UNIVERSITY OF CALIFORNIA
RIVERSIDE

Sleep and Cognition Associations: A Macro and Micro Perspective

A Dissertation submitted in partial satisfaction
of the requirements for the degree of

Doctor of Philosophy

in

Psychology

by

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June 2024

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ACKNOWLEDGEMENTS

I am deeply grateful to my mentors, committee members, family, and friends, whose unwavering support has been instrumental in both embarking on this academic journey and successfully completing this chapter of it. Without each and every one of you, I would not have reached this point.

To my advisor, Dr. Chandra Reynolds:

Your guidance and belief in me have been transformative. Thank you for providing me with the opportunity to further discover my passion for research and for nurturing my growth every step of the way. Your support, patience, and mentorship have been invaluable in shaping me into the academic that I am today. I am privileged to have been mentored by someone as kind, passionate, and supportive as you. From my very first day in your lab to my very last day in your lab, I have looked up to you. Thank you for providing me with the blueprint of how to be an advisor who uplifts their students and fosters a passion for learning.

To my committee members, Dr. Rachel Wu and Dr. Weiwei Zhang:

Your steadfast support and encouragement have been a constant source of strength throughout my journey. From guiding me through various milestones to advocating for my future endeavors, your mentorship and support have been invaluable. I am grateful for the opportunity to have worked alongside and learn from both of you.

To my scientific support:

Lauren Whitehurst, your introduction to research on sleep and cognition has been pivotal in shaping my trajectory. Thank you for believing in me and for igniting my passion for this field. To my lab mates, your brilliance and dedication have inspired me every day. I am lucky to have been surrounded by such amazing people that have provided feedback, encouragement, and support throughout my time at UCR. Thank you to Brittany (Paige) Trubenstein, Elizabeth Munoz, Dianna Phillips, Shandell Pahlen, Anqing Zheng, and Ryan Bruellman. Moreover, a big thank you to the wonderful research assistants that I have had the pleasure working with throughout my time in the Biobehavioral Research Lab. I would like to especially thank Emery Lor and Crystal (Sian) Yu for allowing me to be a part of your academic journey and learn how to be a mentor. Thank you to the Interplay of Genes and Environment across Multiple Studies consortium (IGEMS; NIA AG060470, AG059329) and the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife; NIA AG046938; Reynolds & Wadsworth, MPIs) team for allowing me the opportunity to learn from and work with experts within the field. Lastly, I would like to thank my fellow cohort member, Hea Jung Lee, for your friendship and support over the past five years.

To my family:

Your unwavering love and support have been my anchor during the ups and downs of this journey. Tiffany and BunBun, your continued love and support have been a source of comfort and strength. Mom, thank you for raising me to be a strong and

hardworking woman. To my second family, Kathryn, Edward, Gene, and Sansa, thank you for embracing me with warmth and support. To my partner, Colin, whose early encouragement ignited my passion for research and whose steadfast support has been my anchor throughout this journey, thank you. Your unwavering support has been my greatest blessing. We have been together since the very beginning of my academic journey, and I look forward to seeing where the future will take us. To all those who have been part of my community over the past few years, your involvement has been invaluable. Thank you all.

ABSTRACT OF THE DISSERTATION

Sleep and Cognition Associations: A Macro and Micro Perspective

by

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Doctor of Philosophy, Graduate Program in Psychology
University of California, Riverside, June 2024
Dr. Chandra A. Reynolds, Chairperson

This dissertation aimed to investigate the complex associations between sleep and cognition, shedding light on how sleep may serve as a modifiable factor impacting cognitive functioning and cognitive aging. Through macro and micro perspectives, the research offered a comprehensive understanding of sleep-cognition dynamics. In Study 1, cross-sectional data from mid-to late-life twins within the Interplay of Genes and Environment across Multiple Studies (IGEMS) consortium were leveraged to examine the sleep and cognition relationship while additionally including a polygenic score for Alzheimer's disease (AD) to elucidate the moderating roles both sleep and genetic risk for AD on etiological associations underlying differences in cognitive performance. Findings revealed no statistically significant moderation of sleep disturbances on genetic variance. However, patterns suggested heightened genetic influences with reduced sleep duration or increasing sleep disturbances. Sleep disturbances may moderate common environmental influences for tasks related to attention and working memory. Principally,

Study 1 found higher genetic risk for AD was generally associated with weaker individual-specific environmental influences. In Study 2, we explored micro-level sleep and cognition associations over a two-week period in individuals approaching midlife. Leveraging ambulatory smartphone data from the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife), Study 2 revealed that the between-person average sleep quality (SQ) component exhibited the most influence on performance across episodic memory, working memory, and executive functioning compared to within-person fluctuations in daily SQ. However, variations in daily SQ dynamics exhibited task-specific effects, particularly for working memory and executive functioning tasks. Interactions between SQ and *APOE* genotype indicated momentary improvements in cognitive performance, particularly for executive functioning and working memory, among individuals with increasing scores indexing ε4 dosage experiencing higher-than-usual sleep quality. Together, the dissertation examines both macro-level (Study 1) and micro-level (Study 2) sleep-cognition associations through biometrical twin models that leverage data from IGEMS, comprising data from individuals in mid- to late-life, and from applications of longitudinal time-varying covariate models that leverage ambulatory burst data from CATSLife, comprising data from individuals approaching midlife. Further work is necessary to understand the nuanced relationship between sleep and cognition, particularly with an emphasis on examinations of gene-environment interplay.

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Chapter One:

GENERAL INTRODUCTION

As the prevalence of Alzheimer's disease (AD) and other neurodegenerative disorders continue to rise (Nichols et al., 2022), further investigation is increasingly necessary to understand the connection between potentially modifiable risk factors and early susceptibility to cognitive impairment, cognitive decline, and AD (Matthews et al., 2019; Nichols et al., 2022). Among these factors, sleep features throughout adulthood emerge as a significant area requiring deeper exploration (Livingston et al., 2020; Vo & Reynolds, 2022). Notably, AD is characterized by pronounced disruptions in nighttime sleep architecture, escalating in severity with the progression of the disorder (Wang & Holtzman, 2020). These disruptions encompass reduced deep sleep stages crucial for memory consolidation, diminished lighter sleep stages (i.e., rapid eye movement (REM) sleep), shorter total sleep duration, and decreased sleep efficiency (Wang & Holtzman, 2020; Bliwise, 2004; Bliwise et al., 1995). Moreover, individuals with AD often experience sleep-related difficulties and diminished sleep quality many years before the onset of cognitive impairment or even the condition itself (Bliwise, 2004; Zhang et al., 2019). Maintaining good sleep hygiene is suggested to fortify cognitive integrity and sustain cognitive function (Ferrie et al., 2011). Despite a substantial body of research exploring the link between sleep and cognition, much remains unknown, particularly in the context of aging. For instance, it is currently unclear whether sleep may serve as a risk factor or an early symptom (i.e., prodrome) for AD (Livingston et al., 2020),

necessitating further research to elucidate the influence of sleep on normative cognitive functioning across the lifespan.

While research increasingly underscores the importance of sleep for cognitive and physical health across various life stages – early life (e.g., Bernier, Beauchamp, Bouvette-Turcott, Carlson & Carrier, 2013; Fatima, Doi & Mamun, 2016), midlife (e.g., Waller et al., 2016), and late-life (e.g., Yaffe, Falvey & Hoang, 2014; Reid et al., 2006) – a global issue persists with widespread sleep insufficiency within the population. Insufficient sleep has recently been recognized as a public health epidemic, yet most of the population still exhibit poor sleep hygiene, with chronic under-sleeping prevalent among Americans (Chattu et al., 2018a; 2018b; Centers for Disease Control and Prevention, 2014; National Sleep Foundation, 2019). In our fast-paced 24-hour society (e.g., Coveney, 2014), the crucial importance of sleep is often overlooked for a variety of reasons, including, but not limited to, the demands of shift work (Karthikeyan, Spence, Pandi-Perumal, 2019; Bokenberger, 2018; Bokenberger et al., 2017) and the pressure for increased productivity (e.g., prevalence of all-nighters among college students; Lowry, Dean & Manders, 2010). This trend is reflected in the general decline in average total sleep hours and sleep quality over the past three decades (an estimated reduction of 0.75 minutes/year), reflecting a current global population that is increasingly sleep deprived (Chattu et al., 2019; Matricciani et al., 2017; Hoyos et al., 2015). These reductions in both duration and quality of sleep contribute to adverse health outcomes, including cardiovascular diseases, diabetes, hypertension, and Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD) (Vgontzas et al., 2010; Khalil et al., 2020; Han et

al., 2020; Peter-Derex et al., 2015; Lucey, 2021; Wang & Holtzman, 2020), aligning with the escalating trends in AD and ADRD (Nichols et al., 2022). Indeed, research has found the lowest mortality risk in individuals sleeping within the normative range, while elevated sleep disturbances and poorer sleep efficiency are associated with increased risk of future cognitive impairment and AD pathology (Vgontzas et al., 2010; Tworoger et al., 2006; Ju et al., 2013). Notably, poor sleep not only has long-term consequences but also presents short-term health risks, such as acute increases in stress responsivity (Irwin et al., 1999). Consequently, there is a growing necessity for research aimed at further elucidating the intricate relationship between sleep and cognition, with a particular emphasis on understanding these associations within an aging context, encompassing both long-term and short-term effects.

Sleep and Cognition across the Lifespan

Both sleep and cognition undergo significant and dynamic changes throughout life, with age-dependent alterations to both sleep architecture and cognitive abilities. Research suggests that an individual's sleep architecture is heavily dependent on age, with normative increases in sleep fragmentation and decreases in sleep efficiency (e.g., increased wake after sleep onset (WASO) and sleep latency) and decreases in total sleep time (TST) observed, particularly in the later years (Ohayon et al., 2004; Dorffner et al., 2015; Kocevska et al., 2021; Evans et al., 2021; Scullin & Bliwise, 2015). Moreover, across aging, increasingly less time is spent in bed coupled with shifts in the timing of sleep onset (Kocevska et al., 2021; Evans et al., 2021). These age-related changes are further exacerbated by conditions like AD (Wang et al., 2020). Following the disease

onset, additional and compounded changes to overall sleep architecture and sleep quality occur, including reductions in time in deep sleep, decreases in rapid-eye-movement (REM) sleep, decreases in total sleep time, and increased reports of sleep disorders such as insomnia or excessive daytime sleepiness (Bliwise, 2004; Wang et al., 2019).

Similarly, trajectories of cognitive abilities follow dynamic changes across the aging process as well. Current research indicates that cognitive abilities reach their peaks at various life stages. Processing speed typically peaks earlier in life, around the age of 20, while working memory performance tends to peak during adulthood and established adulthood, which is generally after the age of 30 (Hartshorne & Germine, 2015; Mehta et al., 2020). On the other hand, the latest peak is observed for vocabulary knowledge, occurring in mid-to-late-life, typically between the ages of 50 and 70 (Hartshorne & Germine, 2015; Salthouse, 2009). Within normative adult cognitive development, declines are expected in a wide variety of cognitive abilities ranging from reasoning, spatial visualization, memory, and speed across most individuals, with the exception of increases or relative stability in domains such as vocabulary knowledge (Salthouse, 2009; 2019; Horn & Blankson, 2005). Moreover, peaks in fluid abilities (i.e., the ability to think flexibly) are observed in early adulthood and typically show declines starting in mid-adulthood, whereas peaks in crystallized abilities (i.e., abilities related to experience-based gained intelligence) are observed in late adulthood with declines observed in even later ages (Cattell, 1971; McArdle et al., 2002). As such, prevailing cognitive aging theories and current research posit the maintenance and stability of some cognitive domains and abilities with age, suggesting a non-uniform decline in cognitive functioning

whereby some resilience is observed for some while others exhibit deterioration or declines. Within cognitive aging theories and two-component theories of intelligence (e.g., crystallized and fluid abilities; Horn & Cattell, 1996; Lindenberger et al., 2001), two hypotheses related to cognitive stability (i.e., maintenance) and cognitive change are proposed to understand cognitive aging patterns as they relate to lifestyle factors– preserved differentiation and differential preservation (Salthouse, 2006).

Under the preserved differentiation hypothesis, lifestyle factors associated with cognitive ability may underlie the maintenance of cognitive performance differences across aging, leading to similar aging patterns, such that declines may occur at similar rates but the height of one's trajectory may be dependent on their cognitive ability (Salthouse, 2006). For example, individuals who are more mentally active are also more likely to exhibit higher prior levels of cognitive functioning and these differences are preserved across aging, resulting in less age-related cognitive decline. As such, this viewpoint suggests that one's current cognitive ability may be partly because of one's lifelong mental abilities. Conversely, the differential preservation hypothesis suggests that the extent of cognitive maintenance varies based on lifestyle factors, resulting in diverging cognitive aging trajectories. For example, individuals who engage in more mentally stimulating activities tend to have higher levels of cognitive performance (Salthouse, 2006). As such, under this hypothesis, lifestyle factors like engagement with mental activity may protect against age-related cognitive decline. When applying these hypotheses to understand the relationship between sleep, cognition, and aging, it is possible that individuals with higher cognitive abilities adopt better sleep habits that

support their cognitive function, aligning with the preserved differentiation hypothesis. Alternatively, good sleep quality, which is crucial for cognitive functioning, may protect against cognitive decline with age, aligning with the differential preservation hypothesis. At the core of this discussion lies the impact of lifestyle and environmental factors (e.g., sleep) on one's level of cognitive functioning and rate of cognitive decline. However, indirect pathways between lifestyle and environmental factors on both level and change may also be important to consider (Reuter-Park & Lorenz, 2014). Protective sleep features, such as sleep duration within the normative ranges or good sleep quality, may help counteract age-related declines by enabling compensatory mechanisms (e.g., bilateral recruitment, enhanced fronto-parietal recruitment, strengthened connectivity, recruitment of new brain regions, neurogenesis; Reuter-Lorenz & Park, 2014). In essence, some individuals who vary in terms of risk or protective factors may maintain cognitive functioning across aging by engaging in compensatory mechanisms that are facilitated by environmental factors like sleep. Conversely, others may experience more pronounced declines over time due to the cumulative effects of aging, poor sleep, and genetic predispositions to adverse cognitive outcomes such as AD.

Developmental Perspective: Scaffolding Theory of Aging and Cognition

Recognizing how sleep and cognition may interrelate across the lifespan and understanding how one behavior (e.g., sleep) may impact the other behavior (e.g., cognition) may have important implications for understanding their nuanced interrelationship. As previously mentioned, age-related differences in sleep and cognition associations are prevalent and demonstrate distinct patterns across varying life stages

(Scullin & Bliwise, 2015). Notably, the effects of sleep deprivation and sleep fragmentation on cognitive functioning are often stronger and more pronounced when observed within younger and midlife individuals, as opposed to their older counterparts where effects are lesser, or even null, on reaction time and memory tasks (Bonnet & Rosa, 1987; Sagaspe et al., 2012), and vigilance tasks (Brendel et al., 1990; Stenuit & Kerkhofs, 2005). Interestingly, some studies have also provided support for a facilitating effect of cognitive functioning in poor sleep contexts within older individuals (Lowden, Annund, Kecklund, Peters & Akerstedt, 2009). Specifically, older individuals exhibited both increased power for electroencephalographic (EEG) measurements (e.g., sigma 1 band; 12-14 Hz) and also elevated cortisol levels after sleep deprivation, both of which are suggestive of promoting increased vigilance and protection against sleep-related insults to cognitive functioning, an effect that was not evident in younger age groups (Lowden, Annund, Kecklund, Peters & Akerstedt, 2009).

Older individuals, as compared to younger individuals, may engage in cerebral compensatory recruitment whereby age-related changes to brain anatomy and physiology are compensated through processes such as reorganization of functions and activation patterns which allow for maintained cognitive performance despite the age-related declines (e.g., Hemispheric Asymmetry Reduction in Older Adults (HAROLD); Cabeza, 2001, 2002; Cabeza et al., 1997). As such, in the face of short sleep duration or poor sleep quality, older individuals may also engage in compensatory mechanisms (i.e., recruitment of both hemispheres) that may aid in mitigating and counteracting cognitive decline. For instance, neuroimaging and functional magnetic resonance imaging (fMRI)

studies demonstrate increased blood oxygen level-dependent (BOLD) signal activation in older individuals (i.e., 60+ years old), compared to younger individuals (i.e., 18-39 years old), during sustained attention and response inhibition tasks (i.e., GO-NOGO cognitive tasks), after 36 hours of sleep deprivation (Almklov, Drummond, Orff & Alhassoon, 2015). This increased activation as indexed by the increased BOLD signal for older adults suggests that compensatory mechanisms may be at play such that recruitment of brain regions important to attention and inhibition (e.g., parietal lobe, postcentral gyrus, precuneus, superior parietal lobe, cingulate cortex, and frontal regions) are engaged to aid in cognitive functioning maintenance after poor and/or restricted sleep. Conversely, a simultaneous decrease in the activation of the default mode network (e.g., left posterior cingulate, medial prefrontal cortex, precuneus, and angular gyrus), a network that is primarily active during awake resting states, was observed for older individuals after sleep deprivation, as compared to their younger counterparts (Almklov, Drummond, Orff & Alhassoon, 2015), suggesting that enhancement and activation of brain regions that are more salient to the current demands are recruited and prioritized, at the curtailment of other regions (i.e., DMN) that may not be as essential to the current tasks. Likewise, other research has indicated the engagement in the recruitment of frontal regions by older individuals, and not younger individuals, in tasks assessing spatial working memory (Reuter-Lorenz et al., 2000) and episodic recall (Cabeza et al., 1997), although not specifically with respect to sleep disruptions. Indeed, this compensatory recruitment utilized by older individuals may be further understood within scaffolding frameworks

put forth by Park and Reuter-Lorenz (2009) when examining the sleep-cognition relationship within a developmental psychology perspective.

Specifically, the scaffolding theory of aging and cognition (STAC) and its revised counterpart (STAC-r; Reuter-Lorenz & Park, 2014), which incorporates additional life-course factors (e.g., genetics, environmental factors, health), may yield additional insight on neuroplasticity and compensatory scaffolding mechanisms related to cognitive performance, brain structure, and brain function within the sleep and cognition relationship across the lifespan. STAC-r posits that compensatory scaffolding engaged by aging older individuals through processes such as bilateral recruitment or enhanced recruitment of frontal-parietal regions may enable an individual to mitigate aging-related declines in cognitive functioning and withstand neural insults associated with aging (e.g., volumetric reductions in the brain, elevations in amyloid deposition, reductions in functional connectivity, decreased white matter integrity; Reuter-Lorenz & Park, 2014). Moreover, under the framework of STAC-r, the capacity of an individual's brain to develop and strengthen these compensatory scaffolds may be enhanced through the preservation of brain structure and brain function (i.e., increased brain health, cortical thickness, and synaptic density) afforded by healthy lifestyle choices (e.g., exercise/cardiovascular fitness; Erickson et al., 2014) encompassing a construct termed neural resource enrichment (Reuter-Lorenz & Park, 2014). Alternatively, an individual's capacity to compensate may also be negatively affected and weakened through adverse factors (e.g., depression, low socioeconomic status, presence of the genetic risk allele apolipoprotein Ɛ4 (*APOE* Ɛ4)), which may negatively affect brain structure and function,

encompassing a construct called neural resource depletion (Reuter-Lorenz & Park, 2014). Both neural resource enrichment and neural resource depletion, in addition to biological aging, may directly affect brain structure and brain function, consequently affecting an individual's compensatory scaffolding abilities (Reuter-Lorenz & Park, 2014). However, neural resource enrichment may also directly affect one's compensatory scaffolding abilities through another pathway. Specifically, an individual with more neural resource enrichment (e.g., higher education, higher socioeconomic status, better fitness) may have an increased capacity for compensatory scaffolding despite age-related neural insults to brain structure and brain function, a concept that parallels brain reserve and cognitive reserve theory (Stern, 2012). However, departing from the cognitive reserve theory is the addition of examining the negative effects of neural resource depletion on brain structure, brain function, and compensatory scaffolding abilities (Oosterhuis, May, Slade & Nuttall, 2022). In addition to neural resource enrichment and neural resource depletion factors, behavioral interventions may also contribute to an individual's compensatory scaffolding abilities. Following this framework, compensatory scaffolding then directly affects an individual's rate of cognitive change over time which consequently influences an individual's level of cognitive functioning (Reuter-Lorenz & Park, 2014).

A large body of research has indicated that adequate sleep (both quantity and quality) emerges as a critical factor necessary for optimal cognitive performance and cognitive functioning (e.g., Van Der Werf et al., 2009; Tononi & Cirelli, 2003; Walker, 2008) whereas poor sleep is associated with adverse cognitive health outcomes, including increased neuroinflammation (Irwin & Vitiello, 2019; van Leeuwen et al., 2009;

Vgontzas et al., 2004) and a heightened risk of AD (Benedict et al., 2015). Thus, within the sleep and cognition context, and contextualized within this lifespan perspective of the STAC-r framework, the observed sleep-cognition associations that emerge when comparing midlife to late-life individuals may be due to differential engagement in compensatory scaffolding mechanisms whereby older individuals not only engage in compensatory scaffolding to mitigate neural insults due to biological aging but also to mitigate against neural insults due to poor sleep. Further, various life-course factors, specifically factors related to sleep (e.g., depression, *APOE*, socioeconomic status) may work in tandem with sleep and aging to either further enrich neural resources or further deplete neural resources, ultimately affecting brain status, compensatory scaffolding abilities and overall rate of cognitive change and level of cognitive functioning (Reuter-Lorenz & Park, 2014; Almklov, Drummond, Orff & Alhassoon, 2015). Within this framework, it is plausible that neural resource enrichment influences, neural resource depletion influences, and sleep may work in concert and may directly affect brain structure and brain function while also directly affecting the effectiveness of compensatory scaffolding abilities which will in turn affect an individual's cognitive functioning, in the face of aging (see Figure 0.1; Reuter-Lorenz & Park, 2014; Almklov, Drummond, Orff & Alhassoon, 2015). Whether sleep may act as either a neural resource enrichment factor (i.e., adequate sleep hygiene, adequate duration and quality of sleep) or a neural resource depletion factor (i.e., inadequate sleep hygiene, inadequate duration and quality of sleep), or even as an intervention factor within the current STAC-r framework, suggests sleep plays a role in cognitive functioning and aging. However, the role of sleep

as a modifiable risk factor, or sources of enrichment and depletion, may not be constant across adulthood – that is, sleep dysregulation may act as a risk or a co-occurring feature of neurodegeneration (e.g., Xiong, Tvedt, Akerstedt, Cadar & Wang, 2024; Anderson et al., 2021; Li et al., 2022; Lloret et al., 2020; Ju, Lucey & Holtzman, 2014). Hence, reverse causation may be a bias depending on the age periods when sleep features and cognitive functioning are measured, and the source of measurement (objective or self-reported measurement), as well as whether longitudinal follow-up is available for assessment.

Dual Role of Sleep: Risk Factor and Prodromal Symptom of Alzheimer's Disease

While poor sleep has been posited as a risk factor leading to cognitive decline and neurodegenerative diseases such as AD, it is also been implicated as a potential prodromal symptom of AD, signaling the early stages of cognitive decline associated with AD (Irwin & Vitiello, 2019; Livingston et al., 2020). Sleep dysregulations, including disturbances and inadequate durations, may serve as early indicators of cognitive decline, neurodegeneration, and AD (Bliwise, 2004; Wang et al., 2019; Guarnieri et al., 2012; Ju, Lucey & Holtzman, 2014) and are often reported years before the onset of cognitive impairment or AD (Bliwise, 2004; Wang et al., 2019; Guarnieri et al., 2012; Ju, Lucey & Holtzman, 2014), underscoring the potential of sleep as an informative biomarker for early AD diagnosis (Matsumoto & Tsunematsu, 2021). Furthermore, sleep alterations are more prevalent in individuals with dementia (ranging from 14-69%; Zhao et al., 2016; Zhou et al., 2019; Kabeshita et al., 2017; Guarnieri et al., 2012), although reliability concerns exist regarding self-reported sleep due to cognitive

impairment from AD pathology (Brzecka et al., 2018). Among cognitively normal middle-aged adults, sleep inefficiency and increased frequencies of daytime napping, rather than total sleep time, are associated with elevated amyloid deposition, indicating a link between sleep quality and prodromal AD (Ju et al., 2013). However, other research suggests that increased genetic risk of AD is associated with shorter sleep durations before dementia onset, suggesting sleep duration may be an early AD marker (Leng et al., 2020).

Dysregulated sleep is linked to a heightened risk of AD/ADRD (Bubu et al., 2017; Lim et al., 2013;Shi et al., 2018; Sindi et al., 2018; Chen et al., 2016; Ohara et al., 2018), and lower gray matter volume in vulnerable areas coinciding with AD pathology (e.g., hippocampus, precuneus, cingulate gyrus; Koo et al., 2017; Alperin et al., 2019; Liu et al., 2021; Grau-Rivera et al., 2020). Moreover, individuals with sleep durations at the extremes (i.e., less than 5 hours or more than 10 hours) have increased risk of mild cognitive impairment (Ohara et al., 2018; Sindi et al., 2018; Lutsey et al., 2018). Comparatively, Borges and colleagues (2021) examined subjective sleep parameters in prodromal AD and found that individuals with multi-domain mild cognitive impairment have shorter sleep durations and poorer sleep quality. Furthermore, greater amyloid positivity (i.e., prodromal AD) was associated with longer times in bed, an indication of fragmented sleep and poorer sleep efficiency (Borges et al., 2021), and greater tau deposition in AD-related brain regions (Andrews et al., 2021). Moreover, *APOE* Ɛ4 carriers, even when initially cognitive asymptomatic, are seven times more likely to report sleep disturbances and disruptions in deep sleep stages, compared to the reference

group who did not subsequently receive an AD diagnosis (Burke, Maramaldi, Cadet & Kukull, 2016). *APOE* Ɛ4 carriers with mild cognitive impairment showed more disruptions to deep sleep stages that are crucial for consolidating and strengthening memories (i.e., slow wave sleep; Holz et al., 2012), and shortened rapid-eye-movement (REM) sleep (Hita-Yanez, Atienza & Cantero, 2013). Overall, the existing literature supports a dual role for sleep as both a factor associated with neurodegeneration and AD risk and as a prodrome of AD. The field is extensive, and yet, there remains much to explore in understanding the intricate interplay between sleep and cognition, especially considering the evolving nature of both fields.

Current State of the Field and Further Expansions

The current literature suggests that decreases in sleep duration and declining sleep quality are linked to reductions in various cognitive abilities, including executive function (Regestein et al., 2004), working memory, visual working memory capacity (Xie, Berry, Lustig, Deldin & Zhang, 2019), episodic memory (Aly & Moscovitch, 2010; Inostroza & Born, 2013; Van Der Helm, Gujar, Nishida & Walker, 2011), and attention (Miyata, Noda, Iwamoto, Kawano, Okuda & Ozaki, 2013). Moreover, both excessively short and excessively long sleep durations have been associated with poorer cognitive performance and accelerated rates of cognitive decline (Ma, Liang, Zheng, Shi, Zhong & Xie, 2020; Ferrie, Shipley, Akbaraly, Marmot, Kiyimaki & Singh-Manoux, 2011; Kronholm, Sallinen, Suutama, Sulkava, Era & Partonen, 2009), with these declines becoming observable as early as midlife (Scullin & Bliwise, 2015). However, despite these significant associations, the dynamics underlying the relationship between sleep and

cognition remain elusive. Furthermore, mixed findings in the current cross-sectional studies add complexity to our understanding of these associations, necessitating additional replication as some results currently diverge.

For instance, nocturnal sleep fragmentation was found to be associated with poorer memory performance in one cross-sectional study (Mary, Schreiner & Peigneux, 2013) but not in another study (Foley et al., 1995). Similarly, sleep latency was significantly associated with general cognitive ability in some studies (e.g., Potvin et al., 2012) but not in others (e.g., Habte-Gabr et al., 1991; Newman, Enright, Manolio & Haponik, 1997). Moreover, limited longitudinal studies have focused on examining the sleep and cognition relationship. Often, these studies are assessed with only two timepoints (i.e., baseline and subsequent cognitive performance or pre- and post-designs). These studies have reported evidence of poorer sleep, and sleep disturbances, at baseline, predicting more cognitive complaints two years later (Stenfors, Hanson, Oxenstierna, Theorell & Nilsson, 2013), predicting poorer cognitive performance over two decades later (Virta et al., 2013), and even predicting a subsequent dementia diagnosis (Benedict et al., 2015). However, given the mixed findings that are observed in cross-sectional designs and the limited research examining longitudinal sleep and cognition associations, additional examinations of both cross-sectional and longitudinal associations between sleep and cognition are increasingly necessary.

This dissertation endeavors to address critical gaps in the existing sleep and cognition literature by: 1) integrating methodology from behavioral genetics to deepen our understanding of their relationship beyond phenotypic associations, and 2) leveraging

micro-level timescale assessments to explore the day-to-day associations between sleep and cognition, two areas that have been largely underexplored in the field. Moreover, changes in sleep architecture (Knutson et al., 2010; Ohayon et al., 2004) and changes to cognitive abilities (Salthouse, 2009; McArdle et al., 1998; Horn & Cattell, 1976) are already observable in midlife (Scullin & Bliwise, 2015), underscore the need for deeper investigations into the individual differences that may contribute to variations in cognitive functioning across various stages of the lifespan.

Behavioral and Molecular Genetics within Sleep and Cognition Research

While most individuals will show some form of normative decline in late life, as mentioned previously, there will be other individuals who will show more, or less, rapid declines (Salthouse, 2006). Within the behavior genetic cognitive aging literature, twin studies have yielded evidence supporting robust genetic influences and person-specific environmental influences, and diminishing shared family environmental influences, on individual differences in general cognitive ability across the lifespan (Haworth et al., 2010; Tucker-Drob & Briley, 2014; Lyons et al., 2009; Lyons et al., 2017) as well as specific cognitive abilities (e.g., verbal fluency, spatial ability, memory; Gustavson et al., 2018; Gustavson et al., 2021; Reynolds & Finkel, 2015; Polderman et al., 2015). Applying these informative biometrical approaches to further understand the relationship between sleep and cognitive health, particularly with an aim at disentangling the individual differences that contribute to the development and preservation across the lifespan is vital.

Biometric modelling has been applied within the current sleep literature, albeit not extensively. Research regarding sleep has examined gene-environment interplay between sleep and health (i.e., body mass index; Watson et al., 2010; Watson et al, 2012) and sleep and well-being (i.e., depression; Watson et al., 2014), yielding important implications for the moderating effect of sleep. Specifically, genetic influences on body mass index were highest at short sleep and dissipated at longer sleep durations (Watson et al., 2012) whereas genetic influences on depressive symptoms were highest at both short (i.e., 5 hours) and long sleep (i.e., 10 hours; Watson et al., 2014). Indeed, recent research has examined the moderating role of sleep duration on genetic and environmental influences on cognition (Vo et al., 2022). Specifically, semantic fluency and episodic memory illustrated patterns in which genetic influences were highest at short sleep (i.e., 4 hours) and shared environmental influences were highest at long sleep (i.e., 10 hours), cross-sectionally (Vo et al., 2022). These findings are consistent with the diathesis-stress model (Boardman, Daw & Freese, 2013) whereby genetic influences on health outcomes (e.g. cognitive performance) are predicted to be maximized in adverse environments such as short sleep durations or non-optimal sleep quality. The previous findings of an exacerbation of genetic influences on cognitive performance within short sleep contexts may align with work showing ineffective clearance of neurotoxic waste products such as amyloid- β (Aβ) deposits in shorter sleep durations (Spira et al., 2013), a biomarker that is associated with AD. Further, under the diathesis-stress model, genetic influences are expected to be minimized in more optimal environments such as in the case of adequate and recommended sleep durations. Of note, optimal and adequate sleep is defined as

sufficient sleep quantity based on an individual's age group (i.e., 8 to 10 hours for teens, 7 to 9 hours for young adults and adults, and 7 to 8 hours for older adults; National Sleep Foundation, 2021) and adequate sleep quality (Buysse, 2014). As such, our initial findings demonstrated decreasing genetic influences across four to ten hours of sleep duration.

While the aforementioned studies advanced the sleep research field by applying informative biometrical models to the study of sleep and health, much remains to be understood. Indeed, while prior research has examined gene-environment interplay (e.g., Watson et al., 2010, 2012; Watson et al., 2014; Vo et al., 2022), the specific genetic factors that may be driving the associations are unknown. However, recent findings do suggest a few early candidate genes and pathways that may underly circadian rhythms, sleep disorders, sleep durations, sleep and wake onset times, and sleep patterns (e.g., circadian locomotor output cycles kaput gene (CLOCK; Allebrandt et al., 2010; Patke et al., 2017), aryl hydrocarbon receptor nuclear translocator link (ARNTL; Evans et al., 2013), and 5-hydroxytryptamine transporter linked polymorphic region (5-HTTLPR; Carskadon, Sharkey, Knopik & McGeary, 2012; Brummett et al., 2007). Despite these early candidate genes and pathways that underlie sleep, emerging work on the genes and gene pathways that underlie sleep-cognition associations have considered those that relate to AD risk.

Polygenic risk scores (or polygenic scores; PGS) for AD and the examination of the gene encoding apolipoprotein E (*APOE*), particularly the Ɛ4 allele, have been central in recent sleep, cognition, and AD research (e.g., Spira et al., 2017; Najar et al., 2021;

Leng et al., 2021) and warrant additional investigation. Complex traits such as late-onset AD are polygenic and the associated genetic variants may be aggregated to yield a polygenic score (PGS) that is based on the weighted cumulative estimate of the genetic variant's contribution to a particular trait (e.g., AD-PGS; Leonenko et al., 2021). Recent findings have found associations between higher genetic risk for AD (i.e., higher AD-PGS scores) and shorter sleep duration, particularly in those older than 55 years (Leng, Ackley, Glymour, Yaffe & Brenowitz, 2021). Moreover, higher genetic risk for AD was found to be associated with more daytime sleepiness, associated with an increased need for deep sleep, and associated with more sleep intensity during slow wave sleep (SWS; Muto et al., 2021), within men. Additionally, the *APOE* Ɛ4 allele, the major signal in AD-PGS, was the first established genetic risk factor for late onset AD, and is also associated with increased Aβ deposition (Hwang et al., 2018) and cognitive decline (Rawle et al., 2018). Recent research has revealed that individuals classified as short sleepers (i.e., those sleeping less than 7 hours per night) exhibit shorter telomere length, indicating greater biological aging and cellular senescence (Dhillon et al., 2022). Furthermore, individuals who carry the *APOE* Ɛ4 allele and who are also short sleepers demonstrate the shortest telomere lengths, suggesting a cumulative effect of the risk factors. This combination of being both a short sleeper and an *APOE* Ɛ4 carrier is further associated with lower concentrations of plasma soluble receptor for advanced glycation end product (sRAGE), leading to increased plasma Aβ levels (Dhillon et al., 2022)

Moreover, *APOE* Ɛ4 has also been associated with increased risk for sleep disorders (e.g., sleep-disordered breathing; Kadotani et al., 2001; Gottlieb et al., 2004),

increased risk for shorter sleep durations (Leng, Ackley, Glymour, Yaffe & Brenowitz, 2021), and increased risk for sleep disturbances, sleep latency and sleep efficiency, with stronger associations found in individuals aged 50 or older (Spira et al., 2017). Thus, given the complex relationship between AD-PGS, *APOE* Ɛ4, sleep, and cognition, it is increasingly necessary to incorporate genetic measures into present examinations of sleep and cognition, an area that has been underexplored. This dissertation aims to expand upon gaps within the current literature through the incorporation of measured genetic factors into biometrical models (e.g., Bruins et al., 2022) to further clarify the sleep-cognition associations previously observed.

Sleep-Cognition Timescales

Limited longitudinal studies have explored associations between sleep and cognition, with some evidence suggesting that sleep characteristics may predict future cognitive performance (e.g., Lo et al., 2014). For instance, reductions in sleep duration, even by one hour at baseline, were linked to poorer global cognitive performance as well as increased ventricle expansion after two years, suggestive of a greater decline in cognitive performance as well as greater brain atrophy. Other research has demonstrated associations between baseline impaired sleep quality and baseline sleep efficiency, predictive of faster Aβ accumulation over time (Winer et al., 2021). Moreover, shorter sleep durations, longer sleep durations, and poorer sleep quality, at baseline were predictive of poorer later-life global cognitive functioning (e.g., TELE and Telephone Interview for Cognitive Status (TICS)) in middle-aged individuals (Virta et al., 2013). However, it is noted that most of the previously mentioned examinations of the sleep-

cognition relationship over time have been limited to examinations of global cognitive outcomes or general cognitive functioning as opposed to examinations within specific cognitive domains. Moreover, another notable gap exists within the current literature as very few studies have explored the sleep-cognition association beyond traditional pre- and post- designs, often ones with an intervention, or extended the examination beyond two timepoints (e.g., baseline and the subsequent measurement). This limitation is compounded by the prevalent focus in laboratory settings common in the sleep literature, where the intricate micro-changes, such as daily fluctuations in one's sleep patterns (Knutson et al., 2007), are frequently overlooked, underscoring the critical need for additional examination of the nuanced dynamics within the sleep-cognition relationship. As such, a more comprehensive investigation of sleep and cognition, particularly one that may be more ecologically valid and acknowledges the subtleties that may emerge in daily life, is warranted.

Micro-level assessments of sleep-cognition associations, particularly examinations on burst timescales (i.e., minutes, hours, days) through burst designs would provide ecologically valid measurements as they occur within an individual's daily life (Sliwinski et al., 2018). Moreover, sleep has been shown to impact short-term (i.e., next day) cognitive performance in various domains such as memory, attention, and vigilance (e.g., Miyata et al., 2010, Xu et al., 2011, Durmer & Dinges, 2005, Eugene & Masiak, 2015, Smith et al., 2002). Current work by Lucey and colleagues (2021) explored the daily relationship between objectively measured sleep characteristics and cognitive performance across a neuropsychological testing battery including cognitive tests related

to recall, memory, and processing speed. Performance on the neuropsychological battery was then averaged to index a preclinical Alzheimer Cognitive Composite score. Over the span of six nights, results indicated the lowest performance on the cognitive composite at both higher and lower values of total sleep duration (Lucey et al., 2021). Although this study did not consider subjective measures of sleep, it highlighted the potential for intensive longitudinal assessments, within a burst-design context, in understanding the dynamic interplay between sleep and cognition. Leveraging advancements in technology, such as smartphone applications for ambulatory data collection, could further enhance our understanding of this relationship by examining whether phenotypic associations that are often found in macro-time scales spanning months, years, and decades may also be observable within micro-time scales spanning hours, days and weeks, particularly with the goal of modeling the dynamics and processes between sleep and cognition.

While intensive and burst longitudinal data has been explored in various contexts including sleep and stress (Yap, Slavish, Taylor, Bei & Wiley, 2020; Yap, Bei & Wiley, 2021), sleep and attachment (Haydon & Moss, 2020), sleep and physical activity (Kishida & Elavsky, 2016; Flueckiger, Lieb, Meyer, Witthauer & Mata, 2016), and objectively measured sleep and cognition (Lucey et al., 2021), there is still limited research on the relationship between micro-level sleep and cognition. To our knowledge, only one examination, situated within an ecologically valid context outside of the laboratory setting, of older African American individuals was conducted (Galmaldo et al., 2010). Galmaldo and colleagues (2010) found greater indications of cognitive decline the further an individual deviated from their typical levels of sleep duration. However,

whether these patterns would be preserved in assessments of daily sleep quality, and in more general populations, warrants further attention. Overall, burst ambulatory data analysis could facilitate the further exploration of day-to-day associations between sleep and cognition, capturing the variability and fluctuations in sleep quality across different days (Knutson et al., 2007), providing additional understanding to the complex and dynamic sleep-cognition relationship.

Purpose and Aims of the Dissertation

The primary purpose of this dissertation is to address gaps within the current sleep and cognition literature by assessing the sleep and cognition relationship both at the macro-level (i.e., Study 1) in individuals in mid- to late-life from the Interplay of Genes and Environment across Multiple Studies (IGEMS; Pedersen et al., 2019) and at the micro-level (i.e., Study 2) across individuals who are approaching midlife in the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife; Wadsworth et al., 2019) while incorporating novel approaches that have yet to be applied extensively within the current sleep and cognition literature (e.g., informative twin designs, biometrical approaches, and ecological ambulatory momentary assessments approaches).

The dissertation aims were evaluated within two studies. First, Study 1 of this dissertation aims to expand upon prior work by further examining the sleep-cognition relationship cross-sectionally, while leveraging valuable information from behavioral genetic approaches that utilize twin data and measured genetic influences (i.e., AD-PGS)

to further delve into examining the mechanisms that may underlie the differing patterns of genetic and environmental influences on cognitive performance at varying levels of sleep. Next, Study 2 of this dissertation aims to evaluate whether sleep and cognition associations may hold in burst ambulatory contexts (e.g., day-to-day associations), particularly in individuals approaching midlife across a two-week period, to understand the dynamics and processes between sleep and cognition within the micro-level, while additionally examining the potential moderating role of *APOE*. Moreover, study 2 aims to assess whether macro-level sleep-cognition associations persist and are adequately captured within micro-level timescales.

Aims & Research Questions

Collectively, study 1 and study 2 of this dissertation aims to demonstrate the necessity to further examine sleep (both quantity and quality) as a potential and informative modifiable lifestyle factor that may be intervened and modified prior to the onset of cognitive dysfunction, neurodegeneration, and AD and ADRD onset. Moreover, examining sleep-cognition associations through twin designs and biometrical models that leverage twin data from IGEMS which comprise data from individuals in their mid- to late-life and from leveraging burst and ambulatory data from CATSLife which comprise data from individuals who are approaching midlife, this dissertation aims to yield a broader understanding of sleep-cognition associations across the lifespan. Study 1 leverages informative twin data from samples within the Interplay of Genes and Environment across Multiple Studies (IGEMS) consortium (Pedersen et al., 2019). Study 2 leverages ambulatory burst data from a subsample of participants from the Colorado

Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife; Wadsworth et al., 2019).

Aim 1: Examine the impact of subjective sleep measures across a wide variety of cognitive domains with informative twin designs while incorporating the influences from measured genetic risks (i.e., AD-PGS).

