RESEARCH ARTICLE

The Relationship Between Sleep, Cognition, and Dementia Risk in People With Focal Epilepsy

Xin You Tai,[1,2,3,4] Sijia Zhao,[1,5] Bernard Liem,[2,3,4] Marian Galovic,[6] Masud Husain,[1,2,5] Arjune Sen,[1,2,3,4,*] and Sanjay Manohar[1,2,5,*]

Correspondence
Dr. Tai
xin.tai@ndcn.ox.ac.uk

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Abstract

Background and Objectives

Sleep disruption and cognitive impairment are important comorbidities of focal epilepsy. However, the nature to which sleep affects cognition and long-term dementia risk in focal epilepsy, compared with other brain conditions, remains unclear. We examined the relationship between sleep, cognition, and dementia risk in patients with focal epilepsy compared with healthy controls and stroke patients.

Methods

We conducted an analysis of the prospective UK Biobank cohort study, with baseline assessments performed between 2006 and 2010 and follow-up until 2021. Study groups were mutually exclusive participants with focal epilepsy and stroke at baseline assessment and healthy controls. Sleep characteristics included reports of sleep duration, obstructive sleep apnea, insomnia, napping, and dozing. Main outcomes were risk of incident all-cause dementia and Alzheimer disease from Cox proportional hazard modeling and comparison of executive function measures and brain total hippocampal and gray matter volumes using generalized linear modeling.

Results

We examined a sample of 482,207 participants, aged between 38 and 72 years (mean [SD] 57.6 [8.1] years; 53.8% female), without dementia at baseline and a nested imaging subsample of 42,345 participants. Optimal sleep duration (6–8 hours) was associated with better executive function in control, focal epilepsy, and stroke groups. The impact of optimal sleep was significantly higher in individuals with focal epilepsy compared with controls (interaction term, $p = 0.009$), but not in the stroke group (interaction term, $p = 0.574$). Nonoptimal sleep was associated with worse executive function up to 8 years before the diagnosis of focal epilepsy. A 5-fold increased risk of developing dementia was seen in individuals with focal epilepsy and nonoptimal sleep (hazard ratio [HR] 5.15, 95% CI 3.77–7.04, $p < 0.001$) compared with healthy controls with optimal sleep. This was greater than in stroke individuals with poor sleep (HR 3.48, 95% CI 2.82–4.26, $p < 0.001$). Optimal sleep compared with nonoptimal sleep modified the dementia risk in in individuals focal epilepsy, with a significantly greater improvement compared with healthy controls (interaction term $p = 0.017$), while no significant difference was seen in the stroke group (interaction term $p = 0.991$).

Discussion

Optimal sleep modified both cognitive performance and dementia risk in individuals with focal epilepsy compared with stroke patients and healthy controls. Based on self-reported sleep data, these findings suggest that improving sleep may be an impactful intervention to improve cognition and reduce dementia risk particularly in focal epilepsy.

*These authors contributed equally to this work as co-senior authors.

[1]Nuffield Department of Clinical Neuroscience, University of Oxford, United Kingdom; [2]Division of Clinical Neurology, John Radcliffe Hospital, Oxford University Hospitals Trust, United Kingdom; [3]Oxford Epilepsy Research Group, NIHR Biomedical Research Centre, Nuffield Department Clinical Neurosciences, John Radcliffe Hospital, United Kingdom; [4]Centre for Global Epilepsy, Wolfson College, Oxford, United Kingdom; [5]Department of Experimental Psychology, University of Oxford, United Kingdom; and [6]Department of Neurology, Clinical Neuroscience Center, University Hospital and University of Zurich, Switzerland.

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Glossary

CFA = confirmatory factor analysis; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **NREM** = nonrapid eye movement; **SE** = standard error.

Introduction

Epilepsy, a common neurologic disorder characterized by unprovoked seizures, is associated with cognitive impairment and increased dementia risk in older individuals.[1] These comorbidities are particularly critical considering the aging global population, yet there are no effective interventions to mitigate cognitive decline in people with epilepsy. Sleep is an intriguing line of inquiry, given its role in general cognitive health[2] and evidence that sleep may interact with specific epileptic processes.

In epilepsy, disordered sleep exacerbates seizure activity while seizures themselves can disrupt sleep architecture.[3] Slow-wave sleep, during nonrapid eye movement (NREM) sleep stages, is a state of maximal physiologic synchrony[4] and is associated with increased observation of interictal epileptiform discharges on neurophysiology.[5] Sleep deprivation, conversely, is a well-known precipitant to seizures and can induce more epileptiform discharges.[6] Pathologically, tau and beta amyloid, which link epilepsy and dementia,[1] are the same neurodegenerative proteins removed from the brain through glymphatic clearance pathways during sleep.[7] These hint at an important interplay between epilepsy, sleep, and dementia, but the exact relationships and underlying mechanisms remain unclear.

An important question, therefore, is whether poor sleep and epilepsy are negatively synergistic toward cognitive outcomes or whether both exert a separate negative effect. There is limited literature assessing sleep and cognition in people with epilepsy where disrupted sleep architecture has associated with poor memory performance.[8,9] Interpreting these results are limited by small sample size, a lack of robust controls, and poor comparator data. Further, studies examining the relationship between sleep and epilepsy-related dementia over time are lacking.

