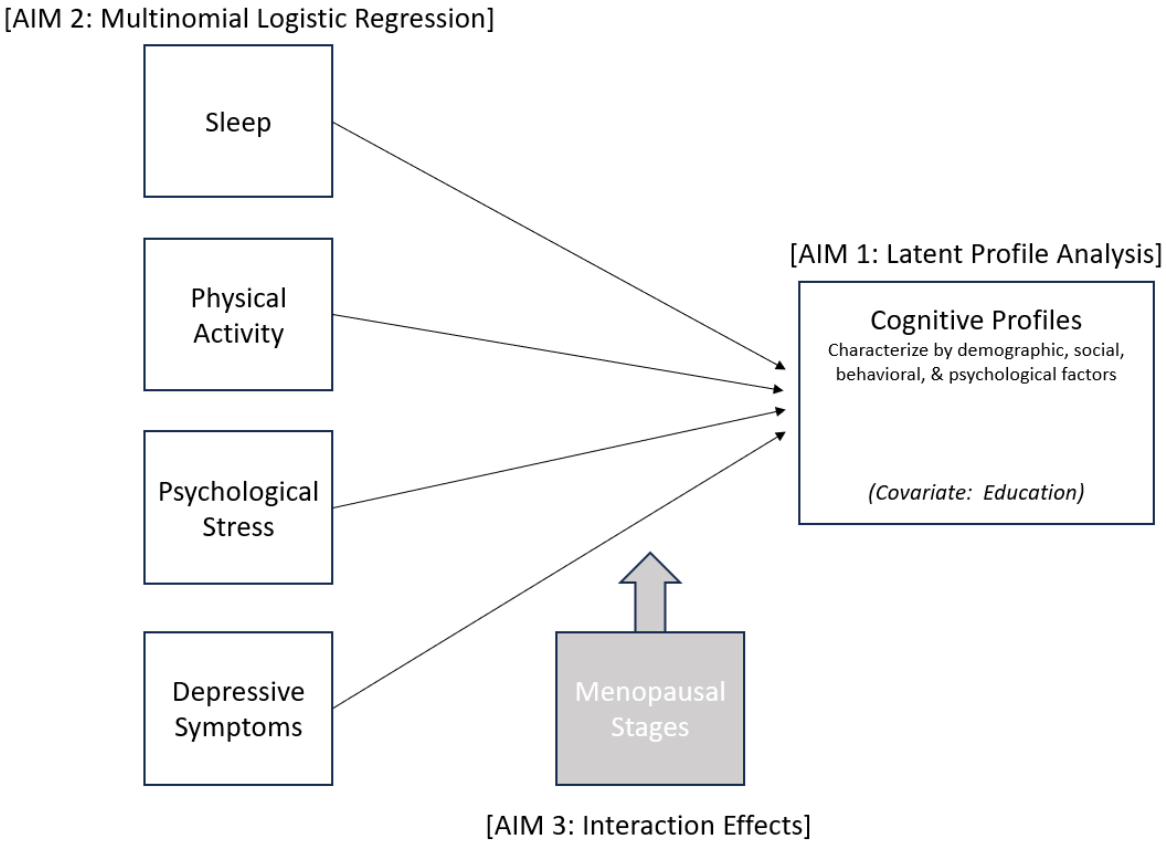
Aim 2: Examine cognitive profile membership by individual factors including sleep, PA, psychological stress, and depressive symptoms.

Hypothesis 2: Health promoting behaviors (good sleep, high PA, low psychological stress, and depressive symptoms) will significantly classify membership in higher-functioning profiles.

Aim 3: In a sub-sample of individuals with confirmed menopausal staging, determine if menopausal staging (pre-menopause; perimenopause; post-menopause) moderates the relation between individual factors and cognitive profiles.

Hypothesis 3: There will be interaction effects of menopause stage and individual factors. Further, it is hypothesized that those in the perimenopause stage will demonstrate larger odds ratios when predicting cognitive profiles by individual factors.

Figure 1. Aims of the Current Study



CHAPTER TWO

METHOD

Participants

A subset of participants from a longitudinal nationally representative dataset [The Human Connectome Project-Aging (HCP-A); Bookheimer et al., 2019] were included in this study. Recruitment took place at active senior centers; places of worship; public lectures and workshops related to aging; advertisements and flyers; Craigslist and social media sites; as well as local businesses, clinics, and events (e.g., city-wide block parties). All sites attempted to achieve a nationally representative dataset based on racial and ethnic identities and socioeconomic brackets (low, middle, and high-income). The primary objective of the larger study is to better understand brain functioning in typical aging and to what extent biological, social, psychological, and/or contextual factors contribute to healthy aging. The study over-recruited females aged 45-59 which is ideal for studying perimenopause and the menopausal transitions during early midlife. The current analytic sample for Aims 1 and 2 includes data collected during the baseline visit and comprises females aged 40-60 (n= 202 M_{age}= 50.46; 60% white, 84% non-Hispanic, 32% having a four-year college education). For Aim 3, a subset of participants who have confirmed menopausal staging (n= 139 M_{age}= 50.87; 60.4% white, 83.5% non-Hispanic, 33.8% having a four-year college education) was used to investigate moderating effects of staging. There were no significant differences in demographic factors including age, education, race, ethnicity, marital status, and number of children between people excluded from Aim 3 (n = 54) and the sub-sample used in Aim 3 (n=139). Participants received compensation

for completing the rigorous, 12-hour protocol ($400). Demographics of the full analytic sample are presented in Table 1 and the descriptive information for both the menopause sub-sample and those without menopause staging are presented in Table 2.

Table 1. Demographic Characteristics of Analytic Sample

	N (%) or M (SD)
Age	50.5 (6.5)
Race	
White	122 (60.4)
Black or African American	47 (23.3)
More than one race	12 (6.2)
Asian	12 (6.2)
Unknown or not reported	9 (4.7)
Ethnicity	
Hispanic or Latino	33
Not Hispanic or Latino	169
Education	
<12th grade	5
12th grade	15
Technical school or 1 year of college	15
2 years of college	28
3 years of college	8
4 years of college (B.A./B.S.)	62
Graduate School (M.A., M.S., J.D., M.D., Ph.D.)	63
Children[a]	
0	9 (6.3)
1	31 (21.8)
2	62(43.7)
3	21 (14.8)
4 or more	19 (13.4)

Marital Status	
Divorced	38 (19.7)
Living as Married	6 (3.1)
Married	86 (44.6)
Never Married	46 (23.8)
Separated	8 (4.1)
Widowed	3 (1.6)
Menopausal Status – confirmed staging[b]	
Reproductive	49 (35.3)
Perimenopause	31 (22.3)
Post menopause	59 (42.4)

[a] missing 51 responses thus only valid percentages provided.
[b] sub-sample of 139 females with confirmed menopause stage.

Table 2. Key Variable Descriptives in the Menopause Sub-sample and Participants without Menopause Staging

Study Variable; *M (SD)*	Excluded from Aims 3 *n* = 54	Sample in Aim 3 *n* = 139	Significance
Age	49.1(5.7)	50.9(6.5)	*p* = .098
Race			*p* = .883
Asian	2	10	
Black or African American	11	31	
More than one race	4	8	
Unknown or not reported	3	6	
White	34	84	
Ethnicity			*p* = .984
Hispanic or Latino	9	23	
Non-Hispanic or Latino	45	116	
MoCA Total	27.1(2.2)	26.8(2.3)	*p* =.409
Marital Status	38.9% Married	46.8% Married	*p* = .108
Children	2.23(1.1)	2.04(1.3)	*p* = .378

Procedure

To determine eligibility, potential participants were invited to complete a screening phone interview. Inclusion criteria included 36 to 100+ years of age and ability to consent. Exclusion criteria focused on diagnoses and treatment for major psychiatric disorders such as schizophrenia, bipolar disorder, or neurological disorders like symptomatic stroke, brain tumors, or other known neurodegenerative diseases (i.e., Alzheimer's disease, Parkinson's disease), as well as individuals who required treatment for a year or longer in the past five years for severe depression. A full list of exclusion criteria is provided in Table 3 (Bookheimer et al., 2019). Following the screening phone call participants were scheduled for a two-day in-person visit. Informed consent was obtained after administering the screening questions again as well as the Montreal Cognitive Assessment (MoCA) which required a cutoff score of 20 or higher to be retained in the study for age group of the current analytic sample. Eligible participants completed a 12-hour protocol across one-to-two days which included collection of biometric data including blood and urine samples as well as vitals (i.e., blood pressure, heart rate, heart rate variability, body weight index), brain imaging (structural and functional), completion of comprehensive cognitive and motor test battery, and self-report questionnaires assessing bleeding patterns according to the Stages of Reproductive Aging Workshop + 10 (STRAW + 10) as well as information regarding the reproductive history, depressive symptoms, perceived stress, sleep quality, and physical activity. All sites attempted to schedule eligible female participants between ages 45 and 55 for blood draws and/or assessment visits during the follicular phase of their menstrual cycle (2-6 days after the commencement of menses) with variable success rates. All participants went into follow-up following their last day of data collection with approximately half being invited for a follow-up visit two years later. This study was approved

by the Washington University Institutional Review Board (IRB) as the coordinating site, as well as the three other data collection site IRBs, including the University of Minnesota, University of California Los Angeles, and Harvard/Massachusetts General Hospital.

Table 3. HCP-A Inclusion/Exclusion Criteria

HCP-A Inclusion Criteria	
1.	Age 36-100+
2.	Ability to give informed consent
HCP-A Exclusion Criteria	
1.	During the participant's lifetime:
	a. Neurologic disease including multiple sclerosis, cerebral palsy, Parkinson's disease, or Alzheimer's disease
	b. Brain surgery
	c. Major psychiatric disorder, such as bipolar disorder or schizophrenia
	d. Hospitalization for 2 days or more for alcoholism or drug dependence
	e. Head injury causing any of the following:
	i. Loss of consciousness for >30 minutes
	ii. Amnesia for >24 hours
	iii. Change in mental status for >24 hours
	iv. Neuroimaging findings consistent with traumatic brain injury
	v. Persistent (>3 months) post-concussive symptoms following concussion or mild TBI
	f. Two or more non-provoked (e.g., not due to fever) seizures after age 5 years or a diagnosis of epilepsy
	g. Any brain tumor including meningiomas
	h. Any cancer treated with chemotherapy and/or radiation to the head or neck, and/or any stage 4 (metastatic) cancer even if no treated
	i. Hospitalization for brain aneurysm, brain hemorrhage, subdural hematoma or stroke (except TIA is allowed)
	j. Rheumatoid arthritis, HIV or lupus or another condition requiring long-term use of steroids or other immunosuppressant

	k. If 80 years old or younger: Diagnosis of macular degeneration
l.	Known genetic disorder (e.g., sickle cell disease or cystic fibrosis)
2.	Within the last 5 years:
	a. Pharmacologic or surgical treatment by a neurologist, or endocrinologist for a period of 12 months or longer, except for thyroid conditions or for back pain or other condition that is clearly not brain related.
	b. Severe depression requiring treatment by a psychiatrist for 12 months or longer
3.	Within the last 1 year:
	a. Diagnosis of thyroid problems and/or changing doses of thyroid medication
	b. Heart attack
4.	Current:
	a. Diabetes that has been diagnosed within the past 3 years (diabetes is OK if it is stably controlled per participant report of either HbA1c <7.0 or stable control for at least 3 months)
	b. Hearing loss sufficient to prevent communication via telephone
	c. Vision worse than 20/200
	d. Current pregnancy
	e. Unsafe metal or devices in body
	f. Moderate to severe claustrophobia
	g. Use of prescription medication to prevent migraines (migraines allowed if not taking daily preventive medications)
	h. Migraine less than 72 hours before the first visit or during the visit
	i. Uncontrolled high blood pressure (>170/100) or working with doctor to stabilize blood pressure
	j. Severe lung, living, kidney or heart disease or other major organ failure
	k. Montreal Cognitive Assessment (MoCA) score of 19 or below for participants aged up to 79 years; MoCA score of 17 or below for participants ages 80-89; MoCA score of 16 or below for participants aged 90 and above
	l. For participants aged 60 – 79, a score of 29 or below on the TICS-M questionnaire. If participants age 80 and above score 29 or below on the TICS-M, we give them a secondary screen to determine their eligibility.