Research Q1: Given the previously found patterns of higher genetic influences at the shorter end of sleep duration (i.e., 4 hours of sleep duration) and higher environmental influences at longer ends of sleep duration (i.e., 10 hours of sleep duration) on cognitive performance, particularly for Verbal Fluency and Episodic Memory (Vo et al., 2022), what is the role of sleep disturbances compared to sleep duration?

Research Q2: What added information do we gain when incorporating measured genetic factors into the analyses, particularly a measured genetic factor of Alzheimer's disease (AD-PGS)?

Aim 2. Examine associations between sleep quality and cognition within a 14-day micro-level timescale repeated measures burst design within individuals approaching midlife.

Research Q1: At the between-person level, is sleep quality a predictor of cognitive performance, across the four cognitive tasks?

Research Q2: At the within-person level, on days in which individuals reported sleep quality above or below their average sleep quality (i.e., person-mean) are there associated decreases or increases in their performance across the four cognitive tasks?

Research Q3: Does *APOE* Ɛ4 status moderate the associations between sleep quality and cognitive performance?

Hypotheses

Hypothesis 1.1

As sleep quality comprises of various attributes related to sleep efficiency, sleep latency, sleep maintenance, and sleep duration (Nelson, Davis & Corbett, 2022) and sleep duration is a sub-component within sleep quality scales (e.g., Pittsburgh Sleep Quality Index; PSQI; Buysse, 1989), the observed patterns for sleep duration will likely be observed and confirmed with sleep quality measures (e.g., sleep disturbances). Based on prior work (e.g., Vo et al., 2022), we expect that elevated genetic influences will be observed within poor sleep contexts, including both shorter sleep durations and increased sleep disturbances, providing a more robust examination of sleep as a moderator of the underlying etiologies of cognition.

Hypothesis 1.2

Previous studies have shown that an elevated genetic risk for Alzheimer's disease is linked to shorter sleep durations, increased daytime sleepiness, and a greater need for deeper and more restorative sleep stages (e.g., Leng et al., 2021; Muto et al., 2021)

whereby the detrimental effects to sleep architecture have been associated with poorer cognitive outcomes (Scullin & Bliwise, 2015; Yafee, Falvey & Hoang, 2014). Furthermore, recent research indicates that genetic susceptibility to Alzheimer's disease is also associated with adverse cognitive outcomes, including poorer cognitive performance (e.g., Gustavson et al., 2023), reduced bilateral hippocampal volumes (Axelrud et al., 2018), and an accelerated rate of cognitive decline (Kauppi et al., 2022; Najar et al., 2023; Ge et al., 2018, Louwersheimer et al., 2016). Building upon these associations, we hypothesize that integrating the AD-PGS within the biometrical twin model, along with age and sleep moderation, will reveal distinct etiological patterns at opposite ends of the spectrum of genetic risk for AD.

Hypothesis 2.1

The current literature suggests sleep quality may be a predictor of cognitive performance with poorer sleep quality being associated with declines in abilities spanning across multiple cognitive domains (e.g., executive functioning, working memory, visual working memory, episodic memory, attention; Regestein et al., 2004; Sternberg et al., 2013; Xie et al., 2019; Aly & Moscovitch 2010; Inostroza & Born, 2013; Van Der Helm et al., 2011; Miyata et al., 2013). We hypothesize that sleep quality, at the between-person level, will be a significant predictor of cognitive performance such that individuals who tend to have better sleep quality will demonstrate better performance across the 14 days on the cognitive tasks spanning perceptual speed, working memory, paired associated memory, and executive functioning (e.g., Symbol Search, Dot Memory, Shopping List, and Stroop Task). In contrast, individuals who tend to have poorer sleep

quality are hypothesized to demonstrate poorer performance on the cognitive tasks across the 14 days.

Hypothesis 2.2

To our knowledge, limited studies have examined micro-level sleep and cognition associations (e.g., Lucey et al., 2021) and only one prior study, specifically examining older African-American individuals, has examined the within-person sleep and cognition associations within an ecologically-valid design (Gamaldo et al., 2010). Gamaldo and colleagues (2010) found that across 14-21 days, individuals who deviated from their expected average sleep duration showed greater indications of cognitive decline (Gamaldo et al., 2010). Based on this prior research, we hypothesize that variations from one's typical pattern (i.e., the within-person effect) will be a significant predictor of cognitive performance across the four cognitive tasks. In other words, we hypothesize that on days in which individuals reported better sleep quality on a particular day, there are associated increases in cognitive performance. On the other hand, we hypothesize that on days in which individuals reported poorer sleep quality on a particular day, there are associated decreases in cognitive performance.

Hypothesis 2.3

As *APOE* Ɛ4 status is an established genetic risk factor for dementia and late-onset Alzheimer's disease as well as showing associations with increased risk for sleep disorders (e.g., sleep-disordered breathing; Kadotani et al., 2001), shorter sleep durations (Leng et al., 2021), and sleep disturbances including both sleep latency and sleep

efficiency (e.g., Spira et al., 2017) we hypothesize that *APOE* Ɛ4 status will moderate the associations between sleep quality and cognitive performance. Specifically, we expect to see patterns in which individuals who have poor sleep quality, and are Ɛ4 carriers, will demonstrate the poorest cognitive performance across all cognitive tasks.

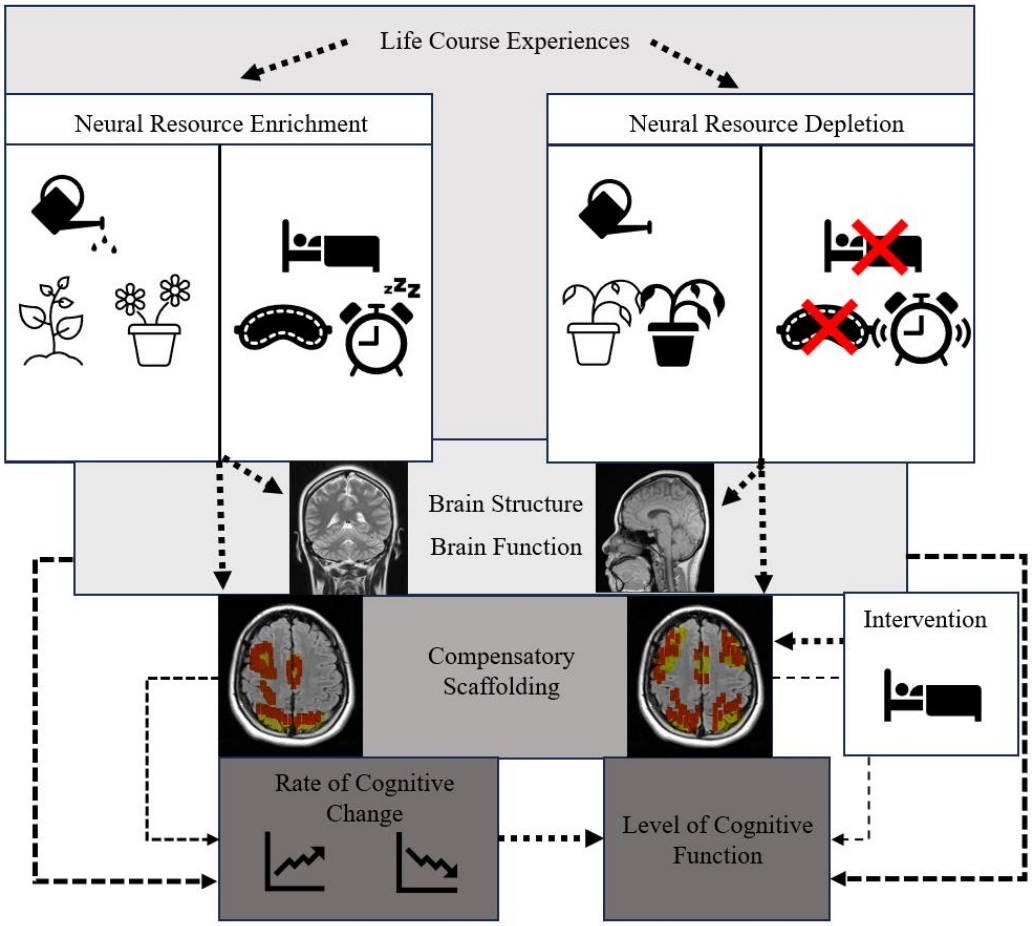

Figure 0.1. Adapted conceptual model of the scaffolding theory of aging and cognition-revised highlighting sleep pathways (STAC-r; Reuter-Lorenz & Park, 2014).

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Chapter Two:

Subjective Sleep Traits and Cognition Across Mid- to Late-Adulthood: a Cross-sectional Study of Gene-Environment Interplay

A significant linkage between sleep and cognitive abilities has been established where poor sleep—including both extreme sleep durations and poorer sleep quality—is associated with poorer cognitive functioning across a wide variety of domains (e.g., Xie, Berry, Lustig, Deldin & Zhang, 2019; Aly & Moscovitch, 2010; Inostroza & Born, 2013; Baldo, Schwartz, Wilkins & Dronkers, 2006), general cognitive decline (Ma, Lian, Zheng, Shi, Zhong & Xie, 2020; Xiong et al., 2024; Yuan et al., 2022), and an increased risk of Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD; Benedict et al., 2015; Peter-Derex, Yammine, Bastuji & Croisile, 2015; Irwin & Vitiello, 2019; Bubu et al., 2017; Xiong et al., 2024). Notably, there are overall decreases in total sleep time, sleep efficiency, and slow-wave sleep as age increases, with concurrent increases in wake after sleep onset (Ohayon et al., 2004), where these disruptions to sleep are further accelerated by AD pathology (Wang & Holtzman, 2020). These age-related alterations in sleep architecture occur alongside normative declines in various cognitive abilities such as reasoning, spatial visualization, memory, and processing speed during late life (e.g., Salthouse, 2009), with varying levels of decline manifesting differentially among individuals (e.g., Salthouse, 2006; Horn & Blankson, 2005; Wilson et al., 2002). While the phenotypic association between sleep and cognition has been well-established, recent advances in behavioral genetic approaches and their application to the examination of sleep, cognition, and their linkage, have shed new light on the contributions of genetic

and environmental factors to individual differences in cognition and cognitive aging. Moreover, these advances have shed additional light on how modifiable factors, such as sleep features commonly associated with aging (e.g., sleep duration; Vo et al., 2022) and sleep disturbances may impact the etiology of cognition, with implications for cognitive aging and AD/ADRD risk.

The behavioral genetic-informed sleep and cognition literature has shown promising strides and advancements over the past two decades, including twin-based studies to estimate genetic and environmental contributions to objectively measured data (e.g., EEG, polysomnography, and actigraphy data; Ambrosius et al., 2008; Rusterholz et al., 2018; Sletten et al., 2013; Breitenstein et al., 2021; Gehrman et al., 2019; Gehrman et al., 2011), and subjectively measured data (e.g., Watson et al., 2014a; Watson et al., 2014b; Barclay et al., 2013). Moreover, molecular genetic approaches and GWAS studies have also increased (e.g., Jansen et al., 2019; O'Connell et al., 2021; Lane et al., 2017). However, while there have been some examinations of gene-environment interplay in the context of sleep and cognition (e.g., Vo et al., 2022), studies that extend the classical twin model to integrate measured genetic factors remain relatively scarce (e.g., Bruins et al., 2022).

The genetic and environmental architecture of the various subcomponents of sleep quality as informed by the Pittsburgh Sleep Quality Index (PSQI) (i.e., subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction), show substantial genetic overlap between the subcomponents, except for sleep medication and daytime dysfunction (Madrid-Valero et.

al., 2022). Heritability estimates ranged from 30%-50% for the global PSQI measure consistent with current research examining overall sleep quality (e.g., Madrid Valero et al., 2022; Madrid-Valero et al., 2020; Kocevska et al., 2021; Gasperi et al., 2017; Genderson et al., 2013) as well as corroborating heritability estimates from research examining sleep apnea and insomnia (e.g., Madrid-Valero et al., 2021; Barclay et al., 2015). Indeed, moderate to high heritability of sleep quality is observed across various ages where genetic factors have been found to account for roughly 34%-43% of the variance in sleep quality across adolescents (Taylor et al., 2015), young adults (Barclay et al., 2010), and adults (Genderson et al., 2013; Madrid-Valero et al., 2018). For sleep duration, heritability estimates had a wider range and ranged from 26%-70% spanning estimates from children, adolescents/early adults, and adults, with the lowest estimates observed in adults (Sletten et al., 2013; Butkovic et al., 2014; Genderson et al., 2013; Madrid-Valero et al., 2018). Gehrman and colleagues (2019) found evidence for a substantial influence of genetic factors on actigraphy-measured sleep traits including total sleep time and sleep efficiency with heritability estimates ranging from 44%-88%, with the heritability for sleep efficiency and periods of restless sleep representing the highest estimates within adults. While the number of twin studies examining the relative genetic and environmental influences on various sleep parameters have increased over the past few decades, there are insufficient studies that examine these associations within the context of gene-environment interplay. To our knowledge, three studies have examined the gene-environment interplay between sleep and health (i.e., body mass index; Watson et al., 2014), sleep and depressive symptoms (Watson et al., 2014), and sleep and

externalizing behaviors (Barclay et al., 2013), with only one prior study having examined gene-environment interplay in the context of sleep and cognition (Vo et al., 2022).

Findings from Vo et al., (2022) suggested genetic and environmental contributions for semantic fluency and episodic memory vary by differing levels of sleep duration. Notably, shorter sleep durations (i.e., 4 hours) were associated with higher additive genetic influences (A) on cognitive function, while longer sleep durations (i.e., 10 hours) showed heightened shared environmental influences (C). Similar trends, although not statistically significant, were observed for processing speed and spatial-visual reasoning. Individual-specific environmental influences (E) on cognition were not significantly moderated by sleep duration. Altogether, the findings align with the diathesis-stress model (Boardman, Daw, & Freese, 2013), suggesting that genetic impacts on health outcomes, i.e. cognitive performance in the present case, are most pronounced in adverse environments such as short sleep durations. Conversely, genetic influences are minimized in more optimal environments, such as with adequate and recommended sleep durations. Different mechanisms underlie shorter versus longer sleep durations and, likewise, poorer or better sleep quality. For instance, shorter sleep durations, longer sleep latency, daytime sleepiness, and nocturnal awakenings (i.e., sleep disturbances) are associated with ineffective clearance and increased accumulation of neurotoxic waste products such as β-amyloid deposits (Aβ), a biomarker linked to Alzheimer's disease (Spira et al., 2013; Shokri-Kojori et al., 2018; Brown et al., 2016; You et al., 2019), albeit typically with sample sizes under 80 (N's ranging from 22 to 77). Similar associations have been observed in diverse samples controlling for the *APOE* genotype, where the ε4

variant is a risk factor for late-onset AD, with short sleep duration associated with poorer memory performance in cognitively unimpaired adults aged 65 and older (Winer et al., 2021). Furthermore, Aβ may accumulate preferentially in hippocampal and thalamic structures even after one night of shortened sleep (Shokri-Kojori et al., 2018), and in the brainstem and precuneus with increased nocturnal awakenings or reduced slow-wave sleep due to disturbances in sleep maintenance (Varga et al., 2016) and daytime sleepiness (You et al., 2019).

Neuroinflammatory processes, such as elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6), are observed in chronic short sleep and sleep deprivation contexts (Krueger, Majde & Rector, 2011; Meier-Ewert et al., 2004; van Leeuwen et al., 2009), as well as in poor sleep quality and increased sleep disturbance contexts (D'Antono & Bouchard, 2019; Irwin, Olmstead & Carroll, 2016), and are adversely associated with cognitive performance (Vgontzas et al., 2004; Hu et al., 2021). Poorer sleep quality is also associated with increased levels of inflammation (D'Antono & Bouchard, 2019) as assessed through a composite inflammation score containing CPR, IL-6, and TNF-α. Increased sleep disturbances are linked to increased systemic inflammation, a mechanism underlying cognitive decline and neurocognitive disorders (Bradburn et al., 2019). Of note, proinflammatory states may modulate sleep features, with heightened inflammation (e.g., increased IL-6) contributing to more sleep disturbances and daytime fatigue (Wang et al., 2019). Sleep disturbances have been shown to predict AD, amyloid accumulation, and cognitive decline (Hahn et al., 2013; Winer et al., 2020; Lucey et al., 2021), with further reports showing that impaired sleep

architecture is associated with increased tau burden (Barthelemy et al., 2020; Winer et al., 2019). Together, the current literature suggests other gene pathways to consider in the interplay between sleep features (both duration and disturbances) and cognitive functioning.

Notwithstanding the progress made by classical twin studies and behavior genetic approaches applied in the previously mentioned studies, a limitation exists in their inability to pinpoint specific genetic factors that might underlie the observed interactions, an aspect where molecular genetic studies prevail. Indeed, phenotypes like sleep and cognition are highly complex and are best explained by polygenic influences (e.g., Tsapanou, Gao, Stern & Barral, 2020; Leonenko et al., 2021). In the present study, we incorporate a PGS for Alzheimer's disease (AD-PGS), derived from large-scale genome wide association studies (Kunkle et al., 2019), as increased risk for cognitive aging and AD has been associated with poorer sleep quality, shorter sleep duration, an increased need for deeper sleep, increased daytime sleepiness, an accelerated rate of cognitive decline, diminished cognitive ability, an increased burden of beta-amyloid in the brain (e.g., Leng et al., 2021; Muto et al., 2021; Kauppi et al., 2020; Porter et al., 2018; Tank et al., 2022; Chaudhury et al., 2019). In addition, Kauppi and colleagues (2020) found that a higher polygenic risk for late-onset Alzheimer's disease (PGS-LOAD) predicted age-related cognitive decline and was a stronger predictor of age-related cognitive decline, above and beyond the *APOE* risk allele Ɛ4, suggesting the saliency to examining AD-PGS within current examinations of sleep and cognition. Moreover, increased PGS-LOAD is associated with poorer performance on fluid intelligence and matrix completion

tasks, as well as smaller left hippocampal volume and total body volume (Tank et al., 2022). However, genetic risk for AD not only confers a risk of greater aggregation of Aβ but may also contribute to heightened susceptibility to cognitive decline in the presence of Aβ accumulation (Ge et al., 2018). However, it is essential to note that not all studies yield supporting evidence for the effect of AD-PGS on cognitive decline (e.g., Harris et al., 2014; Ritchie et al., 2020), warranting additional examinations to clarify the relationship.

In the present study we leveraged measured genotypic information in the form of a PGS for Alzheimer's disease (AD-PGS), which indexes the measured portion of the genetic variance of an otherwise latent additive genetic factor. In other words, the latent additive genetic influences capture the residual genetic variance not explained by the AD-PGS. In expanding the model to include the AD-PGS, we aim to determine if the AD-PGS moderates the relative contribution of environmental influences on cognitive performance, allowing for tests of genotype-environment interplay (e.g., Dolan et al., 2021; Karlsson et al., 2022; Bruins et al., 2022). Within these environment-by-PGS designs, both estimates from the latent PGS and the background latent additive genetic influence are estimated, as well as the latent shared and unique environmental influences on a phenotype (Bruins et al., 2022).

Despite the extensive body of research examining sleep and cognition associations, which has primarily focused on phenotypic links, a significant gap exists in the literature to specify specific etiologies underlying the sleep-cognition relationship. Further, this research gap calls for expanded investigations into measured genetic factors,

offering potentially crucial insights into understanding sleep, cognitive aging, and the risk of AD. The present study utilized archival data from the Interplay of Genes and Environment across Multiple Studies (IGEMS; Pedersen et al., 2013; 2019) consortium which encompasses individuals and their cotwins spanning mid- to late-life adulthood periods. Our investigation seeks to explore additional insights that may be gained by examining sleep disturbance indicators as well as sleep duration measures. Based on our prior work (e.g., Vo et al., 2022), we hypothesize that elevated genetic influences will be observed at shorter sleep durations and increased sleep disturbances. Furthermore, we examine whether individuals at higher genetic risk for AD exhibit similar or differing etiological patterns in cognitive performance compared to those at lower genetic risk for AD. We hypothesize that environmental contributions, shared and person-specific, will show distinct environmental etiologies at opposite ends of the spectrum of genetic risk for AD (PGSxC, PGSxE). Relatedly, we aim to gauge the extent to which AD-PGS accounts for the amplified genetic influences observed at shorter sleep durations as we observed in our prior work (Vo et al, 2022), and extend findings to sleep disturbances.

Methods

Sample

The present sample comprised archival data from the IGEMS consortium (Pedersen et al., 2019) which encompassed individuals and their cotwins spanning mid- to late-life adulthood periods. Specifically, data from seven twin studies were incorporated into the analysis sample and comprised a total of 3900 participants (845

complete pairs of monozygotic (MZ) twins and 1105 complete pairs of dizygotic twins (DZ)). Zygosity was determined through either self-reported questionnaire responses or registry-based information regarding twin and co-twin physical similarities. Zygosity was further validated through DNA analysis and genotyping for select studies (Pedersen et al., 2013; Christiansen et al., 2003). Within the present study, DZ same-sex twins and DZ opposite-sex twins were collapsed into a single DZ group. Furthermore, the analysis sample exclusively included data from twin pairs who both contributed data on the primary moderator variables (i.e., sleep, AD-PGS) and at least one score among the six cognitive tasks. The overall analysis sample ranged from 46-92 years old, with an average age of 62.34 (SD=10.39), and 38.79% female (see Table 1.1). Detailed descriptions of each study are provided below and available elsewhere (Pedersen et al., 2019).

Swedish studies

Swedish Adoption Twin Study of Aging (SATSA)

The Swedish Adoption Twin Study of Aging (SATSA), a longitudinal investigation conducted from 1986-2014, compiled data from both reared-together and apart same-sex adult twins over 30 years and across 19 waves of data collection (Finkel & Pedersen, 2004). Participants were recruited from the Swedish Twin Registry, and SATSA assessments encompassed questionnaires and in-person assessments (IPT) that assessed cognitive and physical function, along with behavioral evaluations. The analysis sample included SATSA data from the 10th in-person assessment (IPT), which included

data on participants' sleep (both duration and disturbances), AD-PGS, and cognitive measures (n = 144; 26 complete MZ pairs and 46 complete DZ pairs, 52.78% *F*; see Table 1.1). The SATSA sample had an age range of 64.21 to 91.37 and an average age of 74.78(SD=5.83).

Origins of Variance in the Old-Old (OCTO-Twin)

The Origins of Variance in the Old-Old (OCTO-Twin) longitudinal study, spanning from 1991 to 2002, collected data from same-sex twins aged over 80 years at the baseline assessment (McClearn et al., 1997). The analysis sample incorporated OCTO-Twin data from the intake wave which included data on participant's sleep (both duration and disturbances), AD-PGS, and cognitive measures (n=58; 22 complete MZ pairs and 7 DZ pairs, 62.07% *F*; see Table 1.1). The OCTO-Twin sample had an age range of 79.4 to 86.7 with an average age of 82.38(SD=1.74).

Longitudinal Study of Gender Differences in Health Behavior and Health among Elderly (GENDER)

The Longitudinal Study of Gender Differences in Health Behavior and Health among Elderly (GENDER) comprised opposite-sex twin pairs (Gold et al., 2002), encompassing only DZ twins born between 1906 and 1925. The analyses incorporated GENDER data from the intake wave which included data on participant's sleep (only sleep disturbances), AD-PGS, and cognitive measures (n=366; 183 complete DZ pairs, 50% *F*; see Table 1.1). The GENDER sample had an age range of 69.8 to 80.7 with an average age of 74.58(SD=2.71).

Danish studies

Middle Age Danish Twins Study (MADT)

The Middle Age Danish Twins Study (MADT) comprises twin pairs recruited from the Danish Twin Registry (Osler et al., 2008; Pedersen et al., 2019). Data for MADT were collected between 1998-2011. The analysis sample incorporated MADT data from the intake wave which included data on participants' sleep (both sleep duration and sleep disturbances), AD-PGS, and cognitive data (*n*=1454; 276 complete MZ pairs, 451 complete DZ pairs, 47.66% *F*; see Table 1.1). The MADT sample had an age range of 46.0 to 68.0 years and had an average age of 55.64(*SD*=5.99).

Longitudinal Study of Aging Danish Twins (LSADT)

The Longitudinal Study of Aging Danish Twins (LSADT) comprises same-sex twin pairs born before 1920, recruited from the Danish Twin Registry (Christensen et al., 1999). The analysis sample incorporated LSADT data from the intake wave which included data on participants' sleep (only sleep disturbances), AD-PGS, and cognitive data (*n*=286; 63 complete MZ pairs, 80 complete DZ pairs, 70.63% *F*; see Table 1.1). The LSADT sample had an age range of 75.0 to 92.0 years and had an average age of 79.54(*SD*=3.78).

United States study

Vietnam Era Twin Study of Aging (VETSA)

The Vietnam Era Twin Study of Aging (VETSA) is a longitudinal study comprising exclusively male twins recruited from the Vietnam Era Twin Registry (Kremen, Franz & Lyons, 2019), who served in the military between 1965 and 1975. The analysis sample incorporated VETSA data from the first intake wave which included data on participants' sleep (both sleep duration and sleep disturbances), AD-PGS, and cognitive data (*n*=1096; 315 complete MZ pairs, 233 complete DZ pairs, 0% *F*; see Table 1.1). The VETSA sample had an age range of 51.1 to 60.7 years and had an average age of 55.9(*SD*=2.5).

Australian study

*Older Australian Twins Study (*OATS)

The Older Australian Twins Study (OATS) consisted of Australian twins aged over 65 years and were drawn from the Australian Twin Registry (Sachdev et al., 2009). The analysis sample incorporated OATS data from the first intake wave which included data on participants' sleep (only sleep disturbances), AD-PGS, and cognitive data (*n*=496; 143 complete MZ pairs, 105 complete DZ pairs, 65.12% *F*; see Table 1.1). The OATS sample had an age range of 65.25-90.06 years and had an average age of 71.28(*SD*=5.5).

Measures

Cognitive Measures.

Cognitive tasks evaluating performance in semantic fluency, episodic memory, attention, working memory, processing speed, and verbal ability were assessed (see Table 1.2). To ensure comparability across all studies, cognitive measures were harmonized across the IGEMS sample (Pahlen et al., 2018; Gatz et al., 2020). Briefly, the harmonization procedure involved converting raw scores to a percent correct scale, followed by T-score transformations based on a referent group standardization sample (age group: 65-69.99; Pahlen et al., 2018). Brief descriptions of the cognitive tasks are provided below.

Episodic Memory (Wordlist)

Episodic memory was assessed using the Wordlist task within six of the studies within our analysis sample (SATSA, GENDER, OATS, VETSA, LSADT, MADT; see Table 1.2), encompassing the single cognitive task with the largest sample size (N=3795). For this task, participants were asked to either listen or read aloud up to 16 related, or unrelated, words and immediately recall as many words as possible. For the two Swedish samples (SATSA and GENDER), episodic memory was assessed through the Consortium to Establish a Registry for Alzheimer's Disease instrument (CERAD; Morris et al., 1993). For the two Danish samples (LSADT, MADT) and the one Australian sample (OATS), episodic memory was assessed through the Rey Auditory Verbal Learning Test (RAVLT). For the one United States study (VETSA), episodic memory was assessed

through the California Verbal Learning Test-Version II (CVLT). The average score for the Word List task within the analysis sample was 51.19(*SD*=11.55).

Semantic Fluency (Animal Naming)

Semantic fluency was assessed using the Animal Naming task within four of the studies within our analysis sample (VETSA, LSADT, MADT, OATS; see Table 1.2). For this task, participants were asked to name as many unique animals as possible within one minute without any duplicates. The average score for the Animal Naming task within the analysis sample was 52.76(*SD*=10.89).

Attention (Digits Forward)

Attention was assessed using the Digits Forward task within six of the studies within our analysis sample (SATSA, OCTO-Twin, OATS, VETSA, LSADT, MADT; see Table 1.2). For this task, participants were tasked to verbally repeat numerical digits in the same sequence in which they were presented. For the Swedish samples (SATSA, OCTO-Twin), the digits forward task was administered through a modified WAIS with a maximum score of 9. For the United States sample (VETSA), the digits forward task was administered through the WMS-III which had a maximum score of 11. For the two Danish samples (LSADT and MADT), the digits forward task was administered through the WAIS which had a maximum score of 14. Lastly, for the Australian sample (OATS), the digits forward task was administered through the WAIS-III which had a maximum score of 9. The average score for the Digits Forward task in the analysis sample was 52.39(*SD*=11.29).

Working Memory (Digits Backward)

Working memory was assessed through the Digits Backward task within six of the studies within our analysis sample (SATSA, OCTO-Twin, OATS, VETSA, LSADT, MADT). For this task, participants were tasked to verbally repeat numerical digits in the reverse sequence in which they were presented. For the Swedish Samples (SATSA, OCTO-Twin), the digits backward task was assessed through a modified Wechsler Adult Intelligence Scale (WAIS) that had a maximum score of 8. For the two Danish samples (LSADT, MADT), the digits backward task was assessed through the WAIS and had a maximum score of 14. For the United States study (VETSA), the digits backward task was administered through the third edition of the Wechsler Memory Scale (WMS-III) which had a maximum score of 10. Lastly, the Australian sample (OATS) administered the digits backward task through the third edition of the Wechsler Adult Intelligence Scale (WAIS-III) which had a maximum score of 8. The average score for the Digits Backward task in the analysis sample was 51.88(*SD*=11.48).

Verbal Ability (Synonyms)

Verbal ability was assessed through the Synonyms task within four of the studies within our analysis sample (SATSA, OCTO-Twin, GENDER, VETSA), encompassing the single cognitive task with the lowest sample size (*N*=1643). Specifically, the Synonyms task measures verbal ability where participants were given a target word and were tasked with providing a selection of a corresponding synonym within a list of provided options. The Swedish samples (SATSA, OCTO-Twin, and Gender)

administered the Synonyms task through the WAIS which had a maximum score of 30. The United States sample (VETSA) administered the Synonyms task through the armed forces qualification test (AFQT) subscale which had a maximum score of 25. The average score for the Synonyms task was 52.95(*SD*=8.19).

Processing Speed (Symbol Digit)

Processing speed and accuracy were assessed through the Symbol Digit task within five of the studies within our analysis sample (SATSA, OCTO-Twin, GENDER, LSADT, MADT). Within the Swedish (SATSA, OCTO-Twin, GENDER) and Danish samples (LSADT, MADT), participants were tasked to verbally state a single digit, ranging from one to nine, that corresponds with a specifically assigned symbol. Participants were asked to respond as quickly and accurately as possible. The average score for the Symbol Digit task in the analysis sample was 52.17(*SD*=11.12).

Sleep.

Sleep Duration

Sleep duration within IGEMS was evaluated through self-reported measures, either by indicating the length of sleep on an average night or by reporting the timing of sleep onset and awakening. To ensure consistency across the diverse range of questions related to sleep duration across the various studies within IGEMS, a harmonization procedure was utilized, resulting in a single measure of sleep duration for each individual (Vo et al., 2022). In instances where sleep duration was assessed through multiple items, such as across different seasons or weekdays versus weekends, an average was computed

to establish a single sleep duration score. For SATSA participants, sleep duration was computed based on average bedtime and waketime. For VETSA participants, sleep duration information was obtained from a single item. Based on guidelines outlined by the National Sleep Foundation, outliers were winsorized by three standard deviations of age-specific sleep norms.

Sleep Quality/Disturbances

Sleep disturbances were assessed through participant self-reports, utilizing a range of questions aimed at gauging sleep quality. Given the diversity and varying quantity of sleep disturbance items across the studies (see supplemental methods in the appendix, Appendix Table A1.1-Appendix Table A1.2), a harmonized measure of sleep disturbances was created. The harmonization process involved consolidating self-report items across IGEMS related to sleeping problems, sleep apnea, insomnia, nightmares, sleep medication usage, restlessness, snoring, and problems related to sleep maintenance into a binary classification of either no endorsement (coded as “0) or some endorsement (coded as “1”). These items were categorized based on clinical information from the 2020 ICD-10 and also aligned with similar items and subcategories within the Pittsburgh Sleep Quality Index (Buysse et al., 1989). For factor score generation, factor scores were generated based on all available items for each individual across the full IGEMS sample, following a similar approach to previous IGEMS work (e.g., Finkel et al., 2022). Initially, the factor analysis supported a two-factor sleep disturbance measure with factor loadings ranging from 0.52 to 0.83 for the first factor, reflecting sleep efficiency (e.g., disruptions to nocturnal sleep, sleep latency, sleep medication usage) and factor loadings ranging

from 0.42 to .62 for the second factor reflecting breathing-related sleep disturbances (e.g., snoring, sleep apnea). However, we proceeded with a one-factor model, despite the two-factor model displaying a more optimal fit, as the factors were highly correlated (r=0.94) and the sample size large (N=12,006, see Appendix Table A1.3). Factor scores were then rank normalized to resolve nonlinearity and skew such that skewness prior to rank normalization was 0.71 and skewness post-rank normalization was 0.06.

AD Polygenic Score

Within IGEMS, subsets of individuals possess extensive genome-wide genotype data, facilitating the computation of polygenic scores (PGS) for traits of interest, such as AD. PGS are genetic scores derived from DNA data that yield a prediction of an individual's genetic susceptibility to a particular trait (e.g., predisposition to AD; Escott-Price, Shoai, Pitcher, Williams & Hardy, 2017). These scores are derived from large-scale genome-wide association studies (GWAS; e.g., Kunkle et al., 2019), which provide effect sizes for numerous genetic variants contributing to a specific phenotype. The aggregated information across all weighted alleles yields a summed polygenic score reflecting the genetic prediction of predisposition for a trait of interest. Within the present subsample from IGEMS, PGS for AD (AD-PGS) are available in three Swedish studies (SATSA, OCTO-Twin, and GENDER), one United States study (VETSA), one Australian study (OATS), and two Danish studies (LSADT and MADT). In cases where only one twin from a MZ pair was genotyped, the PGS of the ungenotyped twin was imputed based on the genotyped twin's PGS. The AD-PGS was adjusted for the first 10 ancestry principal components through a regression procedure to save the residual PGS

scores and the AD-PGS was further standardized (i.e., z-scored) such that the AD-PGS scores had a mean of "0" and a standard deviation of "1".

Statistical Analyses

Phenotypic analyses were conducted in SAS version 9.4 (SAS Institute Inc, 2016). Biometric models were fitted in OpenMx version 2.21.8 (Neale et al., 2016) in R version 4.3.2 (R Development Core Team, 2023). Phenotypic and twin correlations were estimated within the sample, by zygosity group (MZ and DZ; see Table 1.3).

Our model testing procedure was first informed through univariate twin models. In leveraging the distinctive features of the classical twin design, comparisons are made between MZ twins, who share 100% of their genetic material, and DZ twins, who share roughly half of their segregating genetics, to estimate various sources of variation stemming from both genetic and environmental influences. These sources include additive genetic influences (A) which make twins more alike (correlated at 1.0 for MZ twins and 0.5 for DZ twins), shared environmental influences (C) such as shared family environments which make twins, regardless of zygosity, more similar (correlated at 1.0 for both), and non-shared environmental influences (E), encompassing individual-specific factors that make twins more dissimilar and measurement error (uncorrelated for both twin types). Univariate twin models provided a baseline decomposition of the underlying genetic and environmental contributions without the inclusion of moderators (see Table A1.4). Additionally, to assess whether assumptions were met for biometrical modeling, equality tests for means and variances were separately performed for the sleep and

cognitive measures. Specifically, equality tests for means and variances were conducted in successively nested models: 1) means and variances were unconstrained across twin order or zygosity, 2) means were constrained across twins within zygosity groups, 3) means and variances were constrained across twins within zygosity group, and 4) means and variances were constrained across both twin and zygosity group. The LRT model comparisons for these tests yielded non-significant results (all p-values ≥ .11).

Bivariate twin models were then applied to sleep and cognition to examine sources of genetic and environmental variation unique to sleep (i.e., a11, c11, e11) and unique to cognition (i.e., a22, c22, e22), as well as potential genetic and environmental sources of covariation shared between sleep and cognition (i.e., a21, c21, e21; Eaves & Gale, 1974; Martin & Eaves, 1977; see Appendix Table A1.5). Of note, these models were fitted using a direct symmetric approach which allowed for the variances to take on negative values, as opposed to hitting a boundary of zero which has previously been noted to bias the parameter estimates (Verhulst, Prom-Wormley, Keller, Medland & Neale, 2019).

These sources of variation (i.e., genetic and environmental influences; A, C, and E) may then be moderated by an environmental exposure such as sleep (e.g., Vo et al., 2022). Indeed, the above univariate modeling approach (e.g., Purcell, 2002; van der Sluis et al., 2012; Vo et al., 2022) is also readily extended to include the main effect of measured genotypes such as AD-PGS and the moderating effects of the AD-PGS on environmental influences (both shared and nonshared; C and E; Bruins et al., 2023). As such, our model expands upon the Bruins' environment-by-PGS interaction model, which

included only the moderation effect of a PGS, to further include the additional moderators of age and sleep (see Figure 1.1). Of note, while the bivariate models followed a direct symmetric approach, the Bruins' et al. model does not use the direct symmetric approach. Our models, following the Bruins' et al. (2023) approach, incorporated three moderators -- the AD-PGS, age, and sleep (either sleep duration or sleep disturbances) -- to examine the impact of each moderator on the quantitative genetic and environmental influences of cognitive performance. Specifically, we examined whether genetic, shared environmental, and nonshared environmental variance for cognitive performance changed with varying levels of the AD-PGS (i.e., higher versus lower genetic risk for AD) and varying levels of sleep duration (i.e., shorter versus longer sleep duration) or varying levels of sleep disturbances (i.e., less versus more sleep disturbances. By design, to test gene by environment interaction (GxE), the AD-PGS moderated only the environmental pathways (C and E; see Figure 1.1). In other words, the measured genetic influence (i.e., the AD-PGS; A_p) was not allowed to moderate the latent genetic influence (A_L). However, both age and sleep moderated pathways on additive genetic (A_L), measured genetic (i.e., genetic influences attributable to the AD-PGS; A_p), shared environment (C), and nonshared environment (E) contributions to cognition (see Figure 1.1). Age, sex, sleep, and country-level effects contributed to the mean level prediction. Moreover, co-twin sleep also contributed to the mean level prediction by zygosity to adjust for differential MZ and DZ twin resemblance on the sleep moderator (van der Sluis et al., 2012). Covariates of age, sex, and country were constrained across twins and zygosity types. Country-level effects were controlled based

on a series of dummy codes assigned to studies representing Sweden, the United States, and Australia. Within these dummy codes, studies from Denmark were the referent group as they represented the largest sample and were the most represented across the various cognitive tasks. However, for one cognitive task (i.e., Synonyms), the United States sample was the referent group as only the Swedish studies and the United States study contributed samples. The residual variance of cognition, following the regression of covariates on the mean-level of cognition, is partitioned into A_P, A_L, C, and E components of variance, allowing for these components to vary as a function of the moderators (see Figure 1.1). Significant moderators were determined based on estimating 95% confidence intervals and model fit (see Supplemental Table A1.6). Of note, data preprocessing included the standardization of all moderators and outcomes (i.e., z-scored).

Model fit was evaluated using both the Log-likelihood Ratio Test (LRT) and Akaike's Information Criterion (AIC; Akaike, 1987). The LRT assesses the goodness-of-fit between a fuller model and a nested sub-model, with differences in model fits distributed as a chi-square ($\chi 2$) under the null hypothesis. AIC was calculated as -2(log-likelihood) +2K, where K represents the number of parameters within the model. Of note, AIC comparisons for model fit may be made in both nested and unnested model comparisons and AIC provides a penalty-adjusted fit function for model complexity. Models with lower AIC values were better fitting models.

Results

Descriptive Statistics

The average sleep duration for the total analysis sample was 6.96 (*SD*=1.66, *N*=2739; See Table 2), varying from 6.53 hours (SD=1.23) in VETSA to 8.63 hours (SD=1.08) in SATSA, with the largest variation in sleep duration observed for OCTO-Twin (SD=1.38). For sleep disturbance, the average sleep disturbance factor score was -0.17 (SD=1.11), varying from -0.49 (SD=1.34) in GENDER to 0.16 (SD=0.77) in OATS, with the largest variation in sleep disturbance factor scores observed for SATSA (SD=1.67). Overall, sleep duration within this current sample is fairly normative such that the majority of individuals slept within the recommended 7 to 9 hours for this mid-to-late-life age group, in line with expected sleep norms as suggested by the National Sleep Foundation. Moreover, sleep disturbances within this current sample was normally distributed with a skewness of 0.06 post-rank normalization. Additional descriptive statistics on the sleep measures, AD-PGS, and the cognitive measures are depicted in Table 1.2.

Correlations

Phenotypic correlations between the sleep measures and cognitive performance are depicted in Table 1.3. Both sleep measures (sleep duration and sleep disturbances) tend to be negatively correlated with cognitive performance. For sleep duration associations with cognition, statistically significant but nominal associations were observed for Synonyms (r=-0.06, $p < .001$) and for Digits Backward (r=-0.04, $p < .001$),

with nonsignificant associations observed for Synonyms (r=-0.12, p >.05) and Word List (r=-0.04, p = .05). Conversely, sleep disturbance exhibited stronger associations across most cognitive tasks (see Table 1.3). These findings suggest that sleep disturbance may have a more pronounced impact on cognition compared to sleep duration. Overall, while the effect sizes are modest, these correlations indicate a trend towards worsened performance across all cognitive tasks with increasing sleep duration and sleep disturbances. Nonsignificant associations were detected between the sleep measures and the AD-PGS. Similarly, associations between the AD-PGS and cognition were mostly nonsignificant, except for Word List (r=-0.03, p <.05), and in the expected direction of increased genetic risk for AD and poorer cognitive performance.

MZ and DZ twin pair correlations for each cognitive trait, adjusted for age and sex, are depicted in Table 1.3. For sleep duration, the MZ correlation was r=0.34, p<.0001 and the DZ correlation was r=0.18, p<.0001, with similar albeit weaker patterns for sleep disturbances (r_{MZ}=0.21, p<.0001, r_{DZ}=0.18, p<.0001). Twin correlations for MZ and DZ pairs for each cognitive task ranged from 0.30 to 0.63 for MZ pairs and 0.21 to 0.39 for DZ pairs across the six cognitive tasks. Overall, these patterns of twin correlations suggest that genetic influences may contribute to variability in the sleep measures as well as in cognition ($r_{MZ} > r_{DZ}$), while still indicating substantial environmental influences.