In this study, we analyzed cognitive scores and dementia risk in relation to sleep characteristics, focal epilepsy, and stroke in the UK Biobank prospective cohort. Our aim was to understand the extent to which poor sleep was associated with cognitive deficits in people with epilepsy compared with healthy controls. We have previously described an optimal sleep duration, as a proxy for sleep quality, for both cognitive and structural brain health.[2] We hypothesized that suboptimal sleep duration will amplify the cognitive impairment associated with focal epilepsy. In other words, optimal sleep would have a greater benefit in people with focal epilepsy compared with controls. We further postulated that this effect would not be present in stroke, which is another neurologic condition linked to aging and cognitive impairment but not necessarily epileptic seizures. In addition, we examined the extent to which sleep was associated with reduced risk of dementia in epilepsy because this could help inform dementia risk reduction strategies for people with epilepsy.

Methods

This study examined UK Biobank data, a population-based cohort of over 500,000 participants aged between 38 and 72 years at baseline assessment. Participants underwent physiologic measurements and cognitive testing at one of 22 UK centers between 2006 and 2010.[10] A subgroup reattended for brain imaging between 2014 and 2020.[11]

The primary study objective was to investigate the relationship between sleep and epilepsy-related cognitive impairment and incident dementia risk compared with individuals with stroke and healthy controls. Prevalent dementia at baseline assessment (<1%) were excluded along with other neurologic exclusion conditions, including a history of encephalitis, meningitis, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson disease, or previous subdural or subarachnoid hemorrhage. Diagnoses were identified using self-report and hospital inpatient records (UK Biobank codes are given in eTable 1).

Focal Epilepsy Diagnoses

The epilepsy subgroup comprised individuals with focal-onset epilepsy at baseline based on ICD codes. Individuals were excluded based on coding for a genetically associated epilepsy including "generalized idiopathic epilepsy and epileptic syndromes" (G40.3), such as syndromes of juvenile myoclonic epilepsy and childhood absence epilepsies, and "other generalized epilepsy and epileptic syndromes" (G40.4). The latter includes epileptic encephalopathies such as Lennox-Gastaut and West syndrome, as these can be associated with clear cognitive deficits related to an underlying genetic mechanism or developmental delay.[12] A previous study of this cohort identified that the number of antiseizure medications was a surrogate measure of epilepsy severity.[13] Based on this, we investigated the relationship between being on 1 vs 2+ antiseizure medications (less vs more severe epilepsy, list in eTable 2) and cognitive scores and sleep parameters. The molecular target of the antiseizure medication was also considered.

Sleep Characteristics

Sleep characteristics, primarily sleep duration, was investigated. Study participants reported the number of hours

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they sleep every 24 hours and, based on previous work,[2] an "optimal" sleep duration was defined as 6–8 hours while other durations were classified as"poor" sleep duration. Other sleep characteristics inputted in analytic models as binary categories included having obstructive sleep apnea (yes/no), insomnia ("never"/"rarely" vs "sometimes"/"usually"), napping ("never"/"rarely" vs "sometimes"/"usually"), and dozing ("never"/"rarely" vs "sometimes"/"usually").

Cognitive Testing

UK Biobank participants performed computer-based cognitive testing at the initial baseline visit, repeated at the imaging visit and through an online questionnaire. Not all cognitive tasks were performed at each instance while some were repeated. Using data from the first available time point, we analyzed 5 tasks of working memory or speed of processing. This included a pairs-matching and snap reaction time, trail-making, tower-rearranging, and symbol-digit substitution tasks and has been described in detail elsewhere.[2] Reliability along with re-test effect over time has been assessed for these cognitive tasks.[14]

Main Covariates

All full models were adjusted for age (continuous), sex (male vs female), education (categorized as higher [college or university degree or other professional qualification], upper secondary [second or final stage of secondary education], lower secondary [first stage of secondary education], vocational [work-related qualifications], or other), and socioeconomic status (categories derived from Townsend deprivation index[15] quintiles 1, 2 to 4, and 5). We used a previously published cardiovascular risk score[16] where participants were divided into low-risk (score 0), moderate-risk (scores 1 and 2), or high-risk (score 3+) groups based on quintile boundaries 1, 2 to 4, and 5, respectively. Points were given for a diagnosis or treatment of hypertension, high cholesterol, or diabetes (1 point for each condition); waist-to-hip ratio (1 point if greater than sex-specific threshold set by World Health Organization guidelines)[17]; smoking pack-years (1 point if more than 20 pack-years); and APOE e4 allele status (2 points for 2 e4 alleles, 1 point for a single e4 allele, and zero points for any other allele combination or when allele status was unclear).

Brain Imaging Variables

MRI data were acquired on a Skyra 3T scanner (Siemens; Munich, Germany), including high-resolution, T1-weighted, three-dimensional magnetization-prepared gradient-echo structural images and T2-weighted fluid-attenuated inversion recovery images. Imaging summary statistics for total hippocampal and gray matter were used. Full imaging protocols and processing pipeline have been previously described.[18] These were regions of interest as previous studies have found hippocampal atrophy[19-21] in epilepsy while total gray matter volume is a useful measure of widespread, global change.[22] Median absolute deviation was used to exclude outliers, and volumes were adjusted for potentially confounding baseline measures of age, age squared, head size, and imaging site.[18]

Statistical Analysis

A continuous, summary latent measure of working memory and reaction time, which we termed "executive function" for simplicity, was created using confirmatory factor analysis (CFA) on cognitive variables (this method has been previously described).[2,13,16] In brief, cognitive variables were preprocessed to correct for heavily skewed distribution before CFA. Standard fit indices were measured, with higher comparative fit index and Tucker-Lewis Index considered better (>0.9 are commonly used as acceptable fit cutoffs), while lower root mean square error of approximation and standardized root mean square error residual were considered better (<0.06 and <0.08, respectively, are commonly used cutoffs for acceptable fit). Latent variable estimation is methodologically advantageous regarding controlling measurement error that can artificially reduce the relationship between measured variables in standard univariate analyses.[23] Full maximum likelihood was used to estimate missing cognitive data, which gives unbiased parameter estimates and standard errors. Age is a primary confounder when examining cognitive function,[24] so we controlled for age in 2 different ways for robustness—using a model-free, sliding window approach with fixed age-quantile widths moved along the age distribution (described previously,[2,25,26] code: conditionalPlot.m available) or by including age as a covariate in a general linear model.

