STRESS, SLEEP, INFLAMMATION, AND COGNITIVE ABILITY

by

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ABSTRACT

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Under the direction of DR. JANE GAULTNEY

Psychological stress, defined as a relationship between the person and their socioenvironmental context that is appraised as exhausting the resources of a person, has long been shown to affect concurrent and long-term health outcomes. Previous research has focused on the bidirectional natures of stress with biopsychosocial constructs, including sleep, inflammation, and cognition. However, how these factors may be interrelated has been largely unexplored. Thus, our aim was to investigate via multiple path analyses the direct and indirect effects of stress on sleep, inflammation (C-reactive protein, tumor necrosis factor-alpha, and interleukin-6), and concurrent and longitudinal cognitive functioning in middle-aged US adults. Results indicated that stress was a significant predictor of concurrent sleep quality and inflammation. Cross-sectional analyses indicated that there was some support for a pathway from stress to cognitive functioning via sleep and C-reactive protein; however, longitudinally these findings were not replicated when we controlled for cognition at time 1, potentially indicating that the effects of stress on cognition are consistent over time among middle-aged adults. An exploratory moderated mediation indicated that age and sex may mediate the indirect relationship of stress on cognition via inflammation. Overall, we found that to encourage healthy aging and limit cognitive decline over time, stress and inflammation reduction efforts, along with treatment for sleep issues, may improve outcomes among middle-aged adults.

Keywords: Stress, Sleep, Inflammation, Cognition, Middle-Aged Adults

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Stress, Sleep, Inflammation, and Cognitive Ability

Chapter 1: Introduction

The influence of chronic stress on health and well-being has been of interest to the psychologist for the past decades. One of the earlier models of stress is Selye's (1936) general adaption syndrome model. This model focuses on three stages: alarm, resistance, and exhaustion. For instance, a virus may be considered an external stressor. The virus entering into the body will alarm the body, and there will be both innate and adaptive immune responses to counteract the stressor, which would indicate resistance. Exhaustion will occur if or when the body can no longer counteract the stressor. Once exhaustion occurs, the virus will infect the body and remain a stressor, until cytokines and other inflammatory proteins combat the virus.

Stressors to the body are not limited to biological processes but also include social and psychological in conjunction with biological processes. Selye's (1936) stress model suggests that biopsychosocial processes interact with one another and predict favorable or unfavorable health outcomes. This paper details a study that examined the role of psychological stress and health outcomes. Psychological stress here is defined as a relationship between the person and their social and environmental context that is appraised as exhausting the resources of a person, and thus endangers the person's psychological and physical well-being (Spaderna & Hellwig, 2015).

One way stress affects health is through sleep. Psychological stress is associated with reduced sleep duration, efficiency and effectiveness, likely in a bidirectional manner. For instance, perceived stress in middle-aged adults is associated with poor sleep outcomes, such as sleep duration and quality t (Charles et al., 2011; Hu et al., 2020; Zhao et al., 2021). Additionally, poor sleep is associated with a variety of mental health concerns, including depression and anxiety (João et al., 2018; Okun et al., 2018; O'Sullivan et al., 2015), as well as

physical health concerns like coronary heart disease (Davidson et al., 2018; Kwok et al., 2018; Lao et al., 2018) and obesity (Lian et al., 2019; O'Halloran et al., 2021; Rahe et al., 2015),in clinical and non-clinical adult populations. Recent research has particularly highlighted the importance of subjective sleep, or sleep quality, in predicting mental health outcomes, which may be more meaningful than objective sleep recordings (Park & Suh, 2022). According to Buysse et al. (1989), sleep quality is a complex construct including objective measures of sleep, such as time to fall asleep, duration of sleep, number of awakenings, and subjective measures including how restful one's sleep has been. Sleep disturbances are interruptions that can occur in any of these objective and subjective measures of sleep quality.

The purpose of sleep is not definitively established. Various theories have postulated the function of sleep. For example, medical and biological approaches to sleep focus on an inherently biopsychosocial process. From this lens, sleep is evaluated based on changes in the central nervous system, and as such, measured by patterns of electroencephalogram activity, muscular relaxation and activation, eye movement, reduced heart rate, and breathing (Worley, 2018; ZielinskWeet al., 2016; Zisapel, 2007). Adaptive theory suggests that sleep is a state in which an organism is immobile, thereby protecting them during periods of vulnerability (Freiberg, 2020; Roth et al., 2010; Zielinsk et al., 2016). Theories of natural selection propose that being calm and restful during these vulnerable times will reduce the risk of being hurt, decreasing reproductive viability (Freiberg, 2020; Keene & Duboue, 2018; Nunn et al., 2016). According to the energy conservation theory, sleep was evolutionarily used to restore energy expended for hunting, protection, walking excessive distances, and other physical endeavors (Assefa et al., 2015; Brinkman et al., 2022; Freiberg, 2020). Although modern survival requires different skills, conservation theory still purports that restoration via sleep is important to keep

the body in homeostasis, including regulating body temperature and inflammatory biomarkers in the body. Given current theories on the importance of sleep and sleep dysregulation affecting health outcomes, such as inflammation, studying sleep and health is vital to understand its influence on well-being.

