Changes in Composite Sleep Health and Domain-Specific Cognitive Performance in a Community-Based Sample from Two Predominantly African American Neighborhoods in Pittsburgh, PA

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Abstract

Significant evidence exists suggesting sleep health is critical for cognitive health in old age. However, both sleep and cognitive health change notably in late life. As such, identifying associations between longitudinal changes in multidimensional sleep health (SH) in older adults and domain-specific cognitive performance and may be critical for a complete understanding of aging's effect on cognition. Comparing risk of cognitive impairment among those whose SH improved with those whose SH declined throughout the study may also show that longitudinal SH changes, rather than cross-sectional measures, are more relevant for risk of cognitive impairment.

Data for this analysis came from the PHRESHZzz and Think PHRESH studies – two ancillaries from the original PHRESH cohort that used a community-based random sampling strategy to enroll participants from two predominantly Black neighborhoods in Pittsburgh, PA. To analyze the association between changing SH and domain-specific cognitive performance, a multidimensional composite SH score was calculated using both subjective and objective measures of several sleep parameters (duration, efficiency, regularity, timing, and satisfaction). Changing SH was modelled using a linear mixed model with SH as the outcome of interest and time as the main predictor. Subject-specific changes in SH (ΔSH) were modelled using the coefficients from a linear mixed model. These estimates of ΔSH were then included in a series of univariate linear

regressions to determine the association between changing SH and cognition. Odds of cognitive impairment were also assessed using the direction of SH change as a predictor of clinically adjudicated cognitive impairment in a univariate logistic regression. Performance in the executive function (B = 1.67 (95% CI: .35, 3.12)), immediate memory (B = 1.42 (95% CI: .06, 2.84)), and language domains (B = 1.55 (95% CI: .23, 3.01)) were significantly associated with more positive ΔSH scores. The odds of cognitive impairment were lower in the SH improvement group (OR = .632 (95% CI: .37, 1.07) although this result was not statistically significant. The public health significance of this project lies in the underrepresented, underserved study population and the analysis of the relationship between sleep health and cognitive health in old age – two major public health issues.

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1.0 Introduction

Decades of research suggest that sleep health is a critical predictor of cognitive health in old age.[1, 2] Sleep has been directly implicated in neurotoxic metabolite clearance,[3, 4] memory consolidation,[5, 6] regulation of immune function,[7] and the body's response to stress.[8, 9] However, understanding the relationship between sleep health (particularly changes in sleep health across the lifespan) and cognition in older adults remains unclear. Large epidemiologic studies have found that nearly half of older adults experience lower sleep quality, lower sleep satisfaction, and a greater number of sleep disturbances compared to younger populations.[1, 2, 10, 11] These studies have found that consistent age-related changes in sleep occur over time such that shortened sleep duration, decreased efficiency, and an increased number of nightly awakenings are common in old age. As a result, older adults tend to struggle more with falling asleep, sleep for shorter periods of time, and experience more fragmented sleep as they age.[1, 2, 11, 12]

Extensive literature also exists regarding age-related changes in cognitive health in old age.[13-15] Declining cognitive performance is expected among older adults, however, cognition is a complex, multidimensional construct often divided into overarching domains of performance, each of which is characterized by the general cognitive processes involved.[16] While age-related cognitive decline has been well documented, the effect of age on cognition is not constant across all cognitive domains.[13, 14, 17] Performance on neuropsychological tasks involving processing speed, short-term memory, visuospatial ability, and attention[13, 15] generally show the most significant deficits in older adults, whereas performance on tasks assessing recall of remote memories and language skills remain stable or even improve over time.[18]

Considering the parallel declines in both sleep health and several domains of cognitive performance in late life and the necessity of spending nearly 1/3 of our lives asleep, understanding the relationship between sleep health and cognition is crucial for understanding cognitive health in old age. Prior literature suggests that the relationship between sleep disturbances and cognitive performance may be bidirectional; sleep quality worsens as cognitive impairment progresses in adults with neurodegenerative disorders [1, 2, 10, 11] and a greater number of sleep disturbances is associated with greater risk for poor cognitive outcomes in old age.[2, 11] However, poor sleep health is also very common among cognitively normal older adults,[1] which raises the following question; is consistently poor sleep health more detrimental to cognitive performance or are changes in overall sleep health more relevant to poor cognition?

1.1 Cognition and Cognitive Impairment in Older Adults

Cognitive performance is typically characterized according to domains of cognitive function. While some disagreements exist in the literature regarding the organization of these domains, particularly between clinical and research literature on broad domains with multiple component processes [16] there is general consensus regarding the domains discussed here. Additionally, this section is not a comprehensive review of all cognitive domains and their assessment, but rather background information for the domains assessed via the neuropsychological testing battery used in this analysis (outlined below in Section 2.4). Although described here as discrete constructs, it is important to note that these domains seldom function independently, particularly on tasks designed to assess higher-order cognitive processes which require reasoning and problem-solving.[16]

Attention is broadly defined as the selection and sustained processing of information[19] and generally refers to an individual's ability to tend to relevant information.[16] It is usually subdivided into selective attention and sustained attention, with selective attention referring to an individual's ability to identify and tend to important information while ignoring nonrelevant stimuli and sustained attention, or vigilance, referring to their ability to maintain that attention over time.[19] Alternatively, sustained attention is assessed via detection of simple stimuli presented within streams of nonrelevant stimuli.[16]

Visuospatial ability refers to an individual's capacity to identify visual or spatial relationships between objects in space.[20] It is measured by an individual's ability to imagine objects, make global shapes out of smaller components, and understand the differences and similarities between objects.[20] Due to its role in navigation and wayfinding (i.e. these skills are critical for the brain's "where" system[17]), visuospatial ability is considered a critical component of functional independence in older adults.[17]

Language skills include both receptive and productive abilities. Assessments of language skills typically evaluate an individual's ability to identify objects by name and understand either verbal or written instructions then respond with behavioral acts.[16] Measures of fluency, object naming, or behavioral responses to verbal instructions are often used to assess this domain. The language domain is also heavily involved with semantic memory and executive function.[21]

Memory is one of the most complex cognitive domains; within are several subdomains with specific assessments for each component process.[6] These subdomains are generally organized into immediate and delayed components. Delayed memory refers to information that has been encoded, stored, and made available for retrieval at a later time.[6, 16] Delayed memory is

usually further divided into episodic, semantic, and procedural memory, each referring to different types of information being encoded for later retrieval.[6]

Conversely, immediate memory, often referred to as short-term or working memory and often considered an executive function, refers to an individual's ability to hold information in consciousness for short periods of time for adaptive use.[16] The ability to use and manipulate this information in the short term has significant implications for executive function.[6] Generally considered the most complex domain, executive function refers to a set of processes which exert control over other component cognitive abilities to enable reasoning, problem solving, and future planning.[22] Assessments of executive function often evaluate cognitive flexibility (considering new strategies and rapidly rejecting failed efforts in response to feedback, also called mental shifting), inhibition or inhibitory control (suppressing predisposed internal responses to external cues), or working memory (manipulating novel information in the short term).[22] By definition, executive functioning is effortful and deliberate; the previously mentioned component processes require conscious input from the individual and active decision-making.[16] Executive function is critical to cognitive, social, and psychological well-being, as well as functional independence in old age.[18]

Neuropsychological testing can assess functional performance across multiple cognitive domains by evaluating performance within specific subdomains.[16, 23-25] Careful construction of a neuropsychological battery can produce measures of domain-specific cognitive function. By evaluating performance across multiple assessments designed to test component processes within a particular domain, a summary score representing an individual's domain-specific cognitive function can then be created.[25] Cognition is a complex, multidimensional construct, therefore

accurate assessments of overall cognitive performance require measures capable of capturing its nuances, particularly when assessing cognition in old age.

As previously mentioned, cognitive decline is expected in old age, but the rate of decline is inconsistent across domains.[18] Evidence suggests the domains most susceptible to age-related changes are those that rely upon quick processing or transformation of information to complete a task, make a decision, or achieve a goal,[14] particularly implicating attention, visuospatial ability, immediate memory, and executive function.[15, 18] While these deficits are generally a product of structural and functional changes in the brain over the lifespan, they are exacerbated by worsening sensory perception in older adults.[26] As mentioned, cognitive decline in old age does not occur uniformly across domains; performance in some domains may remain stable or even improve over time. Cognitive domains which underlie cumulative knowledge and experiential skills, such as episodic and procedural memory and language skills, are generally preserved with old age, although this preservation is heavily influenced by education, occupation, and experiences throughout the lifespan.[14, 18, 26]

While some cognitive decline is expected in late life, cognitive deficits significant enough to classify as either mild cognitive impairment (MCI) or dementia suggest that an underlying neurodegenerative pathology may be present.[14, 18, 26] MCI is defined as substantive decline in one or more cognitive domains beyond expectation given an individual's age, race, education, and occupation with no impairment of functional abilities.[27] Individuals with MCI show increased risk of mortality, loss of independence, and significant socioeconomic struggles.[18] If there is evidence of functional impairment resulting from significant cognitive decline in one or more domains, a dementia diagnosis may be made.[18] Many forms of dementia exist, each the result of a different

neurodegenerative pathology or mix of pathologies, but unspecified dementia is broadly defined within research contexts as a state of cognitive decline sufficient to cause functional impairment.[28]

Although there is a high rate of progression to dementia amongst those with MCI, many individuals remain at the MCI stage and some even regain their baseline cognitive abilities.[27] In these individuals, it is unlikely that an underlying progressive neuropathology is the cause of their cognitive impairment, which underscores the complexity of studying cognitive impairment in older adults. Determining whether cognitive decline is indicative of preclinical MCI or dementia is significantly complicated by the diversity and complexity of neurodegenerative disease etiologies and the incredibly long preclinical periods of these diseases.[1, 10, 27]

Dementia and MCI pose significant public health issues, exacerbated by increasing life expectancies for many populations around the world as a consequence of the global epidemiologic transition.[2, 29] In a 2013 meta-analysis of studies using both clinical and community samples with ≥300 participants conducted among those aged 60 years or older, estimates for MCI prevalence ranged from 16% - 20%, but study authors note that the true prevalence may be even higher today due to underreporting and diagnostic uncertainty.[27] It is also estimated that around 4.2 million adults in the U.S. and nearly 36 million worldwide had all-cause dementia in 2010 and that it is the fifth-largest contributor to the global burden of disease.[28] However, recent epidemiologic studies of large, nationally representative cohorts have found that the age-adjusted prevalence of dementia is actually decreasing in the U.S. and Europe.[28, 30, 31] Study authors identify increasing levels of education and management of key cardiovascular risk factors as the primary drivers of this decline.[32] A 2020 *Lancet* Commission on dementia prevention actually lists 12 potentially modifiable risk factors for dementia: lower education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol

consumption, traumatic brain injury, and air pollution.[32] Decades of research led to the creation of this list, but we aim to show that sleep health was an important omission that should be included for future consideration. Particularly when considering the long preclinical phase of dementia, determining how changes in sleep health associate with cognition in older adults may help identify another important potentially modifiable risk factor for cognitive impairment.

