Sleep characteristics and risk of stroke and dementia: an observational and Mendelian randomization study

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ABSTRACT

Background and Objectives: Sleep disturbances are implicated as risk factors for both stroke and dementia. However, whether these associations are causal and whether treatment of sleep disorders could reduce stroke and dementia risk remains uncertain. We aimed to evaluate associations and ascertain causal relationships between sleep characteristics and stroke/dementia risk and MRI markers of SVD.

Methods: We used datasets from a multicentre population-based study, and summary statistics from genome-wide association studies (GWAS) of sleep characteristics and outcomes. We analysed 502,383 UK Biobank participants with self-reported sleep measurements, including sleep duration, insomnia, chronotype, napping, daytime dozing, and snoring. In observational analyses, the primary outcomes were incident stroke, dementia, and their subtypes, alongside SVD markers. Hazard ratios (HR) and odds ratios (OR) were adjusted for age, sex, and ethnicity, and additional vascular risk factors. In MR analyses, ORs or risk ratios are reported for the association of each genetic score with clinical or MRI endpoints.

Results: Among 502,383 participants (mean [SD] age, 56.5 [8.1] years; 54.4% female), there were 7,668 cases of all-cause dementia and 10,334 strokes. In longitudinal analyses, after controlling for cardiovascular risk factors, participants with insomnia, daytime napping and dozing were associated with increased risk of any stroke (HR=1.05, 95% CI=1.01-1.11, $p=8.53x10^{-3}$; HR=1.09, 95% CI=1.05-1.14, $p=3.20x10^{-5}$; HR=1.19, 95% CI=1.08-1.32, $p=4.89x10^{-4}$, respectively). Almost all sleep measures were associated with dementia risk (all $p<0.001$ except insomnia). Cross-sectional analyses identified associations between napping, snoring, and MRI markers of SVD (all $p<0.001$). MR analyses supported a causal link between genetically predicted insomnia and increased stroke risk (OR=1.31, 95%CI=1.13-1.51, p=0.00072), but not with dementia or SVD markers.

Discussion: We found multiple sleep measures predicted future risk of stroke and dementia, but these associations were attenuated after controlling for cardiovascular risk factors and were absent in MR analyses for Alzheimer's disease. This suggests possible confounding or reverse causation, implying caution before proposing sleep disorder modifications for dementia treatment.

BACKGROUND

Sleep disorders have been suggested as a causal risk factor for both stroke and dementia[1,2]. Studies investigating associations of sleep have investigated several sleep phenotypes including sleep duration, sleep chronotype, insomnia, napping, daytime dozing, and snoring. Many associations with these measures have been reported: both short and long sleep duration was associated with increased risk of overall cardiovascular diseases mortlaity[3], insomnia was associated with cerebral small vessel disease (SVD) risk[4], and both short sleep duration and insomnia was associated with increased dementia risk[5,6].

Most previous studies investigating sleep associations with stroke and dementia have been cross-sectional, which leaves open questions regarding causality. The previously identified associations with sleep could be due to confounding with vascular risk factors such as smoking and alcohol, or could arise from reverse causation in which subclinical cerebrovascular disease or dementia causes sleep disturbance.

Evidence supporting a causal relationship can be obtained from longitudinal studies evaluating whether risk factors at baseline predict incident stroke and dementia and by using Mendelian randomization (MR). MR is a statistical approach that uses genetic variants as instrumental variables to infer the causal effect of a modifiable exposure (risk factor) on a health outcome (e.g., stroke and dementia)[7].

To investigate the role of sleep characteristics on stroke and dementia risk, we performed longitudinal analyses in over 500,000 individuals from UK Biobank and examined whether six different sleep measures predicted incident stroke (all stroke, ischemic stroke, intracerebral haemorrhage [ICH]) and dementia (all-cause dementia, Alzheimer's disease [AD], vascular dementia, frontotemporal dementia [FTD]). We then performed MR to analyse the causal nature of the associations.

