Cardiovascular Endurance Modifies the Link between Subjective Sleep Quality and Entorhinal Cortex Thickness in Younger Adults

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ABSTRACT

WON, J., A. J. ALFINI, and J. C. SMITH. Cardiovascular Endurance Modifies the Link between Subjective Sleep Quality and Entorhinal Cortex Thickness in Younger Adults. *Med. Sci. Sports Exerc.*, Vol. 53, No. 10, pp. 2131–2139, 2021. **Introduction:** Poor sleep is linked to impaired cognitive function, cortical brain atrophy, and lower cortical thickness. Independently, higher cardiovascular endurance has neuroprotective effects. It remains in question, however, whether cardiovascular endurance moderates the relationship between sleep and brain health. The aims of this study included the following: 1) the association between subjective sleep quality and cognitive performance, hippocampus volume, and entorhinal cortex (EC) thickness, and 2) the moderating effects of cardiovascular endurance on the associations of sleep quality with cognitive and magnetic resonance imaging measures in healthy younger adults. **Methods:** A total of 1095 younger adults (28.8 ± 3.6 yr) from the Human Connectome Project were included in the analyses. The 2-min walk test was used as a proxy of cardiovascular endurance. Self-reported sleep quality was measured using the Pittsburgh Sleep Quality Index. Composite cognitive tests were used to assess global cognition, and T1-weighted structural magnetic resonance imaging data (obtained using Siemens 3T scanner) was used to assess hippocampus volume and EC thickness. Linear regression was used to examine the moderating effects of fitness on the relationships between sleep and each of these neurocognitive outcomes after controlling for age, sex, and education year. **Results:** Poorer sleep quality was associated with both a lower crystalized intelligence score ($B = -0.198$, $P = 0.034$) and lower EC thickness ($B = -0.013$, $P = 0.003$). With greater 2-min walk test score, the association between greater Pittsburgh Sleep Quality Index score and lower EC thickness was attenuated ($B = 0.0008$, $P = 0.028$). **Conclusions:** Higher cardiovascular endurance may mitigate the relationship between poorer subjective sleep quality and lower EC thickness. Future longitudinal studies should examine the interactive effects of sleep and fitness on brain health among older and more vulnerable populations. **Key Words:** CARDIOVASCULAR ENDURANCE, CORTICAL THICKNESS, ENTORHINAL CORTEX, SLEEP, YOUNGER ADULTS

The prevalence of sleep problems is as high as 56% in the general population, which comes with substantial health care costs (1). Inadequate sleep is associated with adverse health outcomes such as cardiovascular disease (2), depression, and anxiety (3). Importantly, poor subjective sleep quality (i.e., assessed by Pittsburgh Sleep Quality Index (PSQI) (4)) has been associated with impaired global cognition, working memory, attentional set-shifting, abstract problem solving, verbal knowledge, long-term memory, and visuospatial reasoning (5–8). In addition, poor subjective sleep quality is associated with adverse neuroimaging outcomes (9). For example, self-reported sleep quality has also been linked to global cortical brain atrophy (10), hippocampal atrophy (11), reduced cortical thickness (12), and lower structural and functional connectivity in temporal and occipital regions (13).

Although the relationship between subjective sleep quality and brain health among older adults has been extensively studied, few studies have examined this relationship among younger adults. Aging is associated with reduced subjective sleep quality (14) and increase in subjectively measured daytime sleepiness (15). These age-related alterations in subjective sleep quality have consistently predicted cognitive decline in older adults (16). Conversely, because younger adults typically exhibit normal cognitive function, it is presumed that poor sleep affects cognition in this population to a lesser degree compared with their older counterparts (17). Nevertheless, subjective measures of poor sleep are not only common in younger adults but also linked with lower cognitive performance, higher rates of depression, and attention-deficit disorder (16). Detecting and improving sleep problems in early adulthood is of significance,

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as the neurocognitive effects of poor sleep may accumulate over time and have deleterious long-term consequences (18).

Independently, higher cardiovascular fitness is associated with better cognitive function, larger cortical volume, and greater cortical thickness across the lifespan (19). For example, cross-sectional studies of younger and older adults have reported that higher cardiovascular fitness was linked to greater gray and white matter volumes in both age groups (20). Another cross-sectional study in younger adults found significant positive relationships between cardiovascular endurance and global cognitive function (21). A randomized controlled trial demonstrated that 6 months of aerobic exercise training improved executive function among cognitively normal adults, regardless of age and, after stratifying by age, showed that younger adults exhibited exercise-induced increases in cortical thickness in a left frontal region (22).

