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Genetic associations between sleep traits and cognitive ageing outcomes in the Hispanic Community Health Study/Study of Latinos

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Summary

Background Sleep phenotypes have been reported to be associated with cognitive ageing outcomes. However, there is limited research using genetic variants as proxies for sleep traits to study their associations. We estimated associations between Polygenic Risk Scores (PRSs) for sleep duration, insomnia, daytime sleepiness, and obstructive sleep apnoea (OSA) and measures of cogntive ageing in Hispanic/Latino adults.

Methods We used summary statistics from published genome-wide association studies to construct PRSs representing the genetic basis of each sleep trait, then we studied the association of the PRSs of the sleep phenotypes with cognitive outcomes in the Hispanic Community Healthy Study/Study of Latinos. The primary model adjusted for age, sex, study centre, and measures of genetic ancestry. Associations are highlighted if their p-value <0.05.

Findings Higher PRS for insomnia was associated with lower global cognitive function and higher risk of mild cognitive impairment (MCI) (OR = 1.20, 95% CI [1.06, 1.36]). Higher PRS for daytime sleepiness was also associated with increased MCI risk (OR = 1.14, 95% CI [1.02, 1.28]). Sleep duration PRS was associated with reduced MCI risk among short and normal sleepers, while among long sleepers it was associated with reduced global cognitive function and with increased MCI risk (OR = 1.40, 95% CI [1.10, 1.78]). Furthermore, adjustment of analyses for the measured sleep phenotypes and *APOE-ε4* allele had minor effects on the PRS associations with the cognitive outcomes.

Interpretation Genetic measures underlying insomnia, daytime sleepiness, and sleep duration are associated with MCI risk. Genetic and self-reported sleep duration interact in their effect on MCI.

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Keywords: Global cognitive function; Mild cognitive impairment; Sleep duration; Insomnia; Daytime sleepiness; Polygenetic risk score

Research in context

Evidence before this study

The authors reviewed the literature using traditional sources. Several publications have shown sleep phenotypes are associated with cognitive aging outcomes. However, there is limited research using genetic variants as proxies of sleep traits to study their associations. The relevant citations are appropriately cited.

Added value of this study

We used Polygenetic Risk Scores (PRSs) to capture the genetic determinants of sleep traits. Higher insomnia PRS was associated with lower global cognitive function and with increased risk of mild cognitive impairment (MCI). There is a sleep duration–genetics interaction, where higher sleep duration PRS was associated with lower MCI risk in short and normal sleepers, but with worse global cognitive change and higher MCI risk in long sleepers.

Implications of all the available evidence

Future studies are needed to (a) study shared biological pathways and causal relationships between sleep and cognitive outcomes; (b) use sleep PRSs for risk stratification and prediction of aging-related cognitive decline and dementia.

Introduction

Alzheimer's Disease and Related Dementias (ADRD), as well as cognitive outcomes that typically precede these disorders such as Mild Cognitive Impairment (MCI) and cognitive decline, are important public health concerns.[1] These disorders and phenotypes are known to be affected by various risk factors including genetics and lifestyle.[2] However, there is limited knowledge regarding genetic risk profiles that predict early cognitive decline and impairment in diverse population. For example, *apolipoprotein E* (*APOE*) alleles are reported to be associated with cognitive decline, MCI, and ADRD in White adults[3] while the associations are weak in Hispanics/Latinos.[4] Compared to Whites, Hispanics/Latinos have a higher prevalence of vascular dementia,[5,6] and a high burden of several cardiovascular risk factors that may drive increased risk of ADRD.[7,8] Therefore, studying cardiovascular risk factors as early markers or mediators of dementia holds potential for early prevention and intervention for declined cognition in Hispanics/Latinos.

Sleep disturbances including insomnia, short or long sleep durations, excessive daytime sleepiness, and obstructive sleep apnoea (OSA) affect ~50% of older adults and are associated with both cardiovascular disease risk and ADRD-related pathologies and other ageing-related cognitive outcomes.[9–11] Sleep disturbances may have multi-faceted associations with cognitive function and ageing, potentially due to common underlying mechanisms as well as direct causal associations.[12] Genetics can be used to assess the shared basis of sleep disorders and cognitive ageing, and genetic markers of sleep phenotypes may help to predict cognitive ageing outcomes. Using genetic variants as proxies of lifetime sleep exposure, rather than directly measured sleep itself, may be especially useful to study sleep-cognitive ageing associations because genetic variants are relatively static over time whereas sleep changes.[13] In addition, there are many ways to measure sleep (e.g., average duration of sleep, average duration spent in the bed, frequency of motion and intensity of movement) and different studies at different time points may apply different procedures,[14] limiting the evaluation and standardization of sleep measures for predicting risk of cognitive ageing. Finally, large strides have been taken to incorporate genetic information into standard health-related data collection, so that genetics-based measures such as Polygenic Risk Scores (PRSs) may become useful and widely adopted for risk stratification.[15]

Sleep duration has a known "U-shape" association with cognitive and cardiovascular outcomes.[16,17] Other researchers used genetics to study the association of sleep duration with cognitive phenotypes, linearly, and while assessing U-shaped or other non-linear association forms. For examples, Henry et al.[18] used Mendelian Randomization analysis (MR) in White individuals from the UK Biobank to show that sleep duration has likely a non-linear relationship with cognitive function, where both long and short sleep durations were associated with negative effects. Li et al.[19] studied, in the same population, the association of sleep duration and its PRS with

cognitive and brain MRI outcomes. They identified a direct effect of the PRS in addition to an indirect effect mediated by sleep duration. They also reported a non-linear association of sleep duration with cognitive outcomes, though these results were not informed by genetic analysis. Yuan et al.,[20] also using UK biobank data, reported no evidence of a causal association of sleep duration (linear) with AD based on MR, but did observe an association between self-reported long sleep (>9 h) with high risk of AD. A study by Tsapanou et al.[21] of mostly non-Hispanic Whites confirmed that sleep duration PRS is associated with sleep duration, and reported that higher PRS values are associated with better cognitive function. In a more recent paper they expanded the work and studied sleep duration PRS association with cognition over time.[22] Higher values of sleep duration PRS were associated with a greater reduction in visuo-spatial ability, but not with other cognitive measures.