A recent hypothesis is that disruption of the glymphatic system may play a key role in SVD, which is a major cause of lacunar stroke, ICH, and vascular dementia. This suggests that sleep disorders might specifically increase SVD risk. To investigate, we also evaluated in 40,000 UK Biobank participants with brain imaging whether sleep measures were associated with MRI features of SVD including white matter hyperintensities (WMH) and markers of white matter ultrastructural damage on diffusion tensor imaging (DTI). We further examined associations between sleep and MRI markers of SVD using MR.

METHODS

Study population

UK Biobank is a prospective cohort study of 502,383 participants (aged 40-69) recruited from 22 centres across the United Kingdom from March 2006 to October 2010[8]. Participants completed self-reported questionnaires, verbal interviews, physical measurements, and blood samples collection. All UK Biobank protocols were approved by external ethics committees (reference 11/NW/0382) and all participants provided informed consent[9].

Sleep measures

UK Biobank recorded information via the touchscreen questionnaire on several sleep measures including sleep duration, chronotype (morning/evening person), daytime napping (short periods of sleep taken throughout the day), sleeplessness/insomnia (the trouble falling asleep at night or wake up in the middle of night), daytime dozing (the inability to stay awake and alert during waking hours), and snoring.

Incident stroke and dementia

Clinical endpoints were recorded for all stroke, ischemic stroke, ICH, all-cause dementia, AD, vascular dementia, and FTD. These were defined based on the earliest recorded case that occurred after baseline assessment and before the end of follow-up period. Data were obtained through self-report at a nurse interview and linkage to hospital admissions from electronic health records and death certificate records. The

lists of clinical codes used to define the clinical endpoints were developed and validated by the UK Biobank Outcome Adjudication Group in conjunction with clinical experts.

MRI markers of SVD

In 2014, UK Biobank commenced an imaging study to conduct MRI scans in a subset of ~100,000 participants[10]. Information for over 40,000 participants has been released so far. Patients with prevalent stroke have been excluded. We examined WMH volume and several DTI metrics, including mean diffusivity (MD) and fractional anisotropy (FA)[11]. We log-transformed the total volume of WMH from T1 and T2 FLAIR images. For the DTI metrics, we performed principal component analyses on 48 markers of FA and MD, respectively, derived by UK Biobank from the FA skeleton of the diffusion MRI data, and used the first principal component from each analysis as a summary measure[12]. Additionally, from DTI scans we calculated peak width of skeletonized mean diffusivity (PSMD), an automated measure based on skeletonization analysis, using a published pipeline[13].

Genetic instruments

Sleep measures were used as instrumental variables. We obtained genome-wide association studies (GWAS) summary statistics from published analyses of UK Biobank participants for sleep duration (N=446,118; 78 loci)[14], chronotype (N=697,828; 351 loci)[15], daytime napping (N=452,633; 123 loci)[15], daytime dozing (N=452,071; 42

loci)[16], and snoring (N=314,449; 41 loci)[17]. For insomnia, the most recent and largest GWAS summary statistics were used, with 554 genetic loci identified in 2,365,010 individuals[18].

For outcome variables, summary statistics for stroke and ischemic stroke subtypes were obtained from participants of European ancestry from the GIGASTROKE Consortium[19], which consisted of 73,652 stroke patients and 1,234,808 controls. We conducted analyses for any stroke (n=73,652 cases), ischemic stroke (n=62,100 cases), cardioembolic stroke (n=10,804 cases), large-artery stroke (n=6,399), and small vessel stroke (n=6,811). We also used summary statistics from a cohort of neuroimaging-confirmed lacunar (small vessel) stroke, which provided more detailed phenotyping of SVS (NC_SVS, N=6,030)[20]. Summary statistics for AD were obtained from the International Genomics of Alzheimer's Project (IGAP) (N=21,982)[21]. For SVD imaging traits, summary statistics for WMH (N=42,310), FA (N=17,663), and MD (N=17,467) were obtained from a GWAS of participants from UK Biobank and the CHARGE Consortium[22]. We obtained summary statistics for PSMD from a currently unpublished GWAS study (N=40,464). A summary for originating GWAS studies can be found in Supplementary Table 1.

