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Authors
Mohlenhoff, Brian S
Insel, Philip S
Mackin, R Scott
et al.

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SCIENTIFIC INVESTIGATIONS

Total Sleep Time Interacts With Age to Predict Cognitive Performance Among Adults

Brian S. Mohlenhoff, MD[1,2,3]; Philip S. Insel, MS[2,4,5]; R. Scott Mackin, PhD[1,2,5]; Thomas C. Neylan, MD[1,3]; Derek Flenniken[2,5]; Rachel Nosheny, PhD[2,5]; Anne Richards, MD, MPH[1,3]; Paul Maruff, PhD[6,7]; Michael W. Weiner, MD[1,2,3,4]

[1]Department of Psychiatry, University of California, San Francisco, San Francisco, California; [2]Center for Imaging of Neurodegenerative Diseases (CIND), San Francisco, California; [3]Mental Health Service, Department of Veterans Affairs Medical Center, San Francisco, California; [4]Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, California; [5]San Francisco Veterans Affairs Medical Center, Veterans Health Research Institute (NCIRE), San Francisco, California; [6]Florey Institute for Neuroscience and Mental Health, University of Melbourne, Parkville, Australia; [7]Cogstate, Ltd., Melbourne, Victoria, Australia

Study Objectives: To investigate interactions between high and low amounts of sleep and other predictors of cognitive performance.
Methods: We used four cognitive tests to determine whether sleep time interacted with age, personal history of a memory problem, parental history of a memory problem, or personal concerns about memory and were associated with cognitive performance. Data were collected from an internet-based cohort study. We used an ordinary least squares regression with restricted cubic splines, controlling for demographic variables and comorbidities.
Results: We found significant nonlinear interactions between (1) total sleep time and age and (2) total sleep time and personal history of a memory problem and cognitive performance. Short and long sleep durations and self-reported memory complaints were associated with poorer performance on a test of attention and this was true to a greater degree in younger and older adults. A repeat analysis excluding subjects reporting dementia was significant only for the test of attention.
Conclusions: These results extend existing data on sleep duration and cognition across the lifespan by combining in a single study the results from four specific cognitive tests, both younger and older adults, and four self-reported risk factors for cognitive impairment. Longitudinal studies with biomarkers should be undertaken to determine whether causal mechanisms, such as inflammation or amyloid buildup, account for these associations.
Keywords: aging, cognition, internet, sleep
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BRIEF SUMMARY
Current Knowledge/Study Rationale: Sleep durations that are comparatively short and long have been associated with poorer cognitive performance but little is known about how total sleep time interacts with other risk factors for poorer cognitive performance. Furthermore, most studies to date have considered only short or long sleep durations, not both.
Study Impact: For the first time, we show that individuals who were concerned about their memory and reported short and long sleep durations performed significantly worse on standardized tests of memory and attention than their peers who reported mid-range sleep durations. Additionally, after excluding subjects with dementia, older individuals who reported short and long sleep durations performed significantly worse on a standardized test of attention than their peers who reported mid-range sleep durations, raising the possibility that older adults are especially susceptible to the effects of irregular sleep durations.

INTRODUCTION

Studies have shown an inverted U-shaped relationship between total sleep time (TST) and cognition such that individuals with TSTs closer to the mean demonstrated better performance than their peers with shorter or longer TST.[1,2] The same U-shaped relationship between cognition and TST has been observed in older adults as well.[3,4] In addition to TST, three other correlates of cognitive performance are age (independent of TST), having a subjective memory complaint or a memory problem, and having a family history of memory problems or dementia.[5–7] No published study has tested whether the association between long and short TST and cognitive dysfunction interacts with these other risk factors (subjective memory complaint, or personal or family history of memory problems) for poorer cognitive performance. Moreover, most studies of TST and cognition have used linear regression analyses using a quadratic term, without evaluating other potential nonlinear shapes of the curve.[8]

The purpose of this study was to test for the presence of a relationship between TST and cognition and determine whether family history, memory concerns, or memory problems show significant interactions with TST in relationship to cognitive function. We hypothesized that self-reported TST would be correlated, in an inverted U-shaped manner, with cognition in adults with other risk factors for poorer cognition, namely (1) a personal history of a memory problem or concern or (2) a family history of a memory problem or dementia. A secondary goal

was to determine whether any such relationships depended on age. We used a large internet-based sample that included at-home cognitive assessments and extensive self-reported behavioral and health information. We used a cubic spline analysis for continuous data to allow for the possibility of nonlinear relationships.