We here expand upon this prior work by including a large sample size of diverse Hispanics/Latinos, by studying interaction between self-reported sleep duration and sleep duration PRS, and by studying the use of PRSs of additional sleep phenotypes in association with cognitive outcomes. Hispanics/Latinos are an understudied and underrepresented minority in the U.S., suffering from a high burden of dementia.[23] Previous studies in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) have demonstrated that OSA, long sleep duration, and longer sleep-onset latency are associated with poor cognitive outcomes.[16,24–26] We leveraged data from the HCHS/SOL and its ancillary study of cognitive ageing in middle-aged and older adults, the Study of Latinos-Investigation of Neurocognitive Aging (SOL-INCA), to assess if genetic determinants of sleep were associated with cognitive ageing. We first used publicly available GWAS summary statistics to develop PRSs for sleep phenotypes, including daytime sleepiness, sleep duration, insomnia, and OSA. Then, we constructed the PRSs in the HCSH/SOL and (after validating the associations with their respective sleep phenotypes) estimated their associations with global cognitive function, global cognitive change, and MCI. The analytic workflow is described in Fig. 1.

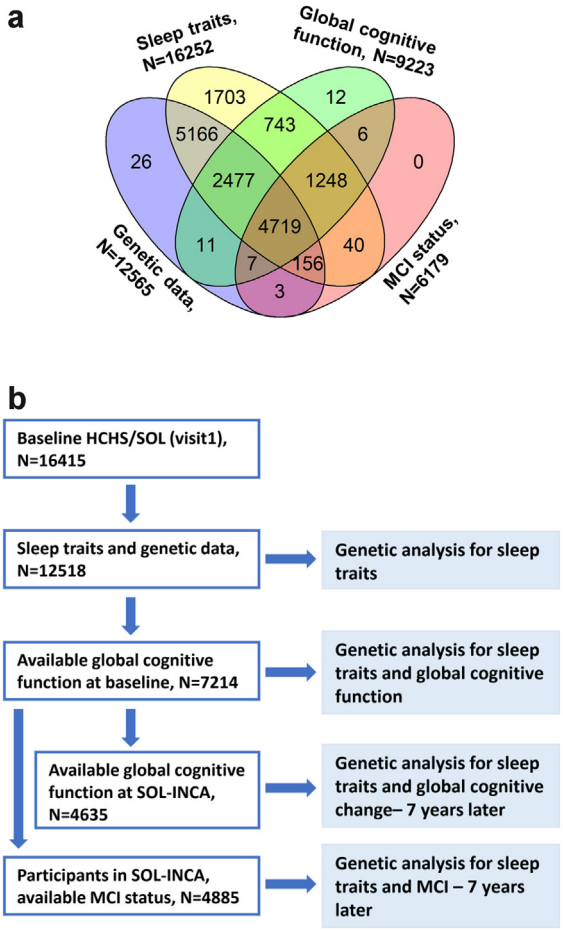

***Fig. 1*: The number of participants included in each stage of the study is summarized by (a) Venn diagram and (b) flowchart.** Participants were included if they had consent for genetic data analysis for HCHS/SOL investigators, had at least one of the primary sleep outcomes, and/or had complete neurocognitive tests used to compute global cognitive function at the HCHS/SOL baseline visit, and/or the global cognitive change from baseline visit to SOL-INCA visit, and/or had inferred MCI status in the SOL-INCA visit, on average 7 years after baseline. Abbreviations: *HCHS/SOL*: Hispanic Community Health Study/Study of Latinos; *MCI*: Mild Cognitive Impairment; *SOL-INCA*: Study of Latinos - Investigation of Neurocognitive Aging.

Methods

Study population

The HCHS/SOL is a longitudinal cohort study aiming to estimate the prevalence and risk/protective factors for chronic diseases in U.S. Hispanics/Latinos.[27,28] During the baseline visit 1 (2008–2011), 16,415 participants aged 18–74 years were recruited from four U.S. regions: San Diego, CA; Chicago, IL; Bronx, NY and Miami, FL. Participants were enrolled using a multi-stage design, where census block units were sampled followed by households with Hispanic/Latino surnames. Individuals were then sampled from households. Sampling weights were developed to account for sampling probability and non-response. Therefore, estimates obtained from analyses that properly account for these sampling weights are unbiased for, or representative of, the HCHS/SOL target population. Data were collected via interviews, physical exams, and questionnaires and included a sleep study and neurocognitive function tests for a subset of individuals aged 45 years. Additional neurocognitive function tests were administered later as

part of the SOL-INCA ancillary study of HCHS/SOL which occurred at or after the second HCHS/SOL exam (average of 7 years post-visit 1).[29] Because the target population of the SOL-INCA ancillary study is different than that of the HCHS/SOL, a separate set of sampling weights was developed to be used when analysing SOL-INCA data.

As described in Fig. 1, participants were included in the current analysis if they consented to genetic data analysis and met the following criteria: had at least one of the primary sleep phenotypes and/or cognitive outcomes described below: (1) complete neurocognitive tests required to compute global cognitive function at the baseline HCHS/SOL exam, and/or (2) global cognitive change between baseline and SOL-INCA, and/or (3) computed MCI status at the SOL-INCA exam. We characterized the HCHS/SOL and the SOL-INCA study populations.

Cognitive outcomes

We studied three neurocognitive outcomes: global cognitive function at baseline, global cognitive change from baseline to the SOL-INCA visit, and MCI. Global cognitive function was calculated as the mean of the z-scores for each of the following cognitive tests: Brief-Spanish English Verbal Learning Test (B-SEVLT) sum and recall (measuring verbal episodic learning and memory respectively)[30]; Word Fluency test (WF; measuring phonemic fluency)[31]; and Digit Symbol Substitution test (DSS; measuring processing speed and executive function).[32] The z-score of global cognitive function at the SOL-INCA visit was computed with the same tests and additionally two Trail Making Tests (TMT-A and TMT-B; measuring executive function), after changing the direction to match that of the other tests, i.e., all test scores were aligned so that high z-scores reflected better cognitive function. To compute z-scores, we used all individuals with cognitive tests at baseline (or at SOL-INCA) regardless of having genetic data. We accounted for the survey design in the computation of the mean and standard deviations of each of the cognitive tests. Global cognitive change was computed as the difference between global cognitive function at the SOL-INCA and the baseline visit.

Individuals were classified as having MCI according to National Institute on Aging-Alzheimer's Association criteria[33] and as previously described by SOL-INCA team.[29] Briefly, MCI classification relied on (1) self-reported significant cognitive decline based on the Everyday Cognition-12 (ECog12),[34] (2) change in any cognitive test between the baseline HCHS/SOL exam and the SOL-INCA exam of ≥−0.055 standard deviation (SD)/year, and low scores for cognitive tests (≤−1 SD) in comparison with SOL-INCA internal norms after adjustment of age, sex, education, and the NIH Toolbox Picture Vocabulary Test (PVT; measuring general premorbid cognitive function),[35] and (3) no or minimal functional impairment in Instrumental Activities of Daily Living.[36] Individuals with severe MCI or suspected dementia (defined by the decline of any cognitive score and functional impairment >−2 SD relative to the normal mean) were excluded from the MCI analysis.