We examined the relationship between executive function and mutually exclusive groups of focal epilepsy, stroke, and healthy controls, stratified by sleep duration. We compared the difference in executive function between condition groups and controls using a generalized linear model including covariates of interest. An interaction term between sleep duration and having focal epilepsy or stroke was included in the model. Executive function was examined within the focal epilepsy subgroup only to examine the effect of epilepsy severity. Brain measures were analyzed in the epilepsy subgroup using the same methods. Prediagnosis executive function was derived based on time *t*, which was the difference between the date of baseline assessment and the date of diagnosis of focal epilepsy during the follow-up period. Specifically, this uses cross-sectional data and provides a model of prediagnosis executive function at a group level, rather than individual longitudinal information. This approach was recently published.[27]

Cox proportional hazard regression models identified hazard ratios (HRs), with time to incident all-cause dementia as the dependent variable. HRs were calculated for mutually exclusive groups of focal epilepsy and stroke, compared with healthy controls as the baseline, with other covariates included in the model. For our main model, we tested the dementia risk associated with having focal epilepsy, stroke, or neither condition, stratified by sleep duration (with optimal sleep duration in healthy controls as the baseline). Cognitive scores were not included in the model because cognitive

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impairment may share the same underlying mechanisms as dementia and it was not our aim to assess whether cognition can predict future dementia risk. For the main exposures and covariates, there were less than 3% missing or unknown data and complete case analysis was applied. In view of having 3 primary questions, we ran 1 main statistical model to test each hypothesis, without correction for multiple comparisons. We tested proportional hazards assumption using Schoenfeld residuals. We expected departure from proportionality, as is common in a cohort of this size from even trivial and clinically irrelevant fluctuations in the data. For completeness, this was further addressed, through secondary analysis such as restricted follow-up windows. Participants were considered at risk of developing dementia from baseline until the date of first diagnosis, death, loss to follow-up, or the last surveyed hospital admission date (March 31, 2021, for England and Scotland and February 28, 2018, for Wales), whichever came first. These censoring dates were recommended by UK Biobank because the data were estimated to be over 90% complete in England, Scotland, and Wales.

Secondary data analyses included a mediation analysis to explore whether short or longer sleep durations had a differential relationship between epilepsy and cognition. We examined dementia risk with different follow-up durations of 5–15 years to control for potential reverse causality; that is, early dementia diagnoses may represent individuals with the clinical syndrome but not given a formal label. The risk of developing Alzheimer disease, instead of all-cause dementia, was examined to focus on amyloid-related and tau-related processes. The association between dementia risk and epilepsy stratified by age at epilepsy diagnosis was tested. Analyses were performed in Matlab R2018a or in R version 4.0.3 using the Lavaan[28] or survival package.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was given by all participants. Ethical approval was given by the North West Multi-centre Research Ethics Committee (REC number 21/NW/0157).

Data Availability

The data analyzed during this study are available from the UK Biobank ukbiobank.ac.uk/researchers/. The variables used are summarized in eTable 1. This research was conducted using the UK Biobank resource under application 9462. Code to generate the cognitive trajectory figures using conditionalPlot.m is available at osf.io/vmabg/

Results

The UK Biobank cohort included 502,486 participants at baseline. Following the exclusion criteria (N = 20,279), our study included 482,207 individuals (flowchart in eFigure 1). Participants had a mean (SD) age of 57.6 (8.1) years, and 53.8% were female (baseline demographics in Table 1). Over 5,647,522 total follow-up years (median 12.0, interquartile range 11.2–12.7), 5,826 cases of all-cause incident dementia were observed. At baseline assessment, 3,788 participants (0.79%) had focal epilepsy only while 6,372 (1.3%) had a history of stroke only. Sleep duration, the primary sleep characteristic, had a Gaussian distribution around 7–8 hours across all groups (eFigure 2). Other sleep characteristics considered included obstructive sleep apnea and tendencies to experience insomnia, napping, or dozing (breakdown in baseline demographics Table 1).

Sleep and Executive Function in Focal Epilepsy, Stroke, and Control Groups

A continuous cognitive function latent variable of executive function was estimated from 5 cognitive tasks of working memory or speed of processing (model and fit indices shown in eFigure 3), controlled for age using a model-free, residual-based method (allowing for nonlinear effects).[2,16] We observed a quadratic relationship between this age-residual executive function and sleep duration (Figure 1). Sleep was further categorized as optimal sleep duration 6–8 hours or poor/nonoptimal sleep duration (either <6 or >8 hours), based on findings from a previous study.[2] At baseline assessment, an optimal sleep duration (6–8 hours) was reported in 407,528 (86.3%); 3,001 (79.2%); and 4,784 (75.1%) individuals in the control, focal epilepsy, and stroke groups, respectively.