METHODS

Data were drawn from a large internet-based cohort study called the Brain Health Registry (BHR). Launched in January 2014, the goal of the BHR is to facilitate the development of treatments for Alzheimer disease and other brain diseases. The BHR collects detailed health information and cognitive data online from a large pool of registrants interested in participating in neuroscience research in order to create a well-characterized cohort that can be accessed for future clinical trials. After registration and consent (the BHR is endorsed by the institutional review board at the University of California, San Francisco), participants complete questionnaires asking about demographics, overall health, medication use, memory, family history of dementia, mood, sleep, diet, and exercise.[9] Early advertising was accomplished through networking presentations at scientific conferences and presence at dementia-related events open to the public. Participation was voluntary and participants received no compensation for completing online questionnaires and tests.

At the time of this study, 5,483 individuals were enrolled in the BHR who had answered a question about sleep—"During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)"—in addition to the three questions pertaining to the other parameters of interest for this study, including questions related to dementia risk. Of this number, cognitive measures were available for 4,012 individuals. The sample used for this study consisted of 3,926 individuals who had provided age and sleep data, underwent cognitive tests, and for whom demographic data were also available. Subjects provided written consent to participate and all work has been approved by the institutional review board at the University of California, San Francisco.

Respondents listed up to nine medications using write-in fields. We identified patients taking either benzodiazepine or nonbenzodiazepine sedative-hypnotic medications. We used the restricted Damerau-Levenshtein distance from the search terms[10] to identify correct and incorrect spellings of medications available in the United States.[11]

To test our hypothesis using the BHR data, we identified two items on the set of initial screening questions that might indicate increased risk of dementia. These were: (1) having personal concerns about their own memory (OMC) or (2) having had a parent with a memory problem including dementia (PMP).[12,13] We also considered respondents who had reported having a personal history of having a memory problem including dementia (OMP) being diagnosed. We controlled for age, number of years of education, sex, scores on the Geriatric Depression Scale, use of sleep medications, and presence or absence of obstructive sleep apnea (with responses to the question, "Have you ever been diagnosed with sleep apnea?"). This information was gathered at the time of initial baseline questionnaire administration. We included subjects between the ages of 18 and 90 years. We ran all analyses first including and then excluding respondents who indicated on their medical history questionnaire that they had dementia (n = 21), Parkinson disease (n = 62), schizophrenia (n = 5), or stroke (n = 63).

Participants also complete online neuropsychological tests including the Cogstate Brief Battery in an unsupervised setting. The Cogstate Brief Battery is a computer-based collection of cognitive tests that have been validated under supervised and unsupervised conditions in a variety of populations.[14–19] Cogstate data included results from four tests, representing four distinct cognitive domains.

The One-Back (ONB) task is a test of working memory.[20] For this task participants are asked "is this card the same as that on the immediately previous trial?" The task has 30 trials. The primary outcome variable for this test is the mean of log-transformed response times for correct answers.

The Identification Test (IDN) is a measure of visual information processing speed (attention). For this test the participant is asked "Is the card red?" and must press either "yes" or "no" as cards are displayed. The primary outcome for this test is reaction time in milliseconds normalized using a logarithmic base 10 (Log 10 transformation).

The One Card Learning (OCL) test is a measure of visual learning and memory based on a recognition paradigm previously described.[21] For this task participants are asked, "Have you seen this card before?" The test contains 80 trials and the primary outcome variable is the proportion of correct responses (accuracy) normalized using an arcsine transformation.

The Detection Task (DET) is a simple reaction time measuring psychomotor speed. In this test the participant must answer the question "has this card turned over?" Participants are to press the spacebar as soon as the card flips over and the test ends after completion of 35 trials. The primary outcome variable for this test is reaction time in milliseconds normalized using a logarithmic base 10 (Log 10 transformation).

The relationships between performance on Cogstate tests and other variables were modeled using ordinary least-squares regression. Performance on each test was modeled separately and included age, sex, education, score on the Geriatric Depression Scale, presence of sleep apnea, sleep medication, and number of hours slept as predictors. Interactions between sleep and (1) family history, (2) memory concern, (3) memory problem, and (4) age were also evaluated, separately. Continuous predictors (age and hours slept) were assessed for potential nonlinear associations with cognition using restricted cubic splines. Answer categories allowed subjects to report TST between 4 and 12 hours in half-hour increments and extremely low and high sleep durations as " < 4" and " > 12" hours. The Akaike Information Criterion (AIC) was used to select the optimal number of spline knots.[22] Both age and hours slept consistently demonstrated significant nonlinear associations with all cognitive responses and were modeled with the two parameters resulting from three-knot splines. AIC was also used to test for the significance of the association between sleep and cognition. Associations were considered significant if the inclusion of the variable

or interaction of interest in the model resulted in a drop of AIC of 2 or more. Two-sided *P* values from *F* tests are reported in **Table 1**. Model fits were inspected by an analysis of residuals. *P* values were not corrected for multiple comparisons. All analyses were done in R v3.1.1 (wwww.r-project.org).