Sleep phenotypes

We used sleep phenotypes in order to validate sleep PRS associations with their sleep phenotypes, as adjusting variables in secondary analyses of sleep PRS associations with cognitive outcomes, and to stratify individuals by categories of sleep duration. Definitions and measurements of sleepiness, insomnia, OSA, and sleep duration are provided in the Supplementary Materials. Based on the number of individuals in each potential category and previously published HCHS/SOL sleep-related manuscripts, we defined short sleep as sleep duration ≤6 h per night, long sleep as sleep duration >9 h per night, and normal sleep duration was defined as average sleep duration longer than 6 and up to 9 h/night.

Genetic data

Genotyping was performed using Illumina custom array genotypes were imputed using the TOPMed Freeze 5b reference panel.[37,38] Genetic Principal Components (PCs) were previously estimated using PC-AiR in the GENESIS R package.[39] 'Genetic analysis groups' were constructed based on a combination of self-identified Hispanic/Latino background and genetic similarity. *APOE* genotyping was performed on 10,934 HCHS/SOL individuals using commercial TaqMan assays.[40] For additional 548 individuals, we inferred *APOE* genotypes based on phased whole-genome sequencing data from the Trans-Omics in Precision Medicine (TOPMed) dataset, Freeze 8.

PRS construction

We identified publicly available summary statistics from GWAS of sleep phenotypes: OSA, daytime sleepiness, insomnia, sleep duration, short sleep, and long sleep duration[41–44] (Supplemental Table S1) and used these to develop PRSs for sleep phenotypes using the clump and threshold method implemented in the PRSice-2 software.[45] We excluded Single Nucleotide Polymorphisms (SNPs) with minor allele frequency <0.01 in HCHS/SOL or, when available, in the GWAS summary statistics. We also excluded SNPs with Hardy–Weinberg equilibrium test p-value $<1 \times 10^{-6}$ and SNPs with imputation quality <0.8. We used the HCHS/SOL genetic data as a Linkage Disequilibrium reference panel and set the clumping parameters to a distance of 1000 kb and $R^2 = 0.1$. Primary PRS included SNPs with

a p-value $<1 \times 10^{-2}$, and we also considered p-values thresholds of 1×10^{-5} and 5×10^{-8}.

Statistical analysis: PRS association analysis

All association analyses were performed using the survey R package version 4.0 to account for the HCHS/SOL survey sampling design, including stratification, clustering, probability sampling, and non-response.[28] Thus, association effect estimates characterize the HCHS/SOL target population.

We first validated the association of each PRS with its corresponding sleep trait in the HCHS/SOL dataset in survey-adjusted association analyses. For binary outcomes we used logistic regression models (setting "quasibinomial" family in the generalized linear model equation code), and linear regression models for continuous outcomes (setting "gaussian" family in the code). PRSs that were associated with their corresponding trait (p-value < 0.05) were carried forward for association analysis with cognitive outcomes, using survey logistic regression for MCI and survey linear regression for global cognitive function and global cognitive change. We estimated the association of the sleep PRSs with cognitive outcomes using three nested regression models, with the goals of both assessing the potential of the PRS for prediction of cognitive outcomes, and to assess the usefulness of a genetic marker compared to measured, time varying risk factors. The primary model 1 adjusted for age, sex, study centre, genetic analysis group, and first 5 PCs representing genetic ancestry. Model 2 also adjusted for education level, and model 3 further adjusted for cardiometabolic risk factors and potential mediators of the PRS associations with cognitive outcomes: body mass index (BMI), alcohol intake, frequency of taking sleep medications per week, depression and anxiety estimated by the Center for Epidemiologic Study Depression (CES-D 10 item)[46] and State Trait Anxiety Inventory (STAI 10 item)[47] scales respectively, and risk of stroke and vascular events as estimated by the Framingham Cardiovascular Risk Score (FCRS).[48,49] When estimating associations with MCI, all models were further adjusted for time between the baseline and the SOL-INCA visit. We also studied whether the sleep PRSs which were associated with MCI are still associated with MCI in a joint model, including all PRS and model 1 covariates. We compared these associations to those from models that included the measured sleep phenotype or additive heritance mode of the *APOE-ε4* allele, in addition to the PRS. To study the known non-linear association of sleep duration with cognitive outcomes, we estimated the association of the sleep duration PRS in strata of short, normal, and long sleepers; computed the MCI prevalence in each sleep duration category; and further stratified by individuals with PRS values below and above the observed sample median of PRS values. To address the differences in how short and long sleep are defined in the literature, we also estimated the association of sleep duration PRS with MCI using multiple accepted thresholds of defining short (<6, ≤ 6, <7) and long (>8, ≥ 9, >9) sleep categories.

In secondary analyses, we estimated the pairwise associations between sleep PRSs and all other sleep traits. Our main results report association effect estimates with 95% confidence intervals. In the Supplementary Information, we also report False Discovery Rate (FDR) adjusted p-values using the Benjamini-Hochberg procedure[50] for all primary (model 1) associations, computed in each set of results. Additionally, we computed the predictive performance of sleep PRSs for their respective binary sleep phenotypes and for MCI by computing the Area Under the Receiver Operative Curve (AUC) statistics using the R package pROC.

Ethics statement

The HCHS/SOL was approved by the institutional review boards (IRBs) at each field centre, where all participants gave written informed consent in their preferred language (Spanish/English), and by the Non-Biomedical IRB at the University of North Carolina at Chapel Hill, to the HCHS/SOL Data Coordinating Center. All IRBs approving the study are: Non-Biomedical IRB at the University of North Carolina at Chapel Hill. Chapel Hill, NC; Einstein IRB at the Albert Einstein College of Medicine of Yeshiva University. Bronx, NY; IRB at Office for the Protection of Research Subjects (OPRS), University of Illinois at Chicago. Chicago, IL; Human Subject Research Office, University of Miami. Miami, FL; Institutional Review Board of San Diego State University, San Diego, CA. The study reported here was approved by the Mass General Brigham IRB under protocol # 2018P001797.

Role of the funding source

The funder did not have any role in the design and execution of the analysis in this manuscript, data interpretation, manuscript writing, and nor in the decision to submit the paper for publication.