Genetic and Environmental Influences

Standardized univariate ACE estimates for the sleep measures and the cognitive measures are provided in the appendix adjusted for age and sex (see Appendix Table A1.4). These standardized ACE estimates describe the estimates of heritability (SA), common environmentality (SC), and nonshared environmentality (SE) of the sleep and cognitive measures. For the sleep measures, the heritability estimates were modest, with lower estimates observed for sleep disturbances compared to sleep duration. Specifically, additive genetic effects accounted for 13% percent of the variance in sleep duration whereas additive genetic effects only accounted for roughly 5% of the variance in sleep disturbances. Meanwhile, the heritability estimates for the cognitive measures were moderate, with the highest estimates observed for the Synonyms task (62%) and the lowest estimates observed for the Word List task (23%).

Bivariate ACE models between sleep duration and cognitive tasks show no significant main effects of sleep duration across the four cognitive tasks (i.e., Wordlist, Animal Naming, Digits Forward, and Digits Backward, all *p's* > 0.05; see appendix Table A1.5). Specifically, dropping the paths specific to genetic (a21), shared environmental (c21) and non-shared environmental (e21) influences of sleep on cognition, resulted in a negligible change in model fit based on AIC and LRT model comparisons (see appendix Table A1.5). Bivariate ACE models between sleep disturbances and cognitive tasks, do suggest a significant main effect of sleep disturbances, particularly for Wordlist ($\chi 2(3) = 15.49$, $p = 0.001$), Digits Forward ($\chi 2(3) = 9.17$, $p = 0.03$), and Digits Backward ($\chi 2(3) = 14.33$, $p = 0.002$), but not for Animal

Naming, Symbol Digit, or Synonyms (all *p's* > 0.05). Across most of these cognitive tasks the best-fitting models tended to be the AE model. However, in some cases (e.g., Word List, Animal Naming, Symbol Digit), the full ACE model was the better-fitting model. As the AE model provided more optimal fit, we proceeded with reporting the results for an AE model for the moderation models, but report parameter estimates from the full ACE models in the appendix (see Table 1.4 and appendix Table A1.6-appendix Table A1.9). Moreover, while no significant main effects of sleep duration were observed, the influences from sleep duration may occur through moderation of genetic and environmental influences. Baron and Kenny (1986) suggest that strong correlations between a moderator and an outcome are not necessary, and it may actually be preferable for a moderator to be uncorrelated with an outcome variable. As such, we proceeded with moderation models even in the absence of significant main effects of sleep duration.

Moderation Models

Informed by the bivariate models, we present the parameter estimates from the better-fitting AE models in the main text and the parameter estimates from the ACE models are presented in the appendix.

Sleep Duration

For models with sleep duration, AD-PGS, and age as moderators, only significant sleep duration moderation was observed for Digits Backward on the E parameter (AE Model; B=-0.04, 95% CI [-0.09, -0.001], see Appendix Table A1.7 and Figure 1.2), suggesting an attenuation of the contributions from the unique environmental influences

with longer sleep durations. The parameter estimate for the variance explained by the AD-PGS (A_p) was not significant and was quite small (B=0.02, 95% CI [-0.02, 0.06]) suggesting that the direct contribution of the AD-PGS to Digits Backward is not significant. Rather, it is only through the PGS' interplay and interaction with the nonshared environment that appears to be significant (AE Model; B=-0.04, 95% CI [-0.06, -0.01], see Appendix Table A1.7 and Figure 1.2), suggesting an attenuation of the contributions from the unique environmental influences with higher genetic risk for AD. Sleep duration did not significantly moderate A_p, the portion of the genetic variance that was indexed by the AD-PGS, (AE Model; B=-0.01, 95% CI [-0.04, 0.03]), nor did it moderate the portion of the genetic variance of the latent (i.e., background) genetic influence (A_L) on differences in cognitive performance (see Appendix Table A1.7).

Moderation of sleep duration on A or E components was localized in only Digits Backward, principally on the nonshared environmental contributions to Digits Backward performance suggesting an attenuation of the person-specific environmental contributions at longer ends of sleep duration (B=-0.04, 95% CI [-0.09, -0.001], see Appendix Table A1.7). Sleep duration moderation model results are presented in the appendix for all cognitive tasks (see Appendix Table A1.7-A1.8 and Appendix Figures A1.1-A1.3). Briefly, the patterns of estimates were consistent with prior findings (Vo et al., 2022), whereby genetic contributions to cognitive performance tended to decrease across increasing levels of sleep duration (see Appendix Figures A1.1-A1.3).

Sleep Disturbances

For Wordlist, an episodic memory task, the variance explained by the AD-PGS was small but significant (B=-0.04, 95% CI [-0.07, -0.01]; see Table 1.4) and significant moderation via the AD-PGS was observed for the E component (AE model; B=-0.03, 95% CI [-0.05, -0.003], see Table 1.4), suggesting significant environment-by-PGS interaction. The estimates suggest an attenuation of the contributions from the unique environmental influences with increasing levels of genetic risk for AD (see Figure 1.3). Of note, no significant moderation via sleep disturbances was observed on the AD-PGS (A_p), nor for A_L, C or E (see Table 1.4 for AE models and Appendix Table A1.9 for ACE models). We note that the full ACE model was a better fitting model in the bivariate models; however, estimates from the full ACE models were consistent with findings from the more parsimonious models.

For Animal Naming, a verbal fluency task, the variance explained by the AD-PGS was small and nonsignificant (B=-0.03, 95% CI [-0.06, 0.01], see Table 1.4). Moreover, no significant moderation via sleep disturbances was observed on the AD-PGS (A_p), A_L, or E contributions in the AE models, nor on the C contributions in the fuller ACE models (see Appendix Table A1.8). Within the fuller ACE models (see Appendix Table A1.9), despite providing poorer model fit, significant moderation via the AD-PGS on the C component was observed (ACE model; B = 0.13, 95% CI [0.01, 0.22]; see Figure 1.4) which suggests a buffering of the attenuation of the shared environmental contributions to verbal fluency performance at higher levels of genetic risk for AD. However, the shared

environmental influences were subsequently dropped in the more parsimonious, and better-fitting, AE model.

For Digits Forward, an attention-based task, the variance explained by the AD-PGS was negligible and nonsignificant (B=0.003, 95% CI [-0.03, 0.04]). No significant moderation via the AD-PGS was observed on the A_L or E contributions to differences in cognitive performance in Digits Forward. Moreover, sleep disturbances did not significantly moderate the AD-PGS (A_p), A_L or E components contributing to differences in performance. Within the fuller ACE models (see Appendix Table A1.9), despite providing poorer model fit, significant moderation via sleep disturbances on the C component was observed (ACE model; B=0.16, 95% CI [0.06, 0.24]; see Figure 1.5), suggesting a slight buffering of the attenuation of the shared environmental contributions to Digits Forward performance at higher levels of sleep disturbances.

For Digits Backward, a working memory task, the variance explained by the AD-PGS was small and nonsignificant (B=0.02, 95% CI [-0.02, 0.05]) and only through the AD-PGS' interplay and interaction with environmental influences appear to be significant. Specifically, significant environment-by-PGS interaction was observed on the E component (B=-0.03, 95% CI [-0.05, -0.002], see Table 1.4) suggesting a reduction in the influences from the non-shared environment on working memory performance at higher levels of risk for AD (see Figure 1.6). Within the fuller ACE models (see Appendix Table A1.9), despite providing poorer model fit, it is noted that significant AD-PGS moderation was observed on the C component (B=0.11, 95% CI [0.04, 0.19]), and significant sleep disturbance moderation was observed on the C component (B=0.24,

95% CI [0.17, 0.30]). This suggests that shared environmental influences on working memory performance increase with higher genetic risk for AD and with increased sleep disturbances. However, the shared environmental component was dropped in the better-fitting AE model and interpretations of significant moderation on the C component should be approached with caution.

Lastly, for Synonyms, a verbal ability task, significant AD-PGS moderation was observed on the E component (B=-0.05, 95% CI [-0.08, -0.02], see Table 1.4), suggesting a decrease in the contributions from the non-shared environmental influences on verbal ability performance with higher genetic risk for AD (see Figure 1.7). However, the AD-PGS, on its own, was not significant (B = -0.02, 95% CI [-0.08, 0.03]) and explained very little of the variance in Synonyms performance (see Table 1.4). Of note, no significant moderation via sleep disturbance was observed on the AD-PGS (A_p), A_L, C, or E components.

For all models with sleep disturbance as a moderator, in addition to the AD-PGS and age, no significant moderation of A_L, C, or E was observed for either the AD-PGS or sleep disturbance for Symbol Digit, a processing speed task. In addition, within these models, sleep did not significantly moderate the portion of the genetic variance indexed by the AD-PGS (A_p) on Symbol Digit performance. The variance explained by the AD-PGS was negligible and nonsignificant (B=-0.03, 95% CI [-0.07, 0.01]; see Table 1.4).

Discussion

The present study aimed to uncover how underlying etiological contributions to cognition may be affected by poor sleep conditions, including both shorter sleep durations and increased sleep disturbances. Across the cognitive tasks, only significant sleep duration and AD-PGS moderation of the nonshared environment was observed for the working memory task, Digits Backward. Specifically, we observed an attenuation of the contributions of individual-specific environmental influences to working memory performance at both longer sleep durations and higher genetic risk for AD. Some indications of sleep disturbance moderation were observed for the common environmental influences within the full ACE models for cognitive tasks tapping the domains of attention and working memory. Further, we evaluated whether measured AD polygenic risk contributions might alter environmental contributions to cognition (environment-by-PGS). While the variance explained by the AD-PGS was negligible and nonsignificant across most cognitive domains except episodic memory, and did not appear to vary by sleep duration or sleep disturbances, we detected environment-by-PGS interaction for episodic memory, verbal fluency, working memory, and verbal ability such that higher genetic risk for AD was generally associated with weaker individual-specific environmental influences.

We evaluated the moderating effects of sleep duration and disturbances on genetic and environmental contributions to cognitive performance, observing more consistent significant findings for sleep disturbances moderating environmental influences. While higher genetic influences were suggested with shorter sleep durations and increasing

levels of sleep disturbances, as found with our prior work (Vo et al., 2022), we did not observe significant moderation of genetic influences on cognition in the present analyses. However, the general etiological patterns, albeit weaker and nonsignificant, may be understood under the diathesis-stress model (Boardman, Daw & Freese, 2013). That is, the adverse sleep environment may act as an environmental stressor, amplifying the expression of genetic vulnerabilities tied to cognitive function (Boardman, Daw & Freese, 2013). While we do not necessarily know what the underlying genetic influences may be, poor sleep may detrimentally affect neurobiological processes crucial for learning and memory, such as synaptic plasticity (Wang et al., 2011). Research suggests that disrupted sleep impairs synaptic plasticity mechanisms essential for neural function and cognitive performance, particularly for learning and memory (Raven, Van der Zee, Meerlo & Havekes, 2018). For instance, synaptic downscaling, as proposed by the synaptic homeostasis hypothesis, is vital for maintaining cellular energy balance during sleep (i.e., restoring cellular homeostasis), involving increased slow-wave activity and global synaptic strength adjustments during sleep, particularly after ongoing long-term potentiation during wakeful states (Tononi & Cirelli, 2003). Disruptions to this process, often influenced by sleep loss and disturbances to sleep, may lead to reduced synaptic efficacy, particularly in the hippocampus, and impacting brain functions tied to alertness, information processing, and memory (Kreutzmann, Havekes, Abel & Meerlo, 2015) and leading to cognitive deficits. Furthermore, sleep disturbances and too short or too long sleep durations, often coupled with aging (Ohayon et al., 2004), may impair glymphatic clearance vital for clearing metabolic and neurotoxic waste products, particularly during

slow-wave sleep, a stage crucial for memory consolidation (Benveniste et al., 2019; Xie et al., 2013; Eide et al., 2022; Hablitz & Nedergaard, 2021). As such, poorer cognitive performance may be partly explained by the accumulation and increased deposition of Aβ in instances of sleep deficits, sleep disturbances, shorter sleep durations, or the increased necessity for excessive daytime sleepiness (Spira et al., 2018; Winer et al., 2020). Lastly, sleep disturbances may disrupt brain connectivity and network dynamics, affecting attention, memory and executive functions. Poor sleep quality and disturbances have been associated with decreased functional and structural connectivity in regions linked to Alzheimer's disease pathology (Amorim et al., 2018; Liu et al., 2018), including the default mode network (McKinnon et al., 2016), where disruptions to the default mode network have been observed in individuals with AD (Jones et al., 2011).

On the other hand, we observed indications of sleep disturbance moderating the common environmental influences, particularly for attention and working memory tasks, within the fuller ACE models, despite AE models often providing the best fit. As such, the results should be interpreted with caution and additional work may be necessary to uncover whether the effects are actually driven by A or C. However, the contrasting results between attention and working memory tasks suggest divergent effects of poor sleep on the influence of shared common environments on cognitive performance. Specifically, increased sleep disturbances were associated with a buffering of the overall decrease in the impact of shared common environments on attention. This may be attributed to the increased variability in environmental exposures associated with poor sleep quality, such as disruptions in regular routines (e.g., daily activities, daily

schedules; Lee, Kim & Chung, 2021), such that inconsistencies in environmental factors may reduce the overall impact of shared common environments on attention. Moreover, individual differences in response to poor sleep may also play a role, as susceptibility to the effects of poor sleep quality on attention varies among individuals (Hudson, Van Dongen & Honn, 2020; Song et al., 2019). Conversely, for working memory, increased sleep disturbances were associated with an increase in the impact of shared common environments. This amplification of environmental influences in poorer sleep contexts may be explained by sleep fragmentation and poor sleep quality, which are often linked to lower cognitive scores and mental fatigue (Low, Wu & Spira, 2019; Alfini et al., 2020). Additionally, poor sleep quality may heighten individuals' susceptibility to environmental stressors (e.g., familial environments/relationships, family strain, low social support, depression; Ailshire & Burgard, 2012; Frazier & Brown, 2023; Aggarwal et al., 2024), potentially having a more pronounced impact on working memory abilities during periods of poor sleep.

The AD-PGS accounted for a negligible proportion of the genetic variance, suggesting additional factors beyond measured genetic risk may contribute to differences in cognitive performance. It must be noted that AD is multifactorial and complex in nature and is highly heritable (Gatz et al., 2006). Indeed, even in examinations of the heritable contributions to AD, the AD-PGS was shown to only contribute to roughly 10% of the risk of AD, with even lower contributions observed for the AD-PGS without the *APOE* region (Karlsson et al., 2022). Moreover, current research suggests no causal relationship between sleep and cognition (Yuan et al., 2022), rather, regardless of varying

levels of genetic risk for AD, longer sleep durations were associated with heightened risk for AD. However, while the contribution from the AD-PGS was small in our present examinations, we were able to detect environment-by-PGS interaction for some of the cognitive tasks. In other words, on its own, the AD-PGS did not contribute very much to the appreciable background genetic variation, but it may contribute to differential responsivity to environmental (both shared and nonshared) influences on cognitive performance. For example, when observing the etiological patterns of episodic memory and working memory tasks, we observe that a higher genetic risk for AD was associated with less nonshared environmental variance contributing to individual differences in working memory and episodic memory performance, particularly when including sleep disturbances as both a main effect and a moderator within the same model. In addition, for both verbal fluency and attention tasks, we observe environment-by-PGS interaction such that higher genetic risk for AD was concurrently observed with attenuation of the shared environmental variance contributing to individual differences in verbal fluency and attention performance. As such, within individuals with high genetic risk for AD, unique environmental factors on memory performance, and common environmental factors on verbal fluency and attention task performance, may be overshadowed by the stronger influence of their genetic predisposition and consequently, the contribution of the nonshared environmental influences to cognitive performance are attenuated. Given the results from recent GWAS showing that susceptibility loci for late-onset AD (LOAD) include the *APOE* gene as the strongest risk factor for LOAD, specifically the ε4 allele (Liu et al., 2013) but also implicates Aβ, tau, immunity, and lipid metabolism (Kunkle et

al., 2019; Shi et al., 2017; Brier et al., 2016), individuals with a higher genetic predisposition to AD may exhibit more pronounced genetic influences on cognitive differences. The *APOE* ε4, for instance, has been consistently linked to poorer cognitive performance and accelerated cognitive decline (El Haj et al., 2016; O'Donoghue et al., 2018), affecting both global cognitive function (Quintino-Santos et al., 2015) and various cognitive domains including memory and executive function (Van der Vlies et al., 2007; Schultz et al., 2008; Kerchner et al., 2014; Sapkota, Backman & Dixon, 2017; Luck et al., 2015). In addition, these patterns are broadly consistent with present work that suggests a less pronounced effect from environmental factors on cognition (e.g., spatial-reasoning, semantic memory, episodic memory) among *APOE* ε4+ carriers, or carriers of putative risk alleles, compared to non-carriers (Reynolds et al., 2016; Reynolds, Gatz, Berg & Pedersen, 2007).

In addition, etiological patterns suggest that environmental factors may exert a more pronounced influence on differences in cognitive performance among individuals with lower genetic susceptibility to AD, reflecting a differential sensitivity to environmental influences based on genotype. Consequently, environmental factors, including sleep and other lifestyle choices, especially those that foster similarities in twins regardless of zygosity, may have a greater influence on differences in cognitive performance among individuals with lower AD risk. These environmental influences manifest in various forms, such as shared upbringing and cultural and physical environments. It is worth noting that even though the twins in our study are older and live apart, they may still share correlated environments (McGue & Christensen, 2007; McGue

& Christensen, 2013; Frederiksen & Christensen, 2003). Individuals with lower genetic predisposition to AD may demonstrate greater responsiveness to environmental factors that could potentially mitigate or safeguard against cognitive decline. These factors encompass modifiable lifestyle choices, dietary habits, physical activity, and, importantly, behaviors conducive to good sleep hygiene (e.g., Livingston et al., 2020), particularly those rooted in earlier life experiences that may contribute to the commonality in cognitive performance among both identical and fraternal twins. Notably, family practices related to sleep hygiene, such as maintaining consistent sleep schedules, limiting screen time before bed, and moderating caffeine intake, have been demonstrated to be protective against sleep disturbances and enhance sleep duration and quality in children and adolescents (Buxton et al., 2015), with plausible suggestions that the protective benefits may extend into adulthood through the maintenance of these learned behaviors. Furthermore, research indicates that better sleep, characterized by shorter sleep latency, is associated with improved performance in tasks related to visuospatial ability, processing speed, and verbal memory in older adults, while poorer sleep, including increased daytime sleep, is linked to significantly worse performance in visuospatial reasoning and processing speed (Cox et al., 2019). Additionally, recent findings by Muto and colleagues (2022) suggest that individuals with lower genetic risk for AD experience less daytime sleepiness and demonstrate a reduced need for slow-wave sleep, contrasting with those at higher genetic risk for AD who exhibit inverse patterns of association. However, additional research and scrutiny may be warranted as the fuller ACE models were not always the best-fitting model.

Limitations

Several limitations need to be acknowledged within this study. Firstly, its cross-sectional design restricts the ability to draw definitive conclusions about how sleep and AD-PGS moderate etiological contributions to cognition over the lifespan. In addition, as we utilized only one timepoint of cognitive ability, we do not account for one's baseline cognitive ability which may provide additional insight on differences in cognitive performance. Next, as the sample is drawn from various studies, the harmonization approach used for sleep measures, particularly sleep disturbances, may potentially obscure some associations. As such, our study's reliance on the simplified categorization of "no endorsement" versus "some endorsement" of sleep disturbances across the studies may lack the nuance needed for precision and statistical power. Utilizing more comprehensive assessments of sleep quality, such as the Pittsburgh Sleep Quality Index (Buysse, 1989), could provide more precise insights into the etiological associations underpinning cognitive performance while further allowing for the examination of the various subcomponents of sleep quality (e.g., subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication, and daytime dysfunction). Next, our sample size may limit our power to detect moderation effects, especially given the requirement that both twins and co-twins must have data on all moderators, including sleep and the AD-PGS. Consequently, power constraints may undermine our ability to detect meaningful effects, including replicating the statistically significant sleep duration moderation of additive genetic influences (Vo et al, 2022). Further, as each cognitive domain was only represented with a single cognitive test, combining cognitive indicators

into a single latent trait may increase our statistical power. However, our sample is limited in this respect as not all cognitive indicators were available across the differing studies. Finally, it must be noted that the *APOE* ε4 allele frequency is reduced with older age (McKay et al., 2011; Tan, Christiansen, Christensen, Kruse & Bathum, 2004; Davidson et al., 2006), where the hazard of death is greatly increased with increasing age due to conditions related to the deleterious effect of ε4 (e.g., cardiovascular disease, diabetes, AD; Lahoz et al., 2001; Liu, Liu, Weng, Gu & Zhong, 2019; Husain, Laurent & Plourde, 2021). As such, future studies may benefit from incorporating an age effect on the PGS, at the mean level, to account for the possibility that PGS scores may vary with advancing age, in addition to accounting for the age effect on cognition.

Conclusion/Future Directions

Overall, this is the first study to examine the role of sleep, genetic risk for Alzheimer's disease, and the varying etiological associations to cognition, capitalizing on the additional information gained from integrating a measured genetic factor into the classical twin model. Although the Alzheimer's disease polygenic score showed limited contribution to genetic variance in the cognitive tasks, we detected significant environment-by-PGS interactions. These interactions revealed that genetic risk was associated with varying responsiveness to environmental influences on cognitive performance. Furthermore, our findings highlighted patterns indicating that poorer sleep conditions, characterized by shorter durations and increased disturbances, were linked to heightened genetic influences on cognitive performance differences. Moving forward, it is essential that future research investigate whether these etiological associations persist

when examining the AD-PGS without the *APOE* region, given its potential modulation of the effect of sleep on AD risk (Wang et al., 2020; Wang et al., 2023; Xu et al., 2024; Baril et al., 2022). Overall, the present study underscores the potential significance of sleep as a target for interventions aimed at enhancing or maintaining cognitive function. Further exploration in this area holds promise for advancing our understanding of mitigating risk for Alzheimer's disease.

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Table 1.1 Demographic Characteristics of the sample

Study	N	%Female	# of Complete Twin Pairs MZ	DZ	Age M(SD)	Cognitive Tasks
Total Sample	3900	38.79	845	1105	62.34(10.39)	WL, AN, DF, DB, SYNM, SYMD
SATSA	144	52.78	26	46	74.78(5.83)	WL, DF, DB, SYN, SYMD
OCTO-Twin	58	62.07	22	7	82.38(1.74)	DF, DB, SYN, SYMD
GENDER	366	50	0	183	74.58(2.71)	WL, SYN, SYMD
VETSA	1096	0	315	233	55.90(2.48)	WL, AN, DF, DB, SYN
LSADT	286	70.63	63	80	79.54(3.78)	WL, AN, DF, DB
MADT	1454	47.66	276	451	55.64(5.99)	WL, AN, DF, DB, SYMD
OATS	496	65.12	143	105	71.28(5.51)	WL, DF, DB, SYMD

Note. MZ=monozygotic, DZ=dizygotic, WL=Wordlist, AN=Animal Naming, DF=Digit Forward, DB=Digit Backward, SYN=Synonyms, SYMD=Symbol Digit

Table 1.2. Descriptives of Measures by Study

	Sleep				PGS	Cognitive						
Study	Sleep Dur.		Sleep Dist.		AD-PGS	All Cognitive Tasks	WL *N*=3795	AN *N*=2825	DF *N*=3522	DB *N*=3519	SYN *N*=1643	SYMB *N*=2347
	N	M(SD)	*N*	M(SD)	M(SD)	*N*	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)
Overall	2739	6.96 (1.66)	3900	-0.17 (1.11)	0.01 (0.99)	1643-3795	51.19 (11.55)	52.76 (10.89)	52.39 (11.29)	51.88 (11.48)	52.95 (8.19)	52.17 (11.12)
SATSA	140	8.63 (1.08)	144	0.13 (1.67)	-0.04 (0.89)	141-143	57.79 (13.54)	--	52.68 (12.44)	54.29 (9.61)	53.29 (10.42)	53.08 (11.80)
OCTO-Twin	49	7.19 (1.38)	58	-0.27 (1.27)	0.03 (0.99)	49-58	--	--	51.20 (10.86)	48.83 (8.55)	46.52 (11.31)	39.53 (11.63)
Gender	--	--	366	-0.49 (1.34)	-0.05 (0.93)	272-359	50.48 (11.74)	--	--	--	50.28 (11.71)	45.97 (10.38)
VETSA	1096	6.53 (1.23)	1096	-0.38 (1.49)	0.03 (1.03)	1088-1096	55.19 (10.61)	53.23 (10.34)	54.94 (11.79	55.13 (12.51)	54.08 (5.57)	--
LSADT	--	--	286	0.12 (0.74)	0.12 (0.74)	285-286	37.98 (11.79)	42.64 (9.64)	49.54 (10.36)	45.76 (9.37)	--	--
MADT	1454	7.11 (0.91)	1454	-0.13 (0.63)	-0.00 (0.99)	1395-1453	51.41 (10.08)	54.40 (10.45)	52.39 (10.87)	51.35 (10.17)	--	55.55 (9.69)
OATS	--	--	496	0.16 (0.77)	0.01 (1.00)	465-491	47.77 (9.45)	--	48.43 (9.99)	49.46 (9.85)	--	46.98 (10.74)

Note. *N*'s for AD-PGS are equivalent to the N's for sleep disturbances. *N*'s for Word List range from 144-1453, *N*'s for Animal Naming range from 286-1450, *N*'s for Digit Forward range from 57-1453, *N*'s for Digit Backward range from 57-1453, *N*'s for Synonym range from 52-1096, *N*'s for Symbol Digit range from 49-1395

Table 1.3 Phenotypic and Twin Correlations

		Phenotypic			Twin Correlations	
Trait		Sleep Duration	Sleep Disturbances	AD-PGS	MZ	DZ
Word List	*r*	*-0.038*	**-0.068****	**-0.033***	**0.30****	**0.25****
	N	2681	3795	3795	803	1081
Animal Naming	*r*	0.001	**-0.059****	-0.025	**0.39****	**0.21****
	N	2539	2825	2825	647	762
Digit Forward	*r*	-0.020	**-0.065****	0.004	**0.46****	**0.27****
	N	2732	3522	3522	838	919
Digit Backward	*r*	**-0.041***	**-0.072****	0.023	**0.43****	**0.22****
	N	2731	3519	3519	835	920
Synonyms	*r*	**-0.059***	**-0.056***	-0.019	**0.52****	**0.39****
	N	1279	1643	1643	359	454
Symbol Digit	*r*	-0.123	-0.013	-0.022	**0.63****	**0.37****
	N	1575	2347	2347	429	692
Sleep Duration	*r*		**-0.147****	-0.007	**0.34****	**0.18****
	N		2739	2739	631	733
Sleep Disturbance	*r*			-0.008	**0.21****	**0.18****
	N			3900	845	1105

Note. *p<.05, **p<.01, twin correlations are adjusted for age and sex

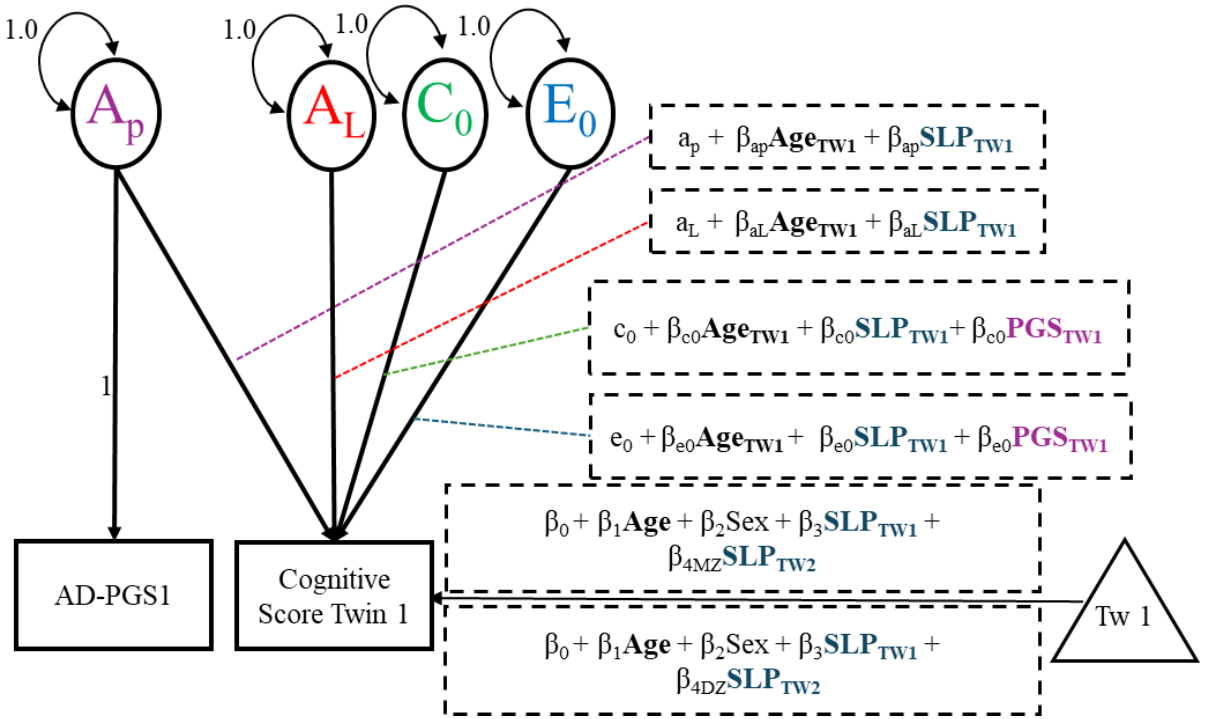
Table 1.4. Parameter Estimates and 95% Confidence Intervals for AE Sleep Disturbance Models

Cognitive Task	Est.	95% CI	Est.	95% CI	Est.	95% CI
Word List	A_p		A_L		E_0	
	-0.04	**[-0.07, -0.01]**	**0.48**	**[0.42, 0.53]**	**0.77**	**[0.74, 0.8]**
AD-PGS					$B_{Ap,E}$	
	--	--	--	--	**-0.03**	**[-0.05, -0.003]**
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$	
	-0.04	**[-0.07, -0.01]**	**0.09**	**[0.04, 0.14]**	-0.01	[-0.04, 0.02]
Sleep Dist.	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$	
	-0.003	[-0.03, 0.03]	0.04	[-0.03, 0.11]	-0.03	[-0.07, 0.01]
Animal Naming	A_p		A_L		E_0	
	-0.03	[-0.06, 0.01]	**0.59**	**[0.54, 0.64]**	**0.73**	**[0.7, 0.77]**
AD-PGS					$B_{Ap,E}$	
	--	--	--	--	-0.01	[-0.04, 0.01]
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$	
	-0.01	[-0.05, 0.03]	0.01	[-0.04, 0.06]	**-0.04**	**[-0.07, -0.005]**
Sleep Dist.	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$	
	0.03	[-0.01, 0.06]	0.01	[-0.06, 0.07]	0.02	[-0.02, 0.07]
Digit Forward	A_p		A_L		E_0	
	0.001	[-0.03, 0.04]	**0.66**	**[0.62, 0.71]**	**0.72**	**[0.69, 0.75]**
AD-PGS					$B_{Ap,E}$	
	--	--	--	--	-0.01	[-0.03, 0.01]
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$	
	-0.01	[-0.05, 0.03]	-0.01	[-0.06, 0.03]	-0.01	[-0.04, 0.022]
Sleep Dist.	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$	
	-0.02	[-0.05, 0.02]	0.05	[-0.01, 0.1]	-0.03	[-0.07, 0.01]
Digit Backward	A_p		A_L		E_0	
	0.02	[-0.02, 0.05]	**0.61**	**[0.57, 0.66]**	**0.74**	**[0.71, 0.77]**
AD-PGS					$B_{Ap,E}$	

Cognitive Task	Est.	95% CI	Est.	95% CI	Est.	95% CI
	--	--	--	--	**-0.03**	**[-0.05, -0.002]**
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$	
	0.00	[-0.04, 0.03]	**-0.06**	**[-0.11, -0.01]**	-0.03	[-0.06, 0.004]
Sleep Dist.	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$	
	0.02	[-0.01, 0.05]	0.04	[-0.04, 0.11]	-0.04	[-0.08, 0.01]
Synonyms	A_p		A_L		E_0	
	-0.02	[-0.08, 0.03]	**0.68**	**[0.63, 0.74]**	**0.63**	**[0.59, 0.67]**
AD-PGS					$B_{Ap,E}$	
	--	--	--	--	**-0.05**	**[-0.08, -0.02]**
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$	
	-0.05	[-0.11, 0.01]	**0.34**	**[0.27, 0.41]**	**0.10**	**[0.06, 0.15]**
Sleep Dist.	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$	
	-0.02	[-0.05, 0.02]	0.01	[-0.04, 0.07]	0.03	[-0.01, 0.07]
Symbol Digit	A_p		A_L		E_0	
	-0.03	[-0.07, 0.01]	**0.70**	**[0.66, 0.74]**	**0.52**	**[0.49, 0.56]**
AD-PGS					$B_{Ap,E}$	
	--	--	--	--	0.01	[-0.02, 0.04]
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$	
	0.003	[-0.04, 0.04]	**0.08**	**[0.04, 0.12]**	0.02	[-0.01, 0.05]
Sleep Dist.	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$	
	0.01	[-0.02, 0.05]	-0.03	[-0.07, 0.02]	0.02	[-0.02, 0.07]

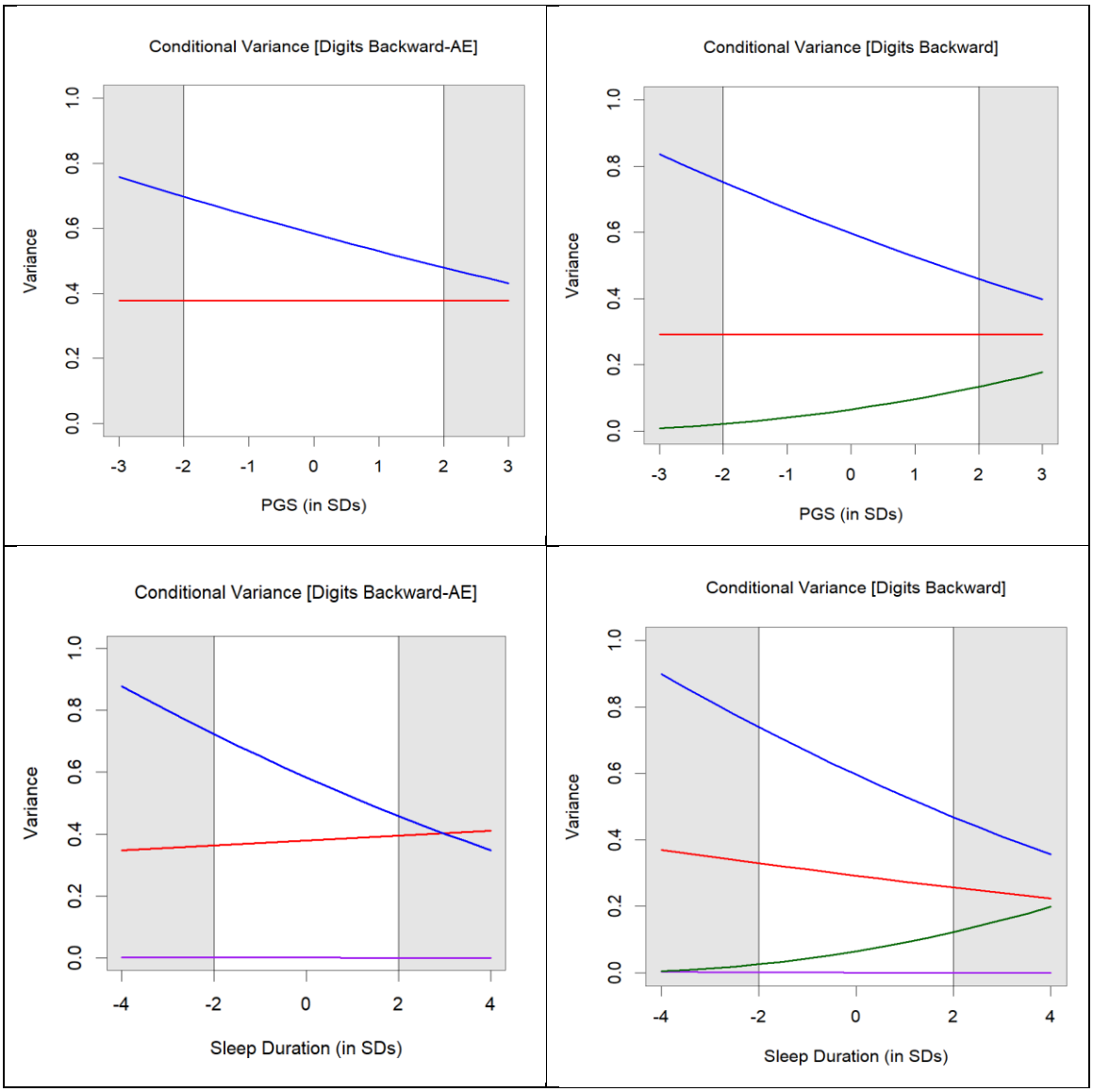
Note. A_p = genetic influences attributable to the AD-PGS, A_L= additive genetic influences, E= non-shared environmental influences, Est.=Estimate. Moderation parameter terms include the AD-PGS, age, and sleep disturbances. Bolded parameters indicate $p < .05$.

Figure 1.1. Biometrical ACE Moderation Model



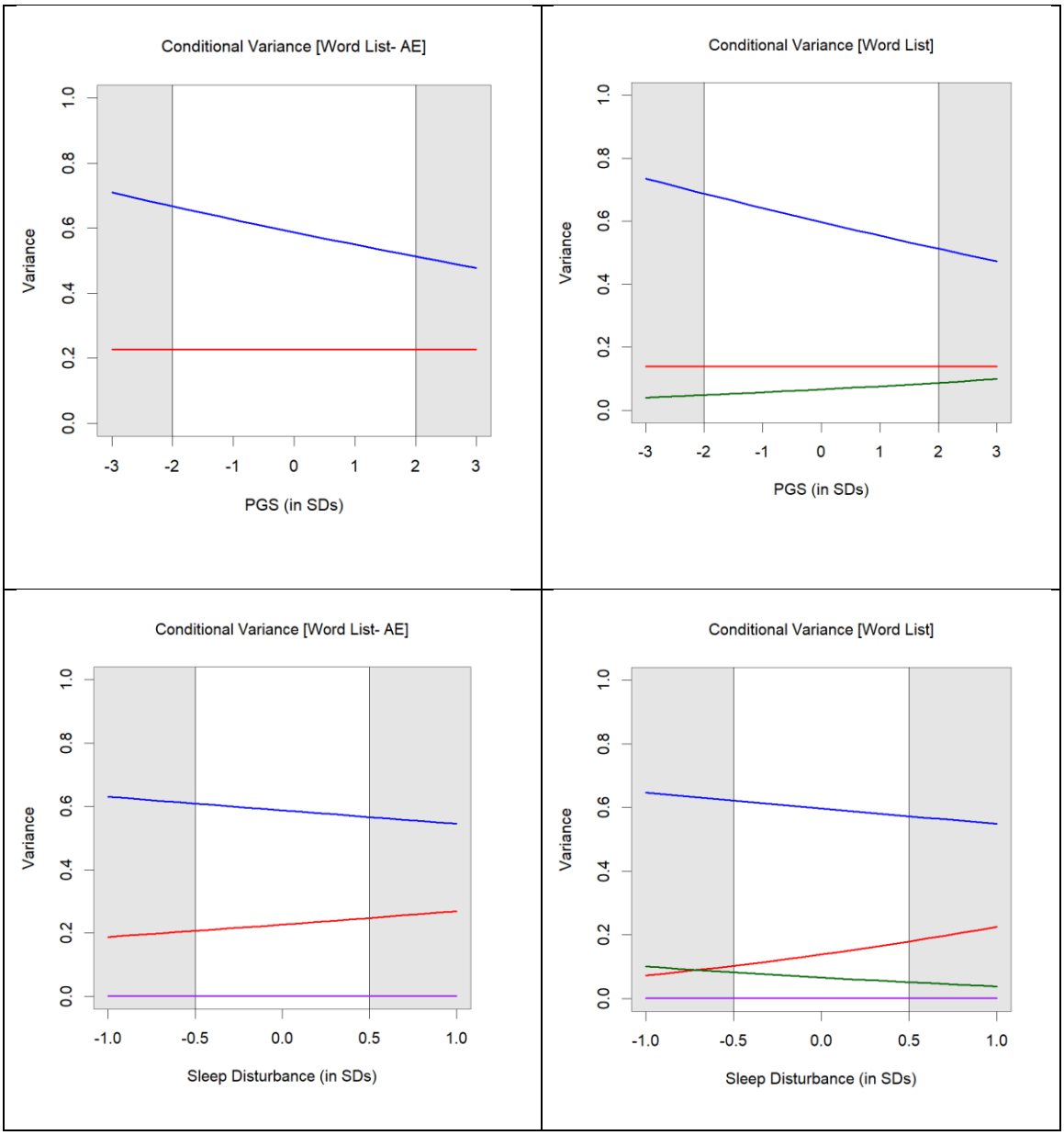
Note. Path diagram of the adapted Bruins et al. (2022) environment-by-PGS interaction model shown for only one twin from a twin pair. A_P=Genetic influence attributable to the AD-PGS, A_L=additive genetic influences, C_0=shared environmental influence, E_0=nonshared environmental influence, TW1=Twin 1, TW2=Twin 2, Circles=latent variables, Squares=observed variables, Triangle=Mean cognitive score/trait.

Figure 1.2. Genetic and environmental variance of Digit Backward, across varying levels of the AD-PGS and varying levels of sleep duration.