Poor and irregular sleep has been associated with chronic inflammation (Dolsen et al., 2019; Hepsomale & Groeger, 2022; Motivala, 2011; Ranjbaran et al., 2007). Chronic inflammation is associated with poor outcomes including the leading cause of death and morbidity. Investigating long-term outcomes from chronic inflammation due to poor sleep may be important, as about 36% of the Western population has poor quality sleep (Hinz et al., 2017), and approximately 33% experience symptoms of insomnia disorder (American Psychiatric Association, 2013). In a longitudinal study, Dowd and colleagues (2011) investigated inflammatory biomarkers and their relation to sleep quality and duration in a Taiwanese sample of older adults. Sleep quality was not associated with inflammation; however, long sleep duration was associated with inflammation. Individuals who slept more than eight hours per night had higher inflammation than individuals sleeping for shorter periods. In contrast, another study by Friedman (2011) found in a national sample of adults in the US that worse sleep quality was associated with higher levels of the pro-inflammatory markers interleukin-6 (IL-6) and E-selectin in both men and women. Among women, greater sleep duration and shorter sleep latency (time to fall asleep) predicted lower levels of IL-6, and greater sleep efficiency predicted lower E-selectin and lower IL-6. However, in adolescents, higher levels of C-reactive protein (CRP), an acute inflammatory marker, correlated with shorter sleep duration, but not poor sleep quality (H. Park et al., 2016). Irwin et al. (2016) conducted a meta-analysis using 72 studies to assess the influence of sleep duration and sleep disturbances on CRP, IL-6, and tumor necrosis

factor-alpha (TNFα). Results indicated that sleep disturbances were associated with high levels of CRP and IL-6 and this relationship was also noted in individuals that slept over 10 hours. Shorter sleep duration from 5 to 7 hours, was associated with high levels of CRP, but not IL-6. This did not apply to less than five hours of sleep. However, TNFα was not associated with sleep disturbance or duration. Thus, how exactly sleep duration and quality, and inflammation work together remains unclear.

Irwin (2019) proposed a model in which disturbances in sleep (infrequent sleep, too short or too long sleep, or poor sleep quality) activate the release of adrenocorticotropic hormone and cortisol from the brain into the bloodstream via the pituitary gland and the hypothalamus. As a result of cortisol?, leukocytes will produce proinflammatory cytokines such as IL-1ß, IL-6, and TNFα and decrease circulating interferon A and B (IFNA & IFNB, respectively). This process is of importance, as it suggests that sleep disturbances influence hormonal balance and immunity. Thus, if sleep is irregular, one may be more prone to illness from the immune system temporarily weakened from fighting the hormonal imbalance. Although Irwin's (2019) model suggests that individuals should have lower inflammation when they sleep better, findings on associations of sleep quality and sleep duration with specific inflammatory biomarkers are inconsistent and may vary with the aspect of sleep measured. Consequently, we know little of the influence of sleep on proinflammatory cytokines.

Stress, Sleep, Inflammation, and Cognitive Ability

One health outcome associated with changes in sleep, stress, and inflammation is the development of cognitive impairment (Bubu et al., 2017; Cochrane et al., 2012; Falck et al., 2020; Ma et al., 2021; Wichmann et al., 2014). Sleep disturbances have been associated with changes in the hypothalamus-pituitary-adrenal (HPA) axis which is associated with increased

inflammation (Irwin, 2019). Irwin and Vitiello (2019) suggest that poorer sleep could be considered a predictor of cognitive decline over time, as poor sleep predicts an increase in the ß-amyloid burden. ß-amyloid is a peptide that is believed to contribute to the development of plaques in the brain, thus affecting the working memory (Murphy & LeVine, 2010). You and colleagues (2019) assessed whether the ß-amyloid deposits in the brain are associated with sleep dysfunction and changes in cognition in participants with cognitive disorders. You et al. (2019) found that nocturnal awakenings were associated with daytime ß-amyloid depositions in the precuneus and poor cognition. Mediation analysis noted that ß-amyloid depositions indirectly predict risk for cognitive impairment through nocturnal awakenings. While findings indicate cross-sectional associations between sleep dysfunction and risk for cognitive impairment, there is little longitudinal evidence for this association.

