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ORIGINAL RESEARCH

Sleep Quality and Cognitive Abilities in the Greek Cohort of Epirus Health Study

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Purpose: Sleep is essential to all human body functions as well as brain functions. Inadequate sleep quantity and poor sleep quality have been shown to directly affect cognitive functioning and especially memory. The primary aim of the present study was to investigate the association of sleep quality with cognitive abilities cross-sectionally in a middle-aged Greek population and secondarily to examine this association prospectively in a smaller group of these participants.

Patients and Methods: A total of 2112 healthy adults aged 25–70 years (mean: 46.7±11.5) from the Epirus Health Study cohort were included in the analysis and 312 of them participated in secondary prospective analysis. Sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI) scale and cognition was assessed in primary cross-sectional analyses with three neuropsychological tests, namely the Verbal Fluency test, the Logical Memory test and the Trail Making test, and in secondary prospective analyses with online versions of Posner cueing task, an emotional recognition task, the Corsi block-tapping task and the Stroop task. Statistical analysis was performed using multivariable linear regression models adjusted for age, sex, education, body mass index and alcohol consumption.

Results: Attention/processing speed was the only cognitive domain associated cross-sectionally with PSQI score. Specifically, participants with better self-reported sleep quality performed faster on the Trail Making Test - Part A (β= 0.272 seconds, 95% CI 0.052, 0.493).

Conclusion: Further studies are needed to clarify the association of sleep quality with cognition, especially in middle-aged people that are still in productive working years.

Keywords: sleep quality, cognition, attention, executive functions, memory, middle-aged

Introduction

Cognitive functions are the mental processes, such as perception, memory, language, planning and problem solving, that are necessary for selection, processing, manipulation, storage and retrieval of information in order for an individual to adapt to the environment.[1] Insufficient sleep quantity[2–4] and poor sleep quality[5,6] have been linked to impaired cognitive functions.

The processes that take place during sleep are vital and serve physiological[7–9] and cognitive functions.[10] Although still not well understood, these processes are thought to restore homeostasis of human body networks, renormalizing the changes occurred while being awake. It is proposed that sleep minimizes energy expenditure, promotes protein synthesis and synaptic strengthening, and eliminates metabolic waste products through glymphatic network.[11] Also, sleep disruptions are linked with higher levels of amyloid plaques and tau tangles,[12–14] a hallmark of cognitive decline and Alzheimer's disease.

Sleep seems to affect particularly learning and memory consolidation, as evidenced in studies of all age ranges.[15–17] Regarding the neurophysiological mechanisms involved, during non-rapid eye movement sleep (or slow-wave sleep), information encoded during wakefulness is repeatedly replayed in hippocampus, distributed and integrated in neocortical

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regions. This strengthens synaptic connections that are renormalized during sleep by slow oscillations. As a result, relevant information becomes more salient and irrelevant information fades away.[18–20]

The association between sleep quality and cognitive function has been examined in previous studies with healthy adults. There are cross-sectional[21–23] as well as longitudinal studies[24–27] that suggested poorer sleep quality is associated with poorer cognitive function in general; and other studies that argued poor sleep quality negatively affects selectively only specific cognitive domains using both cross-sectional[28–30] and longitudinal design.[31] However, there are also studies that did not find an association between sleep quality and cognition cross-sectionally[32,33] or prospectively.[34,35]

Previous studies conducted in Greece that evaluated sleep quality in relation to cognition have shown an association both with objective[36] and with subjective cognitive performance.[37] However, these two studies used sample from the same cohort, aged over 65 years old. It is of note that most previous studies included elderly participants over 60 years. Thus, the relationship between sleep quality and cognition in middle-aged and in younger adults remains unclear.

The aim of this study was to investigate the association between sleep quality, as defined by the Pittsburgh Sleep Quality Index (PSQI) scale, and cognition in a Greek sample of mostly middle-aged participants without any reported neurological or psychiatric diagnosis. We used data from the Epirus Health Study (EHS), a deeply phenotyped ongoing prospective cohort study in Greece involving participants aged 25–70 years.

Materials and Methods

Study Population

The EHS started in June 2019 and is an ongoing population-based prospective cohort study, which aims to investigate the etiology of multifactorial chronic diseases and thus to improve the overall health status of the Greek population. The EHS cohort consists of permanent residents of the Epirus region in Greece, of both sexes, aged 25 to 70 years, without symptoms of active infection at entry into the study. Further details on EHS cohort study design have been published previously.[38] Until 31 October 2022, a total of 2230 participants were recruited to the study and the vast majority of them were residents of the urban city of Ioannina and fluent in the Greek language.