Although the neuroprotective effects of cardiovascular endurance have been well documented, it remains unknown whether cardiovascular endurance might moderate the relationship between poor sleep and structural decline. To address this research gap, we evaluated (a) the main effects of subjective sleep quality on global cognition, hippocampus volume, and entorhinal cortex (EC) thickness, and (b) the interaction of cardiovascular endurance and self-reported sleep quality on cognitive performance and brain structure among younger adults.

For the magnetic resonance imaging (MRI) analyses, the hippocampus and EC were selected as *a priori* regions of interest. Located in the medial temporal lobe, the hippocampus is one of the key regions involved in memory and cortical-hippocampus communication during slow wave sleep is crucial in memory consolidation (23). Moreover, worse self-rated sleep has been associated greater hippocampal atrophy across the adult lifespan (24). The EC is the major information gateway between the hippocampus and neocortex (25). The integrity of this connection is critical for sleep-dependent memory consolidation (26). Several lines of evidence suggest a relationship between poor self-reported sleep and regional cortical thinning (27), and it is worth investigating the link between subjective sleep quality and EC thickness given that EC is affected by sleep disorder (28) and is one of the key indicative regions for cognitive decline through greater tau accumulation, increasing the risk of Alzheimer's disease (29). Lastly, higher cardiovascular endurance is associated with both larger hippocampus volume and greater EC thickness (30,31). We hypothesized that younger individuals with poorer sleep quality would exhibit lower global cognition, a smaller hippocampus volume, and a lower EC thickness; and that greater cardiovascular endurance would reduce the negative relationship between subjective sleep quality and cognitive and cortical volume and thickness.

METHODS

Participants. We utilized publicly available data from the Human Connectome Project (HCP) (32) in which cardiovascular endurance data, self-rated sleep quality, composite cognitive test scores, and structural MRI are available in a large sample of well-characterized younger adults. Using a recruiting strategy reflecting the population distribution of the United States, the HCP recruited healthy younger adults (ranging between 21 and 35 yr of age) from the state of Missouri. Exclusion criteria included 1) psychiatric disorders, substance abuse, neurological disorders, or cardiovascular disease; 2) two or more seizures after age 5 yr or a diagnosis of epilepsy; 3) any genetic disorder, such as cystic fibrosis or sickle cell disease; 4) multiple sclerosis, cerebral palsy, brain tumor, or stroke; 5) premature birth; 6) currently on chemotherapy or immunomodulatory agents, or a history of radiation or chemotherapy; 7) thyroid hormone treatment in the past month; 8) treatment for diabetes in the past month (other than gestational or diet-controlled diabetes); 9) use of daily prescription medications for migraines in the past month; 10) a score of 25 or lower on the Mini Mental State Exam; 11) pregnancy; and 12) any MRI contraindications (e.g., the presence of ferromagnetic material in the body, moderate or severe claustrophobia). Data sharing and experimental procedures were performed in compliance with relevant guidelines and regulations (33). All participants provided written informed consent to the HCP consortium. Participants visited the Washington University of St. Louis on two different days for MRI scanning and cognitive assessments, respectively.

Subjective sleep quality. To evaluate sleep, we used the PSQI (4). The PSQI consists of seven subscales including sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. By summing the subscale scores, a global sleep score reflecting overall sleep quality can be calculated, with higher scores indicating poorer sleep quality. The PSQI is effective in differentiating poor and good sleep quality; a score of >5 is indicative of poor sleep (34). We used the PSQI score as both a continuous and categorical variable to explore between group differences.

Cardiovascular endurance. To measure the ability to sustain effort that requires conjoint work capacities from cardiopulmonary function (i.e., cardiovascular endurance), we used the 2-min walk test (2MWT), which was administered as part of the motor domain of the National Institutes of Health (NIH) toolbox (35). Participants were instructed to walk as fast as they can for 2 min on a 50-ft course (15.24 m). Distance is measured in feet and inches after completion of the test. The raw scores were normalized to the entire NIH Toolbox normative sample (≥18 yr old), regardless of age or any other variable; thus, the scores were normalized to have a mean of 100 with an SD of 15, indicating 100 reflects the national average performance and scores of 85 and 115, respectively, reflect performances 1 SD below and above the national average. Extensive reliability and validity tests demonstrate that the 2MWT has good test–retest reliability (intraclass correlation >0.8) (35).