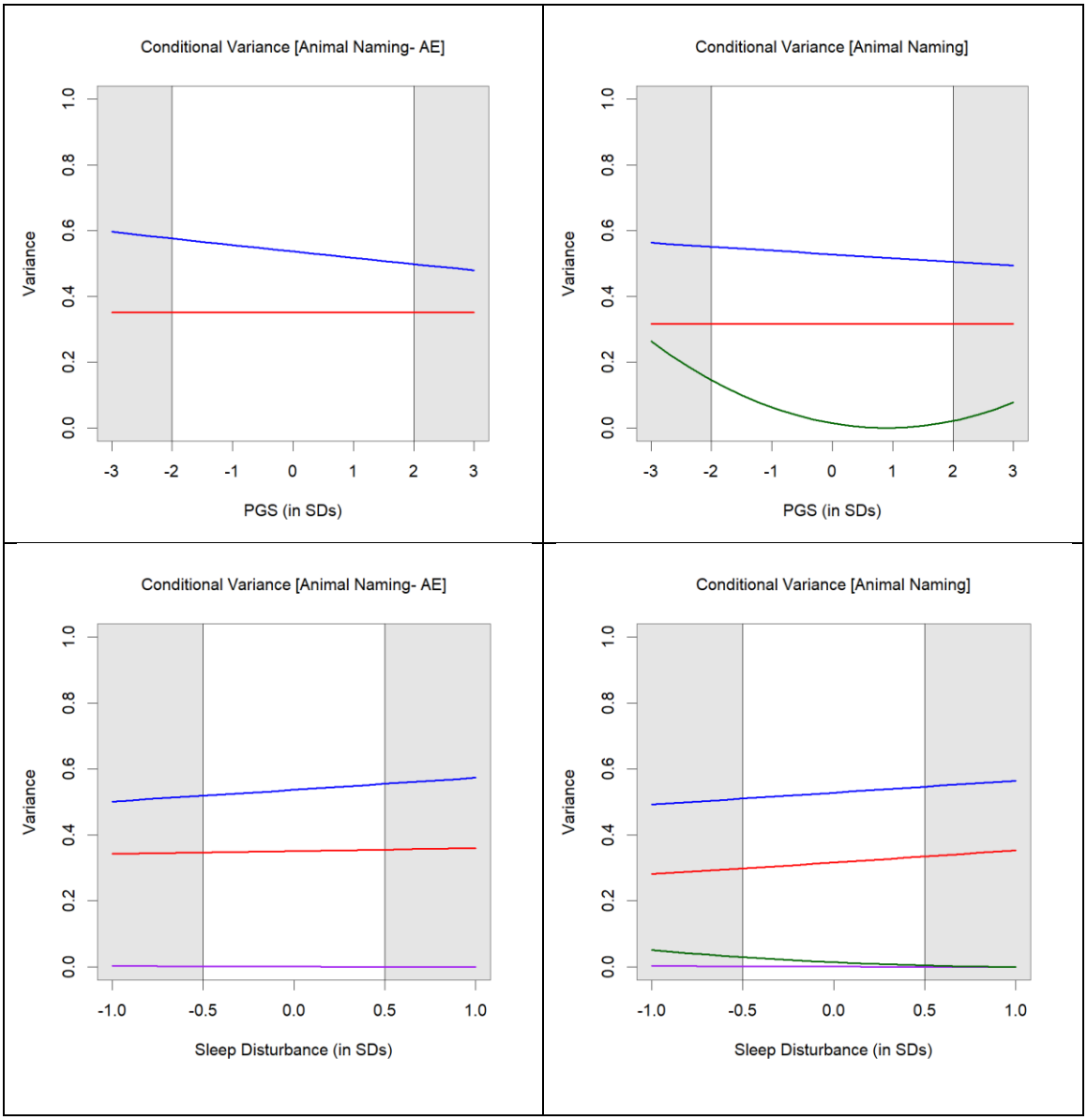
Note. Left panel depicts the AE model and right panel depicts the ACE model. Red Line= additive genetic variance, Purple Line= Proportion of genetic variance attributable to the AD-PGS, Green Line= shared environmental variance, Blue Line=nonshared environmental variance. Shaded blocks indicate a PGS±2-3 SD's or sleep durations ±2-4 SD's from the mean.

Figure 1.3. Genetic and environmental variance of Word List, across varying levels of the AD-PGS and varying levels of sleep disturbances.



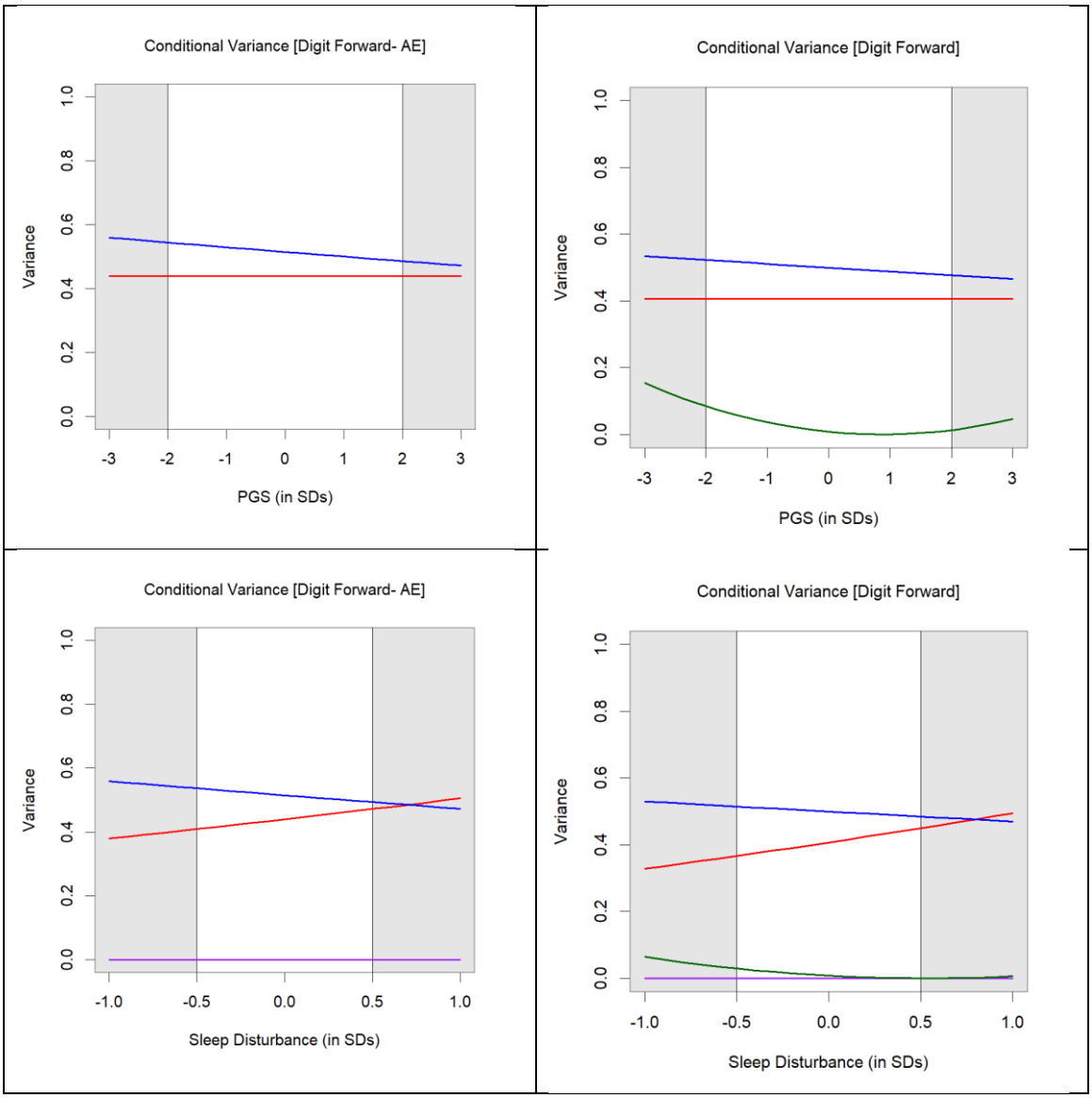
Note. Left panel depicts the AE model and right panel depicts the ACE model. Red Lines=latent additive genetic variance, Purple Line= Proportion of genetic variance attributable to the AD-PGS, Green Lines= shared environmental variance, Blue Lines=nonshared environmental variance. Shaded blocks indicate a PGS±2-3 SD's or Sleep disturbances ±0.5-1 SD's from the mean.

Figure 1.4. Genetic and environmental variance of Animal Naming, across varying levels of the AD-PGS and varying levels of sleep disturbances.



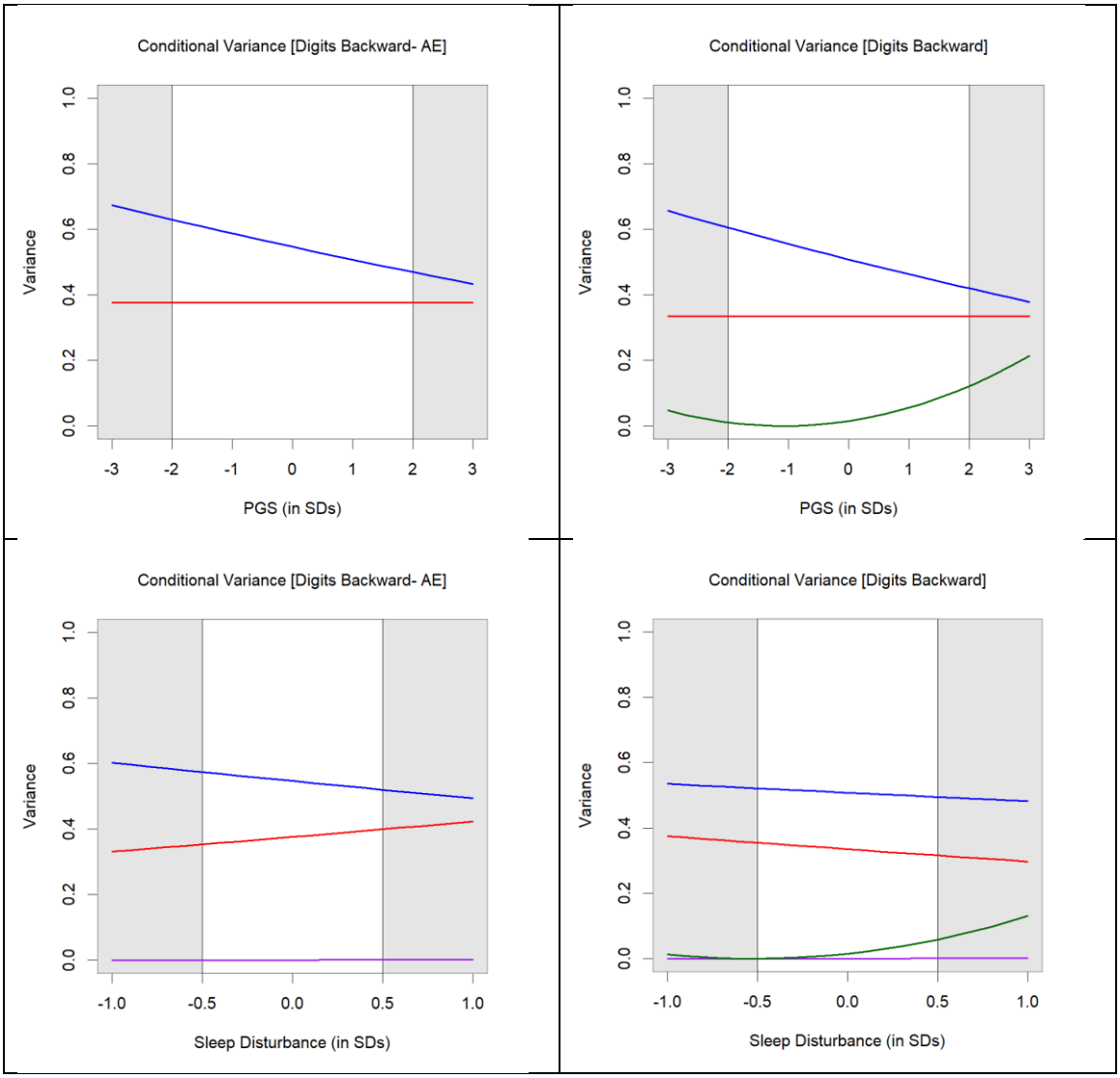
Note. Left panel depicts the AE model and right panel depicts the ACE model. Red Line=latent additive genetic variance, Purple Line= Proportion of genetic variance attributable to the AD-PGS, Green Line= shared environmental variance, Blue Line=nonshared environmental variance. Shaded blocks indicate a PGS±2-3 SD's or Sleep disturbances ±0.5-1 SD's from the mean.

Figure 1.5. Genetic and environmental variance of Digit Forward, across varying levels of the AD-PGS and sleep disturbances



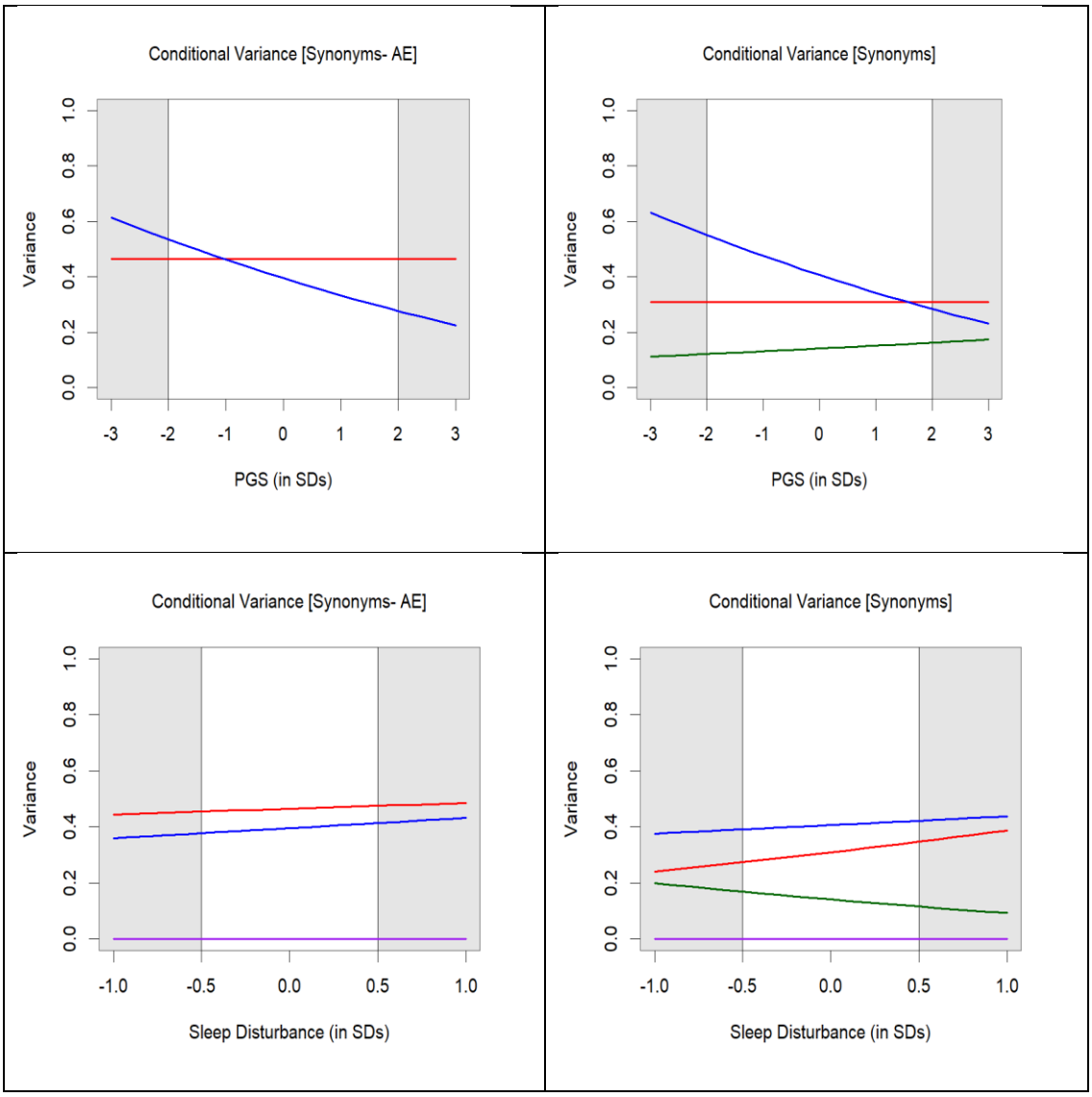
Note. Left panel depicts the AE model and right panel depicts the ACE model. Red Line=latent additive genetic variance, Purple Line= Proportion of genetic variance attributable to the AD-PGS, Green Line= shared environmental variance, Blue Line=nonshared environmental variance. Shaded blocks indicate a PGS±2-3 SD's or Sleep ±0.5-1 SD's from the mean.

Figure 1.6. Genetic and environmental variance of Digit Backward, across varying levels of the AD-PGS and varying levels of sleep disturbances.



Note. Left panel depicts the AE model and right panel depicts the ACE model. Red Line=latent additive genetic variance, Purple Line= Proportion of genetic variance attributable to the AD-PGS, Green Line= shared environmental variance, Blue Line=nonshared environmental variance. Shaded blocks indicate a PGS±2-3 SD's or Sleep disturbances ±0.5-1 SD from the mean.

Figure 1.7. Genetic and environmental variance of Synonym, across varying levels of the AD-PGS and sleep disturbances.



Note. Left panel depicts the AE model and right panel depicts the ACE model. Red Line=latent additive genetic variance, Purple Line= Proportion of genetic variance attributable to the AD-PGS, Green Line= shared environmental variance, Blue Line=nonshared environmental variance. Shaded blocks indicate a PGS±2-3 SD's or Sleep disturbances ±0.5-1 SD's from the mean.

Chapter Three:

Daily Sleep Quality and Cognitive Performance Across two Weeks in Individuals Approaching Midlife

Central to the examination of modifiable factors that may contribute to early cognitive decline and heightened risk for Alzheimer's Disease and Alzheimer's Disease Related Dementias (AD/ADRD) is the role of sleep. Converging evidence illustrates a relationship in which poor sleep is associated with deficits in cognitive performance and cognitive functioning, and increased AD/ADRD risk (e.g., Bubu et al., 2017; Lim et al., 2013; Koo et al., 2017; Alperin et al., 2019; Liu et al., 2021; Grau-Rivera et al., 2020; Minakawa et al., 2019; Sindi et al., 2018; Lutset et al., 2018). However, current research has predominantly focused on either younger individuals, such as college students or young adults (Miyata et al., 2010; Pilcher & Walters, 1997; Amaral et al., 2018; Okano et al., 2019), or older adults above 65 years of age (e.g., Yaffe, Falvey & Hoang, 2014; Brewster, Varrasse & Rowe, 2015; Miyata et al., 2013), leaving a noticeable gap in understanding the sleep-cognition relationship during established adulthood (i.e., between emerging and middle adulthood periods, age 30-45; Mehta et al., 2020). Yet, research focused on examining individuals approaching midlife holds the potential to identify and target modifiable risk factors, particularly sleep, to inform early and proactive intervention opportunities aimed at mitigating cognitive impairment and risk for AD/ADRD. Moreover, sleep extends beyond being a daily routine behavior essential for daily functioning and cognitive functioning. Rather, sleep may reflect and may also be shaped by the diverse environmental influences embedded in individuals' daily lives.

Over time, these individualized factors may accumulate and shape the sleep-cognition associations over longer timescales (Smith, Fang, Thompson & Fogel, 2020; Friedman, Corley, Hewitt & Wright Jr, 2009; Grant & Van Dongen, 2013). However, there remains a gap in understanding short-term dynamics covered in lab-based sleep deprivation studies and the longer-term habitual sleep patterns studied in epidemiolocal studies. Notably, existing research has predominantly focused on between-person differences rather than within-person influences, overlooking the day-to-day fluctuations in sleep quality that merit additional attention.

Previous research has highlighted the age-dependent nature of an individual's sleep architecture (Ohayon et al., 2004), which undergoes changes across the lifespan. Similarly, age-related cognitive changes typically involve declines in reasoning, spatial visualization, memory, and processing speed, while vocabulary knowledge tends to remain stable or even increase over time (Salthouse, 2004), albeit showing substantial variability in cognitive decline among individuals (e.g., Reuter-Lorenz & Lustig, 2005). Despite a surge in research efforts, the longitudinal investigation of the interplay between sleep and cognition remains limited. While some characteristics, like sleep duration and sleep quality at baseline, or improvements in sleep over time, have been linked to subsequent cognitive functioning and markers of neurodegenerative processes including predictions of increased ventricular expansion and accelerated Aβ accumulation over time (Lo et al., 2014; Virta et al., 2013; Gilner et al., 2019; Hua, Sun & Shen, 2020; Hua et al., 2021), few studies have examined how sleep specifically influences various cognitive domains over time. Specifically, existing research tends to focus on broad

cognitive outcomes rather than the nuanced effects of sleep on specific cognitive processes (e.g., Lucey et al., 2021; Gamaldo, Allaire & Whitfield, 2010).

Moreover, given the pronounced links between sleep and Alzheimer's disease (AD; Wang et al., 2020; Spira et al., 2013; Sprecher et al., 2017; Mander et al., 2015), where the focus is predominantly on mid- and later life leaves questions about sleep-cognition dynamics and genetic factors such as apolipoprotein E (*APOE*) gene, particularly the ε4 allele, a genetic risk factor for dementia and late-onset AD. *APOE* ε4 has been linked with sleep disorders, shorter sleep durations, especially in those over 50 (Kadotani et al., 2001; Gottlieb et al., 2004; Leng et al., 2021, Spira et al., 2017), and increased levels of senile plaque density (Schmechel et al. 1993; Rebeck et al., 1993). Extending the examination to the established adulthood period (ages 30-45; Mehta et al., 2020), is crucial for the recognition that aging is a continuous and lifelong journey, not just situated within the latter half of the human lifespan. Declining trends are discernible even before midlife, manifesting as early as around 20 years of age for changes in sleep architecture (Ohayon et al., 2004) and processing speed (Salthouse, 2004), suggesting the potential existence of an earlier risk window that warrants assessment and consideration for possible interventions targeting the intersection of sleep and cognition. As a counterpoint to declines, various mechanisms safeguarding against neurodegenerative shifts and cognitive decline may become apparent in earlier stages of life (e.g., young adult brain capital, cognitive reserve; Farina et al., 2023; Kartschmit et al., 2019). Together, studying these associations in younger cohorts may yield valuable insights and

uncover the potential for early interventions within critical, potentially short-term, windows aimed at mitigating cognitive decline and reducing AD/ADRD risk.

Sleep and cognition associations have been studied in short-term experimental instances aimed at manipulating sleep in the laboratory setting (e.g., sleep deprivation, double-blind placebo-controlled pharmacological assessments; Miyata et al., 2010; Tselha et al., 2018). Results from these short-term sleep manipulation studies have indicated that cognitive detriments can be observed after just one night of poor sleep, affecting memory, attention, and vigilance (e.g., Miyata et al., 2010; Xu et al., 2011; Durmer & Dinges, 2005; Smith et al., 2002). Short-term sleep disruptions have immediate detrimental effects on cognitive performance where detriments in performance reached asymptotic levels by the third hour of extended wakefulness and persisted until the fifth hour (Smith et al., 2002). Moreover, short-term sleep restriction and manipulated sleep curtailment, whether for a single night (e.g., Krueger, Majde & Rector, 2011) or over multiple repeated nights (e.g., Meier-Ewert et al., 2004), were associated with increased levels of pro-inflammatory cytokines including interleukin-6 and C-reactive protein, both of which are linked to adverse cognitive outcomes whereby inflammation is posited as a central mechanism in AD (Kinney et al., 2018). The immediate repercussions of poor sleep underscore the importance of investigating sleep-cognition associations longitudinally, and across varying timescales (e.g., day-to-day), as opposed to the over-reliance on cross-sectional examinations within the current sleep-cognition literature.

The longitudinal studies conducted at a macro-level do not consider the potential impact of daily fluctuations in one's regular sleep patter, which may proximally influence

one's cognitive performance (e.g., Knutson et al., 2007; Lucey et al., 2021; Gamaldo et al., 2010; Lucke et al., 2022). Therefore, expanding the current sleep-cognition literature, especially with advancements in technology enabling the observation of behavior outside laboratory settings (e.g., ambulatory data via phone applications), presents an opportunity to leverage informative data from intensive longitudinal burst assessments of sleep and cognition. Burst assessments allow for investigating whether sleep-cognition associations observed at the macro-level timescale (i.e., months, years, decades) are also present at the micro-level timescales (i.e., hours, days, weeks). This micro-level approach facilitates modeling and understanding the dynamic processes underlying sleep-cognition associations, providing a more comprehensive insight into their relationship. Moreover, micro-level burst assessments offer distinct advantages. Firstly, they are considered more ecologically valid (Sliwinski et al., 2018), providing a more accurate depiction of how daily sleep patterns directly impact cognitive functioning the next day. Secondly, these daily and intensive assessments enable the examination of how variability in typical sleep patterns, which may fluctuate from day-to-day, influences cognitive performance across days, allowing for the disaggregation of between-and within-person associations. While various contexts have been explored using intensive longitudinal data, such as sleep and stress (e.g., Yap, Slavish, Taylor, Bei & Wiley, 2020; Yap, Bei & Wiley, 2021), attachment (e.g., Haydon & Moss, 2020), physical activity (e.g., Kishida & Elavsky, 2016; Flueckiger, Lieb, Meyer, Witthauer & Mata, 2016), and mood (e.g., Lewis et al., 2023) to our knowledge, only a few studies have investigated these associations between

sleep and cognition (Lucey et al., 2021; Gamaldo, Allaire & Whitfield, 2010; Lucke et al., 2022).

For example, Lucey and colleagues (2021) examined whether changes in objectively measured sleep characteristics (i.e., sleep duration, sleep quality, sleep efficiency) were associated with changes in cognitive performance on a preclinical Alzheimer cognitive composite based on a neuropsychological cognitive testing battery across the span of six nights. They found that both lower and higher total sleep duration was associated with lower performance within older individuals (Lucey et al., 2021), suggesting the importance of the between-person differences in sleep duration on subsequent cognitive performance. Galmado and colleagues (2010) explored within-person sleep-cognition associations in older African-American individuals aged 50 to 80 years, revealing lower cognitive performance as individuals deviated from their expected average sleep duration, suggesting the importance of within-person effects between sleep and cognition. Both studies align with recent findings from Lucke and colleagues (2022), where micro-level sleep and working memory were assessed across a seven-day period in individuals aged 66-90 years old, and significant between-person effects of sleep duration were observed, along with within-person associations indicating lower working memory performance in poor sleepers who slept even less than average (Lucke et al., 2022). Overall, the literature emphasizes not only the scarcity of research in micro-level examinations of sleep and cognition but also the scarcity of research in individuals approaching midlife, underscoring the need for further investigation into the relationship between sleep quality and cognitive performance. This gap is especially notable when

considering the potential moderating role of *APOE* status, which has been associated with individual variability in cognition (Rawle, Davis, Bendayan, Wong, Kuh & Richards, 2018), in addition to the aforementioned associations with sleep and AD risk.

The present study seeks to contribute to the existing literature by integrating a novel approach to studying the dynamics of multiple indices of sleep quality and cognition while additionally examining potential moderating effects through *APOE* within a micro-level timescale burst design. Given the prevalence of sleep-cognition associations across aging, with stronger associations observed in midlife, we sought to examine whether these associations are evident within micro-level timescales (e.g., day-to-day observations), particularly in individuals approaching midlife. We sought to answer: 1) whether, at the between-person level, sleep quality is a significant predictor of cognitive performance on cognitive tasks across various cognitive domains (i.e., perceptual speed, working memory, executive functioning, and paired associate memory), 2) whether, at the within-person level, on days in which individuals reported sleep quality above or below their average sleep quality (i.e., person-mean) there are associated decreases or increases in their performance across the cognitive tasks (i.e., Symbol Search, Dot Memory, Shopping List, Stroop Task), and 3) whether *APOE* ε4 status moderates the associations between sleep quality and cognitive performance across the 14-days.

Methods

Participants

The 14-day micro-level ambulatory burst data was examined in a subset of 440 individuals from the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife; Wadsworth et al., 2019). The CATSLife sample is comprised of 1327 participants from two parent studies —the Colorado Adoption Project (CAP; Plomin & Defries, 1983; Rhea et al., 2013) and the Longitudinal Twin Study (LTS; Rhea et al., 2013)—who were invited to participate in a study of established adulthood.

From the CATSLife sample, 440 participants were invited and completed the supplemental smartphone study of daily cognitive functioning (235 CAP, 205 LTS). The analytic sample within this present study comprised up to 431 participants (230 CAP, 201 LTS) who had an average age of 35.79 (SD=5.69, range=28.07 – 51.32) (See Table 2.1) who contributed daily sleep quality and cognitive data. This analytic sample consisted of 57.77% female participants and was primarily White/Non-Hispanic (89.33%). The average participation was 6.86 days (SD=3.91), ranging between 1 to 14 study days. Sample descriptives for the full sample and for CAP and LTS samples are presented in Table 1. Of note, in analyses with the APOE_score, the sample was reduced to 424 due to seven individuals missing on their APOE_score.

Ambulatory Burst Phone Data Procedure

The ambulatory burst smartphone data was collected across up to 14 total study days based on protocols that were adapted from the ESCAPE study (Sliwinski et al., 2018). Participants were provided with a training day prior to the initiation of their 2-week burst participation period to become familiar with the smartphones. Neither the practice day nor any participation beyond the assigned 2-week period were included in the present analyses. The ambulatory assessment comprised two types of surveys: a waking survey (1x/day) and beeped surveys (3x/day) over the course of 14 days. Specifically, the waking survey was administered to all participants at the beginning of each study day and completed prior to the initiation of the beeped surveys. The waking survey asked questions pertaining to the participant's prior night's sleep, among other measures not included in the present study. As such, all participants responded to the waking survey measures (e.g., sleep quality measures) only once per day, at the beginning of their day, before moving on to the beeped surveys, yielding up to 14 maximum observations of one's sleep quality if an individual completed all 14 study days.

Beeped surveys were administered three times a day, and included the beeped measures (e.g., cognitive tasks) that participants were tasked with completing which was distributed throughout the day. These validated cognitive measures lasted roughly 1 minute each and were presented in the following fixed order: Dot Memory, Symbol Search, Stroop Task, and Shopping List (Sliwinski et al., 2018; Friedman et al., 2008; Hassenstab et al., 2018). The maximum completion of beeped survey responses was 42 observations, for each cognitive task, across the 14 study days. Of note, the waking

survey and beeped surveys were calibrated and randomized across the 14 study days based on each participant's self-reported daily sleep schedule to ensure that survey prompts were sent during times in which the participant would naturally be awake. For example, individuals who wake at 9 AM regularly would not be sent a waking survey or beeped surveys before their waking time. An example day may consist of a waking survey being administered at 8:30 AM, a beeped survey at 10:19 AM, another beeped survey at 2:27 PM, and a final beeped survey at 7:58 PM.

Waking Survey Measures

Sleep

Participants self-reported their prior night's sleep quality within the waking survey at the beginning of each study day, across up to 14 study days. The waking survey assessed subjective aspects of one's sleep quality (i.e., "How difficult was it to fall asleep? (SF)", "How was the quality of your sleep? (SQ)", "Did you have trouble staying asleep? (ST)", "Did you feel refreshed when you woke up? (SR)") from the prior night. The response options ranged from "Not difficult" to "very difficult", "very poor" to "very good", "no trouble" to "a lot of trouble", and "not at all" to "very much", respectively. Of note, these responses were presented to the participants on a sliding scale which ranged from "0" to "100". As such, two items assess one's relative sleep quality (i.e., SQ and SR), and two items assess one's relative sleep problems (i.e., SF and ST).

For analysis, we created variables to reflect typical sleep quality across 14 days and deviations from the typical pattern (see Table 1). Following McNeish and Matta

(2020), separable between-person and within-person time-varying covariate (TVC) effects were extracted using restricted maximum-likelihood (REML) for sleep quality measures (i.e., SQ, SR, SF, ST) which captured individual differences in typical levels of sleep quality (i.e., intercepts) versus variations from one's typical pattern to capture momentary associations, i.e. time-point-specific sleep quality values (i.e., residuals). The average-level sleep quality intercepts (i.e., b_SleepTVC) were grand-mean centered and day-specific sleep quality residuals (i.e., r_SleepTVC) were person-mean centered.

Beeped Measures

Four cognitive tasks aimed at assessing perceptual speed, working memory, executive functioning, and paired associate memory performance are assessed through the beeped survey up to three times a day within a 14-day period. The specific cognitive measures are described below, in the order of presentation to the participants.

Dot Memory (Working Memory)

Working memory performance was assessed through the Dot Memory task, where individuals were presented with three dots on a 5x5 grid (Sliwinski et al., 2018). Participants were tasked to remember the location of these dots as the dots disappeared (after 3 seconds) and were then replaced with a distractor task. For the distractor task, the 5x5 grid was populated with 'E's and 'F's and participants were tasked to identify the target 'F's among the field of 'E's. Following the distractor task, participants were presented with an empty grid and were asked to recall where the dots were previously located. As such, this task consists of an encoding phase, a distraction phase, and a

retrieval phase, and five test trials were administered. Accuracy for Dot Memory was assessed based on the average Hausdorrf distance for each beeped session, which assesses the relative distance from a target correct response to an individual's response, for each of the three beeped sessions within each study day (Aspert et al., 2002). More specifically, the Hausdorff distance is a variation of the Euclidian distance and is used to quantify the difference between two points (i.e., participant's responses versus target responses) and quantifies the mismatch as the furthest distance between the three sets of target-response points. As such, lower values will indicate that participants are closer to their target locations whereas higher values will indicate that participant responses are further away from their target responses.

Symbol Search (Perceptual Speed)

Symbol search, a measure of perceptual speed (Sliwinski et al., 2018), tasked participants to correctly identify the matching pair were presented with three pairs of symbols and were tasked with choosing which of two response options were a matching pair. There were 14 total trials within each beeped session. Accuracy for Symbol Search was assessed based on a ratio of correct responses per unit of time. For our present study, throughput was calculated as percent correct divided by reaction time and multiplied by a scaling constant (i.e., 0.6 for seconds; Thorn et al., 2006) to convert the percent correct back to the number of correct responses. As such, utilizing the throughput measure for symbol search is one conceptual approach to account for speed-accuracy tradeoffs. Together, the throughput measure can be understood as a projected number of correct responses per minute of responding time (i.e., if participants were given a whole minute

to respond, the throughput estimate would be their projected number of correct responses).

Stroop Task (Executive Functioning)

Executive function was assessed through the Stroop task (Friedman et al., 2008; Waters et al., 2012). Within this task, participants were presented with color words and were tasked with touching the word at the bottom of the screen that matched the color of the font of the color word displayed. Participants were tasked to respond as quickly and accurately as possible. Accuracy for Stroop was assessed based on an average percentage scale across the trials within each of the three beeped sessions across each study day. Accuracy for Stroop Task performance was based on the combined congruent (i.e., same font color and color word) and incongruent (i.e., font color does not match the color word) trials. Performance accuracy on the incongruent trials alone was assessed separately.

Shopping Task (Paired Associate Memory)

Paired associate memory performance was assessed using the Shopping List task where participants were tasked with two phases (Hassenstab et al., 2018; Aschenbrenner, Hassenstab, Morris, Cruchaga & Jackson, 2023). During the first phase, participants are asked to judge whether the price listed beneath each shopping item was a reasonable price for the item (e.g., $4.25 for a bottle of soap). During the second phase, participants were asked to touch which of two possible prices was associated with the shopping item in the first phase. Accuracy for Shopping List was assessed based on average

performance, on a percentage scale, across the trials within each of the three beeped sessions and across each study day.

Time-Invariant Covariates

Demographic Variables and Covariates

Demographic variables and covariates included: age, mean centered at 35 years, sex (0=Male, 1=Female), weekend/weekday (0=weekend, 1=weekday), adoption status (0=Non-adopted, 1=adopted), combined race/ethnicity (-.5=Non-White/Hispanic, .5=White/Non-Hispanic), and project (0=CAP, 1=LTS).

APOE genotyping

APOE genotyping was ascertained within the CATSLife sample where single nucleotide polymorphisms of rs7412 and rs429358 were used to form the *APOE* haplotypes (c.f. Reynolds et al., 2019, see Table 2). For this analysis, we included *APOE* variants that were imputed from GWAS genotyping and where unavailable, direct genotypes were used (Reynolds et al., 2019). Of note, across the entire sample, the highest genotype frequency was ε33 (57.73%), followed by ε34 (21.82%), ε23 (14.32%), ε44 (2.05%), ε24 (1.59%), and ε2 (1.14%) with 7 (1.59%) individuals missing their *APOE* genotyping and subsequently filtered out of the analyses. Hardy-Weinberg Equilibrium was achieved for both SNPs (rs7412 and rs429358) and in the *APOE* haplotypes formed from the SNPs in the full CATSLife sample (see Reynolds et al., 2019). Consistent with the full CATSLife sample, *APOE* genotypes did not show a significant deviation from Hardy-Weinberg Equilibrium ($\chi^2(3)=2.72$, $p=0.44$) in the

current analytical subsample. Following Leonenko et al. (2019), and with weights derived from the Kunkle et al., 2019 genome-wide association study (GWAS), a weighted *APOE* score was created based on an individual's number of ε2 and ε4 alleles: $APOE\_score = (num_{\varepsilon 2\ alleles} \times -0.47) + (num_{\varepsilon 4\ alleles} \times 1.12)$.

Statistical Analyses

All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC). Specifically, multilevel growth models, both unconditional and conditional models, were fitted with full maximum likelihood that allows for missingness and to account for both the nesting of days within individuals and for the nesting of individuals within sibships. The primary aim was to examine patterns of daily sleep quality and cognitive performance among while incorporating the time-varying covariates (TVC) of the four sleep quality measures (i.e., TVC_SF, TVC_SQ, TVC_ST, and TVC_SR). Moreover, we further examined whether *APOE* moderated the observed relationships. Figure 2.1 represents the model fitted to test our aims.

Overall, the general model-building procedure was as follows: 1) unconditional growth models to evaluate shape (i.e., linear, quadratic), 2) conditional sleep quality time-varying covariate quadratic growth model, 3) the prior model + time-invariant covariates (e.g., age, sex, and covariates), 4) the prior model + *APOE*_score, and 7) the prior model + interactions between the *APOE*_score and the sleep TVCs. For the multi-level models, day was centered on day 7 such that the intercept reflected the projected cognitive score for the midpoint of the study period , the linear trend (day) reflected the

linear rate of change in cognitive performance on day 7, and the quadratic term (day^2) reflected the acceleration (upwards or downwards) in cognitive performance across days. Random effects were estimated for the intercept and slope and further decomposed into within- and between-pair variances based on family to account for the dependencies amongst siblings (i.e., siblings are likely to be more similar in their performance) within our data, whenever allowed, and the time-specific within-person residual which captured unsystematic variance with time.

Minor deviations from the general model-building procedure were present across the various cognitive measures: (1) Shopping List did not support a quadratic model where models failed to converge, and we proceeded with a linear model; 2) separate random effects were not estimated for between and within sibling effects for the Stroop Task; 3) time of the week was not a significant predictor of performance for Symbol Search and Dot Memory but was significant for Shopping List and Stroop Task and was subsequently retained.

To inform model building, correlations between all key measures were conducted for the full sample, by sex, and age, providing support for the necessity to account for both sex and age interactions within most multilevel modeling except for Symbol Search (see Table 2.3). As the data is longitudinal consisting of multiple sessions across up to 14 study days, variables were created to indicate one's average performance (i.e., M_Dot, M_Sym, M_Stroop, and M_shop) as well as standard deviations of performance (i.e., SD_Dot, SD_Sym, SD_Stroop, and SD_Shop) which provide indications of inconsistencies, or variability and patterns of gains, in performance across time. Of note,

while the total sample consisted of 424 individuals with the *APOE* score, the total sample size for these correlations decreased from 424 to 417 due to the exclusion of days with missing data when calculating standard deviations from participant's performance. As these correlations are only meant to inform the subsequent multi-level modeling procedure, we focused on the effect sizes (i.e., *rs* > .10), as opposed to significant p-values, when deciding whether sex or age interactions should be accounted for in our growth models.

Across all models, model fit was assessed via Log-likelihood Ratio Test (LRT) comparisons and Akaike's Information Criterion (AIC; Akaike, 1987) in which LRT assesses the goodness-of-fit between the fuller model to the simpler model (i.e., between nested models). However, it is important to note that the fuller conditional growth models include an increasingly large number of parameters making the LRT model comparison tests increasingly demanding and may mute any significant effects observed. As such, within these final models, we discuss and highlight the results from the individual fixed effect parameters that show significance rather than focus on the LRT model comparisons for model significance.

Results

Descriptive statistics for sociodemographic and study variables are reported in Table 1 and APOE haplotype and score frequencies in Table 2.2. Performance tended to be quite high where average percent correct ranged from 84.55% (i.e., Shopping List) to 97.57% (i.e., Stroop Task), and average Hausdorff distance was 0.67 (*SD*=0.39).

Intraclass correlations (ICCs), calculated to examine between-person variability on the cognitive measures across up to 42 total sessions, suggest that the between-person variability was highest for Symbol Search (ICC=.57), with similar values for Dot Memory and the Stroop Task (ICC's=.50 and .46, respectively), corroborating reliability estimates from Sliwinski et al., 2018. The intraclass correlation for Shopping List was the smallest (ICC=.20), similar to estimates from Aschebrenner et al. (2023).

APOE, Sleep Quality and Cognition Associations

Negligeable to small associations between *APOE*_score and the four sleep TVCs were observed (r's=-0.05-0.03 for the between-person sleep TVCs, and r's=-0.06-0.12 for the within-person sleep TVCs), with larger values noted for M_r_SF and M_r_ST (see Table 2.3). Overall, the *APOE*_score was correlated positively with sleep problems and negatively with sleep quality in general. Across most of the cognitive tasks, negative associations were observed between the *APOE*_score and both average performance (*r's*=-0.03 [-] -0.12; except for Shopping List, *r*=0.12) and variability across days (*r's*=-0.01 [-] -0.05; except for Stroop Task, *r*=0.02) (see Table 3). Sleep quality and cognition associations show general patterns in which better sleep quality was generally observed with better average performance (*r's*= -0.10-0.14) and less variability across days (*r's*=-0.06 [-] -0.02) (see Table 2.4). Correlational patterns across the full sample and by sex and age suggested negligeable associations with Symbol Search. Overall, the correlations suggested the importance of incorporating sex and age interactions within the growth models, particularly emphasizing the necessity to account for age interactions with the sleep quality measures and the *APOE* score.