Statistical analyses

Cross-sectional and longitudinal analyses

Ethnicity, smoking, and alcohol were coded as binary outcomes. For ethnicity,

European was encoded to “0”, whereas all other ethnicities were encoded to “1”; For smoking and alcohol, “Never” was encoded to “0”, whereas “Previous” and “Current” were encoded to “1”. Categorical sleep variables (insomnia, chronotype, napping, dozing) were also reconstructed as binary outcomes. For insomnia, “Never/rarely” was encoded to “0”, whereas “Sometimes” and “Usually” were encoded to “1”; For daytime napping and dozing, “Never/rarely” was encoded to “0”, whereas “Sometimes” and “Often” was encoded to “1”; For chronotype, “Definitely a ‘morning’ person” and “More a ‘morning’ than ‘evening’ person” were encoded to 0, whereas “Definitely a ‘evening’ person” and “More a ‘evening’ than ‘morning’ person” were encoded to 1. The associations between sleep measures and SVD imaging markers (WMH, FA, MD, PSMD), were examined in a cross-sectional analysis using linear regression models. WMH was log-transformed and that you scaled the continuous outcomes to have a mean of 0 and SD of 1. In primary analyses, only age, sex, and ethnicity were adjusted. In secondary analyses, we adjusted for a wider range of vascular risk factors and other potential confounders (age, sex, ethnicity, BMI, blood pressure treatment, systolic blood pressure, diastolic blood pressure, type 2 diabetes, smoking, alcohol, serum cholesterol, and Townsend deprivation score). Sensitivity analyses were performed with further adjustment for major depression and atypical antipsychotic medication usage.

Longitudinal analyses were performed to investigate whether sleep measures predicted incident stroke and dementia. Cox proportional-hazards regression models

were used to examine the association between sleep variables and risk of incident stroke and dementia. Primary analyses were conducted with adjustment for age, sex, and ethnicity. Secondary analyses were conducted with a wide range of vascular risk factors and potential confounders included as described in cross-sectional analyses. Furthermore, sensitivity analyses were performed with further adjustment for major depression and atypical antipsychotic medication usage, and excluding all outcomes of interest that occurred within one year of the baseline assessment. The proportional hazards assumption for was evaluated using Schoenfeld residuals.

Mendelian randomization analyses

A two-sample MR analysis was performed to examine whether there was evidence to support a causal relationship of sleep with stroke, dementia, and SVD imaging markers.

Primary analyses were conducted using two-sample inverse-variance weighted univariable MR (IVW-MR). Independent single-nucleotide polymorphisms (SNPs) ($r2<0.01$ in European ancestry individuals in the 1000 Genomes Project, Phase 3 release [1KG]) that were associated with sleep measures at genome-wide significance ($p<5\times10\text{-}8$) were selected in European ancestry individuals. These SNPs were cross-referenced against the PhenoScanner database of published genetic associations to ensure that they, or their proxies ($r2\geqslant0.8$ in the 1KG project) were not associated with potential confounding factors at genome-wide significance[23]. The detailed SNPs excluded can be found in Supplementary Table 2. For all analyses, palindromic

variants with ambiguous allele frequencies were discarded as were genetic variants with potential strand issues that could not be resolved. Furthermore, all SNPs associated with sleep measures were harmonized with the outcome data to ensure that the effect estimates of each SNP on sleep and the outcome corresponded to the same effect allele.

A range of sensitivity analyses were performed relaxing some of the stricter assumptions underlying the IVW-MR method, including the weighted median estimator, simple and weighted mode-based estimators, MR-Egger regression, and MR pleiotropy residual sum and outlier (MR-PRESSO) methods[24]. These methods are recommended in practice for sensitivity analyses as they require different assumptions to be satisfied, and therefore if estimates from such methods are similar any inferred causal claims are more credible[25]. MR pleiotropy tests were performed which examine the intercept term in MR Egger regression to evaluate whether the result is influenced by directional horizontal pleiotropy. For significant results, reverse MR was performed to examine whether it is the case that the outcome causes the exposure. MR-PRESSO distortion and outlier tests were performed.