1.2 Sleep Health and Its Relationship with Cognitive Health

As mentioned, a growing body of evidence suggests that sleep is critical for optimal cognitive performance in older adults. While identifying the exact neural mechanisms underlying the relationship between sleep and cognition still requires further study, several explanations have been offered. Considering that older adults tend to struggle more to fall asleep, sleep for shorter periods of time, and experience more fragmented sleep over time,[12] age-related functional changes to brain regions regulating circadian rhythms and the sleep-wake cycle and how they may impact cognition have received particular focus in recent years.[33]

Sleep and circadian rhythms are intricately connected, complex processes regulated by dynamic interactions between several neural substrates, changing gene expression, and the environment.[34] While several brain regions are implicated in the regulation of the sleep-wake cycle, two specific regions in the hypothalamus have been identified as relevant to both age- and dementia-related changes in sleep: the ventrolateral preoptic area (VLPO) and the suprachiasmatic nucleus (SCN) of the of the anterior hypothalamus.[34] Studies in animal models suggest that the VLPO plays a role in sleep maintenance via its inhibitory projections to arousal areas of the brain and that lesions in this nucleus result in significant sleep fragmentation.[35] Alternatively, the SCN

is considered an essential mediator of humans' circadian clocks by functioning much like an oscillatory pacemaker within the brain.[33, 36] By generating rhythmic electrical activity in response to external light cues from the retina, synchronizing signals from the SCN help dictate the phases of "peripheral clocks" (i.e. those functioning in other tissues such as the liver, heart, and muscles) which play a critical role in the sleep-wake cycle.[33, 34, 37] Functional changes in these two hypothalamic nuclei are thought to be relevant to disrupted sleep-wake cycles observed in older adults; deterioration of the VLPO may underlie the shortened, less efficient sleep often seen in older adults whereas degeneration of the SCN may drive their changing sleep pattens (i.e. decreased duration and regularity of sleep).[38]

Sleep deprivation and fragmentation have also been shown to induce structural synaptic changes in rodents.[39] The number of dendritic spines (the major postsynaptic site of excitatory glutamatergic neurotransmission[40]) greatly decreases in response to sleep deprivation, particularly in the hippocampus.[39, 40] Dendritic spines have important implications for synaptic regulation and cognition[41] and a decrease in spine density has been shown to be detrimental to hippocampal-dependent memory consolidation (i.e. storage of information in long-term memory) occurring during sleep.[40] These declines are thought to occur with acute sleep deprivation (i.e. 5 hours of extended wakefulness), however, chronic sleep restriction and disruption have been shown to associate with significantly decreased hippocampal volumes in humans with insomnia.[42] While the exact mechanism underlying this reduction in hippocampal volume in humans requires further study, it is possible that these transient reductions in dendritic spine density in response to acute sleep deprivation may persist as an individual is chronically sleep deprived across their lifespan.[39] In older adults, this provides a potential explanation for declining performance on memory-based tasks over time; as sleep duration decreases across the lifespan due to functional changes in brain

regions which dictate sleep-wake cycles, hippocampal-dependent memory consolidation worsens as a result of declining dendritic spine density over time and memory deficits become more pronounced. However, further study is required to confirm this hypothesis.

Sleep has also been implicated in metabolic homeostasis as a regulator of the drainage systems which facilitate clearance of neurotoxic waste products such as β-amyloid (Aβ), α-synuclein, and tau.[3] Via the glymphatic drainage system, cerebrospinal fluid (CSF) is recirculated through the brain, interchanging with the interstitial fluid (ISF) surrounding brain cells in order to clear the previously mentioned neurotoxic proteins which have been implicated in various neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.[3, 4] Impairment of the metabolic waste clearance system may underlie the significantly worsening sleep health of individuals with neurodegenerative diseases as they progress.[43] As these neurotoxic proteins accumulate, cell loss in brain regions involved in the maintenance of sleep (i.e. the VLPO) and the rhythmicity of the sleep-wake cycle (i.e. the SCN) leads to further deterioration of the individual's sleep health. As their sleep health continues to decline, glymphatic clearance worsens even further and pathophysiological changes advance as a result of this damaging positive feedback loop.[43] While this proposed mechanism for worsening sleep health provides a potential explanation for the significantly impaired sleep health observed in older adults with neurodegenerative diseases, it is unclear whether declining sleep health is a cause or consequence of the aforementioned neuropathology.

While the structural and functional implications of poor sleep have received more attention in recent years, literature on the specific neuroanatomical changes associated with consistently poor sleep health across the lifespan remains limited. At present it is unclear whether neuropathology associated with preclinical dementia causes poor sleep health in old age or if poor

sleep is a preceding risk factor for the initiation of neurodegenerative pathology. However, mounting evidence suggests that poor sleep health in old age is associated with worse cognitive health in older adults.[1, 10-12, 14, 26, 38, 44, 45] Exploring this relationship is critical for understanding the role of sleep in cognition. Does poor sleep health only impact certain cognitive domains? Is consistently poor sleep health associated with worse cognitive performance or are changes in sleep health more indicative of poor cognitive outcomes? How do we even define "poor" sleep?

1.3 Sleep Health as a Composite Measure

The idea that sleep can be assessed by simply measuring how long someone sleeps regularly has been challenged in recent years. Buysse et al. (2014) argues for a reevaluation of sleep research; instead of limiting itself to sleep disorders or insufficiencies, Dr. Buysse suggests that sleep research shift its focus to "sleep health" as an assessment of overall quality and wellness, rather than the mere absence of disorder. As Dr. Buysse states, "good sleep is essential for good health" but how good sleep has been defined and assessed in sleep research has been limited. Sleep can be assessed across multiple levels of analysis and past studies have found that several measurable characteristics of sleep are clearly associated with physical, mental, and neurocognitive wellbeing.[46] He proposes a multifaceted construct of sleep health combining both subjective and objects measures of sleep's various dimensions such as duration, timing, efficiency, satisfaction, and alertness. While these dimensions of sleep are associated with several specific health outcomes, he does emphasize that there are many other potential dimensions that can be measured.[46] The importance of a multidimensional measure of sleep health lies in its ability to define "good" vs. "poor" along multiple lines of analysis, reframe sleep health as a continuous

measure that can also define "better" vs. "normal," and more comprehensively measure a universal behavior with significant implications for health and well-being.

While a comprehensive review of all components of sleep health are beyond the scope of this paper, the various dimensions used in this analysis are defined and supported by evidence for their association with cognitive health in older adults in the following sections. In this analysis, sleep duration, efficiency, timing, regularity, and self-reported sleep satisfaction/quality are used to construct a composite sleep health (SH) score, with specific thresholds determined based on a priori knowledge of "good" vs. "poor" sleep (outlined below in Section 1.1).

Furihata et al.(2016) use a similar aggregate measure of self-reported sleep quality spanning 5 dimensions (satisfaction, daytime sleepiness, mid-sleep time, sleep onset latency, and duration) to determine whether self-reported sleep was significantly associated with prevalent and incident depressive symptoms in older women.[47] Desantis et al. (2016) use different waves of the same cohort used in this analysis (the PHRESH cohort described in Section 2.1 Study Population) and a similar methodology for constructing the composite SH measure (described in Section 2.3 Composite Sleep Health Score) to determine whether the association between neighborhood-level factors and sleep quality is mediated by psychological distress.[48] The same group used the same SH score construction in a later analysis published in 2019; however, they also performed analyses using the individual sleep dimensions as predictors in linear regressions of SH with psychological distress, BMI, and physical functioning as well as the overall SH score.[49] Similarly, Bowman et al.'s 2021 paper on the longitudinal association of depressive symptoms and multidimensional sleep health from the SWAN sleep study found that higher depressive symptoms were associated with subsequent poorer overall SH, lower alertness, and satisfaction over time.[50]

To our knowledge, this analysis is the first use of a composite SH metric being applied to longitudinal sleep data in this way. By creating a subject-specific measure of changing SH over time, we are able to determine how changes in SH over time associate with domain-specific cognitive performance measured at a later time. However, identifying which dimensions of sleep health are relevant to cognitive performance in older adults is critical to constructing an appropriate SH score.

1.3.1 *Total Sleep Time and Cognition*

Both short[51-53] and long[10, 11, 51] sleep duration have been shown to associate with poorer overall cognition, risk of dementia, and a host of other adverse health outcomes in cross-sectional studies.[54] While several mechanisms have been proposed for how short sleep duration or insufficient sleep are associated with cognition (i.e. adverse memory formation and consolidation,[51] reduced metabolite clearance,[54] impaired attention,[38, 52, 55-57] and compromised executive function[57, 58]), it is still relatively unclear how long duration associates with dementia risk and cognition mechanistically. Longer sleep duration has been identified as a potential biomarker of dementia with a confounder (such as depression or another sleep disorder) potentially increasing sleep need. [10, 12, 38] However, a causal relationship between long duration and poor cognition is yet to be established. This evidence suggests a possible U-shaped association exists between duration and cognition; healthy adults sleeping less than 6 hours per night and those sleeping more than 8 hours per night tend to show significantly more risk for cognitive decline in comparison to their "normal duration" counterparts (those who consistently get 6 – 8 hours of sleep per night).[59] Evidence for sleep duration's relationship with cognition and risk of cognitive impairment has also been shown in longitudinal studies of aging.[45, 60]

1.3.2 *Sleep Efficiency and Cognition*

Another important component of SH is sleep efficiency (SE), defined here as objectively measured sleep duration divided by the total time spent in bed, as reported by sleep diaries. Sleep efficiency provides a valid measure of sleep disturbance throughout the night which provides insights on an individual's specific sleep-wake pattern and ability to maintain sleep.[60] In Blackwell et al.'s longitudinal study of 2932 women in the Study of Osteoporotic Fractures (SOF) ancillary sleep study, SE was significantly associated with poorer performance on both the Modified Mini Mental State Exam (MMSE; a measure of global cognitive function with components for orientation, concentration, language, praxis and immediate & delayed recall), and Trail Making Test Part B (a validated measure of attention, sequencing, visual scanning, and executive function).[51] Although the threshold used for unhealthy SE was lower in this study compared to the threshold defined in this analysis (Blackwell et al. used ≤70% SE as the defined cut point whereas here we use ≤85%), those who were below this threshold took 9.15% longer (95% CI: 2.41, 28.73) to complete the Trails B task and had a 1.9% (95% CI: 1.38, 2.26) lower score on the MMSE.