Cognitive tests. A comprehensive battery of neuropsychological tests was administered to evaluate cognitive function, including Picture Sequence Memory, Dimensional Change Card Sort, Flanker task, Oral Reading Recognition, Picture Vocabulary, Pattern Comparison, and List Sorting.

Previous studies have described the administration and scoring methods (36,37). The subtest scores were averaged to generate composite scores using the NIH Toolbox Cognition Battery that included 1) total composite score (normalized scores of all subtests); 2) a crystalized intelligence quotient score (normalized crystalized scores such as Picture Vocabulary and Oral Reading tests); 3) an early cognitive composite score (normalized early childhood cognitive battery such as Picture Vocabulary, Flanker, Dimensional Change Card Sort, and Picture Sequence Memory); and 4) fluid intelligence score (normalized fluid ability measures including Flanker, Dimensional Change Card Sort, Picture Sequence Memory, and List Sorting). All cognitive scores were standardized using a mean of 100 and an SD of 15. It has been reported that the composite score from the NIH Toolbox has excellent reliability and validity and can be effectively used in epidemiologic and clinical studies (38). Therefore, we used cognitive composite scores as measurements of cognitive performance for the present analysis.

MRI data acquisition. Whole-brain MRI was conducted using a customized Siemens (Munich, Germany) 3.0 Tesla Skyra MR scanner at Washington University. A 32-channel head coil (SC72) was used for radio frequency transmission and reception. A high-resolution T1-weighted anatomical image was acquired with gradient echo sequence: field of view, 224 mm; voxel size, 0.7 × 0.7 × 0.7 mm; slice thickness, 0.9 mm; repetition time, 2400 ms; echo time, 2.14 ms; inversion time, 1000 ms; flip angle, 8°; and duration, 7:40 min.

MRI data analysis. MRI data were processed using the FreeSurfer (version 5.3.0) automatic cortical reconstruction process for cortical parcellation, and subcortical segmentation (recon-all) (39) was used for brain volume assessment. Briefly, nonbrain tissue was removed by applying a hybrid watershed/surface deformation procedure to volumetric T1-weighted images. Next, automated Talairach transformation was administered before deep gray matter (including the hippocampus) and white matter structures were segmented. Then, intensity normalization, gray and white matter boundary tessellation, automated topology correction, and a surface deformation to estimate the borders between gray/white and gray/cerebrospinal fluid were performed. The closest distance from the gray/white boundary to the gray/cerebrospinal fluid at each vertex was calculated to evaluate cortical thickness. Hippocampal volume (mm^3) and EC thickness (mm) were calculated from this automated segmentation process. We also evaluated the sleep–cardiovascular endurance interaction effects on total gray matter volume to test specificity.

Statistical analyses. All statistical analyses were performed using SPSS Version 26.0 (IBM, Armonk, NY). The Shaprio–Wilk test was used to determine normality of the demographic data, cognitive test scores, and MRI data for the entire sample. First, we investigated the association of sleep with cognitive function. To accomplish this, we used linear regression models in which the PSQI global sleep score (as continuous variable) was the independent variable and the composite cognitive test scores were included as dependent variables. Separate models were estimated for each composite test score (e.g., fluid, early, crystalized, and total). We then tested the relationship between the PSQI global sleep score and MRI variables, using separate models for hippocampus volume, total gray matter volume, and EC thickness. All primary analyses were adjusted for age, sex, and years of education. In addition, total intracranial volume (estimated by FreeSurfer) was included as a covariate when regional brain volume was tested as a dependent variable. This adjustment was based on previous investigations that identified significant sex-related differences in intracranial volume (ICV), with males having a greater ICV than females (40). Benjamini–Hochberg false discovery rate (FDR) correction (41) was conducted to control the family-wise error rate for multiple comparisons on families (i.e., family 1 cognition; family 2, MRI). We also tested the association between the 2MWT score and cognitive test results and brain assessments using the same approach.

Next, using the PSQI as a categorical variable (good sleepers (PSQI ≤5) vs poor sleepers (PSQI >5)) (34), we first evaluated between-group differences in demographic characteristics using independent-samples *t*-tests (or Wilcoxon rank sum tests) for continuous variables and a χ^2 test (or Fisher exact test) for the categorical variable. Between-group differences (good sleepers vs poor sleepers) in cognitive performance and cortical volume/thickness were assessed using linear regression models, with sleep group (categorical variable; good sleepers as a reference group) as an independent variable and cognitive test scores and cortical volume/thickness (both continuous variables) as dependent variables.