Results

Demographics and outcome characteristics of HCHS/SOL study samples

Fig. 1 summarizes the overlap between data types used in the analyses (genetic data, sleep phenotypes, cognitive outcomes; panel a), and the analytic flow and sample sizes used. Table 1 characterizes the study participants, by strata defined by participation in sleep and cognitive outcomes analyses. Data for validating the sleep PRSs were available for 12,518 individuals with sleep and genetic data. There were 7214 individuals with genetic

Measures	Individuals from the baseline visit		Individuals also participated in the SOL-INCA visit		
	With sleep traits data	With global cognitive function data	With global cognitive change data	Without MCI	With MCI
No. of participants	12,518	7214	4635	4417	468
Primary sleep outcomes					
OSA (REI ≥ 5) (n (%))	3461 (31.0)	2680 (41.5)	1732 (41.3)	1636 (40.9)	166 (40.7)
WHIIRS (mean (SD))	7.14 (5.45)	7.73 (5.58)	7.69 (5.54)	7.62 (5.53)	8.96 (5.63)
Sleep duration, h (mean (SD))	7.92 (1.42)	7.80 (1.40)	7.77 (1.36)	7.75 (1.36)	7.91 (1.49)
ESS (mean (SD))	5.78 (4.84)	6.00 (5.02)	6.12 (5.01)	6.04 (5.02)	6.62 (5.18)
Secondary sleep outcomes					
REI, events/h (mean (SD))	6.43 (12.25)	8.31 (13.10)	8.08 (12.58)	8.11 (12.73)	8.34 (13.08)
Insomnia (WHIIRS ≥ 9) (n (%))	4453 (36.5)	2893 (41.2)	1856 (40.9)	1744 (40.3)	226 (49.6)
Sleep category					
Short sleep (≤6 h) (n (%))	1175 (9.8)	770 (11.2)	486 (10.8)	466 (10.9)	53 (11.9)
Intermediate sleep (6< ~ ≤9 h) (n (%))	8613 (72.1)	5089 (73.7)	3354 (74.9)	3199 (75.0)	305 (68.5)
Long sleep (>9 h) (n (%))	2164 (18.1)	1044 (15.1)	640 (14.3)	601 (14.1)	87 (19.6)
EDS (ESS > 10) (n (%))	1947 (15.7)	1210 (17.0)	812 (17.7)	750 (17.2)	96 (21.0)
Covariates					
Age, years (mean (SD))	46.15 (13.86)	55.23 (7.46)	54.91 (7.11)	54.84 (7.07)	57.29 (7.90)
Sex, male (n (%))	5158 (41.2)	2818 (39.1)	1704 (36.8)	1648 (37.3)	152 (32.5)
Education category					
<12 years (n (%))	4626 (37.0)	2933 (40.7)	1742 (37.6)	1720 (38.9)	235 (50.2)
=12 years (n (%))	3223 (25.8)	1584 (22.0)	1025 (22.1)	956 (21.6)	90 (19.2)
>12 years (n (%))	4650 (37.2)	2682 (37.3)	1861 (40.2)	1741 (39.4)	143 (30.6)
BMI category (BMI range, kg/m^2)					
Underweight (<18.5) (n (%))	99 (0.8)	32 (0.4)	16 (0.3)	12 (0.3)	4 (0.9)
Normal (18.5–24.9) (n (%))	2395 (19.2)	1114 (15.5)	715 (15.5)	689 (15.6)	63 (13.5)
Overweight (25–29.9) (n (%))	4695 (37.6)	2861 (39.7)	1863 (40.3)	1795 (40.7)	163 (35.1)
Obesity (≥30) (n (%))	5297 (42.4)	3192 (44.3)	2032 (43.9)	1914 (43.4)	235 (50.5)
Alcohol intake category					
Never (n (%))	2433 (19.4)	1553 (21.5)	1017 (22.0)	955 (21.6)	118 (25.2)
Former (n (%))	4074 (32.6)	2484 (34.4)	1521 (32.8)	1454 (32.9)	167 (35.7)
Current (n (%))	6007 (48.0)	3174 (44.0)	2094 (45.2)	2005 (45.4)	183 (39.1)
Sleep medication frequency					
No (n (%))	10,716 (86.4)	5949 (83.3)	3854 (83.7)	3679 (83.9)	368 (79.8)
Up to 3 weeks (n (%))	730 (5.9)	464 (6.5)	307 (6.7)	288 (6.6)	37 (8.0)
≥4 weeks (n (%))	959 (7.7)	726 (10.2)	446 (9.7)	420 (9.6)	56 (12.1)
FCRS (mean (SD))	0.12 (0.12)	0.14 (0.12)	0.13 (0.12)	0.13 (0.12)	0.17 (0.13)

(Table 1 continues on next page)

Measures	Individuals from the baseline visit		Individuals also participated in the SOL-INCA visit		
	With sleep traits data	With global cognitive function data	With global cognitive change data	Without MCI	With MCI
(Continued from previous page)					
CES-D (mean (SD))	7.37 (6.16)	7.70 (6.43)	7.54 (6.31)	7.46 (6.24)	8.90 (6.70)
STAI (mean (SD))	17.23 (5.88)	17.24 (6.04)	17.07 (5.87)	16.99 (5.83)	18.35 (6.18)
APOE genotypes					
ε2/ε2 (n (%))	33 (0.3)	19 (0.3)	12 (0.3)	12 (0.3)	1 (0.2)
ε2/ε3 (n (%))	849 (7.5)	515 (7.9)	337 (8.1)	324 (8.2)	27 (6.6)
ε2/ε4 (n (%))	131 (1.2)	79 (1.2)	45 (1.1)	46 (1.2)	8 (1.9)
ε3/ε3 (n (%))	7871 (69.3)	4528 (69.2)	2873 (69.3)	2733 (69.1)	280 (68.1)
ε3/ε4 (n (%))	2285 (20.1)	1303 (19.9)	810 (19.5)	782 (19.8)	84 (20.4)
ε4/ε4 (n (%))	188 (1.7)	101 (1.5)	67 (1.6)	61 (1.5)	11 (2.7)

Abbreviations: *APOE*: apolipoprotein E; *BMI*: Body Mass Index; *CES-D*: Center for Epidemiologic Study Depression; *EDS*: Excessive Daytime Sleepiness; *ESS*: Epworth Sleepiness Scale; *FCRS*: Framingham Cardiovascular Risk Score; *HCHS/SOL*: Hispanic Community Health Study/Study of Latinos; *OSA*: Obstructive Sleep Apnea; *REI*: Respiratory Event Index; *SOL-INCA*: Study of Latinos - Investigation of Neurocognitive Aging; *STAI*: State-Trait Anxiety Inventory; *WHIIRS*: Women's Health Initiative Insomnia Rating Scale.