All observational analyses were conducted using Python 3.92 software; MR analyses were conducted in R v4.2.0 using the TwoSampleMR and MR-PRESSO packages. A false discovery rate (FDR) correction was applied with a significance threshold of 0.05.

Standard Protocol Approvals, Registrations, and Patient Consents

All UK Biobank participants provided informed consent as part of the UK Biobank recruitment process to the use of their anonymised data and samples for any health-related research, to be recontacted for further substudies, and for UK Biobank to access their electronic health records. UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. This research was conducted using UK Biobank under application number 36509.

Data Availability

The data supporting the findings of this study are available within the article and its Supplemental Materials. The original data from UK Biobank can be accessed by approved researchers through application to UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research). The summary statistics obtained from the genome-wide association are publicly available. The summary statistics for sleep characteristics can be obtained from the Sleep Disorder Knowledge Portal (https://sleep.hugeamp.org/) and the Complex Traits Genetics Lab (https://ctg.cncr.nl/software/summary_statistics/). The summary statistics for stroke from the GIGASTROKE Consortium can be obtained from the GWAS Catalog (https://www.ebi.ac.uk/gwas/; study accession numbers GCST90104534–GCST90104563). The summary statistics for AD can be obtained from the International Genomics of Alzheimer's Project (IGAP)

(https://www.niagads.org/datasets/ng00075).

RESULTS

Participant characteristics

502,383 participants from UK Biobank were analysed, with mean age 56.5 (SD=8.1) years; 54.4% were female and 94.6% white. Details for other risk factors, sleep measures, and SVD imaging measures are summarized in Table 1.

Association of sleep measures with stroke and dementia - longitudinal analysis

The median number of years follow-up was 13.07 (IQR=1.40) for stroke and 13.08 (IQR=1.39) for dementia. During the follow-up period there were 10,434 (2.07%) incident strokes, 8,785 (1.7%) ischemic strokes, 1,859 (0.37%) cases of ICH, 7,668 (1.5%) cases of all-cause dementia, 3,273 (0.6%) cases of AD, 1,736 (0.34%) cases of vascular dementia, and 264 (0.05%) cases of FTD (Table 2).

All sleep measures except insomnia were associated with all-cause dementia, and all sleep measures except snoring were associated with vascular dementia. After adjusting for vascular risk factors all associations with all-cause dementia remained significant (all $p<0.01$), apart from insomnia which was no longer significant. The association of daytime dozing with vascular dementia attenuated but remained significant after adjusting for vascular risk factors (HR:1.36 [1.10-1.69], p=0.005). Finally, we found insomnia (HR:0.83 [0.77-0.90], $p=9.50\times10^{-6}$) and snoring (HR:1.11 [1.02-1.21], p=0.008) were significantly associated with AD both before and after adjusting for cardiovascular risk factors.

In longitudinal analyses accounting for age, sex, and ethnicity, there were strong associations between insomnia, chronotype, daytime napping, and dozing with all stroke and all ischemic stroke. However, after adjusting for vascular risk factors, only insomnia, daytime napping and dozing showed weak associations with all stroke (HR:1.05 [1.01-1.11], $p=8.53x10^{-3}$ for insomnia; HR:1.09 [1.05-1.14], $p=3.20x10^{-5}$ for napping; HR:1.19 [1.08-1.32], $p=4.89x10^{-4}$ for dozing) and all ischemic stroke (HR:1.08, CI=[1.03-1.13], p=0.002 for insomnia; HR:1.11 [1.06-1.16], $p=4.43x10^{-6}$ for napping; HR:1.24 [1.11-1.37], $p=6.64x10^{-5}$ for dozing). The sensitivity analyses with further adjustment for major depression and atypical antipsychotics medication usage and excluding all outcomes of interest that occurred within one year of the baseline assessment did not find affect any significance level. To evaluate validity of models, scaled Schoenfeld residuals global tests were performed.