The Impact of Optimal Sleep Duration on Executive Function

Lower executive function was observed in individuals with focal epilepsy and stroke compared with healthy controls ($t = -8.336$, standard error [SE] 0.013, $p < 0.001$ and $t = -7.735$, SE 0.009, $p < 0.001$, respectively, general linear model output in eTable 3). Optimal sleep duration was associated with higher executive function within each of the 3 groups (Figure 2). Relationship with other sleep parameters is given in eTable 3. Pairwise correlations were performed between the 5 sleep characteristics to assess potential collinearity. This returned generally low correlation coefficients, with the highest being 0.33 between "napping" and "dozing." The correlation matrix can be found in eTable 4. To examine the association with optimal sleep duration closely, mediation analysis identified that both short (<6 hours) and long (>8 hours) durations were significant mediators of the relationship between having focal epilepsy and worse executive function (Figure 1). In other words, nonoptimal sleep partly explains the worse cognition in focal epilepsy.

Further to mediation, we identified a significant interaction between optimal sleep duration and focal epilepsy ($t = 2.628$, SE 0.015, $p = 0.009$), which represented a positive modifying effect, suggesting that optimal sleep reduces the negative impact of focal epilepsy on executive function more than it does in controls (Figure 2, eTable 3). There was no modifying effect of sleep on the stroke group (interaction term, $t = -0.562$, SE 0.011, $p = 0.574$).

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Table 1 Baseline Characteristics of Study Participants

	Controls		Epilepsy		Stroke	
	No. (proportion)	No. (proportion)	No. (proportion)	No. (proportion)	No. (proportion)	No. (proportion)
	No incident dementia	Incident dementia	No incident dementia	Incident dementia	No incident dementia	Incident dementia
Characteristic	**(n = 466,631)**	**(n = 5,416)**	**(n = 3,684)**	**(n = 104)**	**(n = 6,066)**	**(n = 306)**
Age, mean (SD), y	57.41 (8.09)	65.27 (4.8)	56.81 (8.05)	63.64 (6.46)	61.77 (6.69)	65.45 (4.74)
Sex						
Female	252,257 (0.54)	2,548 (0.47)	1878 (0.51)	41.0 (0.39)	2,444 (0.4)	109 (0.36)
Education[a]						
Higher	77,483 (0.17)	735 (0.14)	625 (0.17)	15 (0.14)	928 (0.15)	40 (0.13)
Upper secondary	25,363 (0.05)	255 (0.05)	192 (0.05)	5 (0.05)	272 (0.04)	16 (0.05)
Lower secondary	58,684 (0.13)	560 (0.1)	500 (0.14)	7 (0.07)	740 (0.12)	29 (0.09)
Vocational	218,345 (0.47)	1,799 (0.33)	1,444 (0.39)	23 (0.22)	2,060 (0.34)	77 (0.25)
Other	86,756 (0.19)	2,067 (0.38)	923 (0.25)	54 (0.52)	2,066 (0.34)	144 (0.47)
Socioeconomic status quintile[b]						
1 (least deprived)	93,859 (0.20)	993 (0.18)	565 (0.15)	14 (0.13)	897 (0.15)	37 (0.12)
2–4	280,267 (0.60)	3,109 (0.57)	2,066 (0.56)	51 (0.49)	3,297 (0.54)	166 (0.54)
5 (most deprived)	91,924 (0.20)	1,308 (0.24)	1,051 (0.29)	39 (0.38)	1,866 (0.31)	103 (0.34)
n/a	581 (0.0)	6 (0.0)	2 (0.0)	0 (0.0)	6 (0.0)	0 (0.0)
Sleep duration						
6–8 h vs other duration	403,287 (0.86)	4,241 (0.78)	2,935 (0.80)	66 (0.63)	4,571 (0.75)	213 (0.70)
Obstructive sleep apnea, Y/N	2,209 (0.0)	58.0 (0.01)	34.0 (0.01)	1.0 (0.01)	78.0 (0.01)	2.0 (0.01)
Insomnia						
Sometimes/always vs never	352,057 (0.75)	4,011 (0.74)	2,765 (0.75)	80.0 (0.77)	4,812 (0.79)	242 (0.79)
Napping						
Never vs sometimes/always	263,248 (0.56)	2,367 (0.44)	1,845 (0.5)	37.0 (0.36)	2,456 (0.4)	99.0 (0.32)
Dozing						
Never vs sometimes/always	353,622 (0.76)	3,490 (0.64)	2,508 (0.68)	60.0 (0.58)	3,922 (0.65)	160 (0.52)
Number of antiseizure medications						
1	4,560 (0.01)	155 (0.03)	1,779 (0.48)	57.0 (0.55)	254 (0.04)	26.0 (0.08)
2+	387 (0.0)	12 (0.03)	2,539 (0.21)	17.0 (0.16)	20.0 (0.0)	2.0 (0.01)

Percentages may not sum to 100 because of rounding.
[a] Higher education defined as college/university degree or other professional qualification; upper secondary, second/final stage of secondary education; lower secondary, first stage of secondary education; and vocational, work-related practical qualifications.
[b] Socioeconomic status assessed on the Townsend deprivation index, which combines information on social class, employment, car availability, and housing.

