RESEARCH ARTICLE

Associations of Chronic Insomnia, Longitudinal Cognitive Outcomes, Amyloid-PET, and White Matter Changes in Cognitively Normal Older Adults

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Abstract

Background and Objectives

The relationship between insomnia and cognitive decline is poorly understood. We investigated associations between chronic insomnia, longitudinal cognitive outcomes, and brain health in older adults.

Methods

From the population-based Mayo Clinic Study of Aging, we identified cognitively unimpaired older adults with or without a diagnosis of chronic insomnia who underwent annual neuropsychological assessments (z-scored global cognitive scores and cognitive status) and had quantified serial imaging outcomes (amyloid-PET burden [centiloid] and white matter hyperintensities from MRI [WMH, % of intracranial volume]). We used mixed-effects models to examine associations between baseline insomnia (independently or with interaction with self-reported changes in habitual sleep duration) and longitudinal cognitive z-scores, log-transformed WMH, and amyloid-PET levels while adjusting for multiple confounders, including sleep apnea diagnosis. The risk of incident cognitive impairment (CI) was estimated using the Cox proportional hazards model.

Results

We included 2,750 participants (mean 70.3 ± 9.7 years old, 49.2% female) in global cognition models and 2,814 in Cox models with median follow-up of 5.6 years. A total of 1,027 and 561 participants were included in WMH and amyloid-PET models, respectively. Insomnia was associated with a 0.011 per year (95% CI −0.020 to −0.001, *p*-interaction = 0.028) faster decline in global cognitive scores and 40% increased risk of CI (hazard ratio [HR] 1.4, 95% CI 1.07–1.85, $p = 0.015$). Insomnia with reduced sleep was associated with baseline cognitive performance (β = −0.211, 95% CI −0.376 to −0.046, *p*-interaction = 0.012), WMH (β = 0.147, 95% CI 0.044–0.249, *p*-interaction = 0.005), and amyloid-PET (β = 10.5, 95% CI 0.5–20.6, *p*-interaction = 0.039) burden. Insomnia participants sleeping more than usual (potentially indicating remission of symptoms) had lower baseline WMH burden (β = −0.142, 95% CI −0.268 to −0.016, *p*-interaction = 0.028). Insomnia was not associated with the rate of WMH or amyloid accumulation over time. In participants with insomnia, hypnotic use was not associated with cognitive scores (β = 0.016, 95% CI −0.201 to 0.233, $p = 0.888$) or incident CI (HR 0.94, 95% CI 0.5–1.6, $p = 0.832$).

Discussion

We found an association between insomnia, cognitive decline, and increased risk for CI. Insomnia with reduced sleep was associated with worse cognitive performance and poorer brain health (WMH and amyloid burden) at baseline. Sleeping more than usual was associated with lower WMH burden.

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Supplementary Material

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Glossary

AD = Alzheimer disease; **BAI** = Beck Anxiety Inventory; **BDI-II** = Beck Depression Inventory-2; **CBT-I** = cognitive behavioral therapy for insomnia; **CDR** = Clinical Dementia Rating; **CI** = cognitive impairment; **CMC** = cardiovascular and metabolic conditions; **HR** = hazard ratio; **ICD** = International Classification of Disease; **IQR** = interquartile range; **MCSA** = Mayo Clinic Study of Aging; **MCI** = mild cognitive impairment; **OSA** = obstructive sleep apnea; **REP** = Rochester Epidemiology Project; **SUVR** = standardized uptake value ratio; **TIV** = total intracranial volume; **WMH** = white matter hyperintensity.

Introduction

Insomnia is characterized by persistent difficulty initiating or maintaining sleep, often with early morning awakenings and poor sleep quality. These symptoms are associated with daytime functional impairment, including fatigue, mood disturbance, and impaired cognitive function.[1-4] Insomnia symptoms increase with aging,[5,6] with annual incidence rate of approximately 5%,[7] and affect 36.2%–74.8% of older adults.[3,5,6,8] Large scale meta-analytic studies have shown that insomnia is associated with an increased risk of cognitive decline or dementia.[9-12] However, validity and generalization of these findings is limited because of frequent multimorbidity,[13-15] including higher prevalence of comorbid obstructive sleep apnea (OSA) in older adults with insomnia,[16] and possible hypnotic treatment effects, which were often not accounted for.[9,10]

Changes in sleep duration may also be an important factor when considering insomnia risks. Different phenotypes of insomnia based on sleep duration have been proposed, with those having objectively short sleep being more likely to develop cardiometabolic morbidity and impaired cognition.[17,18] Moreover, both objective and self-reported short and/or long sleep duration, respectively, have been associated with increased risk of cognitive decline or dementia.[9,12,19-24] In individuals with insomnia, changes in sleep duration may also be associated with disease severity[25] and/or remission of symptoms. However, cohort studies considering the relationship between insomnia and sleep duration in the risk of cognitive decline remain scarce.[26]

Despite growing evidence linking insomnia to incident dementia, underlying pathologic changes contributing to cognitive decline remain unclear. Although there is more evidence supporting an increased risk for Alzheimer disease (AD),[10,27,28] chronic insomnia has also been linked to cardiovascular and cerebrovascular disease,[29-33] which may underlie vascular contributions to cognitive impairment/dementia.[34] Therefore, it is probable that mixed AD and cerebrovascular pathology exist,[35] consistent with evidence supporting a relationship between insomnia and increased risk of both AD and vascular dementia.[36]

This study aimed to examine associations between insomnia and longitudinal cognitive outcomes (continuous measures and incident CI) while taking into consideration a comprehensive set of confounders, including OSA diagnosis; changes in habitual sleep duration; and their interaction with insomnia. Our secondary aim was to investigate whether insomnia (independently or with changes in sleep duration) was associated with longitudinal imaging biomarkers of cerebrovascular disease (white matter hyperintensity [WMH]) or AD (global amyloid-PET burden). Finally, we explored whether hypnotic use is associated with cognitive or neuroimaging biomarker outcomes in participants with insomnia. We hypothesized that insomnia with reduced sleep drives the association between insomnia and cognitive decline, and is independently associated with WMH and amyloid accumulation.