Associations between hours of sleep and potential covariates were evaluated using the Wilcoxon rank-sum test for categorical variables (sex, sleep apnea, sleep medication, family history of dementia, diagnosed memory problem, memory concern) and Spearman correlation for either continuous or ordered categorical variables (age, education). Education was parameterized as an ordered factor with three groups: some college or less, college graduate, and graduate school.

RESULTS

Demographics

The demographic data in **Table 1** include the 3,926 subjects in BHR who reported on their age, sleep, and demographics, and completed at least one cognitive task (54 subjects completed one task and the remainder completed all 4 tasks). The average age was 60 years (standard deviation [SD] 13.4). Of this number, 70.4% were female. A total of 80% of respondents (n = 3,103) reported having either a bachelor's degree or higher, 21% (n = 823) reported having earned a 2-year college degree or less, and 3% (n = 121) reporting having taken no college courses at all. A total of 11.5% of respondents endorsed having obstructive sleep apnea. About half of respondents (49.4%) reported having a parent with a memory problem or dementia. The mean age of respondents endorsing a parent with a memory problem or dementia was 62 (SD 10.5) years, with 21.3% of this group reporting less than a college education. A total of 4.2% of subjects reported taking benzodiazepine or nonbenzodiazepine sedative-hypnotic sleep medications. There was a statistically significant but small difference between the age of subjects who did not report memory problems in their parents (average 59 years) and those who did (62 years). The correlation between age and personal memory problems did not reach statistical significance (*P* = .38).

Table 1—Sample data (n = 3,926).

	Sleep (hours)		
	Average	SD	*P*
Total	8.18	2.05	–
Age	–	–	< .001*
Sex			
Male (n = 1,161)	8.03	2.05	.001*
Female (n = 2,765)	8.24	2.05	
Education			
< College (n = 823)	7.88	2.23	< .001*
College (n = 1,359)	8.19	1.95	
> College (n = 1,744)	8.31	2.02	
Sleep apnea			
No (n = 3,474)	8.21	2.02	.002*
Yes (n = 452)	7.91	2.27	
PMP			
No (n = 1,962)	8.18	2.03	.623
Yes (n = 1,916)	8.17	2.07	
OMP			
No (n = 3,738)	8.17	2.02	.49
Yes (n = 140)	8.16	2.80	
OMC			
No (n = 2,835)	8.29	1.92	< .001*
Yes (n = 1,512)	8.00	2.23	
Sleep medications			
No (n = 3,762	8.20	2.04	.001
Yes (n = 164)	7.71	2.19	

For categorical variables, *P* is derived from Wilcoxon rank-sum tests, for ordered categorical or continuous variables, *P* is derived from Spearman correlation coefficients. * = significance using $P \leq .05$. AIC = Akaike Information Criterion, OMC = personal memory concern, OMP = personal memory problem, PMP = parent with memory problem, SD = standard deviation, TST = total sleep time.

Sleep

Table 2 shows that most respondents (88.5%) reported that they usually slept between 6 and 9 hours nightly. TST showed positive correlation with age ($r = .085$, $P < .001$). Those respondents reporting a personal or parental history of memory problem or dementia had no difference in TST compared to their peers who did not report a personal or parental or history of memory problem or dementia. Respondents who indicated that they were concerned about their memory reported a TST that was 15 minutes shorter than those of their peers (6.99 versus 7.14, $P < .001$).

Cognitive Testing

Sleep

All four cognitive domains tested showed significant nonlinear relationships with hours of sleep (**Table 2** lists statistical test values and **Figure 1** and **Figure 2** demonstrate the nonlinear relationship between cognition and sleep). Performance was best at a TST in a midrange—approximately 8.0 hours, depending on the particular test—whereas performance was significantly lower at higher and lower TST.