Sleep Duration and Executive Function in Relation to Epilepsy Severity

Based on previous findings that the number of antiseizure medications was a surrogate marker of epilepsy severity within this cohort,[13] we examined people with epilepsy on a single antiseizure medication ("less severe" epilepsy) and those on 2+ antiseizure medications ("more severe" epilepsy). More severe epilepsy was associated with worse executive function ($t = -2.23$, $p = 0.026$, Figure 2), with a significant interaction between epilepsy severity and optimal sleep duration

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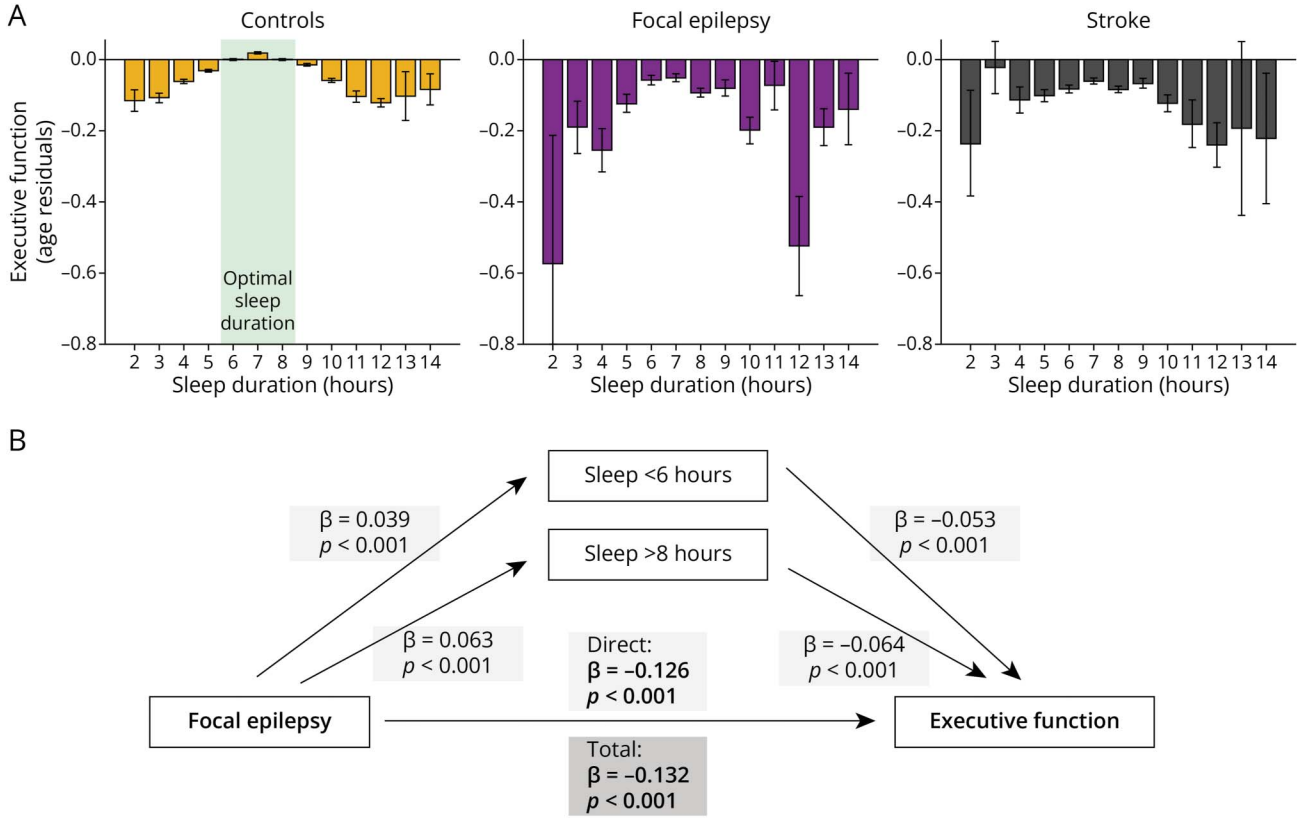
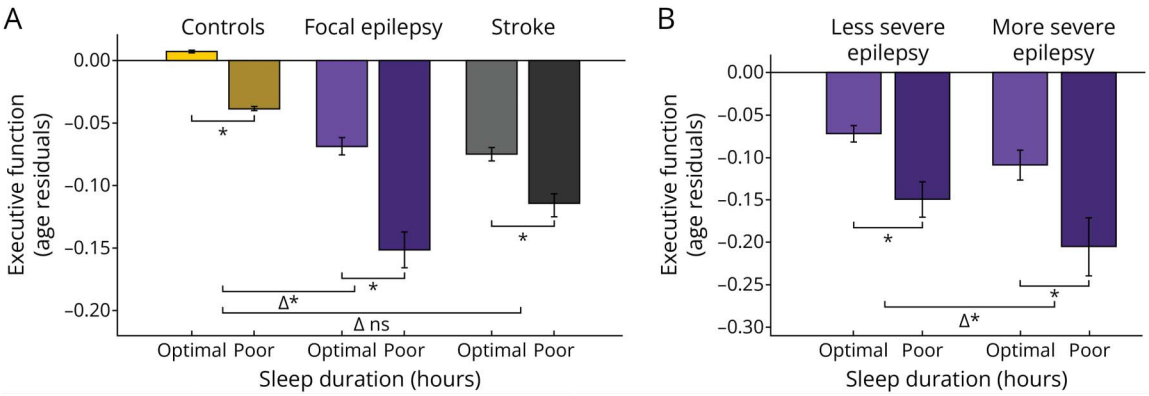
Figure 1 Relationship Between Executive Function and Sleep Duration in Control, Focal Epilepsy, and Stroke Groups As Well As Mediation Analysis Between Focal Epilepsy and Executive Function



(A) In healthy controls, a quadratic relationship between executive function (z-scored) and reported hours of sleep was observed, including an optimal sleep duration (6–8) for cognitive and brain health (previously described[2]). There was a similar pattern in participants with focal epilepsy and stroke. (B) Both short (<6) and long (>8) sleep durations significantly mediated the relationship between focal epilepsy and were associated with worse executive function.