Methods

Participant Selection

From the population-based prospective longitudinal cohort of Olmsted County (Minnesota) residents enrolled in the Mayo Clinic Study of Aging (MCSA),[37] we initially selected MCSA participants aged 50 and older with a complete cognitive assessment as of June 2023 (n = 6,278). We then excluded participants with (1) baseline or incident major neurologic or psychiatric disorders during the study, (2) insomnia diagnosis deemed inconclusive per criteria outlined below, (3) with less than 2 valid cognitive assessments, and (4) with missing covariate data (Figure 1).

Standard Protocol Approvals, Registrations, and Patient Consents

Institutional review boards at Mayo Clinic and Olmsted Medical Center approved the study. All participants provided written informed consent.

Clinical Assessment

Medical comorbidities were abstracted by nurses using the Rochester Epidemiology Project (REP) medical records linkage system.[38] A composite score of cardiovascular and metabolic conditions (CMC) was calculated by the summation of the presence of any of the 7 indicators of vascular health (hypertension, hyperlipidemia, cardiac arrhythmias, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke), as proposed by the U.S. Department of Health and Human Services. The CMC score has been validated as a measure highly associated with neuroimaging biomarkers of brain health.[39,40] Chronic pain was assessed by chronic usage of analgesic medication (acetaminophen or any nonsteroidal anti-inflammatory drugs except for aspirin) on a daily basis. We also obtained APOE genotyping.[41] Participants with at least 1 APOE ε4 allele were classified as APOE ε4 carriers.

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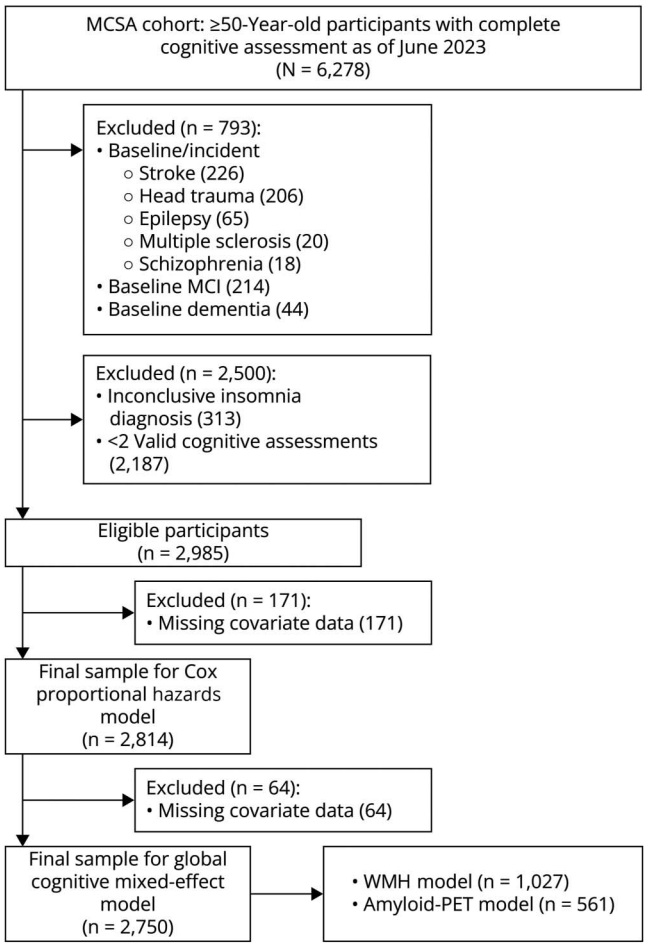
Figure 1 Flow Diagram of Participant Selection



MCI = mild cognitive impairment; MCSA = Mayo Clinic Study of Aging; WMH = white matter hyperintensity.

Mental Health Assessment

Participants completed the Beck Depression Inventory-II (BDI-II)[42] for assessment of symptoms of depression, the Beck Anxiety Inventory (BAI)[43] for assessment of symptoms of anxiety, and the CAGE questionnaire[44] for assessment of symptoms of alcoholism. Major depression was defined by BDI-II score >13. Anxiety disorder was defined by a BAI score >7. Alcoholism was defined by a CAGE score ≥2 or history of alcohol use disorder from chart abstraction.

Sleep Assessment

Participants with at least 2 occurrences of International Classification of Diseases (ICD)-9 and/or ICD-10 diagnostic codes related to insomnia (by electronic medical records and REP data) at least 30 days apart were classified as having chronic insomnia, similar to other epidemiologic studies.[45,46] Participants without any instance of insomnia diagnoses were deemed negative for insomnia. Participants not meeting either criteria were excluded because of inconclusive diagnosis to prevent inclusion of acute insomnia, inaccurate documentation, or referrals. In chronic insomnia participants, initial valid time point for analysis of baseline MCSA characteristics and assessments was set as any time point between 6 months before the first clinical insomnia diagnosis to the first time point available after clinical insomnia diagnosis, whichever came first. Assessments before 6 months of initial diagnosis were excluded from the analysis. However, the number of assessments until first valid assessment was accounted for in cognitive models. Insomnia diagnostic code timespan was estimated by calculating the time between first and last code occurrence. For patients without insomnia, baseline characteristics and assessments were drawn from initial evaluation in the MCSA.