Sleep and Age

We found a nonlinear interaction between age and TST that was associated with better cognitive performance at mid-range TST (**Table 2** and **Figure 1**) but only in the cognitive domains of working memory and attention. Subjects in the middle range of our cohort in terms of age demonstrated better cognitive performance at high and low sleep durations compared with both their younger and older peers. In other words, the U-shaped curves describing cognitive performance in relation to TST were less pronounced. The results of tests for combined effects of age and TST on measures of learning and psychomotor speed did not achieve significance.

Sleep and Other Variables

We found significant nonlinear interactions between TST and OMP on memory and attention (**Table 2** and **Figure 2**).

Table 2—Summary of results.

Outcome	Variable	n	*F*	*P*	ΔAIC
ONB	TST	3,887	5.18	.006	−6.38
	TST × age	3,887	2.69	.029	−2.80
	TST × PMP	3,841	0.39	.68	3.22
	TST × OMP	3,841	2.60	.075	−1.21
	TST × OMC	3,858	0.40	.67	3.20
IDN	TST	3,877	12.29	< .001	−20.56
	TST × age	3,877	5.04	< .001	−12.18
	TST × PMP	3,831	0.52	.60	2.97
	TST × OMP	3,831	5.73	.003	−7.48
	TST × OMC	3,848	0.06	.95	3.89
OCL	TST	3,942	3.95	.02	−3.90
	TST × age	3,942	0.30	.88	6.80
	TST × PMP	3,894	0.96	.38	2.07
	TST × OMP	3,894	0.07	.93	3.86
	TST × OMC	3,913	2.49	.08	−1.00
DET	TST	3,849	3.46	.03	−2.94
	TST × age	3,849	0.57	.68	5.73
	TST × PMP	3,804	0.50	.61	2.99
	TST × OMP	3,804	0.20	.82	3.60
	TST × OMC	3,820	0.21	.81	3.58

AIC = Akaike Information Criterion, DET = Detection Task of reaction time, IDN = Identification Test of information processing speed (attention), OCL = One Card Learning test of visual learning and memory, OMC = personal memory concern, OMP = personal memory problem, ONB = One-Back test of working memory, PMP = parent with memory problem, TST = total sleep time.

Subjects reporting a memory problem performed worse on measures of memory and attention at both higher and lower TST than their peers who did not report personal memory problems (**Figure 2**). The results of tests for effects of OMP and TST on measures of learning and psychomotor speed did not achieve significance. All tests related to reported history of having a PMP or a OMC did not achieve significance.

Post Hoc Analyses

We conducted a *post hoc* analyses excluding subjects who endorsed "dementia" on a health questionnaire. After these subjects were removed, TST was associated with performance on tasks of working memory, attention, and psychomotor speed but not visual learning. An interaction between age and sleep was associated with attention only (**Figure S1** in the supplemental material). In each case, subjects reporting middle-range TST performed the best. Other tests showed a similar trend but did not reach the level of statistical significance (**Figure S2** in the supplemental material).