Figure 2 Relationship Between Executive Function and Optimal Sleep Duration in Control, Focal Epilepsy, and Stroke Groups As Well As Based on Epilepsy Severity



(A) Participants with focal epilepsy or stroke had lower executive function (z-scored) compared with controls (t = −8.34, $p < 0.001$, and t = −7.74, $p < 0.001$, respectively). Optimal sleep duration (6–8 hours) was associated with higher executive function ($t = 21.41$, $p < 0.001$) compared with poor sleep duration. The difference in executive function associated with optimal sleep duration was significantly greater in individuals with focal epilepsy compared with controls (interaction term $p = 0.009$) but not with stroke patients (interaction term $p = 0.574$) based on a generalized linear model. (B) Using the number of antiseizure medications as an index for epilepsy severity, based on previous findings,[13] more severe epilepsy (2+ anti-seizure medication) was associated with worse executive function (t = −2.66, $p = 0.008$). Optimal sleep duration modified this effect with a significant interaction between epilepsy severity and optimal sleep duration (interaction term $p = 0.046$).

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(interaction term $p = 0.038$). This indicated that the cognitive impact of worse epilepsy severity on executive function was less in those with optimal sleep (eTable 5). In contrast to the number of medications, no specific antiseizure medication target (ion channel blocker, GABAergic agent, SV2A modulator, mixed mechanisms) was associated with worse cognition.

Worse Executive Function Was Associated With Poor Sleep Several Years Before the Diagnosis of Focal Epilepsy

We examined cognitive data from 2,511 individuals who went on to develop focal epilepsy during the follow-up period of the study. Using a previously published nonlinear model-free approach to analyze group-level cognitive trajectory,[27] individuals with focal epilepsy who reported poor sleep showed worse prediagnosis executive function compared with those in the optimal sleep group, up to 8 years before their epilepsy diagnosis (Figure 3). This difference in cognition widens between the sleep groups leading up to their diagnosis.

Association Between Sleep and Brain Volumes in Focal Epilepsy

Focal epilepsy and poor sleep duration were both associated with reduced hippocampal and total gray matter volume (eTable 6). While individuals with focal epilepsy and poor sleep had a lower total hippocampal volume compared with those with optimal sleep duration, the interaction term was not significant for either brain measure (eFigure 4).

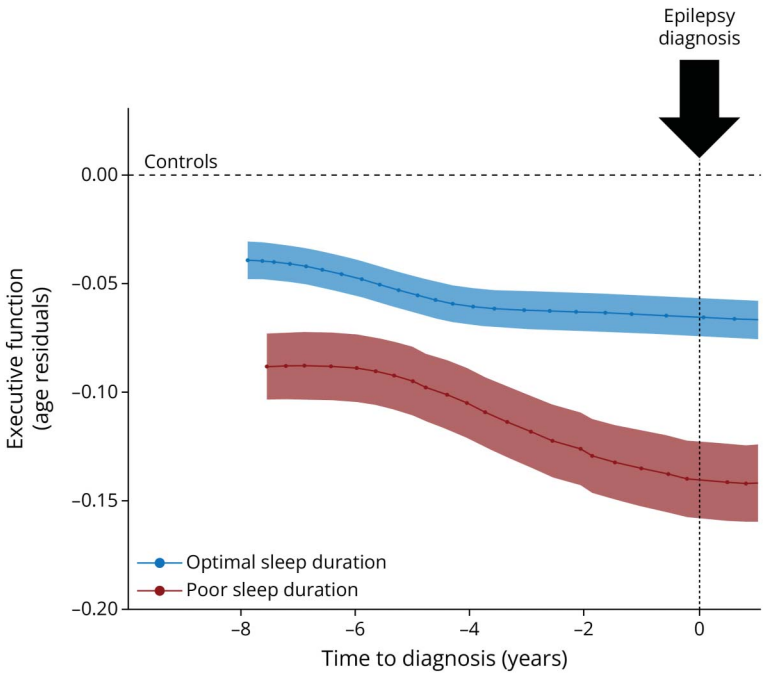
Dementia Outcomes Associated With Sleep Duration

During the study follow-up, the adjusted HR for incident dementia was 1.39 (95% CI 1.31–1.49, $p < 0.001$) for controls with poor sleep duration compared with a baseline group of controls with optimal sleep (HR 1) (Figure 4). Of participants with focal epilepsy and poor sleep duration, 4.8% developed dementia (HR 5.15, 95% CI 3.77–7.04) while this occurred in 2.2% of individuals with focal epilepsy and optimal sleep duration (HR 2.56, 95% CI 1.72– 2.77). Individuals in the stroke group also had a greater risk of developing dementia compared with baseline controls with optimal sleep. It is important to note that the difference in dementia risk between optimal and poor sleep durations in individuals with focal epilepsy was significantly larger than in controls (interaction term $p = 0.017$), representing a modifying effect of optimal sleep to improve dementia risk in focal epilepsy (eTable 7). Conversely, there was no significant difference in dementia risk between optimal and poor sleep in the stroke group compared with controls (interaction term $p = 0.991$). Schoenfeld residuals showed that the global test indicated a departure from the proportional hazard assumption ($\chi^2 = 73.4$, $p < 0.001$).