For the purposes of the current study, we excluded participants who self-reported serious neurological (n=1 Alzheimer's disease, n=2 Parkinson's disease, n=19 epilepsy) or psychiatric conditions (n=57 major depression disorder and n=1 bipolar disorder). Also, we excluded 20 participants with missing data on cognitive tests and 18 participants with missing data of sleep quality scores. Thus, the analyses were performed on the remaining 2112 participants, as described in Figure 1.

The study was approved by the Research Ethics Committee of the University of Ioannina and is conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their participation in the study.

Data Collection

The EHS collects information on socio-demographic characteristics, general health status and lifestyle data, as well as anthropometric and clinical measurements. Specifically, all study participants were interviewed using a standard close-ended questionnaire at recruitment by two trained interviewers regarding socio-demographic characteristics (ie, sex, age, level of education, place of birth and income), general health status and lifestyle factors (ie, physical activity, alcohol consumption, smoking habits). Weight, standing height and waist circumference were measured using SECA equipment.

Pittsburgh Sleep Quality Index (PSQI)

Sleep quality was assessed using the PSQI, a tool designed by Buysse et al in 1989,[39] which provides a subjective measure of sleep quality and sleep patterns. It consists of 19 self-rated questions focusing on sleep quality and disturbances in the past month, of which 4 are open-ended and the remaining 15 are closed-ended (Likert-type). The 19 items generate seven component scores and then are summed to yield the total PSQI score. The seven components of PSQI are subjective sleep quality, sleep latency, sleep duration, sleep disturbances, habitual sleep efficiency, use of sleep medications and daytime dysfunction. Each component score ranges from 0 to 3, and the total PSQI score ranges from 0 to 21, with higher scores indicating severe sleep difficulties. Furthermore, a total score above five indicates poor sleep quality.

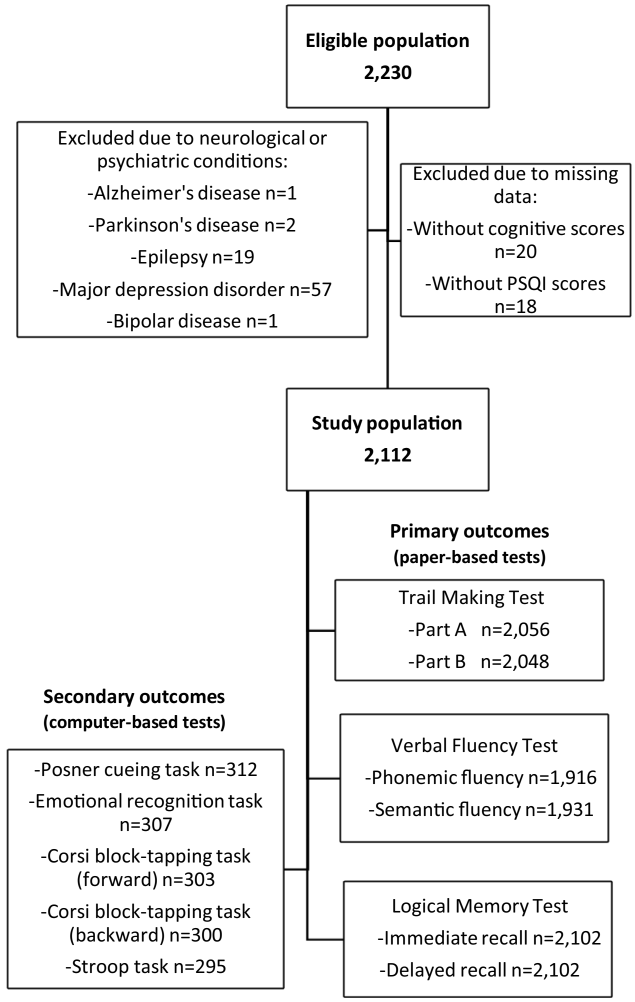

Figure 1 Flowchart for the identification of the study population.
Note: Each outcome was determined independent of the other outcomes.

Cognitive Measurements

Assessment of cognitive functions at recruitment was conducted through standardized neuropsychological tests, the Greek versions of the Trail Making Test (TMT),[40] the Verbal Fluency test (VF)[41] and the Logical Memory test (LM).[42,43] These tests were chosen because they are widely used to assess cognitive function and are sensitive to the presence of any cognitive decline that may occur even in preclinical stages.[44] Additionally, stratification by age and level of education is performed for the available normative data concerning the Greek population, which provides useful cut-off values for cognitive impairment.