Certain pro and anti-inflammatory markers have also been associated with cognitive ability. Pro-inflammatory cytokines often worsen a disease, while anti-inflammatory counteract the disease and promote healing (Dinarello, 2000). One pro-inflammatory marker, TNFα, may be involved in the pathophysiology associated with cognitive dysfunction (McCaulley & Grush, 2015; Tarkowski, 2003). TNFα inhibitors may aid in lowering concentrations of TNFα, yet, are too large to cross the blood-brain barrier and cannot reverse cognitive decline overtime (Chang et al., 2017; Ou et al., 2021; Pardridge, 2010). Further, CRP is present in increased amounts in the brain of those experiencing memory loss and may further increase the risk for individuals to develop neurocognitive disorders, which is highly associated with mortality (Kravitz et al., 2009; Ran et al., 2020; Zhu & Liao, 2020). Interleukin-1 plays an integral role in local tissue reactions within the central nervous system, including neuroinflammation, leukocyte recruitment, and downstream signaling of ß-induced inflammasomes, which can lead to ß-amyloid depositions

(Shaftel et al., 2008; Wang & Wang, 2017) resulting in an influence on spatial learning, memory retention and mood alterations (DiSabato et al., 2021; Liśkiewicz et al., 2019). In addition, Wichmann et al. (2014) indicated based on a 20-year cohort study that repeated high or increasing IL-6 increases the likelihood of cognitive impairment. Thus, given the involvement of these cytokines with cognitive functioning, monitoring and potentially reducing them may reduce the risk for cognitive decline.

Aim and Hypotheses

This proposed study aimed to further investigate the association of concurrent and longitudinal self-reported stress, sleep (operationalized as self-reported sleep quality), and immune function with cognitive changes in middle-aged Americans. (H1) We hypothesized that higher stress, worse sleep quality, greater inflammation at time 1, and cognitive functioning at time 1 and 2 would correlate. We expected positive correlations between sleep quality (higher numbers indicate worse quality) and stress with IL 1ß, Il 6, CRP and TNFα. (H2) We hypothesized that stress, sleep and inflammation at T1 would directly predict cognitive functioning at T2. (H3) Furthermore, we proposed that stress at T1 would directly predict cognitive functioning at T2, as well as indirectly through T1 sleep, and T1 inflammation. (Exploratory Hypothesis) Finally, we explored whether a test of moderated mediation would indicate that age and biological sex moderate these indirect relationships. This model is illustrated in Figure 1.

Chapter 2: Method

Overview and Design

To investigate whether psychological stress predicts cognition directly or indirectly via sleep and inflammation and whether this relationship is moderated by age and sex, a secondary analyses of longitudinal data from the Midlife in the United States 2 (MIDUS 2) was conducted (http://midus.wisc.edu/). The MIDUS 2 dataset contains longitudinal information on the health and well-being of a nationally representative sample of middle-aged healthy adults in the United States in terms of race and gender at the time of data collection. Data collection was conducted at the University of Wisconsin-Madison, and samples were drawn from a 10-year follow-up of MIDUS 1. The sample was nationally representative at the time of collection.

Measures

Psychological stress. Psychological stress was assessed via the Perceived Stress Scale, which is a 24-item scale assessing the perceived stress (Cohen et al., 1983). Items are scored on a 5-point scale from *0 never* to *4 very often.* Example items included *In the last month, how often have you been upset because of something that happened unexpectedly?* and *In the last month, how often have you been able to control irritations in your life?* Items 4, 5, 7, and 8 were reverse-scored, and then all items were summed. The perceived stress scale scores ranged from 0 to 40. Scores ranging from 0 to 13 indicated low stress, item scores from 14 to 26 indicated moderate stress, and scores of 27-40 indicated high perceived stress. A meta-analysis reported Cronbach's alpha was >.70 in 11 different studies in which the tool was evaluated (Lee, 2012).

Sleep quality. Sleep quality was defined as how restorative sleep obtained at night is and operationalized via the Pittsburgh Sleep Quality Global Index (PSQI; Buysse et al., 1989). This self-report measure assessed sleep quality and had 7 components: subjective sleep quality (*How*

do you rate your sleep overall?), sleep latency (*How often do you have trouble sleeping because you could not get to sleep within 30 minutes?*), sleep duration (*How many hours of actual sleep did you get?*), sleep disturbance (*How often did you have trouble sleeping or waking up in the middle of the night?*), use of sleep medication (*How often have you taken medication to help you sleep*), habitual sleep efficiency (*when have you usually gone to bed at night?*) and daytime dysfunction (*How often do you have trouble staying awake while driving, eating meals, or engaging in the social activity?*). The PSQI consisted of 15 four-point items (*0 not during the past month - 3 three or more times a week*), as well as 4 open-ended values (0-3). Higher scores indicate worse sleep quality with a global score above 5 indicated poor sleep quality (Buysse et al., 2008). The PSQI is a valid and reliable measure in assessing sleep quality in midlife adults. A systematic review found that the global PSQI had a fair or good internal consistency with a Cronbach's alpha coefficient ranging from .64 to .83 (Zhang et al., 2020).