For the assessment of changes in habitual sleep duration patterns, we used the response from group statement #16 ("Changes in Sleep Pattern") of the BDI-II. The BDI-II asks individuals to select the statement that best describes the way they have been feeling during the past 2 weeks. Participants who answered sleeping somewhat (1b) or a lot (2b) less than usual or reported waking up 1–2 hours earlier and not being able to get back to sleep (3b) were classified as having "reduced sleep." Participants who answered sleeping somewhat (1a) or a lot (2a) more than usual or most of the day (3a) were classified as "sleeping more." Otherwise, they did not observe change in habitual sleep duration (0). As initial assessment of habitual sleep duration change in the MCSA was not time aligned with initial insomnia diagnosis occurrence determined by clinical evaluation (median 7.3 [interquartile range (IQR) 1.9–12.3] years difference), habitual sleep duration change reflects sleep characteristics at baseline cognitive assessments, not at initial insomnia diagnosis. We also abstracted information on the use of any hypnotic medication at each annual MCSA visit. As the MCSA was not originally designed to systematically assess hypnotic prescription or over-the-counter use, we could not reliably determine frequency and duration of usage for most participants. In addition, we abstracted the diagnosis of OSA from medical records using a similar approach (≥2 instances of diagnoses in separate dates), which reliably identifies diagnosed OSA cases at our institution (positive predictive value = 100%, 95% CI 97%–100%).[47] Given the epidemiologic nature of this study, OSA severity, treatment adherence and efficacy was not available. For assessment of individuals at high risk for undiagnosed OSA, we collected information from participants with informants (bed partners, close relatives) who answered question #6 of the Mayo Sleep Questionnaire[48]: "Does the patient ever seem to stop breathing during sleep?," consistent with our previous work.[49] Witnessed apneas have shown satisfactory sensitivity (73%–83%) for detecting OSA in previous studies.[50] A positive response in patients without OSA diagnosis was considered high risk for undiagnosed disease.

Cognitive Assessment

Annual comprehensive neuropsychological assessments were performed,[37] assessing 4 cognitive domains (executive, language, memory, and visual spatial). Individual test scores were

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Table 1 Demographic, Clinical, and Imaging Characteristics of Participants Included in Mixed-Effects Models

Demographic characteristics	All (n = 2,750)	Chronic insomnia		*p* Value
		No (n = 2,307)	Yes (n = 443)	
Age at baseline, y, mean ± SD	70.3 ± 9.7	70 ± 9.7	72.1 ± 9.3	<0.001
Sex, female, n (%)	1,352 (49.2)	1,092 (47.3)	260 (58.7)	<0.001
APOE ε4, any allele, n (%)	745 (27.1)	633 (27.4)	112 (25.3)	0.350
Education, y, median (IQR)	14.5 (12–16)	15 (12–16)	14 (12–16)	0.128
Cognitive assessment				
Baseline Global Cognitive Score (z-scored)	0.11 ± 0.98	0.14 ± 0.97	−0.02 ± 1.01	0.003
Last Global Cognitive Score (z-scored)	0.02 ± 1.23	0.06 ± 1.22	−0.21 ± 1.26	<0.001
Valid follow-up duration, y, median (IQR)	5.6 (2.8–8.9)	5.9 (2.9–8.9)	5.1 (2.7–8.4)	0.017
Valid cognitive assessments, median (IQR)	4 (2–7)	4 (2–7)	4 (2–6)	0.011
Incident cognitive impairment, n (%)	297 (10.8)	234 (10.1)	63 (14.2)	0.014
Age at change in cognitive status, mean ± SD	81.2 ± 8	81.1 ± 8.6	81.4 ± 8.6	0.823
Clinical/mental health assessment				
Cardiometabolic comorbidities (CMC score)	1.9 ± 1.3	1.8 ± 1.3	2.2 ± 1.4	<0.001
Chronic analgesic use, n (%)	370 (13.5)	290 (12.6)	80 (18.1)	0.003
BDI-II score, median (IQR)	3 (1–6)	3 (1–6)	5 (1–9)	<0.001
Major depression (BDI-II >13), n (%)	112 (4.1)	73 (3.2)	39 (8.8)	<0.001
BAI score, median (IQR)	1 (0–3)	1 (0–3)	2 (0–5)	<0.001
Anxiety (BAI >7), n (%)	228 (8.2)	161 (7)	67 (15.1)	<0.001
Alcoholism, n (%)	105 (3.8)	83 (3.6)	22 (5)	0.169
Sleep assessment				
OSA, n (%)	472 (17.2)	337 (14.6)	135 (30.5)	<0.001
Habitual sleep duration change				<0.001
No change, n (%)	1,697 (61.7)	1,493 (64.7)	204 (46)	
Reduced sleep, n (%)	622 (22.6)	452 (19.6)	170 (38.4)	
Sleeping more, n (%)	431 (15.7)	362 (15.7)	69 (15.6)	
Hypnotic use, n (%)	113 (4.1)	44 (1.9)	69 (15.6)	<0.001
Antihistamines, n (%)	37 (1.3)	27 (1.2)	10 (2)	0.079
Antidepressants, n (%)	27 (1.0)	5 (0.2)	22 (5.0)	<0.001
Z-drugs, n (%)	28 (1.0)	8 (0.3)	20 (4.5)	<0.001
Benzodiazepines, n (%)	10 (0.4)	2 (0.09)	8 (2.0)	<0.001
Combined class exposure, n (%)	11 (0.4)	2 (0.09)	9 (2.0)	<0.001
Imaging assessment				
Age at baseline MRI, y, mean ± SD	71.9 ± 8.7	69.9 ± 8.7	71.0 ± 8.2	0.002
Baseline WMH, %TIV, median (IQR)	0.37 (0.18–0.77)	0.37 (0.17–0.74)	0.43 (0.18–0.89)	0.169
Age at baseline amyloid-PET	66.1 ± 8.1	66.0 ± 8.3	66.6 ± 7.3	0.186
Baseline global amyloid-PET, CL, mean ± SD	15.1 ± 19.7	14.6 ± 19.5	18.3 ± 20.7	<0.001

Abbreviations: BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-2; CL = centiloid; MCI = mild cognitive impairment; OSA = obstructive sleep apnea; TIV = total intracranial volume; WMH = white matter hyperintensity volume.

