HHS Public Access

Author manuscript

Ann Neurol. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Ann Neurol. 2021 January ; 89(1): 177–181. doi:10.1002/ana.25910.

Genetic Risk of Alzheimer's Disease and Sleep Duration in Non-Demented Elders

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Abstract

Growing evidence has suggested an association between sleep duration and Alzheimer's disease (AD), but it is unclear if sleep duration is a manifestation of the AD disease process. We studied whether genetic liability for AD predicts sleep duration using a genetic risk score (GRS) for AD (AD-GRS), in 406,536 UK Biobank participants with European ancestry and without dementia at enrollment. Higher AD-GRS score was associated with shorter sleep (b = −0.014, 95% confidence interval [CI] = −0.022 to −0.006), especially in those aged 55+. Using AD-GRS as an instrumental variable for AD diagnosis, incipient AD reduced sleep duration by 1.87 hours (95% CI = 0.96, 2.78). Short sleep duration might be an early marker of AD.

One of the most exciting recent advances in dementia research is the identification of a bidirectional relationship between sleep disturbances, such as insomnia, sleep disordered breathing, and Alzheimer's disease (AD). Sleep disturbances are highly prevalent in patients with AD,[1] and have also been suggested as a modifiable risk factor for AD in healthy older adults.[2,3] However, the relationship between sleep duration and AD is controversial.

Epidemiological studies have had conflicting findings, with many suggesting a U-shaped or J-shaped relationship: both short and long sleep duration has been associated with an increased risk of cognitive impairment.[4–6] However, it is challenging to use a conventional observational study design to establish temporal order or to rule out residual confounding or

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Author Contributions

Y.L., K.Y., and W.D.B. contributed to the conception and design of the study. W.D.B., S.A., and M.M.G. contributed to the acquisition and analysis of data. Y.L. and W.D.B. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

shared etiologies. Especially in older adults, it is possible that early neurodegenerative changes might affect sleep duration.

Mendelian randomization (MR) uses genetic variants as instrumental variables and was developed to address limitations in drawing causal inference in observational data, specifically confounding and reverse causation.[7] Genes are determined at conception prior to dementia onset, so if genetic factors related to AD predict sleep it is likely that sleep is a manifestation of the AD disease process or a shared etiology. Recent MR study using data from UK Biobank suggested that genetic liability to long sleep duration results in worse cognitive performance.[8] However, this does not rule out that sleep duration may be altered as a result of preclinical AD; and it remains unclear whether shared etiologic factors alter sleep duration prior to cognitive impairment.

We applied known genetic variation in AD risk, which is established at birth, to test the hypothesis that shared genetics or incipient AD may influence sleep duration (Fig). We also examined whether this influence differed by age, sex, and APOE ε4 status.

Methods

Study Setting and Participants

UK Biobank is an ongoing study of over 500,000 adults. Participants aged 39 to 73 years old were recruited from 2006 to 2010 from across the United Kingdom to provide detailed information about themselves via computerized questionnaires, provide biologic samples, undergo clinical measurements, and have their health followed prospectively.[9] Our analyses focused on 406,536 participants with European genetic ancestry, complete genetic and sleep duration data, and without dementia at baseline assessment. Ethical approval was obtained from the National Health Service National Research Ethics Service; all participants provided written informed consent.

Sleep Duration

Average sleep duration was assessed at the baseline touchscreen questionnaire by asking: “About how many hours sleep do you get in every 24 hours? (please include naps).” Answers were open ended (in hours): we categorized participants into short sleep duration (< 6 hours), average (6–9 hours), and long sleep duration (10+ hours), following prior studies.[5]

Genetic Risk Score for AD

Genotyping of UK Biobank samples was conducted with 2 closely related arrays (Affymetrix using a bespoke BiLEVE Axiom array and Affymetrix UK Biobank Axiom array) and all genetic data were quality controlled and imputed (https://www.ukbiobank.ac.uk/scientists-3/genetic-data/). The AD genetic risk score (GRS) was based on 23 loci associated with AD, including 2 single nucleotide polymorphisms (SNPs) used to characterize APOE ε4 status, which were obtained from the 2013 International Genomics of Alzheimer’s Project meta-analyzed genomewide association study stage I results (17,008 Alzheimer’s disease cases and 37,154 controls).[10] The AD-GRS was

calculated multiplying each individual's risk allele count for each locus by the β coefficient (expressed as the log odds ratio [OR]) for that polymorphism and summing the products for all 23 loci[11]; PLINK (https://www.cog-genomics.org/plink/1.9/general_usage#cite). We also created a 21 SNP AD-GRS without 2 loci associated with APOE, and we derived a categorical variable noting number of APOE ε4 alleles.