Other Sensitivity Analyses

Similar patterns of association were observed when considering risk of incident dementia using a follow-up period of 5–15 years, performed to mitigate potential for reverse causation with undiagnosed cases at baseline (eFigure 5). We also

Figure 3 Prediagnosis Cognitive Profile in Participants With Focal Epilepsy



In participants with focal epilepsy, poor sleep duration was associated with worse prediagnosis executive function compared with those in the optimal sleep group up to 8 years before their epilepsy diagnosis. At a group level, the difference in executive function increased between the sleep groups leading up to their diagnosis.

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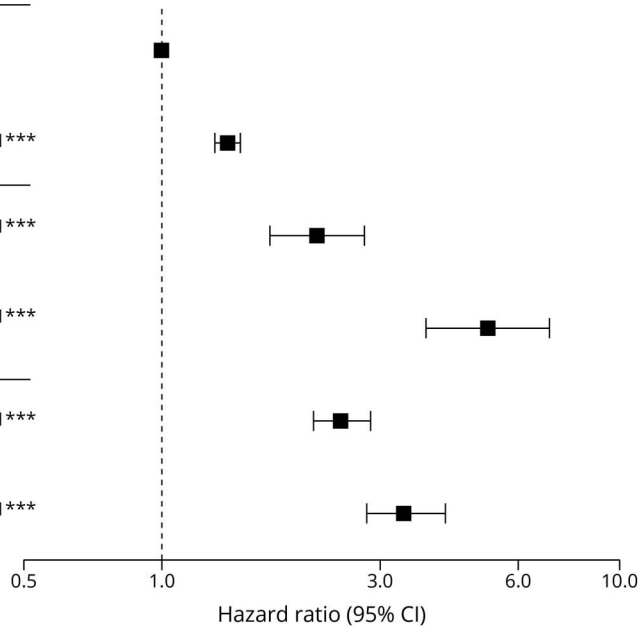
Figure 4 Risk of Incident Dementia Associated With Epilepsy and Stroke According to Optimal Sleep Duration

Group	Total number of participants	Number of dementia cases	Hazard ratio (95% CI)	*p* Value
Controls | optimal sleep	420,082	4,325	1 (reference)	
Controls | poor sleep	66,565	1,201	1.39 (1.31–1.49)	<0.001***
Focal epilepsy | optimal sleep	3,112	69	2.19 (1.72–2.77)	<0.001***
Focal epilepsy | poor sleep	821	40	5.15 (3.77–7.04)	<0.001***
Stroke | optimal sleep	5,005	217	2.46 (2.15–2.85)	<0.001***
Stroke | poor sleep	1,667	95	3.48 (2.82–4.26)	<0.001***



Data are HRs for incident dementia, associated with mutually exclusive groupings of controls, focal epilepsy only, and stroke only, stratified by sleep duration groups (optimal vs poor). A significant interaction is present between focal epilepsy and optimal sleep duration compared with controls, but not in the stroke group. The model has been adjusted for age, sex, education, socioeconomic status, and assessment center. Horizontal bars indicate 95% CIs. CVS = cardiovascular; HR = hazard ratio.

examined the risk of developing Alzheimer disease (N = 2,454) instead of all-cause dementia during the study follow-up period (eFigure 6). This showed similar results, with 2.1% of individuals with focal epilepsy and poor sleep developing dementia (HR 5.06, 95% CI 3.14–8.16) compared with 0.4% in the baseline control with optimal sleep. There was no significant difference between individuals with focal epilepsy with optimal sleep (HR 1.69, 95% CI 1.12–2.55) and the controls with poor sleep (HR 1.20, 95% CI 1.08–1.33) although confidence intervals were large in the epilepsy group. Again, there was a significant interaction between having focal epilepsy and poor sleep duration in developing Alzheimer disease. Similarly, we considered a model that included mental health (history of depression or schizophrenia/psychosis) and cardiovascular health comorbidities (cardiovascular risk score). Individuals in the control group who later developed epilepsy were excluded. The same pattern of association was observed with increased risk of developing dementia in individuals with focal epilepsy (HR 3.70, 95% CI 2.68–5.11) and a significant interaction term when considering optimal sleep and having focal epilepsy (p = 0.009, eTable 8). When considering age at epilepsy diagnosis, poor sleep was associated with a higher dementia risk in both younger-onset (<50 years) and older-onset (>50 years) epilepsy groups (eTable 9); however, only younger-onset individuals showed a significant interaction with poor sleep on dementia risk (interaction term $p < 0.001$). In addition to the summary measure of executive function, we examined the relationship between the reaction time task and the working memory pairs-matching task with focal epilepsy, stroke, optimal sleep duration, and other parameters as 2 different subdomains of cognition incorporated into the executive function latent variable (eTable 10).

Discussion

We show that sleep can modify cognitive impairment associated with focal epilepsy in midlife to late-life individuals. In other words, optimal sleep duration compared with other durations was associated with an improvement in cognitive performance in individuals with focal epilepsy, which was significantly higher than in controls or stroke patients. Optimal sleep may affect epilepsy-related cognitive impairment up to 8 years before epilepsy diagnosis and further modify the risk of developing dementia in the future.