The results for longitudinal studies after adjusting for confounders and vascular risk factors are summarized in Figure 1. Detailed association results can be found in Supplementary Table 3 for primary analyses, Supplementary Table 4 for secondary analyses, Supplementary Table 5 and 6 for sensitivity analyses, and Supplementary Table 7 for scaled Schoenfeld residual tests.

Association of sleep measures with MRI markers of SVD; cross sectional analysis

After adjustment for sex, age, and ethnicity daytime napping was associated with higher WMH (OR:1.99, $p=5.56x10^{-13}$ [1.95,2.03], FA (OR:1.24, $p=7.21x10^{-7}$ [1.14-1.35]), MD (OR:1.17, $p=2.82x10^{-4}$ [1.07.1.27]), and PSMD (OR:1.05, $p=2.26x10^{-8}$

[1.03,1.07]). Furthermore, insomnia (OR:1.16, p=0.002 [1.06,1.27]) and snoring (OR:0.97, p=0.004 [0.78-0.93]) were associated with FA, while chronotype (OR:0.89, p=0.006 [0.81-0.97]) and snoring (OR:1.12, p=0.01 [1.03-1.22]) were associated with MD.(Table 3) After further adjusting for vascular risk factors, napping showed strong evidence of a weak association with WMH (OR:1.05, $p=1.49x10^{-6}$ [1.03,1.07]), FA (OR:1.13, p=0.005 [1.04-1.23]), MD (OR:1.14, p=0.002 [1.05-1.24]), and PSMD (OR:1.03, $p=2.84x10^{-4}$ [1.02-1.05]). Evening chronotype people was related to higher MD (OR:0.9, p=0.017 [0.83-0.98]). However, other associations were no longer statistically significant.

Mendelian randomization analyses

MR analyses found no significant association of genetically determined napping and dozing with all stroke, ischemic stroke, SVS, neuroimaging-confirmed lacunar stroke, cardioembolic stroke, and AD (all p>0.2, Figure 2). Genetically elevated propensities for napping and dozing were associated with higher risk of large-artery stroke (OR:1.90 [1.04, 3.47], p=0.035 for napping; OR:3.47 [1.09-16.57], p=0.037 for dozing), but the results were no longer significant after FDR correction. Genetically elevated levels of insomnia were associated with increased risk of all stroke (OR:1.27 [1.10, 1.47], p=0.00072) and all ischemic stroke (OR:1.31 [1.13-1.51], p=0.0003) after FDR correction. Insomnia was also significantly associated with SVS (OR:1.56 [1.03-2.36], p=0.03), but not after FDR correction. No reverse causality was observed for either all stroke (p=0.56) or all ischemic stroke (p=0.19).

There were no statistically significant associations between any sleep measures and WMH, FA, or MD. All other results were not statistically significant. There was no evidence for pleiotropy (Supplementary Table 11), and the MR-PRESSO distortion test detected one outlier for insomnia and all stroke, two outlier between insomnia and ischemic stroke. The outlier-corrected results were still statistically significant (OR:1.28 [1.17-1.49], p=0.0006 for AS; OR:1.32 [1.14-1.53], p=0.0002 for AIS). All MR-PRESSO global test, outlier test, distortion test, and outlier-corrected results are summarized in Supplementary Table 13, 14, 15, and 16.

DISCUSSION

We investigated the relationship of sleep with stroke and dementia, using both observational and genetic data, in over 500,000 individuals. Our observational study found associations between multiple sleep measures and both stroke and dementia, as well as associations between napping and snoring with SVD imaging traits. The association of insomnia with stroke was confirmed in our MR analyses.