Measures

Demographics

Participants completed demographic questionnaires, including their age, race/ethnicity, education, socioeconomic status, marital status, child status, and household size.

Cardiovascular and Metabolic Health

Health-related factors were based on 10 variables which have been previously linked to cardiovascular and metabolic health. The protocol called for fasting blood draws immediately after the initial informed consent and final screening evaluation at the beginning of the study session. In addition to blood samples, vitals, weight, and height were measured at the beginning of the study session. *Of the various labs and vitals collected, the following biomarkers were utilized in this current study as important markers of cardiovascular and metabolic health*: immune markers [C-reactive protein (CRP), albumin], vascular [blood pressure (BP), creatinine clearance], metabolic (BMI, hemoglobin A1c, total LDL and HDL cholesterol, triglycerides, and vitamin D) (Rashid et al., 2023). Blood pressure was additionally categorized into risk zones as established by the American Heart Association (Whelton et al., 2018).

Medications

Each participant provided a list of current medications. The use of the medications was assessed via the following categories: hormone replacement therapy, hormone birth control, medications treating hyperlipidemia, hypertension, thyroid disease, diabetes, narcotics, anticholinergic and psychotropics. Each medication was coded “1” for the presence of that medication and a “0” for the absence of that medication and summed for each medication category. For example, if an individual reported two hormone replacement therapies this was coded as “2” and if they reported two hypertensive medications that was coded as “2.”

Menopausal Status

Menopausal staging was classified objectively using validated criteria, specifically the Current Menstrual State and Menstrual History survey (Harlow et al., 2012). For the current study, menopausal staging was determined by responses to a questionnaire asking about the nature of their menstrual cycles and bleeding which provides a crude estimate of staging (reproductive stages range from -5 to -3a; menopausal transition ranges from -2 to -1; perimenopause spans -2 through +1a; final menstrual period is 0; and post menopause is +1a through +2; see Table 4). The premenopausal/late reproductive (-3b through -3a) group was defined as females who have experienced either no change to their menstrual cycle or very subtle changes to their cycle (i.e., typically shorter cycles). The perimenopause (stages -2 through +1a) group was defined as females who report variability in menstrual cycle length. Specifically, this was defined as at least two cycles having a difference of seven days or more in the length of consecutive cycles within 10 cycles. The post menopause (stages +1b through +2) group was defined by >12 consecutive months without menses. Additionally, there were multiple hormonal measures obtained for participants of all ages and genders, including serum estradiol (E2), testosterone, Luteinizing hormone (LH), and Follicle Stimulating Hormone (FSH), in addition to relevant hormone therapy (HT) information. E2 and FSH can be used to help define the menopausal stage of participants in conjunction with the other STRAW 10+ criteria. Due to variable hormone levels across the menstrual cycle, which are particularly evident during perimenopause, the protocol called for collection of blood samples for females 45-55 years old to be collected 2-6 days after the start of their cycle. However, each site encountered several barriers to completing this protocol, including participant cooperation, time constraints on 3T magnets, and difficulty in tracking ovulation for females with PCOS and surgical history positive

for partial oophorectomy. Therefore, a subset of females who were able to schedule their blood draws 2-6 days post commencement of menses will be analyzed in the context of their responses to the Menstrual Questionnaire and Menopause screener (Harlow et al., 2012), which evaluate menstrual timing (e.g., age of menarche, date of last menstrual cycle, cycle length, menstrual flow, etc.) to elucidate reproductive staging. Additional information regarding surgical interventions, diagnoses impacting menstrual cycles (PCOS, etc.), hormone replacement therapy, and hormonal birth control use was collected to determine if lack of menses was due to menopause or birth control. This information will help verify correct staging in the current study.

Table 4. The STAW 10+ Staging System for Reproductive Aging

Terminology	**Stage**	**Duration**	**Menstrual Cycle**
Reproductive			
Early	-5	variable	Variable to regular
Peak	-4	variable	Regular
Late	-3b -3a	variable	Regular Subtle changes in flow & length
Menopausal Transition			
Early	-2	variable	Variable length persistent >7 day difference in length of consecutive cycles
Late	-1	1-3 years	Interval of amenorrhea of >=60 days
Post menopause	0		Final Menstrual Period
Early	+1a +1b	2 years	
	+1c	3-6 years	
Late		Rest of years	

Note: Perimenopause spans stages -2 through +1a. Table is adapted from Harlow et al. (2012).

Cognitive Functioning: Performance-Based Measures

For the current study, the NIH Toolbox for the Assessment of Neurological and Behavioral Function Cognitive, Motor, and Emotion modules were utilized (Weintraub et al., 2013; Zelazo et al., 2013). This includes tasks that measure multiple domains of cognition including Executive Function, Episodic Memory, Language, Processing Speed, Working Memory, and Attention as well as emotional functioning. Details of each test are outlined in more detail below.

*Attention***:** The NIH Toolbox's Flanker Inhibitory Control and Attention Test was used to measure participant's ability to inhibit attention to irrelevant stimuli, a key component of executive function. While ignoring the direction of the distractor arrows (called 'flankers'), participants were instructed to indicate the direction that the target arrow was pointing for each trial. The task included congruent and incongruent trials, where flanker arrows face the same direction as target arrows in congruent trials, and in the opposite direction to the target arrow in the incongruent trials. Total scores were based on both accuracy and reaction time, and uncorrected standard scores were used in analysis.

Cognitive Flexibility/Task Switching: Cognitive flexibility and task switching, a key aspect of executive function, was measured via the NIH Toolbox's Dimensional Change Card Sort (DCCS) test. Participants must match visual target stimulus to one of two stimuli based on the color or the share. Sometimes the dimension being matches is switched, which requires cognitive flexibility to change sorting rules and then match the correct stimulus. Scoring is like the flanker inhibitory control and attention test, meaning it is based on a combination of accuracy and reaction time and then converted to uncorrected standard scores. Mental flexibility and divided attention were also measured via the Trail Making Test Trial B (TMT-B; Bowie &

Harvey, 2006; Salthouse, 2011). On this task, participants were asked to connect circled numbers and letters in alternating numeric and alphabetical sequence as quickly as possible. The score is the number of seconds it took participants to complete the task with lower scores indicating higher ability. Because this is the opposite valiance as other performance-based tasks included in this analysis, TMT-B was scaled so the valiance would match other cognitive tasks, thus higher scores indicate higher ability after scaling.

Processing Speed: The NIH Toolbox's Pattern Completion Processing Speed (PCPS) test measures processing speed. Participants indicated whether the two adjacent pictures were different or the same. The total score was based on the number of items correct within a 90-second time limit and then converted to uncorrected standard scores for analysis.

Working Memory: Working memory was assessed using the List Sorting Working Memory Test from NIH Toolbox, where participants were presented with oral (spoken names) and visual (pictures) information about various foods and animals. In the first list condition, participants are shown and asked to verbally order animals or foods from smallest to largest. For the second list condition, participants are given both animal and food lists and asked to verbally order each list by increasing the size of the items. The number of list items increases with subsequent trials, and the task is discontinued after two successive incorrect trials. Total correct items were summed and then converted to an uncorrected standard score.

Visual and Verbal Memory: The NIH Toolbox's Picture Sequence Memory test (PSMT) objectively evaluates visual episodic memory. Each trial illustrates objects and actions that are presented one at a time, arranged into a demonstrated order, and then back to a random order. These picture sequences included 15 pictures total. Next, the participant moved the pictures into the correct demonstrated order. Scores were determined based on the total number of correctly

positioned adjacent pairs of pictures over the three learning trials and converted to uncorrected standard score. Additionally, a more comprehensive assessment of verbal episodic memory that is widely used in research and neuropsychological measurement, the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941) was administered. The RAVLT was altered to optimize the time spent onsite. Thus, the 20-minute delay recall was excluded from the protocol. For AIM 1, the uncorrected standardized score from NIH-Toolbox PSM and the short delay recall and total learning scores from the RAVLT will be utilized to represent visual and verbal memory, respectively.

Language: The NIH Toolbox Picture Vocabulary Task (TPVT) (Gershon et al., 2014) was used to measure receptive language abilities. Participants were asked to select one out of four presented photos that best fits the auditorily presented word. A score known as a theta score was automatically calculated for each participant, representing the relative overall ability or performance, which was then converted to an uncorrected standardized score.

Sleep Disturbance

Participants completed the Pittsburg Sleep Quality Index (PSQI) which evaluates sleep quality and disturbance. The PSQI consists of 19 items within a one-month time frame for seven distinct content domains, each ranging from 0 to 3, with 3 indicating the greatest dysfunction in that domain (Buysse et al., 1989). PSQI item content focuses on distinct domains including (1) sleep duration, (2) sleep disturbance, (3) sleep latency, (4) daytime dysfunction due to sleepiness, (5) sleep efficiency, (6) overall sleep quality, and (7) sleep medication use. The sleep domain scores are summed to produce a total score that ranges from 0 to 21 with higher scores (“global score”) indicating worse sleep quality. In the present sample, internal consistency was good (α=.7).

Physical Activity

Physical activity was measured with the International Physical Activity Questionnaire-Short Form (IPAQ-SF; Lee et al., 2011). The IPAQ is one of the most widely used physical activity questionnaires and was developed for its cost effectiveness. Participants were asked to recall the amount of moderate activity, vigorous activity, walking, and sedentary time spent over the past week (seven days). The IPAQ-SF has been used successfully in both younger and older adults (Cleland et al., 2018). In the present sample, physical activity was captured by the total physical activity with the continuous total IPAQ score (total Met-minutes of activity during the week).

Perceived Stress

The NIH Toolbox's Perceived Stress Survey (PSS) was administered to all participants. Using FF, the PSS consisted of 10 items, within a one-month time frame, that evaluated individual perception of the nature of various events and their relation to the values and coping resources available to an individual. Respondents were asked to indicate their responses via a 5-point Likert scale, from 1 (*never*) through 5 (*very often*), with higher scores indicating more perceived stress and a range of 10-50. In the present sample, internal consistency was good (α=.88).