***Table 1*: Demographics, health, and lifestyle characteristics of the HCHS/SOL study population in each of the study stages.**

and global cognitive function data, 4635 individuals with genetic and global cognitive change data, and 4885 individuals with genetic and MCI data. Of the study participants, depending on the specific analysis, ~11% were categorized in the short sleep (≤ 6 h) stratum and ~15% were categorized in the long sleep (>9 h) stratum. Table 2 summarizes the global cognitive function, global cognitive change, and cognitive tests scores for both visits, with the SOL-INCA visit further stratified by MCI status. Supplemental Table S2 reports the number and proportions of participants by each potential definition of short and long sleep categories.

PRSs for sleep traits

We constructed PRSs for OSA, insomnia, sleepiness, and continuously measured sleep duration (primary phenotypes) as well as for short and long sleep (secondary phenotypes). Supplemental Fig. S1 presents the associations of these sleep PRSs with the corresponding sleep traits in HCHS/SOL. It also provides results from secondary analyses considering a more stringent p-value threshold for SNP inclusion in the PRSs, and estimated associations of sleep duration PRS with short and long sleep phenotypes. As expected, PRSs using SNPs with $p < 1 \times 10^{-2}$ (primary PRSs) had the strongest associations for each of the four primary sleep traits (all association p-values < 0.01). In secondary analyses, PRSs for short and long sleep were not associated with their respective phenotypes, and sleep duration PRS was not associated with short and long sleep at the p-value <0.05 level.

Supplemental Table S3 reports AUCs for each of insomnia, OSA, sleep duration, and sleepiness PRS in predicting the respective binary phenotypes (short and long sleep for sleep duration PRS), and compares them to AUCs of models without the PRS. Compared to models using clinical covariates, AUCs were often just slightly higher for models that added in the PRS, suggesting that, despite strong associations, these PRS may not improve prediction models for these sleep phenotypes.

The association of sleep traits' PRSs with cognitive outcomes

Fig. 2 visualizes the associations of sleep trait PRSs with cognitive outcomes. PRS for insomnia was significantly associated with lower global cognitive function in model 1 (estimate = –0.04 per 1 SD increase in the PRS, 95% CI [–0.06, –0.01], p-value = 0.003). Further adjustments in model 2 and model 3 only slightly attenuated the association. PRSs for the other three primary sleep traits, daytime sleepiness, sleep duration, and OSA, were not associated with global cognitive function in any of the three models (all p-values > 0.05). None of the sleep trait PRSs were associated with global cognitive

Measures for each cognitive domain	Characteristics from baseline visit		Characteristics from SOL-INCA visit			Characteristics change between visits
	With global cognitive function	With global cognitive change	With global cognitive change	None-MCI	MCI	With global cognitive change
No. of participants	7214	4635	4635	4417	468	4635
Global cognitive function						
Z-score	0.02 (0.76)	0.10 (0.73)	0.07 (0.74)	0.13 (0.71)[a]	−0.65 (0.75)[a]	−0.04 (0.53)
Psychomotor speed						
DSS	34.10 (13.39)	35.44 (12.84)	33.60 (12.72)	33.87 (12.85)	22.98 (11.25)	−1.84 (7.36)
Verbal learning, memory						
B-SEVLT (sum)	22.78 (5.54)	23.17 (5.44)	23.41 (5.68)	23.66 (5.56)	18.29 (5.68)	0.24 (5.27)
B-SEVLT (recall)	8.29 (2.88)	8.49 (2.79)	8.54 (2.93)	8.68 (2.85)	6.02 (2.87)	0.05 (2.90)
Phonemic fluency						
WF	18.33 (7.20)	18.93 (7.15)	18.59 (7.11)	18.73 (7.16)	13.19 (6.61)	−0.34 (5.44)
Executive function						
TMT-A	na	na	59.49 (35.44)	60.19 (37.36)	88.00 (55.00)	na
TMT-B	na	na	152.80 (63.08)	150.40 (62.40)	185.19 (62.54)	na

Cognitive measures are presented as mean and standard deviation (SD). The global cognitive function at baseline and SOL-INCA visit were calculated as the mean of the z-scores for each of the four and six cognitive tests listed in the table respectively. The direction of all tests to compute z-score was matched i.e., high z-scores were always interpreted as better cognitive function. Note that the average global cognitive function is not zero because was computed using all individuals with available cognitive function data at baseline, but presented here over the smaller set of individuals who also had genetic data. Abbreviations: *B-SEVLT*: Brief-Spanish English Verbal Learning Test; *DSS*: Digit Symbol Substitution test; *HCHS/SOL*: Hispanic Community Health Study/Study of Latinos; *MCI*: Mild Cognitive Impairment; *na*: not available; *SOL-INCA*: Study of Latinos - Investigation of Neurocognitive Aging; *TMT-A*: Trail Making Test, Part A; *TMT-B*: Trail Making Test, Part B; *WF*: Word Fluency. [a]The sample sizes for none-MCI and MCI groups used to compute global cognitive function from SOL-INCA visit are 4217 and 426 respectively.

Table 2: **Cognitive characteristics of HCHS/SOL cohort at the baseline and SOL-INCA visits.**

change. In association analysis with MCI, PRS for insomnia was associated with an increased risk of MCI in all three models (model 1: OR = 1.20, 95% CI [1.06, 1.35], p-value = 0.005). Higher PRS for sleep duration was associated with lower MCI risk in all three models (model 1: OR = 0.86, 95% CI [0.76, 0.98], p-value = 0.02). PRS for daytime sleepiness was associated with an increased risk of MCI in the first two models only