In longitudinal analyses evaluating whether sleep measures led to incident stroke and dementia, the results revealed that insomnia, chronotype, daytime napping, daytime sleepiness, and snoring were associated with all stroke and ischemic stroke, suggesting a strong relationship between sleep and stroke, consistent with previous evidence[26–28]. After adjusting for confounders and vascular risk factors, the associations for insomnia, daytime napping, and dozing attenuated, but remained statistically significant, in accordance with previous work which found that daytime napping was associated with increased risk of stroke[29]. We also found that sleep duration, chronotype, daytime napping, daytime sleepiness, and snoring were associated with all-cause dementia, which is consistent with many previous studies associating sleep duration, chronotype, daytime napping, and daytime sleepiness with dementia risk[30–33]. However, after adjusting for vascular risk factors, only the associations with daytime sleepiness remained statistically significant. This suggests that relationship between sleep measures and dementia risk may be mediated by conventional cardiovascular risk factors such as blood pressure, smoking, and alcohol

consumption. Although we found a statistically significant association of increased insomnia with reduced risk of AD in the longitudinal analyses, there was no evidence to support a causal association since the Mendelian randomization analyses showed only a weak association of genetically determined insomnia with increased risk of AD which was not statistically significant. Although the analyses were adjusted for a wide range of potential confounders and vascular risk factors, there could still be other confounders that may have led to the observed association in the longitudinal analyses. In view of recent hypotheses that sleep is a risk factor for SVD and that this could partially mediate the associations between sleep and dementia, possibly via the glymphatic system, we examined associations between sleep and MRI markers of SVD in over 40,000 individuals with available brain MRI scans. As well as evaluating the conventional marker WMH, we also examined associations with DTI measures of white matter ultrastructure; such measures have been shown to be more strongly associated with cognitive impairment than WMH[13,34]. FA measures directionality of diffusion, MD measures the extent of diffusion, and PSMD is an automated metric that measures MD within the white matter tracts[13]. Fewer associations than with stroke and dementia persisted after controlling for cardiovascular risk factors, although daytime napping was consistently associated with WMH and all DTI measures after adjusting for vascular risk factors which aligns with previous findings[35]. Snoring was associated with both diffusivity measures, MD and PSMD[27,28]. This suggests that napping and snoring may be risk factors for SVD, although the analysis was cross-sectional and needs to be replicated in a longitudinal study to reduce risk of confounding.

To further investigate the causal nature of these associations, our MR analyses found evidence of causal associations linking genetically determined insomnia to risk of stroke and ischemic stroke. Our MR results did not support causal relationships of genetically determined daytime napping, sleepiness, and snoring with stroke, dementia, and imaging markers, indicating that these relationships may be confounded by other variables. Our MR analysis did not support a causal association between sleep characteristics and dementia, which is consistent with a previous study[36]. There was no evidence of a causal relationship of genetically determined insomnia with SVD imaging markers.

Several reasons might explain the lack of significant associations in the MR analyses for daytime napping and dozing. Confounding factors may have played a role in the identified associations in the observational study. Although our study included demographics and vascular risk factors, it is possible that other implicit confounders were not accounted for[37]. Additionally, the possibility of reverse causality, where stroke survivors or patients with SVD experience increased daytime sleepiness and napping, cannot be ruled out[32]. It is possible that patients surviving from stroke have increased levels of daytime sleepiness and napping[30].

Previous studies have implicated sleep apnoea as a risk factor for stroke[38], and snoring may be indicative of sleep apnoea syndrome. However, we found no associations of

snoring with stroke in either the observational or Mendelian randomization analyses. The previously reported association might be confounded by other cardiovascular comorbidities such as hypertension and type 2 diabetes, and we included controlling for these in our primary analysis. Consistent with this, previous MR studies have reported no association between sleep apnoea and stroke[39], supporting potential confounding of the previously reported epidemiological associations[38].

Our study has several strengths. The use of UK Biobank enabled a very large sample size of well characterized individuals with long-term follow-up to be analysed, of whom over 40,000 had brain MRI scans available. We also combined both observational and MR analyses to characterize the nature of the associations and assess causality, which increased the reliability of the findings. Our study is more comprehensive than previous analyses in the large sample size, the use of multiple sleep variables as exposures, and multiple outcome variables including stroke, dementia, and SVD markers, which may provide mechanistic insights.