Depressive Symptoms

For the current study, the NIH-Toolbox included multiple surveys evaluating different dimensions of depressive symptoms including three surveys that capture negative affect and mood states including sadness, fear, and anger (Pilkonis et al., 2013; Salsman et al., 2013). The NIH TB uses both fixed-form (FF) and computer adaptive test (CATs) surveys. For FF, each item is administered to every participant. CATs are types of measures in which the questions a

person responds to are tailored to them based on previous responds, with each response refining the person's score and requires administration through iPad via NIH TB application. CATs surveys begin from an item bank that all measure the same construct (i.e., sadness) starting with an item in the "middle" range of severity. With each response, an estimated score is calculated, and the CAT algorithm selects the best item in the item bank for refining that estimated score until the stopping rule is met. Due to the length of testing administration involved in the current study, CATs were utilized on various measures because (1) it is brief, usually ranging from 4-12 items and can be completed in under a minute, (2) high precision, low error rates, (3) highly tailored content, and (4) they cover a wide range of function or symptoms within a given construct or domain. The stopping rule for the current study included a minimum of four items administered until 12 items are administered or the standard error was below a threshold (e.g., 0.3 on the theta metric or 3.0 on the T-score metric) (Babakhanyan et al., 2018). Details of each survey are outlined in more detail below.

*Sadness***.** Using CAT format, respondents were asked to think about the past seven days and respond to items related to symptoms of depression (item bank of 28) on a 5-point scale from 1 (*never*) to 5 (*always*). These surveys evaluated low levels of positive affect and taped into affective (low mood) and cognitive (negative self-view, negative worldview) dimensions of depression. Higher scores indicate more feelings of sadness.

Fear Anxiety. Using CAT format, respondents were asked to think about the past seven days and respond to items related to symptoms of anxiety (item bank of 29) such as fear and panic on a 5-point scale from 1 (*not at all*) to 5 (*extremely*). This survey evaluated feelings of fear including panic and fearfulness, related to anxiety. Higher scores indicate more fearfulness and panic symptoms.

Anger Affect. Using CAT format, respondents were asked to indicate on a 5-point scale from 1 (*never*) to 5 (*always*) whether 21 items describe them in the past seven days with one item asking is "just being around people irritated me" on a 5-point scale from 1 (*never*) to 5 (*always/very much*). This survey evaluated anger as an emotion and includes constructs such as irritability and frustration, with higher scores indicating more feelings of irritability and frustration.

Proposed Analyses

Descriptive Statistics

Descriptive statistics were calculated in R-Studio to determine the psychometric properties of all measures, which included means, standard deviations, Cronbach's alpha (where applicable), and scale ranges. Outlier (as defined by a z-score > 4) and skewness analyses were conducted. To obtain comparable scales prior to hypothesis testing, all performance-based measures within each cognitive domains (attention, cognitive flexibility/task switching, processing speed, working memory, episodic memory, and language) were scaled to have comparable valence. Lastly, correlations were computed on all key variables.

Aim 1: Identifying and characterizing cognitive profiles. To identify profiles of cognitive functioning, a latent profile analysis (LPA) was run using *Mplus* 8.1 (Muthén & Muthén, 2017). The selection of the nine LPA indicators (i.e., performance-based measures of attention, cognitive flexibility/task switching, processing speed, working memory, visual and verbal memory, and language) was be based on summation of the extant literature (e.g., cognitive domains associated with independent variables) and availability of performance-based tasks in the dataset. LPA can capture variation in performance patterns between individuals and the assignment of an individual to a subgroup (i.e., class) is based on the degree of similarity of

performance across the nine objective cognitive assessments between individuals. Although the LPA indicators are continuous, and maximum likelihood (ML) estimation is typically appropriate, due to the number of missing data in the indicator variables and nonnormal distribution of some indicators a Full Information Maximum Likelihood estimation with robust standard errors (MLR) was utilized. Because extreme outliers can bias the outcome, outliers (as defined by a z-score > 4) within the indicators were identified and excluded.

For the LPA, initially the maximum *K* (number of subgroups) was determined using both practical and theoretical insight (Nagin, 2014; Nagin & Tremblay, 2005; Spurk et al., 2020; van der Nest et al., 2020). Therefore, the current study predicted the number of identifiable subgroups would be three to four, resulting in a maximum *k*=5. Weber et al (2021) found four cognitive profiles when investigating longitudinal data in a perimenopausal sample thus we expect to find a solution that approximates their findings, though it may be different due to the current study using cross-sectional data with fewer data points in a sample containing pre-peri-and-and post-menopausal females. Additionally, education was included as a covariate on the indicator level because research has documented education to be a strong predictor of cognitive performance. Model fit was evaluated by using a multiple fit indices taken into consideration in tandem with prior research, theory, and clinical interpretability regarding cognitive profiles (Frankfurt et al., 2016a; Spurk et al., 2020; van de Schoot et al., 2017; van der Nest et al., 2020). It is important to consider both statistical and conceptual issues when deciding the best model fit. Importantly, fit statistics do not provide absolute benchmarks for “accuracy” or “exactness” but instead compare relative fit among models (Frankfurt et al., 2016a).

For this study the following information criteria (IC) related to parsimony were utilized: the Bayesian Information Criterion (BIC), sample-size adjusted Bayesian Information Criterion

(SABIC), Akaike's Information Criterion (AIC), Consistent AIC (CAIC) and Approximate Weight of Evidence Criterion (AWE). Generally, model selection is based on the lowest value for ICs. Each IC varies in their level of penalization for model complexity which can be considered on a continuum. The AIC has the lowest penalty (e.g., favoring more classes) and BIC/CAIC have the highest penalty (e.g., favoring fewer classes), and SABIC approximately somewhere in the middle. Next, there is the likelihood-based test, bootstrapped likelihood ratio test (BLRT) which provides a p value which assesses whether adding a class will lead to a statistically significant improvement in the model fit. For example, a BLRT with a non-significant p value for *k* class solution would thus support the *k* -1 solution. In addition to the ICs listed above, entropy-based ICs were also used. Entropy-based measures are based on whether the model produces classes that are well separated. Additionally, the Vuong-Lo-Ruben Likelihood Ratio test (VLRT) was used to help determine the best class salutation. These measures help with selecting a model with optimal class separation which is important because it allows for confidence in the class membership assignment (van de Schoot et al., 2017). The following entropy-based ICs (related to clustering) were used: Classification likelihood criterion (CLC), normalized entropy criterion (NEC), and Entropy (E). Like BIC, SABIC, AIC, and CAIC, smaller values for CLC are preferred. For example, a NEC of 0 would indicate a perfect clustering. For entropy, the range is 0 to 1 with higher values preferred. Specifically, an entropy of >.8 is best with ~.7 indicating generally acceptable classification (Frankfurt et al., 2016a; van de Schoot et al., 2017). Because the current analytic sample is modest, to ensure the most accurate class assignment, ICs related to clustering and implicated as better ICs for small sample sizes (SABIC) were prioritized. These statistics (e.g., SABIC, BIC, etc.) have been compared to the adjusted R^2 since it incorporates model complexity and overall fit, penalizing convoluted

solutions. Although including covariates during clustering analyses is possible, it is best practice to proceed with the class enumeration process (i.e., deciding on the number of classes) without covariates because they will change the latent class estimation (van de Schoot et al., 2017). However, educational attainment is significantly associated with performance based cognitive tasks and therefore education was included as a covariate on the indicator level.

Once cognitive profiles were enumerated, emergent cognitive profiles were characterized in terms of demographic, cardiovascular and metabolic health indicators, and medication use by using nonparametric Kruskal-Wallis (K-W) tests. K-W tests were utilized rather than a MANOVA due to the skewed distribution of blood-based labs and demographic factors (W> 1.5). Post hoc pairwise Wilcoxon rank sum tests determined which groups differed significantly from each other, and Bonferroni correction was used to account for multiple comparisons (Benjamini & Hochberg, 1995). For categorical variables, such as race, ethnicity, blood pressure category, a Fisher's Exact analysis was utilized.

Aim 2: Predicting cognitive profiles membership with behavioral and psychological factors. Multinomial logistic regression models are effective when the dependent variable is three or more levels and is generalized from the binary logistic regression. This statistical analysis allowed for the simultaneous comparison of multiple independent variables. This analysis was used with sleep, PA, depressive symptoms, and psychological stress variables classifying cognitive profile membership. The profiles identified in Aim 1 were used as the dependent variable in the multinomial logistic regression. One class served as the reference group. Typically, this reference group would be the "normative" group and in the current study, the group with the largest number of participants was used as the reference group.

Aim 3: In a sub-sample of females with confirmed menopause staging, examine whether associations between psychological and behavioral factors and cognitive profiles differed based on staging. Individual psychological and behavioral factors may interact with menopause stage as it relates to cognitive performance. Therefore, in Aim 3, interaction terms were added, stepwise, to a logistic regression. Fixed effects for the moderator, along with interaction terms (menopause status x each individual variable) were added to the model. Significant interaction terms were further probed. These analyses aimed to identify for whom the relations between sleep, PA, perceived stress, and depressive symptoms and cognitive profile membership may differ.

Sensitivity Analysis

The extant literature suggests for LPA there are several factors that impact statistical power to detect the accurate number of classes, including sample size, number of indicators, and inter-class separation. Tein and colleagues (2013) demonstrate the complexities in their simulation study which overall found that out of seven models none were adequately powered to select the correct number of classes when class separate was small to medium. When inter-class distance between latent classes were very large (Cohen's d = 1.5), they found that certain fit indices were adequate in class section, while a large degree of separation (d =.8) meant the number of indicates and sample size were important factors in estimating statistical power. Notably, they explain that it is impossible to calculate the inter-class distance between latent classes prior to the analysis (Tein et al., 2013). Thus, in the current study post-hoc analysis was included and calculated the inter-class distance between latent classes to determine which goodness-of-fit indices to prioritize in the context of the degree of separation.

For Aim 2, sensitivity analyses were run using G*Power (Faul et al., 2007) as a rough approximation of detectible effect size for the proposed regression analyses. For the current study, a total sample size of 202 was used. The effect size that can be detected when assuming the present study is adequately powered at 80% is $f^2 = .08$, which represents a small effect. Additionally, the inclusion of interaction parameters likely renders the sample underpowered to detect small effects. Despite being underpowered, the study aims to add to the literature on a historically understudied group.

CHAPTER THREE

RESULTS

Preliminary Analyses

Descriptive statistics for all key study variables are reported in Table 5. After creating composite scores, all variables were examined for outliers, internal consistency, and skewness. Multiple outliers (as defined by a z-score > |4|) were identified and removed. Specifically, two participants were excluded because of the PA variable; one participant for the immediate memory variable, one for the flanker inhibitory control test, two for the DCCS task switching, and three for TMT-B (total of 9 excluded) leaving a total analytic sample of 193 participants. All measures had a good internal consistency (α >0.8).