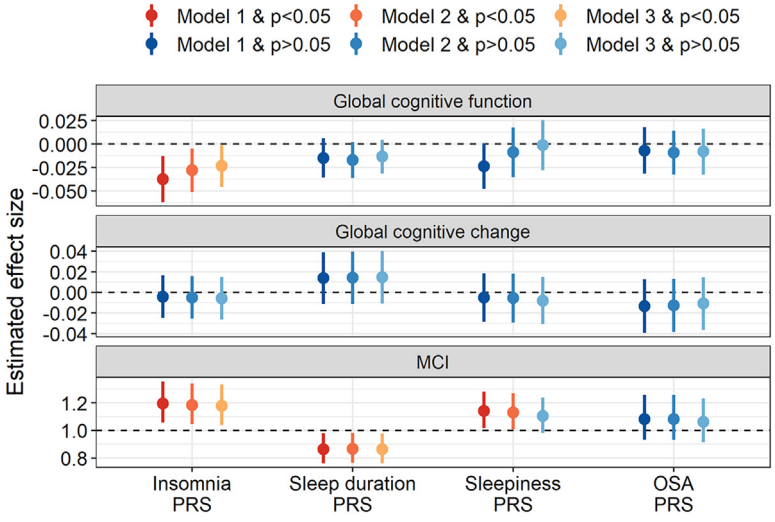

Fig. 2: **Estimated associations between sleep traits' PRSs with cognitive outcomes.** Each dot and line represent the estimated effect size per 1 SD increase in the PRS and its 95% confidence interval. Global cognitive function and global cognitive change are treated as a continuous variable and MCI as a binary variable. Model 1. Adjusted for age, sex, field centre, genetic analysis group, and the first 5 PCs of genetic data. Model 2. Adjusted for model 1 covariates with further adjustment for education. Model 3. Adjusted for model 2 covariates, and additionally to BMI, alcohol intake, sleep medication frequency per week, depression, anxiety, and FCRS. Abbreviations: *BMI*: Body Mass Index; *FCRS*: Framingham Cardiovascular Risk Score; *MCI*: Mild Cognitive Impairment; *OSA*: Obstructive Sleep Apnea; *PCs*: Principal Components; *PRS*: Polygenic Risk Score.

(model 1: OR = 1.14, 95% CI [1.02, 1.28], p-value = 0.02). PRS for OSA was not associated with MCI in any models (all p-values > 0.05). Observed associations tend to weaken slightly upon adjustment for the measured sleep phenotype to *APOE-ε4*, except for the sleep duration PRS in association with MCI which became a bit stronger after adjusting for self-reported sleep duration (Supplemental Fig. S2). When combining the three associated sleep PRSs in the same model, all associations weakened. This is likely due to the association between the sleep PRSs, as demonstrated by the results of the secondary analysis of association between sleep PRSs and other sleep phenotypes (Supplemental Fig. S5). All estimated effect sizes, SEs, and raw and False Discovery Rate (FDR) adjusted p-values are provided in Supplemental Tables S4 and S5.

Supplemental Table S3 reports AUCs for each of insomnia, OSA, sleep duration, and sleepiness PRSs in predicting MCI, and compares them to AUCs of models without the PRSs. As for prediction of sleep phenotypes, here as well sleep PRSs did not sufficiently improved performance of MCI predictive models compared to models without the PRSs, suggesting that these PRSs are not ready for implementation within a predictive modelling framework.

The association of sleep duration PRS with cognitive outcomes stratified by sleep duration categories

Because sleep duration has a known U-shaped association with cognitive outcomes, including in HCHS/SOL,[16] we estimated the association between sleep duration PRS and cognitive outcomes in strata of short, normal, and long sleepers (Fig. 3a). In all strata and models, sleep duration PRS was not significantly associated with global cognitive function at baseline (p-values > 0.05). In contrast, sleep duration PRS was associated with a decline in global cognitive function only in long sleepers (model 1: estimate = –0.079, 95% CI [–0.124, –0.033], p-value = 0.001). Further, the sleep duration PRS was associated with MCI in all three sleep duration strata, with evidence of interaction. Among short and normal sleepers, sleep duration PRS was associated with reduced MCI risk (model 1 OR in short sleepers = 0.53, 95% CI = [0.37, 0.78], [p-value = 0.001] and in normal sleepers OR = 0.79, 95% CI [0.68, 0.93], [p-value = 0.003]) while among long sleepers it was associated with increased MCI risk (model 1: OR = 1.40, 95% CI [1.10, 1.78], p-value = 0.006). The associations remained similar in models further adjusted for sleep duration or *APOE-ε4*, with slightly weakened PRS associations with MCI in long sleepers (Supplemental Fig. S3). All estimated effect sizes, standard errors (SEs), p-values, and False Discovery Rate (FDR) adjusted p-values are provided in Supplemental Table S6.

Fig. 3 panel b further visualizes the raw interaction association between sleep duration category, sleep duration PRS, and MCI. MCI prevalence recapitulates the interaction observed in the statistical analysis: while in short and normal sleepers MCI prevalence is lower among people with high sleep duration PRS values compared to those with lower sleep duration PRS values (e.g., 20.3% versus 5.3% MCI prevalence in short sleepers with below-median compared to above-median PRS values), in long sleepers the pattern is reversed with 7.1% versus 13.9% MCI prevalence in individuals with below-median compared to above-median PRS values.

Supplemental Table S7 provides AUCs of association models of sleep duration PRS and MCI within short, normal, and long sleep categories, and compares them to AUCs from models that did not include PRS. While AUCs were not improved by PRS in the normal sleep duration strata, AUCs were higher in models with sleep duration PRS in short and long sleep strata. For example, in model 1, AUC for MCI in short sleepers was 0.64 when including duration PRS, compared with 0.59 without, and in long sleepers, the AUC was 0.66 compared to 0.62 without the PRS.

Supplemental Fig. S4 provides association results from secondary analysis of sleep duration PRS with MCI within alternative categories of short and long sleep duration. The results suggest that the categories selected in the main analysis indeed demonstrate strong non-linear association, where higher PRS values have strong risk protective association within short sleepers and strong risk increasing association within long sleepers. The pattern is slightly weaker in other potential short and long sleep categories.

Secondary analysis of associations between sleep traits

We estimated the association of the four sleep traits PRSs with the other sleep traits in HCHS/SOL (Supplemental Figs. S5 and S6). PRS for insomnia was associated with shorter sleep duration (model 1: estimate = –0.04, 95% CI [–0.07, –0.006], p-value = 0.02). Additionally, both insomnia PRS and sleepiness PRS were associated with an increased risk of OSA (insomnia PRS model 1: OR = 1.11, 95% CI [1.05, 1.18], p-value = 0.001, sleepiness PRS model 1: OR = 1.10, 95% CI [1.03, 1.17], p-value = 0.003). All estimated effect sizes, SEs, and p-values from these association analyses are provided in Supplemental Table S8 (continuous sleep outcomes) and 9 (binary sleep outcomes).