Similarly, Bernstein et al (2019) analyzed the cross-sectional association of objectively measured sleep and cognitive functioning in older adults (n=489) and found that poorer SE was associated with poorer conceptual flexibility in both younger and older adults.[61] Although literature on its inclusion in an overall SH score is limited, several studies have analyzed SE as an independent predictor and found significant associations with between lower SE and poorer performance on tasks assessing executive function, attention, and orientation.[61-63]

1.3.3 *Sleep Regularity and Cognition*

As previously mentioned, sleep studies focusing on older adults' sleep-wake cycles suggest that circadian rhythms may degenerate somewhat over time (i.e. older adults' daily sleep-wake patterns become less closely synchronized to external cues leading to irregular sleep durations over time).[36, 52, 53, 56] Additionally, the various lifestyle changes that come with aging (changing social roles, fewer responsibilities in retirement, different caregiving responsibilities, etc.) may also influence changing sleep patterns.[12] As such, sleep regularity (SR; defined here as the within-person standard deviation in objectively measured sleep duration) is thought to increase over time. In other words, sleep becomes more irregular in older adults as the standard deviation of their average nightly sleep duration increases with age. In prior insomnia treatment studies, an SR $\geq$ 60 min was used as the threshold to differentiate individuals with insomnia from their healthy counterparts.[62, 63] There is a significant paucity of research on the specific relationship between SR and cognition, but its inclusion in our composite SH score calculation is necessary considering its ability to capture information regarding the regularity of an individual's sleep-wake patterns.

1.3.4 *Sleep Timing and Cognition*

Another important component of healthy sleep focuses on which hours of the 24-hour daily cycle are spent sleeping. Sleep timing (ST), defined in this analysis as the midpoint between sleep onset and final awakening according to analysis of actigraphy data during the sleep period, has important implications for the body's circadian rhythm and natural sleep-wake cycle.[48] As noted above, disrupted circadian rhythms and breakdowns in the regularity of the sleep-wake cycle have been associated with increased risk for a variety of adverse health outcomes.[33, 49, 59, 60] But

evidence suggests that older adults who go to bed later (even if they do so regularly) may be at a similarly increased risk.[50] Evidence for these associations come from the University of Manchester's Longitudinal Study of Cognition in Normal Healthy Old Age. In a 2019 study of sleep chronotype (i.e. daily sleep preferences), Didikoglu et al. found that over the extended follow-up period (up to 35.5 years for a significant proportion of the 6375 participants initially enrolled) those with a later sleep chronotype showed higher risk for hypertension, decreased socialization, depression, diabetes, and all-cause mortality. Additionally, those with regularly delayed sleep schedules (i.e. bedtime procrastinators) and shift workers also showed increased risk for a host of adverse health outcomes.[60] While ST has not been used as an individual predictor of cognitive performance in previous literature, it reflects a critical component of the sleep-wake cycle which has been previously implicated in changing cognition in older adults.[10, 12, 38]

1.3.5 *Sleep Satisfaction and Cognition*

The final component of composite SH considered in this analysis is subjective sleep satisfaction. Sleep satisfaction (an inherently subjective measure) has physiologic correlates to slow-wave sleep and EEG delta activity, two objective measures of deep sleep.[46] In older adults, particularly those with cognitive impairment, concerns regarding the accuracy of individuals' sleep-reports have been realized in studies comparing the differential relationships of objective and subjective measures of sleep quality.[48] Prior research has shown that the validity of perceived satisfaction as a standalone assessment of overall sleep quality in older adults with significant cognitive decline is limited, considering the potential for misreporting.[54] However, it is still an essential component of overall SH that's been shown to associate with aspects of executive functioning. Bernstein et al.'s 2019 analysis of 489 adults who completed one week of actigraphy-

measured sleep and a self-reported sleep measure found that subjective sleep quality was associated with poorer conceptual flexibility and global executive function in older adults.[49]

1.4 Summary of Major Gaps in Literature

While sleep research and studies of sleep's role in cognition across the lifespan have garnered significant attention in recent years and decades, significant gaps in the literature still exist. Recent technological advances have also made the collection of objectively measured sleep data in large samples more feasible.[61] But limitations related to both sample size and sleep assessment persist; many large epidemiologic studies still rely solely upon self-reported sleep, and many of those who do use objective assessments of sleep are underpowered.[64] As previously mentioned, subjective sleep measures have shown internal validity in studies on the relationship between sleep and cognition, particularly with measures of executive function.[54] They are also essential components of overall sleep health because they represent an individual's beliefs about the sleep they obtain, as opposed to the actual sleep hygiene and obtained sleep captured by objective measures.[61] However, previous studies have shown that older adults, particularly those with cognitive impairments and decreased functional capacities, are at a higher risk for misestimating their sleep quantity and quality compared to younger adults.[65] Therefore, sleep studies which exclusively rely upon subjective measures of sleep in older adults are prone to information biases resulting from misreporting and misclassification.[66] In recent years, these issues have led to calls for the increased use of both objective and subjective measures of sleep health in sleep research, particularly in studies on aging and cognition.[67]

Previous studies on sleep and cognition have also been limited by the use of single age groups (i.e. no cross-sectional comparators),[61] singular measures of global cognition (i.e. MMSE as main cognitive outcome measure),[38] and the inclusion of "unhealthy" adults only (i.e. those with a sleep disorder or some form of cognitive impairment).[1, 61] As such, studies on community-dwelling older adults with multifaceted predictors and outcomes are critical for the advancement of research on the role of sleep in cognitive health.

Finally, research on aging and cognitive health have well-documented issues with under-representation of highly vulnerable minority populations.[68, 69] By and large, most samples in aging and dementia research are white, educated, and of high socioeconomic status [68, 70] While decades of research have characterized the trajectory of impairment-free normative cognitive aging, participants in aging and dementia research in the U.S. have been overwhelmingly white historically.[70] This is problematic because between group differences in socioeconomic status, healthcare quality and access, and educational quality and attainment likely influence racial and ethnic differences in cross-sectional performance on neuropsychological testing.[71] However, representation issues have made race/ethnicity-specific normative standards in cognitive health research difficult to establish for minority populations.[69] There is also a significant lack of attention regarding methodological issues related to the recruitment and retention of racially diverse samples, further perpetuating vulnerable populations' issues with underrepresentation in geriatric research.[70]

In the U.S., health disparities (referring to between group differences in disease burden) and healthcare disparities (referring to differences in health insurance coverage, quality of care, and healthcare access/utilization) are some of the most severe among all wealthy nations.[72] Minority groups in the U.S. are particularly vulnerable as a consequence of complex and

interrelated social, economic, and environmental factors.[72] While there has been a more concerted effort to identify and address these disparities through research in recent years, there is still a severe paucity of research on aging processes and changes in cognitive health over time among highly vulnerable populations.[70]

1.5 Aims and Hypotheses

Aim 1: To assess how longitudinal changes in individual SH associate with domain-specific cognitive performance assessed at the end of follow-up in a highly vulnerable sample of community dwelling older adults. This will be done by modelling the subject-specific change in composite SH from 2013-2018 then analyzing its association with domain-specific measures of cognitive performance measured in 2019-2020.

H1: Improvements in SH (i.e. positive SH per year) will correlate with better performance in the executive function, immediate memory, and attention domains in line with prior literature regarding the relationship between sleep and these domains.[5, 18, 38, 40, 52, 57, 73-75] Changing SH and performance in the delayed memory, language, and visuospatial domains are unlikely to show an association with composite sleep health considering the lack of evidence supporting a relationship between SH and these domains.

Aim 2: Determine how changing SH relates to risk of clinically adjudicated cognitive impairment by using longitudinal regression to assess the risk of cognitive impairment among those whose SH improved vs. those whose SH declined.

H2: Risk of cognitive impairment will be significantly lower among those with a positive ΔSH (i.e. those whose SH improved over study time) compared to those with a negative ΔSH (or

those whose SH declined) as evidenced by the wealth of literature demonstrating declining SH among those with cognitive impairment.[1, 10-12, 53, 76, 77]

2.0 Methods

2.1 Study Population

The study population used for this analysis comes from the Pittsburgh Hill/Homewood Eating, Shopping, and Health (PHRESH) cohort. PHRESH is an NIH-funded study designed to analyze how revitalization efforts in one of the neighborhoods (the Hill District) impacted residents' health outcomes in relation to residents of the other neighborhood (Homewood) by recruiting a random sample of households from both. Both Homewood and the Hill District are low-income, predominantly African American neighborhoods in Pittsburgh, PA, and until 2013, both were also food deserts. At that time, the Hill District opened its first full-service grocery store as a part of its economic revitalization efforts and has since received significant investment for housing and greenspace renovations and improvement. The PHRESH Study was originally conceived as a natural experiment on the influence of neighborhood conditions on health.

The original PHRESH cohort included a randomly selected sample of households from Homewood and the Hill District drawn from a full list of residential addresses in both neighborhoods generated by the Pittsburgh Neighborhood and Community Information System. Participants were recruited for the original PHRESH cohort beginning in 2011 via door-to-door recruitment by neighborhood data collectors (residents of these neighborhoods recruited and trained to enroll selected households). The primary food shopper was recruited, resulting in a predominantly female sample. Data used in this analysis were collected in two of the PHRESH Study's ancillary projects; the Pittsburgh Hill/Homewood Research on Neighborhood Change and Sleep study (PHRESHZzz) and the Think PHRESH cognitive outcomes study.