We also evaluated the association of cardiovascular endurance with cognitive function and MRI data using linear regression method described above and corrected for multiple comparisons on families (i.e., family 1, cognition; family 2, MRI). For the significant correlation between PSQI and cognitive performance and cortical volume, cortical thickness (PSQI as a continuous variable), 2MWT, and interaction term (PSQI–2MWT) were further added into the linear regression model to evaluate the moderating effects of cardiovascular endurance in the relationship between sleep and cognitive performance and cortical volume. Lastly, we administered a sensitivity analysis by adding additional covariates (income and race) into the regression models. The statistical significance was determined using a two-tailed $\alpha = 0.05$.

RESULTS

Participants. Among the 1206 participants who completed the study protocol, 111 individuals were excluded due to missing data (cognitive tests, $n = 16$; cardiovascular endurance, $n = 2$; cortical volume/thickness, $n = 93$). The total analytic sample included 1095 participants (Table 1).

Association between self-reported sleep (as a continuous variable) and cortical volumes, thickness, and cognitive function. A greater PSQI score predicted a lower crystalized intelligence score ($B = -0.198$; 95% confidence interval (CI), −0.381 to −0.014; $P = 0.034$). However, this association did not survive FDR correction ($P = 0.012$). There were

TABLE 1. Demographic data of the participants.

	Total Sample (n = 1095)	Good Sleepers (PSQI ≤5; n = 749)	Poor Sleepers (PSQI >5; n = 346)	Group Differences P Value (Cohen's d)
Demographics				
Age, mean ± SD, yr	28.8 ± 3.6	28.8 ± 3.7	28.7 ± 3.5	0.725 (0.022)
Female, n (%)	595 (54.3)	400 (53.4)	195 (56.3)	0.327_F
White, n (%)	814 (74.3)	582 (77.7)	232 (67.0)	0.002_F
Education years, mean ± SD	14.9 ± 1.8	15.0 ± 1.7	14.6 ± 1.9	0.00006 (0.263)
Sleep				
PSQI total score, mean ± SD	4.7 ± 2.7	3.2 ± 1.3	8.0 ± 2.1	2.6483e–247 (2.889)
Aerobic fitness				
2-min walk test, mean ± SD	110.1 ± 12.0	110.8 ± 11.9	108.6 ± 12.0	0.005 (0.182)

Group differences were calculated using independent-samples t-test or Wilcoxon rank sum tests for continuous variables and Fisher exact tests for categorical variables ($_F$).

no associations between PSQI score and other cognitive composite scores ($P \geq 0.127$).

Findings also revealed that greater PSQI score was linked to lower EC thickness ($B = -0.013$; 95% CI, −0.022 to −0.004; FDR corrected, $P = 0.003$), whereas there were no significant associations between PSQI score and total gray matter or hippocampal volumes ($P \geq 0.291$; Table 2). The pattern of results from the sensitivity analysis remained the same (i.e., negative associations between PSQI and crystalized composite score ($P = 0.047$) and EC thickness ($P = 0.008$)). Detailed results of the sensitivity analysis are provided in Supplementary Table 2 (Table, Supplemental Digital Content, Appendix, http://links.lww.com/MSS/C332). The relationship between PSQI as a categorical variable (good sleepers (PSQI ≤5) vs poor sleepers (PSQI >5)) and cognitive test results and brain assessments are also available in Supplementary Material 2 (Supplemental Digital Content, Appendix, http://links.lww.com/MSS/C332).

Association between cardiovascular endurance and cortical volumes, thickness, and cognitive function. Greater 2MWT score was associated with consistently better cognitive performance including fluid composite score ($B = 0.196$; 95% CI, 0.136–0.255; FDR corrected, $P < 0.001$), early composite score ($B = 0.194$; 95% CI, 0.141–0.248; FDR corrected, $P < 0.001$), crystalized composite score ($B = 0.142$; 95% CI, 0.096–0.187; FDR corrected, $P < 0.001$), and total composite score ($B = 0.276$; 95% CI, 0.207–0.345; FDR corrected, $P < 0.001$).