Discussion

In this work, we used PRSs to capture the genetic determinants of sleep traits, and studied whether they predicted cognitive outcomes. Higher insomnia PRS was associated with both lower global cognitive function and with increased risk of MCI; higher sleepiness PRS was associated with increased MCI risk; and higher

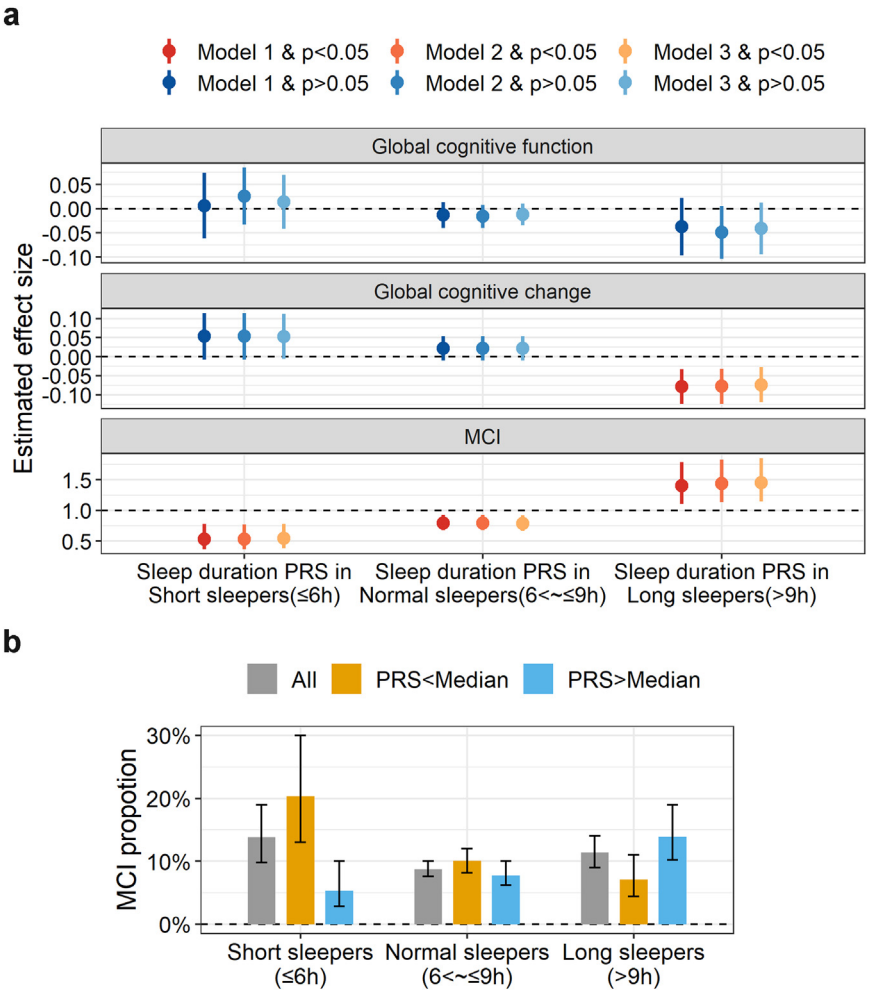

Fig. 3: **Estimated association between sleep duration PRS and cognitive outcomes stratified by sleep duration categories. (a)** Associations of 1 SD increase in sleep duration PRS with global cognitive function, global cognitive change and MCI stratified by sleep duration categories, short (≤6 h of usual sleep), normal (6< ~ ≤9), and long sleepers (>9). Each dot and line represent the estimated effect size and its 95% interval. Global cognitive function is treated as a continuous variable and MCI as a binary variable. Model 1. Adjusted for age, sex, field centre, genetic analysis groups, and the first 5 PCs of genetic data. Model 2. Adjusted for model 1 covariates with further adjustment for education. Model 3. Adjusted for model 2 covariates, and additionally to BMI, alcohol intake, sleep medication frequency, depression, anxiety, and FCRS. **(b)** Proportion of individuals with MCI in each of the sleep duration categories, divided by PRS classification: total individuals, individuals with PRS below the sample median, and individuals with PRS above the sample median. Abbreviations: *BMI*: Body Mass Index; *FCRS*: Framingham Cardiovascular Risk Score; *MCI*: Mild Cognitive Impairment; *PRS*: Polygenic Risk Score.

sleep duration PRS was associated with lower MCI risk. Adjustment of analyses for the measured sleep phenotypes and *APOE-ε4* had minor effects on the PRS associations with the cognitive outcomes, suggesting that sleep PRSs have the potential to be used for risk stratification for cognitive ageing phenotypes without collecting detailed sleep phenotypes. Further stratified association of sleep duration PRS and cognitive outcomes in short, normal, and long sleepers revealed an interaction effect where higher sleep duration PRS was associated with lower MCI risk in short and normal sleepers, but with worse global cognitive change and higher MCI risk in long sleepers.

PRSs can capture lifetime sleep exposures, potentially providing insights into the influences of sleep across the life course on both brain development and accelerated brain ageing[51,52]- both of which are important for cognition and cognitive decline as shown by experimental, clinical and epidemiological studies.[53] The importance of sleep for cognition and more generally for brain health is supported by experimental studies identifying the roles of sleep for promoting both synaptic homeostasis and plasticity as well as the clearance of toxic brain waste products (e.g., beta amyloid) through the perivascular central glymphatic system.[54,55] Additionally, given pleiotropy among sleep, cognitive,

mood, and health-related factors,[56] the sleep PRSs also capture information on general brain and body health. The findings of associations between the PRSs for insomnia, sleep duration and sleepiness with one or more cognitive outcomes is therefore consistent with a broad literature implicating poor sleep quality, short and long sleep duration, and excessive daytime sleepiness as risk factors for cognitive impairment and decline. In contrast, the PRS for OSA was not associated with cognitive outcomes. In this regard, the literature is mixed as to whether OSA and its attendant intermittent hypoxemia and sleep fragmentation are associated with increased risk for cognitive impairment, with sources of discrepancies potentially related to the severity and duration of untreated OSA, and the need to consider the potential protective effects of mild intermittent hypoxemia on cognitive outcomes.[57,58]

Novel findings emerged regarding sleep duration in analyses stratified by sleep phenotypes, expanding on the prior literature by explicitly considering the interaction between genetic propensity for sleep duration (as assessed by sleep duration PRS) and extreme and intermediate sleep duration phenotypes. As expected, genetic predisposition for longer sleep duration (higher PRS values, modelled continuously) was protective in its associations with MCI in strata of short and normal sleep duration: in short and normal sleepers, the association with MCI was protective: OR = 0.53 in short sleepers, and OR = 0.79 in normal sleepers (per 1 SD increase in the PRS). In contrast, sleep duration PRS was associated with an increased risk for MCI in individuals with extreme long sleep duration (OR = 1.40). For comparison, this estimated association is larger than the estimate association of an Alzheimer's Disease PRS with MCI in SOL-INCA (OR = 1.34, unstratified).[59] Further, when computing AUCs, measuring predictive potential of the PRS for MCI risk, sleep duration PRS increased AUC compared to a baseline model without the PRS only in short and long sleepers: from 0.60 to 0.64 (model 1, short sleepers), and from 0.62 to 0.66 (model 1, long sleepers). This interaction may explain some of the conflicting results, where higher sleep PRS values were found to be associated with both improved[21] and reduced[22] cognitive function. Extreme long sleep duration is a risk factor for multiple adverse health outcomes and appears to be associated with a "high sleep propensity" phenotype and genetic variants preferentially expressed in brain tissues.[42] Therefore, it is possible that individuals with both a genetic predisposition to longer sleep and sleeping in the range considered extremely long are at particularly high risk for developing MCI. Since the PRS associations with MCI did not substantially change after adjusting for self-reported sleep duration, the findings suggest that it is not recent long sleep per se that drives an association with cognition, but a genetic predisposition to long sleep, which may reflect multiple pathophysiological processes related to sleep-wake control and general health.