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converted to z-scores using the mean and SD of this sample, and were averaged across all domains to yield a global cognitive score, weighted to the 2013 Olmsted County population. Cognitive status was determined at each annual visit by a collective agreement among the examining physician, neuropsychologist, and study coordinator.[37] Briefly, criteria for cognitively unimpaired required normal neuropsychological evaluation, normal examination, and Clinical Dementia Rating (CDR) Scale = 0.[37] Participants with a CDR ≥1 and meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for dementia,[e1] were classified as demented. Participants not meeting either criteria with concern for CI in ≥1 domains despite normal functional activities were diagnosed with mild cognitive impairment (MCI).[37,e2] Dementia subtype classification was based on published research criteria.[e3-e6]

Imaging Assessment

Brain MRI scans were acquired on 3T GE MRI scanners (GE Healthcare, Chicago, IL) or Siemens (Siemens Healthineers, Erlangen, Germany) with median interval between scans of 2.3 years (IQR 1.25–2.75). FLAIR-MRI images were analyzed using an automated algorithm,[e7] with adjustment for total intracranial volume (TIV)[e8] to estimate WMH as a percentage of TIV, after excluding areas with infarcts, if present.[e9] Estimations were harmonized across scanner types.[e10]

Serial amyloid-PET scans using 11(C-PiB)[e11] were conducted with a median interval of 2.5 years (IQR 2.25–3.7). Each scan included four 5-minute dynamic frames acquired 40–60-minute postinjection. Data were processed at each time point using a validated, fully automated in-house pipeline.[e12,e13] Processing steps included coregistration to structural MRI and exclusion of voxels more likely to represent CSF than gray or white matter. Regional uptake values were extracted from bilateral Aβ-vulnerable regions of interest,[e14,e15] including the orbitofrontal, prefrontal, anterior cingulate (anterior and mid cingulate), posterior cingulate/precuneus, parietal, and temporal regions. Standardized uptake value ratios (SUVRs) were calculated by normalizing median uptake in each region to that of the cerebellar crus gray matter.[e16] Global PiB SUVRs were computed as a weighted average across these regions and converted to centiloid units for comparability with other studies.[e17]

Statistical Analysis

Demographic and clinical characteristics are described as mean ± SD or median (IQR) depending on variable distribution. For numerical group comparison between participants without or with insomnia, *t* tests or Mann-Whitney *U* tests were performed for parametric and nonparametric data, respectively. Categorical variables were compared by means of χ^2 tests or Fisher exact tests.

We assessed for a relationship between baseline chronic insomnia diagnosis and longitudinal global cognitive z-scores, log-transformed WMH, and amyloid PET levels, respectively, using a similar approach. For these analyses, we used linear mixed-effects models fit by maximum likelihood using random subject-specific intercepts and slopes, which were deemed necessary. We included covariates and their interactions with time as fixed factors initially using an unstructured covariance matrix (greater flexibility). For all models, baseline insomnia and habitual sleep duration change (no change, reduced sleep, or sleeping more) were included as fixed factors along with their interaction, and its 3-way interaction with time. We then used a backwards elimination procedure ($p \geq 0.05$), respecting the hierarchical principal for interactions, to remove unnecessary predictors and to form the most parsimonious model. Once the true relationship between repeated measures became apparent, we optimized model covariance structure type if it improved model fitness or as necessary for convergence. To assess goodness of fit, we estimated the R^2 related to fixed factors alone (marginal R^2) and for the full model with both fixed and random effects (conditional R^2).[e18]

For the global cognitive performance model, we also included the following baseline characteristics as fixed factors in initial models: age, sex, education (years), APOE ε4 status, CMC score, BDI-II score, BAI score, alcoholism, chronic analgesic use, and OSA diagnosis. Two-way interactions between insomnia and (1) APOE ε4 status, (2) CMC scores, and (3) baseline OSA were also included. Number of cognitive assessments and time from baseline were included as both fixed and random effects. Model fit was obtained with first-order autoregressive structure with heterogenous variances.

For log-transformed WMH and amyloid-PET level models, we also included the following baseline characteristics as fixed factors in initial models: age at initial scan, sex, APOE ε4 status, CMC score, and OSA diagnosis. Time from baseline scan was included as both a fixed and random effect. MRI manufacturer was included in WMH models as a random factor to adjust for possible residual variability not accounted for by harmonization. For best model performance, WMH models used first-order autoregressive structure and amyloid models used unstructured.

Next, we used the Cox proportional hazards model to calculate the risk of developing CI (MCI or dementia) in patients with an insomnia diagnosis vs those without while adjusting for the same baseline covariates that were significant in mixed-effects models: age, sex, APOE ε4 status, education (years), CMC score, alcoholism, depression (BDI-II score >13), and habitual sleep duration change. We also checked for an interaction between insomnia and sleep duration change. The backward selection procedure ($p \geq 0.05$) was applied to reach the most parsimonious model. Survival probability was calculated at each time point based on estimated hazard function to generate survival curves for CI incidence.

We also performed exploratory analyses using linear mixed-effects models and Cox proportion hazards model, respectively,

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to assess the relationship between hypnotic use and all outcomes described above in participants with insomnia, while adjusting for the most important covariates and propensity scores (predicted probability of hypnotic treatment) to avoid confounding effect related to participant characteristics that might have led to treatment assignment (e.g., greater psychiatric disease burden). Propensity scores were derived from binary logistic regression estimates, including these predictors: baseline age, sex, BDI-II score, BAI score, OSA diagnosis, education, chronic analgesic use, alcoholism, sleep duration change, insomnia diagnostic code timespan, and number of occurrences of insomnia diagnosis code (Nagelkerke R^2 0.4) with assessment for collinearity.

Finaly, we performed multiple sensitivity analyses in subgroups with informant-reported witnessed apneas by replacing OSA diagnosis with a composite OSA risk category variable in final models. OSA risk category was defined as (1) no diagnosis, low risk; (2) no diagnosis, high risk; and (3) diagnosed OSA.