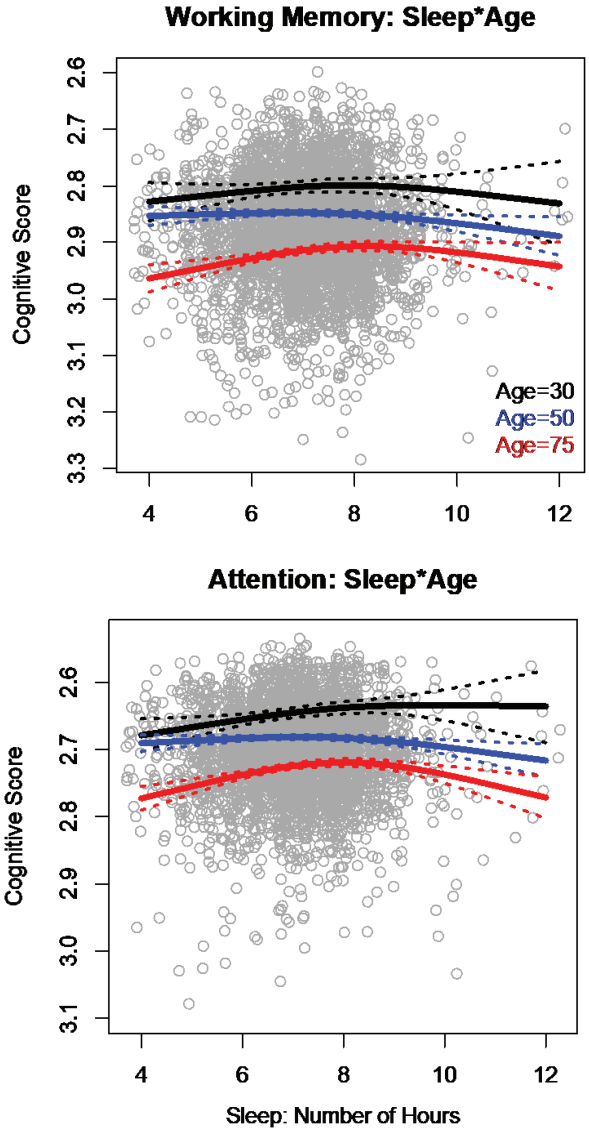
DISCUSSION

Our data show that concern about memory problems and age altered the relationship between sleep cognitive performance. In this study of adults, in each scenario tested, subjects in the middle range of our cohort in terms of age demonstrated better cognitive performance at high and low sleep durations compared with both their younger and older peers who reported similar sleep times (importantly, the same U-shaped relationship between sleep and cognitive performance existed at every age). Our work expands on previous findings of this same relationship between TST and cognition using four specific tests of cognitive performance. In the realms of memory and attention, we found that individuals who were concerned about their memory and reported long and short TST demonstrated cognitive performance that was significantly poorer than that of their peers who reported mid-range sleep durations. Additionally, TST interacted with age such that younger and older subjects reporting relatively short and long TST demonstrated the poorest performance on tests. Inversely, subjects in the middle age range who reported middle-range TST demonstrated the best cognitive performance in a group that was similar demographically and in terms of dementia risk factors.

When we repeated our analyses excluding individuals who had reported dementia on the medical screening portion of their baseline questionnaires, the only interaction that still reached statistical significance was for the relationship between TST and age and poorer performance on tests of attention. Thus, although these data are only partially supportive of our initial hypothesis, they demonstrate that TST interacts with at least one other specific predictor of cognitive performance, even in subjects denying dementia. Although previous studies have shown relationships between TST and cognitive performance and between age and cognitive performance, our findings demonstrate the complexity of the relationships between age, TST and cognitive performance.

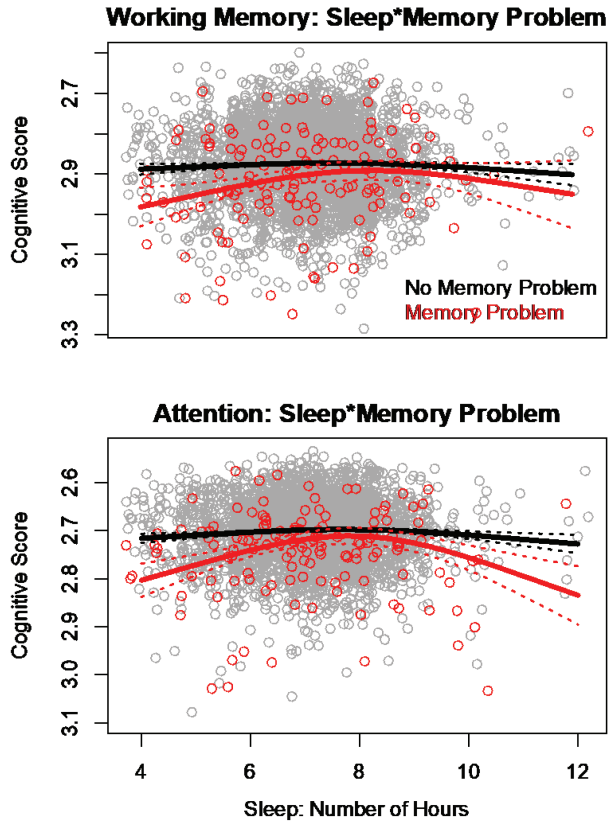
The association between middle-range TST and better cognitive performance may be causal: it may be that short and long

Figure 1—Cognitive performance and TST by age.



Graphs of cognitive performance in two tested domains based on self-reported TST and age. Shown are tests of working memory (ONB; top) and processing speed (IDN, attention; bottom). Age was modeled continuously, but for graphical purposes, three age groups are plotted. Solid lines indicate means and dashed lines indicate 95% confidence intervals. TST = total sleep time.

Figure 2—Cognitive performance and TST by reported personal memory problem.