There was a significant association between greater 2MWT score and greater total gray matter volume ($B = 274.16$; 95% CI, 106.362–441.958; $P = 0.001$; FDR threshold $P = 0.012$). Conversely, there were no significant associations between 2MWT results and hippocampal volume or EC thickness ($P \geq 0.531$; Table 3). The pattern of results from the sensitivity analysis remained the same for the association between 2MWT and cortical volume and cognitive test results. Detailed results of the sensitivity analysis are available in Supplementary Table 3 (Table, Supplemental Digital Content, Appendix, http://links.lww.com/MSS/C332).

The moderating effects of cardiovascular endurance on relations between self-reported sleep and cognitive function and cortical thickness. There was a significant PSQI (continuous variable)–2MWT interaction on EC thickness ($B = 0.0008$; 95% CI, 0.00008–0.0015; $P = 0.028$), such that the association between greater PSQI score and reduced EC thickness was attenuated by 0.0008 mm with each 1-unit increase in 2MWT (i.e., greater fitness). The moderating effects of 2MWT remained significant for sensitivity analysis ($B = 0.0007$; 95% CI, 0.00001–0.0014; $P = 0.044$) (see Fig. 1).

DISCUSSION

The present study investigated the moderating effects of cardiovascular endurance on the association between sleep and brain health in healthy younger adults. Our results provide evidence that poorer self-reported sleep quality is linked to a lower crystalized composite score and lower EC thickness. Although greater cardiovascular endurance was consistently associated with better cognitive function and greater total gray matter volume, there were no associations between cardiovascular endurance and hippocampal volume or EC thickness. Importantly, the association between poorer subjective sleep and lower EC thickness was reduced with greater cardiovascular endurance.

Our findings indicate that poorer self-rated sleep quality is associated with lower crystalized composite score in younger

TABLE 2. Association between PSQI score (as a continuous variable) and cortical volume, thickness, and cognitive test results.

	B Coefficient	t	P	95% CI for B
Cortical volume and thickness				
Total gray matter volume, mm^3	−361.696	−1.055	0.291	−1034.365 to 310.971
Hippocampal volume, mm^3	4.877	0.656	0.511	−9.709 to 19.463
Entorhinal cortex thickness, mm	−0.013	−2.949	0.003	−0.022 to −0.004
Cognitive function				
Fluid composite	−0.074	−0.605	0.544	−0.316 to 0.166
Early composite	−0.110	−0.992	0.320	−0.330 to 0.108
Crystalized composite	−0.198	−2.115	0.034	−0.381 to −0.014
Total composite	−0.220	−0.152	0.127	−0.502 to 0.062

PSQI was used as a continuous variable. Regression analyses were adjusted for age, sex, education, and ICV for hippocampal volume. Regression analyses were adjusted for age, sex, and education for cognitive tests and entorhinal cortex thickness.

TABLE 3. Association between 2-min walk test score (as a continuous variable) and cortical volume, thickness, and cognitive test results.

	B Coefficient	*t*	*P*	95% CI for *B*
Cortical volume and thickness				
Total gray matter volume	274.16	3.206	0.001	106.362 to 441.958
Hippocampal volume	1.166	0.626	0.531	–2.487 to 4.820
Entorhinal cortex thickness	0.0004	0.427	0.669	–0.001 to 0.002
Cognitive function				
Fluid composite	0.196	6.477	1.413e–10	0.136 to 0.255
Early composite	0.194	7.118	1.978e–12	0.141 to 0.248
Crystalized composite	0.142	6.154	1.057e–09	0.096 to 0.187
Total composite	0.276	7.877	8.068e–15	0.207 to 0.345

PSQI was used as a continuous variable. Regression analyses were adjusted for age, sex, education, and ICV for hippocampal volume. Regression analyses were adjusted for age, sex, and education for cognitive tests and entorhinal cortex thickness.

adults. However, other studies have demonstrated no associations between PSQI score and working memory, executive function, and procedural learning performances (17). Although episodic memory (Picture Sequence Memory) and language tasks (Picture Vocabulary) were included, most tasks consisting of the fluid composite, early composite, and total composite scores are executive function (Flanker, Dimensional Change Card Sort), processing speed (Pattern Comparison), and working memory tasks (List Sorting). Therefore, our findings demonstrating no associations between PSQI score and fluid

