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Original Article

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Sex differences in the role of sleep on cognition in older adults

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Abstract

Study Objectives: The study aimed to investigate sex differences in the relationship between sleep quality (self-report and objective) and cognitive function across three domains (executive function, verbal memory, and attention) in older adults.

Methods: We analyzed cross-sectional data from 207 participants with normal cognition (NC) or mild cognitive impairment (89 males and 118 females) aged over 60 years. The relationship between sleep quality and cognitive performance was estimated using generalized additive models. Objective sleep was measured with the GT9X Link ActiGraph, and self-reported sleep was measured with the Pittsburgh Sleep Quality Index.

Results: We found that females exhibited lower executive function with increased objective total sleep time, with a steeper decline in performance after 400 minutes ($p = .015$). Additionally, longer objective sleep correlated with lower verbal memory linearly ($p = .046$). In males, a positive linear relationship emerged between objective sleep efficiency and executive function ($p = .036$). Self-reported sleep was not associated with cognitive performance in females and males with NC. However, in males with cognitive impairment, there was a nonlinear positive relationship between self-reported sleep and executive function ($p < .001$).

Conclusions: Our findings suggest that the association between sleep parameters on cognition varies between older males and females, with executive function being most strongly associated with objective sleep for both sexes top of form. Interventions targeting sleep quality to mitigate cognitive decline in older adults may need to be tailored according to sex, with distinct approaches for males and females.

Key words: sleep; cognition; aging; sex differences; actigraphy

Statement of Significance

This research is significant as it addresses the gap in a previously underexplored area of sex differences in the interplay between sleep quality and cognitive function in older populations. By examining both objective and self-reported sleep measures across three cognitive domains, the study provides valuable insights into how sleep impacts various cognitive domains differently in older males and females. Notably, the findings suggest that interventions to improve sleep quality and potentially mitigate cognitive decline may need to be sex specific regarding which sleep parameters to target.

The impact of aging on sleep and cognition is well documented in the literature. Aging has been associated with fragmented sleep and decreased sleep quality, which could exacerbate the cognitive decline that occurs with aging [1]. However, the literature on sex differences in sleep and its interaction with cognition in older adults is still limited. Females experience dramatic hormonal and physiologic developmental changes (puberty, pregnancy, and menopause) across the lifespan that contribute to alterations in sleep patterns and a higher number of reported sleep complaints [2]. Moreover, females have twice the risk of developing Alzheimer's disease (AD), for which poor sleep is a risk factor [3, 4]. Understanding how males and females differ in their sleep

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health and the implications of these differences on cognition is vital for designing effective interventions and prevention strategies for AD.

Advancing age is associated with physiological changes, among which are the alterations of sleep architecture (i.e. stages of sleep) and circadian rhythm. Older adults have a shorter slow-wave sleep duration and activity, as well as shorter rapid eye movement sleep and more frequent awakenings during the night [5, 6]. Additionally, they tend to go to bed earlier in the evening and wake up earlier in the morning [7]. These changes, along with other common occurrences due to aging (e.g. medical comorbidities and medications), contribute to the high prevalence of sleep disturbances experienced by this population [8, 9]. Previous studies reported that up to 75% of older adults experienced sleep difficulty [10–12]. Because one of the roles of sleep is to clear out neurotoxic waste products produced during the day, poor sleep has been found to exacerbate cognitive decline and neuropathological markers of AD, such as beta-amyloid and tau deposition [13–15].

However, the broader investigation of the interrelationships between aging, sleep, and cognition has been relatively inconclusive and marked by variability in findings, potentially due to methodological variations and differences in operationalizing sleep metrics across studies. In older adults with normal cognition (NC), both short (<6 hours) and long (>9 hours) sleep durations have been linked to reduced global cognition and memory [16, 17]. However, Sabeti et al. [18] observed this association solely in older adults with cognitive impairment. In a 2-year longitudinal study, it was found that older females who slept for only 4 hours exhibited a more significant cognitive decline compared with those who slept for 7 hours. Notably, individuals who slept for 9 hours did not experience any cognitive decline during the same period [19]. Conversely, Faubel et al. [20] indicated that older adults who slept for 11 hours demonstrated lower cognitive performance compared with those who slept for 7 hours. In addition to global cognition and memory, sleep disturbances have been reported to impact other cognitive domains, including attention and executive function, in older populations. Specifically, Blackwell et al. [21] and Wilckens et al. [22] revealed a negative correlation between frequent nighttime awakenings and performance on executive function and attention. However, Wilckens et al. [22] did not find a significant association between sleep duration and cognitive performance in their study.

Biological sex is another major factor that influences sleep. Research investigating sex differences in self-reported sleep quality suggests that middle-aged and older females take longer to fall asleep, have shorter sleep duration, and have lower sleep efficiency (SE) [23, 24]. However, this result is contradicted by studies looking at objective sleep quality between older males and females using actigraphy and polysomnography (PSG). A meta-analysis including studies on sleep characteristics across three countries reported that older females had longer sleep duration and higher SE based on actigraphy data [25]. Studies using PSG show that reduced slow-wave sleep due to age is more pronounced in males than in females [26, 27]. The discrepancy between self-reported and objective sleep could be due to males and females having different perceptions or requirements of restful sleep [28, 29].