Graphs of cognitive performance in two tested domains based on self-reported history of having a memory problem/dementia/Alzheimer's disease. Shown are tests of working memory (ONB; top) and processing speed (IDN, attention; bottom). Solid lines indicate means and dashed lines indicate 95% confidence intervals. TST = total sleep time.

amounts of sleep have detrimental effects on cognition. This could mean that, in older individuals and in those in whom a diagnosis has been made who suspect that they have memory problems, it is more important to get "the right amount" of sleep—that is, an optimal average TST that is closer to the population mean. These individuals may be especially susceptible to subtractions from performance by biological factors associated with insufficient sleep. It is difficult to imagine a single disease process that would have the same effect on cognition at both short and long TST.

Studies of insomnia, acute sleep deprivation or chronic partial sleep deprivation all show poorer cognition.[23–25] Short sleep duration is associated with a wide range of poorer health outcomes including diabetes and heart disease as well as all-cause mortality. [26] We have controlled for a variety of factors that have been previously described as leading to both cognitive and sleep problems. These include age,[27] presence of depression,[28–30] education level,[31] use of sleep medications,[32–34] and presence or absence of obstructive sleep apnea.[35] Aside from indirectly affecting cognition via these mediating health factors, multiple possible mechanisms could account for the association between shorter sleep duration and poorer cognition, including impaired neural plasticity and inflammation.[36,37] Less is known about associations between poor health and cognition and longer sleep durations. There are very few studies of experimental increases in sleep in humans who sleep normally, as this is a problematic intervention. One mechanism by which increased sleep duration might affect cognition is via increased inflammatory mediators such as C-reactive protein.[38,39] It is possible that inflammation causes direct harm to memory networks or inhibits consolidation of new memories.[40] It is also possible that longer sleep durations associated with poorer cognitive performance do not promote a distinct disease process

but instead represent incomplete compensation for impaired sleep quality by increased TST.

Another possibility is that the relationship between cognition and short and long TST seen in our study are both caused by some neurological insult or early disease process that could not be identified in our sample. If a neurological disease leads to deviations in TST as well as cognitive dysfunction, then TST in certain populations may be a useful predictor of poorer cognitive performance. Both short[41] and long[42,43] TST have been shown to be associated with cognitive decline or subsequent cognitive impairment,[44] though this has been less extensively studied and some studies[4,45,46] have not found this association. It would be interesting to conduct a similar study while controlling for other known predictors of cognitive decline, disease, and dementia, such as amyloid burden. It is quite possible that short and long sleep durations are associated with poorer cognitive performance for different reasons.

Because all cognitive tests considered depended on attention, it is possible that this cognitive domain drove all other results prior to removing from analyses those subjects reporting dementia. Alternatively, it is possible that only the most robust finding remained true after removing subjects who were most impaired. Previous studies have shown measures of attention to be particularly sensitive to sleep loss.[23] Our results suggest that this is true even in the setting of dementia. Importantly, our data showed that performance on a measure of attention is also lower among subjects reporting longer sleep durations.

This study has several important limitations. Volunteer studies are inherently at risk of sampling bias. Our sample was older, more highly educated, and contained more female subjects than other previous studies of sleep duration and cognition and the generalizability of our results may be limited. Additionally, self-reported sleep duration has been shown in some studies to have poor correlation with objectively measured sleep duration.[47] It is possible that subjects who had memory concerns may have estimated their sleep times more or less accurately than their peers without memory concerns, introducing bias into our results. Reassuringly, in a study of 78 older adults, accuracy of individuals' estimations of sleep time was not correlated with cognitive performance as measured by the Montreal Cognitive Assessment.[48] It is also possible that lack of an objective assessment for sleep apnea resulted in an underappreciation of the prevalence of that condition in our sample, though our finding of 11.5% reporting sleep apnea is higher than other estimates ranging from 2% to 7% in adults.[49] However, given that the average age of subjects in this study was 60 years and 70% female, our sample might be expected to have a somewhat higher prevalence of sleep apnea, though perhaps not as high as 28% in men and 20% in women (using an apnea-hypopnea index of greater than or equal to 5) as found in another study of adults of average age 72.5 years.[50] Another potential limitation is that asking subjects to complete Cogstate tests under unsupervised conditions introduced a bias into our assessments. The Cogstate tests have been validated in a variety of populations but administration of the tests under unsupervised conditions has been validated only in a sample of younger adults, whereas our sample contained predominantly older adults.[14–18]

Important next steps in research on cognitive performance and sleep time might include conducting studies similar to ours in which biological data, such as inflammatory markers and brain and cerebrospinal fluid amyloid beta burden, could be considered. Furthermore, outcomes such as mortality and incident dementia will be available for our study subjects, allowing for the consideration of actual risk of cognitive decline in relation to TST and other variables of interest.