Inflammatory biomarkers. Inflammatory biomarkers were assessed through blood assays conducted during initial data collection. Collecting inflammatory information via blood has shown to be more accurate than via salivary or urinary analyses (Watson et al., 2019). Inflammatory markers included in this analysis are IL-6, CRP, and TNFα.

Cognitive ability. To assess for cognitive ability, the brief test of adult cognition by telephone (BTACT; Lachman et al., 2014) was used. The BTACT consisted of several brief cognitive tasks, including the Rey Auditory Verbal Learning Test (measureing attention, memory and learning ability; Lezak, 1995), the Digits Backward Test (assessing working memory; Psychological Corporation & Tulsky, 1997), Category Fluency (assessing the integrity of sematic memory; Drachman & Leavitt, 1972), the Stop and Go (to assess response inhibition; Logan & Cowan, 1984), Task Number Series problem-solving(to measure problem-solving;

Salthouse & Prill, 1987), and 30 Seconds and Counting Task (to assess processing speed; Lachman et al., 2014). In the cognitive battery, scoring was completed manually. Latencies were calculated manually from the sound field and then transferred to a selected database via an iterative sound latency processing algorithm. Responses were recorded and accuracy was scored by a computer analysis program (Tun & Lachman, 2006). Higher scores indicated better cognitive performance.

Exploratory moderators. Age and sex were entered as potential moderators of the indirect pathways. Previous work suggests age is a strong predictor of cognitive decline (Roland et al., 2020). Biological sex was included as the literature suggests that women have a greater cognitive reserve than men, but also a faster cognitive decline (Levine et al., 2021; Mielke, 2018; Plassman et al., 2007).

Plan of Analyses

An a-priori power analysis was conducted using G*Power v3.1 (Faul et al., 2009) which indicated that a sample size of n = 115 with a power of .95 would yield a significant result at p = .05 for linear multiple regression with a R^2 increase. This is further supported by Fritz et al. (2012) who suggest that a mediation analysis should have > 100 participants. Further, given that the mediation analysis will be bootstrapped 1000 times, power issues are uncommon (Preacher et al., 2007).

IBM SPSS v27 (IBM Corporation, Armonk NY, USA, 2020) was used for all analyses. First, descriptive analyses were performed. Then, preliminary correlational analyses were completed to investigate whether all variables are associated independently at time 1 (psychological stress, sleep quality, inflammation, and cognitive functioning) and time 2 (cognitive functioning). In this correlational analysis, (H1) we expected worse sleep quality to be

positively associated with higher levels of inflammation. Further, we expected lower cognition to be associated with poorer sleep quality and higher concentrations of proinflammatory biomarkers. After the preliminary analyses, a path analysis was conducted to examine whether perceived stress at time 1 would indirectly predict cognition at time 2 via different proinflammatory cytokines (IL-6, TNFα, CRP) and/or sleep at time 1. (H2 & H3) We expected higher psychological stress at time 1 to be directly predictive of poorer cognition, as well as indirectly through higher concentrations of inflammatory biomarkers. Finally, given the findings of associations between gender and age with cognition among older adults, an exploratory moderated mediation using PROCESS macro for SPSS (Model 8; Hayes, 2018) tested whether any indirect pathways from sleep to cognitive function at time 2 via inflammation or via sleep was moderated by gender or age.

Chapter 3: Results

Demographic Information and Preliminary Correlational Analyses

Descriptive and preliminary correlational analyses are presented in Tables 1 and 2, respectively. Over half of the sample identified as female, and the average age was 55.41(*SD* = 12.45, range 28-84). The majority of participants were White.

Hypothesis 1 predicted that higher stress, poorer sleep quality, increased inflammation at time 1 and cognitive functioning at times 1 and 2 are correlated. This was assessed using bivariate correlational analyses. Primary variables correlated in the expected directions. Thus, hypothesis 1 was partially supported. Stress correlated with lower cognition at time 2, and higher (worse) sleep quality, and higher CRP and IL6. Worse sleep quality correlated negatively with cognition at time 2, and positively with CRP, IL6, and TNFα. Also, CRP correlated negatively with cognition at times 1 and 2, and positively with IL6 and TNFα. Similarly, IL6 was negatively correlated with cognition at time 1 and time 2, and TNFα. Further, TNFα negatively correlated with cognition and time 1 and time 2. Finally, cognition at time 1 strongly correlated with cognition at time 2.