Pearson and Kendall Tau's correlations were conducted to examine associations between performance-based tasks, psychological and behavioral factors, as well as demographic and cardiovascular and metabolic health factors (see Table 5). Results revealed several significant correlations between age and cognitive performance, sleep disturbance, household size, and menopause staging. Specifically, negative associations between age and picture sequencing, verbal learning, processing speed, inhibitory control, and task switching were observed, suggesting that as age increases abilities decrease. Interestingly, there were no significant associations with age and other tasks including verbal memory, picture vocabulary, working memory, and divided attention. Notably, education was significantly positively associated with all performance-based cognitive tasks *except* for the working memory. Sleep disturbance was significantly and positively associated with perceived stress, anger-affect, and menopause

Table 5. Means, Standard Deviations, and Correlations of Key Study Variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1. Age	-																					
2. Picture Sequence	-.233**	-																				
3. Short Delay	-.138	.196*	-																			
4. Total Learning	-.154*	.450**	.699**	-																		
5. Processing Speed	-.273**	.222**	.144	.234**	-																	
6. Picture Vocabulary	.049	.365**	.294**	.409**	.291**	-																
7. Working Memory	-.093	.345**	.235**	.316**	.271**	.486**	-															
8. Inhibitory Control	-.174*	.350**	.208**	.399**	.553**	.380**	.291**	-														
9. Task Switching	-.171*	.269**	.177*	.315**	.475**	.394**	.351**	.655**	-													
	-.037	.311**	.229**	.329**	.375**	.512**	.427**	.446**	.484**	-												
10. Divided Attention																						
	.178*	-.015	-.047	-.027	.105	.050	.082	.004	-.122	-.045	-											
11. Sleep Disturbance																						
12. Perceived Stress	-.097	-.019	-.001	.046	.176*	-.018	-.062	.210**	.074	.018	.284**	-										
13. Physical Activity	-.122	-.142	-.110	-.171*	-.059	-.090	-.036	-.096	-.061	-.009	-.052	-.012	-									
14. Education	-.078	.220**	.257**	.370**	.162*	.375**	.115	.277**	.170*	.204**	.000	-.058	-.116	-								
15. Sadness	-.028	-.234**	-.061	-.218**	-.021	-.206**	-.222**	-.092	-.179*	-.162*	.040	.057	.235**	-.042	-							
16. Fear-Affect	-.026	-.204**	-.064	-.186*	-.081	-.125	-.229**	-.140	-.146	-.149	.052	.277**	.063	-.046	.350**	-						
17. Anger-Affect	.012	-.151*	.011	-.072	.044	.038	-.019	-.050	-.133	-.081	.220**	.312**	.009	-.051	.351**	.554**	-					
18. BMI	-.118	-.081	-.107	-.141	-.077	-.071	-.082	-.141	-.165*	-.121	.037	.127	.094	-.208**	.083	.252**	.168*	-				
19. House Income	-.065	-.063	.013	.046	-.085	.100	.026	.016	-.069	-.019	-.224**	-.215**	-.026	.154*	.009	-.007	-.113	-.045	-			
20. Household Size	-.303**	.181*	.033	.074	.109	-.018	.021	.131	.092	.048	-.220**	.124	.032	-.003	-.001	.026	-.090	.023	.173*	-		
21. Pregnancies	-.018	-.010	-.040	-.079	.016	-.183*	-.048	-.041	-.086	.035	-.105	.125	.104	-.202**	.031	-.022	-.059	.173*	-.026	.555**	-	
22. Children	-.105	.085	-.101	-.125	.000	-.061	-.019	.010	-.067	.049	-.060	.048	.178*	-.144	-.095	-.032	-.196*	.199*	.001	.482**	.708**	-
	.690**	-.139*	-.100	-.078	-.210**	.056	-.135	-.138*	-.072	-.065	.136*	-.161*	-.040	-.103	-.051	-.081	-.070	-.109	-.097	-.249**	-.023	-.095
23. [a]Menopause Stage																						
Mean (SD)	50.4(6.4)	107(15)	5.7(1.8)	49.4(9.4)	106(16)	110(11)	103(12)	99(6.8)	106(7)	62" (27)	4.66(2.6)	23.3(6)	2871(2894)	17 (2)	9.1(2.7)	9.4(2.9)	13(3.4)	27.6(5.6)	98449	2.6(1.4)	2(1.5)	2.1(1.1)

Note. M and *SD* are used to represent mean and standard deviation, respectively. * Indicates $p < .05$. ** indicates $p < .01$; [a]Kendall's tau Correlation

staging, suggesting that worse sleep is associated with more stress, irritability, and later menopause staging. Small to medium-sized associations were observed between stress and fear-affect and irritability. Contrary to hypotheses and prior research, physical activity was positively associated with sadness and number of children and was negatively associated with verbal learning. Feelings of sadness were negatively associated with some performance-based cognitive tasks. Specifically, higher levels of reported sadness were associated with poorer performance in picture sequencing, verbal learning, picture vocabulary, working memory, task switching, and divided attention. Negative associations between sleep disturbance and annual household income and size emerged, suggesting those who have both more material wealth and people living in their household sleep better. Negative associations between perceived stress and household income were also observed.

Latent Profile Analysis

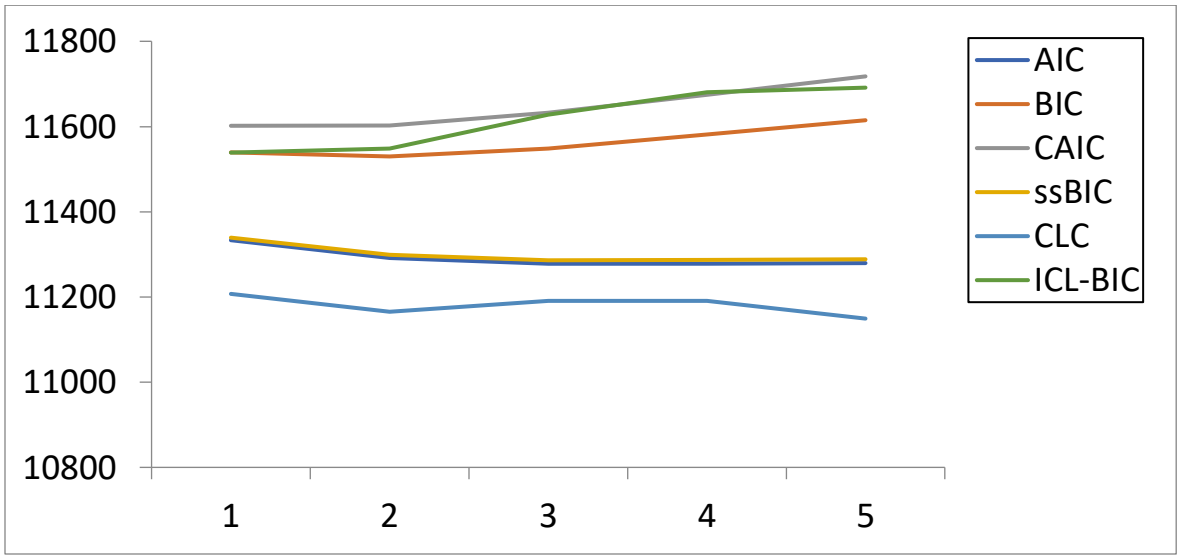
To elucidate cognitive profiles in a sample of midlife females utilizing nine performance-based cognitive tasks as indicators, two- through five-class LPAs were investigated while accounting for education on the indicator level (see Figure 2). Multiple class solutions had the lowest parsimony ICs, as a four-class solution had the lowest AIC, two-class solution had the lowest BIC and CAIC, and the three- and four-class solution had approximately the same, and lowest, SABIC (see Table 6). Next, the clustering IC statistics were examined, which revealed that the five- and two-class solution had the best fit. While deciding between a two-, three-, or four-class solutions, all IC statistics, prior research, and clinical utility were considered. The two-class solution was not chosen because there was large variability within class and a poor distribution between classes (24 vs. 169 participants). The three-class solution was not chosen because although it did technically have the lowest SABIC, this was only lower by 0.71 than the

four-class solution. Notably, when comparing the three- and four-class solutions, entropy statistics (CLC, NEC, and E) all favored a four-class solution. Finally, most parsimony and clustering ICs had less than a 10-point difference between three- and four- class solutions, which suggests that the three-class solution does not definitively fit better than the four-class solution for most ICs (Frankfurt et al., 2016). Taken together, a four-class solution was retained as the best model to fit the data based on the low log likelihood value, AIC, BIC, and SABIC values, high entropy value, a non-significant LMR test, the smallest class containing more than 5% of the sample, and the profiles demonstrating spread in verbal learning and memory tasks, which theoretically aligns with the extant literature. Finally, postdoc inter-class distance was calculated using Euclidean distances between centroids obtained from the latent profile analysis. The distances represent the dissimilarities between centroids of the latent profiles in a multidimensional space. Specifically, the distance between cognitive profile 1 and cognitive profile 2 is 1.28, indicating moderate dissimilarity between the two cognitive profiles. Similarly, the distance between cognitive profile 2 and cognitive profile 3 is approximately 1.26 (Tein et al., 2013).

Table 6. Fit Indices for Two-to-Five Class Solutions of Latent Profile Models

				Parsimony Criteria				**Clustering Criteria**			**Both**
Classes	**N**	**parms**	**LL**	**AIC**	**BIC**	**CAIC**	SABIC	**CLC**	**NEC**	**E**	**ICL-BIC**
2	193	73	-5572.800	11291.60	11529.78	11602.78	11298.53	11164.60	0.31	0.929	11548.77
3	193	83	-5556.100	11278.20	11549.00	11632.00	11286.08	11191.08	0.83	0.814	11627.88
4	193	93	-5545.980	11277.96	11581.39	11674.39	11286.79	11190.42	0.85	0.816	11679.85
5	193	103	-5536.340	11278.68	11614.74	11717.74	11288.46	11149.20	0.57	0.857	11691.26

Figure 2. Plot of Fit Indices for Class Enumeration



Note. To decide on the number of classes identified using LPA, several fit indices were calculated. This figure is a visualization of the differences in fit by plotting the values of the penalized likelihood indices.

These four profiles suggest that 6% of the sample (*n* = 11, Profile 1 "mixed") demonstrated strengths in pattern recognition and picture vocabulary, with weaknesses in verbal memory and inhibitory control. Profile 2 accounted for 39% of the sample (*n* = 76, Profile 2 "weakness in verbal learning and memory") whose performance revealed a weakness in verbal learning and memory. Another 12% of the sample (*n* = 23, Profile 3 "weakness in executive functions") demonstrated weakness in divided attention, picture vocabulary, working memory, and task switching. Finally, the majority (43%) of individuals (*n* = 83, Profile 4 "strength in verbal learning and memory") demonstrated a strength in verbal learning and memory. Importantly, education was accounted for at the indicator level, meaning that these group differences are not due to educational attainment as the LPA accounted for the variance shared between indicators and education. Z-scores for the performance-based tasks for each of the groups are plotted in Figure 3 and displayed in Table 7.