Data Availability

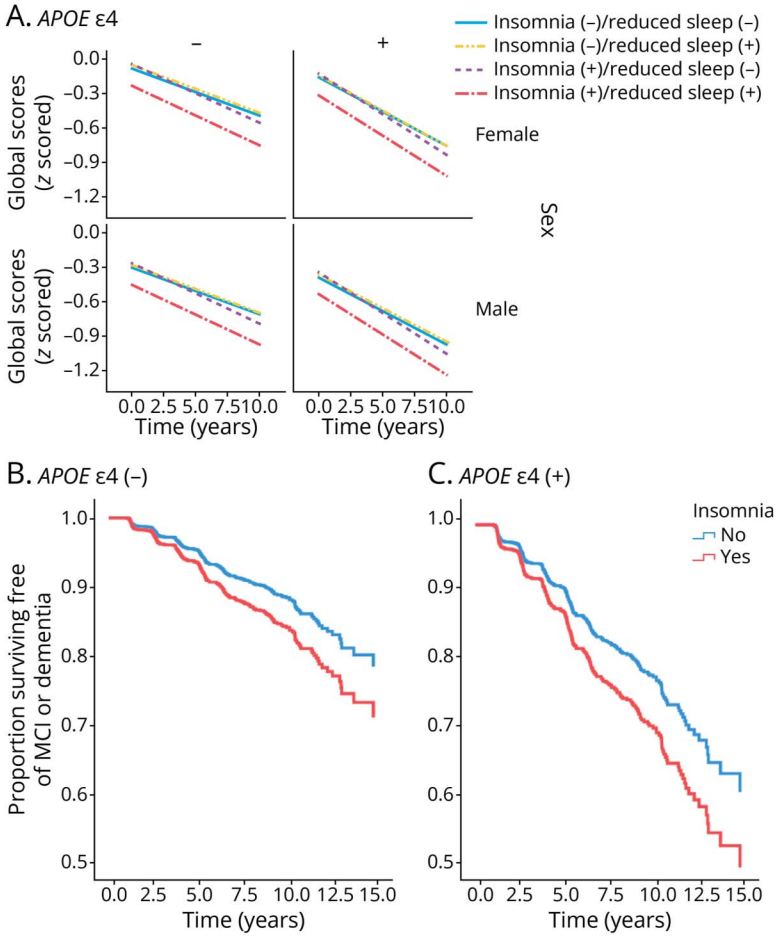
MCSA data are available to qualified investigators by request through the MCSA website.[e19]

Results

Demographic and Clinical Characteristics

A total of 2,750 participants were included in the global cognitive mixed-effects model and 2,814 in the Cox proportional hazards model after exclusions (Figure 1). A total of 1,027 participants were included in WMH models (n = 711 with ≥2 scans) and 561 in amyloid-PET models (n = 353 with ≥2 scans). In mixed-effects model analysis, 443 (16.1%) were classified as having chronic insomnia. Median insomnia diagnostic code timespan was 9.2 (IQR 3.3–17.4) years based on median of 5 (IQR 3–8) insomnia diagnosis occurrences. Because baseline assessment was defined by diagnosis occurrence in participants with insomnia, they were slightly older at baseline (72.1 ± 9.3 vs 70 ± 9.7, $p < 0.001$). Insomnia participants were more likely to be female and to have lower baseline cognitive scores, while having greater incidence of CI (MCI or dementia). They had more cardiometabolic comorbidities, higher frequency of chronic analgesic use, higher depression and anxiety scores, and more frequent comorbid OSA. Refer to Table 1 for full demographic and clinical details. Similar findings were observed in cohorts used

Figure 2 Predicted Cognitive Decline and Survival Free of Cognitive Impairment



Panel A shows the effect of chronic insomnia and its interaction with self-reported reduced sleep on predicted global cognitive score (z-scored) change over time, according to sex and APOE ε4 carrier status, estimated for 70-year-old participants with 12 years of education, 2 cardiometabolic comorbidities, minimal depression symptoms (BDI-II score of 13), without OSA or alcoholism, starting out at 3rd assessment (to reduce initial practice effect). Habitual sleep duration change categories are shown according to their relevance to the models. As sleeping more was not different than no changes in sleep pattern, it was omitted from figures to avoid redundancy. Panels B and C show predicted survival probability (based on cox proportional hazard model estimates) for incident cognitive impairment (MCI or dementia) for participants according to history of chronic insomnia and depending on their APOE ε4 carrier status (B: negative; C: positive), having mean covariate characteristics at baseline (70.4 years old, 14.8 years of education, 2 medical comorbidities, no depression, or alcoholism). BDI-II = Beck Depression Inventory-2; MCI = mild cognitive impairment; OSA = obstructive sleep apnea.

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for Cox proportional hazards, WMH, and amyloid-PET models (eTables 1 and 2).

Insomnia, Cognition, and Incident CI

We assessed the association between insomnia (and its interaction with sleep duration change) and global cognitive decline using mixed-effects models. Insomnia with reduced sleep was significantly associated with lower baseline global cognition (β = −0.211, 95% CI −0.376 to −0.046, *p*-interaction = 0.012), comparable with being 4 years older. Insomnia was also associated with a 0.011 per year faster decline in global cognitive z-scores (95% CI −0.020 to −0.001, *p*-interaction = 0.028), representing nearly 60% of the annual decline seen with APOE ε4 or 2 additional cardiometabolic comorbidities (Figure 2A, Table 2).

We then assessed whether chronic insomnia was associated with incident CI (MCI/dementia) using Cox proportional hazard models. Chronic insomnia was associated with higher risk of incident CI (hazard ratio [HR] 1.4, 95% CI 1.07–1.85, p = 0.015), comparable with 3.5 additional years of age (Figure 2, B and C, Table 3). The interaction with sleep duration change was not significant.