Cross-Sectional Analyses

Hypothesis 2 predicted that stress would directly predict cognitive functioning at time 1 and 2 after accounting for indirect effects. Further, hypothesis 3 predicted that stress at time 1 would indirectly predict cognitive functioning at time 1 and 2 via sleep quality and inflammation. This was analyzed using three path analyses that explored direct and indirect effects from stress to concurrent cognitive ability via sleep quality and immune function at time 1. Because inflammatory markers may be differently affected by stress and sleep, the three

markers of immune function were analyzed separately. Three additional path analyses examined direct and indirect paths from time 1 predictor to time 2 cognition.

Stress, Sleep Quality, CRP, Cognition. See Figure 2. Stress significantly predicted worse sleep quality. Worse sleep quality was a significant direct predictor of CRP, but not cognition. CRP directly predicted cognition. There was no direct effect of stress on cognition; therefore hypothesis 2 was not supported by the cross-sectional data. An indirect association of stress→sleep quality→CRP→cognition at time 1 partially supported H3.

Stress, Sleep Quality, IL6, Cognition. See Figure 3. Given that the association of stress with sleep quality was the same for each of the three analyses, that finding was not reiterated here. When using IL6 as the measure of inflammation, worse sleep quality did also not significantly predict IL6 or cognition. However, IL6 predicted cognition. There were no other significant direct or indirect pathways. Therefore, hypotheses 2 and 3 were not supported when using IL6 as an inflammatory marker.

Stress, Sleep Quality, TNFα, Cognition. As illustrated in Figure 4, stress predicted TNFα, but not cognition. Worse sleep quality did not predict TNFα or cognition. TNFα, however, was a significant predictor of cognition. There was no significant direct effect of stress on cognition; therefore hypothesis 2 was not supported. There was partial support for hypothesis 3 as indicated by the indirect association between stress→TNFα → cognition.

In summary, analyses of the cross-sectional data suggested no support for a direct effect of stress on concurrent cognition when including measures of sleep quality and measures of immune function; therefore hypothesis 2 was not supported in the cross-sectional data. Support for the prediction of indirect associations between stress and cognition via sleep quality and/or immune markers was mixed.

Longitudinal Analyses

Stress, Sleep Quality, CRP, Cognition. The next three analyses used time 1 measures of stress, sleep quality, and immune markers as predictors of cognitive functioning at time 2 (10 years after time 1). We controlled for cognitive functioning at time 1. Because the "a" pathways from stress to sleep quality and each of the three immune markers were the same as reported above, we report here only the "b," "c'," and indirect pathways. Neither the "b," or "c," nor the indirect paths yielded significance after controlling for cognitive functioning at time 1.

Stress, Sleep Quality, IL6, Cognition. When assessing the longitudinal path model using IL6 as the measure of immune function, stress was a significant predictor of cognition at time 2. The indirect paths did not yield significance.

Stress, Sleep Quality, TNFα, Cognition. Finally, stress again predicted cognition at time 2 when the immune marker TNFα was included in the model. None of the indirect paths yielded significance.

In summary, the longitudinal data did not suggest support for a direct effect of stress at time 1 on cognition at time 2 (hypothesis 2). Further, H3 stress→sleep →inflammation→ cognition at time 2 was not supported when we controlled for cognitive functioning at time 1. Because of the strong association of cognition at time 1 and time 2, none of the longitudinal analyses produced a significant pathway when controlling for cognition at time 1.

Exploratory Moderated Mediation

Following the planned analyses, we examined tests of moderated mediation to determine if any indirect paths were modified by sex or age for either concurrent or longitudinal measures of cognition. This was determined by examining the index of moderated mediation generated by Hayes' PROCESS model 85. While some of the stress x age and stress x sex interaction terms

were significant predictors of sleep quality and cognition, only sex mediated the indirect relationship between stress → TNFα → cognition at time 1, with women showing a higher likelihood for this interaction (CIs = .0007 - .0053). However, this finding is weakened given a nonsignificant index of moderated mediation. When controlling for cognition at time 1, the indirect relationship of stress → TNFα →cognition at time 2 became insignificant.

Further, we examined the effects moderated by age. Age mediated the indirect effect of stress → TNFα → cognition at time 1 (CIs .0004 - .0038). The trend was strongest among adults from the middle third of the sample (ages 55 to 68); however, once again the index of moderated mediation did not reach significance. As was true for the path analyses, the correlation between time 1 and time 2 was so strong that other effects were possibly masked. Given the tentative nature of the moderated mediation models, no conclusions are proposed.