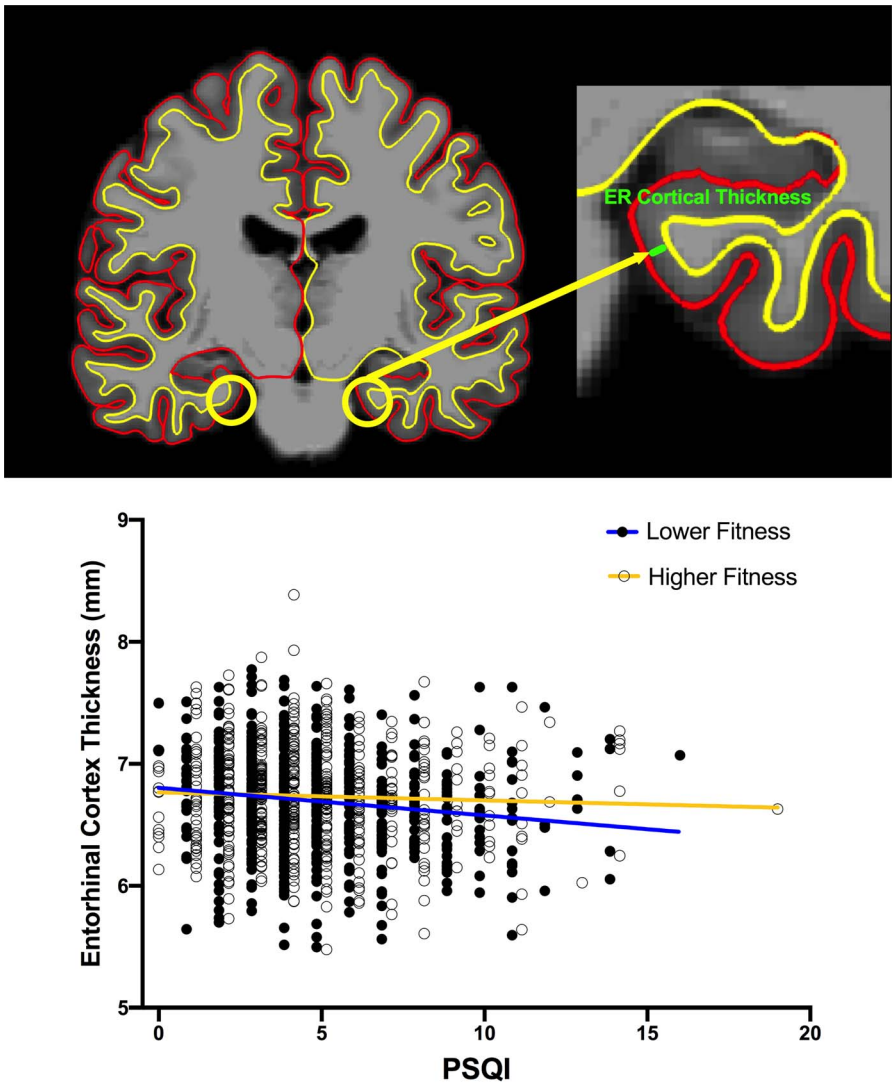

FIGURE 1—PSQI (continuous variable)–2MWT (continuous variable) interaction on bilateral EC thickness (B = 0.0008; 95% CI, 0.00008–0.0015; P = 0.028). To visualize the interaction, we incrementally tested the relationship between continuous PSQI and EC thickness at specific levels of the 2MWT score. We identified the significant inflection point (where the PSQI and EC thickness relationship becomes significant) at the 2MWT score of 110. Thus, 2MWT score of 110 (high fitness, 2MWT score ≥110; low fitness, 2MWT score <110) was used as cutoff to create two groups for the interaction figure. Regression results for lower fitness are r = 0.144, r^2 = 0.021, P = 0.0004, and those for higher fitness are r = 0.031, r^2 = 0.001, P = 0.335.

composite, early composite, and total composite performances partly agree with the previous study (17). In contrast, the crystalized composite measure is normalized scores of Picture Vocabulary and Oral Reading tests, indicating that poorer subjective sleep quality may be associated with poorer language and vocabulary comprehension. Thus, the present results complement the previous investigation (17), with evidence that although poorer self-reported sleep may not be associated with impaired executive function, it may predict lower language and vocabulary acquisition in healthy younger adults. This is supported by the sleep group comparison in this study such that the good sleep group (PSQI ≤5) demonstrated better crystalized cognitive composite score compared with the poor sleep group (PSQI >5). However, it is important to note that the main effect of sleep on cognition is small and does not survive FDR. This may not be unexpected in younger adults who are cognitively healthy and have multiple avenues of cognitive reserve that may be able to overcome poor sleep at their age. Longitudinal studies in chronic poor sleepers are needed to understand how this effect may increase over time and what lifestyle behaviors continue to be protective.