For the secondary prospective analyses, the neuropsychological tests used were the online versions of the Posner cueing task,[45] an emotional word recognition task,[46] the Corsi block-tapping task[47] and the Stroop task.[48] Participants were invited to complete the computer-based neuropsychological tests through the online platform PsyToolkit.[49,50] An invitation was sent via email on 28/9/2021 to all participants recruited until August 2021, and on the last day of each month to participants recruited ever since. Until 31st October 2022, 312 participants had completed the computer-based neuropsychological tests, and secondary prospective analyses were performed on 154 participants that had completed the online neuropsychological examination at least 6 months after their initial neuropsychological examination at recruitment.

TMT, Posner cueing task and Stroop task assess attention and processing speed; VF and Stroop task assess executive functions and LM, the emotional word recognition task and Corsi block-tapping task assess memory. Total scores of VF, LM, the emotional word recognition task, and Corsi block-tapping task are the sum of correct responses and higher

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scores indicate better performance. Total score of TMT is the seconds needed to complete each subtest and thus, lower scores indicate better performance. Scores of Posner cueing task and Stroop task are both correct responses and seconds needed to complete each condition of test. Further details for each neuropsychological test and scoring are provided in the supplementary material (Supplementary File 1).

Statistical Analysis

Baseline characteristics of the study sample were summarized using means and standard deviations (SD) or percentages, as appropriate for continuous and categorical variables, respectively. Also, baseline sample characteristics and scores of cognitive tests were analyzed according to PSQI using independent sample *t*-tests or x^2 tests.

PSQI scores were examined both as continuous and as categorical variables in separate models. Continuous scores of PSQI were transformed according to the cut-off score for good sleep quality (0–5 points) and poor sleep quality (6–21 points).

Multivariable linear regression analysis was used to investigate the cross-sectional association of sleep quality, measured by PSQI score, with cognition, measured by the continuous scores of the three cognitive tests conducted at recruitment. In addition, multivariable linear regression analysis was performed to examine the prospective association of sleep quality with cognition using PSQI score and the continuous scores of the four computer-based cognitive tests. We also applied multivariable linear regression analysis using binary categories of PSQI scores and continuous scores of the cognitive tests.

All models were first adjusted for age (continuous), sex and level of education (primary and secondary school, high school, and higher education) and additionally adjusted for body mass index (BMI, continuous) and alcohol consumption (never, less than once/month, 1–3 times/month, 1–2 times/week, almost every day).

Interaction analyses according to sex and age groups (young: <40 years, middle-aged: 40–59.9 years, old: ≥60 years) were performed in the fully adjusted models to test whether the associations could be modified by these factors.

A sensitivity analysis was performed after excluding participants that were not born in Greece (N=181) to control for possible language difficulties that could affect the performance on cognitive tests. However, results remained similar and consequently they are no further discussed.

Statistical analyses were performed using STATA (version 13.1; StataCorp, College Station, TX, USA). A p-value of less than 0.05 was considered statistically significant for all main analyses, but the interactions were interpreted more conservatively given the higher sample size needed for such analyses.

Results

In Table 1, sociodemographic characteristics of the study participants are presented overall and by the binary PSQI score. Overall, the mean age of participants was 46.7 (SD=11.4) years and most of them belonged to the age group 40–59 years (57.48%). Women (60.1%) and individuals of higher education (64.1%) predominated in the sample. The mean PSQI score was 4.6 points (SD=2.3), ranging from 1 to 18 and suggesting a moderate sleep quality. The majority of participants (73.2%) reported good sleep quality. The mean BMI was 26.5 kg/m2 (SD=4.9). Regarding the alcohol consumption among participants, 29.7% consumed alcoholic beverages less than once a month and 29.7% consumed alcoholic beverages once or twice a week.

Participants with poor sleep quality were older, more often women and of lower education in comparison with participants with good sleep quality. Also, participants with poor sleep quality had worse cognitive scores in both subtests of TMT (Part A and Part B) and VF (semantic and phonemic), whereas they had similar performance with participants with good sleep quality in the rest cognitive tests (Supplementary Table S1).