Chapter 4: Discussion

We aimed to investigate whether psychological stress, sleep quality, inflammatory markers, and cross-sectional and longitudinal cognition were directly or indirectly related cross-sectionally or longitudinally. First, we investigated whether psychological stress, sleep quality, CRP, IL6, TNFα, and cognition at time 1, as well as cognition at time 2, would be correlated. Our analyses suggested that in our sample, high stress at time 1 was associated with poor sleep quality, higher levels of CRP and IL6, and poor cognition at time 2. Interestingly, we found that cognition at time 2 was unfavorably associated with all variables at time 1, suggesting that unfavorable health conditions, such as high stress, poor sleep quality, and accumulation of inflammatory markers, may be related to poorer cognition, and cognitive decrease over time.

When exploring direct associations from stress at time 1 to cognition at times 1 and 2, we did not find a direct pathway of stress to cognition. One thing we noted is that when we did not control for cognition at time 1, there was a direct path from stress to cognition at time 2. However, once we controlled for time 1, this association was non-significant. Our findings were different from previous findings on cross-sectional data that found perceived stress predictive of cognitive functioning at the same time point (Oumohand et al., 2020). Further, our findings differ from other literature suggesting that chronic stress is a significant predictor of future cognitive decline (Sussams et al., 2020; Turner et al., 2017), as well as Alzheimer's disease (Bisht et al., 2018; Jeong et al., 2006; Sharma et al., 2021). This reflects the addition of sleep and immune markers to the model.

In the present study, stress had a direct effect on sleep quality at the same time point. Similar associations had been drawn in prior research (Charles et al., 2011; Chen et al., 2022; Dolsen et al., 2019; Hu et al., 2020). One possible reason for the stress-sleep association could be

that high levels of stress influence sleep onset, due to rumination, worrying, or other unfavorable cognitive processes that prevent sleep (Thorsteinsson et al., 2019). In addition, being exposed to higher levels of stress may increase elevations in the body's stress response system, the HPA, and increase levels of cortisol, both of which could unfavorably affect the quality of sleep (Buckley & Schatzberg, 2005). Buckley and Schatzberg (2005) indicate that when the HPA axis functions normally and stress is controlled, cortisol levels will decline throughout the day and increase at night and early morning while an individual is asleep. However, if cortisol remains high before times of sleep due to existing psychological stress, these high levels may dysregulate the circadian rhythm, making the act of sleeping less restful and restorative.

Data examining the relationship between stress and cognition via the different inflammatory markers produced mixed results. All of the markers of inflammation, CRP, IL-6, and TNFα, predicted cognition at times 1 suggesting that higher concentrations of inflammatory biomarkers are directly related to cognition. The indirect pathways of stress to cognition at time 1, via the three cytokines were significant for only one cytokine, CRP. Previous research implied that CRP is highly reactive, and will rapidly increase in response to an inflammatory, usually physical, stimulus in the body (Sproston & Ashworth, 2018). While IL-6 and TNFα also have acute response properties, these are not as rapid as for CRP. Thus, the increase in only CRP may be related to design of the study as stress and inflammation were measured at the same time, and higher stress at a particular time may act as a strong inflammatory stimulus for CRP.

Analyses indicated an additional significant indirect path in the cross-sectional analyses from stress to cognition via sleep quality to CRP (Stress→Sleep Quality→CRP→cognition). Given that cortisol and CRP are commonly associated, it is possible that disturbances in the HPA axis increase cortisol in the bloodstream adversely affect sleep quality. Poor sleep quality may

increase CRP, which in turn lays the groundwork for reduced cognition (Buckley & Schatzberg, 2005). Alternatively, as implied by Irwin (2019), cortisol may rise as a response to poor sleep, which then causes an increase in CRP. Given that the analyses were correlational, and that stress, sleep quality, and CRP levels were measured simultaneously, no strong claims are made here regarding directionality.

Finally, we also conducted an exploratory moderated mediation, to assess whether the direct or indirect paths found were modified by biological sex and age. Sex modified direct relationships between stress, TNFα, and cognition, with women having a higher likelihood of high stress associated with high concentrations of TNFα. Age x stress moderated multiple associations. As expected, being of higher age was associated with higher concentrations of inflammation, which could be related to a higher risk of illness or higher accumulation of adverse experiences (Rasmussen et al., 2020; Rea et al., 2018). Age, but not sex, was also associated with sleep quality, indicating that individuals of higher age may have poorer sleep quality. Similar findings can be found in existing literature (Madrid-Valero et al., 2017). Possible explanations could include that increase in age is associated with higher cortisol, that as discussed, can impact the restorativeness of the sleep (Buckley & Schatzberg, 2005; Yiallouris et al., 2019). Further, factors such as pain and illness, which tend to be more prevalent as individuals age, may decrease the overall sleep quality (BiharWeet al., 2012; Sheffler et al., 2022; Vitiello et al., 2002). None of the indices of moderated mediation were clearly significant, suggesting that indirect paths were not modified or perhaps that other models and operationalization of stress and sleep should be explored

Overall, our findings suggested that stress, sleep, and inflammation are related to some extent and, if not managed, may interact in a way that could negatively impact cognition. Our

biopsychological approach to investigating direct and indirect associations of cognition over time is unique as it utilizes variables that have been associated independently with cognition but have not been comprehensively explored in a model. In order to better understand the interactions explored in this study, other relevant markers, such as chronic stress (as opposed to acute), pain, illness, and body composition need to be explored. Further, future research should focus on stress reduction strategies that demonstrate decreases in sleep disturbances and inflammation to prevent cognitive decline over time. Further, our model should be extended focusing specifically on Alzheimer's disease and whether interactions of stress, sleep, and inflammation over time affect the beta-amyloid acquisition, increasing the risk of the disease.