However, the study also has limitations. First, most of sleep measures were derived from self-reported questionnaires. Recently, derived accelerometery data, including measures of sleep duration, have been released in UK Biobank, which provide more precise measures of sleep not subject to recall bias. Future work should use these data and compare the results to the current study. Several factors may have also reduced the ability of MR analyses to identify associations. We used UK Biobank for

the observational analyses and large GWAS datasets including UK Biobank and the GIGASTROKE Consortium for the genetic analyses, which provided much higher statistical power. However, some of the datasets used for the genetic associations with the sleep measures and outcomes were derived at least partially from UK Biobank. This overlap in participants may have contributed to some degree of over-fitting and weak instrument bias. GIGASTROKE included 12% of cases from UK Biobank for all stroke. However, previous MR studies excluded the overlapping participants obtained similar results with the main analyses [19], demonstrating that due to large sample sizes of respective studies the bias due to sample overlap is expected to be very small. Each sleep measure has specified a time frame pertaining to the last four weeks. Therefore, it is possible that the questionnaire may not be capturing a long-term exposure, as changes in sleep quality that occurred months or years before the baseline assessment may be relevant to long-term effects on health outcomes. Moreover, due to the lack of sufficiently large datasets for genetic associations with dementia subtypes, we were only able to conduct MR analyses using AD summary statistics from IGAP; future work should conduct MR analyses on other types of dementia, including vascular dementia and FTD when these data become available. Although sensitivity tests were performed, the MR results are still likely to be impacted by horizontal pleiotropy and reverse causality, which is a technical limitation in this method. Finally, if relationships are U-shaped relationship, as was suggested for sleep duration and SVD traits[40], these may not be detected by MR.

The findings of this study have important implications for clinical research and practice. For dementia, our observational analyses identified multiple associations of almost all sleep measures with dementia even after controlling for cardiovascular risk factors, although none persisted in the MR analyses. This may reflect limitations in the genetic instruments we had available but raises caution as to the causality of the observational associations. This is important since correction of sleep disorders has been suggested as preventative therapy for dementia, but our findings highlight that randomized controlled trials are required before routine sleep interventions should be recommended as a proven treatment. For stroke, we found multiple observational associations but many of these were no longer significant after controlling for cardiovascular risk factors. However, the associations with insomnia and napping persisted after adjustment, and importantly our MR analyses found associations of genetically determined insomnia with stroke risk and of napping with risk of large-artery stroke, supporting a causal relationship. This raises the possibility that treating insomnia may reduce stroke risk and recurrence, but again this needs testing in clinical trials. Lastly, our study does not provide strong evidence that sleep disturbances are a strong risk factor for SVD or that there is a major mechanism linking sleep with dementia. Although associations with napping and snoring were identified on observational studies, our MR analyses did not confirm evidence of a causal relationship.

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Author Contributions

CG, ELH, and HSM conceived and designed the study. CG and ELH analyzed the genetic and phenotypic data. CG, ELH, and HSM interpreted the data. All authors contributed to writing the first and subsequent versions of the manuscript.

Conflict of Interest Disclosures

The authors report no competing interests.

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The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Access and Responsibility

ELH and HSM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Characteristics of participants. Mean and standard deviation are presented for numerical variables, while the frequency and percentage are shown for categorical variables.

Characteristics	Mean (SD) or n(%)	N
Risk factors		
Female sex	273,169 (54.4%)	502,011
Age at recruitment (years)	56.53 (8.10)	502,383
Ethnicity (White)	472,642 (94.6%)	499,667
Townsend deprivation index	-1.29 (3.09)	501,760
Body mass index (BMI) (kg/m2)	27.43 (4.80)	499,391
Systolic blood pressure (mm Hg)	137.92 (18.69)	501,095
Diastolic blood pressure (mm Hg)	82.24 (10.17)	501,097
Current smoker	52,969 (10.6%)	499,569
Alcohol user	459,059 (91.7%)	500,746
Type 2 diabetes mellitus	47,822 (9.5%)	502,326
Taking blood pressure medication	103,035 (20.8%)	494,987
Serum cholesterol	5.69 (1.15)	470,734
Sleep measures		
Sleep duration (hours/day)	7.10 (1.30)	501,514
Insomnia	141,363 (28.2%)	500,898
Morningness chronotype	247,099 (55.5%)	444,946
Daytime napping	219,500 (43.8%)	500,508
Daytime dozing	14,092 (2.8%)	498,667
Snoring	173,329 (37.2%)	465,360
SVD MRI markers		
WMH volume (mm^3)	8.02 (1.01)	41,623
Fractional anisotropy (FA)	0.00017 (4.43)	40,746
Mean diffusivity (MD)	0.00011 (4.52)	40,746
Peak width of skeletonized mean diffusivity (PSMD) (mm^2/s)	0.00023 (4.1E-05)	40,464

Table 2. Clinical end point (stroke and dementia) and CSVD data for participants.