Insomnia, WMH, and Amyloid Burden

Next, we examined associations between insomnia (and its interaction with sleep duration change) and longitudinal WMH burden and amyloid-PET levels, respectively, using mixed-effects models. Insomnia with reduced sleep was associated with higher baseline WMH burden (β = 0.147, 95% CI 0.044–0.249, *p*-interaction = 0.005), while participants with

Table 2 Fixed Effect Estimates for Covariates Included in Final (Most Parsimonious) Mixed-Effects Model for Global Cognitive Score (Z-Scored)

Covariates	β (95% CI)	*p* Value
Insomnia (yes)	0.033 (−0.073 to 0.139)	0.543
Insomnia × time	−0.011 (−0.020 to −0.001)	0.028
Insomnia × reduced sleep	−0.211 (−0.376 to −0.046)	0.012
Insomnia × sleeping more	−0.090 (−0.303 to 0.123)	0.406
Habitual sleep duration change (ref: no change)		
Reduced sleep	0.021 (−0.060 to 0.101)	0.616
Sleeping more	0.065 (−0.022 to 0.153)	0.144
Baseline OSA (yes)	0.110 (0.036 to 0.185)	0.004
Intercept	2.30 (2.02 to 2.58)	<0.001
Time (from baseline, y)	0.272 (0.246 to 0.299)	<0.001
Baseline age (y)	−0.052 (−0.056 to −0.049)	<0.001
Baseline age × time	−0.004 (−0.004 to −0.003)	<0.001
Baseline cognitive assessment (#)	0.036 (0.013 to 0.060)	0.003
Assessment × time	−0.008 (−0.011 to −0.005)	<0.001
Sex (male)	−0.224 (−0.279 to −0.168)	<0.001
APOE ε4 carrier (yes)	−0.081 (−0.141 to −0.021)	0.008
APOE ε4 × time	−0.019 (−0.026 to −0.011)	<0.001
Education (y)	0.121 (0.110 to 0.131)	<0.001
CMC (score)	−0.032 (−0.055 to −0.008)	0.009
CMC × time	−0.005 (−0.008 to −0.002)	<0.001
BDI-II (score)	−0.018 (−0.025 to −0.011)	<0.001
Alcoholism (yes)	−0.181 (−0.322 to −0.041)	0.011
Model performance		
Marginal R^2 (fixed factors)	0.52	
Conditional R^2 (full model)	0.93	

Abbreviations: BDI-II = Beck Depression Inventory-2; CMC = cardiometabolic comorbidities; OSA = obstructive sleep apnea.

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Table 3 Cox Proportional Hazards Model Estimates

Covariates	HR (95% CI)	*p* Value
Insomnia (yes)	1.40 (1.07 to 1.85)	0.015
Baseline age (y)	1.10 (1.08 to 1.12)	<0.001
Education (y)	0.90 (0.86 to 0.94)	<0.001
APOE ε4 carrier (yes)	2.07 (1.64 to 2.62)	<0.001
Cardiometabolic comorbidities (CMC score)	1.14 (1.04 to 1.25)	0.005
Depression (BDI-II >13) (yes)	2.04 (1.08 to 3.84)	0.028
Alcoholism (yes)	1.95 (1.19 to 3.19)	0.008

Abbreviations: BDI-II = Beck Depression Inventory-2 Score.

insomnia sleeping more had lower baseline WMH burden (β = −0.142, 95% CI −0.268 to −0.016, *p*-interaction = 0.028) (Figure 3A, Table 4), indicating comparable effect sizes in opposite directions, equivalent to ±4.5 years of age at baseline, respectively. There were no significant interactions with time.

Insomnia with reduced sleep was associated with higher amyloid-PET burden at baseline (β = 10.5, 95% CI 0.5–20.6, *p* = 0.039), with an effect size comparable with that of APOE ε4 carrier status (β = 12.2, 95% CI 8.6–15.9, *p* < 0.001) (Figure 3B, Table 4). However, insomnia (with or without reduced sleep) did not change the rate of accumulation longitudinally.

Hypnotic Use, Cognition, and Neuroimaging Biomarkers

We conducted exploratory analyses examining associations between hypnotic use in participants with insomnia and cognitive and neuroimaging outcomes, respectively. Hypnotic use was not associated with global cognitive z-scores (β = 0.016, 95% CI −0.201 to 0.233, *p* = 0.888), incident CI (HR 0.94, 95% CI 0.5–1.6, *p* = 0.832), WMH (β = −0.089, 95% CI −0.215 to 0.036, *p* = 0.161), or amyloid-PET burden (β = −10.3, 95% CI −23.7 to 3.15, *p* = 0.132) (eTables 3 and 4). Owing to limited sample size in neuroimaging models, we performed sensitivity analyses in the full sample using final model covariates plus hypnotic use and propensity scores (for hypnotic treatment). No associations were found between hypnotic use and WMH (β = −0.029, 95% CI −0.110 to 0.051, *p* = 0.479) or amyloid-PET burden (β = −6.2, 95% CI −17.1 to 4.8, *p* = 0.269). However, adding an interaction with sleep duration change showed that hypnotic use in participants with reduced sleep was associated with lower baseline WMH (β = −0.216, 95% CI −0.380 to −0.053, *p*-interaction = 0.009) in the full sample and lower baseline amyloid-PET burden (β = −26.3, 95% CI −48.3 to −4.2, *p*-interaction = 0.020) in participants with insomnia. These findings were not consistent across samples: no significant associations were detected for WMH in insomnia participants with reduced sleep (β = −0.217, 95% CI −0.436 to 0.002, *p*-interaction = 0.052) or for amyloid-PET burden in all participants with reduced sleep (β = −19.9, 95% CI −41.0 to 1.2, *p*-interaction = 0.065), precluding any definite conclusion or generalization regarding potential protective effects of hypnotics in these subgroups.

Sensitivity Analyses

In the subgroup with informant-reported witnessed apneas, replacing the OSA diagnosis with (or adding) the OSA risk category variable in the parsimonious models did not significantly alter the main results (eTables 5–7).

Discussion

We found that chronic insomnia diagnosis in cognitively unimpaired older adults was associated with a faster rate of cognitive decline and incident MCI/dementia. Insomnia with self-reported reduced sleep was associated with worse global cognitive performance at baseline, along with greater WMH and amyloid-PET burden. Participants with insomnia who reported sleeping more had attenuation of baseline WMH. Hypnotic use was not associated with cognitive decline, WMH, or global amyloid accumulation.