Although there were no associations between comprehensive PSQI score (as a continuous variable) and total cognitive composite score in the present study, Grumbach and colleagues (42) found that self-reported sleep duration, which is one component of PSQI questionnaires, predicted greater total cognitive composite score in the same HCP sample. This suggests that, although overall sleep quality may be associated with language and reading acquisition, sleep duration may be an important predictor for global cognition in younger individuals. A caveat for interpreting the results from Grumbach et al. (42) is that only a single subcomponent of the PSQI showed significant relationship to the total cognitive composite sore. Given that self-reported sleep duration is often underestimated by individuals (43), caution should be taken when using a single PSQI subscore as a predictor. Conversely, global PSQI scores not only demonstrated high retest reliability and validity (44–46) and are consisted of seven distinct sleep subcomponents (4), representing overall dimensions of sleep quality. Thus, our results add to the exiting literature by investigating the association between global subjective sleep quality and cognitive function in younger adults.

Same patterns in the relationship between self-reported sleep quality and cognitive function were observed for the sleep group comparison (good vs poor sleepers). In the sleep group comparison, there was a strong trend toward a negative association between PSQI score and total cognitive composite score (i.e., measurement of global cognition). Although it was not statistically significant ($P = 0.061$), the effect of the finding should not be diminished given the large sample size ($n = 1095$). Classifying sleep groups based on the PSQI cutoff is clinically relevant to differentiate good (PSQI ≤5) and poor sleepers (PSQI >5) because a global PSQI score of ≤5 correctly identified 89.6% of healthy control and 84.4% of insomnia patients (4). Hence, the present study adds further weight to this notion that subjective sleep quality using PSQI can have its own exploratory value for exploring the relationship between subjective sleep and brain health in younger adults.

The present study also found that subjectively measured poor sleep was linked to lower EC thickness in healthy younger adults. The association between sleep and cortical thickness has been previously reported. For example, lower sleep slow waves density (i.e., hallmark feature of stage 3 and 4 non–rapid eye movement) was associated with significantly lower cortical thickness in a sample that included younger adults (47). Compared with good sleepers, patients diagnosed with persistent insomnia demonstrated lower cortical thickness (48). In older individuals with amnestic mild cognitive impairment, shorter rapid eye movement sleep duration was associated with lower cortical thickness (49). Furthermore, sleep deprivation disrupted neurotransmitter receptors (i.e., ionotropic glutamate receptors) mediating the synaptic activity that excites cellular activity within the EC (50). There was a positive association between sleep apnea and accelerated EC tau accumulation, one of the key biomarkers for Alzheimer's disease leading to neurodegeneration in the EC and hippocampal regions (29). Extending the collective evidence supporting the relationship between sleep disorder, objectively measured sleep, and EC, our results elucidate that subjectively poorer sleep may be associated with lower EC thickness in younger adulthood.

The present results also suggest that there may be no linkage between subjective sleep quality and hippocampal volume in younger adults. This finding is partly consistent with Sexton et al. (12) in which no relationship between subjective sleep quality assed by PSQI and hippocampal volume was found in middle-age adults. One other study also found no association between self-rated sleep and hippocampal volumes in older adults who are older than 90 yr (51). Conversely, poorer subjective sleep was associated greater hippocampal atrophy across the adult lifespan (24), and there was an association between higher PSQI scores and lower CA1 volume in individuals with primary insomnia (52). Given these mixed findings, the relationship between subjective sleep quality and hippocampal volume remains speculative. Various aspects of hippocampus, beyond hippocampal volume, such as hippocampal subfield volume, cerebral blood flow, and functional connectivity need to be explored in the future to extend our understanding about the relationship between subjective sleep and hippocampus.