Other Covariates

Age and ethnicity were reported during baseline assessment. UK Biobank provides sex determined by genetic analysis and principal components (PCs) related to genetic population stratification. We used the first 10 PCs to adjust for confounding by population stratification. Dementia diagnosis was defined using the UK Biobank algorithmic dementia definition, which is based on International Classification of Disease (ICD) 9th and 10th editions codes for all-cause dementia from hospitalizations, death records, and self-report until 2018.

Statistical Analysis

Following the general approach of an MR study, we evaluated the relationship between sleep duration and cognition utilizing genetic risk as an analytic tool.[12,13] First, we used linear regression with the AD-GRS as the predictor and sleep duration as a continuous outcome. Next, we evaluated the association between AD-GRS and categories of sleep duration (< 6, 6–9, and 10+) with a multinomial logistic regression (with 6–9 hours as the reference group). We tested for interactions by age and sex. As sensitivity analyses, we examined whether any significant associations with the AD-GRS were driven or modified by APOE genotype. We assessed associations with (1) the AD-GRS without APOE and (2) APOE ε4 allele on it's own. We also tested for an interaction between APOE ε4 allele and the AD-GRS without APOE.

We used a traditional 2-stage least squares instrumental variable model to predict effects on sleep duration using the AD-GRS as an instrument for dementia diagnosis made at any point during follow-up. We used eventual dementia diagnosis over follow-up as a proxy for incipient AD. This analysis provides an estimate for the magnitude of the effect of incipient AD on sleep duration and can be directly compared to the observational estimates of sleep patterns and AD/dementia.[14] In secondary analysis, we ran this analysis again after excluding new dementia diagnoses made within 3 years of the sleep assessment.

All models included adjustment for age, sex, and 10 PCs to account for ancestry differences. Analyses were conducted in STATA (version 14); tests were 2-sided with $\alpha = 0.05$ and we report 95% confidence intervals (CIs).

Results

Participants reported an average sleep duration of 7.2 hours (standard deviation [SD] = 1.1) and had an average AD-GRS of 0.11 (SD = 0.40; range −1.15 to ~ 1.85; Table 1). Higher AD-GRS score was associated with shorter sleep duration (hours; b = −0.014, 95% CI = −0.022 to −0.006), and this was only evident among those aged 55 years and older (b = −0.023, 95% CI = −0.033 to −0.012) when stratified by age (Table 2) (p for interaction = 0.009). Primary results did not differ by sex (p for interaction = 0.42). In categorical models

in the older adults, AD-GRS was associated with increased odds of shorter sleep duration but not longer sleep duration.

APOE ε4 allele on its own was associated with shorter sleep duration among older aged participants (1 allele b = −0.02, 95% CI = −0.03 to −0.01; 2 alleles b = −0.04, 95% CI = −0.07 to −0.02, compared to no allele). Using the AD-GRS without APOE, estimates were slightly weaker and imprecise but in the same direction (b = −0.01, 95% CI = −0.03 to 0.01). The effect did not differ by APOE ε4 allele status (p for interaction = 0.17).

Using the AD-GRS as an instrument for eventual dementia diagnosis in a 2-stage least square analysis suggested that incipient AD was associated with 1.87 hours (b = −1.87, 95% CI = −2.78 to −0.96) shorter sleep duration among those aged 55 years and older. Results were similar after excluding dementia diagnoses made within 3 years of the sleep assessment (b = −2.11, 95% CI = −2.78 to −0.96).

Discussion

We found that higher AD-GRS was associated with shorter sleep duration, in a large sample of middle-aged to older-aged adults without dementia at baseline. This was only observed among those aged 55 years and older, and the association did not differ by sex. Using the AD-GRS as an instrumental variable, we estimated that participants aged 55 to 73 years with a subsequent dementia diagnosis had almost 2 hours shorter sleep duration at baseline compared to those without a dementia diagnosis. This evidence supports the hypothesis that AD genetic risk influences sleep duration prior to onset of dementia; thus sleep duration might be used as an early marker for AD.

Short and/or long sleep duration are associated with increased risk of dementia in observational studies, with the majority showing a stronger association for long sleep duration.[4–6,15,16] Because there are no known biological mechanisms that explain why long sleep might cause cognitive impairment, it is often speculated that short sleep could be a risk factor for dementia, whereas long sleep is more likely to be prodromal. However, causal inferences from conventional analyses of observational data are quite speculative. One prior MR study found evidence suggesting longer sleep duration increases cognitive decline.[8] Our findings using an MR framework suggest that genetic risk for AD and incipient AD leads to shorter sleep duration in older ages. Based on our findings of no association between AD-GRS and long sleep, the association between long sleep duration and cognitive impairment is unlikely to be due to the genetic liability for AD.