Figure 3. Plot of Z-scores of Sadness and Fear Anxiety per Cognitive Profile

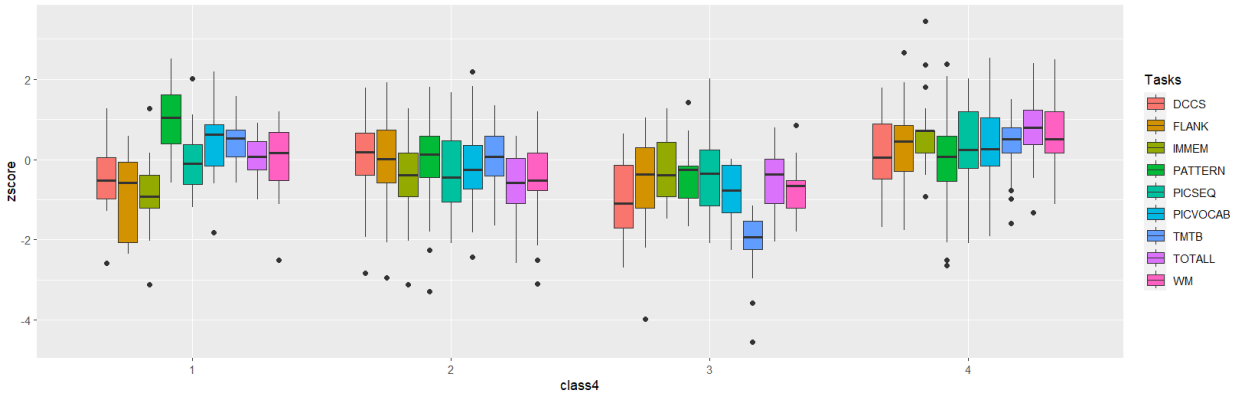


Table 7. Z-scores of Performance-based Cognitive Tasks per Cognitive Profile

Cognitive Tasks; *M (SD)*	"Mixed" Profile 1 *n*=11 *(6%)*	"Weakness in verbal learning & memory" Profile 2 *n*=76 (39%)	"Weakness in executive functions" Profile 3 *n*=23 (12%)	"Strength in verbal learning and memory" Profile 4 *n*=83 (43%)
Picture Sequence	0.02 (.95)	-0.28 (.94)	-0.38 (1.1)	0.35 (.95)
Short Delay – Verbal Memory	-0.88 (1.14)	-0.41 (.88)	-0.24 (.81)	0.56 (.84)
Total Verbal Learning	0.02 (.61)	-0.68 (.81)	-0.56 (.79)	0.77 (.63)
Processing Speed	0.96 (.89)	-0.02 (.95)	-0.45 (.80)	0.00 (1.03)
Picture Vocabulary	0.39 (1.09)	-0.22 (.92)	-0.83 (.73)	0.37 (.93)
Working Memory	-0.10 (1.06)	-0.39 (.90)	-0.75 (.65)	0.57 (.85)
Inhibitory Control	-0.91 (1.08)	0.01 (.97)	-0.61 (1.19)	0.29 (.80)
Task Switching	-0.50 (1.00)	0.16 (.98)	-0.99 (1.01)	0.20 (.84)
Divided Attention	0.41 (.63)	0.08 (.65)	-2.07 (.82)	0.44 (.54)

Characterization of Emergent Profiles

The four profiles were characterized based on demographic factors, cardiovascular and metabolic health indicators, and medication use by using K-W tests or Fisher's Exact tests for categorical variables (see Table 8). Though Fisher's Exact tests did not reveal differences in ethnicity (Hispanic or Latino vs. Non-Hispanic or Latino) between cognitive profiles, there were significant differences between cognitive profiles in terms of race ($\chi^2(12) = 35.4$, $p < .001$, $\varphi = .428$). Specifically, more Black females were represented in cognitive profile 2 "weakness in verbal learning and memory" (n = 25; %) than any other profile, and there were significantly more white females represented in cognitive profile 4 "strength in verbal learning and memory" (n = 64) than in cognitive profiles 1 "mixed" or 3 "weakness in executive functions" (see Table 8). Beyond racial differences between cognitive profile groups, differences emerged for hemoglobin A1c ($H(3) = 8.03$, $p = .045$, $\eta 2 = 0.03$). Results suggest a small effect size for hemoglobin A1c. Regarding hemoglobin A1c levels, cognitive profiles 3 and 4 were significantly different ($p = .016$) until multiple comparison corrections were applied ($p = .099$) (see Table 7). Medication use for blood pressure, cholesterol, psychotropic, hormonal birth control, hormone replacement therapy, and thyroid disease medications did not differ between the cognitive profile groups. All cognitive profile characteristics can be found in Table 8.

Table 8. Characteristics of Emergent Cognitive Profiles

Study Variable; *M (SD)*	"Mixed" Profile 1 *n*=11 *(6%)*	"Weakness in verbal learning & memory" Profile 2 *n* = 76 (39%)	"Weakness in executive functions" Profile 3 *n* = 23 (12%)	"Strength in verbal learning and memory" Profile 4 *n* = 83 (43%)	Significance
Age	50.7 (6.5)	50.4 (6.6)	50.5 (6.9)	50.4 (6.1)	$p = .993$
MoCA Total	27.2 (2.8)	26.2 (2.2) *	25.5 (2.2) *	27.9 (1.8) *	$p < .001$
Race[a]					$p < .001$
Asian	1 (8.3)	6 (50)	0	5 (41.7)	
Black or African American	0	25 (59.5)	9 (21.4)	8 (19)	
More than one race	0	4 (33.3)	2 (16.7)	6 (50)	
Unknown or not reported	1 (11.1)	5 (45.5)	3 (33.3)	0	
White	9 (7.6)	36 (30.5)	9 (7.6)	64 (54.2)	*118*
Ethnicity[a]					$p = .084$
Hispanic or Latino	2	15	7	8	
Not Hispanic or Latino	9	61	16	75	
Menopause Stage[a¥]					$p = .828$
Reproductive	4	18	7	20	
Perimenopause	1	11	2	17	
Post Menopause	3	26	7	23	
Blood Pressure Risk[a]					$p = .126$
At Risk	2	10	2	11	
Stage 1 High Blood Pressure	3	29	9	28	
Stage 2 High Blood Pressure	1	15	4	16	
Normal	5	22	6	28	
BMI	29.5 (5.5)	27.8 (6.4)	28.8 (4.9)	26.7 (4.9)	$p = .216$
Total Cholesterol	120.4 (28.4)	114.6 (27.8)	115.3 (31)	117.2 (27.4)	$p = .613$
Hemoglobin A1c (%)	5.2 (0.5)	5.4 (0.6)	5.4 (0.4)	5.2 (0.4)	$p = .045$
Albumin	4.4 (0.2)	4.4 (0.3)	4.4 (0.3)	4.4 (0.3)	$p = .621$
Creatinine	0.7 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	$p = .125$
Number of Medications	2.5 (1.5)	2.3 (1.9)	2.2 (1.7)	2..6 (2.0)	$p = .583$
Hormonal Birth Control	0 (0)	0.1 (0.2)	0 (0)	0 (0.2)	$p = .616$
HTR	0 (0)	0 (0.3)	0.1 (0.3)	0.1 (0.5)	$p = .322$
BP Medications	0 (0)	0.3 (0.6)	0.3 (0.5)	0.2 (0.4)	$p = .313$
Psychotropic Medications	0 (0)	0.2 (0.4)	0 (0.2)	0.3 (0.7)	$p = .175$
Cholesterol Medications	0 (0)	0.1 (0.3)	0.1 (0.3)	0.1 (0.2)	$p = .357$
Thyroid HRT	0.1 (0.3)	0 (0.2)	0.1 (0.3)	0.1 (0.3)	$p = .476$
Annual House Income	96,500 (66,167)	100,667 (154,259)	95,070 (110,858)	97,676 (59,536)	$p = .267$
Children	2.38 (1.4)	2.31 (1.2)	1.88 (1.2)	1.92 (.99)	$p = .242$

*Group differences via Wilcoxon rank sum tests; [a]Fisher's Exact Test; [¥] Confirmed Menopause Staging Sub Sample (n = 139)

Multinomial Logistic Regression

To predict the classification of participants into cognitive profiles, a multinomial logistic regression was conducted using the "normative" group (profile 4 "strength in verbal learning and memory") as the reference class. Preliminary inspection of the data did not indicate a possibility of multicollinearity. The multinomial logistic regression model used to predict membership via individual factors into one of the four cognitive profiles included the following predictors: sleep disturbance, physical activity, perceived stress, and depressive symptoms as measured by sadness, fear anxiety, and anger affect (irritability) scales. Overall, this model was significantly predictive of group classification, χ^2 (18) =30.55, p=.032; Nagelkerke R^2 = .246 and correctly classified 52.9% of all participants. Specifically, 71.6% of those in the cognitive profile 4, "strength in verbal learning and memory," were classified correctly. However, 0% of cognitive profile 1 "mixed", 53.6% of cognitive profile 2 "weakness in verbal learning and memory," and 10% of cognitive profile 3 "weakness in executive functions" participants were classified accurately. There were no significant findings between the reference group, cognitive profile 4 "strength in verbal learning and memory," and cognitive profile 1 "mixed." When classifying individuals into cognitive profile 4 "strength in verbal learning and memory" vs. cognitive profile 2 "weakness in verbal learning and memory," both sadness and fear anxiety emerged as significantly predictive. The results show that individuals in cognitive profile 2 "weakness in verbal learning and memory" reported greater levels of sadness and fear anxiety than compared to cognitive profile 4 "strength in verbal learning and memory" (sadness M = 9.6 vs.8.4; fear anxiety M = 9.9 vs. 8.7). When classifying individuals into cognitive profiles 3 "weakness in executive functions" and 4 "strengths in verbal learning and memory," only sadness emerged as significant. This means that individuals who were in cognitive profile 3 "weakness in executive

functions" reported significantly higher levels of sadness as compared to those in cognitive profile 4 "strengths in verbal learning and memory" (M = 10.3 vs. 8.4). Raw scores have been plotted for sadness and fear anxiety survey in Figure 4. In contrast to stated hypotheses, physical activity, sleep disturbance, perceived stress, and anger affect (irritability) did not significantly classify membership into any of the groups (see Table 9).

Table 9. Psychological and Behavioral Predictors for the Classification of Cognitive Profile Groups

						95% Confidence Interval for Exp(B)	
Cognitive Profiles[a]		B	Std. Error	Sig.	Exp(B)	Lower Bound	Upper Bound
1 Mixed	Intercept	-1.896	.352	<.001			
	Sadness	-.039	.153	.800	.962	.713	1.299
	Sleep Disturbance	-.026	.130	.840	.974	.755	1.256
	Total PA	.000	.000	.902	1.000	1.000	1.000
	Stress	.015	.064	.816	1.015	.896	1.150
	Fear anxiety	.101	.166	.544	1.106	.799	1.532
	Irritability	.078	.128	.541	1.081	.841	1.391
2 Weakness in verbal learning and memory	Intercept	-.047	.182	.797			
	Sadness	.161	.076	.034	1.175	1.012	1.364
	Sleep Disturbance	-.106	.074	.151	.900	.779	1.039
	Total PA	.000	.000	.905	1.000	1.000	1.000
	Stress	.011	.033	.734	1.011	.947	1.080
	Fear anxiety	.223	.094	.017	1.250	1.040	1.503
	Irritability	-.102	.082	.211	.903	.769	1.060
3 Weakness in executive functions	Intercept	-1.411	.293	<.001			
	Sadness	.234	.111	.035	1.264	1.016	1.572
	Sleep Disturbance	.111	.104	.286	1.117	.911	1.369
	Total PA	.000	.000	.254	1.000	1.000	1.000
	Stress	-.060	.050	.230	.942	.854	1.039
	Fear anxiety	.180	.126	.156	1.197	.934	1.533
	Irritability	-.006	.112	.960	.994	.799	1.237

[a]The reference category is: Cognitive Profile 4 (strength in verbal learning and memory).