PHRESHZzz invited participants to undergo 7 days of continuous sleep assessments in three separate waves (2013, 2016, and 2018) with all sleep data collected via wrist actigraphy and daily sleep diaries (described below in Section 2.2). The Think PHRESH ancillary study then recruited participants from the PHRESHZzz sample (those with at least one wave of sleep and blood pressure assessments in 2016 or 2018) to complete a comprehensive neuropsychological assessment battery. Data collection for Think PHRESH occurred between March 2019 – February 2020. All study participants provided informed consent and all study protocols and procedures were approved by RAND Institutional Review Board.

2.2 Actigraphy-based Sleep Assessment

PHRESHZzz used the Actigraph GT3X+, which has been validated as a measure of sleep-wake cycles in accordance with both polysomnography and other forms of wrist actigraphy.[64] Participants were instructed to wear the device on their non-dominant wrist for 7 consecutive days and complete a daily sleep diary over the same time period. Data were then separated into sleep and wake periods using data on bedtimes and waketimes from the diaries then further confirmed via visual inspection of the actigraphic recordings. Sleep data were then scored using the Cole-Kripke algorithm to determine sleep and wake periods before primary sleep measures were derived (described below). These sleep measures were then averaged across all nights of each assessment period to establish an estimate of normal sleep-wake cycles across all available nights of data collection.

2.3 Composite Sleep Health Score

Formulation of the composite SH score followed a similar methodology to Desantis et al.'s analysis.[49] Support for the selected thresholds delineating "healthy" vs. "unhealthy" ranges for each sleep parameter are provided in Introduction (Section 1.3). Briefly, the composite SH score was calculated by assigning a value of 1 for those who fell within the "healthy" range and 0 for those who fell in the "unhealthy" range then calculating the sum of all sleep parameters to produce a summary score with a range of 0 to 5 representing overall SH. The thresholds used here are:

- *Total Sleep Time (TS):* measured as total time asleep from actigraphy trace
  - 0 = average sleep duration <6 hours or >8 hours
  - 1 = average sleep duration ≥6 – 8≤ hours
- *Sleep Efficiency (SE)*: measured as total sleep time divided by total time in bed according to daily sleep diary
  - 0 = < 85% efficiency
  - 1 = ≥ 85% efficiency
- *Sleep Regularity (SR):* measured as standard deviation for within-person total sleep time over the week of data collection
  - 0 = standard deviation ≥ 60 min.
  - 1 = standard deviation < 60 min.
- *Sleep Timing (ST):* measured as midpoint between sleep onset and final awakening on actigraphy trace
  - 0 = midpoint at 4:00 am or later
  - 1 = midpoint prior to 4:00 am

- *Sleep Satisfaction (SS):* measured by diary-assessed rating of sleep quality on a 5-point Likert scale (0 = "Very poor" to 5 = "Very good") following each night of actigraphy
    - 0 = average rating < 4
    - 1 = average rating ≥ 4

While our and Desantis et al.'s analyses[49] of composite SH are both based on Buysse's conception of a multidimensional SH construct,[46] neither include a measure of daytime alertness, a notable deviation from Dr. Buysse's original concept. Although our parameters vary slightly, the predictors used in our analyses still provide a comprehensive measure of overall sleep health, especially in comparison to analyses which rely upon a single measure of sleep.

2.4 Neuropsychological Testing Battery and Domain-Specific Z-scores

Think PHRESH participants completed the neuropsychological battery described below (Table 1). Trained study personnel administered all tests either in-home, at the PHRESH field office, or at one of Pitt's Community Engagement Centers (whichever the participant preferred).

Z-scores for each cognitive domain were calculated using a regression-based norming approach based on the distribution of aggregated scores on neuropsychological tasks assessing the same domain and adjusted for within-sample age, gender, and years of education.

Table 1: PHRESH Cognitive Assessment Battery

Domains	**Neuropsychological Assessment(s)***
Attention	Digit Span Subtest (WMS-III),[78] Digit Symbol Coding Total and Copy Scores (WAIS-III)[78]
Visuo-Spatial Ability	Visual Reproduction Copy (WMS-III)[78]
Language	Boston Naming,[79] Letter Fluency,[23] Category Fluency[79]
Immediate Memory	Logical Memory I (WMS-III),[78] CERAD Word List Learning,[80] Visual Reproduction (WMS-III)[78]
Delayed Memory	Logical Memory II (WMS-III),[78] CERAD Word List Learning[80], Visual Reproduction Delayed Memory
Executive Function	Ratio of Trail Making Test Part B to Part A time, [23] Golden Stroop Color-Word Test,[23] Digit Ordering Test,[81] Clock Drawing Test

***A detailed description of each assessment provided within the respective listed references**

2.4.1 *Cognitive Impairment Adjudication*

A common method for determining cognitive impairment indicative of dementia in research uses neuropsychologic assessment; an individual's performance on a neuropsychological assessment battery is compared to their expected performance.[25] This expected performance is based on a normative standard adjusted for various sociodemographic factors (here, those factors were education, race, and occupation).[25] In this analysis, a team of neuropsychologists and a psychiatrist reviewed all participants' cases to perform clinical adjudications of cognitive impairment. Any individual who performed more than 2 standard deviations below expected on any of the neuropsychological tasks and met other criteria agreed upon by the clinical group was

classified as having either no cognitive disorder, MCI, or dementia. In addition to performance on the cognitive battery, all clinically relevant criteria were considered by the group such as proxy reports on cognitive and behavioral changes, participant behavior during the study visit, subjective complaints of impairment, literacy, educational attainment, occupation, etc. Consensus within the group had to be reached for an adjudication to be made.

Very few of the subjects were classified as having dementia during the adjudication meetings. In the interest of preserving sample size, the 4 individuals classified as having dementia were combined with the 110 MCI cases as a generalized "cognitively impaired" group (N=114).

2.5 Individual Level Covariates

Prior to starting the 7-days of actigraphic sleep assessment at each wave of data collection, participants completed an in-person interview with study personnel to assess sociodemographic variables such as age, household income, neighborhood of residence, education, and complete other assessments of relevant health covariates. Psychological distress was assessed by the Kessler 6 (K6) scale. The K6 is a validated assessment that asks participant, "During the last 30 days, about how often did you you feel…" "hopeless?" "restless or fidgety?" "that everything was an effort?" "nervous?" or "worthless?" Higher scores are indicative of greater distress with participants responding on a scale of 1 (none of the time) to 4 (all of the time). Ratings were summed to create a composite score with a range of 0 – 24. In this analysis, a score ≥8 was used to create a dichotomous variable indicating the presence or absence of psychological distress.

Additionally, participants were asked, "Did you take any sleep medication to help you fall asleep tonight? (yes or no)" in the daily sleep diaries they were asked to complete. Based on this

response, sleep medication usage was included as a dichotomous covariate indicating sleep medicine usage at any timepoint during data collection. A complete list of the relevant demographic variables and health behaviors used in this analysis are listed below in Table 2. The variables included in this analysis are mostly from the 2018 wave of data collection, as this was the closest timepoint to the completion of the neuropsychological assessments, the greatest proportion of participants had complete covariate data at this time point, and these variables generally did not change across the 3 waves of data collection. The main exceptions are age at baseline, as this was determined from the age at the first study visit, or 2013, in order to establish age at baseline, and the education variable, which was measured continuously at the Think PHRESH neuropsychological evaluation.

2.6 Statistical Analyses

All statistical analyses were performed using SAS 9.4. The mean (with standard deviation), median (with interquartile range), or *N* (percent) of each individual-level covariate was calculated for the study sample. The proportions of individuals falling in the "healthy" range of each sleep parameter included in the composite SH score were compared using a Chi square test of homogeneity. The distributions of SH score at each wave of data collection were also compared using histograms.

A linear mixed model including a random intercept and time in years as a random effect was constructed using composite SH score as the outcome of interest. Time was coded as the number of years from baseline, defined here as the date at each participant's interview at their first wave of sleep data collection. With time encoded this way, baseline was not the same for all

participants. The interview date of a participant's last wave of sleep data collection was encoded as the end of study time in this analysis, so the LMM models change in SH across the years of sleep data collection.

Age at baseline, sleep medicine usage, psychological distress (defined as a score ≥8 on the K6 self-report assessment of non-specific psychological distress), neighborhood, and educational attainment were all included as covariates in the model. Although only inclusion of age at baseline contributed significantly to model adequacy, all covariates were kept in the model based on *a priori* knowledge regarding the association of these covariates and SH. The neighborhood indicator variable was included as a study design variable to control for the PHRESH sampling strategy.

The final model used in this analysis is included below:

Model 1:

$$SH_{ij} = \beta_0 + \beta_1 * age_{ij} + \beta_2 * sleepmeds_{ij} + \beta_3 * psychdistress_{ij} + \beta_4 * neighborhood_{ij} + \beta_5 * education + \beta_6 * time_{ij} + b_{0i} + b_{1i} * time$$

In the model above, the subscript *i* represents the *i*th individual and the subscript *j* represents the *j*th time point. b_{1ij} corresponds to the subject-specific random effect of time on composite SH score (i.e. b_{1ij} = ΔSH - $\beta_{6,}$ or the subject-specific deviation of change in SH composite score per year from the sample average). b_{0ij} represents a random intercept, or the subject-specific difference in SH score at baseline as estimated by the model.

By including time as both a fixed and random effect, the coefficients obtained from the model provide information regarding the influence of time on SH, for each subject as well as the overall sample. Fixed effects in a linear mixed model represent the average change in the outcome of interest in the entire sample for each 1-unit change in the continuous predictor (i.e. the fixed

effect of time represents the average effect of a 1-year increase in time on SH). Conversely, random effects are subject-specific and dependent upon the slope of each individual's change in SH score over time. The coefficient for a random effect in a linear mixed model represents each subject's deviation from the sample average change in the outcome over time. The sum of a model's fixed and random effect coefficients estimate the subject-specific change in the outcome per unit time.

Using the time variable as an example, the fixed effect of time would be the average change in SH score per 1-year increase in time across the whole sample. The random effect of time represents each subject's deviation from that average change in SH score. For each subject *i* at every timepoint *j*, the change in SH score per year can be modelled via the following calculation:

$$\Delta SH = b_{1ij} + \beta_6$$

This calculation was performed for each subject, then used to create a new variable (ΔSH) representing each individual's change in SH score per year of the study period. A similar calculation was performed to estimate each subject's baseline SH using the random and fixed effects of the intercept.