Follow-up period ranged from 6 months to 2 years (mean period 1.4 years) (Supplementary Table S1). Participants that had completed the prospective computer-based cognitive tests were of younger age and higher education and had lower BMI compared with participants that did not complete the prospective neuropsychological examination (Supplementary Table S2).

Table 2 presents the results of multivariable linear regression models that investigated the cross-sectional association between continuous scores of PSQI and the three primary cognitive tests. No significant associations were observed between continuous scores of PSQI and memory tests of LM immediate recall and delayed recall. We observed some

Table 1 Sociodemographic and Lifestyle Characteristics of Epirus Health Study Participants by Level of Sleep Quality

Characteristics	All Participants (N=2112)	Sleep Quality[†]		*p*-value
		Good (N=1546)	Poor (N=566)	
Age	46.7 ± 11.4	46.1 ± 11.3	48.1 ± 11.7	<0.001[a]
Female	1268 (60.1)	873 (56.5)	395 (69.8)	<0.001[b]
Education				<0.001[b]
Primary and secondary school*	167 (7.9)	92 (6.0)	75 (13.3)	
High school**	590 (28.0)	421 (27.3)	169 (29.9)	
Higher education***	1353 (64.1)	1032 (66.8)	321 (56.8)	
PSQI score	4.6 ± 2.3	1546 (73.2)	566 (26.8)	
BMI	26.5 ± 4.9	26.4 ± 4.9	26.6 ± 4.8	0.498[a]
Alcohol consumption				0.153[b]
Never	280 (13.3)	201 (13.0)	79 (14.0)	
Less than once / month	627 (29.7)	444 (28.7)	183 (32.3)	
1–3 times / month	312 (14.8)	237 (15.3)	75 (13.3)	
1–2 times / week	628 (29.7)	477 (30.9)	151 (26.7)	
Almost everyday	265 (12.6)	187 (12.1)	78 (13.8)	

Notes: [†]Sleep Quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) score. Good and poor sleep quality were defined if PSQI ranged between 0–5 and 6–21, respectively. *Elementary school or junior high school, up to 9 years of education. **High school, up to 12 years of education. ***University degree/MSc/PhD/Postdoc, more than 13 years of education. [a]Comparisons using *t*-test. [b]Comparisons using x^2 test. Mean ± standard deviation and frequency (percentage) are presented for continuous and categorical variables, respectively.
Abbreviations: PSQI, Pittsburgh Sleep Quality Index; BMI: body mass index.

Table 2 Results of Multivariable Linear Regressions for the Cross-Sectional Association Between Sleep Quality (Continuous Score) and Cognitive Function (Continuous Score) Among Epirus Health Study Participants

Cognitive Function Scores	Sleep Quality[†]					
	Model 1[a]			Model 2[b]		
	Beta	95% CI	*p*-value	Beta	95% CI	*p*-value
Verbal Fluency						
Semantic	−0.113	−0.227, 0.001	0.051	−0.109	−0.223, 0.006	0.063
Phonemic	−0.223	−0.550, 0.104	0.182	−0.069	−0.140, 0.002	0.057
Logical Memory						
Immediate recall	0.050	−0.039, 0.139	0.273	0.051	−0.039, 0.141	0.264
Delayed recall	0.010	−0.036, 0.056	0.669	0.012	−0.034, 0.058	0.615
Trail Making Test						
Part A	0.271	0.050, 0.493	**0.016**	0.272	0.052, 0.493	**0.016**
Part B	0.283	−0.069, 0.636	0.115	0.286	−0.063, 0.635	0.108

Notes: [†]Sleep Quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) score. [a]Adjusted for age (continuous), sex, education. [b]Adjusted for age (continuous), sex, education, BMI and alcohol consumption. Bold values indicate statistical significance at the p < 0.05 level.
Abbreviation: CI, Confidence interval.

trends toward significant associations between continuous scores of PSQI and VF semantic (b=−0.109, p=0.063) and phonemic (b=−0.069, p=0.057) subtest. A significant association was found only between PSQI and TMT A test both in basic adjusted model (b=0.271, p=0.016) and in the fully adjusted model (b=0.272, p=0.016).

In the secondary prospective analyses that used computer-based cognitive tests to examine the association between continuous scores of PSQI and cognition, no significant associations were found (Table 3).