Our findings corroborate previous literature describing an association between insomnia and longitudinal cognitive decline in older adults[e20,e21] but differs from other studies suggesting no association or better cognitive outcomes.[e22-e24] The risk of CI associated with insomnia in this study (HR 1.4, 95% CI 1.07–1.85) was comparable with that of meta-analytic studies assessing risk for AD dementia (RR 1.38–1.43),[10,28] or all-cause cognitive decline (RR 1.16–1.27).[9,12]

Our study supports previous research suggesting that insomnia with objectively confirmed short sleep may be an important phenotype associated with CI[18] and extends these findings by indicating that even perceived reduced sleep may be relevant. It is noteworthy, however, that the main effect of insomnia with reduced sleep on cognition and neuroimaging outcomes occurred at baseline, reflecting the chronic nature of the sleep disturbance, which remains widely undiagnosed and undertreated in the community.[e25,e26]

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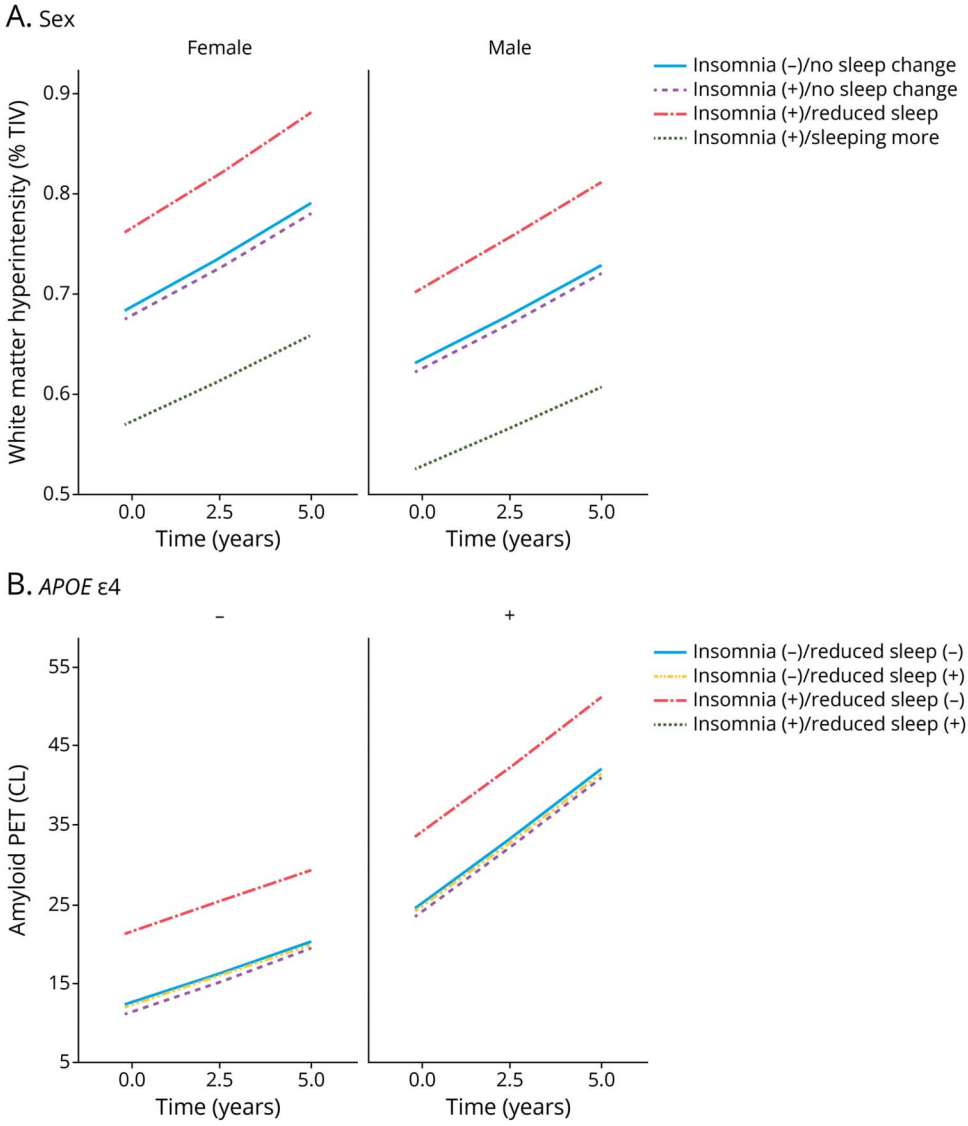
Figure 3 Predicted Changes in White Matter Hyperintensity Volume and Amyloid-PET Levels



The effect of chronic insomnia and its interaction with self-reported habitual sleep duration change on predicted white matter hyperintensity volume (% total intracranial volume) (A) or amyloid-PET level (centiloid units) (B) change over time for a 70-year-old participant with 2 cardiometabolic comorbidities, depending on sex (A) or APOE ε4 carrier status (B), respectively. Sleep duration change categories are shown according to their relevance to each model. As sleeping more was not different than no changes in sleep pattern in amyloid models, it was omitted from the figure to avoid redundancy.

However, only chronic insomnia (not its interaction with reduced sleep) was associated with incident CI. This may reflect limited power to detect interactions because of the low incidence of CI in insomnia participants. Still, it is consistent with studies reporting no association between sleep duration and incident cognitive decline,[e27-e29] despite broader evidence suggesting otherwise.[9,12] Inconsistencies may stem from differences in sleep duration assessment or categorization, the possible time-varying nature[e30] or remission[e31] of insomnia, and the possibility that reporting less or more sleep than usual may not reflect clinically meaningful changes or their timing. Self-reported sleep duration in insomnia can be challenging due to frequent sleep-wake state misperception, leading to underestimation.[e32] Moreover, chronic insomnia involves not only changes in sleep duration but also prolonged sleep latency[e29,e33-e37] and sleep maintenance issues (poor sleep efficiency,[e29,e33,e37,e38] increased wake after sleep onset,[e33,e38-e40] and early morning awakenings[2,e41]), which have been associated with poorer cognitive outcomes.[9,28] However, these associations vary across studies.