Strength and Limitations

One significant strength was the large sample size available in the MIDUS data set. Thus, we had enough power to test our model, which is often a challenge when conducting path analyses (Willaby et al., 2015). Further, our analyses benefitted from utilizing both cross-sectional and longitudinal data measure of cognition. We found multiple predictive associations on sleep quality and inflammatory markers at a prior time-point may predict cognitive decline over time.

Numerous limitations need consideration when reviewing our findings. For instance, inflammatory markers and stress and sleep data were available at only time 1. More specifically, the PSQI assessed sleep quality over one month, while the inflammatory markers were specific to the day they were measured. Past research has suggested that sleep quality remains relatively stable over time. For example, Knutson et al. (2006) found that in over 600 middle-aged adults, 76% of adults had the same PSQI dichotomous classification in values taken one year apart from one another. However, inflammatory markers are much more sensitive and tend to change more

frequently. For example, CRP levels can increase 1000 times within a few hours with the onset of infection (Szczerska et al., 2022). Nevertheless, past research has found that systemic inflammation during midlife is a significant driver of cognitive decline 20 years later (Walker et al., 2019).

Finally, our study did not utilize an objective measure of sleep, such as sleep duration or sleep efficiency through polysomnography. Instead, we relied on self-reported sleep quality. However, Kaplan et al. (2017) suggest that sleep quality in midlife is a good predictor of health outcomes and that overall there is little variance in objective and subjective measures of sleep when assessing for health.

To conclude, our study demonstrated an indirect effect of stress on cognition, via sleep and some indices of inflammation. These results show that, of the inflammatory markers assessed, CRP was most predictive of cognitive outcome and was associated with stress and sleep quality. To encourage healthy aging and limit cognitive decline over time, stress and inflammation reduction efforts, along with treatment for sleep issues, should be considered in middle-aged adults.

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Table 1

Sociodemographic Information

		n	Valid %
Sex			
	Female	2646	53.3
	Male	2316	46.7
Race			
	White	4473	90.6
	Black	229	4.6
	Alaskan Native/Native American	77	1.6
	Other	160	3.2
Education			
	Did not complete high school	309	6.2
	Obtained GED	61	1.2
	Some college	1094	22.1
	Obtained college/associates degree	1347	27.2
	Some graduate education/Obtained professional degree	879	17.7

Note. $f = 5415$.

Table 2

Correlational Data

Variables	*n*	*M*	*SD*	1	2	3	4	5	6
1.Stress	1249	22.24	6.34	-					
2.Worse Sleep	1172	6.23	3.68	.368**	-				
3.CRP	1235	3.02	4.78	.065*	.117**	-			
4.IL6	1243	3.04	3.04	.080**	.113**	.391**	-		
5.TNFα	1241	2.22	.95	-.034	.082**	.172**	.252**	-	
6.Cog1	3972	0.00	1.00	-.061	-.047	-.072*	-.115**	-.155**	-
7.Cog2	3043	0.00	1.00	-.158**	-.124*	-.101**	-.149**	-.098**	.776**

Note. CRP = C-reactive protein; IL6 = Interleukin-6; TNFα = Tumor necrosis factor alpha; Cog 1 and Cog 2 = Cognition at time 1 and 2, respectively.

* $p < .05$. ** $p < .01$.