Recent studies from the Cohorts for Heart and Ageing Research in Genomic Epidemiology (CHARGE) consortium reported modifications of SNP effects on blood pressure and lipids in short and long sleepers.[60,61] Our study adds to the evidence of gene-sleep duration interaction effects on health. A potential approach to investigate the non-linearity of these associations would be to study PRS for short and long sleep duration in association with cognitive outcomes. A hypothesis for such analysis would be that short and long sleep PRSs associated with lower global cognitive function and with increased risk for MCI. However, short and long sleep PRSs were not associated with short duration and long duration sleep in HCHS/SOL, therefore we could not test this hypothesis. Short (<7 h) and long (≥9 h) sleep GWAS relative to sleep duration of 7–8 h were performed in UK Biobank using the same population that was used in the sleep duration analysis, but their GWAS resulted in a lower number of genome-wide significant loci (27 for short sleep, 8 for long sleep) compared to sleep duration analysis (78 loci).[44] It is possible that short and long sleep GWAS are less useful for PRS construction. The PRS associations with MCI did not substantially change upon adjustment to the self-reported sleep duration. As the germline genetic sequences do not change over the life course, the PRS represent an "exposure" over the lifetime, while self-reported sleep duration changes with ageing and with life circumstances. Thus, it may not be surprising that both genetically determined and self-reported sleep duration contribute to MCI risk.

Our study has notable strengths. First, we focused on an understudied population of Hispanics/Latinos in the U.S., which is the largest minority group and with a relatively high projected rates of incident dementia.[62] Further, in this population, traditional ADRD genetic risk factors are relatively weakly associated with cognitive ageing outcomes, and therefore there is a great need in identifying robust predictors of cognitive ageing. Second, we applied PRS analysis to estimate the genetic determinants sleep traits. These genetic data are fixed at birth and do not change over time, representing important tools for improving and researching health. We considered PRSs for multiple important clinical sleep phenotypes, including insomnia, daytime sleepiness, and OSA, which were not studied in prior literature to the same extent as sleep duration PRS with relation to cognitive outcomes. Finally, the analysis of sleep duration PRS association within strata of sleep duration opens new avenues for futures studies of patient stratification for potential intervention to reduce risk of ADRD outcomes.

Our study also has limitations. First, we could not assess the causality of associations between sleep phenotypes and cognitive outcomes due to the nature of the

observational data and the inability to apply Mendelian Randomization (MR) analysis due to the lack of GWAS for the specific cognitive outcomes. Second, GWAS summary statistics used for the construction of sleep PRSs were based on European populations, limiting the strength of PRS in our Hispanic/Latino dataset. Third, some of the sleep phenotypes, including sleep duration, are self-reported and therefore subject to misreporting or misclassification.

Our study suggests multiple important directions for future work. First, it would be important to study shared biological pathways and causal relationships between sleep and cognitive outcomes. For example, genome-wide significant genetic signals for insomnia showed enrichment in cognition-associated tissues and cell types in the brain including cortex, hypothalamic neurons, etc.[63] suggesting shared genetic mechanisms to insomnia and cognitive ageing. Second, sleep PRSs could be applied for risk stratification and prediction models of ageing-related cognitive decline and dementia. Third, the observed interaction between sleep duration and sleep duration PRS may result in novel approaches for studying the association of long sleep with cognitive ageing.

In summary, we comprehensively estimated the associations between the genetic components of sleep phenotypes with cognitive ageing outcomes in a large sample of Hispanics/Latinos. We concluded that genetic determinants for insomnia, daytime sleepiness, and sleep duration are associated with MCI risk. Also, there is interaction effect between genetic and self-reported sleep duration on MCI. These findings may contribute to the development of future strategies for decelerating cognitive ageing.

Contributors

Study conceptualisation: Y. Zhang and T. Sofer. Data curation: W. Tarraf, S. Wassertheil-Smoller, C.R. Isasi, M.L. Daviglus, R. Kaplan, S. Redline, H.M. González. Formal analysis: Y. Zhang, M. Elgart, T. Sofer. Funding acquisition: T. Sofer. Methodology: Y. Zhang, M. Elgart, E. Granot-Hershkovitz, W. Tarraf. Supervision: T. Sofer. Visualisation: Y. Zhang. Writing – original draft: Y. Zhang, E. Granot-Hershkovitz, T. Sofer. Writing – review & editing: Y. Zhang, M. Elgart, H. Wang, W. Tarraf, A.R. Ramos, A.M. Stickel, D. Zeng, T.P. Garcia, F.D. Testai, S. Wassertheil-Smoller, C.R. Isasi, M.L. Daviglus, R. Kaplan, M. Fornage, C. DeCarli, S. Redline, H.M. González, T. Sofer. T. Sofer and M. Elgart had full access to all the data in the study and take responsibility for the accuracy and integrity of the work. T. Sofer and Y. Zhang were responsible for the decision to submit the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

HCHS/SOL data are available via controlled-access application to dbGaP (study accession phs000810) or via approved data use agreement with the Data Coordinating Center of the HCHS/SOL and the University of North Carolina. For more details see https://sites.cscc.unc.edu/hchs.

The supplementary materials include additional description of sleep phenotypes, sources of GWAS summary statistics; Supplementary Tables: Supplemental Tables S1–S9; Supplementary Figures: Supplemental Figs. S1–S6.

Declaration of interests

S.R. report receiving consulting fees from Jazz Pharma, Eli Lilly, and Apnimed; a contract from Jazz Pharma, with payments made to the institutions; being a volunteer on patient advocacy group of the Alliance for Sleep Apnoea Partners; and receiving loaned equipment from Philips Respironic and Nox Medical for an NIH multi centre trial. All other authors have not made any declarations.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2022.104393.

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