Regarding the cognitive implications of poor sleep, limited research has been conducted to investigate sex differences in this topic. Notably, it has been observed that sleep deprivation affects working memory to a greater extent in young females compared with males [30, 31]. However, whether the same findings apply to older populations is still not well understood. This lack of research leaves an important gap in our understanding of how sleep impacts cognitive function across the lifespan.

In this study, we investigated sex differences in the relationship between sleep quality (self-reported and objective measures) and cognitive performance in a clinical cohort of older individuals. Because the research on this topic is limited, the goal of this paper was to generate hypotheses and identify potential patterns that can be explored further in subsequent studies. We were also interested in exploring the relationship between these two sleep quality measures and in assessing whether these relationships varied between males and females. Finally, we explored whether cognitive performance was better explained by an objective measure, a self-reported measure, or a combination of both.

Materials and Methods

Participants

Participants were recruited from the University of Kansas Alzheimer's Disease Research Center (KU-ADRC) Clinical Cohort, an ongoing longitudinal observational study to support regional and national research on aging, cognition, and AD. This study collects demographic, medical, psychological, and cognitive data annually, and imaging and biospecimen data as needed if participants opt in. Participants could opt to partake in the Physical Activity and Sleep Study (PASS), a substudy of the Clinical Cohort initiated on July 29, 2015, in which participants completed self-report sleep questionnaires annually and wore an actigraph every 2 years until May 27, 2021. During this time, the KU-ADRC Clinical Cohort enrolled over 1000 participants. To be eligible for the Clinical Cohort study, participants had to be at least 60 years, native English speakers, and not exhibit the following conditions: significant depressive symptoms, untreated thyroid dysfunction, visual or auditory impairment, active (<2 years) ischemic heart disease, and uncontrolled insulin-dependent diabetes mellitus.

In the current analysis, we included 207 participants with NC or mild cognitive impairment (MCI), as indicated by clinical dementia rating (CDR) scores of 0 and greater than 0, respectively. Among these participants, 161 exhibited NC, while 46 had MCI with a CDR of 0.5 ($n = 36$) or 1 ($n = 10$). We excluded those who had progressed to dementia. The research was approved by the KU-ADRC's Institutional Review Board, and all participants provided written informed consent separately for both the KU-ADRC Clinical Cohort and the PASS study.

Sleep quality measures

Actigraphy.

ActiGraph GT9X Link accelerometers (Pensacola, FL) are body-worn monitors that measure objective sleep patterns. Our study used placement on the nondominant wrist to estimate sleep parameters. The GT9X devices were programmed to collect data at a sample rate of 30 Hz. ActiLife software version 6.13.2 or 6.13.4 (ActiGraph, LLC) was used to process and analyze the raw actigraphy data using the Cole–Kripke algorithm [32]. Wear time was measured using the Choi algorithm, and a valid wear time included a minimum of 10 hours per day, at least 1 weekend day, and a minimum of 4 days [33]. Participants were also provided with a sleep diary to document the timing and length of their sleep during the day and at night. They were asked to note how long it took them to fall asleep, record any instances of waking

up during the night, and track the time they woke up and got out of bed.

We included SE and total sleep time (TST) in this analysis due to the prevalent occurrence of sleep disturbances and variations in sleep duration and SE among older adults. Wake after sleep onset was not included because it was highly correlated with SE ($r = -.95$) in our sample. SE refers to the percentage of total time spent asleep during the total time in bed (time asleep/time in bed). TST refers to the time spent asleep in bed (in minutes) at night. TST was calculated by subtracting the duration of falling asleep and awakening from the total amount of time in bed (in minutes; out of bedtime—in bedtime). A higher TST means a longer sleep duration. For each night's data, sleep intervals recorded by ActiGraph were compared with the participants' sleep diaries to check for discrepancies. When the sleep diary entries were closely aligned (within a 30-minute margin) with the ActiGraph-identified sleep period, the sleep period identified by ActiGraph was used. In cases where the discrepancy exceeded 30 minutes, the researchers manually evaluated the sleep data in ActiLife by looking for significant changes in activity levels. This manual assessment was also automatically initiated whenever participants did not submit or complete their sleep diaries.

The Pittsburgh Sleep Quality Index.

The Pittsburgh Sleep Quality Index (PSQI) is a self-report questionnaire consisting of 10 items measuring sleep quality over the past month. The total score of PSQI is calculated by summing its seven subscales, with scores ranging from 0 (indicating "good sleep quality") to 21 (indicating "poor sleep quality"). The PSQI is a reliable measure to distinguish between good and poor sleepers (PSQI > 5), with a sensitivity of 89.6% and a specificity of 86.5% [34]. It is also valid to use for clinical and research purposes. In exploratory analyses, we also selected two of these subscales (scores range from 0 to 3), specifically SE and duration, for comparison with SE and TST, as measured by actigraphy.

Cognitive performance

As part of the Clinical Cohort study annual evaluation, participants completed a cognitive test battery, specifically the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), and several additional tests. The UDS was designed to measure cognitive performance in MCI or dementia due to AD by the Alzheimer's Disease Centers Clinical Task Force established by the National Institute on Aging. The subtests included in the present analyses were the Wechsler Adult Intelligence Scales-Revised (WAIS-R; digit symbol substitution test) [35], two subtests from the Wechsler Memory Scale-Revised (WMS-R; letter-number sequencing and digit span forward and backward) [36], the Stroop test (interference condition) [37], the Craft Story 21 Immediate and Delayed recall [38], the free and cued selective reminding test [39], two tests of semantic verbal fluency (animal and vegetable naming) [40], and trail making test B [41]. The administration procedures of the subtests are described in their respective references.