The most notable finding in this study was the moderating effects induced by cardiovascular endurance on the relationship between subjective sleep and EC thickness. According to a prior investigation in younger adults, greater cardiovascular fitness predicted greater right EC volume (31) and EC thickness (53). In a cross-sectional study of older adults, longer self-reported walking distance predicted greater EC volume (54). In another study of cognitively intact middle-age and older adults, higher levels of self-rated sedentary behavior were relevant to lower EC volume (55). Rodent work reported that enriched environment (e.g., running wheels) increased EC thickness (56). In contrast to

these findings, the present study did not observe a significant association between cardiovascular endurance and EC thickness. Best and colleagues (57) examined the association between physical fitness (including body mass index, 2MWT, and grip strength) and neuroimaging markers using the same HCP sample. They found that body mass index was negatively associated with fractional anisotropy in several white matter regions and positively correlated with right superior parietal lobe thickness. However, there were no significant relationships between cardiovascular endurance and brain structure including hippocampal volume and EC thickness, which aligns with the results found in this study. The lack of cardiovascular endurance–EC thickness association makes the moderating effects more notable, as this highlights the role of cardiovascular endurance as a moderator in the relationship between subjective sleep and thickness of the brain region that is important for cognitive function. Collectively, the present study has an important implication that poorer subjective sleep predicts lower EC thickness in younger adults, which could be linked to higher risk of accelerated brain deficits in later life (18), and greater cardiovascular endurance may mitigate the negative relationship between poor subjective sleep and lower EC thickness from younger adulthood.

Strengths and limitations. One of the major strengths of the present study was a large and well-characterized sample of younger and healthy individuals ($n = 1095$). The present study also used cognitive composite scores from a comprehensive neuropsychological battery that robustly tested a wide range of cognitive domains using the NIH Toolbox. In addition, investigations into subjective sleep quality and brain assessments in younger adults are relatively scarce. Our results add to the current body of knowledge by suggesting that poorer subjective sleep is associated with lower EC thickness, which is moderated by cardiovascular endurance in younger adults. There are several limitations to this study that warrant caution when interpreting the results. First, cross-sectional design limits interpreting the directionality of the current results. Further longitudinal and interventional studies will be necessary to clarify the role of fitness in modulating the sleep-related impairment in brain health. Second, we used self-reported sleep data and a proxy of cardiovascular endurance. Although 2MWT is a proxy of cardiovascular endurance, 2MWT results demonstrated high relevance to those of 6-min walk test, which demonstrated significant associations between brain assessments including brain volume and cognitive function (58). Next, objective measurement of sleep (e.g., polysomnography, actigraphy, and sleep disordered breathing) and direct measure of fitness (e.g., maximal or sub-maximal graded exercise test) need to be used in the future. Lastly, future longitudinal and intervention studies should examine if the moderating effects of higher cardiovascular endurance on cognitive function and on brain structure are inter-related.

CONCLUSIONS AND FUTURE DIRECTIONS

In healthy younger adults, greater PSQI score predicted a lower crystalized composite score (e.g., language and vocabulary abilities) and EC thickness. Moreover, the association between poorer subjective sleep quality and less EC thickness was attenuated with greater cardiovascular endurance. The participants in this study exhibited cardiovascular endurance that was slightly above but within 1 SD of the normative data. Considering the importance of early detection and prevention of poor sleep-related cognitive and brain dysfunction, which may accumulate over time and may have long-term consequences in the late adulthood, clinical implication of the present study is the importance of maintaining cardiovascular endurance from early adulthood to mitigate the association between poor subjective sleep and lower cortical thickness. Furthermore, this study will also help develop therapeutic strategies to improve sleep and offset negative health effects of subjective poor sleep quality. The relationship between poor subjective sleep and cognitive and structural deficits is more evident in older adults (8,9), and our results suggest the possible moderating effects of cardiovascular endurance on the link between subjective sleep and brain health in older individuals, which should be investigated in future. Lastly, the present study expands on the prior work demonstrating the joint effects of sleep and exercise on cognitive (59) and brain function (60). Despite the significance of the present study, our results should be viewed cautiously because of cross-sectional study design, self-reported sleep data and a proxy of cardiovascular endurance, and inclusion of individuals with normal sleepers. Future work should explore the interaction between cardiovascular endurance and sleep on brain function using longitudinal study design and objective measurement of sleep and cardiovascular fitness.

We thank Human Connectome Project Team for sharing the data. All participants provided written informed consent to the HCP consortium, and the HCP was approved by the institutional review board at Washington University and was conducted in accordance with the Helsinki Declaration of 1975. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and the results of the present study do not constitute endorsement by the American College of Sports Medicine.

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