Figure 1

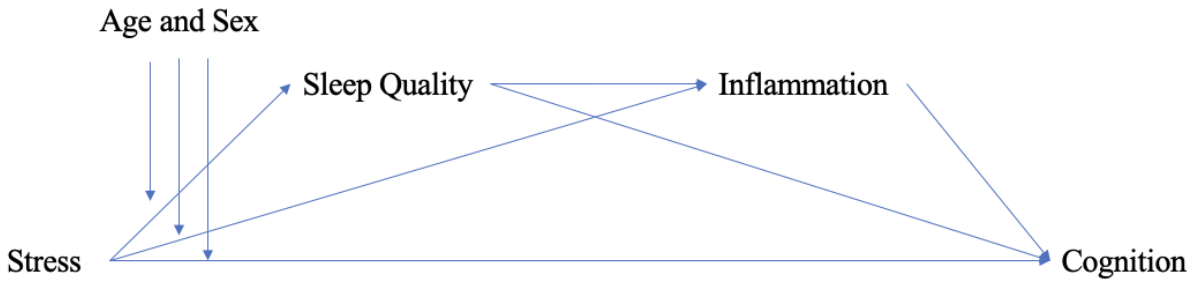
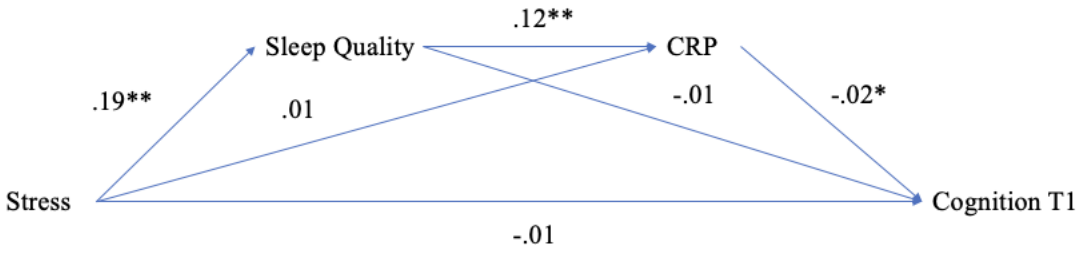


Figure 1: Hypothesized Model.

Figure 2

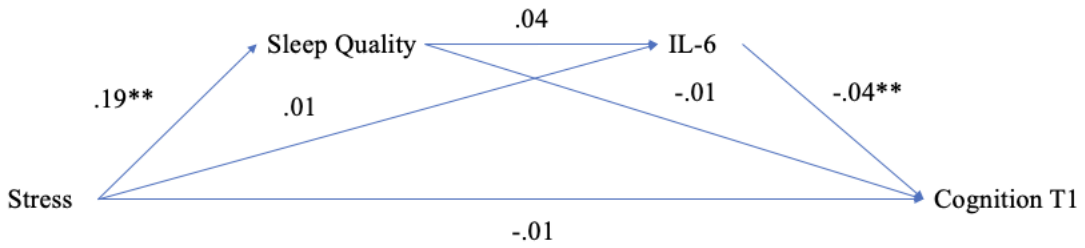


Direct Effect	*b*	CIs
Stress -> Cog	-.0071	-.0172, .0030
Indirect Effects		
Stress -> PSQI -> Cog	-.0013	-.0048, .0022
Stress -> CRP -> Cog	-.0002	-.0011, .0006
Stress -> PSQI -> CRP-> Cog	-.0003	-.0008, -.0001

Figure 2. Direct and indirect effects of stress on cognition via sleep quality and CRP. R^2 = .01.

* p < .05. **p < .01.

Figure 3

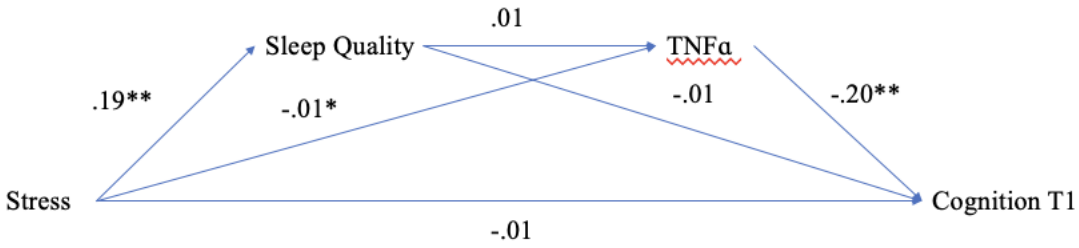


Direct Effect	*b*	CIs
Stress -> Cog	-.0064	-.0058, .0014
Indirect Effects		
Stress -> PSQI -> Cog	-.0014	-.0049, .0021
Stress -> IL-6 -> Cog	-.0004	-.0016, .0007
Stress -> PSQI -> CRP-> Cog	-.0003	-.0010, .0001

Figure 3. Direct and indirect effects of stress on cognition via worse sleep quality and IL6. R^2 = .02.

* $p < .05$. **$p < .01$.

Figure 4



Direct Effect	*b*	CIs
Stress -> Cog	-.0086	-.0186, .0014
Indirect Effects		
Stress -> PSQI -> Cog	-.0013	-.0047, .0023
Stress -> TNFα -> Cog	-.0018	.0003, .0036
Stress -> PSQI -> TNFα > Cog	-.0004	-.0012, .0002

Figure 4. Direct and indirect effects of stress on cognition via worse sleep quality and TNFα. R^2 =.03.

* $p < .05$. **$p < .01$.