The present study used cognitive factor scores derived from a confirmatory factor analysis, and the scores can be interpreted similarly to a Z-score (a positive score indicates above-average performance, while a negative score suggests below-average performance). This approach reduces type 1 error resulting from multiple testing and improves measurement accuracy by combining common variance across multiple subtests while accounting for measurement error. The details of this analysis can be found elsewhere [42]. The result yielded three factors: verbal memory (immediate and delayed logical memory, selective reminding test trials sum), attention (digits forward, digits backward, and letter-number sequencing), and executive function (category fluency sum of animals and vegetables, Stroop color-word interference, trail making test B, and digit symbol substitution test).

Statistical analysis

We compared demographics (age and education) between males and females using an independent *t*-test. Analysis of covariance (ANCOVA) was used to compare the three cognitive domains and sleep variables (TST, SE, and PSQI) between sexes, adjusting for age and CDR, with education included as a covariate exclusively for the cognitive domains. We implemented Bonferroni correction to correct the type I error rate to adjust for multiple comparisons at $p < .008$.

We implemented generalized additive models (GAMs) with the mgcv package in R to analyze the relationship between sleep and each cognitive domain (executive function, verbal memory, and attention). Because previous studies have suggested that males and females have different sleep patterns and perceptions of sleep quality, we chose to perform the analyses separately for males and females to allow for clearer interpretations. We selected GAMs because previous research has shown that sleep and cognition were nonlinearly correlated in older adults [43]. GAMs are suitable for accounting for nonparametric and nonlinear relationships. The spline fitting of the sleep parameters, a method to find the best fit of the data points, was estimated using restricted maximum likelihood (REML). REML is particularly adept at reducing bias in the estimation of variance components. It adjusts for the degrees of freedom used by the fixed effects, allowing for more accurate and less biased estimates of the random effects variance.

There was 14% ($n = 29$) of missing data in the PSQI variable, which was imputed with multiple imputation chained equation with 25 iterations using the mice package in R. All variables were included in the imputation, except for the dependent variables (i.e. the three cognitive domains). The imputation was performed by dividing the dataset into two: the NC and MCI groups. This was done because previous research has shown that cognitively impaired older adults have skewed awareness, resulting in inaccurate self-reporting [44]. Other variables, such as age, years of education, and CDR, that affect cognitive performance were added as covariates. The results of the 25 iterations were pooled with the median *p*-value, a simple pooling procedure that has been shown to perform similarly or better than other pooling approaches (e.g. the "D2" method, the Cauchy combination test) [45]. The figures represented the results of the iteration corresponding to the median *p*-value.

$$\text{Cognition} \sim s(\text{TST}) + s(\text{SE}) + s(\text{PSQI, by} = \text{CDR}) + \text{age} + \text{education} + \text{CDR}$$

Exploratory analysis

We conducted Spearman's correlation analysis to explore the relationship between sleep parameters (TST and SE) measured by actigraphy and PSQI, and to examine potential variations based on sex and CDR status. We also performed model comparisons to assess which model best explains the relationship between sleep and cognition. Specifically, we compared models based on actigraphy-measured sleep parameters, self-reported sleep parameters from the PSQI, a combination of both, and the original model. All models were estimated using GAM, and model

comparisons were based on the Akaike information criterion (AIC). Both correlation and model comparisons were pooled using Rubin's Rules [46].

Model I: $\text{cognition} \sim s(\text{TST}) + s(\text{SE}) + \text{age} + \text{education} + \text{CDR}$

Model II: $\text{cognition} \sim \text{PSQI sleep duration} + \text{PSQI SE} + s(\text{PSQI}) + \text{age} + \text{education} + \text{CDR}$

Model III: $\text{cognition} \sim s(\text{TST}) + s(\text{SE}) + \text{PSQI sleep duration} + \text{PSQI SE} + s(\text{PSQI}) + \text{age} + \text{education} + \text{CDR}$

Model IV: $\text{cognition} \sim s(\text{TST}) + s(\text{SE}) + s(\text{PSQI, by} = \text{CDR}) + \text{age} + \text{education} + \text{CDR}$

Results

The summary of participants' demographics is presented in Table 1. Most participants were white (93.70%), were college-educated (16.4 years), and had NC (i.e. CDR = 0; 77.78%). Our results revealed that females outperformed males in verbal memory ($\beta = 0.32$, $p = .03$) accounting for age, educational level, and CDR score. However, the sex differences in verbal memory were no longer significant after correcting for type I errors using Bonferroni correction at $p < .008$. The average number of days that actigraphy was completed in our sample was seven, indicating valid wear-time. We did not find significant differences in executive function, attention, TST, SE, and PSQI between males and females.

Sleep and cognitive function

The GAMs revealed some significant correlations between sleep parameters and cognitive function in older adults after accounting for age, education, and CDR score. The statistical parameters of the results are presented in Table 2 for executive function, Table 3 for verbal memory, and Table 4 for attention. In older females, TST showed a slightly nonlinear association with executive function ($p = .015$; Figure 1A) and a linear association with verbal memory ($p = .046$; Figure 2A). In executive function, the correlation with TST was slightly negative up to approximately 400 minutes of TST, beyond which a steeper decrease in executive function was observed. The pattern of the relationship varied in verbal memory in which the decline in performance was consistent with a longer TST. Additionally, TST presented a negative linear relationship with attention but did not reach statistical significance ($p = .067$; Figure 3A). Among older males, there were no significant associations between TST and cognitive performance across the three domains: executive function ($p = .148$; Figure 1A), verbal memory ($p = .060$; Figure 2A), and attention ($p = .206$; Figure 3A).