Growth Models

Dot Memory

The best fitting unconditional model for Dot Memory was a quadratic growth model with sibling random effects on the intercept (Table A2.1), suggesting a linear decrease in the average Haussdorf distance (i.e., participants were closer to their targets) from day 7 (b=-0.02, SE=0.001, p<.001), with a buffering of the gains in accuracy (b-0.001, SE=0.003, p<.001) from the nonlinear quadratic term across days (see Table 2.5). Weekend/weekday effects were not significant and were not retained. Building upon this model, we included the TVC sleep quality parameters observing that the effects of SQ were significant ($\chi 2(2)=6.8$, $p<.05$) but not the other sleep TVCs (see Table 2.6). The next set of conditional growth models include the TICs, principally age, sex, and the *APOE*_score (see Tables A2.2, and A2.3). Significant sex effects were observed across each of these fullest models such that females were estimated to be further from their target locations (b=0.20, SE=0.04). Significant between-person TVC effects for SQ were observed such that better sleep quality is associated with closer responses to the targeted location (b=-0.004, SE=0.002) and more sleep problems (i.e., ST and SF) are associated with responses that are further away from the targeted locations (b=0.004, SE=0.002; b=-0.005, SE=0.002, respectively). Across the 14 study days, participants are generally closer to their target locations (b's = -0.01, all *p*'*s*<.05) albeit the effects are attenuated with the nonlinear term (day2).

Figure 2 shows the predicted Dot Memory scores across the 14-days for the TVC of SQ (see appendix for all four sleep TVCs, Appendix Figure A2.1). Generally, participants are closer to their targets across the study days. Here, we observe that younger ε34 individuals, with sleep quality one standard deviation above the average sleep quality, are closer to their targets and are outperforming the ε33 homozygous groups. However, while the younger ε34 individuals have an advantage, the advantage does dissipate across the days where these individuals also become less accurate over time. The older ε34 individuals are further from their target locations, plateau earlier, and are less accurate, albeit some gain is observed for those who have better sleep quality. Lastly, the ε33 homozygous group's performance on Dot Memory remains quite stable over time. Indeed, patterns were similar across the various sleep quality TVCs (see Appendix Figure A2.1).

Symbol Search

The best fitting unconditional model for Symbol Search was a quadratic growth model with sibling random effects on the intercept (see Table A2.1), suggesting a linear increase from day 7 (b=0.81, SE=0.04, p<0.0001), with a buffering of gains across days (b=-0.08, SE=0.01, p<.0001) from the nonlinear quadratic term across days (see Table 5). Weekend/weekday effects were not significant. However, as the correlation patterns between the *APOE*_score, sleep quality, and Symbol Search were not meaningful (r's < .10, *p*'s > .05) we did not build upon this model to include the TVC sleep quality parameters nor the TICs or the *APOE*_score.

Stroop Task

The best fitting unconditional model for the Stroop Task was a quadratic growth model with no sibling random effects on the intercept (Table A2.1), suggesting a nonsignificant linear increase in performance from day 7 (b=0.04, SE=0.02, p >.05), with an attenuation of the gains in accuracy (b=-0.001, SE=0.01, p > .05) from the nonlinear quadratic term across days (see Table 2.7). Weekend/weekday effects were significant ($\chi 2(5)=24.2$, p<.0001), suggesting better performance on weekdays, and were retained in the following models. Building upon this model, we included the TVC sleep quality parameters and observed only a significant main effect for the between-person TVC for SQ ($\chi 2(2)=7.2$, p<.05), suggesting better SQ is associated with better performance (b=0.03, SE=0.01, p <.05). No significant main effects were observed for the within-person sleep TVCs. The next set of conditional growth models include the TICs, principally age, sex, and the APOE_score (see Tables A2.2, and A2.4). No significant main effects of sleep quality (or any sleep TVCs) or APOE_score were observed (see Table A2.4; similar results observed when assessing only the incongruent trials, see Table A2.5). However, patterns suggest that a higher APOE_score, indexing the contribution of ε4, were associated with poorer performance on Stroop (b=-0.21, SE=0.01, p > .05). Moreover, performance was further decreased in older individuals with a higher dosage of ε4 across the days (b=-0.01, SE=0.001, p >.05), with a buffering in the decline if they had better average sleep quality (b=0.01, SE=0.003, p<.05). Moreover, a momentary gain in performance is observed when individuals with higher e ε4 dosage had better sleep quality than average on a particular day (b=0.01, SE=0.004, p < .05) and a further boost

in gain for older individuals (b=0.001, SE=0.001, p <.05). Of note, the patterns are similar and slightly stronger when assessing the incongruent trials (see Table A2.5).

Figure 2.3 shows the predicted Stroop Task scores across the 14-days for the TVC of SQ (see all Sleep TVCs in the appendix, Figure A2.2, see all sleep TVCs for Stroop Incongruent trials in Figure A2.3) contrasting expected trajectories of *APOE* ε33 versus *APOE* ε34 individuals. Here, we observe that ε34 individuals with poor sleep quality generally perform worse in comparison to those with ε33. However, ε34 individuals who have good sleep quality (i.e., +1 SD above the mean) performed just as well, if not better, compared to those with ε33. The worst performance was observed in individuals with ε34, who had poor SQ, and who were age 40. Moreover, when individuals with ε34 were above their usual SQ or SR (see Appendix Figure A2.2) on a particular day, there is a little bit of gain in performance.

Shopping List

The best fitting unconditional model for Shopping List was a linear model with no random effects (Table A2.1). Weekend/weekday effects significantly improved model fit (χ2(4)=12.1, p=.02) and were retained. This model suggested a linear decrease in performance from day 7 (b=-0.22, SE=0.04, p <.05), with a trend significant boost in performance on weekdays (b=0.56, SE=0.29, p=0.057). Building upon this model, we included the TVC sleep quality parameters, observing that the effects of the between-person SQ, SF, and ST effects were significant, with trend effects for SR (see Table 2.9) whereby relative increases in performance were suggested by SQ (b=0.045, SE=0.02, p

<.05) and SR (b=0.033, SE=0.02, *p* =0.06) and relative decreases in performance were suggested by ST and SF (b's=-0.04 [-] -0.07, all *p's* < 0.05). No significant main effects were observed for the within-person sleep quality TVCs. The next set of conditional growth models include the TICs and the APOE_score (see Tables A2.2 and A2.6). Significant between-person TVC effects were observed for SQ such that better SQ on average was associated with better performance (b=0.07, SE=0.03, *p* < .05). On the other hand, significant between-person TVC effects for sleep problems (i.e., TVC_ST and TVC_SF) were observed, such that having more sleep difficulties were associated with decreases in Shopping List performance (b=-0.08, SE=0.03; b=-0.10, SE=0.03, all *p's* < .05; respectively). Significant linear effects are observed across all four fullest models and across the four sleep TVCs indicating worsening performance across study days beyond day 7 (b's=-0.17 [-]-0.19, all *p's* > .05). Older individuals show a heightened decrease in performance across days (b=-0.01, SE-0.01). The main effect of *APOE*_score was a significant predictor of Shopping List performance, albeit in an unexpected positive direction (b's= 1.35-1.61, all *p's* < .05) suggesting that increasing dosage of ε4 is associated with better performance on Shopping List. An interesting between-person sleep TVC x Age x APOE_score effect was observed across all TVCs such that better sleep quality (SQ and SR) on average, older age, and more positive APOE_score were associated with better performance (b=0.02, SE=0.006, b=0.02, SE=0.006, respectively, all *p's* < .05) whereas more sleep difficulties (i.e., ST and SF) on average, older age, and increased dosage of ε4 on the *APOE*_score were associated with poorer cognitive performance (b=-0.01, SE=0.005, b=-0.01, SE=0.005, respectively, all *p's* < .05).

Figure 2.5 shows the predicted Shopping List scores across the 14-days for the TVC of SQ (see all of the sleep TVCs in Appendix Figure A2.3). Here, we observe that individuals who are *APOE* ε34 who are one standard deviation above the average sleep quality are predicted to outperform those with ε33. Moreover, they tended to remain quite stable in their performance over time. Individuals who are *APOE* ε34 who have poor sleep quality tended to perform worse over time in comparison to their counterparts with better sleep quality as well as those who are *APOE* ε33.

Discussion

The present study examined the association between sleep quality and cognitive performance in adults within established adulthood over a two-week period, as individuals went about their daily routines. Additionally, we considered the day-to-day sleep quality and explored whether *APOE* ε4 positivity moderated sleep and cognition associations. At the between-person level, significant effects were observed for sleep quality across paired associated memory, executive functioning, and working memory, indicating that one's average sleep quality significantly influenced cognitive performance. Moreover, day-to-day sleep difficulties were associated with deficits in paired associated memory performance. Day-to-day sleep quality associations with cognitive performance were less pronounced overall, apart from working memory where individuals were more successful in performance on days with higher sleep quality levels. *APOE* ε4+ individuals tended to outperform non- ε4+ individuals in paired associated memory at higher typical levels of sleep quality and at younger age, but otherwise poorer sleep quality and older ages led to more comparable or worse performance. For executive

functioning, older age, poorer sleep, and greater *APOE* ε4 positivity was associated with poorer performance, but on days with better sleep quality, ε4+ individuals has a boost in executive functioning performance was observed.

We observed the most pronounced between-person sleep TVC effects for paired associated memory and executive functioning, with somewhat weaker evidence for working memory. Our findings align with existing research that links better sleep quality to better cognitive performance and poorer sleep quality with cognitive deficits (e.g., Lo et al., 2016; Satterfield & Killgore, 2019; Anderson et al., 2009; Tucker et al., 2010; Holanda Junior & Almondes, 2016; Sen & Tai, 2023; Tai, Chen, Manohar & Husain, 2022). Better cognitive performance in individuals who tend to have better sleep quality may be supported by prominent theories such as the default mode network (DMN) activation theory (Horovitz et al., 2009). The DMN activation theory suggests that areas within the DMN, comprising of areas often implicated within AD pathology (e.g., medial prefrontal cortex (mPFC), posterior cingulate cortex, precuneus, and angular gyrus), may be shaped by sleep (Horovitz et al., 2009). Moreover, it is suggested that the prefrontal cortex (PFC), a brain region that supports functions related to working memory and executive functions, may be particularly sensitive to poor sleep (Alvarez & Emory, 2006; Harrison, Horne & Rothwell, 2000). Increased neuronal activity within the DMN is observed in poor sleep quality contexts (Horovitz et al., 2009; Jones et al., 2011; Gujar, Yoo, Hu & Walker, 2010; Dai et al., 2020) co-occurring with cognitive deficits, mild cognitive impairment, and Alzheimer's disease (Sorg et al., 2007; McKinnon et al., 2016; Lunsford-Avery et al., 2020). Furthermore, regions within the DMN, such as the

prefrontal cortex (PFC; and dorsolateral PFC) play pivotal roles in executive function and working memory, contributing to coordination and attention distribution in executive control (Jones & Harrison, 2001; Blumenfeld & Ranganath, 2007). Dai and colleagues (2020) found enhanced functional connectivity in the dorsal attention network (DAN) and the DMN after sleep deprivation which was negatively associated with working memory performance. Therefore, modulations in functional connectivity in brain regions within the DMN, due to poor sleep, may be one physiological basis for the observed findings of poor sleep quality, on average, being associated with worse cognitive performance. Consistently sleeping poorly has been suggested to likely impair higher-order functioning as well as reduce vigilance and attentional abilities (Frenda et al., 2016). Poor sleep quality may impair cognitive performance by disrupting subcomponents of the Multi-Component Model of Working Memory (Baddeley, Hitch & Allen, 2021), notably the central executive. Linked to attention, task switching, problem-solving, decision-making, working memory updating, inhibition of irrelevant information, and cognitive flexibility, the central executive's abilities are crucial for adequate cognitive performance on complex tasks (Baddeley, Hitch & Allen, 2021). Studies, such as those utilizing N-back tasks, have demonstrated that total sleep deprivation can impair the central executive system (Choo, Lee, Venkatraman, Sheu & Chee, 2005).

The evidence supporting the within-person day-to-day effects of sleep quality was minimal, with only some evidence observed for working memory and executive functioning, suggesting that the fluctuations in sleep quality and the dynamics of sleep

quality may be task-specific. Indeed, research corroborates this finding as working memory has been found to be most sensitive to the effects of sleep deprivation (Chee et al., 2006; Martinez-Cancino et al., 2015) with increasing levels of sleep deprivation being associated with both increased response times and decreased accuracy (Tempesta et al., 2017; Harrington et al., 2018). As such, working memory's reliance on executive functions and its interplay with attention, memory consolidation, and cognitive control, as seen with the demands of the central executive may underscore our finding regarding one's deviations from their average sleep quality being influential on cognitive performance, notably on days in which one slept better than usual. Even one night of poor sleep or sleep deprivation may impair components of executive functioning including sustained attention, reaction time, and components of working memory (Krause et al., 2017). Sleep fragmentation has been associated with diminished executive function (Oosterman et al., 2009). Interestingly, the immediate and dynamic influence of sleep and cognition aligns with sleep "banking" whereby the influence of poor sleep on cognition may be offset by a prior period of extended or above-average sleep (e.g., Rupp et al., 2009). Specifically, Rupp and colleagues (2009) found that increasing one's sleep by even just under two hours per night resulted in significantly increased time in deep sleep stages which was associated with faster rebound on psychomotor vigilance task performance compared to the control group after sleep deprivation. Similar results emerged for tasks related to sustained attention and memory whereby short-term sleep extension was found to offset the effect of poor sleep (Arnal et al., 2015; Stepan et al., 2019). However, current work suggests that within-person links between sleep and

cognition may still depend on one's average levels (Lucke et al., 2022). That is, people who are poor sleepers performed worse on working memory tasks when they slept even less than usual during the night prior (Lucke et al., 2022).

Importantly, a complex interplay between genetic factors and sleep quality influencing cognitive performance was observed, with implications for gene-environment interplay. Research has found that *APOE* ε4 individuals often report poor sleep quality and too short or too long sleep durations (Basta et al., 2021; Leng et al., 2021). Furthermore, poor sleep quality and extreme sleep durations have been linked to greater Aβ burden and poorer cognitive performance across various cognitive domains (Winer et al., 2021). Importantly, the nuanced relationship between within-person sleep quality TVC effects and executive functioning performance becomes evident only its interaction with *APOE.* As such, executive functioning may be more sensitive to the combined influence of *APOE* and sleep quality. The findings may be attributed to the cognitive demands inherent in the Stroop task, which necessitates cognitive flexibility, selective attention, and inhibitory control, particularly evident during congruent and incongruent trials. The emphasis on response inhibition within the task likely contributes to the observed outcomes. Prior studies have identified deficits in Stroop performance within AD patients, particularly on incongruent trials (e.g., Bondi et al., 2002; Fisher, Freed & Corkin, 1990) with deficits observable even in the early stages of AD pathology (Bondi et al., 2002). Furthermore, insights from Wetter and colleagues (2005) suggest a distinct effect of *APOE* ε4 positivity on inhibition/switching abilities: non-demented *APOE* ε4 individuals exhibited poorer performance specifically in the inhibition/switching

condition of the D-KEFS Color-Word Interference Test, an adapted version of the Stroop test.

The unexpected findings regarding paired associated memory reveal a unique pattern where *APOE* ε4+ individuals, particularly in the younger age group, were predicted to outperform the other groups. This unexpected result may be understood through the context of antagonistic pleiotropy (Tuminello & Han, 2011; Han & Bondi, 2008), which proposes that ε4+ carriers may exhibit enhanced cognitive performance in early life, as observed in this study's sample, followed by a subsequent decline in later years, exhibiting a tradeoff between the advantageous and disadvantageous effects of *APOE* ε4 on cognition. However, it is important to interpret these results cautiously, as antagonistic pleiotropy was not evident in the other cognitive tasks, and the intraclass correlation for this task was low, suggesting lower reliability of between-person differences. Further examinations, particularly longitudinal analyses, are warranted to validate these findings.

The present study had many strengths. Indeed, this is the first study to examine sleep quality-cognition associations within micro-level timescales in individuals within established adulthood which allowed for examinations of daily fluctuations in sleep quality while additionally examining the moderating role of *APOE*. Limited prior work has examined the within-person sleep and cognition associations within this age group (e.g., ages 50+; Lucey et al., 2021, Gamaldo, Allaire & Whitfield, 2010; Lucke et al., 2022) and none have examined whether *APOE* moderated the associations. In addition to examining just one measure of sleep quality, we examined various aspects of sleep

quality related to sleep problems, sleep efficiency, and how refreshed one felt the next morning. The findings from this study provide additional insight into how sleep-cognition associations may have momentary associations across day-to-day observations while also discerning whether and how effects accumulate and contribute to performance in smaller timescales, with implications for how these effects may also play out over larger timescales and how they may be observed at much younger ages.

While the present study had many strengths, the present study also had several limitations. Firstly, the sample size comprised only a subset of individuals from CATSLife who participated in the ambulatory smartphone substudy (i.e., N=440 in the substudy, further reduced to N=424, versus N=1327 in CATSLife). As such, our findings may not generalize to the full CATSLife sample as these individuals who opted to participate in the supplemental ambulatory smartphone substudy may differ from the entire sample. Moreover, the CATSLife sample, while representative of the Colorado population (Rhea et al., 2013a; Rhea et al., 2013b), both the CATSLife sample and the subsample analyzed in this present study are ethnically and racially homogenous with most of the sample being comprised predominantly of White or non-Hispanic individuals. Although the current examination is valuable regardless of being ethnically and racially homogenous, more can be known about the dynamics of sleep-cognition associations in more diverse ethnic backgrounds. Indeed, research has found that racial/ethnic minority groups are more likely to report shorter sleep durations (i.e., less than 6 hours of sleep), more likely to experience poor sleep quality, more likely to experience increased daytime sleepiness, and more likely to report sleep complaints, relative to non-Hispanic Whites

(Johnson et al., 2019; Nunes et al., 2008; Grandner et al., 2010). As such, our present findings are limited in generalizability to other diverse populations, particularly in populations where sleep-health disparities are prevalent. Next, while the present study examined sleep quality, recent literature suggests that perhaps beyond sleep quality and beyond sleep duration, sleep regularity (i.e., consistency of one's sleep-wake timing) may be a better predictor of health outcomes (Windred et al., 2023). As such, future work may benefit from also examining one's sleep regularity across day-to-day observations and examine whether deviations from one's typical sleep-wake schedule may be associated with any detriments to cognitive functioning the following day. Lastly, future work may benefit from directly modeling the mean and the intraindividual variability of sleep and cognition (e.g., mixed-effect location scale models; Ying et al., 2021; Ong et al., 2016).

Despite the limitations, our study stands as the first to explore micro-level associations between sleep and cognition over a two-week period among individuals within established adulthood while additionally examining the moderating role of *APOE*. Leveraging the burst nature of the data, we were able to capture day-to-day variations in sleep quality, thereby enhancing the ecological validity of our design. Overall, our findings highlight the interplay between daily and average sleep quality with cognitive performance, particularly evident in working memory, executive functioning, and paired associated memory, even among a younger sample and within a micro-level timescale. Notwithstanding the saliency of the influence of average sleep quality on cognition, daily fluctuations in sleep quality appear to also impact executive functioning and working memory performance, with significant interactions with *APOE*. These results underscore

the importance of examining such associations across micro-level timescales to understand their cumulative effects, with implications for larger timescales among individuals approaching midlife. Notably, some associations observed over longer timescales persist in day-to-day observations, emphasizing the relevance of studying sleep-cognition dynamics at earlier life stages rather than solely focusing on older adults where cognitive aging is already evident.

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Table 2.1. Descriptives of CATSLife Smartphone Subsample

		Analysis Sample		CAP		LTS
Sample Descriptives	*N*	Frequency (%)	*N*	Frequency (%)	*N*	Frequency (%)
%Female	431	57.77%	230	58.26%	201	57.21%
Adopted	431	19.26%	230	36.09%	201	0%
White/Non-Hispanic	431	89.33%	230	93.04%	201	8.07%
Hispanic/Non-White	431	10.67%	230	6.96%	201	14.93%
Sample Descriptives	*N*	Mean (SD)	*N*	Mean (SD)		Mean (SD)
Age (SD)	431	35.79(5.69)	230	40.14(4.02)	201	30.882(2.16)
Age Range	431	28.07-51.32	230	31.01-51.32	201	28.07-35.78
*APOE*_Score (SD)*	424	0.22 (0.62)	223	0.21(0.59)	201	0.23(0.65)
Days (SD)	431	6.93(3.89)	2794	6.93(3.87)	2364	6.93(3.91)
M_Dot (SD)	424	0.71(0.40)	223	0.73(0.44)	201	0.69(0.42)
SD_Dot (SD)	417	0.40(0.13)	220	0.40(0.12)	197	0.39(0.13)
M_Sym (SD)	424	96.06(2.75)	223	96.17(2.72)	201	95.93(2.78)
SD_Sym (SD)	417	4.97(2.56)	220	4.95(2.45)	197	4.99(2.47)
M_Stroop (SD)	424	97.57(4.43)	223	97.36(5.75)	201	97.79(2.17)
SD_Stroop (SD)	417	3.53(2.85)	220	3.68(3.40)	197	3.38(2.05)
M_Shop (SD)	424	84.55(7.50)	223	84.60(6.77)	201	84.48(8.26)
SD_Shop (SD)	417	12.02(3.56)	220	12.20(3.44)	197	11.82(3.68)
b_SQ (SD)	424	0.10(16.44)	223	0.59(16.03)	201	-0.43(16.90)
M_r_SQ (SD)	424	0.02(0.74)	223	-0.02(0.76)	201	0.06(0.70)
b_SF (SD)	424	0.10(18.62)	223	-0.49(17.75	201	0.76(19.56)
M_r_SF (SD)	424	0.03(0.72)	223	0.06(0.77)	201	0.0004(0.67)
b_SR (SD)	424	0.15(17.64)	223	0.16(18.04)	201	0.13(17.23)
M_r_SR (SD)	424	-0.00(0.67)	223	0.01(0.79)	201	-0.01(0.52)
b_ST (SD)	424	0.11(19.29)	223	-0.2(19.37)	201	0.43(19.24)
M_r_ST (SD)	424	-0.01(0.75)	223	0.02(0.88)	201	-0.05(0.58

Note. CATSLife=Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging, CAP=Colorado Adoption Project, LTS=Longitudinal Twin Study. M_=Average performance, SD_= Standard deviations of performance (i.e., one's standard deviations from their performance, capturing variability/patterns of gains across time), Dot=Dot Memory, Sym=Symbol Search, Stroop=Stroop Task, Shop=Shopping List, SQ=Sleep Quality TVC, SF=Sleep Fall TVC, SR= Sleep Refresh TVC, ST=Sleep Trouble TVC.

Table 2.2 *APOE* haplotype, SNP, and score frequencies

APOE	rs429358	rs7412	APOE_Score	N	Percent
ε22	T/T	T/T	-.94	5	1.14
ε23	T/T	C/T	-.47	63	14.32
ε24	C/T	C/T	.65	7	1.59
ε33	T/T	C/C	0.00	253	57.50
ε34	C/T	C/C	1.12	96	21.82
ε44	C/C	C/C	2.24	9	2.05

Note. Nmissing *APOE*=7

Table 2.3. Partial Correlations between APOE_Score, cognitive performance, and sleep quality measures.

		APOE_Score				
Sample		Full *N*=417	Females *N*=241	Males *N*=176	Younger *N*=210	Older *N*=207
M_Dot	*r*	-0.04	-0.04	-0.03	**-0.16**	0.09
SD_Dot	*r*	-0.01	-0.05	0.06	*-0.12*	*0.14*
M_Sym	*r*	-0.03	0.03	-0.10	0.05	-0.11
SD_Sym	*r*	0.01	-0.06	0.12	-0.06	0.09
M_Stroop	*r*	**-0.12**	**-0.13**	-0.10	*0.13*	**-0.23**
SD_Stroop	*r*	0.02	-0.02	0.08	**-0.14**	*0.13*
M_Shop	*r*	**0.12**	0.10	*0.15*	**0.20**	0.02
SD_Shop	*r*	-0.05	-0.06	-0.04	**-0.18**	0.12
b_SQ	*r*	-0.05	-0.03	-0.08	0.08	**-0.10**
M_r_SQ	*r*	-0.06	-0.10	-0.01	-0.04	-0.10
b_SF	*r*	0.03	0.08	-0.03	-0.01	0.08
M_r_SF	*r*	**0.12**	**0.16**	0.06	0.11	*0.12*
b_SR	*r*	-0.03	-0.03	-0.04	0.07	*-0.14*
M_r_SR	*r*	-0.01	-0.03	0.02	0.01	-0.03
b_ST	*r*	0.01	0.01	0.01	-0.07	0.11
M_r_ST	*r*	**0.10**	0.09	0.11	0.06	*0.14*

Note. Full correlations are partialed for age and sex. Female and Male correlations are partialed for age. Younger and Older correlations are partialed for sex. The total sample size decreased from 424 to 417 due to data exclusion from individuals who scored perfectly across all days and sessions and/or the data exclusion due to missing sleep items when calculating standard deviations from one's performance. M_=Average performance, SD_= Standard deviations of performance, Dot=Dot Memory, Sym=Symbol Search, Stroop=Stroop Task, Shop=Shopping List, SQ=Sleep Quality TVC, SF=Sleep Fall TVC, SR= Sleep Refresh TVC, ST=Sleep Trouble TVC. Bolded parameters are statistically significant at $p < .05$, Italicized parameters are trend significant $p < .07$.

Table 2.4. Partial Correlations between cognitive performance and sleep quality measures.

	Full (N=417)							
	b_SQ	M_r_SQ	b_SF	M_r_SF	b_SR	M_r_SR	b_ST	M_r_ST
M_Dot	**-0.10**	0.04	**0.10**	-0.01	-0.06	-0.01	0.06	-0.01
SD_Dot	-0.02	0.02	0.04	-0.05	-0.06	0.01	0.04	-0.02
M_Sym	-0.00	0.07	-0.00	-0.00	-0.04	0.07	-0.00	-0.07
SD_Sym	-0.02	-0.09	0.02	0.01	0.01	-0.05	0.03	0.10
M_Stroop	**0.13**	**0.13**	-0.05	**-0.13**	0.06	0.07	-0.06	**-0.11**
SD_Stroop	-0.06	-0.03	-0.00	-0.04	-0.04	-0.04	0.07	0.04
M_Shop	**0.14**	0.09	**-0.19**	**-0.11**	**0.12**	0.04	**-0.14**	-0.03
SD_Shop	-0.06	-0.06	**0.11**	**0.10**	-0.06	-0.03	0.08	0.01

Note. Full correlations are partialled for age and sex. The total sample size decreased from 424 to 417 due to the exclusion of days with missing data when calculating standard deviations from participant's performance. M_=Average performance, SD_= Standard deviations of performance (i.e., one's standard deviations from their performance, capturing variability/patterns of gains across time), Dot=Dot Memory, Sym=Symbol Search, Stroop=Stroop Task, Shop=Shopping List, SQ=Sleep Quality TVC, SF=Sleep Fall TVC, SR= Sleep Refresh TVC, ST=Sleep Trouble TVC. Bolded parameters are statistically significant at $p < .05$, Italicized parameters are trend significant $p < .07$. Total sample size is reduced from 424 to 417 due to missing data for specific days.

Table 2.5. Best Fitting Unconditional Growth Models across the four Cognitive Tasks.

	Dot Memory	Symbol Search	Stroop Task	Shopping List
Fixed Effects	b(SE)	b(SE)	b(SE)	b(SE)
1. Intercept	**0.677(0.023)**	**41.072(0.558)**	**97.509(0.228)**	**84.101(0.418)**
2. Day	**-0.015(0.001)**	**0.806(0.044)**	0.037(0.024)	**-0.221(0.037)**
3. Day^2	**0.001(0.0003)**	**-0.076(0.008)**	-0.001(0.005)	
4.Weekend/Weekday	--	--	**0.205(0.103)**	*0.560(0.293)*
Random Effects				
σ^2_{1BW}	**0.047**	**30.347**	**17.896**	**10.968**
σ^2_{1WI}	**0.141**	**83.240**		**33.355**
σ_{21WI}	**0.003**	**4.702**	**-0.698**	**0.726**
σ^2_{2WI}	**4.0E-04**	**0.571**	**0.199**	**0.124**
σ_{31WI}	**-7.9E-04**	**-0.675**	**-0.087**	--
σ_{32WI}	**-5.0E-05**	**-0.021**	**-0.018**	--
σ^2_{3WI}	**1.0E-05**	**0.012**	**0.005**	**--**
σ_{41WI}	--	--	**-1.621**	-4.620
σ_{42WI}	--	--	-0.052	0.303
σ_{43WI}	--	--	**0.025**	**--**
σ^2_{4WI}	--	--	**0.848**	**4.651**
σ^2_u	**0.156**	**50.868**	**15.941**	**150.680**
N Observations	10997	10991	10977	10954
N Sibling Identifiers	337	337	--	337
N Individuals	431	431	431	431

Note. Bolded parameters are significant $p<.05$. Italicized parameters are trend significant $p=0.06$. Day=Linear effect, Day^2=Quadratic Effect, BW=between-family, WI=within family. Numbered subscripts reference the numbered fixed effects. For example, $\sigma_2{}^2{}_{WI}$ = linear variance, σ_{31WI} = Covariance between the Intercept and the Quadratic.

Table 2.6. Conditional Growth Model Fixed Effects for Sleep Predictors: Dot Memory

	Model_SQ		Model_SR		Model_SF		Model_ST	
Fixed Effects	b	SE	b	SE	b	SE	b	SE
Intercept	**0.677**	**0.023**	**0.677**	**0.023**	**0.676**	**0.023**	**0.677**	**0.023**
Day	**-0.015**	**0.001**	**-0.015**	**0.001**	**-0.015**	**0.001**	**-0.015**	**0.001**
Day^2	**1.3E-03**	**3.3E-04**	**1.3E-03**	**3.3E-04**	**1.3E-03**	**3.3E-04**	**1.3E-03**	**3.3E-04**
r_SleepTVC	**-4.6E-04**	**2.4E-04**	-3.9E-04	2.4E-04	-2.6E-04	2.2E-04	2.7E-04	2.1E-04
b_SleepTVC	-2.0E-03	1.2E-03	-1.6E-03	1.1E-03	1.9E-03	1.0E-03	9.5E-04	1.0E-03
Goodness of Fit								
Neg 2 LL	12413.6		12415.8		12415.6		12417.9	
AIC	12439.6		12441.8		12441.6		12443.9	
AICC	12439.6		12441.8		12441.7		12444	
BIC	12489.3		12491.4		12491.3		12493.6	
K	13		13		13		13	
Model Comparisons								
$\Delta\chi 2$	6.8		4.6		4.8		2.5	
df	2		2		2		2	
P	0.033		0.100		0.09		0.29	

Note. Model comparisons are between the current model to the best-fitting unconditional model. Day=Linear Effect, Day^2=Quadratic Effect, r_SleepTVC=within-person sleep time-varying covariate effect, b_SleepTVC=between-person sleep time-varying covariate effect, SQ=Sleep Quality, SR=Sleep Refresh, SF=Sleep Fall, ST=Sleep Trouble. Bolded parameters are significant p <.05. $N_{Siblings}$=337, N_{Unique}=431, $N_{Observations}$=10977.

Table 2.7: Conditional Growth Model Fixed Effects: Stroop Task

	SQ		SR		SF		ST	
Fixed Effects	b	SE	b	SE	b	SE	b	SE
Intercept	**97.510**	**0.228**	**97.510**	**0.229**	**97.510**	**0.228**	**97.511**	**0.228**
Day	0.037	0.024	0.037	0.024	0.037	0.024	0.037	0.024
Day^2	-0.001	0.005	-0.001	0.005	-0.001	0.005	-0.001	0.005
Weekend/Weekday	**0.204**	**0.103**	**0.204**	**0.103**	0.202	0.103	**0.205**	**0.103**
r_SleepTVC	0.000	0.002	0.000	0.003	0.001	0.002	-0.002	0.002
b_SleepTVC	**0.027**	**0.010**	0.014	0.009	-0.005	0.009	-0.008	0.009
Goodness of Fit								
Neg 2 LL	63777.7		63782.6		63784.4		63783.3	
AIC	63811.7		63816.6		63818.4		63817.3	
AICC	63811.7		63816.7		63818.5		63817.4	
BIC	63880.8		63885.7		63887.5		63886.5	
K	17		17		17		17	
Model Comparisons								
$\Delta\chi 2$	7.2		2.3		0.5		1.6	
df	2		2		2		2	
p	0.03		0.32		0.78		0.45	

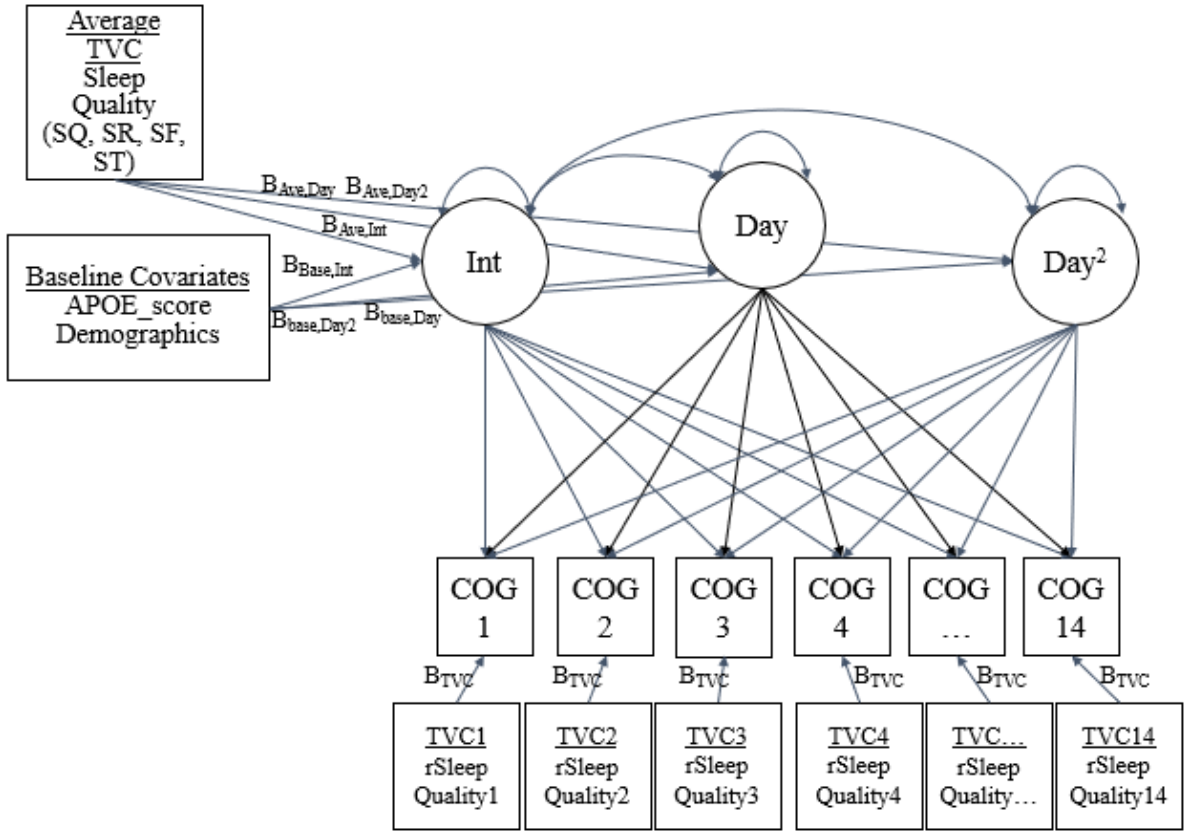
Note. Model comparisons are between the current model to the best-fitting unconditional model. Day=Linear Effect, Day^2=Quadratic Effect, r_SleepTVC=within-person sleep time-varying covariate effect, b_SleepTVC=between-person sleep time-varying covariate effect. Bolded parameters are significant $p < .05$. N_{Unique}=431, N observations=10977

Table 2.8: Conditional Growth Model Fixed Effects: Shopping List

	SQ		SR		SF		ST	
Fixed Effects	b	SE	b	SE	b	SE	b	SE
Intercept	**84.094**	**0.415**	**84.094**	**0.417**	**84.105**	**0.412**	**84.114**	**0.413**
Day	**-0.220**	**0.037**	**-0.221**	**0.037**	**-0.221**	**0.037**	**-0.220**	**0.037**
Weekend/Weekday	0.572	0.294	0.571	0.294	0.565	0.294	0.561	0.294
r_SleepTVC	0.011	0.007	0.005	0.008	-0.002	0.007	-0.011	0.007
b_SleepTVC	**0.046**	**0.020**	0.033	0.018	**-0.065**	**0.017**	**-0.039**	**0.017**
Goodness of Fit								
Neg 2 LL	86986.3		86990.6		86980.7		86986.3	
AIC	87012.3		87016.6		87006.7		87012.3	
AICC	87012.4		87016.7		87006.7		87012.3	
BIC	87062		87066.3		87056.3		87062.0	
K	13		13		13		13	
Model Comparisons								
$\Delta\chi 2$	8		3.7		13.6		8	
df	2		2		2		2	
p	0.02		0.16		0.001		0.02	

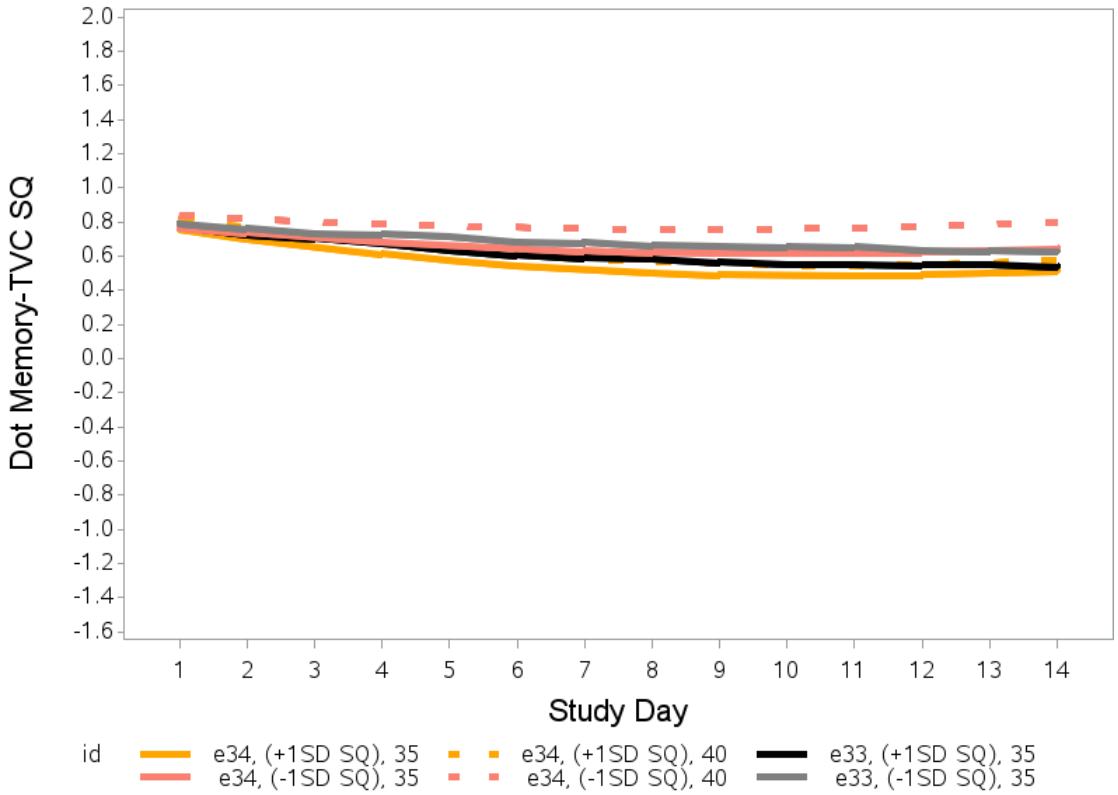
Note. Model comparisons are between the current model to the best-fitting unconditional model. Day=Linear Effect, r_SleepTVC=within-person sleep time-varying covariate effect, b_SleepTVC=between-person sleep time-varying covariate effect. Bolded parameters are significant p <.05. $N_{sibling}$=337, N_{Unique}=431, N observations=10954.

Figure 2.1. Model fitted to assess Sleep and Cognition Associations across 14 days.