An unstructured G matrix was used to specify the variance-covariance structure of the random effects included in this model (intercept and time). This matrix represents the variance-covariance structure used to model the variance in ΔSH (i.e. the between-subject variability in ΔSH) and the covariance between their deviation from the sample mean baseline SH (i.e. the random intercept from LMM) and ΔSH (i.e. the random effect of time.) It is subject-specific and allows the model to account for baseline SH score when estimating overall ΔSH by including the covariance between the subject-specific random intercept and random effect of time. This greatly increases the complexity of the model because an unstructured G matrix accounts for the

dependence between individuals' baseline SH and ΔSH. It also does not assume a specific mathematical relationship between them, but rather, models the relationship between them as a function of their actual covariance.

To determine whether declining SH increased risk for cognitive impairment, an indicator variable was created to indicate whether a subject's ΔSH was positive or negative. This variable was assigned a value of 1 for those with a positive ΔSH (i.e. SH improvement) and 0 for those who had a negative ΔSH (i.e. SH decline) then used in a univariate logistic regression with cognitive impairment used as the outcome of interest. No participants had an exact ΔSH = 0, so all participants were assigned either a 0 or 1 representing SH decline or improvement, respectively. A Fischer's Exact Test was used to assess whether the rows and columns of the SH improvement/decline by cognitive impairment status were truly independent.

3.0 Results

Sociodemographic characteristics and relevant covariates are described below in Table 3. In the final analytic sample, mean age at first sleep assessment was 60.3 years (±9.20). As a reminder, for anyone who did not have valid sleep data at the 2013 wave of data collection, their 2016 data were used as baseline (N = 51). Nearly 83% of the sample were female and over 95% were African American. Median household income at baseline was $12,500 with an interquartile range (IQR) of $17,500 indicating that income was widely dispersed in this sample. The 75th percentile of household income was $25,000, just below the 2020 federal poverty line for a family of 4 ($26,500)[82] indicating that a significant proportion of this sample come from a low socioeconomic background. Education also varied significantly across the sample. Measured continuously as years of school completed, mean educational attainment was 12.6 years (±2.24) and ranged from 5 to 20 years in this study sample. Additionally, 67.1% of the PHRESH sample were residents of the Hill District neighborhood, 15.6% had taken sleep meds at any time during data collection, and 18.6% were classified as having psychological distress on the Kessler 6 questionnaire (i.e. scored ≥8, described in Section 2.5).

Table 2: Sociodemographic Characteristics and Covariates Included in Linear Mixed Model (Measured at Time of Neuropsychological Testing)

Sociodemographic Factor n = 243	**Mean (SD), Median (IQR), or N (%)**
Age at baseline*	60.3 (9.20)
Female	201 (82.7%)
African American	231 (95.1%)
Median Annual Household Income	$12,500 (17,500)
Hill District Residents	163 (67.1%)
Years of Education	12.6 (2.24)
Other Relevant Covariates	
Took Any Sleep Medications	37 (15.6%)
Psychological Distress	45 (18.6%)

***Baseline defined as first PHRESHZzz study visit**

Table 3, below, lists the proportion of the sample who met the "healthy" threshold in each sleep parameter as well as the mean SH score at each wave of data collection. Sleep efficiency and duration had the lowest proportion of individuals classified in the "healthy" range; however, these parameters did not show similar longitudinal trends. The proportion of individuals who met the sleep efficiency criteria (those who slept ≥85% of the time between going to bed and waking up) declined significantly over the course of the study. Considering that mean SH score also varies significantly across the waves of data collection, worsening sleep efficiency in a large proportion of the sample may be a significant contributor to the change in mean SH over time. While individual sleep parameters were not used as predictors in this analysis, this finding is unsurprising considering the extensive literature showing that sleep

efficiency decreases in old age as nightly sleep disruptions become more common.[1, 10-12, 33, 38, 83, 84]

Table 3: Sample Size, Proportion of Sample in "Healthy" Range by Sleep Parameter, Mean SH Score by Waves of PHRESHZzz Data Collection

Parameter N_{total} = 243	**2013** N = 192	**2016** N = 226	**2018** N = 216	**p-value**
Duration	36%	34.6%	33.9%	.86
Efficiency	35.5%	14.3%	9.6%	<.0001
Regularity	58.9%	55.9%	61.3%	.51
Timing	59.4%	67.7%	65.7%	.18
Satisfaction	43.6%	42.1%	46.3%	.65
Mean SH Score (SD)	2.33 (1.41)	2.14 (.94)	2.16 (.95)	<.0001

While it's clear that mean SH does change over the study period, the magnitude and trajectory of that change is not constant over time and the influence of individual longitudinal changes in SH is unclear. Visual inspection of the distribution of mean SH score at each wave of data collection (shown below in Fig. 1) does show a notable increase in the proportion of lower scores at each successive wave of data collection, suggesting that SH may be declining in a significant proportion of subjects. However, modelling individual trajectories of SH via LMM provides an estimation of both the magnitude and direction of those changes for each subject over time. From this information, we can determine whose sleep improved or declined and by how much and how those changes associate with cognitive performance.

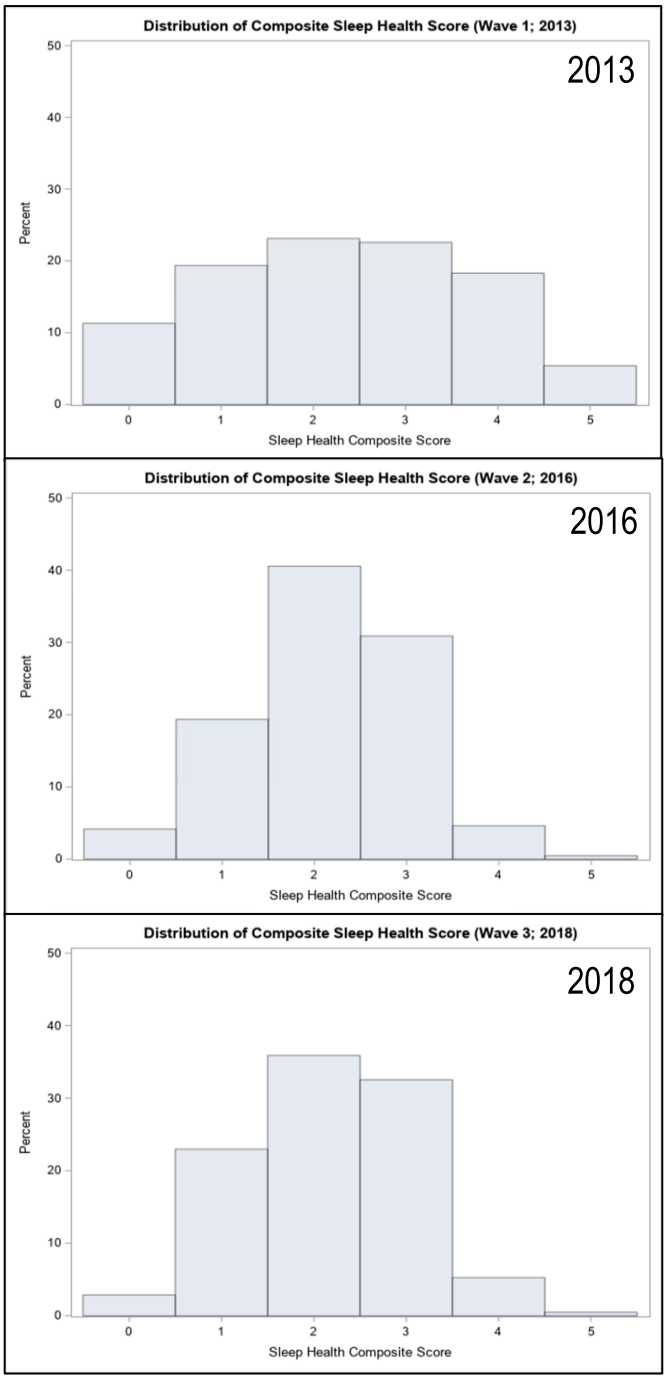

Figure 1: Distribution of Composite SH Score by Wave of Data Collection

3.1 Linear Mixed Model: Modelling the Effect of Time on SH score

Table 4: Coefficients for the Fixed Effects Included in Model 1 - Time as Main Predictor of SH, Adjusted for Relevant Covariates

Parameter	Model Coefficient (SE)	p-value
Intercept	1.44 (.42)	.009
Time	-0.026 (.02)	.23
Age at baseline	0.013 (.01)	.03
Sleep Medicine Usage	-0.26 (.15)	.09
Psychological Distress (K6 score ≥8)	-0.05 (.14)	.72
Neighborhood	0.12 (.12)	.21
Education	-0.002 (.03)	.93

The estimates above in Table 4 for the fixed effects included in Model 1 can be interpreted as the average difference in composite SH score for each 1 unit increase in the predictor in question for the continuous variables listed. For example, each year in the study was associated with a .026-point decline in average SH score across the sample. Although the fixed effect of time was not a statistically significant predictor of SH (i.e. there was a significant difference in how SH changed from year to year between subjects), the statistically significant difference in SH between the 3 waves of data collection and the negative value for the Time coefficient suggest that SH is declining on average over time in this sample.

Figure 2 shows the distribution of baseline SH score across the sample. The estimate for the fixed intercept indicates that the average SH score at baseline in this sample was 1.44. Of note, the

fixed intercept of this model was statistically significant, indicating that there was significant heterogeneity in composite SH score at baseline. A statistically significant fixed intercept suggests that including a random intercept was appropriate. A random intercept in an LMM allows the model to assume significant variability in baseline SH score and adjust estimates for change in SH by accounting for this variability.