Menopause Stage as a Moderator

Because the subsample of females with confirmed menopause staging reduced the total sample from 193 to 139 individuals, a Fisher's Exact test of cognitive profile by menopause stage was utilized. This revealed some cells only included as low as 1 participant with others containing 2 or 3 (see Table 8). When it was determined that there was insufficient power to predict membership into the four cognitive profiles identified through Aim 1 with a categorical moderator due to unacceptable cell sizes, cognitive profiles 1 "mixed" and 3 "weakness in executive functions" were removed for multiple reasons. First, these profiles were significantly smaller than the others. Second, cognitive profile 2 is marked by significantly worse verbal learning and memory than cognitive profile 4 which had notable strengths in verbal learning and memory. Theoretically, verbal learning and memory are cognitive functions most supported by the literature as being impacted during the menopausal transition (Maki & Weber, 2021; Weber et al., 2013). Therefore, to investigate whether confirmed menopause staging moderated the effects of psychological and behavioral factors in predicting membership in the cognitive profiles, the two profiles with contrasting performance in verbal learning and memory and sufficient power were retained given adequate sample size and theoretical relevance (see Table 8 and Figure 4). Next, logistic regression was performed to examine whether sleep disturbance, physical activity, perceived stress, depressive symptoms (i.e., sadness, fear anxiety, anger affect (irritability), menopause stage, and interaction effects of menopause stage on these variables predicted group membership into cognitive profile 2 "weakness in verbal learning and memory" or 4 "strength in verbal learning and memory." Overall, the model which included sleep disturbance, physical activity, perceived stress, sadness, fear anxiety, anger affect (irritability), menopause stage, and interaction effects of menopause stage on these variables was not

significantly predictive of profile classification, χ^2 (13) =21.78, p = .059; Nagelkerke R^2 = .252 but correctly classified 68.3% of all participants. Specifically, 60% of those in cognitive profile 2 "weakness in verbal learning and memory" and 75.9% of those in cognitive profile 4 "strength in verbal learning and memory" were classified correctly. The overall model did not reach statistical significance and there were no significant main or interaction effects observed (see Table 10). Additionally, because race emerged as significantly different between cognitive profiles and the literature documents existing health disparities in reproductive aging (Cortés & Marginean, 2022; Harlow et al., 2022; Paramsothy et al., 2017), a post hoc analysis was conducted that additionally included race and the interaction effects of menopause stage on race in a logistic regression.

Figure 4. Plot of Z-scores of Sadness and Fear Anxiety per Cognitive Profile

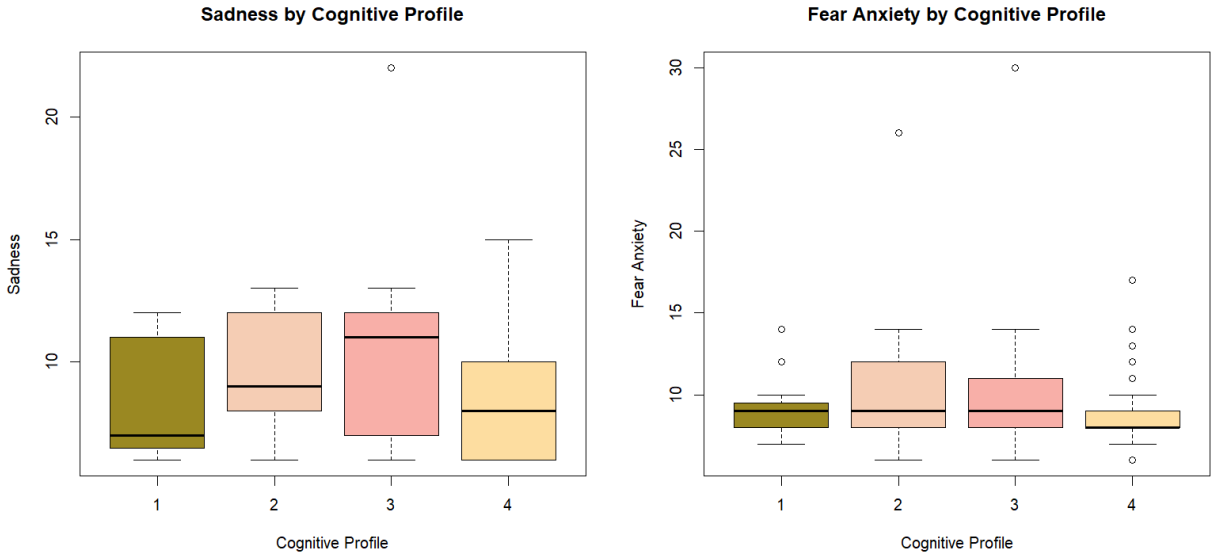
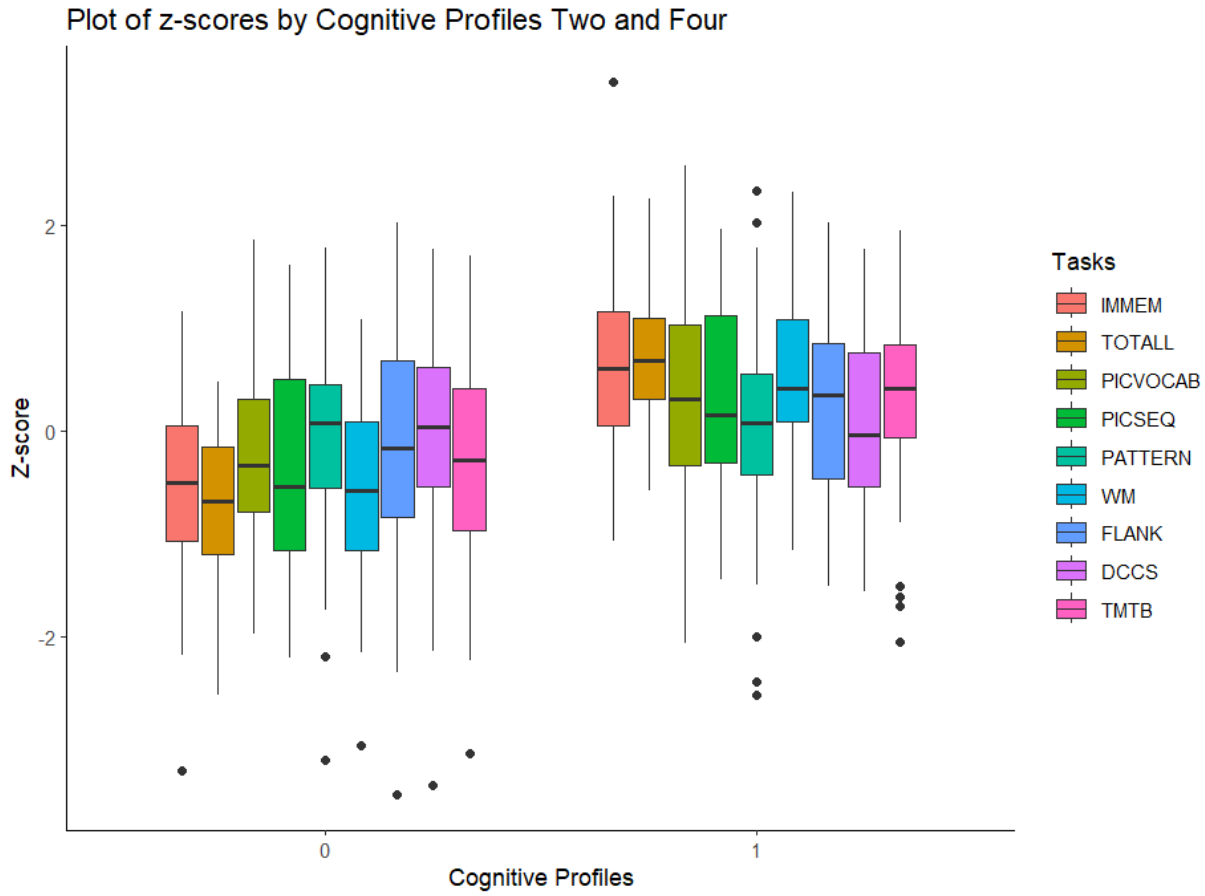


Table 10. Interaction Between Menopause Stage and Predictors for the Classification of Cognitive Profile 2 (Weakness in verbal learning and memory) and 4 (Strength in verbal learning and memory)

Variables in the Equation	B	S.E.	Wald	df	Sig.	Exp(B)
Sleep Disturbance	.143	.160	.799	1	.371	1.154
Total PA	.000	.000	.151	1	.698	1.000
Stress	.136	.085	2.563	1	.109	1.146
Sadness	-.242	.159	2.317	1	.128	.785
Fear anxiety	-.416	.251	2.742	1	.098	.660
Irritability	.104	.178	.342	1	.558	1.110
Menopause Stage	-.160	.281	.322	1	.571	.852
Sleep x MS	-.005	.110	.002	1	.962	.995
PA x MS	.000	.000	.381	1	.537	1.000
Stress x MS	-.072	.054	1.749	1	.186	.931
Sadness x MS	.000	.112	.000	1	.997	1.000
Fear anxiety x MS	.094	.160	.350	1	.554	1.099
Irritability x MS	.063	.140	.202	1	.653	1.065
Constant	.342	.402	.725	1	.395	1.408

MS = Menopause Stage

Figure 5. Plot of Z-scores of Cognitive Tasks per Cognitive Profile's Two and Four



CHAPTER FOUR

DISCUSSION

This study aimed to provide a greater understanding of cognitive functioning during midlife in females- a group that is disproportionately affected by AD – and chronically understudied. The purpose of this study was to use a data-driven approach to characterize the heterogeneity in performance-based cognitive functioning in a sample of midlife females and to provide much-needed clarity on objectively measured cognitive outcomes of this crucial transitional period in the context of individual psychological and behavioral factors. To better understand the complexities of cognitive functioning in midlife - a time marked by hormonal shifts that impact psychological and behavioral factors - this study first elucidated cognitive profiles and then characterized emergent profiles in terms of psychological, behavioral, demographic, cardiovascular and metabolic health indicators, and medication use, including hormone replacement therapy (HRT). Additionally, this study sought to extend prior research suggesting that female midlife cognitive functioning is related to psychological and behavioral factors by investigating emergent cognitive profiles to better understand how psychological and behavioral factors might contribute. Prior research has demonstrated a positive association between cognitive functioning and various psychological (e.g., depressive symptoms, psychological stress) and behavioral (e.g., sleep disturbance, physical activity) factors, but most of these studies are either cross-sectional in nature, did not include cognitive profiles, or did not use a person-centered approach. No prior research has examined cross-sectional cognitive

profiles in conjunction with measures of psychological, behavioral, demographic, and cardiovascular and metabolic health factors in relation to menopause staging.

Preliminary analyses revealed that older age was significantly associated with worse performance on picture sequencing, verbal learning, processing speed, inhibitory control, and task switching but *not* verbal memory, picture vocabulary working memory or divided attention. This finding is interesting because prior research suggests that cognitive abilities decline over the lifespan (Dahl et al., 2013; Dixon et al., 2021; Narbutas et al., 2019). As expected, higher education was significantly associated with better performance across cognitive domains, except within the working memory task. Not surprisingly, higher household income and size was associated with less stress and better sleep. Contrary to prior research, more physical activity was related to more feelings of sadness. Negative associations between sadness and picture sequencing, verbal learning, picture vocabulary, working memory, task switching, and divided attention were observed. Indeed, this aligns with prior research suggesting that negative mood states impact executive function via alterations in the fronto-parietal and DMN networks (Brzezicka, 2013).