ABBREVIATIONS

AIC, Akaike Information Criterion
BHR, Brain Health Registry
DET, Detection Test
IDN, Identification Test
OCL, One Card Learning
OMC, own memory concerns
OMP, own memory problem
ONB, One-Back Test
PMP, parent memory problem
SD, standard deviation
TST, total sleep time

REFERENCES

1. Sternberg DA, Ballard K, Hardy JL, Katz B, Doraiswamy PM, Scanlon M. The largest human cognitive performance dataset reveals insights into the effects of lifestyle factors and aging. *Front Hum Neurosci.* 2013;7:292.
2. Xu L, Jiang CQ, Lam TH, et al. Short or long sleep duration is associated with memory impairment in older Chinese: the Guangzhou Biobank Cohort Study. *Sleep.* 2011;34(5):575–580.
3. Gildner TE, Liebert MA, Kowal P, Chatterji S, Snodgrass JJ. Associations between sleep duration, sleep quality, and cognitive test performance among older adults from six middle income countries: results from the Study on Global Ageing and Adult Health (SAGE). *J Clin Sleep Med.* 2014;10(6):613–621.
4. Devore EE, Grodstein F, Duffy JF, Stampfer MJ, Czeisler CA, Schernhammer ES. Sleep duration in midlife and later life in relation to cognition. *J Am Geriatr Soc.* 2014;62(6):1073–1081.
5. Hedden T, Gabrieli JDE. Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci.* 2004;5(2):87–96.
6. Cipolli C, Neri M, Andermarcher E, Pinelli M, Lalla M. Self-rating and objective memory testing of normal and depressed elderly. *Aging (Milano).* 1990;2(1):39–48.
7. Debette S, Wolf PA, Beiser A, et al. Association of parental dementia with cognitive and brain MRI measures in middle-aged adults. *Neurology.* 2009;73(24):1–8.
8. Durrleman S, Simon R. Flexible regression models with cubic splines. *Statist Med.* 1989;8(5):551–561.
9. Weiner MW, Nosheny R, Camacho M, et al. The Brain Health Registry: an internet-based platform for recruitment, assessment, and longitudinal monitoring of participants for neuroscience studies. *Alzheimers Dement.* 2018;14(8):1063–1076.
10. van der Loo MP. The stringdist package for approximate string matching. *R J.* 2014;6(1):111–122.
11. Schatzberg AF, Cole JO, DeBattista C. *Manual of Clinical Psychopharmacology.* 7th ed. Washington, DC: American Psychiatric Association Publishing; 2010.
12. Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatr Scand.* 2014;130(6):439–451.