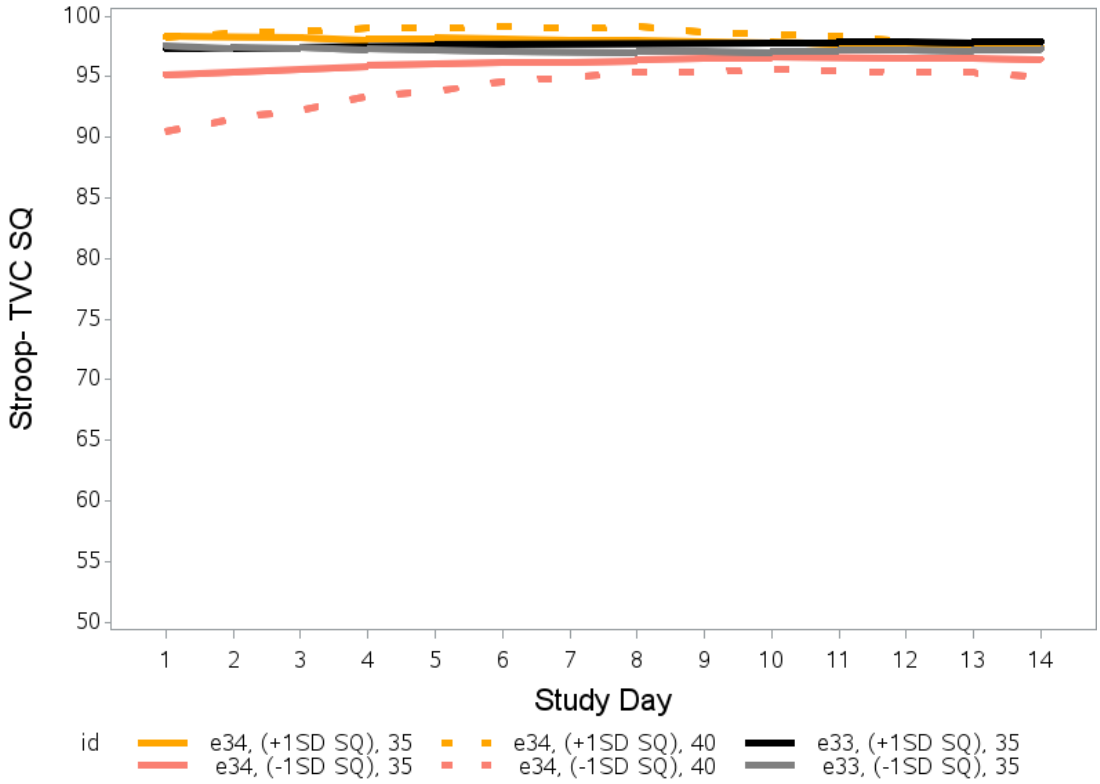
Note. TVC=Time-varying covariate, SQ=Sleep quality, SR=Sleep refresh, SF= Sleep fall, ST=Sleep trouble, Cog=cognitive tasks (Dot Memory, Symbol Search, Stroop Task, Shopping List), Day=Linear effect, Day^2=Quadratic effect, B_TVC=between-person effect, rSleepQuality=within-person effect.

Figure 2.2. Trajectories of Dot Memory across 14 study days.



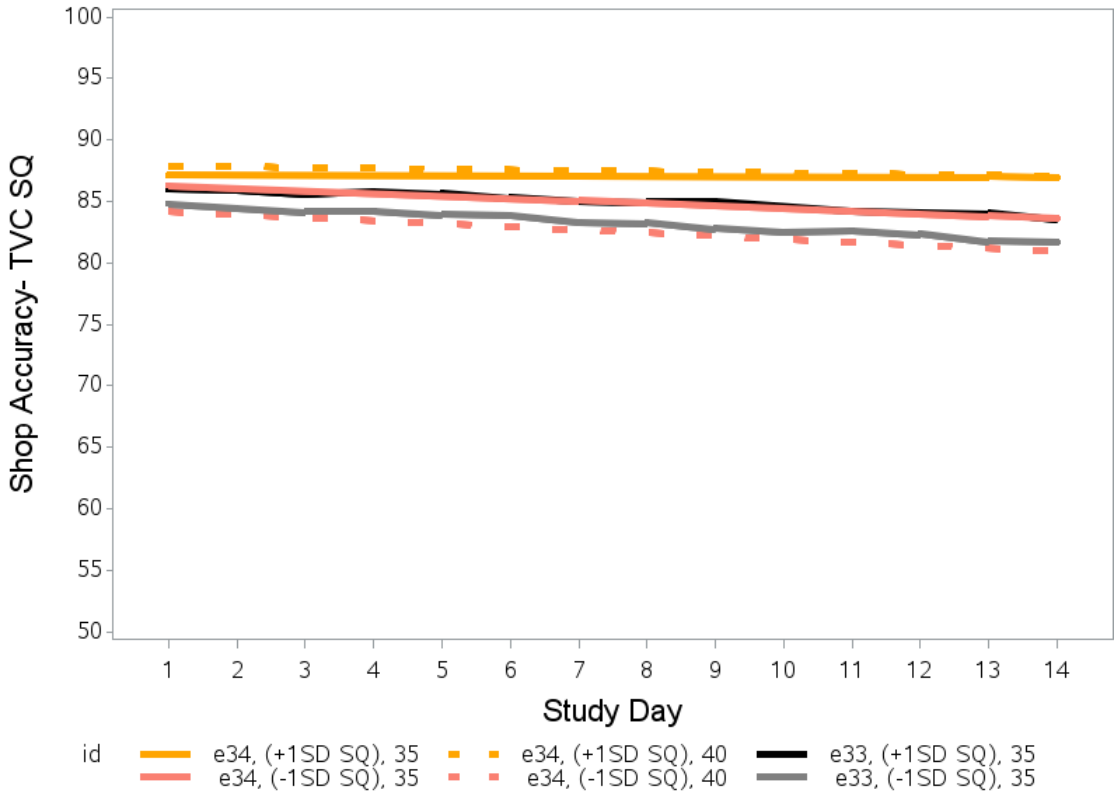
Note. All plotted quadratic models centered at day 7 represent expected trajectories for Dot Memory performance, adjusting for age, sex, adoption status, race/ethnicity, and project. Orange lines depict ε34 individuals with poor (i.e., 1 standard deviation below the average) sleep quality. Gold lines depict ε34 individuals with good (i.e., 1 standard deviation above the average) sleep quality. Black lines depict the ε33 homozygous group. Dashed Line= Age 40, Solid Lines=Age 35, TVC=Time-varying covariate, SQ=sleep quality, SR=sleep refresh, SF=sleep fall, ST=sleep troubles

Figure 2.3. Trajectories of Stroop Task across 14 study days.



Note. All plotted quadratic models centered at day 7 represent expected trajectories for Stroop Task performance, adjusting for age, sex, adoption status, race/ethnicity, and project. Orange lines depict ε34 individuals with poor (i.e., 1 standard deviation below the average) sleep quality. Gold lines depict ε34 individuals with good (i.e., 1 standard deviation above the average) sleep quality. Black lines depict the ε33 homozygous group. Dashed Line= Age 40, Solid Lines=Age 35, TVC=Time-varying covariate, SQ=sleep quality, SR=sleep refresh, SF=sleep fall, ST=sleep troubles.

Figure 2.4. Trajectories of Shopping List across 14 study days.



Note. All plotted linear models centered at day 7 represent expected trajectories for Symbol Search performance, adjusting for age, sex, adoption status, race/ethnicity, and project. Orange lines depict ε34 individuals with poor (i.e., 1 standard deviation below the average) sleep quality. Gold lines depict ε34 individuals with good (i.e., 1 standard deviation above the average) sleep quality. Black lines depict the ε33 homozygous group. Dashed Line= Age 40, Solid Lines=Age 35, TVC=Time-varying covariate, SQ=sleep quality, SR=sleep refresh, SF=sleep fall, ST=sleep troubles

Chapter Four:

GENERAL DISCUSSION

The relationship between sleep and cognition is complex, particularly when considering it in the context of aging and its implications for cognitive aging, cognitive decline, and the risk of Alzheimer's disease and related dementias (AD/ADRD). Indeed, sleep has been suggested as a potential modifiable risk factor for AD (Ju, Lucey & Holtzman, 2014; Musiek & Ju, 2022; Brenowitz et al., 2021; Livingston et al., 2020; Vo & Reynolds, 2022). Yet, uncertainties remain regarding whether sleep acts as a risk factor or a prodrome for AD (Livingston et al., 2020; Vo & Reynolds, 2022), especially in the literature focused on late-life stages (e.g., Blackwell et al., 2014; Yaffe et al., 2011; Yaffe, Falvey & Hoang, 2014; Leng et al., 2016) where the onset of AD is closer in proximity. Concerns about reverse causality are raised in part due to the emergence of AD pathogenesis and the accumulation of Aβ deposits and tau protein in the brain typically occurring decades before cognitive decline and disease manifestation (Jack et al., 2018; Monsell et al., 2014; Villemagne et al., 2011; Swerdlow, 2007; Beason-Held et al., 2013; Amieva et al., 2005). Concurrently, there is also an observed increase in sleep complaints and sleeping problems manifesting many years prior to Alzheimer's disease onset (Bliwise et al., 2004). This ambiguity underscores the necessity for research elucidating the impact of sleep on normative cognitive functioning across different life stages and across varying timescales. Furthermore, while the phenotypic relationship

between sleep and cognition is well-established, there is a lack of research exploring how genetic and environmental contributions to cognition may vary depending on an individual's aging-related sleep characteristics (Ohayon et al., 2004), highlighting the importance of further investigations of gene-environment interplay. Moreover, whether these sleep and cognition associations persist even within day-to-day observations and within younger individuals such as ones within established adulthood (Mehta et al., 2020) is still unclear. Notwithstanding the current progress of the field, even less research has examined how genetic risk for AD (i.e., AD-PGS and *APOE*) may moderate these associations between sleep and cognition, particularly with a focus on gene-environment interplay in both macro-level and micro-level timescales.

Numerous factors, including genetic predisposition, environmental influences, and lifestyle behaviors such as adherence to sleep hygiene practices, may play a significant role in facilitating both cognitive development and decline (Livingston et al., 2020; Minakawa et al., 2019; Kazem et al., 2015; Garcia & Gunstad, 2016). In this dissertation, we examined the moderating effects of sleep duration and sleep quality/disturbances on cognitive functioning. Our exploration encompassed both examinations of genetic and environmental pathways and considerations of various timescales to address existing gaps in the current literature on sleep, cognition, and aging. The research carried out in this dissertation represents a notable advancement in the field, particularly due to its utilization of methodological approaches that are rarely employed in studies focusing on sleep and cognition. Across both studies, we investigated five

essential research questions concerning macro- and micro-level investigations of sleep and cognition:

1.1 Given the previously found patterns of higher genetic influences at the shorter end of sleep duration (i.e., 4 hours of sleep duration) and higher environmental influences at longer ends of sleep duration (i.e., 10 hours of sleep duration) on cognitive performance, particularly for Verbal Fluency and Episodic Memory (Vo et al., 2022), what is the role of sleep disturbances in conjunction with sleep duration?

2.1 What added information do we gain when incorporating measured genetic factors into the analyses, particularly a measured genetic factor of Alzheimer's disease (AD-PGS)?

2.2 At the between-person level, is sleep quality a predictor of cognitive performance, across the four cognitive tasks?

2.3 At the within-person level, on days in which individuals reported sleep quality above or below their average sleep quality (i.e., person-mean) are there associated decreases or increases in their performance across the four cognitive tasks?

2.4 Does *APOE* Ɛ4 status moderate the associations between sleep quality and cognitive performance?

Summary of General Findings

Study 1.

The first study of this dissertation sought to explore macro-level sleep-cognition associations by leveraging twin data from mid- to late-life individuals within the Interplay of Genes and Environment across Multiple Studies (IGEMS) consortium (Pedersen et al., 2019). Within this study, we investigated how sleep disturbances, or sleep duration, may moderate the underlying etiology (i.e., genetic and environmental contributions) to cognitive performance across six different cognitive domains, expanding upon our prior work (Vo et al., 2022) which examined only the moderating effects of sleep duration. Moreover, by extending the model to integrate a measured genetic susceptibility indicator of Alzheimer's disease (AD-PGS), combining the effect of both latent and observed genetic information within the same model, we aimed to gauge the extent to which the AD-PGS may play a role in moderating the etiological contributions to cognition, particularly environmental factors (i.e., environment-by-PGS interactions; Bruins et al., 2022), an endeavor that has not been done within the field prior to this dissertation.

Overall, results from Study 1 suggest that the AD-PGS explained minimal variance across our six cognitive tasks tapping cognitive domains related to working memory, episodic memory, verbal fluency, attention, verbal ability, and processing speed. However, we identified significant interactions between environmental factors (both shared and nonshared environmental influences) and the AD-PGS for some of the cognitive tasks (e.g., episodic memory, verbal fluency, working memory, attention), suggesting environment-by-PGS interaction. Specifically, etiological patterns suggested that higher genetic risk for AD was associated with an attenuation of the influences from

the nonshared environmental influences contributing to differences in performance on working memory and episodic memory tasks. Additionally, for verbal fluency and attention tasks, higher genetic risk for AD was associated with a buffering of the attenuation of the influences from the shared environmental influences contributing to differences in performance, despite the AE model indicating better fit. Conversely, shared environmental influences on working memory performance increased with higher genetic risk for AD. As for the effects of sleep, results suggest significant moderation effects of sleep disturbances on the etiological contributions, mainly the shared environmental contributions, to cognitive performance, especially in domains related to verbal fluency, attention, and working memory. General etiological patterns, albeit nonsignificant, suggest increasing contributions from genetic influences (i.e., latent genetic contributions) at higher levels of sleep disturbances across our cognitive tasks. Despite these general patterns, we observed no significant moderation of sleep on the measured genetic contributions (i.e., AD-PGS), and our results did not replicate prior findings for sleep duration (Vo et al., 2022). However, the sample utilized in the present study was a reduced sample, and further replication with larger samples is warranted.

Study 2.

The second study within this dissertation sought to explore micro-level associations between sleep and cognition, leveraging ambulatory burst data from a subset of individuals in established adulthood (Mehta et al., 2020) from the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife; Wadsworth et al., 2019). Within this study, our investigation focused on day-

to-day associations, spanning up to 14 days, between individuals' typical sleep quality and deviations from their usual patterns, and their associations with daily cognitive performance. Additionally, we explored whether an *APOE* score that indexed the contribution of ε2 alleles (lower score) and ε4 alleles (higher score) significantly moderated these associations. In this study, we assessed four cognitive domains – processing speed, working memory, executive functioning, and paired associated memory – alongside four sleep quality indicators: overall sleep quality perception, sleep onset difficulty, sleep maintenance issues, and morning refreshment. Our goal was to ascertain whether sleep quality significantly predicted cognitive performance both between individuals and within individuals, and whether these relations were influenced by *APOE* genotype. Using longitudinal time-varying covariate models, we extracted separate effects for between-person and within-person variations in daily sleep quality measures. This enabled us to capture the individual differences in typical sleep quality levels (between-person effect) and one's deviations from their typical patterns (within-person effect) on a particular day, thereby shedding light on both stable traits (i.e., typical levels) and momentary (i.e., day-to-day) associations between sleep and cognition.

Overall, results from Study 2 underscore the nuanced impact of sleep quality on cognitive performance over a micro-level two-week period. At the between-person level, individuals' average sleep quality emerged as a significant predictor of cognitive performance, particularly in performance on tasks related to paired associated memory, executive functioning, and working memory domains. These results suggest a lasting influence of overall sleep quality levels on cognitive performance, across the two-week

period. However, within-person fluctuations in daily sleep quality exhibited less pronounced effects on cognitive performance, with the between-person component exhibiting the most influence on performance across the four cognitive tasks. Significant interactions were observed for the between-person sleep quality and the *APOE* score, such that individuals with increasing scores indexing the dosage of *APOE* Ɛ4 who also experienced better sleep quality on average, were expected to perform the best on paired associated memory. Nonetheless, variations in daily sleep quality dynamics appeared to influence cognitive performance in a task-specific manner, with a greater impact of the within-person sleep quality effect observed in domains related to executive functioning. Furthermore, significant interactions between the within-person sleep quality and the *APOE* score were observed, indicating gene-environment interplay. Specifically, ε34 individuals, or instances of increased dosage of ε4, who experienced daily sleep quality above their typical levels, showed slight improvements in executive functioning, suggesting momentary associations between daily sleep quality and cognitive performance, particularly in this domain.

Implications

Current demographic projections anticipate a twofold increase in the older population (aged 60 years or older) over the next three decades, with the estimated global population exceeding 2 billion, and individuals over 80 years surpassing 420 million (World Health Organization, 2022). Concurrently, two discernible trends emerge in dementia demographics. Firstly, projections suggest a threefold rise in dementia cases within the next three decades (by 2050; Nichols et al., 2022), reflecting the potential

impact from the increasingly aging population. Secondly, while dementia rates may decline in recent generations in some countries with historically high rates, they may rise in certain regions where rates were historically lower (Livingston et al., 2020). The increasing aging population likely drives the first trend, while the latter might be influenced by delaying factors such as the adoption of healthy lifestyle habits reducing risk (e.g., diet, exercise, sufficient/adequate sleep), and conversely, the adoption of unhealthy behaviors increasing risk (e.g., smoking, alcohol, insufficient/poor sleep; Livingston et al., 2020). Emerging research highlights that inadequate sleep quantity, extreme sleep durations (i.e., too short or too long), and poor sleep quality may increase the risk of dementia (Shi et al., 2018; Sindi et al., 2018; Xu, Ta, Zou, Cao & Tan, 2020; Bubu et al., 2017). Furthermore, studies indicate a reduction of gray matter volume in vulnerable areas coinciding with AD pathology in poor sleep contexts (Koo et al., 2017; Alperin et al., 2019; Liu et al., 2021; Grau-Rivera et al., 2020). However, there is a need for further research to deepen our understanding of the relationship between sleep and cognition. Existing research has primarily focused on phenotypic examinations between sleep and cognition, leaving crucial gaps regarding how sleep may influence the underlying etiology of cognitive performance and the interaction between genetic factors and environmental factors. Notably, few studies have explored this relationship until this dissertation.

The present dissertation endeavored to consider sleep features across adulthood as a key factor associated with cognitive decline and ADRD, within an aging and developmental context, shedding light on gene-environment interplay. Particularly, gene-

environment interplay was a focal point of this dissertation, explaining the interplay between genetic risk for AD and measured environmental influences, such as sleep, and how their interaction may shape cognitive outcomes. This emphasis is motivated by the fact that genetic predispositions to AD are not entirely deterministic of disease onset and poor cognitive outcomes (e.g., probabilistic epigenesis; Gottlieb, 2007). Rather, these effects may emerge and be modified, either attenuated or amplified, by environmental exposures, in this case, better or poorer sleep, whereby individuals at higher genetic risk for AD may be more vulnerable to the cognitive effects of unfavorable sleep. Overall, disentangling the precise interplay between genetic risk for AD and sleep may then be leveraged to understand the critical importance of sleep on cognitive functioning, particularly among the most vulnerable individuals.

Scaffolding Theory of Aging and Cognition: Revisited

Notably, revisiting the scaffolding theory of aging and cognition (STAC) and its revised counterpart (STAC-r; Reuter-Lorenz & Park, 2014) discussed in Chapter 1 of this dissertation, sleep is positioned as a multifaceted factor that may function as a neural resource enrichment factor, a neural resource depletion factor, or even as an intervention factor. Together, these factors are posited to influence overall cognitive functioning, in the context of aging, directly and indirectly affecting brain structure, brain function, and compensatory scaffolding abilities (Reuter-Lorenz & Park, 2014). Under this framework, this dissertation views sleep as a complex "environmental" exposure that may be influenced by both genetic and environmental influences, albeit with more environmental influences, that may either support or undermine cognitive functioning and the

effectiveness of cognitive scaffolds, and these effects may be further attenuated or bolstered, through interactions with genetic factors (i.e., genetic risk for AD).

Specifically, within Study 1, we observed that within a poor sleep setting, characterized by increased sleep disturbances, with similar patterns with shorter sleep durations, albeit failing to reach significance, the impact of genetic influences on cognitive performance appears to become more pronounced. Our analyses incorporated the AD-PGS derived from AD-genome-wide association studies (GWASs; Kunkle et al., 2019), which encompass genes implicated in inflammatory pathways, as well as beta-amyloid (Aβ) and tau. Despite including the AD-PGS, particularly with consideration of the *APOE* region, we still observed a moderation effect of sleep on genetic influences, challenging the notion that *APOE* and it is association with perturbations in Aβ clearance may fully explain this relationship. In other words, the AD-PGS does not appear to account for the patterns of sleep moderation despite its presumed association with Aβ clearance in poor sleep contexts. Indeed, the existing literature suggests associations between poor sleep and upregulated neuroinflammatory processes, including the interleukin-6 (IL-6) pathway, and ineffective beta-amyloid (Aβ) clearance (e.g., Irwin et al., 2016; Meier-Ewert et al., 2004; van Leeuwen et al., 2009; Vgontzas et al., 2004; Haack, Sanchez & Mullington, 2007; Taveras et al., 2011) whereby suggestions regarding the reciprocal nature of sleep and immune responses are suggested (Zielinski & Krueger, 2011; Krueger, Rector & Churchill, 2007). Within poor sleep contexts, often observed in extreme sleep deprivation contexts, there is an observed upregulation of neuroinflammatory processes, including the overexpression of proinflammatory

cytokines (e.g., IL-6, C-reactive protein (CRP); tumor necrosis factor- α (TNF-α); Heneka et al., 2015; Fraga et al., 2019) and an accumulation of metabolites and toxins such as Aβ. These factors may possibly elicit synaptic dysfunction and blood brain barrier dysregulation (Ferreira, Clarke, Bomfim & De Felice, 2014; Wang, Tan, Yu & Tan, 2015; Elwood, Lim, Naveed & Galea, 2017; He et al., 2014), which in turn may affect brain structure and brain function. Consequently, compensatory mechanisms necessary for adequate cognitive functioning may be inhibited. Moreover, systemic inflammation increases with increasing age, a term coined "inflamm-aging" (Ferrucci & Fabbri, 2018). Indeed, research suggests elevated signs of inflammation in the hypothalamus and hippocampus in AD patients, compared to controls (Silva et al., 2021). In instances of partial sleep deprivation, short sleep durations, and sleep disturbances, increased levels of plasma IL-6 were observed in humans (Irwin et al., 2016; Meier-Ewert et al., 2004; van Leeuwen et al., 2009; Vgontzas et al., 2004; Haack, Sanchez & Mullington, 2007; Taveras et al., 2011). In addition, sleep fragmentation in older adults was associated with increased neocortical expression of genes characteristic of aged microglia, where microglia play a crucial role in immune defense, synaptic pruning (Choudhury et al., 2020; Choudhury et al., 2021), and maintenance of brain health, and excessive microglial activation promotes neuroinflammation (Kaneshwaran et al., 2019; Woodburn, Bollinger & Wohleb, 2021; Smagula et al., 2016). As such, a "glial connection" between sleep disturbances and AD has been suggested (Sunkaria & Bhardwaj, 2022). Moreover, overexpression of IL-6 in mice has been associated with cognitive dysfunction through impairing neurotransmission in the hippocampus and

prefrontal cortex, impaired hippocampus neurogenesis (Vallieres et al., 2002), decreases in synaptic plasticity, and impairment of excitatory synaptic activity (Biber et al., 2008), impairing learning and memory (Sparkman et al., 2006; Zhu et al., 2012), and age-related decline in cognition (Parks et al., 2020). In middle-aged adults, an overexpression of IL-6 was found to be associated with hippocampal gray matter volume (Marsland et al., 2008), and dysregulation of IL-6 has been found to modulate various cognitive functions including learning, memory, and synaptic plasticity (Donzis & Tronson, 2014; Elderkin-Thompson, Irwin, Hellemann & Kumar, 2012), as well as being associated with AD (Swardfager et al., 2010; Lai et al., 2017). High levels of IL-6 at baseline were associated with nearly 1.5 times higher risk of global cognitive decline at follow-up (2-7 years; Bradburn, Sarginson & Murgatroyd, 2018), declines in executive function and memory (Singh-Manoux et al., 2014; Metti et al., 2015). Cross-sectional studies have shown associations with high IL-6 and lower performance in executive function and memory (Schram et al., 2007). Similarly, overexpression in TNF-α is associated with decreased passive avoidance memory, synaptic plasticity, and cerebellar learning (Fiore et al., 2000; Butler et al., 2004; Paredes, Acosta, Gemma & Bickford, 2010). Moreover, in mice, increased levels of TNF- α was associated with an accumulation of Aβ and decreased clearance of Aβ, synaptic dysfunction, and cognitive deficits (Chang, Yee & Sumbria, 2017). Despite these current associations, the implication from our study suggests a more nuanced relationship between sleep, genetic risk for AD, *APOE*, and cognition. Given that the AD-PGS accounts for only roughly 10% of the risk in AD (Karlsson et al., 2022), it may not fully capture all genetic factors relevant to sleep-cognition relationship, and

additional genetic or non-genetic factors (e.g., lifestyle factors, physical environments, socioeconomic status, depression, diet, physical activity; Hunter et al., 2018; Gildner et al., 2014; Machado et al., 2022; Zhao et al., 2018) may play a role. Further research is warranted to elucidate the underlying mechanisms underpinning this complex relationship.

Moreover, our results from Study 1 suggest support for a hypothesis that suggests within poor sleep contexts, compensatory mechanisms necessary for adequate cognitive functioning may be inhibited, meaning that poor sleep may act as a neural resource depletion factor within the STAC-r model (Reuter-Lorenz & Park, 2014), attenuating an individual's ability to mitigate aging-related declines in cognitive functioning and impairing their ability to withstand neural insults associated with aging. Through these adverse mechanisms, further depletion of neural resources may occur, ultimately affecting brain status, compensatory scaffolding abilities, and overall rate of cognitive change and level of cognitive functioning (Reuter-Lorenz & Park, 2014). However, further work is necessary to elucidate the direct relationship between sleep, brain structure, brain function, and compensatory abilities. Moreover, whether these associations play out within younger versus older individuals in our sample requires further examinations.

On the other hand, Study 2 provides support and implications for the role of sleep as a neural enrichment factor. Even within the micro-level burst study design, spanning only a 14-day period, we found compelling evidence linking better sleep quality to enhanced cognitive performance across individuals in established adulthood, and those

who are younger compared to the sample in Study 1. Notably, while the effects of average-level sleep quality were modest, even subtle improvements in overall sleep quality can positively impact cognitive performance among individuals who are already performing quite well. In addition, we found significant within-person sleep quality effects, particularly for working memory and executive functioning tasks, such that even short-term variations in sleep quality may have immediate effects on cognitive functioning. Current literature examining short-term manipulations of sleep has shown cognitive detriments even after one night or poor sleep (e.g., Xu et al., 2011), across a wide variety of domains. Moreover, short-term effects of sleep on cognitive performance may also be understood within the context of the short-term benefits of naps. Specifically, napping has been suggested to benefit cognitive domains such as episodic memory, executive function, and alertness (e.g., Scullin et al., 2017; Dutheil et al., 2021; Leong, Lo & Chee, 2022; McDevitt et al., 2018; Chen, Whitehurst, Naji & Mednick, 2020), where benefits of naps are sometimes found to be stronger in younger individuals and benefits decrease for older individuals (e.g., Scullin et al., 2017). Our findings from Study 2 suggest that even just one night of sleep quality above one's typical levels is associated with increases in cognitive performance, albeit modest effects. However, while modest, these results corroborate current research on short-term effects of sleep, both in pre- and post- laboratory manipulation designs as well as research on short-term effects of naps (e.g., Scullin et al., 2017; Dutheil et al., 2021; Leong, Lo & Chee, 2022; McDevitt et al., 2018; Chen, Whitehurst, Naji & Mednick, 2020). Moreover, the significant interaction effects between sleep and *APOE* observed within Study 2 suggest a

cumulative and compounded effect between both poor sleep quality and genetic risk for AD (e.g., *APOE* Ɛ4; Ates, Karaman, Guntekin & Ergun, 2016; Neu et al., 2017), both neural resource depletion factors. Conversely, the results also show a compensated effect such that better sleep quality on a particular day was able to offset some of the negative effects of *APOE*. Further, *APOE* Ɛ4 has been found to significantly moderate the relationship between Aβ accumulation and sleep latency in older adults (Hwang et al., 2018), coupled with additional associations that the *APOE* Ɛ4 genotype may confer further cognitive impairment due to disturbed sleep (Hita-Yanez et al., 2012; Palpatzis, Bass, Jones & Mukadam, 2021; Wei, Wang, Shi & Li, 2022). As such, within the STAC-r framework, and while not directly tested, this dissertation postulates that older individuals, especially those at higher genetic risk, may bolster cognitive scaffolds to compensate for detriments to memory consolidation and cognitive processing through sufficient sleep. Conversely, disrupted sleep may compromise the effectiveness of cognitive scaffolds and accelerate cognitive decline in individuals at greatest risk (i.e., individuals who are older and who are at greater AD risk). Indeed, current research suggests a cumulative and compounded nature of multiple risk factors on risk for AD (Nianogo et al., 2022). Moreover, our results emphasize the importance of investigating gene-environment interaction, a facet not explicitly addressed in the STAC-r framework (Reuter-Lorenz & Park, 2014). Yet, the STAC-r framework lays a solid foundation for understanding how these interactions between genetic and environmental factors may affect cognitive aging. As such, implications from the work within this dissertation suggest a cumulative nature to enrichment and depletion factors whereby their interplay

may yield added and compounded risk or mitigate and attenuate risk, a notion not adequately addressed by the current STAC-r framework (Reuter-Lorenz & Park, 2014), and yet a notion that importantly points towards the necessity of examining gene-environment interplay.

Limitations and Future Directions

Sleep Measurement and Additional Sleep Parameters

One limitation both in our work and the broader field is the lack of consensus regarding how to measure sleep quality, a complex construct notoriously challenging to define (Buysse et al., 1989). In this dissertation, sleep quality was indexed through various indicators. In Study 1, we utilized clinical information from the 2020 ICD-10 and items resembling subcategories within the Pittsburgh Sleep Quality Index (Buysse, 1989) to assess sleep disturbances, including sleep issues such as sleep apnea, insomnia, restlessness, nightmares, and snoring. In Study 2, we indexed sleep quality via individuals' perceptions of their prior night's sleep, morning refreshment, sleep maintaining, and difficulty falling asleep. By incorporating input from clinical sleep dysfunction evaluations (Buysse, 1989; Mollayeva et al., 2016), we aimed to capture the multifaceted nature of sleep quality, encompassing concerns related to nighttime sleep adequacy, daytime consequences of poor sleep, and nocturnal behaviors. Notably, in Study 1, we observed more intriguing etiological patterns stemming from moderation via sleep disturbances, rather than sleep duration. In Study 2, we found significant between-person and within-person effects of sleep quality across cognitive tasks, underscoring the

importance of sleep quality associations with cognition. However, it is important to acknowledge the variability in how sleep quality is measured across the field, often yielding diverging results (Scullin & Bliwise, 2015). Definitions range from the field of sleep medicine, which often include objectively measured polysomnographic or actigraphy-derived parameters like sleep efficiency, total wake/sleep time, and sleep efficiency (Krystal & Edinger, 2008), to subjective assessment tools such as the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale (Buysse, 1989; Natale et al., 2015; Thorndike et al., 2011; Johns, 1991; Carney et al., 2012). Yet, while measures such as the PSQI are widely used and considered the "gold standard" for subjectively measured sleep quality, they do not always align closely with polysomnographic measures which are considered the "gold standard" for objectively measured sleep quality (Jackowska, Dockray, Hendrickx & Steptoe, 2011). To enhance the validity of sleep quality assessments, we advocate for integrating both subjective and objective measures in future research. For instance, employing the concurrent use of PSQI and actigraphy could provide a more comprehensive understanding of individuals' sleep quality (Landry, Best, Liu-Ambrose, 2015; Hughes et al., 2018). Furthermore, we suggest that future work could aim to deepen our comprehension of the interplay between sleep and cognition by broadening the scope beyond just nighttime sleep duration and quality. Exploring additional facets such as daytime naps, chronotype, total 24-hour sleep duration, and regularity in the timing of sleep may provide valuable insights into how different aspects of sleep may influence cognitive function (e.g., Leng et al., 2020; Alvarez-Bueno et al., 2022; Pengsuwankasem et al., 2023; Windred et al., 2024; Sauers

et al., 2024; Sauers et al., 2023; Spira et al., 2018). Lastly, to further understand whether sleep may subsequently influence one's compensatory mechanisms, future work should integrate information from neuroimaging studies (e.g., Li et al., 2022; Hernandez et al., 2023; Alfini, Tzuang, Owusu & Spira, 2020; Spira et al., 2016) to further assess brain structure and brain function, both cross-sectionally and longitudinally.

Sociocultural Factors

Another limitation of our present work lies in the lack of diversity within both the IGEMS (Pedersen et al., 2019) and CATSLife (Wadsworth et al., 2019) samples across Study 1 and Study 2. While both samples provided rich and informative data, we were constrained in our ability to explore associations between sleep and cognition while considering social factors such as racial and ethnic inequalities in both sleep, cognition, and ADRD risk, especially to address questions related to the promotion of sleep-health equity. Particularly, limited studies have considered, or have been adequate powered, to examine sleep-health associations across different racial/ethnic groups, particularly in Asian, Native Hawaiian and Pacific Islander, and American Indian and Alaska Native groups (Johnson et al., 2019). Overall, individuals from ethnic and racial minority groups are more likely to report less than 6 hours of sleep, more likely to experience poor sleep quality, more likely to experience increased daytime sleepiness, and more likely to report sleep complaints, relative to non-Hispanic Whites (Johnson et al., 2019; Nunes et al., 2008; Grandner et al., 2010). In addition, African American individuals are disproportionately at higher risk for both poor sleep quality and adverse health outcomes (e.g., Alzheimer's disease and related dementias; Matthews et al., 2019; Barnes &

Bennett, 2014; Rottapel et al., 2020). Further, Asian Americans report shorter sleep compared to White individuals and longer sleep than Black and Hispanic individuals but represent the group with the lowest prevalence of dementia (Matthews et al., 2019; Guglielmo et al., 2018). Of note, emerging research suggests that *APOE* may hold similar predictive value for dementia risk and memory performance across a range of ethnic and racial backgrounds (Llibre-Guerra et al., 2022). Despite the current research field moving towards more racially/ethnically diverse research, current work has focused on disparities between racial/ethnic minority groups in comparison to White groups, but less work has focused on within-group variation. Indeed, some evidence has found that African Americans with higher SES have poorer sleep quality than African Americans with lower SES and greater variability in sleep duration and quality was observed within Latino groups based on factors such as nativity status and country of origin (Patel et al., 2010; Garcia et al., 2020). Even less is known regarding within-group variability among Asian groups and lesser-studied populations. Taken together, other socio-contextual factors, socio-cultural factors, and social determinants that may disparately influence an individual's sleep and health warrant further attention, particularly with a focus on an individual's intersecting identities (i.e., race/ethnicity, sex, SES, culture, sleep attitudes and beliefs) both within- and between-groups and with further examinations into understudied groups. As such, we advocate for future research to consider sleep and cognition associations under an intersectional framework and examine how certain health disparity causes and health determinants may have effects on health disparity outcomes, such as higher incidence prevalence including earlier disease onset or more aggressive

progression of the disease. In addition, we advocate for additional work to shift from a deficit-based framework to a resilience-based framework, particularly with an aim to understand how sleep might promote health within various groups.

Conclusion

The collective findings from this dissertation contribute to the literature in fundamental ways that illuminate the complex interplay between genetics and environments, with implications toward cognitive aging, cognitive functioning, and ADRD risk, specifically with a focus on understanding the complex relationship between sleep and cognition. Collectively, this dissertation addressed gaps within the literature concerning the lack of examinations of gene-environment interplay as well as gaps concerning the lack of examining the effects of daily fluctuations in sleep and the relation to cognition. Overall, these findings suggest that tailored therapeutic or pharmacological interventions may be necessary to support cognitive health in individuals with different sleep durations, different sleep qualities, momentary dynamics of sleep, and varying levels of genetic predispositions to AD. Rather than applying a universal approach, these insights emphasize the importance of personalized interventions in precision medicine approaches.

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Appendices

Appendix 1. Supplemental Methods and Supplemental Tables and Figures (Study 1)

Appendix 2. Supplemental Tables and Figures (Study 2)

Appendix 1. Supplemental Methods and Supplemental Tables and Figures (Study 1)

Supplemental Methods

Sleep Disturbance Factor Score Sample Description

A harmonized measure of sleep disturbances was created which involved consolidating self-report items across multiple studies within the Interplay of Genes and Environment across Multiple Studies (IGEMS) consortium (Pedersen et al., 2019). Ten IGEMS studies included measures related to sleep disturbances, spanning items pertaining to sleeping problems, sleep apnea, insomnia, nightmares, sleep medication usage, restlessness, snoring, and problems related to sleep maintenance. Detailed descriptions of the studies within the IGEMS consortium may be found in Pedersen et al. (2019). Briefly, within the present sample, three Swedish studies contributed sleep disturbance data: The Swedish Adoption/Twin Study of Aging (SATSA; Finkel & Pedersen, 2004), Origins of Variance in the Old-Old (OCTO-Twin; McClearn et al., 1997), Aging in Women and Men: A longitudinal Study of Gender Differences in Health Behavior and Health among Elderly (GENDER; Gold et al., 2002). Additionally, OCTO-Gender twins from the fourth follow-up of GENDER who followed the OCTO-Twin protocol were also included. Of note, OCTO-Gender twin pairs did not overlap with GENDER twin pairs. Three United States studies contributed sleep disturbance data: Vietnam Era Twin Study of Aging (VETSA; Kremen, Franz & Lyons, 2013), Midlife in the United States (MIDUS; South & Krueger, 2012), and the Minnesota Twin Study of Adult Development (Finkel & McGue, 1993). Additionally, two Danish studies contributed sleep disturbance data: Middle Age Danish Twins Study (MADT; Osler et al., 2008; Pedersen et al., 2019) and the Longitudinal Study of Aging Danish Twins

(LSADT; Christensen et al., 1999). Lastly, the Older Australian Twins Study (OATS; Sachdev et al., 2009) was the only Australian study that contributed sleep disturbance data. Of note, while all available IGEMS studies with sleep disturbance data contributed to the sleep disturbance harmonization and factor score generation, not all studies were utilized in the present biometrical analyses reported in Chapter Two which required having the Alzheimer's disease polygenic score available.

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Table A1.1 Sleep Disturbance Factor Score Descriptives by Study

Study	Sleep Disturbances		
	N	M	SD
Overall	12006	-4E-15	0.97
SATSA	238	0.24	1.56
OCTO-Twin	591	-0.05	1.16
GENDER	488	-0.47	1.34
VETSA	1291	-0.35	1.49
LSADT	2362	0.14	0.74
MADT	4305	-0.13	0.63
OATS	598	0.16	0.77
MTSADA	801	0.36	0.49
MIDUS	1178	0.45	1.22
OCTO-Gender	154	-0.17	1.21

Note. SATSA= Swedish Adoption/Twin Study of Aging, OCTO-Twin= Origins of Variance in the Oldest Old, GENDER= Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behavior and Health among Elderly, OCTO-Gender=Older GENDER participants who followed the OCTO-Twin protocol, MIDUS= Midlife in the United States, MTSADA= Minnesota Twin Study of Adult Development and Aging, VETSA= Vietnam Era Twin Study of Aging, MADT=Middle Age Danish Twins Study, LSADT=Longitudinal Study of Aging Danish Twins, OATS= Older Australian Twin Study. All available IGEMS studies with sleep disturbance data contributed to sleep disturbance harmonization and factor score generation. However, not all studies presented in this table were included in the present biometrical model analyses as not all IGEMS studies had scores for the Alzheimer's disease polygenic score.