SE demonstrated a significant positive relationship only in male executive function in a linear manner ($p = .036$; Figure 1B). SE did not show significant associations with verbal memory ($p = .699$; Figure 2B) and attention ($p = .103$; Figure 3B). In females, SE did not demonstrate significant relationships in all cognitive domains: executive function ($p = .201$; Figure 1B), verbal memory ($p = .120$; Figure 2B), and attention ($p = .258$; Figure 3B). The overall pattern demonstrated that a higher SE correlated with a higher performance.

Total PSQI scores did not exhibit significant associations in females with NC across three cognitive domains: executive function ($p = .190$; Figure 1C), verbal memory ($p = .492$; Figure 2C), and attention ($p = .515$; Figure 3C). The overall trend of these associations was that a more severe self-reported sleep contributed to a worse performance. In males with NC, the PSQI also had no significant relationships with executive function ($p = .566$; Figure 1C), verbal memory ($p = .666$; Figure 2C), and attention ($p = .603$; Figure 3C). However, the trend was the opposite from females with NC.

Table 1. Descriptive Statistics on Demographics, Sleep, and Cognitive Performance

	Males ($n = 89$)		Females ($n = 118$)		Total ($N = 207$)	
Participants' characteristics	***M***	***SD***	***M***	***SD***	***M***	***SD***
Age (years)	76.1*	6.9	74*	6.6	74.9	6.8
Education (years)	16.7	2.8	16.1	3	16.4	2.9
	N	**%**	***N***	**%**	***N***	**%**
Race						
White	86	96.6	108	91.5	194	93.7
African American	2	2.3	8	6.8	10	4.8
Asian	1	1.1	2	1.7	3	1.5
CDR = 0	63	70.8	98	83.1	161	77.78
	M	***SD***	***M***	***SD***	***M***	***SD***
Actigraphy						
TST (minutes)	409.7	68.3	419.8	60.4	415.5	64
SE (%)	85.4	7	86.6	6	86.1	6.4
PSQI	3.7	2.7	4.6	3.2	4.2	3.1
Sleep duration	0.2	0.5	0.4	0.7	0.3	0.6
Sleep efficiency	0.6	0.9	0.5	0.9	0.5	0.9
Verbal memory	0.4*	1.3	0.9*	1.2	0.7	1.3
Executive function	0.1	0.9	0.4	0.8	0.3	0.8
Attention	0.1	0.4	0.2	0.4	0.2	0.4

CDR, clinical dementia rating; M, mean; PSQI, Pittsburgh Sleep Quality Index; SE, sleep efficiency; TST, total sleep time.
*Differences between males and females, $p < .05$.

Table 2. Range of Parameter Estimates and the Median *P*-Value of Generalized Additive Models of the Relationship Between Sleep Quality (Total Sleep Time, Sleep Efficiency, and PSQI) and Executive Function

	Females			Males		
Sleep	**EDF**	**F-test**	**MPV**	**EDF**	**F-test**	**MPV**
TST	1.371–2.218	3.358–4.700	0.015	1.000	1.869–2.743	0.148
SE	1.657–2.003	1.228–1.776	0.201	1.000	3.915–5.365	0.036
PSQI (CDR = 0)	1.000–1.001	0.261–5.208	0.190	1.000	0.021–1.410	0.566
PSQI (CDR > 0)	1.000–2.094	0.597–2.724	0.391	2.630–2.894	4.777–5.961	0.001
Covariate	**Estimate**	**SE**	**MPV**	**Estimate**	**SE**	**MPV**
Age	(−0.025)–(−0.023)	0.008	0.005	(−0.034)–(−0.030)	0.010	0.002
Education	0.041–0.047	0.018	0.015	0.014–0.020	0.025	0.514
CDR > 0	(−0.978)–(−0.932)	0.157–0.165	<0.001	(−1.126)–(−1.018)	0.156–0.163	<0.001

CDR, clinical dementia rating; EDF, estimate degree of freedom (quantification of model's flexibility); MPV, median *p*-value; PSQI, Pittsburgh Sleep Quality Index; SE, standard error; SE, sleep efficiency; TST, total sleep time.

Table 3. Range of Parameter Estimates and the Median *P*-Value of Generalized Additive Models of the Relationship Between Sleep Quality (Total Sleep Time, Sleep Efficiency, and PSQI) and Verbal Memory

	Females			Males		
Sleep	**EDF**	**F-test**	**MPV**	**EDF**	**F-test**	**MPV**
TST	1.000	3.360–4.863	0.046	1.000	3.186–4.156	0.060
SE	1.000	1.728–3.742	0.120	1.000	0.060–0.294	0.699
PSQI (CDR = 0)	1.004–2.243	0.033–1.856	0.492	1.000–1.257	0.003–1.043	0.666
PSQI (CDR > 0)	1.000–4.656	0.562–3.422	0.083	1.000–1.520	1.839–7.214	0.050
Covariate	**Estimate**	**SE**	**MPV**	**Estimate**	**SE**	**MPV**
Age	(−0.066)–(−0.059)	0.013–0.014	<0.001	(−0.063)–(−0.029)	0.017–0.018	0.078
Education	0.071–0.087	0.027–0.029	0.005	(−0.002)–0.087	0.043–0.045	0.939
CDR > 0	(−1.328)–(−1.062)	0.248–0.266	<0.001	(−1.683)–(−1.092)	0.273–0.286	<0.001

CDR, clinical dementia rating; EDF, estimate degree of freedom (quantification of model's flexibility); MPV, median *p*-value; PSQI, Pittsburgh Sleep Quality Index; SE, standard error; SE, sleep efficiency; TST, total sleep time.