13. Mayeux R, Sano M, Chen J, Tatemichi T, Stern Y. Risk of dementia in first-degree relatives of patients with alzheimer's disease and related disorders. *Arch Neurol.* 1991;48(3):269–273.
14. Maruff P, Lim YY, Darby D, et al. Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *BMC Psychol.* 2013;1(1):30.
15. Maruff P, Thomas E, Cysique L, et al. Validity of the CogState Brief Battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Arch Clin Neuropsychol.* 2009;24(2):165–178.
16. Lees J, Applegate E, Emsley R, et al. Calibration and cross-validation of MCCB and CogState in schizophrenia. *Psychopharmacology.* 2015;232(21–22):3873–3882.
17. Lim YY, Ellis KA, Harrington K, et al. Use of the CogState Brief Battery in the assessment of Alzheimer's disease related cognitive impairment in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. *J Clin Exp Neuropsychol.* 2012;34(4):345–358.
18. Cromer JA, Harel BT, Yu K, et al. Comparison of cognitive performance on the cogstate brief battery when taken in-clinic, in-group, and unsupervised. *Clin Neuropsychol.* 2015;29(4):542–558.
19. Mielke MM, Weigand SD, Wiste HJ, et al. Independent comparison of CogState computerized testing and a standard cognitive battery with neuroimaging. *Alzheimers Dement.* 2014;10(6):779–789.
20. Kirchner WK. Age differences in short-term retention of rapidly changing information. *J Exp Psychol.* 1958;55(4):352–358.
21. Stark SM, Yassa MA, Stark CEL. Individual differences in spatial pattern separation performance associated with healthy aging in humans. *Learn Mem.* 2010;17(6):284–288.
22. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr.* 1974;19(6):716–723.
23. Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol.* 2005;25(1):117–129.
24. Reynolds AC, Banks S. Total sleep deprivation, chronic sleep restriction and sleep disruption. *Prog Brain Res.* 2010;185:91–103.
25. Goel N, Rao H, Durmer J, Dinges D. Neurocognitive consequences of sleep deprivation. *Semin Neurol.* 2009;29(4):320–339.
26. Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. *Sleep Med.* 2017;32:246–256.
27. Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging.* 2009;30(4):507–514.
28. O'Connor DW, Pollitt PA, Roth M, Brook PB, Reiss BB. Memory complaints and impairment in normal, depressed, and demented elderly persons identified in a community survey. *Arch Gen Psychiatry.* 1990;47(3):224–227.
29. McIntyre RS, Cha DS, Soczynska JK, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety.* 2013;30(6):515–527.
30. Millan MJ, Agid Y, Brüne M, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov.* 2012;11(2):141–168.
31. Schmand B, Smit J, Lindeboom J, et al. Low education is a genuine risk factor for accelerated memory decline and dementia. *J Clin Epidemiol.* 1997;50(9):1025–1033.
32. Rush CR, Griffiths RR. Zolpidem, triazolam, and temazepam: behavioral and subject-rated effects in normal volunteers. *J Clin Psychopharmacol.* 1996;16(2):146–157.
33. Pompeia S, Lucchesi LM, Bueno OFA, Manzano GM, Tufik S. Zolpidem and memory: a study using the process-dissociation procedure. *Psychopharmacology.* 2004;174(3):327–333.
34. Vermeeren A, Coenen AML. Effects of the use of hypnotics on cognition. *Prog Brain Res.* 2011;190:89–103.
35. Naegele B, Pepin JL, Levy P, Bonnet C, Pellat J, Feuerstein C. Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. *Sleep.* 1998;21(4):392–397.
36. Kreutzmann JC, Havekes R, Abel T, Meerlo P. Sleep deprivation and hippocampal vulnerability: changes in neuronal plasticity, neurogenesis and cognitive function. *Neuroscience*. 2015;309:173–190.
37. Mohlenhoff BS, O'Donovan A, Weiner MW, Neylan TC. Dementia risk in posttraumatic stress disorder: the relevance of sleep-related abnormalities in brain structure, amyloid, and inflammation. *Curr Psychiatry Rep.* 2017;19(11):89.
38. Dowd JB, Goldman N, Weinstein M. Sleep duration, sleep quality, and biomarkers of inflammation in a Taiwanese population. *Ann Epidemiol.* 2011;21(11):799–806.
39. Mantua J, Spencer RMC. The interactive effects of nocturnal sleep and daytime naps in relation to serum C-reactive protein. *Sleep Med.* 2015;16(10):1213–1216.
40. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol.* 2007;7(2):161–167.
41. Lo JC, Loh KK, Zheng H, Sim SKY, Chee MWL. Sleep duration and age-related changes in brain structure and cognitive performance. *Sleep.* 2014;37(7):1171–1178.
42. Benito-Leon J, Bermejo-Pareja F, Vega S, Louis ED. Total daily sleep duration and the risk of dementia: a prospective population-based study. *Eur J Neurol.* 2009;16(9):990–997.
43. Benito-León J, Louis ED, Villarejo-Galende A, Romero JP, Bermejo-Pareja F. Long sleep duration in elders without dementia increases risk of dementia mortality (NEDICES). *Neurology.* 2014;83(17):1530–1537.
44. Potvin O, Lorrain D, Forget H, et al. Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. *Sleep.* 2012;35(4):491–499.
45. Blackwell T, Yaffe K, Laffan A, et al. Associations of objectively and subjectively measured sleep quality with subsequent cognitive decline in older community-dwelling men: the MrOS sleep study. *Sleep.* 2014;37(4):655–663.
46. Tworoger SS, Lee S, Schernhammer ES, Grodstein F. The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women. *Alzheimer Dis Assoc Disord.* 2006;20(1):41–48.
47. van den Berg JF, van Rooij FJA, Vos H, et al. Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons. *J Sleep Res.* 2008;17(3):295–302.
48. Landry GJ, Best JR, Liu-Ambrose T. Measuring sleep quality in older adults: a comparison using subjective and objective methods. *Front Aging Neurosci.* 2015;7(325):342–310.
49. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thoracic Soc.* 2008;5(2):136–143.
50. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. *Sleep.* 1991;14(6):486–495.

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SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Brian S. Mohlenhoff, MD, Veterans Administration Medical Center, Department of Mental Health, 4150 Clement Street (116P), San Francisco, CA 94121; Tel: (415) 221-4810 x2-4801; Email: brian.mohlenhoff@ucsf.edu

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