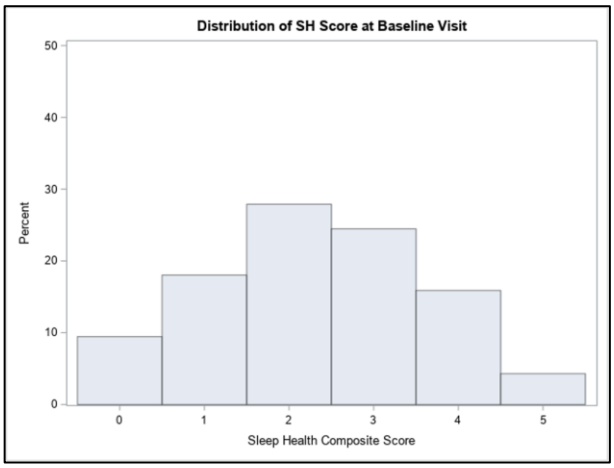

Figure 2: Distribution of Individuals' Baseline SH Score

It should be noted that an intrinsic relationship between ΔSH and baseline SH score exists such that those who scored a 5 at baseline could technically only have a negative ΔSH while the opposite is true for those who scored 0 at baseline. In addition, those with a higher SH at baseline are capable of experiencing a more significant decline over time (i.e. their range in ΔSH is larger and more negatively skewed than those with a low baseline SH). They are also more likely to experience those declines considering more components of their multidimensional SH score could potentially dip below the predefined thresholds and lower their score. Figure 3 above shows that nearly 10% of the study sample had an SH score of 0 at baseline and about 5% had an SH score of 5. To account for the true covariance between baseline SH and ΔSH, the linear mixed model used

in this analysis included an unstructured G matrix variance-covariance structure. A more detailed description of the variance-covariance structure used can be found above in Section 2.6. In brief, using an unstructured variance-covariance structure allows the model to account for the natural covariance between a subject's random intercept and the random effect of time, adjusting model estimates to reflect this dependence.

3.2 Estimation of ΔSH from LMM and Associations with Domain-Specific Z-score

In order to address aim 1, each subject's ΔSH was calculated using a linear mixed model including a fixed and random effect of time. Figure 2 below shows the distribution of ΔSH from the linear mixed models in this sample. The calculation for ΔSH can be found above in Section 2.6.

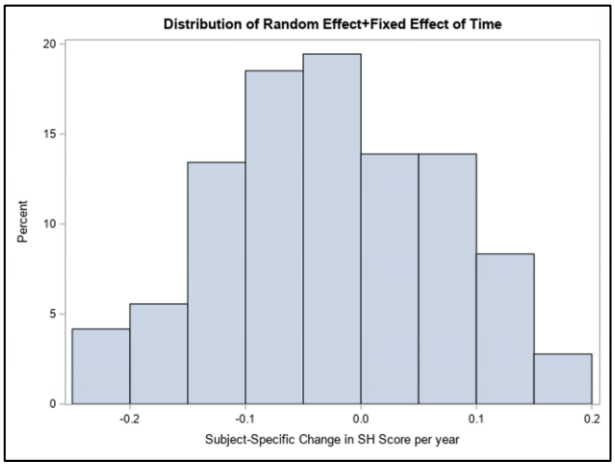

Figure 3: Distribution of SH Score at Baseline Visit

ΔSH ranged from -.23 to .18 in this study, indicating that the greatest improvement in SH was .18 points per year and the greatest decline was .23 points per year with a standard deviation

of .096. As mentioned previously, the model coefficient for the fixed effect of time was -.026. This suggests that, according to the model, mean SH score decreased by .026 points for every year of the study. Because this estimate represents a sample average, it may indicate that a majority of participants' SH declined over the course of the study, but it is possible that those who experienced SH decline had a greater change in SH score, on average, than those whose SH improved. From Fig. 2 above, it appears that this overall decline may be due to the former as much of the distribution in ΔSH is <0 with no significant outliers.

To determine how longitudinal changes in SH associate with cognitive performance, ΔSH was used in a series of univariate linear regressions with domain-specific z-score used as the outcome of interest. Table 5 reports the regression coefficients and their 95% confidence intervals. The association between ΔSH and the executive, immediate memory, and language domain z-scores were statistically significant at p=.05. Figure 4 shows the linear correlations of ΔSH and each domain z-score with the fitted model and 95% confidence intervals included.

Table 5: Linear Regressions of ΔSH as Predictor of Domain Z-score

Domain	**ΔSH Regression Estimates (*B* (95% CI)**
Attention	0.78 (-.53, 2.18)
Visuospatial	0.41 (-1.06, 1.93)
Language	**1.55 (.23, 3.01)
Immediate Memory	**1.42 (.06, 2.84)
Delayed Memory	0.90 (-.45, 2.33)
Executive	**1.67 (.35, 3.12)

****indicates statistical significance at a = .05**

From the univariate linear regressions performed (Table 5), the association between ΔSH and the executive function (B = 1.67 (.35, 3.12)), immediate memory (B = 1.42 (.06, 2.84)), and language (B = 1.55 (.23, 3.01)) domains were all significant. It should be noted that R^2 was very small for all of these correlations, with a maximum of .03 across all 6 regressions, although this is an unsurprising finding considering the variability in ΔSH and domain z-scores. Figure 4 below shows the positive associations between ΔSH and domain-specific z-score such that positive ΔSH was significantly associated with a high z-score in the executive function,

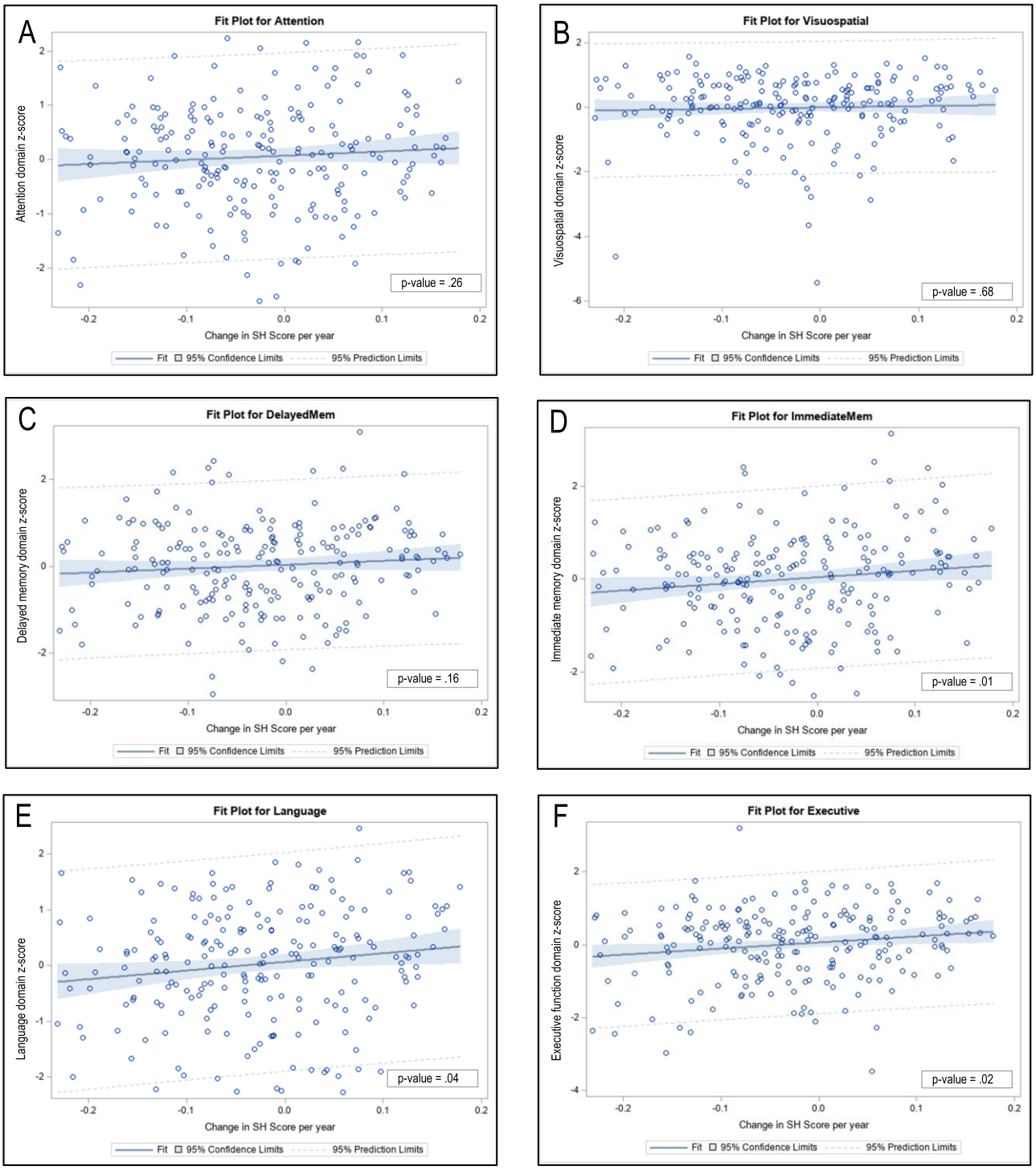

Figure 4: Regressions of ΔSH per year and Domain-Specific z-Scores.

ΔSH as predictor of: a.) Attention b.) Visuospatial c.) Delayed Memory d.) Immediate Memory e.) Language f.) Executive Function domain z-scores

3.3 ΔSH and Risk of Cognitive Impairment

Table 6 below shows the number of participants in the improve and decline groups and the number of each who were either cognitively impaired or had no cognitive disorder (NCD). Surprisingly, a greater proportion of the sample had a positive ΔSH (i.e. the SH improvement group was larger). Because the estimate of ΔSH from Table 4 (ΔSH = -.026) represents a sample average, this indicates that those who experienced SH decline had a more significant change in SH over time, thus producing a negative model estimate. The magnitude of change was greater in the SH decline group, on average, so the overall sample trend was negative. Notably, an equal number of individuals in the SH improvement group were cognitively impaired or had NCD. Conversely, there were much more individuals with cognitive impairment than NCD in the SH decline group.

Table 6: Cognitive Impairment or NCD by SH Improvement or Decline

N (%)	**Cognitively Impaired**	**NCD**	**Total**
SH Improvement	75 (30.9)	75 (30.9)	150
SH Decline	57 (23.5)	36 (14.8)	93
Total:	132	111	243

A Fischer's Exact Test was used to assess the independence of the rows and columns in Table 6 above. The p-value for this test of significance was p = .11, indicating that cognitive impairment status may be independent from the direction of ΔSH.

A univariate logistic regression in which SH improvement was used as a predictor of cognitive impairment was also performed. No covariates were included in this regression as all model estimates from Model 1, the linear mixed model from which the ΔSH estimates were

calculated, were already adjusted for relevant covariates. From this regression, we found that odds of cognitive impairment in the SH improvement group were .63 times lower (OR = .63 (.37, 1.07); p-value=.08) than that of the SH decline group. While this result is non-significant at a=.05, it does trend toward statistical significance and does support the findings above in Table 6; a greater proportion of the SH decline group was cognitively impaired at follow-up than the SH improvement group.