Table 3 Results of Multivariable Linear Regressions for the Prospective Association Between Sleep Quality (Continuous Score) and Cognitive Function (Continuous Score) Among Epirus Health Study Participants

	Sleep Quality†					
Cognitive Function Scores	**Model 1[a]**			**Model 2[b]**		
	Beta	**95% CI**	***p*-value**	**Beta**	**95% CI**	***p*-value**
Posner cueing						
Total correct	−0.443	−1.339, 0.453	0.330	−0.546	−1.428, 0.337	0.224
Mean reaction time-valid trials	0.008	−0.003, 0.019	0.152	0.006	−0.005, 0.018	0.276
Mean reaction time-invalid trials	−0.002	−0.013, 0.010	0.757	−0.002	−0.014, 0.010	0.759
Emotional word recognition						
Total correct	0.183	−0.322, 0.687	0.476	0.144	−0.375, 0.663	0.584
True positive	−0.039	−0.313, 0.235	0.780	−0.016	−0.300, 0.267	0.909
True negative	0.221	−0.112, 0.555	0.191	0.161	−0.175, 0.496	0.345
Corsi block-tapping						
Forward	−0.026	−0.177, 0.125	0.734	−0.035	−0.193, 0.123	0.660
Backward	−0.019	−0.172, 0.135	0.811	−0.033	−0.194, 0.129	0.687
Stroop						
Total correct	−0.477	−1.568, 0.614	0.389	−0.602	−1.708, 0.504	0.283
Mean reaction time-congruent trials	−0.003	−0.019, 0.013	0.724	−0.002	−0.019, 0.014	0.776
Mean reaction time-incongruent trials	0.010	−0.012, 0.032	0.387	0.013	−0.009, 0.036	0.247

Notes: †Sleep Quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) score. [a]Adjusted for age (continuous), sex, education. [b]Adjusted for age (continuous), sex, education, BMI and alcohol consumption.
Abbreviation: CI, Confidence interval.

When binary categories of PSQI scores were used, significant associations were found for both subtests of TMT ($b_{TMT\ A}$=1.274, p=0.028, $b_{TMT\ B}$=1.934, p=0.036 for basic adjusted Model 1 and $b_{TMT\ A}$=1.175, p=0.042, $b_{TMT\ B}$=1.806, p=0.048 for fully adjusted Model 2) (Supplementary Tables S3 and S4), but not for the other primary or secondary cognitive tests.

When multivariable linear regression analyses using the interaction terms by age groups and sex were performed, there was no evidence for interaction for cognitive test scores (Table 4, Supplementary Tables S5 and S6).

Table 4 Results of Multivariable Linear Regressions for the Association Between Sleep Quality and Cognitive Function (Continuous Score) with the Interaction Terms by Age Groups and Sex Among Epirus Health Study Participants

	Sleep Quality†					
Cognitive Function Scores	**Interaction with Age**			**Interaction with Sex**		
	Beta	**95% CI**	***p*-value**	**Beta**	**95% CI**	***p*-value**
Verbal Fluency						
Semantic	0.001	−0.009, 0.011	0.852	0.017	−0.229, 0.264	0.891
Phonemic	−0.002	−0.008, 0.005	0.607	0.030	−0.123, 0.183	0.701
Logical Memory						
Immediate recall	−0.003	−0.011, 0.005	0.439	−0.032	−0.225, 0.162	0.749
Delayed recall	0.000	−0.004, 0.004	0.861	0.029	−0.071, 0.128	0.573
Trail Making Test						
Part A	0.013	−0.007, 0.032	0.198	−0.108	−0.581, 0.366	0.655
Part B	0.025	−0.005, 0.056	0.101	0.112	−0.639, 0.863	0.770

Notes: †Sleep Quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) score. Adjusted for age (continuous), sex, education, BMI and alcohol consumption.
Abbreviation: CI, Confidence interval.

Discussion

In the present analysis, the main purpose was to investigate the association between sleep quality and cognitive abilities both in a cross-sectional and prospective setting, although the prospective analysis was conducted in a small subsample. The results showed a significant association between sleep quality and cognitive ability, only in the cognitive test that measures attention and processing speed assessed cross-sectionally. Namely, higher PSQI scores, implying poorer sleep quality, predicted higher scores in TMT A, indicating slower processing speed and response time in this test.