A crucial takeaway of this study is that distinct patterns of cognitive performance emerged from the analytic sample. After accounting for educational attainment, four distinct cognitive profiles were identified in the current analytic sample that significantly differed based on race and hemoglobin A1c levels. Cognitive profiles are often used in clinical evaluations to determine patterns of strengths and weaknesses, which aid in the understanding of cognitive functioning across the menopausal transition. The current study documented profiles that were distinguished by strengths and weaknesses in various cognitive domains. For example, profile 1 was notable for mixed performance such as weaknesses in verbal memory and inhibitory control

but had better performances in pattern recognition and picture vocabulary tasks. Profile 2 was notable for a weakness in verbal learning and memory, while profile 3 demonstrated weaknesses in many executive function tasks (divided attention, working memory, task switching). Finally, profile 4, which included most of the participants (43%) demonstrated strengths in verbal learning and memory. The current study is the first to use this type of data-driven analysis to investigate psychological and behavioral differences between identified groups. By comparing these profiles via potentially modifiable factors - not just demographic information - possible interventions can be explored further. Specifically, the study aimed to determine whether specific individual factors (i.e., sleep, physical activity, and psychological wellbeing) significantly differentiated certain cognitive profiles.

The current study found that higher levels of depressive symptoms, specifically sadness and fear anxiety symptoms, significantly classified membership into the cognitive profile 2 which was marked by a weakness in verbal learning and memory and cognitive profile 3 which was marked by executive dysfunction. This finding is important for many reasons. First, it aligns with research that documents an association between depressive symptoms and cognitive functioning, and second, it highlights the importance of screening for depressive symptoms in females spanning the menopausal transition. Mood symptoms are well documented to have associations with cognitive functioning, which additionally impacts quality of life and ability to engage in vocational and social activities. For example, one study in older adults found that cognitive functioning (executive function and episodic memory domains) and depressive symptoms significantly impacted activities of daily living (De Paula et al., 2015). Furthermore, cognitive deficits in executive function, memory, attention, and learning were found to have a considerable impact on vocational functioning, particularly in remitted depressive disorder

(Woods et al., 2016). However, contrary to stated hypotheses, in the sub-sample of females with confirmed menopause staging, no interaction effects emerged, suggesting that the association between depressive symptoms and cognitive profiles did not differ based on menopause stage. Research indeed suggests that there are key differences between pre-peri- and post-menopausal levels of mood and sleep symptoms, though this variation was not identified in the current study via interaction effects.

Importantly, race significantly differed between cognitive profiles as demonstrated in Table 8. The cognitive profile marked by a weakness in verbal learning and memory (profile 2) had significantly more Black females than the other profiles, while profile 4, marked by strengths in verbal learning and memory, had more white females. However, there were no significant differences between race and menopause stage. Considering the enormous menopause symptom burden shouldered by racially marginalized females, it is interesting that the cognitive profile observed to have weakness in verbal learning and memory (i.e., cognitive functions most notably impacted across the menopausal transition) is comprised of a disproportionate number of Black females as compared to other profiles. Though there were no observed differences between menopause stage and cognitive profile or menopause stage and race, it may be that known menopause symptoms (e.g., disruptive hot flashes, sleep disturbance, and mood changes) were felt disproportionally by Black participants, helping explain the current findings. Of note, not only are there known health disparities in the context of reproductive aging, but there also continues to be discussion regarding racial and ethnic biases identified within neuropsychological assessments that impact both the evaluation and treatment of individuals from diverse backgrounds in the context of cognitive evaluations. For example, Cory (2021) delineates examples of how white privilege within neuropsychology contributes to and

perpetuates health care disparities. Indeed, the field continues to grapple with these detrimental issues, including the lack of appropriately validated instruments and normative comparison data available for ethnically and linguistically diverse individuals (Hilsabeck & Rivera Mindt, 2021). For instance, neuropsychological research, including test development, validation, and normative data studies are often lacking in regards to representation of Black individuals (Pugh et al., 2022; Ray et al., 2022) which has clear and dangerous implications for evaluating cognitive functioning in addition to appropriately evaluating differential diagnoses. Byrd and Rivera-Mindt (2022) aptly point out that neuropsychology is rife with racial disparities and as a field needs to work toward ameliorating the need for race-based norms by focusing on the systemic inequities that create a need for race-based norms in the first place.

Considering the intersection of racial and gender identities, Black females face psychosocial stressors that are known to negatively impact psychological, physical, and cognitive health. In the context of subjective cognitive complaints, one study found that experiences of gendered racism across the lifespan were significantly associated with subjective cognitive complaints in older Black and African American females. Interestingly, this association was mediated by depressive symptoms and disengagement coping techniques (Hill-Jarrett & Jones, 2022). Additionally, Dixon and colleagues (2021) conducted longitudinal research using the SWAN study data investigating predictors of cognitive decline during midlife which revealed significant and important findings that depressive symptoms predicted poor cognitive functioning in Black females but not Asian American or white females. The current study indeed found that depressive symptoms as well as race significantly differed between cognitive profiles, though mediating effects were not evaluated nor were subjective cognitive complaints evaluated. Research has delineated clear associations between experiences of racism

at the institutional, cultural, and individual level and depressive symptoms in Black females as well as the deleterious effects of systematic oppression on mental and physical health (Lewis et al., 2017; Moise & Hankerson, 2021). In sum, to address the existing racial health disparities in both reproductive aging and cognitive health, it is imperative that researchers and clinicians advocate for the eradication of systemic oppression and challenge systems of power that continue to marginalize Black females.

Limitations and Future Directions

There were several limitations to this study. First, there are noteworthy sampling limitations. The sample is majority white (60+), highly educated, and socioeconomically secure. Secondly, the current study includes only 139 participants with a confirmed menopause stage. This greatly limited the statistical power needed to evaluate differences between menopause stages as sensitivity analyses demonstrated that even small effect sizes may not be possible with this sample size. In the current study, no association was found between LPA-identified cognitive profiles and sleep disturbance, physical activity, perceived stress, or irritability. Prior cross-sectional research would suggest that these constructs would be predictive of cognitive profile membership due to the robust association between sleep, physical activity, stress, and cognitive function, but these variables did not reach significance in classifying individuals into cognitive profiles. For example, research has shown that high PA levels are associated with a lower incidence of menopausal symptoms and those with low PA levels reported more severe menopausal symptoms such as vasomotor (e.g., hot flashes, night sweats), vaginal dryness, depression, irritability, headache, and sleep disturbance (Dąbrowska-Galas et al., 2019; El Hajj et al., 2020). Similarly, the literature suggests a strong association between perceived stress and cognitive functioning. In a recent longitudinal study, Christensen and colleagues (2023) found

that after a 29-year interval, higher perceived stress during midlife predicted greater decline in IQ after accounting for educational attainment, prior IQ performance, and parental socioeconomic factors. However, the current study did not document any associations between PA, perceived stress, cognitive profiles, or menopause stage. As discussed previously, this may be due to the uneven distribution of participants between subgroups, for example in multinomial logistic regressions it is much harder to classify smaller groups. The current study had a group that was comprised of only 11 individuals. This greatly limited the study.

In addition to sampling limitations, physical activity was operationalized via a self-report while objective measures of physical activity would better capture this construct. Future research should utilize accelerometer or performance-based measures of PA and sleep as research using self-report is often biased. Additionally, a significant limitation in the current study is the lack of menopause symptom reporting, such as vasomotor symptoms (hot flashes). There are widely used, well validated self-report questionnaires such as the Menopause Rating Scale (MRS) (Heinemann et al., 2016), the MenoScores questionnaire (Lund et al., 2018) and the Menopause-Specific Quality of Life (MENQOL) questionnaire (Hilditch et al., 1996; Koo et al., 2017) which would have greatly benefited the current study by allowing for investigation and further understanding of subjective experiences of menopause symptoms on cognitive performance. Additionally, measuring menopause symptoms such as vasomotor symptoms and sleep objectively would also be advantageous. Research has demonstrated that objectively measured vasomotor symptoms and sleep are associated with white matter hyperintensities, particularly for females experiencing night-time hot flashes, most consistently associated with hyperintensities within the frontal lobe (Thurston et al., 2023). This is interesting because frontal lobe damage has been associated with depressive symptoms (Pizzagalli & Roberts, 2022). Another limitation

is that the current study did not properly evaluate experiences of anhedonia, a key symptom of depression.

Future research could address some of the limitations of the current study. Including data that evaluates both subjective cognitive complaints and objective cognitive performance in the context of objectively measured vasomotor symptoms, sleep, and physical activity is advised. Additionally, the current study is cross-sectional. Following individuals across the menopausal transition would yield far more reliable information regarding associations between cognitive performance, depressive symptoms, behavioral factors, and cardiovascular and metabolic health indicators. Additionally, accounting for premorbid IQ as opposed to education is advised, as education is merely a proxy for premorbid intelligence, and other factors such as oral reading performance may be a better indicator.

Further research is also needed to establish causal relations between depressive symptoms, menopause stage, and specific cognitive outcomes to develop effective interventions for improving cognitive functioning during and beyond. Indeed, this study confirms prior research findings that suggest negative mood states, particularly sadness and anxiety, are prevalent during the menopausal transition and are related to verbal learning and memory. Finally, health inequities need further investigation and careful attention as the current study documented that race significantly differed between emergent cognitive profiles. As the extant literature has clearly documented, Black females have a higher menopause symptom burden which contributes to and is a result of greater health inequities experienced by this historically and currently marginalized population. Future research should investigate cardiovascular and metabolic health risks as it relates to menopause symptoms and length of menopausal transition

in Black females to help develop tailored interventions in hope to mitigate subjective experiences of cognitive disruptions during this transition.

Conclusion

The menopausal transition is an inevitable experience for half the population, whether induced by surgery or medications or through the natural reproductive aging process. Research has documented significant psychological, behavioral, biological, and social shifts that occur during this developmental period that impact quality of life, including significant vasomotor symptoms, increases in negative mood states, disrupted sleep, and, for some, cognitive difficulties (Maki & Weber, 2021; Weber et al., 2013, 2014). Identifying those who might be at higher risk for worse cognitive, psychological, or behavioral outcomes is critical. The complexity of menopause symptoms certainly requires more research, primarily directed at understanding the unique forms of stress and coping mechanisms related to menopause including those unique to sexual and racial minoritized females as they experience heightened chronic stress due to structural racism and heteronormative cultures (Everett et al., 2021). The current study documented four distinct cognitive profiles which were significantly different based on race, with the females in the profile group marked by weaknesses in verbal learning and memory reporting significantly high levels of depressive symptoms. Considering these findings, clinicians might ponder early intervention for females entering late reproductive stages who have a history of mood disorder or come from a marginalized background. In sum, the current study examined an understudied population and examined whether psychological and behavioral factors differentiated cognitive profiles across the menopausal transition. Distinct cognitive profiles emerged with clear strengths and weaknesses, with higher levels of depressive symptoms significantly classifying individuals into profiles with weaknesses in verbal learning and

memory. Though menopause stage did not moderate this association, the current study reinforces the need for clinicians to examine and treat depressive symptoms for midlife females.