Epilepsy, sleep, and cognition are closely intertwined. Sleep deprivation leads to worse cognition in healthy individuals[29] while focal epilepsy is associated with cognitive impairment[13] and poor sleep is both observed in epilepsy and a risk factor of worse and more frequent seizures.[6] Improved sleep may have a profound effect on cognition in epilepsy; however, this has been poorly examined. Two investigations in adults with

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epilepsy showed improved verbal and nonverbal memory after a period of sleep compared with wakefulness,[30,31] but these changes were either similar to controls or lacked a comparison group. Others have found no significant improvement in memory retention scores after sleep.[32,33] In a study of 15 people with epilepsy, neurophysiologic markers of disrupted sleep architecture negatively correlated with IQ[8] while other authors have found similar results across different cognitive domains.[31,34-36]

Our investigation, with a sample size 2 orders of magnitude greater, identified that optimal sleep duration was linked to less cognitive deficit in people with epilepsy, more so than with controls and stroke patients. Lower cognitive scores associated with worse epilepsy severity were significantly moderated by optimal sleep. These findings highlight sleep as a potential modifiable risk factor that may rescue individuals from the cognitive effects of focal epilepsy. Sleep quality should be the focus of investigation, but this may be difficult to quantify directly[37] and often, including in this study, surrogate measures such as sleep duration are used. The advent of new technologies in accelerometry and longer-term EEG will be key to better quantitative assessment of sleep.[38]

To our knowledge, no study has examined sleep and long-term dementia risk associated with focal epilepsy. We showed that optimal sleep duration substantially mitigates risk of dementia in individuals with epilepsy compared with healthy controls within a follow-up period of up to 15 years. This reflects how poor sleep and having epilepsy have synergistically negative effects on developing dementia, something which was not seen in stroke. These findings were robust to covariates for psychiatric and cardiovascular factors.[13] Therefore, while no causal inference can be made from this study, the results implicate a specific role for sleep in underlying mechanisms of cognitive impairment in people with epilepsy.

Based on the recent literature, 2 potential mechanisms to explain these findings involve subclinical interictal epileptic spikes that occur in the absence of overt seizures[35] and clearance of neurodegenerative proteins through the glymphatic system. Intracranial recordings in 20 people with epilepsy showed that hippocampal epileptic spike frequency during sleep, but not during wakefulness, negatively correlated with verbal memory retention over a week.[39] A rat model of temporal lobe epilepsy observed that hippocampal interictal epileptiform discharges correlate with impaired memory consolidation, and this may be due to disruption of physiologic hippocampal-to-neocortical ripple-spindle coupling during NREM sleep.[40] Furthermore, glymphatic system clearance of tau and beta-amyloid proteins is maximal during slow-wave sleep,[7,41,42] which is supressed by epileptic activity.[34] This may accelerate accumulation of neurodegenerative pathology observed in focal epilepsy.[43,44] Good sleep is critical for cognitive health, and epileptic activity may disrupt important physiologic processes during this time.

Our study has several limitations. Medical information was based on hospital records, death certificate data, or self-report, which may be incorrect.[45] We identified individuals with nongenetic or "focal-onset" epilepsy through medical coding. This does, however, have limitations because we do not have information on seizure origin, laterality, frequency, or, for example, presence of hippocampal sclerosis, which may affect cognitive performance. Such epilepsy characteristics were not captured by the UK Biobank, which was designed to recruit healthy individuals with no single disease in focus. Results of specific clinical investigations, such as EEG, are not available although these would clearly be a beneficial addition to future data releases of the study. Sleep parameters in UK Biobank were self-reported, which are a possible imperfect surrogate measure of sleep quality. While no polysomnography or overnight EEG data were obtained in this cohort, future development of actigraphy data may provide valuable quantitative measures of sleep quality. The cognitive testing available in the UK Biobank included robustly tested visual-based attention, working memory, processing speed, and executive control. Given the multiple-domain impairment documented in epilepsy-related cognitive impairment, it would have also been useful to include measures of other cognitive domains such as verbal fluency and episodic memory, but these data are currently unavailable in the UK Biobank cohort. Furthermore, our approach to modeling the prediagnosis cognitive profile[27] requires several assumptions such as stability of certain health characteristics. Sleep duration reported has been shown to be largely stable over a median of 8.9 years in the imaging subcohort of this group.[2] As such, we believe that our approach balances other potential confounders with the insight that this large sample size provides. There are no longitudinal data on people with epilepsy before diagnosis, which would represent the gold-standard approach. It is important to note that prediagnosis modeling of cognition was separate from any postdiagnosis analysis as the diagnosis of epilepsy introduces several potential confounders, including initiation of antiseizure medications, which may affect sleep architecture. There may be unmeasured confounders and potential for reverse causality although we tried to account for this through the relatively long follow-up period and additional analysis of dementia incidence from 5 to 15 years. The UK Biobank cohort is generally considered healthy and likely to be from less deprived areas.[46] Therefore, the effects studied may be greater in a more representative cohort.

In conclusion, people with focal epilepsy who reported optimal sleep duration had higher cognitive scores than those with poor sleep duration. This difference in cognition was significantly greater than that seen with optimal sleep duration in the control and epilepsy group. Furthermore, optimal sleep duration moderated dementia risk, specifically in people with epilepsy. In the absence of treatment to mitigate cognitive impairment and dementia risk in epilepsy, targeting sleep as a modifiable risk factor could offer an effective and affordable management strategy.

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Author Contributions

X.Y. Tai: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. S. Zhao: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. B. Liem: drafting/revision of the manuscript for content, including medical writing for content. M. Galovic: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. M. Husain: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. A. Sen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. S. Manohar: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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