The results of our study could be explained based on the Controlled Attention Hypothesis, which posits that simpler and basic cognitive processes, such as processing speed, are more easily affected by sleep quality, in contrast with more complex cognitive processes, such as memory and executive functions.[51] This can be attributed to the greater top-down control from higher-order brain areas that is needed to sustain optimal performance in more complex and challenging tasks, such as memory recall. On the contrary, vigilance tasks, assessing processing speed and reaction time, are more sensitive to sleep of insufficient quality because they demand mainly bottom-up processes that are based on prefrontal cortex,[52] a brain area associated also with sleep quality.[52,53] Consequently, this theory states that sleep does not affect universally cognitive functions but rather its effect is selective, depending on the characteristics of the task and the specific cognitive processes needed.

Some previous studies reported null results and supported a lack of cross-sectional association between sleep quality and executive functions[30] and memory[30,35] in particular. However, these findings contradict other studies that argue that poor sleep quality is cross-sectionally detrimental to both the aforementioned cognitive domains,[28,54] including one study conducted in Greek older adults,[36] as well as to general cognitive functioning.[21] Moreover, there are longitudinal studies that confirm the negative association of sleep quality and cognition.[24,27,31] Of note, one of these studies[30] found only a significant relationship between sleep quality and attention using the same cognitive test but a different cut-off score for poor sleep quality compared to our study.

To the best of our knowledge, the present study is one of the few that investigated the association between sleep quality and cognitive abilities in a middle-aged population, recruited from the community with no reported neurological or psychiatric conditions. Previous studies in middle-aged healthy adults reported a negative cross-sectional association of sleep quality with memory[28,29] and a negative prospective association with general cognitive levels,[24,27,55] and only one study with younger mean age showed no cross-sectional associations with sleep quality.[32]

Disparate results possibly could not be attributed in differences in exposure measurement since both studies that found significant results between sleep quality and cognition[21,22,24–26,28–31] and studies that did not report significant results,[32,33,35] used PSQI to measure sleep quality. There were only five studies[23,27,34,36,37] that used other types of self-reported questionnaires to measure sleep quality, and only one of them reported non-significant results.[34]

However, outcome measurement differed considerably among the aforementioned studies. It is noteworthy that most of the studies that reported non-significant results evaluated cognitive function with Mini-Mental State Examination (MMSE),[33–35] a short screening test of global cognition, rather than domain-specific tests, that were used in studies reporting significant associations between sleep quality and cognition.[23,24,28–30,36] Nevertheless, there are also studies that found significantly worse performance in participants with poor sleep quality compared with participants with good sleep quality using MMSE.[21,22,26,31]

Moreover, age of participants could contribute to diversity in results, as larger number of studies that found significant results included participants older than 60 years old[21–23,25–28,30,31,36,37] and only two studies included middle-aged participants.[24,29] In our study, we did not find a moderation effect of age, probably due to the small number of older participants included.

The results of the present study confirm the association between poor sleep quality and cognitive deficits, even in healthy middle-aged adults. In contrast with the previous studies, deficits were specific to the domain of attention. These findings indicate the need for more extensive neuropsychological assessment in individuals reporting sleep difficulties, as they may be at greater risk for cognitive impairment state.

There are potential limitations of the present study to be noted. The primarily cross-sectional design of the study prohibits the investigation of a causal relationship between sleep and cognitive deficits. Also, data on sleep quality were collected with self-reported questionnaires rather than from objective measurements, which would have provided more valid and reliable estimates. However, PSQI has been validated in the Greek population[56] and it is one of the most commonly used tools worldwide. Furthermore, participants of the present study were of middle age and of higher educational level compared to different demographic characteristics of other studies, which poses limits to the potential generalization of the results.

On the other hand, several strengths of our study are noteworthy. First, the PSQI scale and cognitive tests are reliable and standardized measures with age- and education-specific normative data, resulting in increased measurement accuracy. They are also the Greek versions of widely used diagnostic tools for cognitive decline. In addition, we prospectively administered computer-based tests (although in a smaller population sample). Finally, the analyses were performed in a large population-based sample and various sociodemographic factors that could act as potential confounders in the associations between cognitive function and sleep quality were controlled for.

Conclusion

The current study suggested that sleep quality is related to attention and processing speed in a Greek population with mainly middle-aged participants. No heterogeneity of associations by sex and age were observed. Given the evidence linking poor sleep quality to cognitive dysfunction, and considering the rising number of sleep problems, it is necessary to conduct further population and intervention studies using both objective and subjective measures to examine the association of sleep quality with specific cognitive domains, which can lead to the design of targeted strategies for public health promotion.

Data Sharing Statement

Data may be available upon reasonable request to the corresponding authors.

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Disclosure

The authors report no conflicts of interest in this work.

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