Participants with high AD-GRS are disproportionately likely to be experiencing early neurodegenerative changes due to AD even if they do not have clinical dementia.[11] Our finding of an association between high genetic risk for AD and short sleep duration that was only observed among those aged 55 years and older is consistent with short sleep in older adults being caused by or a marker for early AD-related neurodegeneration. Results from our secondary analyses suggest that sleep may be affected years prior to dementia diagnosis. Our findings add to prior evidence that AD pathology leads to increased wakefulness and high sleep fragmentation in transgenic mouse models,[17,18] and results in neuronal loss in the

suprachiasmatic nucleus (SCN), the master circadian clock in mammals, and the locus coeruleus, which is critical for maintaining normal wakefulness.[19,20] Future research will be necessary to fully explore whether AD-related pathology causes shorter sleep duration in older adults (Fig a) or if high genetic liability for AD directly influences sleep duration, not mediated by neurodegenerative changes (Fig b). Regardless, either of these 2 explanations indicates the potential of sleep duration as a preclinical marker for AD. Although APOE ε4 allele on its own was associated with shorter sleep duration, we found stronger effects on sleep duration by using the genetic risk score for AD compared to using APOE4 alleles alone. Future studies may be able to elucidate other pathways further by examining the impact of individual genes/genetic pathways in the AD-GRS, extending these findings to early-onset AD cohorts, or testing for mediation by AD biomarkers or other AD risk factors, such as cardiovascular disease or diabetes.

Our study has several strengths, including a large sample size and a novel analytical approach. A key challenge in sleep and AD research is determining whether preclinical AD causes sleep disruption or vice versa. By using a polygenic risk score for AD, we overcame this challenge. We tested the hypothesis that genetic risk for AD might influence sleep duration, and additionally tested this hypothesis stratifying by age, sex, and APOE ε4 status. There are also several limitations. Selfreported sleep duration might be biased by initial cognitive status or depressive symptoms, factors that may be more likely in those with high AD-GRS. However, it is noted that individuals with high AD-GRS were generally cognitively normal and healthy at baseline and few developed dementia over follow-up. The AD-GRS only explains part of the risk for AD and could have limited our ability to detect associations. We also cannot exclude the possibility of pleiotropic effects of AD-GRS. Given the long preclinical window of AD, it is challenging to determine if the effects of AD-GRS on sleep duration are independent of subtle cognitive decline or early neurodegenerative changes.

Using a polygenic risk score for AD and novel analytical approach, we found shared genetic pathways between sleep duration and AD. Greater genetic risk for AD was associated with shorter sleep duration. This study helps to clarify the direction and nature of the connection between sleep duration and AD. Although future research is needed to confirm these findings; short sleep duration might be an early marker of AD.

Acknowledgments

Financial Support

Y.L. is supported by the National Institute on Aging (NIA) (R00AG056598), and received funding from GBHI, Alzheimer's Association, and Alzheimer's Society (GBHI ALZ UK-19-591141), the UCSF Claude D. Pepper Older Americans Independence Center, and from the UCSF Weill Institute for Neurosciences. W.D.B. is supported by NIA grants K01AG062722, and the Alzheimer's Association grant AARF-18-565846. and the UCSF Claude D. Pepper Older Americans Independence Center funded by National Institute on Aging, P30 AG044281. Support was provided by NIA grant K24AG031155, awarded to Dr. Yaffe.