Table 4. Range of Parameter Estimates and the Median *P*-Value of Generalized Additive Models of the Relationship Between Sleep Quality (Total Sleep Time, Sleep Efficiency, and PSQI) and Attention

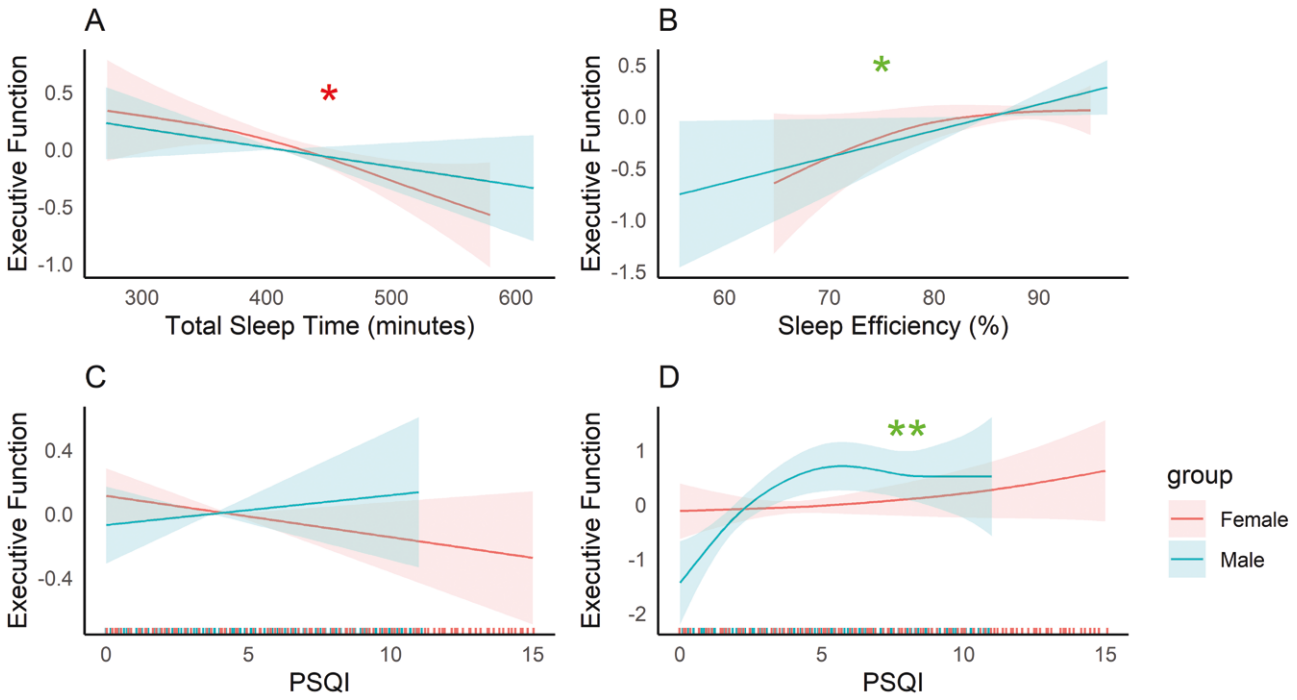
	Females			Males		
Sleep	**EDF**	**F-test**	**MPV**	**EDF**	**F-test**	**MPV**
TST	1.000	3.066–4.027	0.067	1.000	1.465–1.876	0.206
SE	2.083–2.433	1.178–1.551	0.258	1.000	2.267–3.079	0.103
PSQI (CDR = 0)	1.000–2.789	0.002–1.329	0.515	1.000	0.000–1.627	0.603
PSQI (CDR > 0)	1.000–1.800	0.695–1.409	0.498	1.792–2.039	0.844–1.101	0.379
Covariate	**Estimate**	**SE**	**MPV**	**Estimate**	**SE**	**MPV**
Age	(−0.019)–(−0.017)	0.006	0.001	(−0.016)–(−0.015)	0.006	0.010
Education	0.016–0.019	0.012	0.148	0.015–0.017	0.015	0.294
CDR > 0	(−0.323)–(−0.302)	0.105–0.110	0.005	(−0.449)–(−0.424)	0.093–0.096	<0.001

CDR, clinical dementia rating; EDF, estimate degree of freedom (quantification of model's flexibility); MPV, median *p*-value; PSQI, Pittsburgh Sleep Quality Index; SE, standard error; SE, sleep efficiency; TST, total sleep time.

Among participants with MCI, the PSQI was only significantly associated with executive function in males ($p = .001$; Figure 1D), exhibiting a nonlinear positive relationship. The PSQI was not significantly correlated with verbal memory ($p = .050$; Figure 1D) and attention ($p = .379$; Figure 3D) in males and across all three cognitive domains: executive function ($p = .391$; Figure 1D), verbal memory ($p = .083$; Figure 2D), and attention ($p = .498$; Figure 3D) in females.