4.0 Discussion

In this study of cognitive performance in a sample of mostly African American women from two sociodemographically similar neighborhoods in Pittsburgh, PA, we found that the subject-specific change in composite SH adjusted for age, sleep medication use, psychological distress, education, and neighborhood was significantly associated with performance in the domains of executive function, immediate memory, and language. These results indicate that SH improvement over time was associated with better performance in the executive function, immediate memory, and language domains compared to those whose SH declined over the study period. In this, we address aim 1; individuals whose SH score improved were more likely to perform outperform their peers in these cognitive domains. While we supported our hypothesis regarding the association between ΔSH and performance in the executive function and immediate memory domains, we did not support our hypothesis that the same would be true for attention. While it's unclear why did not find a significant association between attention and ΔSH, the association between ΔSH and language is a surprising finding considering the scarcity of literature on the specific relationship between SH and performance in the language domain.

Although associations between changing sleep patterns and performance in several cognitive domains have been studied in prior literature,[34, 74, 75, 77] to our knowledge, this is the first study on the association of longitudinal changes in objectively measured composite sleep health with a robust assessment of domain-specific cognitive performance at follow-up. A previous study conducted in a large sample of Chinese older adults, the Singapore Chinese Health Study, found that changing sleep duration is associated with an increased risk of impaired cognition (as defined by a threshold score on the MMSE).[92] However, this study relied upon self-reported measures of

sleep duration and they only used the MMSE to assess cognition. Another longitudinal cohort study with long-term follow-up, the Whitehall II study, surprisingly found that increasing sleep duration from just 7 to 8 hours per night was associated with decreased verbal memory, inductive reasoning, verbal and semantic fluency, and MMSE performance.[92] But this study also relied upon a self-reported measure of sleep (i.e. duration on an "average" week night) which similarly limits the validity of its findings.

Previous studies analyzing associations of cross-sectional actigraphy-measured sleep with repeated measures of cognition have found that various measures of sleep disturbance (i.e. reduced SE, increased sleep latency, or shortened TST) in old age are associated with impaired executive function,[92] multidimensional cognitive decline (assessed by repeated measures of the Montreal Cognitive Assessment),[93] declines in verbal learning, memory and word fluency,[92] impaired episodic memory,[92] and risk for incident Alzheimer's[91] and amnestic MCI.[87]

Considering these prior findings, it is unsurprising that improving SH was associated with better performance in executive function and immediate memory. However, it does lend support for the validity of composite SH as a measure of sleep. Agreement with prior literature relying upon individual sleep parameters (many of which were used in our composite SH score calculation) as predictors of cognitive performance, decline, or impairment suggests that this multidimensional approach to measuring sleep health is appropriate.

While our results using the cognitive impairment adjudication data to address aim 2 were not statistically significant, they did trend toward significance which is still meaningful. Surprisingly, more individuals in this analysis demonstrated an improved SH over time ($N_{improve} = 150$, $N_{decline} = 93$). Table 6 also shows that nearly twice as many individuals who had a negative ΔSH were cognitively impaired. Considering the fixed effect of time from the linear

mixed model (which estimated a .026-unit decline in mean SH per year), these data suggest that the decliners had more significant changes to their SH score than the improvers. Figure

A significant amount of evidence exists showing that those with cognitive impairment have substantial declines in SH which progress rapidly in parallel with the disease itself.[1, 10, 11, 28, 34, 38, 44, 56, 76, 83] However, it is unclear whether sleep disruption and declining sleep quality precede the onset of dementia-related neurodegeneration, or if worsening SH is a consequence of underlying, pre-clinical pathology. Our results may not definitively settle this debate, but they do suggest that significantly declining SH in older adults not diagnosed with a neurodegenerative disorder may be an indicator of cognitive impairment. Unfortunately, longitudinal assessments of cognition were not available in this study, so this claim cannot be made definitively.

The use of a comprehensive cognitive assessment battery is a major strength of this analysis. Six cognitive domains were assessed with validated measures of cognitive performance within each domain, providing for a robust assessment of multidimensional cognition. Many studies on sleep and cognition have been limited by the cognitive measures they use; many rely on singular measures of global cognition (through assessments like the MMSE) or focus on the relationship between sleep and a singular domain. The use of actigraphic measures of sleep to construct a composite SH score reflecting overall sleep health is another significant strength which hopes to build on prior literature regarding the use of a composite SH index in sleep studies.[46, 48, 49] The benefit of using a comprehensive assessment of sleep is enhanced by the longitudinal design of the PHRESHZzz study. By collecting repeated measures of SH over time, the study design allows for novel analyses of changes in SH and their association with various outcomes. Future studies may be able to do further analyses on the specific drivers of an individual's changing SH

over time. Determining which facet(s) of composite SH is/are driving notable changes in overall sleep may be clinically useful because it could identify potential areas for intervention.

Finally, this study's most significant strength lies in the study population from which participants were recruited. PHRESH used a community-based random sampling strategy to create a representative sample of individuals from two highly vulnerable neighborhoods which represent a historically underrepresented group in cognitive outcomes and dementia research.[85] The generalizability of these results may be limited as a consequence of the homogeneity in race and gender of this sample, but these generalizability concerns are entirely offset by the scarcity of research on aging, cognition, and sleep in this population.[68, 70, 72]

Despite the significant strengths of this analysis, several limitations are present. First, the composite SH score described here may be limited somewhat by its construction. Although 5 parameters of sleep reflecting both objective and subjective components are included, each parameter is weighted equally, and all parameters are included as dichotomous variables based on predefined thresholds. These thresholds were decided with support from prior literature and this systematic approach does simplify the analysis, however, further study on the construction of a composite SH score may find that different sleep parameters contribute differently to overall SH. This may call for differential weighting of certain parameters or more complex composite score construction, but how comprehensively this novel measure captures an individual's sleep compensates for this uncertainty. Finally, the cross-sectional analysis of cognitive performance is a limitation because it does not allow for any assessment of change in cognitive performance over time. As such, any findings can only be interpreted as associational and no inferences can be made regarding causality or longitudinal cognitive decline.

Future research should use longitudinally collected objective measures of sleep health as well as longitudinal assessments of cognitive outcomes to definitively assess how changes in sleep health over time associate with or predict changes in cognitive performance in old age. Additionally, more complex methods for the construction of a composite SH score should be explored as they may be able to capture overall sleep health with greater granularity and accuracy. Finally, trials using interventions specifically designed to improve SH in more generalizable samples should be conducted to validate the associations discussed here and establish causality in broader populations.

Few studies have explored the association between changing SH over time and cognitive outcomes. This analysis adds to existing literature on sleep and cognitive performance by using a novel methodology for measuring SH in a longitudinal fashion. The association of these longitudinal trends in SH and cognitive performance identifies a modifiable behavior that should be studied further as a potential intervention for the prevention of cognitive decline and cognitive impairment in older adults.

Bibliography

1. Dzierzewski JM, Dautovich N, Ravyts S. Sleep and cognition in older adults. Sleep Med Clin 2018;13:93-106.

2. Wennberg AMV, Wu MN, Rosenberg PB, Spira AP. Sleep disturbance, cognitive decline, and dementia: A review. Semin Neurol 2017;37:395-406.

3. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science 2013;342:373-377.

4. Boland B, Yu WH, Corti O, et al. Promoting the clearance of neurotoxic proteins in neurodegenerative disorders of ageing. Nat Rev Drug Discov 2018;17:660-688.

5. Rasch B, Born J. About sleep's role in memory. Physiol Rev 2013;93:681-766.

6. Robertson LT. Memory and the brain. J Dent Educ 2002;66:30-42.

7. Besedovsky L, Lange T, Born J. Sleep and immune function. Pflugers Arch 2012;463:121-137.

8. Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. Semin Neurol 2009;29:320-339.

9. Kim E-J, Dimsdale JE. The effect of psychosocial stress on sleep: a review of polysomnographic evidence. Behav Sleep Med 2007;5:256-278.

10. Porter VR, Buxton WG, Avidan AY. Sleep, cognition and dementia. Curr Psychiatry Rep 2015;17:97.

11. Scullin MK, Bliwise DL. Sleep, cognition, and normal aging: integrating a half century of multidisciplinary research. Perspect Psychol Sci 2015;10:97-137.

12. Li J, Vitiello MV, Gooneratne NS. Sleep in normal aging. Sleep Med Clin 2018;13:1-11.

13. Crossley M. F.I.M. Craik, & T.A. Salthouse (Eds.) The Handbook of Aging and Cognition (2nd ed.). Mahwah, NJ: Lawrence Erlbaum, 2000. Can J Aging 2001;20:590-594.

14. Murman DL. The Impact of Age on Cognition. Semin Hear 2015;36:111-121.

15. Salthouse TA. Trajectories of normal cognitive aging. Psychol Aging 2019;34:17-24.

16. Harvey PD. Domains of cognition and their assessment. Dialogues Clin Neurosci 2019;21:227-237.

17. Pal A, Biswas A, Pandit A, et al. Study of visuospatial skill in patients with dementia. Ann Indian Acad Neurol 2016;19:83-88.

18. Craik FIM, Salthouse TA. The handbook of aging and cognition, 2nd ed. Mahwah, N.J.: Lawrence Erlbaum Associates, 2000.

19. Cohen RA. Attention. In: Kreutzer JS, DeLuca J, Caplan B, eds. Encyclopedia of clinical neuropsychology. New York, NY: Springer New York, 2011: 282-292.

20. Irani F. Visual-Spatial Ability. In: Kreutzer JS, DeLuca J, Caplan B, eds. Encyclopedia of clinical neuropsychology. New York, NY: Springer New York, 2011: 2652-2654.

21. Wright HH. Cognition, language and aging. Available at https://hdl.loc.gov/loc.gdc/gdcebookspublic.20160052362016.

22. Diamond A. Executive functions. Annu Rev Psychol 2013;64:135-168.

23. Nici J. A compendium of neuropsychological tests, 2nd ed. Arch Neurol 2000;57:278-278.

24. Zucchella C, Federico A, Martini A, Tinazzi M, Bartolo M, Tamburin S. Neuropsychological testing. Pract Neurol 2018;18:227-237.

25. Casaletto KB, Heaton RK. Neuropsychological Assessment: Past and Future. J Int Neuropsychol Soc 2017;23:778-790.

26. Anderson ND, Craik FI. 50 Years of Cognitive Aging Theory. J Gerontol B Psychol Sci Soc Sci 2017;72:1-6.

27. Roberts R, Knopman DS. Classification and epidemiology of MCI. Clin Geriatr Med 2013;29:753-772.

28. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med 2014;30:421-442.

29. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. 1971. Milbank Q 2005;83:731-757.

30. Hudomiet P, Hurd MD, Rohwedder S. Dementia prevalence in the united states in 2000 and 2012: estimates based on a nationally representative study. J Gerontol B Psychol Sci Soc Sci 2018;73:S10-S19.

31. Richardson C, Stephan BCM, Robinson L, et al. Two-decade change in prevalence of cognitive impairment in the UK. Eur J Epidemiol 2019;34:1085-1092.

32. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413-446.

33. Hofman MA, Swaab DF. Living by the clock: the circadian pacemaker in older people. Ageing Res Rev 2006;5:33-51.

34. Kondratova AA, Kondratov RV. The circadian clock and pathology of the ageing brain. Nat Rev Neurosci 2012;13:325-335.

35. Kroeger D, Absi G, Gagliardi C, et al. Galanin neurons in the ventrolateral preoptic area promote sleep and heat loss in mice. Nat Commun 2018;9:4129.

36. Hofman MA, Swaab DF. Alterations in circadian rhythmicity of the vasopressin-producing neurons of the human suprachiasmatic nucleus (SCN) with aging. Brain Res 1994;651:134-142.

37. Wang JL, Lim AS, Chiang W-Y, et al. Suprachiasmatic neuron numbers and rest-activity circadian rhythms in older humans. Ann Neurol 2015;78:317-322.

38. Wennberg AMV, Wu MN, Rosenberg PB, Spira AP. Sleep disturbance, cognitive decline, and dementia: A review. 2017.

39. Areal CC, Warby SC, Mongrain V. Sleep loss and structural plasticity. Curr Opin Neurobiol 2017;44:1-7.

40. Havekes R, Park AJ, Tudor JC, et al. Sleep deprivation causes memory deficits by negatively impacting neuronal connectivity in hippocampal area CA1. Elife 2016;5.

41. Nimchinsky EA, Sabatini BL, Svoboda K. Structure and function of dendritic spines. Annu Rev Physiol 2002;64:313-353.

42. Riemann D, Voderholzer U, Spiegelhalder K, et al. Chronic insomnia and MRI-measured hippocampal volumes: a pilot study. Sleep 2007;30:955-958.

43. Sun BL, Wang LH, Yang T, et al. Lymphatic drainage system of the brain: A novel target for intervention of neurological diseases. Prog Neurobiol 2018;163-164:118-143.

44. Lim ASP, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident alzheimer's disease and cognitive decline in older persons. Sleep 2013;36:1027-1032.

45. Gildner TE, Salinas-Rodríguez A, Manrique-Espinoza B, Moreno-Tamayo K, Kowal P. Does poor sleep impair cognition during aging? Longitudinal associations between changes in sleep duration and cognitive performance among older Mexican adults. Arch Gerontol Geriatr 2019;83:161-168.

46. Buysse DJ. Sleep health: can we define it? Does it matter? Sleep 2014;37:9-17.

47. Furihata R, Hall MH, Stone KL, et al. An Aggregate Measure of Sleep Health Is Associated With Prevalent and Incident Clinically Significant Depression Symptoms Among Community-Dwelling Older Women.

48. DeSantis A, Troxel WM, Beckman R, et al. Is the association between neighborhood characteristics and sleep quality mediated by psychological distress? An analysis of perceived and objective measures of 2 Pittsburgh neighborhoods. Sleep Health 2016;2:277-282.

49. DeSantis AS, Dubowitz T, Ghosh-Dastidar B, et al. A preliminary study of a composite sleep health score: associations with psychological distress, body mass index, and physical functioning in a low-income African American community. Sleep Health 2019;5:514-520.

50. Bowman MA, Kline CE, Buysse DJ, et al. Longitudinal association between depressive symptoms and multidimensional sleep health: the SWAN sleep study. Ann Behav Med 2021.

51. Blackwell T, Yaffe K, Ancoli-Israel S, et al. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 2006;61:405-410.

52. Yeh A-Y, Pressler SJ, Algase D, et al. Sleep-Wake Disturbances and Episodic Memory in Older Adults. Biol Res Nurs 2021;23:141-150.

53. Yoon I-Y, Kripke DF, Elliott JA, Youngstedt SD, Rex KM, Hauger RL. Age-related changes of circadian rhythms and sleep-wake cycles. J Am Geriatr Soc 2003;51:1085-1091.

54. Bernstein JPK, DeVito A, Calamia M. Subjectively and objectively measured sleep predict differing aspects of cognitive functioning in adults. Archives of Clinical Neuropsychology 2019;34:1127-1137.

55. Ohayon MM, Vecchierini M-F. Daytime sleepiness and cognitive impairment in the elderly population. Arch Intern Med 2002;162:201-208.

56. Wams EJ, Wilcock GK, Foster RG, Wulff K. Sleep-Wake Patterns and Cognition of Older Adults with Amnestic Mild Cognitive Impairment (aMCI): A Comparison with Cognitively Healthy Adults and Moderate Alzheimer's Disease Patients. Curr Alzheimer Res 2017;14:1030-1041.

57. Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. Lancet Neurol 2014;13:1017-1028.

58. Mirelman A, Herman T, Brozgol M, et al. Executive function and falls in older adults: new findings from a five-year prospective study link fall risk to cognition. PLoS ONE 2012;7:e40297.

59. Didikoglu A, Maharani A, Payton A, Pendleton N, Canal MM. Longitudinal change of sleep timing: association between chronotype and longevity in older adults. Chronobiol Int 2019;36:1285-1300.

60. Hicklin D, Schwander J. [shift work and sleep]. Praxis (Bern 1994) 2019;108:119-124.

61. Bernstein JPK, DeVito A, Calamia M. Subjectively and Objectively Measured Sleep Predict Differing Aspects of Cognitive Functioning in Adults. Arch Clin Neuropsychol 2019;34:1127-1137.

62. Smagula SF, Sofer T, Guo N, et al. Spectral sleep electroencephalographic correlates of sleep efficiency, and discrepancies between actigraphy and self-reported measures, in older men. Journal of Sleep Research 2021;30:e13033.

63. Hughes JM, Song Y, Fung CH, et al. Measuring sleep in vulnerable older adults: A comparison of subjective and objective sleep measures. Clin Gerontol 2018;41:145-157.

64. Zinkhan M, Berger K, Hense S, et al. Agreement of different methods for assessing sleep characteristics: a comparison of two actigraphs, wrist and hip placement, and self-report with polysomnography. Sleep Med 2014;15:1107-1114.

65. Van Den Berg JF, Van Rooij FJ, Vos H, et al. Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons. J Sleep Res 2008;17:295-302.

66. Baker FC, Maloney S, Driver HS. A comparison of subjective estimates of sleep with objective polysomnographic data in healthy men and women. J Psychosom Res 1999;47:335-341.

67. Sadeh A. The role and validity of actigraphy in sleep medicine: an update. Sleep Med Rev 2011;15:259-267.

68. Brewster P, Barnes L, Haan M, et al. Progress and future challenges in aging and diversity research in the United States. Alzheimers Dement 2019;15:995-1003.

69. National Research Council (US) Panel on Race E, and Health in Later Life; Anderson NB, Bulatao RA, Cohen B, editors. Ethnic Differences in Dementia and Alzheimer's Disease. Critical Perspectives on Racial and Ethnic Differences in Health in Late Life. Washington (DC)2004.

70. Napoles AM, Chadiha LA, Resource Centers for Minority Aging R. Advancing the science of recruitment and retention of ethnically diverse populations. Gerontologist 2011;51 Suppl 1:S142-146.

71. Gross AL, Mungas DM, Crane PK, et al. Effects of education and race on cognitive decline: An integrative study of generalizability versus study-specific results. Psychol Aging 2015;30:863-880.

72. 2021 Alzheimer's disease facts and figures. Alzheimers Dement 2021;17:327-406.

73. Parker D, Bucks RS, Rainey-Smith SR, et al. Sleep Mediates Age-Related Executive Function for Older Adults with Limited Cognitive Reserve. J Int Neuropsychol Soc 2020:1-11.

74. Hua J, Sun H, Shen Y. Improvement in sleep duration was associated with higher cognitive function: a new association. Aging (Albany NY) 2020;12:20623-20644.

75. Ferrie JE, Shipley MJ, Akbaraly TN, Marmot MG, Kivimäki M, Singh-Manoux A. Change in sleep duration and cognitive function: findings from the Whitehall II Study. Sleep 2011;34:565-573.

76. Lloret M-A, Cervera-Ferri A, Nepomuceno M, Monllor P, Esteve D, Lloret A. Is sleep disruption a cause or consequence of alzheimer's disease? reviewing its possible role as a biomarker. Int J Mol Sci 2020;21.

77. Wu J, Cheng GHL, Sheng L-T, et al. Prospective associations between change in sleep duration and cognitive impairment: Findings from the Singapore Chinese Health Study. J Affect Disord 2021;281:125-130.

78. Tulsky DS, Price LR. The joint WAIS-III and WMS-III factor structure: development and cross-validation of a six-factor model of cognitive functioning. Psychol Assess 2003;15:149-162.

79. Lucas JA, Ivnik RJ, Smith GE, et al. Mayo's Older African Americans Normative Studies: norms for Boston Naming Test, Controlled Oral Word Association, Category Fluency, Animal Naming, Token Test, WRAT-3 Reading, Trail Making Test, Stroop Test, and Judgment of Line Orientation. Clin Neuropsychol 2005;19:243-269.

80. Beeri MS, Schmeidler J, Sano M, et al. Age, gender, and education norms on the CERAD neuropsychological battery in the oldest old. Neurology 2006;67:1006-1010.

81. Hoppe CD, Müller UD, Werheid KD, Thöne AD, von Cramon YD. Digit Ordering Test: clinical, psychometric, and experimental evaluation of a verbal working memory test. Clin Neuropsychol 2000;14:38-55.

82. 2021 Poverty Guidelines | ASPE.

83. Gooneratne NS, Vitiello MV. Sleep in older adults: normative changes, sleep disorders, and treatment options. Clin Geriatr Med 2014;30:591-627.

84. Ohayon MM, Vecchierini M-F. Normative sleep data, cognitive function and daily living activities in older adults in the community. Sleep 2005;28:981-989.