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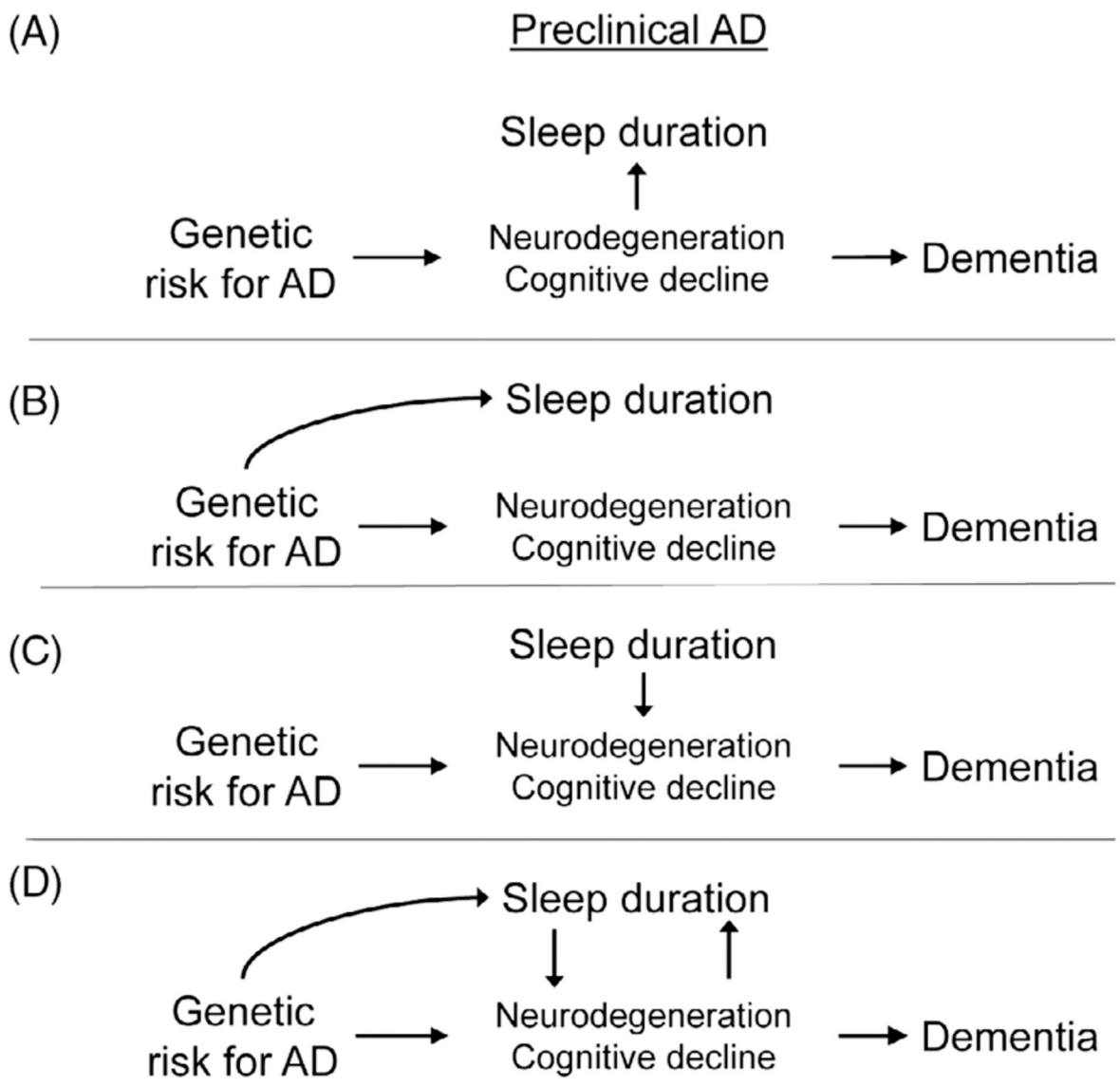

FIGURE:

Hypothesized pathways linking sleep duration and Alzheimer's disease (AD). In both (a) and (b), AD-genetic risk score (GRS) is hypothesized to be associated with sleep duration, directly (b) or indirectly as mediated by early neurodegenerative change (a). Sleep duration may be a prodrome of AD, such that early AD-related neurodegenerative change or subtle cognitive decline during the preclinical stage affects sleep duration (a). Sleep duration may also be directly affected by genetic liability to AD (b). Alternatively, sleep duration changes may contribute to neurodegeneration and increase risk of dementia (c). In this case, sleep duration could be considered as a risk factor for AD. In reality multiple pathways may occur, and there is likely to be a bidirectional link between sleep duration and AD (d).

TABLE 1.

Characteristics of UK Biobank Participants Included in the Analyses (n = 406,536)

Participant characteristics	Mean (SD) or N (%)
Age, yr, 39–73	56.9 (8.0)
Female	219,573 (54.0)
AD-GRS, 1 unit = log OR AD	0.11 (0.40)
AD-GRS without APOE	−0.07 (0.17)
Dementia diagnosis in follow-up	2,004 (< 1)
APOE ε4 allele	
0	289,329 (71.2)
1	107,411 (26.4)
2	9,796 (2.4)
Sleep duration, h	
Short	96,849 (23.8)
Average	302,493 (74.4)
Long	7,194 (1.8)

AD = Alzheimer's disease; GRS = genetic risk score; OR = odds ratio.

TABLE 2.

Estimates for the Association Between AD-GRS and Sleep Measures

Sleep measures	**Age 39–54 (N = 148,796)**	**Ages 55–73 (N = 257,740)**
Sleep duration	β (95% CI)	β (95% CI)
Continuous	0.000 (−0.013 to 0.013)	−0.023 (−0.033 to −0.012)
Categorical	OR (95% CI)	OR (95% CI)
Short	0.991 (0.962 to 1.021)	1.025 (1.002 to 1.049)
Average	Reference	Reference
Long	0.962 (0.863 to 1.074)	0.969 (0.902 to 1.041)

Adjusted for age, sex, 10 PCs to account for confounding by population stratification.

AD = Alzheimer's disease; CI = confidence interval; GRS = genetic risk score; OR = odds ratio; PC = principal components.