Table A1.2 Individual Sleep Disturbance Items from IGEMS

Category	Studies	Item	Response Options
Wake_early			
	*LSADT	"Do you wake up early in the morning without being able to fall asleep again?"	Original: 1= most of the time 2= sometimes 3= no Recoded: 1,2= 1 some endorsement 3= 0 no endorsement
	*MADT	"Do you wake up early in the morning without being able to fall asleep again?"	Original: 1= most of the time 2= sometimes 3= no Recoded: 1,2= 1 some endorsement 3= 0 no endorsement
	MIDUS	“Wake up too early frequency, please indicate how often you experience each of the following: wake up too early in the morning and be unable to get back to sleep”	Original: Never (0 times), rarely (once a month or less), sometimes (2-4 times per month), often (2-3 times per week), almost always (4 or more times per week) Recoded: Never=0 no endorsement Everything else= 1 some endorsement
	*SATSA	“Has it occurred to you that you have woke up too early and was not able to fall asleep?”	Original: 1=never 2=rarely 3= sometimes 4= most often 5=always

Category	Studies	Item	Response Options
			Recoded: 0=no endorsement, 1 =some endorsement
	*GENDER	"I wake up in the early hours of the morning"	Original: 0=no 1=yes Recoded: 0=No endorsement 1=some endorsement
Wake_night			
	MIDUS	"Wake up during the night frequency, please indicate how often you experienced each of the following: wake up during the night and have difficulty going back to sleep"	Original: Never (0 times), rarely (once a month or less), sometimes (2-4 times per month), often (2-3 times per week), almost always (4 or more times per week) Recoded: 0=No endorsement 1=some endorsement
	*VETSA	"Wake up in the middle of the night or early morning-trouble sleep"	Original: 1= not during the past month 2= less than once a week 3= once or twice a week 4= three or more times a week Recoded: 1=0 no endorsement, 2-4=1 some endorsement
	*SATSA	"Have you woken up in the middle of the night and have had trouble falling asleep?"	Original: 1=never 2=rarely 3= sometimes 4= most often

Category	Studies	Item	Response Options
			5=always Recoded: 1=0 no endorsement, 2-5= 1 some endorsement
Restless			
	*VETSA	"Sleep was restless"	Original: 1=rarely or none of the time (less than 1 day) 2= some or little of the time (1-2 days) 3= occasionally or a moderate amount of time (3-4 days) 4= most or all of the time (5-7 days) Recoded: 0=no endorsement, 1=some endorsement
	MTSADA	"Sleep was restless"	Original: rarely or none of the time, some of the time, occasionally, most of the time Recoded: 0=no endorsement, 1=some endorsement
	*OCTO-Twin	"Sleep was restless"	Original: rarely or none of the time, some of the time, occasionally, most of the time Recoded: 0=no endorsement, 1=some endorsement
	OCTO-Gender	"Sleep was restless"	Original: rarely or none of the time, some of the time, occasionally, most of the time

Category	Studies	Item	Response Options
			Recoded: 0=no endorsement, 1=some endorsement
	*SATSA	"Did not sleep well/Restless sleep"	Original: 1=Never/almost never 2=rather seldom 3=Quite often 4= always/almost always Recoded: 0=no endorsement, 1= some endorsement
	*GENDER	"Slept poorly/restless sleep"	Original: 0=seldom or never 1=rather seldom 2=rather often 3=almost always or always Recoded: 0=no endorsement, 1=some endorsement
Snore			
	*SATSA	"Have you been severely snoring?"	Original: 1=never 2=rarely 3=sometimes 4=most often 5=always Recoded: 0=no endorsement, 1=some endorsement
	*VETSA	"Trouble sleep-snore, how often have you had trouble sleeping because you cough or snore loudly"	Original: 1= not during the past month 2= less than once a week 3= once or twice a week

Category	Studies	Item	Response Options
			4= three or more times a week Recoded: 0= no endorsement, 1=some endorsement
	*OATS	"Do you snore"	Original Coding: 1=yes 2=no Recoded: 0=no endorsement 1=some endorsement
Apnea			
	*VETSA	"Have you ever been told by a physician that you had any of the following conditions or illnesses? - sleep apnea"	Original: 1=yes, 2=no Recoded: 0= no endorsement, 1=some endorsement
	*OATS	"Diagnosed with sleep apnoea"	Original Coding: 1=no 2=yes Recoded: 0=no endorsement 1=some endorsement
Nightmare			
	MTSADA	"Do you have nightmares?" Variable name: nightmare	Original Coding: 1=no 2=yes Recoded: 0=no endorsement 1=some endorsement
	*SATSA	"Have you had nightmares?"	Original Coding: 1=never 2=rarely

Category	Studies	Item	Response Options
			3=sometimes 4=most often 5=always Recoded: 0=no endorsement 1=some endorsement
	*VETSA	"Trouble sleep-Have bad dreams"	Original Coding: 1= no during the past month 2= less than once a week 3= once or twice a week 4= three or more times a week Recoded: 0=no endorsement 1=some endorsement
Sleep Medication			
	*GENDER	"I take tablets to help me sleep"	Original Coding: 0=No 1=yes Recoded: 0=No endorsement 1=Some endorsement
	*VETSA	"Taken meds to help sleep"	Original Coding: 1= no during the past month 2= less than once a week 3= once or twice a week 4= three or more times a week Recoded: 0=no endorsement

Category	Studies	Item	Response Options
			1=some endorsement
	MIDUS	"Used sedatives on own ever (12 mo)"	Original Coding: 1=yes 2=no Recoded: 0=no endorsement 1=some endorsement
Latency			
	*SATSA	"Have you had problems falling asleep in the evening?"	Original Coding: 1= never 2=rarely 3=sometimes 4= most often 5= always Recoded: 0=no endorsement 1= some endorsement
	*GENDER	"It takes me a long time to get to sleep"	Original Coding: 0=no 1=yes Recoded: 0=no endorsement 1=some endorsement
	*VETSA	"Trouble sleep-cannot sleep within 30 min"	Original Coding 1= No during the past month 2= less than once a week 3= once or twice a week 4= three or more times a week Recoded: 0=no endorsement 1= some endorsement

Category	Studies	Item	Response Options
	MIDUS	"Trouble falling asleep frequency-(30 days)"	Original Coding: 1= almost every day 2= several times a week 3= once a week 4= several times a month 5= once a month 6= not at all Recoded: 0= no endorsement 1= some endorsement
	*OCTO-Twin	"Difficulty sleeping"	Original Coding: 0=no 1=yes Recoded: 0= no endorsement 1= some endorsement
	OCTO-Gender	"Difficulty sleeping"	Original Coding: 0=no 1=yes Recoded: 0= no endorsement 1= some endorsement

Note. * = Sample was utilized in the present analyses. SATSA= Swedish Adoption/Twin Study of Aging, OCTO-Twin= Origins of Variance in the Oldest Old, GENDER= Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behavior and Health among Elderly, OCTO-Gender=Older GENDER participants who followed the OCTO-Twin protocol, MIDUS= Midlife in the United States, MTSADA= Minnesota Twin Study of Adult Development and Aging, VETSA= Vietnam Era Twin Study of Aging, MADT=Middle Age Danish Twins Study, LSADT=Longitudinal Study of Aging Danish Twins, OATS= Older Australian Twin Study. All available IGEMS studies with sleep disturbance data contributed to sleep disturbance harmonization and factor score generation. However, not all studies presented in this table were included in the present biometrical model analyses as not all IGEMS studies had scores for the Alzheimer's disease polygenic score.

Table A1.3 Factor Loadings and Model Fit Statistics for Confirmatory Factor Analysis of Sleep Disturbances

	Model 1 (One Factor CFA)		Model 2 (Two Factor CFA) FS1		Model 2 (Two Factor CFA) FS2	
Item	Estimate	SE	Estimate	SE	Estimate	SE
Wake_early	0.83	0.03	0.83	0.03	--	--
Wake_night	0.75	0.03	0.75	0.03	--	--
Snore*	0.35	0.04	--	--	0.62	0.12
Medication Usage	0.52	0.04	0.52	0.04	--	--
Restless	0.78	0.03	0.78	0.03	--	--
Latency	0.62	0.02	0.62	0.02	--	--
Apnea*	0.29	0.07	--	--	0.42	0.09
Nightmare	0.65	0.04	0.65	0.04	--	--
Model Fit Statistics						
AIC	27791.643				27785.875	
BIC	27909.933				27911.559	
Sample-Size Adjusted BIC	27859.087				27857.535	
Number of Free Parameters	16				17	
Correlation FS1 & FS2	--				.94	

Note. CFA=Confirmatory Factor Analysis, Model 1= One-factor CFA with separate factor loadings for each item category (wake_early, wake_night, snore, sleep medication, restless, latency, apnea, nightmare). Model 2= Two-factor CFA with separate factor loadings where the first factor reflected sleep efficiency (wake_early, wake_night, medication usage, restless, latency, nightmare) and the second factor reflected breathing-related sleep disturbances (snore, apnea). *= Items on the second factor. Despite Model 2 providing a more optimal model fit, we proceeded with Model 1 as both factors in Model 2 were highly correlated and the sample size was large (N=12006).

Table A1.4 Univariate Standardized Variance Estimates

	SA	SC	SE
Sleep Duration	0.13 [-0.05, 0.31]	0.24 [0.09, 0.38]	0.63 [0.57,0.70]
Sleep Disturbances	0.05 [-0.12, 0.22]	0.17 [0.04, 0.30]	0.78 [0.72, 0.84]
Word List	0.23 [0.08, 0.38]	0.17 [0.05, 0.29]	0.60 [0.55, 0.66]
Animal Naming	0.41 [0.25, 0.58]	0.06 [-0.07, 0.20]	0.52 [0.47, 0.58]
Digits Forward	0.37 [0.22, 0.52]	0.10 [-0.03, 0.22]	0.53 [0.48, 0.58]
Digits Backward	0.40 [0.24, 0.55]	0.05 [-0.08, 0.17]	0.56 [0.51, 0.61]
Synonyms	0.62 [0.45, 0.79]	0.06 [-0.09, 0.20]	0.32 [0.27, 0.39]
Symbol Digit	0.43 [0.30, 0.56]	0.29 [0.17, 0.40]	0.28 [0.25, 0.33]

Note. Models were adjusted for age and sex. SA=heritability, SC=common environmentality, SE=nonshared-environmentality

Table A1.5 Fit Statistics for Bivariate ACE Models

Models	K	-2LL	df	AIC	$\Delta\chi^2$	*Δdf*	*p*
Word List							
Sleep Duration							
1. ACE (Sleep Duration and Cognition)	15	27565.80	5390	27595.80			
2. AE (Sleep Duration and Cognition)	12	27572.99	5393	27596.99	7.19	3	0.066
3. CE (Sleep Duration and Cognition)	12	27575.21	5393	27599.21	9.41	3	0.024
4. E (Sleep Duration and Cognition)	9	27750.24	5396	27768.24	184.44	6	0.000
5. Drop A21, C21, E21	12	27570.43	5393	27594.43	4.63	3	0.201
Sleep Disturbances							
1. ACE (Sleep Disturbances and Cognition)	15	39739.91	7680	39769.91			
2. AE (Sleep Disturbances and Cognition)	12	39754.24	7683	39778.24	14.33	3	0.002
3. CE (Sleep Disturbances and Cognition)	12	39743.40	7683	39767.40	3.49	3	0.322
4. E (Sleep Disturbances and Cognition)	9	39976.68	7686	39994.68	236.77	6	0.000
5. Drop A21, C21, E21	12	39755.40	7683	39779.40	15.49	3	0.001
Animal Naming							
Sleep Duration							
1. ACE (Sleep Duration and Cognition)	15	26334.08	5252	26364.08			
2. AE (Sleep Duration and Cognition)	12	26336.10	5255	26360.10	2.02	3	0.569
3. CE (Sleep Duration and Cognition)	12	26362.69	5255	26386.69	28.61	3	0.000
4. E (Sleep Duration and Cognition)	9	26556.34	5258	26574.34	222.25	6	0.000
5. Drop A21, C21, E21	12	26336.72	5255	26360.72	2.64	3	0.451
Sleep Disturbances							
1. ACE (Sleep Disturbances and Cognition)	15	31968.41	6710	31998.41			
2. AE (Sleep Disturbances and Cognition)	12	31973.85	6713	31997.85	5.44	3	0.143
3. CE (Sleep Disturbances and Cognition)	12	31991.40	6713	32015.40	22.99	3	0.000
4. E (Sleep Disturbances and Cognition)	9	32187.08	6716	32205.08	218.67	6	0.000
5. Drop A21, C21, E21	12	31972.74	6713	31996.74	4.32	3	0.229

(Table A1.5 continued)

Models	K	-2LL	df	AIC	$\Delta\chi^2$	*Δdf*	*p*
Digits Forward							
Sleep Duration							
1. ACE (Sleep Duration and Cognition)	15	28140.73	5434	28170.73			
2. AE (Sleep Duration and Cognition)	12	28144.94	5437	28168.94	4.21	3	0.239
3. CE (Sleep Duration and Cognition)	12	28164.85	5437	28188.85	24.12	3	0.000
4. E (Sleep Duration and Cognition)	9	28444.85	5440	28462.85	304.12	6	0.000
5. Drop A21, C21, E21	12	28143.47	5437	28167.47	2.74	3	0.433
Sleep Disturbances							
1. ACE (Sleep Disturbances and Cognition)	15	37617.88	7407	37647.88			
2. AE (Sleep Disturbances and Cognition)	12	37624.93	7410	37648.93	7.05	3	0.070
3. CE (Sleep Disturbances and Cognition)	12	37641.79	7410	37665.79	23.92	3	0.000
4. E (Sleep Disturbances and Cognition)	9	37963.15	7413	37981.15	345.28	6	0.000
5. Drop A21, C21, E21	12	37627.05	7410	37651.05	9.17	3	0.027
Digits Backward							
Sleep Duration							
1. ACE (Sleep Duration and Cognition)	15	28097.56	5433	28127.56			
2. AE (Sleep Duration and Cognition)	12	28099.51	5436	28123.51	1.95	3	0.583
3. CE (Sleep Duration and Cognition)	12	28125.04	5436	28149.04	27.48	3	0.000
4. E (Sleep Duration and Cognition)	9	28347.79	5439	28365.79	250.23	6	0.000
5. Drop A21, C21, E21	12	28100.59	5436	28124.59	3.03	3	0.387
Sleep Disturbances							
1. ACE (Sleep Disturbances and Cognition)	15	37512.79	7404	37542.79			
2. AE (Sleep Disturbances and Cognition)	12	37518.16	7407	37542.16	5.38	3	0.146
3. CE (Sleep Disturbances and Cognition)	12	37540.58	7407	37564.58	27.79	3	0.000
4. E (Sleep Disturbances and Cognition)	9	37807.19	7410	37825.19	294.40	6	0.000
5. Drop A21, C21, E21	12	37527.12	7407	37551.12	14.33	3	0.002

(Table A1.5 continued)

Models	K	-2LL	df	AIC	$\Delta\chi^2$	*Δdf*	*p*
Synonyms							
Sleep Disturbances							
1. ACE (Sleep Disturbances and Cognition)	15	22201.83	5528	22231.83			
2. AE (Sleep Disturbances and Cognition)	12	22207.39	5531	22231.39	5.56	3	0.135
3. CE (Sleep Disturbances and Cognition)	12	22242.02	5531	22266.02	40.19	3	0.000
4. E (Sleep Disturbances and Cognition)	9	22487.50	5534	22505.50	285.67	6	0.000
5. Drop A21, C21, E21	12	22206.11	5531	22230.11	4.28	3	0.233
Symbol Digit							
Sleep Disturbances							
1. ACE (Sleep Disturbances and Cognition)	15	27986.48	6232	28016.48			
2. AE (Sleep Disturbances and Cognition)	12	27994.68	6235	28018.68	8.21	3	0.042
3. CE (Sleep Disturbances and Cognition)	12	28027.08	6235	28051.08	40.60	3	0.000
4. E (Sleep Disturbances and Cognition)	9	28384.01	6238	28402.01	397.53	6	0.000
5. Drop A21, C21, E21	12	27988.99	6235	28012.99	2.51	3	0.473

Note. A=additive genetic influences, C=shared environmental influences, E=non-shared environmental influences. A21, C21, E21= genetic and environmental influences shared between sleep and cognition.

Table A1.6 Fit Statistics for Moderation Models

Models	K	2LL	df	AIC	$\Delta\chi^2$	*Δdf*	*p*
Word List (PGS, Sleep Duration, Age)							
1. ACE	23	13066.38	4712	13112.38			
2. AE	19	13076.03	4716	13114.03	9.65	4	0.05
3. CE	17	13076.26	4718	13110.26	9.88	6	0.13
4. E	13	13149.97	4722	13175.97	83.59	10	9.90E-14
Word List (PGS, Sleep Disturbances, Age)							
1. ACE	24	18012.64	6709	18060.64			
2. AE	20	18015.88	6713	18055.88	3.25	4	0.52
3. CE	18	18029.99	6715	18065.99	17.36	6	0.01
4. E	14	18119.61	6719	18147.61	106.97	10	2.17E-18
Animal Naming (PGS, Sleep Duration, Age)							
1. ACE	22	12385.77	4458	12429.77			
2. AE	18	12388.47	4462	12424.47	2.69	4	0.61
3. CE	16	12403.77	4464	12435.77	18.00	6	0.01
4. E	12	12508.45	4468	12532.45	122.67	10	1.45E-21
Animal Naming (PGS, Sleep Disturbances, Age)							
1. ACE	22	13505.12	4967	13549.12			
2. AE	18	13509.79	4971	13545.79	4.67	4	0.32
3. CE	16	13532.37	4973	13564.37	27.24	6	1.30E-04
4. E	12	13655.10	4977	13679.10	149.98	10	3.76E-27
Digit Forward (PGS, Sleep Duration, Age)							
1. ACE	23	13235.15	4787	13281.15			
2. AE	19	13237.36	4791	13275.36	2.21	4	0.70
3. CE	17	13256.93	4793	13290.93	21.78	6	1.33E-03
4. E	13	13434.61	4797	13460.61	199.47	10	2.09E-37
Digit Forward (PGS, Sleep Disturbances, Age)							
1. ACE	24	16935.61	6166	16983.61			
2. AE	20	16946.76	6170	16986.76	11.15	4	0.02
3. CE	18	16972.79	6172	17008.79	37.18	6	1.62E-06
4. E	14	17200.79	6176	17228.79	265.18	10	3.46E-51
Digit Backward (PGS, Sleep Duration, Age)							
1. ACE	23	13227.23	4784	13273.23			
2. AE	19	13230.17	4788	13268.17	2.94	4	0.57
3. CE	17	13241.30	4790	13275.30	14.07	6	0.03
4. E	13	13374.70	4794	13400.70	147.47	10	1.24E-26

Models	K	2LL	df	AIC	$\Delta\chi^2$	*Δdf*	*p*
Digit Backward (PGS, Sleep Disturbances, Age)							
1. ACE	24	16910.90	6161	16958.90			
2. AE	20	16939.31	6165	16979.31	28.41	4	1.03E-05
3. CE	18	16959.69	6167	16995.69	48.79	6	8.23E-09
4. E	14	17138.52	6171	17166.52	227.62	10	2.71E-43
Synonyms (PGS, Sleep Disturbances, Age)							
1. ACE	22	7548.11	2871	7592.11			
2. AE	18	7553.13	2875	7589.13	5.03	4	0.28
3. CE	16	7562.63	2877	7594.63	14.52	6	0.02
4. E	12	7721.72	2881	7745.72	173.61	10	4.96E-32
Symbol Digit (PGS, Sleep Disturbances, Age)							
1. ACE	23	10442.70	4032	10488.70			
2. AE	19	10448.03	4036	10486.03	5.33	4	0.26
3. CE	17	10492.74	4038	10526.74	50.04	6	4.62E-09
4. E	13	10755.62	4042	10781.62	312.92	10	2.88E-61

Note. Shaded rows indicate the best-fitting model based on AIC.

Table A1.7 Parameter Estimates and 95% confidence intervals for AE Sleep Duration Models

Cognitive Task	Est.	95% CI	Est.	95% CI	Est.	95% CI
Word List		A_p		A_L		E_0
	-0.02	[-0.06, 0.02]	**0.49**	**[0.41, 0.55]**	**0.84**	**[0.8, 0.88]**
AD-PGS						$B_{Ap,E}$
	--		--		**-0.03**	**[-0.06, -0.01]**
Age		$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$
	-0.04	[-0.08, 0.01]	**0.14**	**[0.07, 0.21]**	**-0.05**	**[-0.08, -0.01]**
Sleep Duration		$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$
	-0.01	[-0.05, 0.03]	0.01	[-0.08, 0.1]	0.005	[-0.05, 0.06]
Animal Naming		A_p		A_L		E_0
	-0.02	[-0.06, 0.02]	**0.61**	**[0.56, 0.67]**	**0.78**	**[0.74, 0.82]**
AD-PGS						$B_{Ap,E}$
	--		--		-0.01	[-0.04, 0.02]
Age		$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$
	-0.002	[-0.04, 0.04]	0.03	[-0.03, 0.09]	-0.02	[-0.05, 0.02]
Sleep Duration		$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$
	-0.005	[-0.04, 0.03]	-0.05	[-0.12, 0.02]	0.003	[-0.05, 0.05]
Digit Forward		A_p		A_L		E_0
	0.01	[-0.03, 0.05]	**0.67**	**[0.62, 0.72]**	**0.73**	**[0.69, 0.76]**
AD-PGS						$B_{Ap,E}$
	--		--		-0.01	[-0.04, 0.02]
Age		$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$
	0.02	[-0.03, 0.07]	0.04	[-0.01, 0.1]	0.01	[-0.02, 0.05]
Sleep Duration		$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$
	-0.03	[-0.09, 0.02]	-0.03	[-0.09, 0.02]	0.002	[-0.04, 0.05]
Digit Backward		A_p		A_L		E_0
	0.02	[-0.02, 0.06]	**0.62**	**[0.56, 0.67]**	**0.76**	**[0.73, 0.8]**
AD-PGS						$B_{Ap,E}$

	--		--		**-0.04**	**[-0.06, -0.01]**
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,E}$	
	0.02	[-0.02, 0.06]	**-0.07**	**[-0.14, -0.01]**	0.03	[-0.01, 0.07]
Sleep Duration	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,E}$	
	-0.01	[-0.04, 0.03]	0.01	[-0.05, 0.07]	**-0.04**	**[-0.09, -0.001]**

Note. A=additive genetic, C=shared environment, E=nonshared environment, PGS-AD-Polygenic Score, Est.=Estimate. Moderation parameter terms include the AD-PGS, sleep, and age.

Table A1.8. Parameter Estimates and 95% confidence intervals for ACE Sleep Duration Models

Cognitive Task	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI
Word List	A_p		A_L		C_0		E_0	
	-0.02	[-0.06, 0.02]	0.23	[-0.27, 0.5]	0.36	[-0.04, 0.47]	**0.85**	**[0.8, 0.89]**
AD-PGS					$B_{Ap,C}$		$B_{Ap,E}$	
	--		--		0.03	[-0.06, 0.17]	**-0.04**	**[-0.08, 0]**
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,C}$		$BA_{ge,E}$	
	-0.04	[-0.08, 0.01]	-0.08	[-0.24, 0.17]	**0.14**	**[0.03, 0.24]**	-0.02	[-0.07, 0.02]
Sleep Duration	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$		$B_{SD,E}$	
	-0.01	[-0.05, 0.03]	-0.14	[-0.25, 0.03]	0.06	[-0.07, 0.22]	0.02	[-0.03, 0.072]
Animal Naming	A_p		A_L		C_0		E_0	
	-0.02	[-0.06, 0.02]	**0.54**	**[0.38, 0.65]**	0.23	[-0.42, 0.42]	**0.78**	**[0.74, 0.82]**
AD-PGS					$B_{Ap,C}$		$B_{Ap,E}$	
	--		--		-0.04	[-0.2, 0.2]	-0.01	[-0.04, 0.03]
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,C}$		$BA_{ge,E}$	
	-0.001	[-0.04, 0.04]	0.08	[-0.02, 0.17]	-0.10	[-0.21, 0.21]	-0.02	[-0.05, 0.02]
Sleep Duration	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$		$B_{SD,E}$	
	-0.01	[-0.05, 0.03]	-0.08	[-0.17, 0.06]	0.05	[-0.19, 0.18]	0.004	[-0.05, 0.05]
Digit Forward	A_p		A_L		C_0		E_0	
	0.01	[-0.06, 0.05]	**0.59**	**[0.43, 0.72]**	-0.29	[-0.47, 0.47]	**0.74**	**[0.67, 0.78]**

Cognitive Task	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI
AD-PGS					$B_{Ap,C}$		$B_{Ap,E}$	
	--		--		-0.004	[-0.33, 0.33]	-0.01	[-0.06, 0.05]
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,C}$		$BA_{ge,E}$	
	0.02	[-0.06, 0.1]	0.07	[-0.09, 0.16]	0.06	[-0.19, 0.19]	0.01	[-0.03, 0.08]
Sleep Duration	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$		$B_{SD,E}$	
	-0.04	[-0.1, 0.004]	-0.01	[-0.16, 0.08]	0.04	[-0.24, 0.24]	-0.003	[-0.05, 0.07]
Digit Backward	A_p		A_L		C_0		E_0	
	0.02	[-0.02, 0.06]	**0.54**	**[0.36, 0.65]**	0.25	[-0.44, 0.44]	**0.77**	**[0.73, 0.81]**
AD-PGS					$B_{Ap,C}$		$B_{Ap,E}$	
	--		--		0.06	[-0.2, 0.2]	**-0.05**	**[-0.08, -0.01]**
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$B_{Age,C}$		$BA_{ge,E}$	
	0.02	[-0.02, 0.07]	-0.04	[-0.12, 0.04]	-0.08	[-0.16, 0.16]	0.03	[-0.01, 0.06]
Sleep Duration	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$		$B_{SD,E}$	
	-0.01	[-0.05, 0.03]	-0.02	[-0.1, 0.07]	0.05	[-0.06, 0.14]	**-0.04**	**[-0.09, -0.002]**

Note. A=additive genetic, C=shared environment, E=nonshared environment, PGS-AD-Polygenic Score. Moderation parameter terms include the AD-PGS, sleep, and age.

Table A1.9 Parameter Estimates and 95% confidence intervals for ACE Sleep Disturbance Models

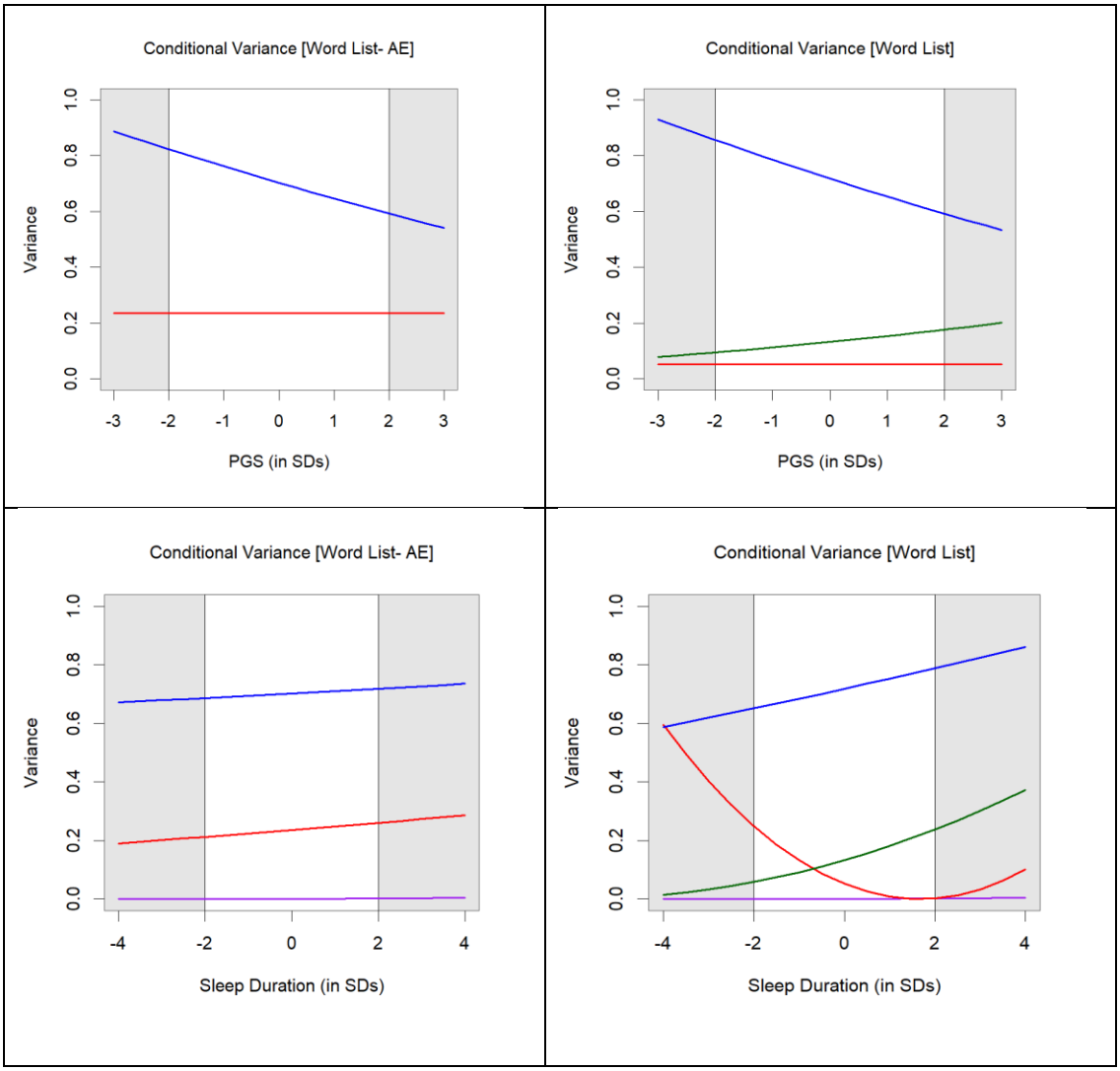
Cognitive Task	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI
Word List	A_p		A_L		C_0		E_0	
	-0.04	[-0.07, -0.01]	**0.37**	**[0.09, 0.5]**	0.26	[-0.4, 0.4]	**0.77**	**[0.74, 0.81]**
AD-PGS					$B_{Ap,C}$		$B_{Ap,E}$	
	--		--		0.02	[-0.15, 0.15]	-0.03	[-0.06, 0.001]
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,C}$		$BA_{ge,E}$	
	-0.04	**[-0.07, -0.01]**	0.06	[-0.08, 0.18]	0.07	[-0.2, 0.2]	-0.01	[-0.04, 0.02]
Sleep Dist.	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$		$B_{SD,E}$	
	-0.004	[-0.03, 0.03]	0.10	[-0.13, 0.19]	-0.06	[-0.15, 0.15]	-0.03	[-0.07, 0.007]
Animal Naming	A_p		A_L		C_0		E_0	
	-0.03	[-0.07, 0.01]	**0.56**	**[0.48, 0.62]**	-0.12	[-0.29, 0.15]	**0.73**	**[0.69, 0.76]**
AD-PGS					$B_{Ap,C}$		$B_{Ap,E}$	
	--		--		**0.13**	**[0.01, 0.22]**	-0.01	[-0.04, 0.02]
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,C}$		$BA_{ge,E}$	
	-0.01	[-0.05, 0.03]	-0.01	[-0.04, 0.06]	0.02	[-0.1, 0.12]	**-0.04**	**[-0.07, -0.002]**
Sleep Dist.	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$		$B_{SD,E}$	
	0.03	[-0.01, 0.06]	0.03	[-0.04, 0.11]	0.11	[-0.03, 0.19]	0.02	[-0.02, 0.07]
Digit Forward	A_p		A_L		C_0		E_0	
	0.003	[-0.03, 0.04]	**0.64**	**[0.48, 0.69]**	-0.09	[-0.4, 0.36]	**0.71**	**[0.67, 0.74]**
AD-PGS					$B_{Ap,C}$		$B_{Ap,E}$	
	--		--		0.10	[-0.04, 0.24]	-0.01	[-0.04, 0.02]
Age	$B_{Age,Ap}$		$B_{Age,AL}$		$BA_{ge,C}$		$BA_{ge,E}$	
	-0.01	[-0.05, 0.03]	-0.02	[-0.08, 0.05]	-0.03	[-0.14, 0.08]	-0.01	[-0.04, 0.023]
Sleep Dist.	$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$		$B_{SD,E}$	
	-0.02	[-0.05, 0.02]	0.07	[-0.09, 0.18]	**0.16**	**[0.06, 0.24]**	-0.02	[-0.06, 0.02]

Cognitive Task	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI
Digit Backward		A_p		A_L		C_0		E_0
	0.01	[-0.02, 0.05]	**0.58**	**[0.49, 0.63]**	0.12	[-0.05, 0.3]	**0.71**	**[0.68, 0.75]**
AD-PGS						$B_{Ap,C}$		$B_{Ap,E}$
	--		--		**0.11**	**[0.04, 0.19]**	**-0.03**	**[-0.06, -0.005]**
Age		$B_{Age,Ap}$		$B_{Age,AL}$		$B_{Age,C}$		$BA_{ge,E}$
	-0.01	[-0.04, 0.03]	-0.05	[-0.1, 0.01]	-0.06	[-0.14, 0.03]	-0.02	[-0.05, 0.01]
Sleep Dist.		$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$	$B_{SD,E}$	
	0.02	[-0.01, 0.06]	-0.03	[-0.14, 0.06]	**0.24**	**[0.17, 0.3]**	-0.02	[-0.06, 0.02]
Synonyms		A_p		A_L		C_0		E_0
	-0.02	[-0.07, 0.03]	**0.56**	**[0.31, 0.69]**	**-0.38**	**[-0.57, -0.01]**	**0.64**	**[0.59, 0.69]**
AD-PGS						$B_{Ap,C}$		$B_{Ap,E}$
	--		--		-0.01	[-0.1, 0.06]	**-0.05**	**[-0.09, -0.02]**
Age		$B_{Age,Ap}$		$B_{Age,AL}$		$B_{Age,C}$		$BA_{ge,E}$
	-0.05	[-0.11, 0.01]	**0.26**	**[0.12, 0.41]**	**-0.22**	[-0.35, 0.01]	**0.11**	**[0.07, 0.172]**
Sleep Dist.		$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$		$B_{SD,E}$
	-0.02	[-0.06, 0.02]	0.07	[-0.17, 0.15]	0.07	[-0.17, 0.18]	0.02	[-0.02, 0.08]
Symbol Digit		A_p		A_L		C_0		E_0
	-0.03	[-0.07, 0.01]	**0.65**	**[0.55, 0.73]**	0.24	[-0.39, 0.4]	**0.52**	**[0.48, 0.56]**
AD-PGS						$B_{Ap,C}$		$B_{Ap,E}$
	--		--		0.05	[-0.17, 0.14]	0.001	[-0.03, 0.03]
Age		$B_{Age,Ap}$		$B_{Age,AL}$		$B_{Age,C}$		$BA_{ge,E}$
	0.004	[-0.04, 0.05]	0.05	[-0.02, 0.16]	0.07	[-0.21, 0.21]	0.02	[-0.01, 0.059]
Sleep Dist.		$B_{SD,Ap}$		$B_{SD,AL}$		$B_{SD,C}$		$B_{SD,E}$

Cognitive Task	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI
	0.02	[-0.02, 0.05]	-0.07	[-0.14, 0.09]	0.12	[-0.21, 0.22]	0.02	[-0.02, 0.07]

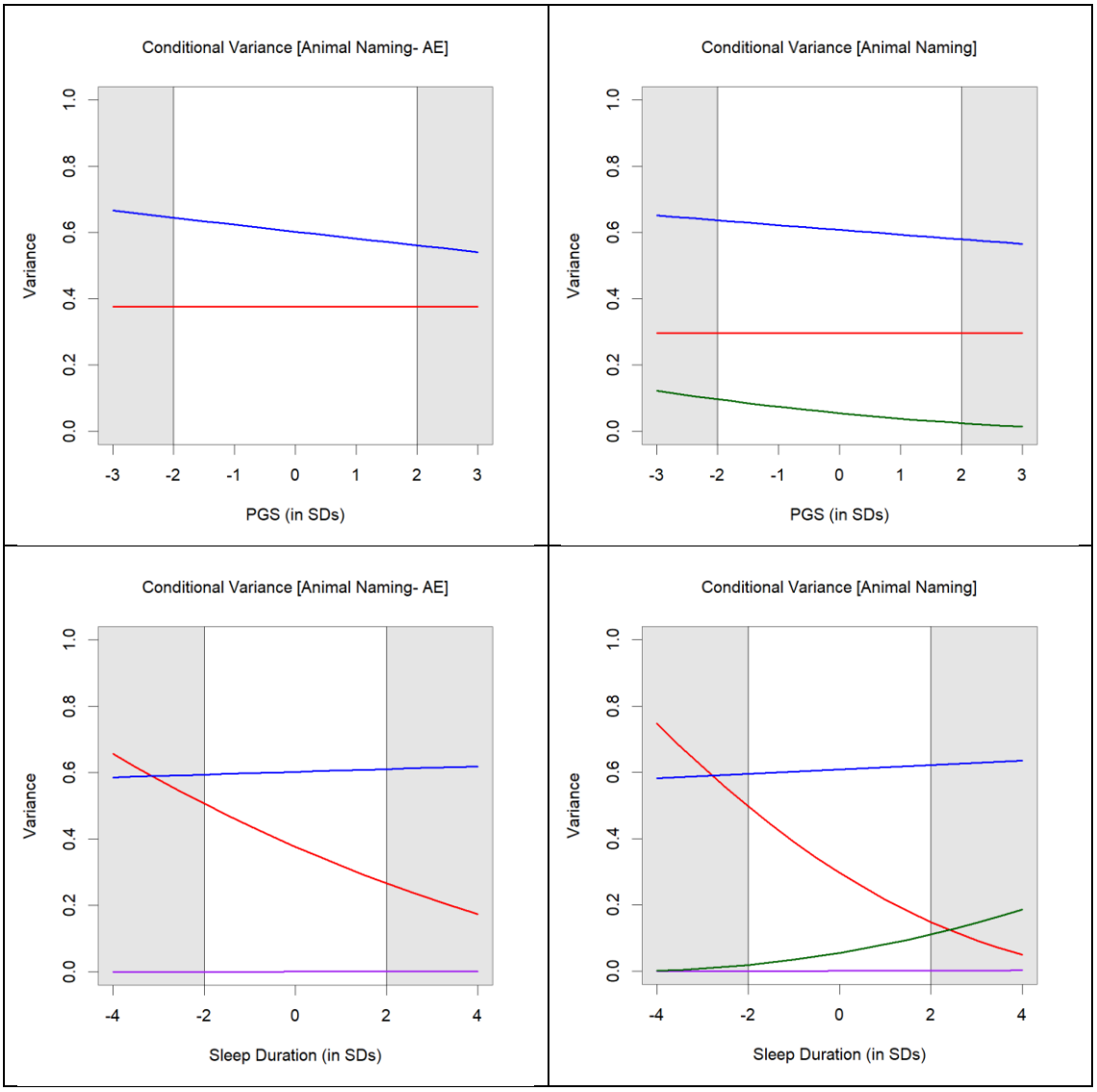
Note. A=additive genetic, C=shared environment, E=nonshared environment, PGS-AD-Polygenic Score. Sleep Dist.=Sleep Disturbance. Moderation parameter terms include the AD-PGS, sleep, and age.

Figure A1.1. Genetic and environmental variance of Word List, across varying levels of the AD-PGS and varying levels of sleep duration.



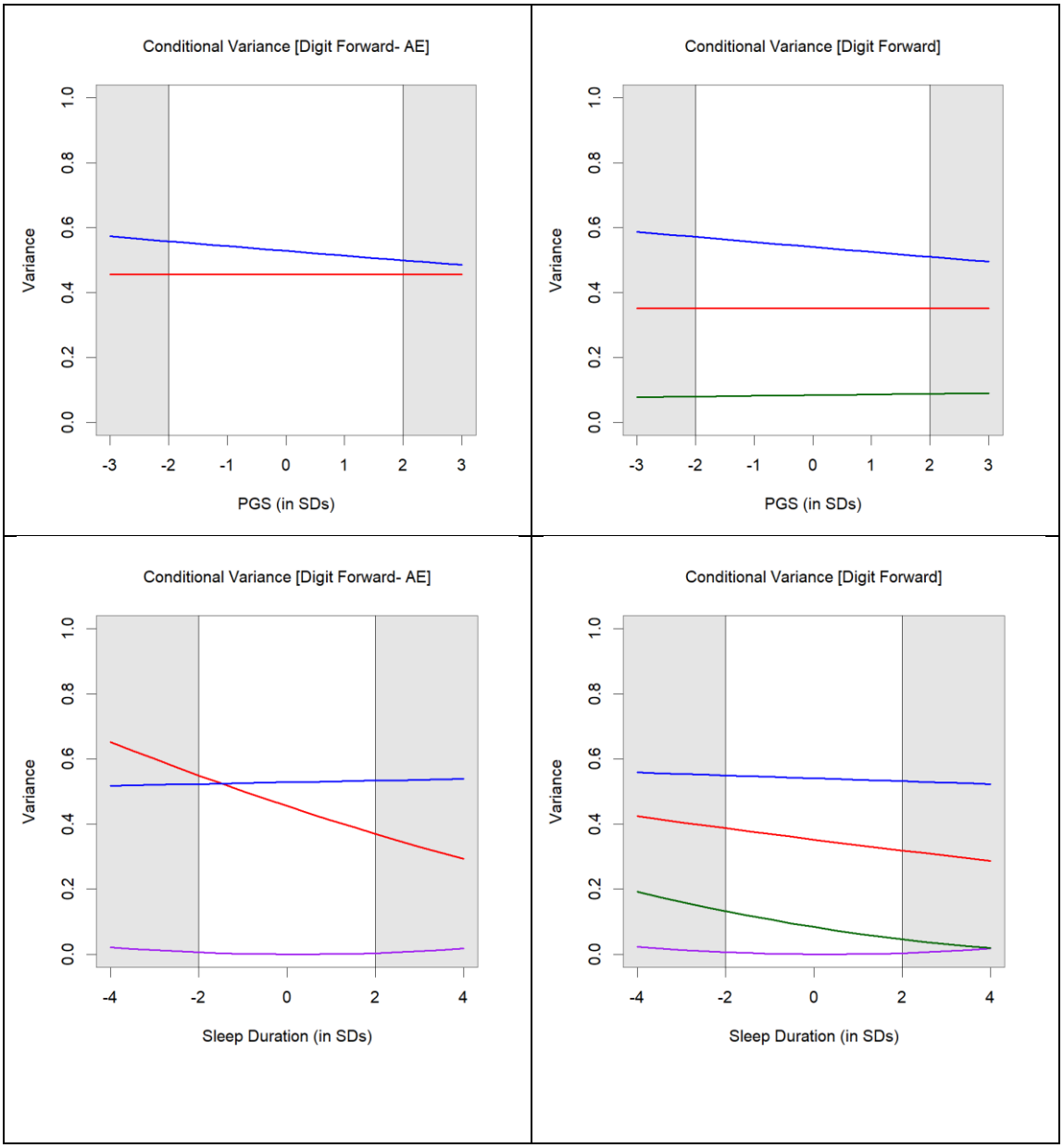
Note. Left panel depicts the AE model and right panel depicts the ACE model. Red Line= latent additive genetic variance, Purple Line= Proportion of genetic variance attributable to the AD-PGS, Green Line= shared environmental variance, Blue Line=unshared environmental variance. Shaded blocks indicate a PGS±2-3 SD's or Sleep durations ±2-4 from the mean.

Figure A1.2. Genetic and environmental variance of Animal Naming, across varying levels of the AD-PGS and varying levels of sleep duration.



Note. Left panel depicts the AE model and right panel depicts the ACE model. Red Line=latent additive genetic variance, Purple Line= Proportion of genetic variance attributable to the AD-PGS, Green Line= shared environmental variance, Blue Line=unshared environmental variance. Shaded blocks indicate a PGS±2-3 SD's or Sleep durations ±2-4 from the mean.

Figure A1.3 Genetic and environmental variance of Digits Forward, across varying levels of the AD-PGS and varying levels of sleep duration.



Note. Left panel depicts the AE model and right panel depicts the ACE model. Red Line=latent additive genetic variance, Purple Line= Proportion of genetic variance attributable to the AD-PGS, Green Line= shared environmental variance, Blue Line=unshared environmental variance. Shaded blocks indicate a PGS±2-3 SD's or Sleep durations ±2-4 from the mean.