Exploratory results

We identified a significant moderate correlation between objective TST and self-reported sleep duration only in males with NC



(A) partial effects of total sleep time on executive function (N = 207); (B) partial effects of sleep efficiency on executive function (N = 207); (C) partial effects of PSQI on executive function in normal cognition (N = 161); (D) partial effects of PSQI on executive function in mild cognitive impairment (N = 46).
* indicates a significant relationship at ($p < 0.05$). ** indicates a significant relationship at ($p < 0.01$)

Figure 1. Partial effects of total sleep time, sleep efficiency (SE), and Pittsburgh Sleep Quality Index (PSQI) on executive function.

($r = -.49$; Supplementary Table S1). This finding indicated that NC males with a longer objective TST reported a lower severity of sleep duration in the PSQI. Regarding the model comparisons, we found that the original model (model 4) showed the lowest AIC values in executive function (male = 179.60; female = 211.53) and verbal memory (male = 279.95; female = 322.72), as shown in Supplementary Table S2, suggesting that this model best explains the associations. For attention, the actigraphy-based model (model 1) showed the lowest AIC values for males (85.53) and females (116.36).

Discussion

Our study examined whether objective and self-reported sleep quality, as measured by actigraphy and a self-reported questionnaire, were associated with cognitive performance, specifically verbal memory, executive function, and attention, within an older adult clinical population. Concurrently, we investigated potential sex-related disparities in this association while accounting for age, education, and cognitive status. We did not find significant differences in TST, SE, and self-reported sleep symptoms between the two sexes. Further research is needed to determine what constitutes optimal sleep for older females and males.

Based on our analysis, we found that TST was a significant predictor, among older females but not older males, of executive function and memory, while attention was not associated in both sexes. The presence of both nonlinear and linear relationships across various cognitive areas suggests that effects were not uniform but rather specific to distinct cognitive domains. This implies that each aspect of cognition may have its own threshold and optimal conditions for sleep duration and quality. To elucidate the sources of this heterogeneity, more research is required to unravel the complexities of how different cognitive functions are differentially affected by sleep and vice versa. Meanwhile, low SE was associated with lower executive function in older males. These findings suggest that sleep duration and SE may have different effects on cognitive function between older females and males. Additionally, the results could indicate that sleep could have more pronounced effects on higher-order cognitive processes, such as memory and executive function [22] and less attention which is considered a more basic cognitive process. Prior studies reported that acute sleep loss impacts different types of attention from the one focused on in our study, such as sustained attention, processing speed, and vigilance [47, 48]. It is noteworthy that our study concentrated on attention more closely aligned with working memory and short-term attention span, which could contribute to different findings from previous research.

We noted that those with MCI and more sleep disturbances tended to exhibit better performance in most of the cognitive domains, specifically in executive function among males. This observation raises certain considerations. Existing research has proposed that those with cognitive impairment might have diminished self-awareness (i.e. anosognosia) [44], potentially leading to inaccuracies in their self-reports. This cautions against relying solely on self-report data when assessing individuals with cognitive impairment and highlights the importance of obtaining collateral information from caregivers. Another plausible explanation could be that sleep may no longer play as a significant role in cognition because these individuals may have already