APPENDIX A

DEMOGRAPHIC INFORMATION

1. Date of Birth _____

2. Age (in years) _____

3. Race
    a. American Indian or Alaska Native
    b. Asian
    c. Hawaiian or Pacific Island
    d. Black or African American
    e. White
    f. More than one race
    g. Unknown or not reported

4. Ethnicity
    a. Hispanic or Latino
    b. Not Hispanic or Latino
    c. Unknown or not reported

5. Years of Education Completed
    a. 1st grade
    b. 2nd grade
    c. 3rd grade
    d. 4th grade
    e. 5th grade
    f. 6th grade
    g. 7th grade
    h. 8th grade
    i. 9th grade
    j. 10th grade
    k. 11th grade
    l. 12th grade, no diploma
    m. High school graduate
    n. GED or equivalent
    o. Some college, no degree
    p. Associate degree: occupational, technical, or vocational program
    q. Associate degree: academic program
    r. Bachelor's degree (BA, AB, BS, BBA)
    s. Master’s degree (MA, MS, MENG, MED, MBA
    t. Professional school degree (MD, DDS, DVM, JD)
    u. Doctoral degree (PhD, EDD)

6. Are you presently married or are you widowed, separated, divorced, living as married, or have you never been married? [CODE RELIGIOUS ANNULMENT AS DIVORCED. CODE LEGAL ANNULMENT AS NEVER MARRIED]

a. Never married
b. Living with partner
c. Married
d. Separated
e. Divorced
f. Widowed

7. How many times have you been pregnant?
   [FREE TEXT]

8. What is your current household size?
   [FREE TEXT]

9. How many children have you had, not counting any who are yours by adoption, who are stepchildren, or who were stillborn?
   [FREE TEXT]

10. What is your current household gross income? Please state your TOTAL COMBINED FAMILY INCOME for the past 12 months? This should include income (before taxes and deductions) from all sources, wages, rent from properties, social security, disability and/or veteran's benefits, unemployment benefits, workman's compensation, help from relatives (including child payments and alimony), and so on.
    [FREE TEXT]

APPENDIX B

PITTSBURG SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?
   BED TIME _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? NUMBER OF MINUTES ___
3. During the past month, what time have you usually gotten up in the morning?
   GETTING UP TIME _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)
   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

f) Feel too cold

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

g) Feel too hot

Not during the	Less than	Once or twice	Three or more

past month_____ once a week_____ a week_____ times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe

How often during the past month have you had trouble sleeping because of this?
Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____ Fairly good _____ Fairly bad_____ Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____
Only a very slight problem _____
Somewhat of a problem _____
A very big problem

10. Do you have a bed partner or room mate?

No bed partner or room mate	_____
Partner/room mate in other room	_____
Partner in same room, but not same bed	_____
Partner in same bed	_____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
_____	_____	_____	_____

b) Long pauses between breaths while asleep

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
_____	_____	_____	_____

c) Legs twitching or jerking while you sleep

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
_____	_____	_____	_____

d) Episodes of disorientation or confusion during sleep

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
_____	_____	_____	_____

e) Other restlessness while you sleep; please describe _____

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
_____	_____	_____	_____

APPENDIX C

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   days per week _____ No vigorous physical activities→Skip to question 3

2. How much time did you usually spend doing vigorous physical activities on one of those days?

   hours per day _____

   minutes per day_____

   Don't know/Not sure

Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   days per week_____ No moderate physical activities →Skip to question 5

4. How much time did you usually spend doing moderate physical activities on one of those days?

   hours per day _____

   minutes per day_____

   Don't know/Not sure

Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?

   days per week_____ No walking → Skip to question 7

6. How much time did you usually spend walking on one of those days?

hours per day _____

minutes per day_____

Don’t know/Not sure

The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the last 7 days, how much time did you spend sitting on a week day?

hours per day _____

minutes per day_____

Don’t know/Not sure

This is the end of the questionnaire, thank you for participating.

APPENDIX D

PERCEIVED STRESS – FIXED FORM

Please respond to each question or statement by marking one box per row.

	In the past month…	Never	Almost Never	Sometimes	Fairly Often	Very Often
SC001	How often have you been upset because of something that happened unexpectedly?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC002	How often have you felt that you were unable to control the important things in your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC003	How often have you felt nervous and "stressed"?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC006_R	How often have you felt confident about your ability to handle your personal problems?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC007_R	How often have you felt that things were going your way?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC008	How often have you found that you could not cope with all the things that you had to do?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC009_R	How often have you been able to control irritations in your life?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC010_R	How often have you felt that you were on top of things?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC011	How often have you been angered because of things that happened that were outside of your control?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC014	How often have you felt difficulties were piling up so high that you could not overcome them?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

APPENDIX E

SADNESS/DEPRESSION – ITEM BANK

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
Depression30	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression31	I felt that I had nothing to look forward to	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression32	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression33	I withdrew from other people.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression34	I felt that nothing could cheer me up.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression35	I felt that I was not as good as other people.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression36	I felt sad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression37	I felt that I wanted to give up on everything.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression38	I felt that I was to blame for things	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression39	I felt like a failure	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Depression40	I had trouble feeling close to people.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression41	I felt disappointed in myself	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression42	I felt that I was not needed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression43	I felt lonely	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression44	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression45	I had trouble making decisions	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression46	I felt discouraged about the future	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression47	I found that things in my life were overwhelming	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression48	I felt unhappy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression49	I felt I had no reason for living	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression50	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Depression51	I felt ignored by people	□ 1	□ 2	□ 3	□ 4	□ 5
Depression52	I felt upset for no reason	□ 1	□ 2	□ 3	□ 4	□ 5
Depression53	I felt that nothing was interesting	□ 1	□ 2	□ 3	□ 4	□ 5
Depression54	I felt pessimistic.	□ 1	□ 2	□ 3	□ 4	□ 5
Depression55	I felt that my life was empty	□ 1	□ 2	□ 3	□ 4	□ 5
Depression56	I felt guilty	□ 1	□ 2	□ 3	□ 4	□ 5
Depression57	I felt emotionally exhausted.	□ 1	□ 2	□ 3	□ 4	□ 5

ITEM BANKS ARE NOT INTENDED TO BE ADMINISTERED IN THEIR ENTIRETY.

APPENDIX F

FEAR ANXIETY – ITEM BANK

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Anxiety36	I felt fearful	□ 1	□ 2	□ 3	□ 4	□ 5
Anxiety37	I felt frightened.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anxiety38	It scared me when I felt nervous	□ 1	□ 2	□ 3	□ 4	□ 5
Anxiety39	I felt anxious.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anxiety40	I felt like I needed help for my anxiety	□ 1	□ 2	□ 3	□ 4	□ 5
Anxiety41	I was concerned about my mental health..	□ 1	□ 2	□ 3	□ 4	□ 5
Anxiety42	I felt upset	□ 1	□ 2	□ 3	□ 4	□ 5
Anxiety43	I had a racing or pounding heart.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anxiety44	I was anxious if my normal routine was disturbed.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anxiety45	I had sudden feelings of panic.....	□ 1	□ 2	□ 3	□ 4	□ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Anxiety46	I was easily startled	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety47	I had trouble paying attention	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety48	I avoided public places or activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety49	I felt fidgety.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety50	I felt something awful would happen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety51	I felt worried.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety52	I felt terrified.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety53	I worried about other people's reactions to me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety54	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety55	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety56	I had twitching or trembling muscles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Anxiety57	I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety58	I felt indecisive.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety59	Many situations made me worry.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety60	I had difficulty sleeping.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety61	I had trouble relaxing.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety62	I felt uneasy.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety63	I felt tense.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anxiety64	I had difficulty calming down.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

ITEM BANKS ARE NOT INTENDED TO BE ADMINISTERED IN THEIR ENTIRETY.

APPENDIX G

ANGER – ITEM BANK

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Anger30	When I was frustrated, I let it show.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anger31	I was irritated more than people knew.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anger32	I felt envious of others.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anger33	I disagreed with people	□ 1	□ 2	□ 3	□ 4	□ 5
Anger36	I felt angry	□ 1	□ 2	□ 3	□ 4	□ 5
Anger37	When I was mad at someone, I gave them the silent treatment.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anger38	I felt like breaking things.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anger39	I felt like I was ready to explode.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anger40	When I was angry, I sulked.....	□ 1	□ 2	□ 3	□ 4	□ 5
Anger41	I felt resentful when I didn't get my way...	□ 1	□ 2	□ 3	□ 4	□ 5
Anger42	I felt guilty about my anger	□ 1	□ 2	□ 3	□ 4	□ 5
Anger43	I felt bitter about things.....	□ 1	□ 2	□ 3	□ 4	□ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Anger44	I felt that people were trying to anger me .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anger46	I held grudges towards others.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anger48	I was grouchy.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anger49	I was stubborn with others.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anger50	I felt annoyed.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anger51	I had a bad temper.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anger52	I had trouble controlling my temper	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anger55	I felt like I needed help for my anger.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Anger57	I felt like yelling at someone	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		Not at all	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Anger58	Just being around people irritated me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

ITEM BANKS ARE NOT INTENDED TO BE ADMINISTERED IN THEIR ENTIRETY.

APPENDIX I

MENSTURAL STATE AND HISTORY SURVEY

1. At what age did your menstrual cycle begin? _____ years
2. Hypothyroidism? 1=Yes; 2=No
3. Hypothyroidism age at onset ____ Years
4. Hyperthyroidism? 1=Yes; 2=No
5. Hyperthyroidism age at onset ____ Years
6. Do you have regular menstrual cycles? 1=Yes; 2=No
    a. IF NO, Explain:
7. About how long is (was) your entire cycle? (i.e. how long between start dates)
    a. 1= less than every 25 days;
    b. 2= between 25-35 days;
    c. 3= more than every 35 days
8. What was the first day of your most recent menstrual cycle [DATE]
9. Other Endocrine problem. 0 = No;1 = Yes
    a. IF YES, Other Endocrine problem Age at onset (years)
10. Have you had a period in the past year (12 months)? 1 = Yes ; 0 = No
11. When was your last period? Choose one of the following.
    a. 1 = less than two years ago;
    b. 2 = 2-3 years ago;
    c. 3 = 3-6 years ago;
    d. 4 = more than 6 years ago
12. Why do you think your periods stopped? Please choose the best answer below. (read through all).

a. 1 = They stopped naturally as a I grew older and became postmenopausal - done with 'the change'?;
b. 2 = I have had a hysterectomy or endometrial ablation;
c. 3 = I am pregnant or breast feeding;
d. 4 = I am taking medications such as a birth control injection or an intrauterine device (e.g., Mirena IUD) that makes my periods stop;
e. 5 = I had chemotherapy and/or other treatments for cancer, and my periods stopped;
f. 6 = I have dramatic weight loss (for example due to HIV or other medical condition or stressful/traumatic life experience) and my periods stopped. ;
g. 7 = Other;
    i. Why do you think your periods stopped? If other, fill in:
h. 999 = Don't know

13. In the past 12 months, have you skipped or missed a period? In other words, have you ever gone 60 days, or two months, without a period? 1 = Yes; 0 = No
14. Did you skip periods because you are getting older? 1 = Yes; 0 = No; 999 = Don't Know
15. Choose one of the following reasons why you skipped periods.
    a. 1 = I am/was pregnant or breast feeding. ;
    b. 2 = I have had a hysterectomy or endometrial ablation;
    c. 3 = I am/was taking medications such as a birth control injection that makes my periods stop;
    d. 4 = I had chemotherapy and my periods stopped;
    e. 5 = Other;

i. If other, fill in:

f. 999 = Don't know

16. Have you noticed that your period comes earlier or later than you expected? 1 = Yes; 0 = No
17. Has your period come late or early by at least a week? 1 = Yes; 0 = No; 999 = Don't Know
18. Did that happen two times or more over the past year (12 months)? 1 = Yes; 0 = No
19. Have you noticed that the length of your period (# of bleeding days) is shorter or longer than usual for you? 1 = Yes; 0 = No ; 999 = Don't Know
20. Have you noticed that the amount of bleeding during your period is more or less compared to what is normal for you? 1 = Yes; 0 = No ; 999 = Don't Know

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VITA

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