Appendix 2. Supplemental Tables and Figures (Study 2)

Table A2.1 Model Fit Statistics for Unconditional Growth Models

	K	-2lnL	AIC	AICC	BIC	Δχ2	df	p
Dot Memory								
M1: No Growth	3	12865.4	12871	12871.4	12883.6			
M1a: No Growth (sibling)	4	12851.2	12859	12859.2	12874.4	14.2	1	1.6E-04
M2a: Linear Growth (sibling intercept only)	7	12503.4	12517	12517.4	12544.1	347.8	3	4.5E-75
M3b: Quadratic (sibling intercept only)	11	12420.4	12442	12442.4	12484.4	83	4	4.0E-17
Symbol Search								
M1: No Growth	3	79706.7	79713	79712.7	79724.9			
M1a: No Growth (sibling)	4	79693.2	97901	79701.3	79716.5	13.5	1	2.4E-04
M2: Linear Growth (sibling)	9	77098.2	77116	77116.2	77150.6	2595	5	0.0E+00
M2a: Linear Growth (sibling intercept only)	7	77099.6	77114	77113.6	77140.3	1.4	2	5.0E-01
M3b: Quadratic (sibling intercept only)	11	76689.1	76711	76711.2	76753.2	410.5	4	1.5E-87
*Stroop Task**								
M1: No Growth	3	65033.3	65039	65039.3	65051.5			
M2: Linear Growth	6	64099.3	64111	64111.3	64135.7	934	3	3.7E-202
M2a: Linear Growth (no random effects)	4	65027.7	65036	65035.7	65052	928.4	2	2.5E-202
M3: Quadratic	10	63809.1	63829	63829.1	63869.7	290.2	4	1.4E-61
M3a: Quadratic (no random effects)	7	64099.9	64113	64113.3	64141.7	290.8	3	9.7E-63
M4: Quadratic + Weekend/Weekday	15	63784.9	63815	63814.9	63875.9	24.2	5	2.0E-04
Shopping List								
M1: No Growth	3	87093.1	87099	87099.1	87111.3			
M1a: No Growth (sibling)	4	87086.5	87095	87094.5	87109.8	6.6	1	1.0E-02
M2: Linear Growth (sibling)	9	87004.3	87022	87022.3	87056.7	82.2	5	2.9E-16
M2a: Linear Growth (sibling intercept only)	7	87006.4	87020	870202.4	87047.1	2.1	2	3.5E-01
M3: Linear Growth (sibling intercept only) + Weekend/Weekday	13	86993.8	87018	87017.8	87063.6	12.6	6	5.0E-02

Note. Not all model runs are shown as some models ran into model convergence issues. Best-fitting models are highlighted in blue. Total N=337-431, Total Observations=10954-10997. Sibling= random effects between siblings. *Stroop task is modeled only at the individual-level.

Table A2.2. Model Fit Statistics for Conditional Growth Models

	K	-2lnL	AIC	AICC	BIC	Δχ2	df	p
Dot Memory								
M5a: TVC SQ	30	12099.1	12159.1	12159.3	12273.3			
M5b: TVC SQ	38	12089.7	12161.7	12162.0	12298.7	9.4	8	0.31
M5c: TVC SQ	44	12083.2	12171.2	12171.6	12338.6	6.5	6	0.37
M5a: TVC SR	30	12109.0	12169.0	12169.2	12283.2			
M5b: TVC SR	38	12099.1	12171.1	12171.4	12308.1	9.9	8	0.27
M5c: TVC SR	44	12094.6	12182.6	12182.9	12350.0	4.5	6	0.61
M5a: TVC ST	30	12100.6	12160.6	12160.8	12274.8			
M5b: TVC ST	38	12087.5	12163.5	12163.8	12308.1	13.1	8	0.11
M5c: TVC ST	44	12079.1	12167.1	12167.5	12334.6	8.4	6	0.21
M5a: TVC SF	30	12104.0	12164.0	12164.2	12278.1			
M5b: TVC SF	38	12093.6	12165.6	12165.9	12302.6	10.4	8	0.24
M5c: TVC SF	44	12085.3	12173.3	12173.7	12340.7	8.3	6	0.22
Stroop Task								
M5a: TVC SQ	34	62389.2	62457.2	62457.4	62594.9			
M5b: TVC SQ	40	62345.5	62425.5	62425.8	62587.5	43.7	6	0.00
M5c: TVC SQ	48	62297.9	62393.9	62394.4	62588.3	47.6	8	0.00
M5a: TVC SR	34	62400.7	62468.7	62469.0	62606.4			
M5b: TVC SR	40	62353.3	62433.3	62433.7	62595.3	47.4	6	0.00
M5c: TVC SR	48	62334.0	62430.0	62430.5	62624.4	19.3	8	0.01
M5a: TVC ST	34	62401.5	62469.5	62469.7	62607.2			
M5b: TVC ST	40	62355.2	62435.2	62435.5	62597.2	46.3	6	0.00
M5c: TVC ST	48	62321.7	62417.7	62418.1	62612.0	33.5	8	0.00
M5a: TVC SF	34	62399.5	62467.5	62467.7	62605.2			

M5b: TVC SF	40	62353.9	62433.9	62434.3	62595.9	45.6	6	0.00
M5c: TVC SF	48	62335.3	62431.3	62431.8	62625.7	18.6	8	0.02
Shopping List								
M5a: TVC SQ	26	85058.2	85110.2	85110.4	85209.2			
M5b: TVC SQ	30	85050.0	85110.0	85110.2	85224.1	8.2	4	0.08
M5c: TVC SQ	36	85037.7	85109.7	85110.0	85246.7	12.3	6	0.06
M5a: TVC SR	26	85065.1	85117.1	85117.2	85216.0			
M5b: TVC SR	30	85056.8	85116.8	85117.0	85231.0	8.3	4	0.08
M5c: TVC SR	36	85044.3	85116.3	85116.6	85253.3	12.5	6	0.05
M5a: TVC ST	26	85054.7	85106.7	85106.8	85205.6			
M5b: TVC ST	30	85046.7	85106.7	85106.8	85220.8	8	4	0.09
M5c: TVC ST	36	85037.4	85109.4	85109.7	85246.4	9.3	6	0.16
M5a: TVC SF	26	85051.5	85103.5	85103.7	85202.5			
M5b: TVC SF	30	85043.3	85103.3	85103.4	85217.4	8.2	4	0.08
M5c: TVC SF	36	85032.4	85104.4	85104.6	85241.4	10.9	6	0.09

Note. M5a= Model includes the time-varying covariate of sleep, time-invariant covariates (i.e., age, sex) and additional covariates (project, race/ethnicity, adopted). M5b=M5a + APOE_score. M5c=M5b+ APOE_score interactions with time-varying covariates of sleep.

Table A2.3. Conditional Growth Model (Fullest Model) Fixed Effects: Dot Memory

Model (M) parameters	TVC SQ		TVC SR		TVC ST		TVC SF	
	b	SE	b	SE	b	SE	b	SE
Intercept	**0.539**	**0.060**	**0.533**	**0.060**	**0.542**	**0.060**	**0.541**	**0.059**
Project	0.061	0.069	0.065	0.070	0.061	0.069	0.061	0.069
Adopted	0.104	0.055	**0.110**	**0.055**	0.107	0.055	0.097	0.055
Race/Ethnicity	-0.055	0.064	-0.058	0.064	-0.055	0.064	-0.054	0.064
Sex	**0.197**	**0.044**	**0.205**	**0.045**	**0.199**	**0.045**	**0.202**	**0.044**
b_SleepTVC	**-4.4E-03**	**1.9E-03**	-2.6E-03	1.8E-03	**3.7E-03**	**1.7E-03**	**3.7E-03**	**1.7E-03**
Sex*b_SleepTVC	3.5E-03	2.3E-03	2.1E-03	2.2E-03	**-4.1E-03**	**2.0E-03**	**-4.7E-03**	**2.0E-03**
Age	0.006	0.006	0.007	0.006	0.006	0.006	0.005	0.006
b_SleepTVC*Age	3.0E-04	2.5E-04	2.5E-04	2.4E-04	-9.0E-05	2.0E-04	-7.0E-05	2.4E-04
Day	**-0.01**	**2.4E-03**	**-0.01**	**2.4E-03**	**-0.01**	**2.4E-03**	**-0.01**	**2.4E-03**
Sex*Day	-2.9E-03	3.0E-03	-2.6E-03	3.0E-03	-2.2E-03	3.0E-03	-2.4E-03	3.0E-03
Age*Day	4.0E-05	2.7E-04	5.8E-05	2.7E-04	-1.0E-05	2.7E-04	1.6E-05	2.7E-04
b_SleepTVC*Day	**-2.0E-04**	**9.4E-05**	-1.3E-04	8.9E-05	1.2E-04	8.0E-05	1.1E-04	8.7E-05
b_SleepTVC*Age*Day	1.0E-05	1.6E-05	1.2E-05	1.6E-05	6.6E-06	1.4E-05	-3.7E-07	1.6E-05
Day^2	**1.2E-03**	**5.3E-04**	**1.3E-03**	**5.3E-04**	**1.1E-03**	**5.2E-04**	**1.2E-03**	**5.3E-04**
Sex*Day^2	1.4E-04	6.7E-04	-4.0E-05	6.7E-04	2.8E-04	6.7E-04	1.4E-04	6.8E-04
Age*Day^2	-8.0E-05	6.0E-05	-6.0E-05	6.0E-05	-8.0E-05	6.0E-05	-6.0E-05	6.0E-05
b_SleepTVC*Day^2	2.8E-05	2.1E-05	1.0E-05	2.0E-05	-3.0E-05	1.8E-05	9.2E-06	1.9E-05
b_SleepTVC*Age*Day^2	**-8.3E-06**	**3.6E-06**	-5.6E-06	3.6E-06	**7.5E-06**	**3.0E-06**	6.1E-06	3.6E-06
r_SleepTVC	-6.8E-04	4.2E-04	-4.8E-04	4.3E-04	2.9E-04	3.6E-04	2.0E-04	3.9E-04
Sex*r_SleepTVC	1.4E-04	5.0E-04	-4.0E-05	5.2E-04	6.1E-05	4.5E-04	-5.9E-04	4.7E-04
Age*r_SleepTVC	4.7E-05	4.5E-05	5.2E-06	4.6E-05	1.3E-05	3.9E-05	-4.0E-05	4.4E-05
APOE	-0.053	0.037	-0.049	0.037	-0.048	0.037	-0.044	0.036

Age*APOE	1.1E-02	6.9E-03	1.3E-02	6.8E-03	1.3E-02	6.8E-03	**1.5E-02**	**6.8E-03**
APOE*day	-6.9E-04	2.5E-03	-2.1E-04	2.5E-03	-1.7E-04	2.5E-03	-9.2E-06	2.5E-03
Age*APOE*Day	5.0E-04	4.6E-04	6.7E-04	4.6E-04	7.3E-04	4.6E-04	6.9E-04	4.6E-04
APOE*Day^2	1.0E-03	5.5E-04	1.0E-03	5.5E-04	1.0E-03	5.5E-04	9.2E-04	5.5E-04
Age*APOE*Day^2	2.7E-05	1.0E-04	-3.2E-06	1.0E-04	2.0E-05	1.0E-04	-1.0E-05	1.0E-04
b_SleepTVC*APOE	-6.1E-04	2.1E-03	4.8E-05	2.0E-03	-1.0E-04	1.9E-03	2.3E-03	1.9E-03
b_SleepTVC*Age*APOE	-6.3E-04	3.6E-04	-4.0E-04	3.9E-04	3.2E-04	3.4E-04	2.3E-04	3.4E-04
b_SleepTVC*APOE*Day	-8.0E-05	1.5E-04	-4.8E-07	1.4E-04	2.3E-05	1.3E-04	3.3E-05	1.3E-04
b_SleepTVC*Age*APOE*Day	-5.0E-05	2.8E-05	-4.0E-05	2.7E-05	-3.0E-05	2.5E-05	1.3E-05	2.5E-05
b_SleepTVC*APOE*Day^2	4.0E-06	3.2E-05	-1.0E-05	3.1E-05	-2.0E-05	2.9E-05	-2.0E-05	2.9E-05
b_SleepTVC*Age*APOE*Day^2	9.9E-06	6.1E-06	3.5E-06	6.1E-06	-8.5E-06	5.6E-06	**-1.0E-05**	**5.4E-06**
APOE*r_SleepTVC	3.7E-04	3.6E-04	4.9E-04	3.8E-04	-6.1E-04	3.3E-04	-2.8E-04	3.4E-04
Age*APOE*r_SleepTVC	-2.0E-05	6.9E-05	-4.0E-05	7.3E-05	1.1E-04	6.4E-05	8.9E-05	7.2E-05
Goodness of Fit								
Neg 2 LL	12083.2		12094.6		12079.1		12085.3	
AIC	12171.2		12182.6		12167.1		12173.3	
AICC	12171.6		12182.9		12167.5		12173.7	
BIC	12338.6		12350		12334.6		12340.7	
Number of Observations Used	10749		10749		10749		10749	
Sibships	332		332		332		332	
Unique Individuals	424		424		424		424	

Note. Fullest Model across the four sleep TVCs. APOE= APOE_score; B_SleepTVC=between-person sleep quality component, r_SleepTVC= within-person sleep quality component. Bolded parameters indicate $p < .05$.

Table A2.4 Conditional Growth Model (Fullest Model) Fixed Effects: Stroop Task

Model (M) parameters	TVC SQ		TVC SR		TVC ST		TVC SF	
	b	SE	b	SE	b	SE	b	SE
Intercept	**97.225**	**0.529**	**97.208**	**0.537**	**97.276**	**0.535**	**97.171**	**0.536**
Project	0.432	0.586	0.403	0.596	0.457	0.592	0.477	0.595
Adopted	0.367	0.461	0.282	0.467	0.234	0.468	0.345	0.471
Race/Ethnicity	-0.288	0.536	-0.150	0.544	-0.163	0.542	-0.163	0.546
Sex	0.384	0.411	0.331	0.420	0.201	0.419	0.287	0.419
b_SleepTVC	0.022	0.017	0.010	0.016	-0.008	0.015	-0.012	0.016
Sex*b_SleepTVC	-0.010	0.020	-0.005	0.019	-0.002	0.017	0.011	0.018
Age	0.050	0.056	0.047	0.057	0.056	0.056	0.059	0.057
b_SleepTVC*Age	-0.001	0.002	-0.001	0.002	-0.001	0.002	-0.002	0.002
Weekend/Weekday	0.176	0.105	0.187	0.105	0.189	0.106	0.185	0.105
Day	-0.004	0.037	0.002	0.038	-0.005	0.037	-0.007	0.038
Sex*Day	0.033	0.047	0.024	0.048	0.034	0.047	0.040	0.048
Age*Day	**0.011**	**0.004**	**0.013**	**0.004**	**0.012**	**0.004**	**0.013**	**0.004**
b_SleepTVC*Day	2.4E-03	1.5E-03	1.9E-03	1.5E-03	-1.2E-03	1.3E-03	-1.1E-04	1.4E-03
b_SleepTVC*Age*Day	**-6.7E-04**	**2.7E-04**	**-6.2E-04**	**2.7E-04**	5.7E-04	2.2E-04	**7.1E-04**	**2.7E-04**
Day^2	0.004	0.007	0.004	0.007	0.004	0.007	0.004	0.007
Sex*Day^2	-0.002	0.009	-0.002	0.009	-0.001	0.009	-0.002	0.009
Age*Day^2	-1.0E-03	8.1E-04	-1.1E-03	8.1E-04	-1.1E-03	8.0E-04	-1.2E-03	8.1E-04
b_SleepTVC*Day^2	-3.1E-04	2.8E-04	-1.9E-04	2.7E-04	1.9E-04	2.4E-04	1.6E-04	2.6E-04

b_SleepTVC*Age*Day^2	8.8E-05	4.9E-05	7.8E-05	4.9E-05	-6.0E-05	4.1E-05	-3.0E-05	4.9E-05
r_SleepTVC	-0.006	0.004	-0.004	0.004	0.001	0.004	0.002	0.004
Sex*r_SleepTVC	0.004	0.005	0.004	0.005	-0.002	0.005	-0.001	0.005
Age*r_SleepTVC	-8.3E-04	4.6E-04	**-9.7E-04**	**4.8E-04**	4.2E-04	4.1E-04	2.8E-04	4.5E-04
APOE	-0.211	0.337	-0.347	0.340	-0.389	0.340	-0.425	0.338
Age*APOE	-0.069	0.063	-0.124	0.063	-0.112	0.063	-0.122	0.063
APOE*Day	0.013	0.039	0.036	0.039	0.020	0.038	0.040	0.039
Age*APOE*Day	0.014	0.007	**0.020**	**0.007**	**0.016**	**0.007**	**0.017**	**0.007**
APOE*Day^2	-0.010	0.007	-0.012	0.007	-0.010	0.007	-0.012	0.007
Age*APOE*Day^2	**-0.006**	**0.001**	**-0.006**	**0.001**	**-0.006**	**0.001**	**-0.006**	**0.001**
b_SleepTVC*APOE	0.032	0.019	0.008	0.019	-0.002	0.018	-0.031	0.018
b_SleepTVC*Age*APOE	**0.014**	**0.003**	**0.010**	**0.004**	**-0.007**	**0.003**	**-0.009**	**0.003**
b_SleepTVC*APOE*Day	**-0.007**	**0.002**	-0.003	0.002	**0.007**	**0.002**	**0.004**	**0.002**
b_SleepTVC*Age*APOE*Day	**-9.5E-04**	**4.1E-04**	-7.7E-04	4.2E-04	**1.4E-03**	**3.8E-04**	3.7E-05	3.8E-04
b_SleepTVC*APOE*Day^2	5.3E-04	4.3E-04	2.2E-04	4.1E-04	-6.8E-04	3.8E-04	-4.1E-04	3.9E-04
b_SleepTVC*Age*APOE*Day^2	1.7E-05	8.0E-05	-4.0E-05	8.0E-05	-1.2E-04	7.3E-05	-9.3E-07	7.2E-05
APOE*r_SleepTVC	**0.010**	**0.004**	**0.008**	**0.004**	-0.006	0.003	-0.002	0.004
Age*APOE*r_SleepTVC	**1.4E-03**	**7.1E-04**	1.4E-03	7.6E-04	-1.1E-04	6.6E-04	2.1E-04	7.4E-04
Goodness of Fit								
Neg 2 LL	62297.9		62334		62321.7		62335.3	
AIC	62393.9		62430		62417.7		62431.3	
AICC	62394.4		62430.5		62418.1		62431.8	
BIC	62588.3		62624.4		62612		62625.7	

Number of Observations Used	10729	10729	10729	10729
Unique Individuals	424	424	424	424

Note. Fullest model across the four sleep TVCs. APOE= APOE_score; B_SleepTVC=between-person sleep quality component, r_SleepTVC= within-person sleep quality component. Stroop task is modeled only at the individual-level. Bolded parameters indicate $p < .05$.

Table A2.5 Conditional Growth Model (Fullest Model) Fixed Effects: Stroop Task Incongruent Trials

Model (M) parameters	TVC SQ		TVC SR		TVC ST		TVC SF	
	b	SE	b	SE	b	SE	b	SE
Intercept	**95.362**	**1.017**	**95.292**	**1.033**	**95.431**	**1.029**	**95.152**	**1.029**
Project	0.752	1.132	0.709	1.152	0.845	1.142	0.887	1.145
Adopted	0.714	0.891	0.554	0.903	0.492	0.903	0.734	0.907
Race/Ethnicity	0.106	1.035	0.421	1.050	0.395	1.045	0.347	1.050
Sex	0.723	0.791	0.638	0.809	0.329	0.807	0.640	0.805
b_SleepTVC	0.030	0.034	0.010	0.032	-0.002	0.030	-0.031	0.031
Sex*b_SleepTVC	-0.011	0.038	0.003	0.036	-0.009	0.034	0.021	0.036
Age	0.020	0.107	0.015	0.110	0.033	0.109	0.040	0.109
b_SleepTVC*Age	-0.001	0.004	-0.002	0.004	-0.002	0.004	-0.003	0.004
Weekend/Weekday	0.368	0.176	0.393	0.176	0.395	0.176	0.385	0.176
Day	0.021	0.071	0.032	0.073	0.016	0.071	0.016	0.072
Sex*Day	0.081	0.090	0.064	0.093	0.086	0.091	0.094	0.092
Age*Day	**0.021**	**0.008**	**0.023**	**0.008**	**0.022**	**0.008**	**0.023**	**0.008**
b_SleepTVC*Day	0.004	0.003	0.003	0.003	-0.003	0.002	-0.001	0.003
b_SleepTVC*Age*Day	**-0.001**	**0.001**	**-0.001**	**0.001**	0.001	0.000	**0.002**	**0.001**
Day^2	-0.002	0.014	-0.002	0.014	-0.002	0.014	0.000	0.014
Sex*Day^2	-0.004	0.017	-0.004	0.017	-0.003	0.017	-0.006	0.017
Age*Day^2	-0.001	0.002	-0.001	0.002	-0.001	0.002	-0.001	0.002
b_SleepTVC*Day^2	-0.001	0.001	0.000	0.001	0.000	0.000	0.001	0.000
b_SleepTVC*Age*Day^2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
r_SleepTVC	-0.009	0.008	-0.004	0.008	0.003	0.007	0.006	0.007
Sex*r_SleepTVC	0.004	0.009	0.003	0.009	-0.005	0.008	-0.002	0.008
Age*r_SleepTVC	0.000	0.001	**-0.001**	**0.001**	0.000	0.001	0.000	0.001

APOE	-0.508	0.648	-0.803	0.654	-0.879	0.655	-0.955	0.648
Age*APOE	-0.138	0.121	-0.241	0.121	-0.228	0.122	*-0.237*	0.121
APOE*Day	0.011	0.074	0.052	0.075	0.023	0.073	0.058	0.074
Age*APOE*Day	0.030	0.014	**0.040**	**0.014**	**0.034**	**0.013**	**0.035**	**0.014**
APOE*Day^2	-0.019	0.014	-0.022	0.014	-0.020	0.014	-0.023	0.014
Age*APOE*Day^2	**-0.012**	**0.003**	**-0.012**	**0.003**	**-0.011**	**0.003**	**-0.012**	**0.003**
b_SleepTVC*APOE	0.075	0.037	0.021	0.037	-0.011	0.034	-0.064	0.034
b_SleepTVC*Age*APOE	**0.028**	**0.007**	**0.021**	**0.007**	**-0.013**	**0.006**	**-0.019**	**0.006**
b_SleepTVC*APOE*Day	**-0.013**	**0.004**	-0.006	0.004	**0.013**	**0.004**	**0.009**	**0.004**
b_SleepTVC*Age*APOE*Day	**-0.002**	**0.001**	-0.001	0.001	**0.002**	**0.001**	0.000	0.001
b_SleepTVC*APOE*Day^2	0.001	0.001	0.000	0.001	-0.001	0.001	-0.001	0.001
b_SleepTVC*Age*APOE*Day^2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
APOE*r_SleepTVC	**0.019**	**0.007**	**0.015**	**0.007**	-0.010	0.006	-0.003	0.006
Age*APOE*r_SleepTVC	**0.003**	**0.001**	0.003	0.001	-0.001	0.001	-0.001	0.001
Goodness of Fit								
Neg 2 LL	74549.9		74590.5		74579.7		74586.1	
AIC	74645.9		74686.5		74675.7		74682.1	
AICC	74646.3		74687.0		74676.2		74682.5	
BIC	74840.3		74880.9		74870.1		74876.5	
Number of Observations Used	10729		10729		10729		10729	
Unique Individuals	424		424		424		424	

Note. Fullest model across all four sleep TVCs. APOE= APOE_score; B_SleepTVC=between-person sleep quality component, r_SleepTVC= within-person sleep quality component. Stroop task is modeled only at the individual-level. Bolded parameters indicate $p < .05$.

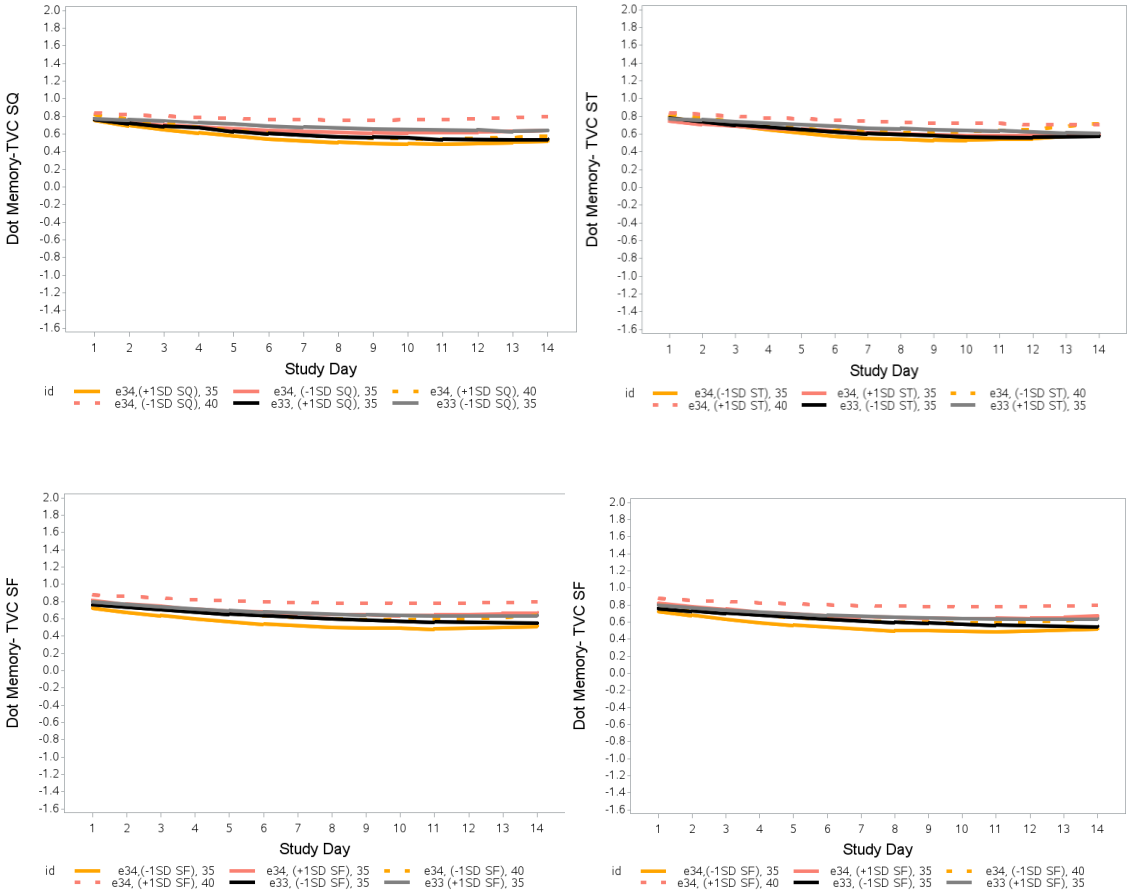
Table A2.6 Conditional Growth Model (Fullest Model) Fixed Effects: Shopping List

Model (M) parameters	TVC SQ		TVC SR		TVC ST		TVC SF	
	b	SE	b	SE	b	SE	b	SE
Intercept	**84.047**	**1.018**	**84.215**	**1.022**	**83.907**	**1.017**	**84.020**	**1.015**
Project	-1.580	1.189	-1.942	1.196	-1.498	1.188	-1.467	1.190
Adopted	-0.776	0.940	-1.001	0.942	-0.844	0.944	-0.822	0.943
Race/Ethnicity	1.312	1.099	1.421	1.100	1.503	1.098	1.085	1.104
Sex	0.440	0.686	0.443	0.694	0.471	0.690	0.501	0.686
b_SleepTVC	**0.066**	**0.031**	0.034	0.029	**-0.076**	**0.028**	**-0.095**	**0.028**
Sex*b_SleepTVC	-0.032	0.039	-0.004	0.037	0.047	0.035	0.041	0.035
Age	-0.130	0.104	-0.153	0.105	-0.117	0.104	-0.101	0.104
b_SleepTVC*Age	-0.003	0.004	-0.002	0.004	0.003	0.003	0.003	0.004
Weekend/Weekday	0.555	0.301	0.553	0.301	0.523	0.299	0.516	0.301
Day	**-0.176**	**0.059**	**-0.173**	**0.059**	**-0.181**	**0.059**	**-0.189**	**0.059**
Sex*Day	-0.083	0.075	-0.094	0.075	-0.075	0.075	-0.070	0.075
Age*Day	**-0.013**	**0.007**	-0.012	0.007	**-0.013**	**0.007**	-0.012	0.007
b_SleepTVC*Day	2.2E-03	2.3E-03	-5.2E-04	2.2E-03	-2.5E-03	2.0E-03	-2.9E-03	2.2E-03
b_SleepTVC*Age*Day	-6.6E-04	4.0E-04	-2.9E-04	4.1E-04	3.8E-04	3.4E-04	4.6E-04	4.0E-04
r_SleepTVC	0.014	0.013	0.010	0.014	**-0.027**	**0.011**	-0.014	0.012
Sex*r_SleepTVC	0.005	0.016	0.003	0.016	0.017	0.014	0.008	0.015
Age*r_SleepTVC	2.5E-04	1.4E-03	-1.7E-04	1.4E-03	-1.1E-03	1.2E-03	-7.7E-04	1.4E-03
APOE	**1.607**	**0.578**	**1.587**	**0.576**	**1.437**	**0.574**	**1.349**	**0.570**
Age*APOE	-0.056	0.107	-0.111	0.106	-0.083	0.106	-0.116	0.106
APOE*Day	0.098	0.062	0.096	0.062	0.091	0.062	0.099	0.062

Age*APOE*Day	3.0E-03	0.012	0.001	0.011	0.003	0.012	-0.001	0.012
b_SleepTVC*APOE	0.010	0.033	0.011	0.032	0.002	0.029	-0.010	0.029
b_SleepTVC*Age*APOE	**0.019**	**0.006**	**0.018**	**0.006**	**-0.014**	**0.005**	**-0.012**	**0.005**
b_SleepTVC*APOE*Day	0.003	0.004	0.002	0.003	0.000	0.003	-0.004	0.003
b_SleepTVC*Age*APOE*Day	5.6E-04	7.2E-04	2.9E-04	6.9E-04	-4.3E-04	6.4E-04	-1.9E-04	6.3E-04
APOE*r_SleepTVC	-0.016	0.011	-0.020	0.012	0.017	0.010	**0.024**	**0.011**
Age*APOE*r_SleepTVC	-3.0E-04	2.2E-03	9.7E-04	2.3E-03	1.1E-03	2.0E-03	1.0E-03	2.3E-03
Goodness of Fit								
Neg 2 LL	85037.7		85044.3		85037.4		85032.4	
AIC	85109.7		85116.3		85109.4		85104.4	
AICC	85110		85116.6		85109.7		85104.6	
BIC	85246.7		85253.3		85246.4		85241.4	
Number of Observations Used	10706		10706		10706		10706	
Sibships	332		332		332		332	
Individuals	424		424		424		424	

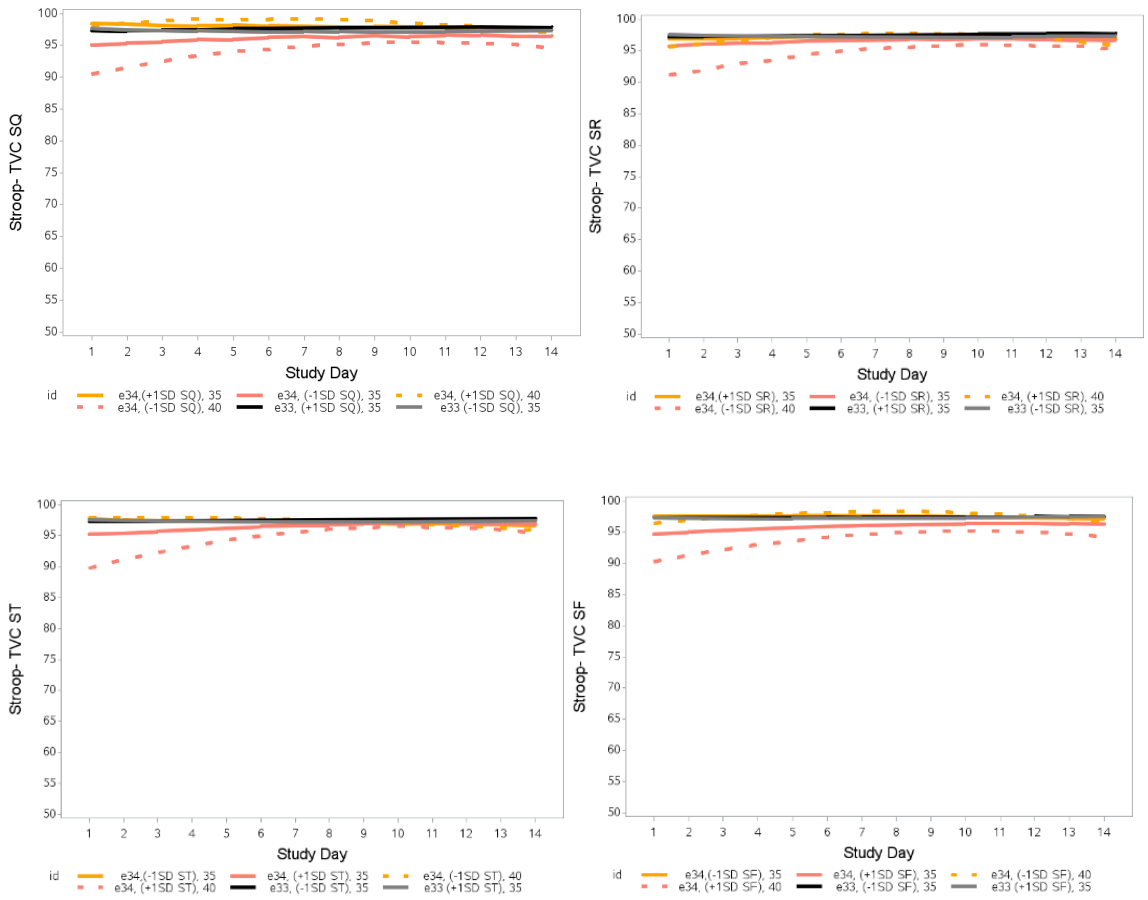
Note. Fullest model across all four sleep TVCs. APOE= APOE_score; B_SleepTVC=between-person sleep quality component, r_SleepTVC= within-person sleep quality component. Bolded parameters indicate $p < .05$.

Figure A2.1. Trajectories of Dot Memory across 14 study days.



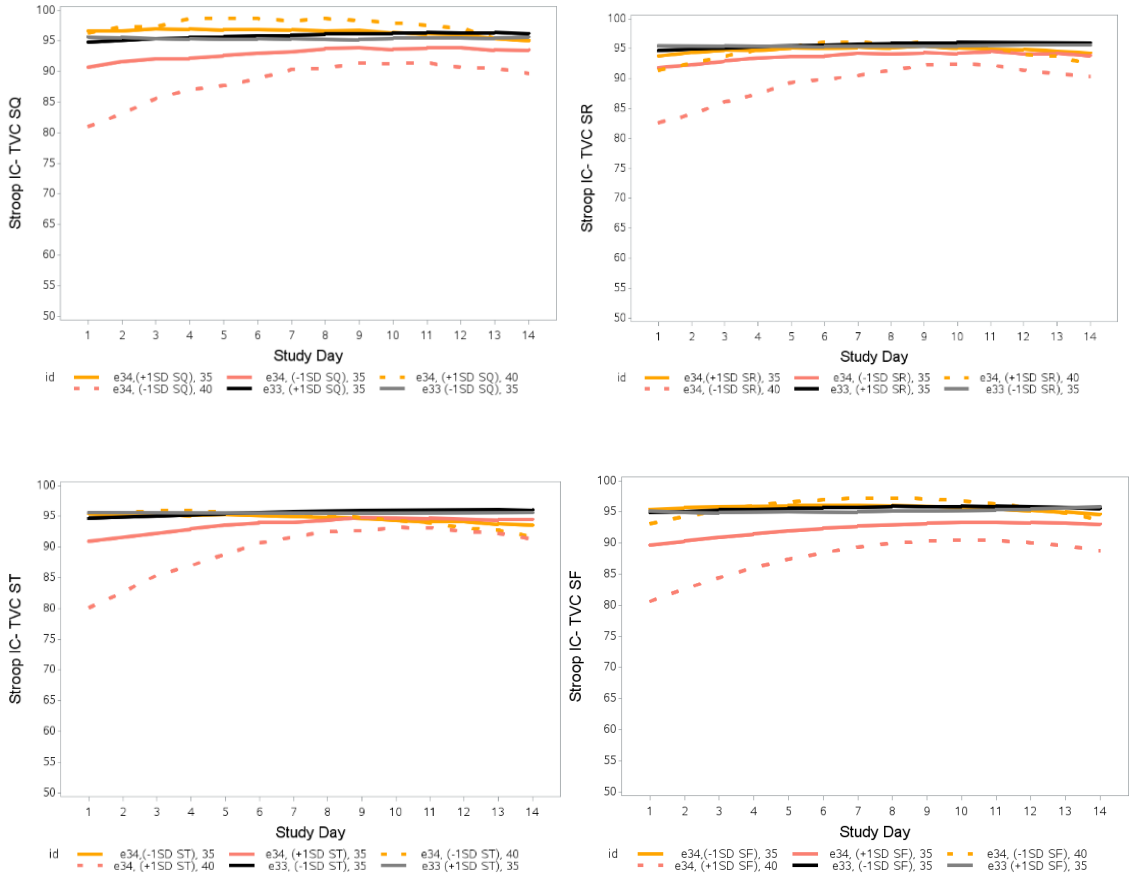
Note. All plotted quadratic models centered at day 7 represent expected trajectories for Dot Memory performance, adjusting for age, sex, adoption status, race/ethnicity, and project. Orange lines depict ε34 individuals with poor (i.e., 1 standard deviation below the average) sleep quality. Gold lines depict ε34 individuals with good (i.e., 1 standard deviation above the average) sleep quality. Black lines depict the ε33 homozygous group. Dashed Line= Age 40, Solid Lines=Age 35, TVC=Time-varying covariate, SQ=sleep quality, SR=sleep refresh, SF=sleep fall, ST=sleep troubles

Figure A2.2. Trajectories of Stroop Task across 14 study days.



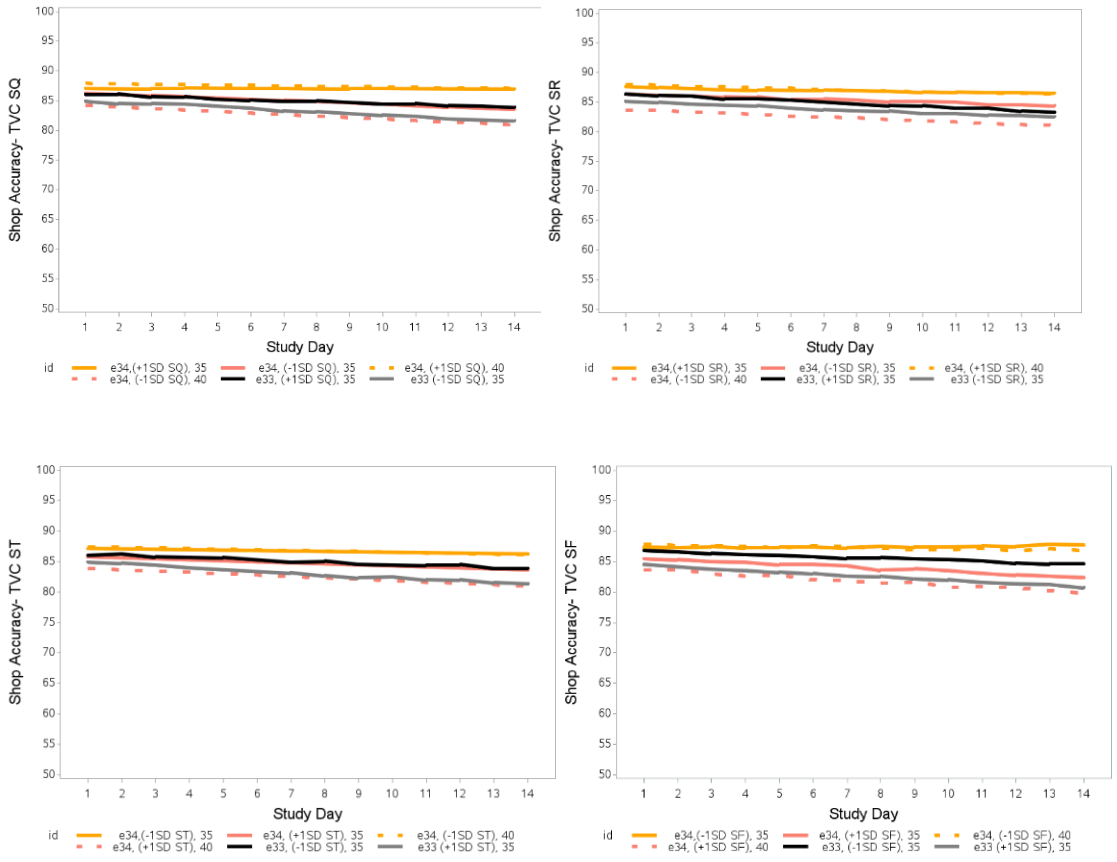
Note. All plotted quadratic models centered at day 7 represent expected trajectories for Stroop Task performance, adjusting for age, sex, adoption status, race/ethnicity, and project. Orange lines depict ε34 individuals with poor (i.e., 1 standard deviation below the average) sleep quality. Gold lines depict ε34 individuals with good (i.e., 1 standard deviation above the average) sleep quality. Black lines depict the ε33 homozygous group. Dashed Line= Age 40, Solid Lines=Age 35, TVC=Time-varying covariate, SQ=sleep quality, SR=sleep refresh, SF=sleep fall, ST=sleep troubles

Figure A2.3. Trajectories of Stroop Task (Incongruent Trials) across 14 study days.



Note. All plotted quadratic models centered at day 7 represent expected trajectories for Stroop Task performance, adjusting for age, sex, adoption status, race/ethnicity, and project. Orange lines depict ε34 individuals with poor (i.e., 1 standard deviation below the average) sleep quality. Gold lines depict ε34 individuals with good (i.e., 1 standard deviation above the average) sleep quality. Black lines depict the ε33 homozygous group. Dashed Line= Age 40, Solid Lines=Age 35, TVC=Time-varying covariate, SQ=sleep quality, SR=sleep refresh, SF=sleep fall, ST=sleep troubles

Figure A2.4. Trajectories of Shopping List across 14 study days.



Note. All plotted quadratic models centered at day 7 represent expected trajectories for Stroop Task performance, adjusting for age, sex, adoption status, race/ethnicity, and project. Orange lines depict ε34 individuals with poor (i.e., 1 standard deviation below the average) sleep quality. Gold lines depict ε34 individuals with good (i.e., 1 standard deviation above the average) sleep quality. Black lines depict the ε33 homozygous group. Dashed Line= Age 40, Solid Lines=Age 35, TVC=Time-varying covariate, SQ=sleep quality, SR=sleep refresh, SF=sleep fall, ST=sleep troubles.