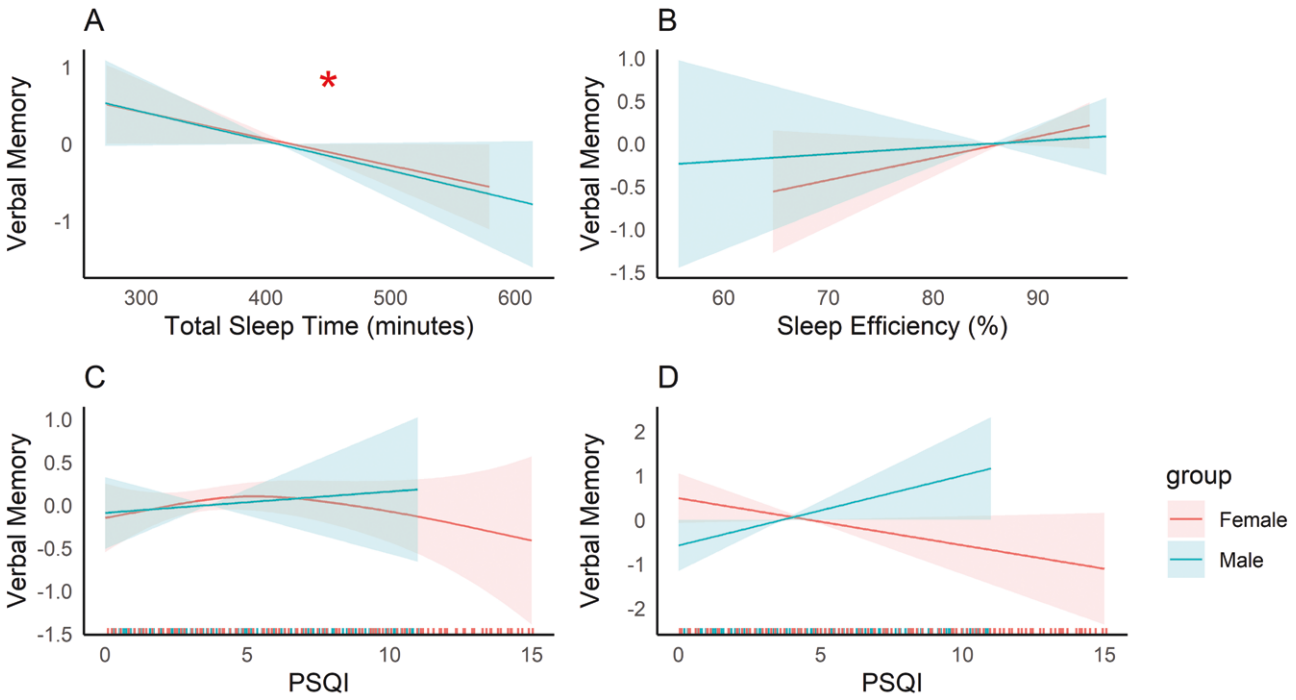


Figure 2. Partial effects of total sleep time, sleep efficiency (SE), and Pittsburgh Sleep Quality Index (PSQI) on verbal memory.

surpassed a critical threshold in their cognitive decline. Our findings need to be interpreted with caution due to the small sample size of individuals with MCI in our study.

In terms of sex differences in perceiving sleep quality, previous research suggests that females generally have a more accurate perception [49, 50]. Our results suggested a trend among females with NC, where poorer self-reported sleep quality was associated with lower cognitive performance, while males with NC demonstrated increased cognitive performance with more severe self-reported sleep quality. However, when comparing the TST and SE measured by actigraphy with self-reported data from our sample, we found a significant correlation in the sleep duration of males with NC, which contradicted previous findings of females having a more accurate perception. Another possible explanation is that females may have different optimal sleep requirements. It is important to note that most of our sample scored in the "better" range on the sleep duration and efficiency subscales of the PSQI. To better understand the relationship between objective and self-reported sleep measures, future research should involve a larger and more diverse sample, including individuals with varying sleep quality.

One main difference between our study and most studies that investigate sleep and cognition in a sex-dependent manner is that prior research typically induces sleep loss to investigate the effects of acute or chronic sleep loss on cognitive performance, resulting in a significant impact on memory and executive function [30, 31], as opposed to real-world observations in our study. Furthermore, the majority of our participants exhibited ideal SE levels (around 85%). Studies that include those with lower SE may yield different results and provide insights into the cognitive sequelae of clinically impaired sleep.

Our study has several strengths. First, we used a comprehensive neuropsychological battery to gauge participants' cognitive performance, opting for a more in-depth assessment rather than relying on a simple test battery (e.g. the mini-mental state examination), which is less sensitive to subtle cognitive impairment. Second, we included composite scores of cognitive domains generated through confirmatory factor analysis to represent each cognitive domain using multiple tests. This approach allows for a better representation of each cognitive domain. Third, we employed GAMs to capture nonlinear relationships between sleep quality and cognitive performance without imposing symmetrical curves. Moreover, GAMs have the built-in capability to determine the appropriate level of smoothness for each predictor, ensuring an optimal fit. Fourth, we objectively measured TST and SE over multiple nights allowing for a more representative result of typical sleep and compared it with self-reported measures to evaluate distinctions between the two common types of measures.

Several limitations should also be acknowledged. First, the present study is limited by the characteristics of the sample. The participants were primarily white, highly educated, relatively healthy, and motivated to engage in research, leading to limited generalizability of the findings. Most of the participants in this study had relatively healthy sleep patterns. Second, we did not include daytime napping in the TST because previous research suggests that daytime sleep and nighttime sleep have different impacts on cognitive processes [51]. Therefore, excluding daytime naps helped to isolate the specific effects of nighttime sleep, ensuring a clearer understanding of how it relates to cognitive performance. Third, we acknowledged the