Clinical end points	n (%)	N
Incident all stroke case	10,434 (2.07%)	502,383
Incident ischemic stroke case	8,785 (1.7%)	502,383
Incident intracerebral hemorrhage case	1,859 (0.37%)	502,383
Incident all-cause dementia case	7,668 (1.5%)	502,383
Incident Alzheimer's disease case	3,272 (0.6%)	502,383
Incident vascular dementia case	1,736 (0.34%)	502,383
Incident frontotemporal dementia case	264 (0.05%)	502,382

Table 3. Association of each sleep variable with each MRI marker of SVD both after controlling for age, sex and ethnicity and after controlling for both demographic and cardiovascular risk factors.

			Controlling for age, sex, and ethnicity			Controlling for demographic and cardiovascular risk factors		
Sleep measures	**Outcome**	**N**	**Beta**	**SE**	**P**	**Beta**	**SE**	**P**
Sleep duration	WMH	41535	0.0001	0.0045	0.982	0.002656	0.004513	0.556
Insomnia	WMH	41498	0.0241	0.0107	**0.024**	0.007863	0.010788	0.466
Chronotype	WMH	37199	-0.0177	0.0097	0.067	-0.01322	0.009789	0.177
Napping	WMH	41511	0.0688	0.0095	**5.56E-13**	0.046697	0.009702	**1.49E-06**
Dozing	WMH	41459	0.0293	0.320545	0.360	0.021213	0.032208	0.510
Snoring	WMH	39200	-0.0284	0.009977	0.004	0.02211	0.010349	0.0327
Sleep duration	FA	40643	0.0038	0.0202	0.849	0.00949	0.020239	0.639
Insomnia	FA	40624	0.1488	0.04801	**0.002**	0.091216	0.048207	0.0585
Chronotype	FA	36398	-0.0919	0.043747	**0.036**	-0.07045	0.044017	0.109
Napping	FA	40636	0.2129	0.042946	**7.21E-07**	0.121745	0.043419	**0.005**
Dozing	FA	40584	0.1631	0.144319	0.258	0.109374	0.144243	0.448
Snoring	FA	38379	-0.1612	0.045017	**0.0003**	0.011804	0.046441	0.799
Sleep duration	MD	40643	0.0393	0.02	0.050	0.03174	0.02013	0.115
Insomnia	MD	40624	0.0429	0.047696	0.368	0.02187	0.04796	0.648
Chronotype	MD	36398	-0.1198	0.043388	**0.006**	-0.10413	0.043717	**0.017**
Napping	MD	40636	0.1550	0.04267	**0.0003**	0.132881	0.043196	**0.002**
Dozing	MD	40584	0.0858	0.143382	0.550	0.101172	0.143508	0.826
Snoring	MD	38379	0.1146	0.044676	**0.010**	0.148667	0.04615	**0.001**
Sleep duration	PSMD	40364	0.0025	0.004292	0.559	0.005335	0.004328	0.218
Insomnia	PSMD	40345	0.0003	0.010219	0.979	-0.01268	0.010309	0.219
Chronotype	PSMD	36155	-0.0058	0.009292	0.530	-0.00256	0.009393	0.785
Napping	PSMD	40357	0.0511	0.009144	**2.26E-08**	0.033715	0.009289	**0.0003**
Dozing	PSMD	40306	0.0236	0.030695	0.442	0.01445	0.030825	0.639
Snoring	PSMD	38122	-0.0116	0.009575	0.226	0.024362	0.009924	**0.014**