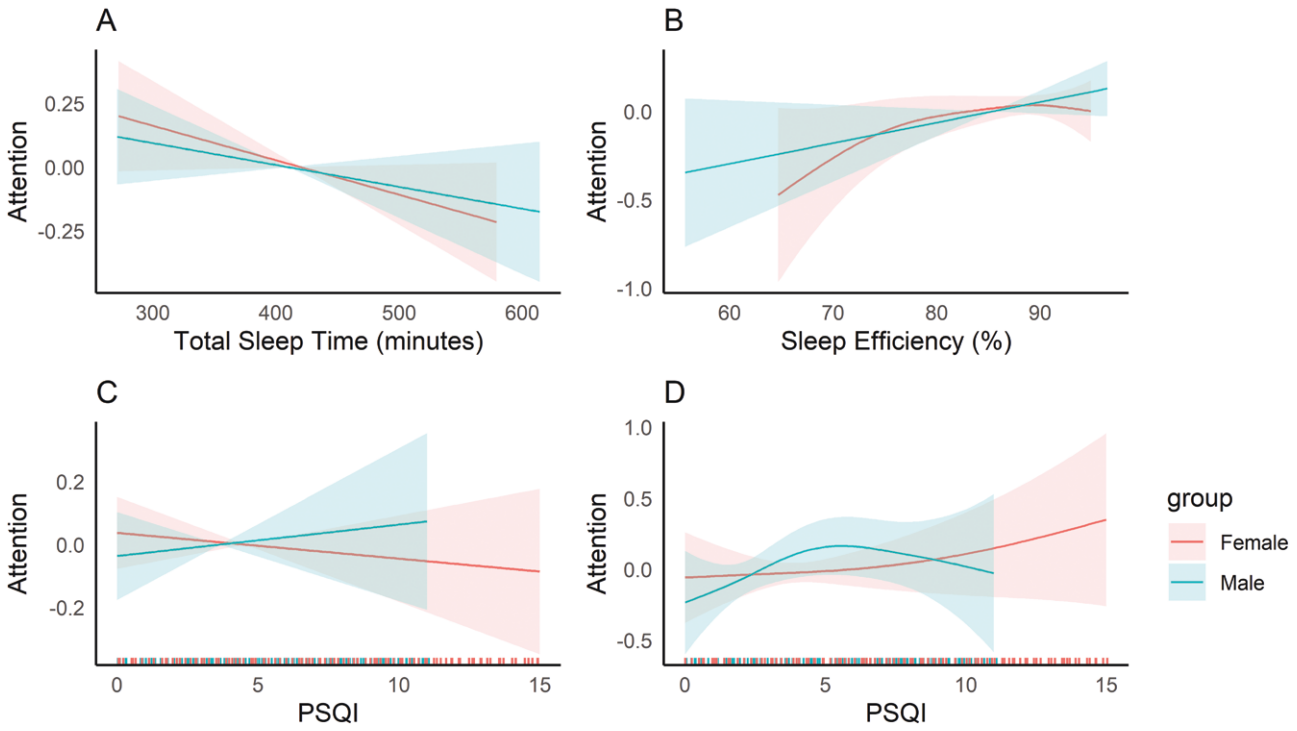


Figure 3. Partial effects of total sleep time, sleep efficiency (SE), and Pittsburgh Sleep Quality Index (PSQI) on attention.

potential challenges of using the PSQI in individuals with MCI, particularly regarding their ability to recall sleep details over the past 30 days. Despite these concerns, we found that the instrument has been extensively used in research involving MCI populations, as reported in a literature review [52], which supports our decision to include participants with normal and mildly impaired cognition in our analysis, allowing for a more comprehensive exploration of the relationship between sleep quality and cognitive function across a spectrum of cognitive statuses. Moreover, the potential influence of cognitive impairment on self-reported sleep quality was mitigated by incorporating the CDR into the analysis as a covariate. We also stratified the relationship between PSQI and cognitive outcomes by CDR levels. Fourth, while the median *p*-value has been suggested to be a valid pooling approach following multiple imputations, there has not been a valid way to pool the effective degree of freedom (EDF), which elaborates the linearity of the associations. We reported the range of the EDF from the 25 imputations; however, this approach introduces high variability in the linearity of the imputed values or the PSQI in our case. More robust methods to pool the EDF are necessary to get clear results of the nature of the relationships.

Our study has yielded foundational evidence of the association between sleep and cognitive health in older females and males, with effects across distinct cognitive domains. Our findings suggest that studies focusing on determining the optimal sleep characteristics required to maintain cognitive health in individuals of different sexes are warranted. Utilizing our findings, the design of future sleep interventions for older females should assess the optimization of sleep duration and monitor self-reported sleep quality to maintain optimal cognitive function. For older males, studies assessing enhancing SE or reducing awakenings could be tested toward supporting higher-order cognitive processing. Future investigations should also consider the role of neurological changes due to aging when investigating the associations of sleep with cognition. While our analysis adjusted for cognitive status and age, further investigation is necessary to understand the directionality of these variables.

Future research should also explore the long-term effects of midlife hormonal changes on sleep and cognitive health in aging populations, using longitudinal analysis, since this period is notable for hormonal shifts. Midlife may serve as an optimal window for intervention, as cognitive decline resulting from sleep deprivation tends to be less severe at this stage. Such studies could also provide critical insights into the temporal dynamics of sleep and cognitive decline, identifying potential periods of vulnerability and opportunities for preventive interventions. Moreover, future research should incorporate information regarding stages of sleep measured by PSG to provide a more detailed understanding of how sleep architecture contributes to cognitive function and whether these effects vary by sex. The implications of future findings have the potential to shape public health policies and strategies for aging. Healthcare professionals should consider recommending regular sleep assessments as part of a comprehensive checkup to promote cognitive well-being in aging populations.

Supplementary material

Supplementary material is available at *SLEEP Advances* online.

Author Contributions

Yumiko Wiranto (Conceptualization [equal], Formal analysis [lead], Methodology [equal], Visualization [lead], Writing—original draft [lead]), Catherine Siengsukon (Writing—review & editing [supporting]), Diego Mazzotti (Supervision [lead], Writing—review & editing [supporting]), Jeffrey M. Burns (Conceptualization [lead], Funding acquisition [lead], Methodology [lead], Project administration [lead], Resources [lead], Supervision [supporting], Writing—review & editing [supporting]), and Amber Watts (Funding acquisition [supporting], Methodology [supporting], Supervision [supporting], Writing—review & editing [lead])

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Disclosure Statements

Conflict of interest: CS is the owner and Chief Executive Officer of Sleep Health Education, LLC. A preprint of this manuscript is available on medRxiv, DOI: https://doi.org/10.1101/2024.01.08.24300996

Data Availability

The dataset presented in this article is not readily available because dataset requests must be made directly to the KU-ADRC. Those interested in accessing the dataset should be directed to the following website where they can complete a data request form: https://www.kumc.edu/research/alzheimers-disease-research-center/research/resources-for-researchers-and-principal-investigators.html.

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