A proposed bidirectional relationship between aging/neurodegeneration and altered sleep likely underlies the association between insomnia and cognitive decline. Aging may promote insomnia by reducing homeostatic sleep pressure,[e42-e44] possibly due to decreased adenosine sensitivity.[e45] Aging is also associated with decreased amplitude of the circadian rhythm,[e46-e48] affecting sleep propensity at the desired time or after awakenings. Coincidentally, aging has been associated with reduced sleep duration, prolonged sleep latency, and reduced sleep efficiency[e49,e50]; potentially reflecting age-related neuronal loss and/or early AD pathology preferentially involving circadian rhythm,[e51,e52] sleep-promoting,[e53,e54] and wake-promoting[e54-e56] areas.

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Table 4 Fixed Effect Estimates for Covariates Included in Final (Most Parsimonious) Mixed-Effects Model for WMH and Global Amyloid-PET Level (CL)

Models	WMH (%TIV, log)		Amyloid-PET (CL)	
Covariates	**β (95% CI)**	***p* Value**	**β (95% CI)**	***p* Value**
Insomnia (yes)	−0.013 (−0.079 to 0.054)	0.711	−1.1 (−7.3 to 5.1)	0.731
Insomnia × reduced sleep	0.147 (0.044 to 0.249)	0.005	10.5 (0.5 to 20.6)	0.039
Insomnia × sleeping more	−0.142 (−0.268 to −0.016)	0.028	−1.1 (−12.6 to 10.4)	0.851
Habitual sleep duration change (ref: no change)				
Reduced sleep	−0.026 (−0.071 to 0.019)	0.258	−0.4 (−4.6 to 3.8)	0.846
Sleeping more	−0.027 (−0.076 to 0.022)	0.275	2.8 (−2.2 to 7.7)	0.270
Intercept	−2.590 (−2.720 to −2.461)	<0.001	−36.8 (−49.1 to −24.6)	<0.001
Baseline scan age (y)	0.031 (0.029 to 0.033)	<0.001	0.7 (0.6 to 0.9)	<0.001
Time from baseline scan (y)	0.029 (0.015 to 0.042)	<0.001	1.6 (1.3 to 1.9)	<0.001
Sex (male)	−0.081 (−0.114 to −0.048)	<0.001	—	
CMC (score)	0.019 (0.005 to 0.033)	0.009	—	
APOE ε4 carrier (yes)	—		12.2 (8.6 to 15.9)	<0.001
APOE ε4 × time	—		1.9 (1.4 to 2.5)	<0.001
Model performance				
Marginal R^2 (fixed factors)	0.69		0.27	
Conditional R^2 (full model)	0.93		0.98	

Abbreviations: CL = centiloid unit; CMC = cardiometabolic comorbidities; TIV = total intracranial volume; WMH = white matter hyperintensity.

We hypothesize that altered sleep physiology due to aging/neurodegeneration may increase the vulnerability to, and is exacerbated by, chronic insomnia, which involves a hyperarousal state,[e57,e58] with increased faster brain activity during wake and sleep.[e59,e60] As sleep is proposed to support memory consolidation,[e61] synaptic homeostasis,[e62] glymphatic function,[e63] and cardiometabolic regulation,[e64,e65] poor and/or reduced sleep in participants with insomnia may impair memory processes,[e66] increase synaptic activity (promoting increased amyloid/tau production),[e67-e69] reduce amyloid[e70] and tau[e71] clearance, and promote cerebrovascular disease,[30,31] respectively, ultimately contributing to cortical neurodegeneration[e72-e74] and dementia.

This hypothesis is supported by our findings of increased WMH and amyloid burden in participants with insomnia, which may independently contribute to cognitive decline.[35] These associations were stronger in participants with self-reported reduced sleep, aligning with findings linking short sleep to reduced white matter integrity[e75-e77] and increased amyloid burden,[e78-e80] despite other findings related to sleep duration and insomnia symptoms.[e81-e84] Of interest, one study showed that insomnia moderated the relationship between amyloid and cognitive decline.[e85] Increased sleep latency, a common feature of insomnia, has also been associated with WMH[e86] and amyloid burden.[e87,e88] Consistent with our findings of lower WMH in insomnia participants who reported sleeping more than usual, longer sleep duration in patients with insomnia was associated with decreased odds of MCI.[e89] Better sleep consolidation has also been shown to attenuate the effect of the ε4 allele on longitudinal cognitive decline, AD risk, and neurofibrillary tangle density.[e90] In patients with MCI, cognitive behavioral therapy for insomnia (CBT-I) improved sleep and executive function.[e91] However, evidence for long-term cognitive and neuroimaging benefits is lacking.

Regarding hypnotics, the data are conflicting.[e92-e95] Similar to our findings, a large meta-analysis found no association between hypnotic use (benzodiazepines and z-drugs) and dementia risk in patients with a history of insomnia.[e92] Another meta-analysis did not show a relationship between hypnotic use (benzodiazepines, z-drugs, antipsychotics) and dementia after adjusting for age, while antidepressant use showed a borderline association (odds ratio 1.06–1.42).[e93]

Although our findings suggesting a potential protective effect of hypnotic use on WMH and amyloid burden in participants with reduced sleep are exploratory, they align with a retrospective longitudinal observational study that reported a slower rate of cognitive decline over 4 years in patients using trazodone, compared with propensity-matched nonusers.[e96] A large case-control study also showed a potential protective effect from benzodiazepine/z-drug use in dementia risk after

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median 6.1 years.[e97] This is consistent with evidence supporting better sleep quality in older adults, including with AD, with different hypnotics.[e98-e101] Of interest, chronic benzodiazepine use has been associated with global brain metabolism upregulation, lower amyloid-PET burden, and larger hippocampi in older adults,[e102-e104] though controversy remains.[e105] A recent experimental study showed acute decreases in CSF pTau-t181 and β-amyloid with suvorexant when compared with placebo in late middle-aged healthy adults, also suggesting a potential neuroprotective effect.[e106]

We hypothesize that some of the associations between hypnotics and poorer cognitive outcomes may reflect confounding of more severe insomnia and greater neuropsychiatric comorbidity in participants on hypnotics, particularly at higher doses or longer exposure. Most studies reporting such associations did not compare individuals with or without hypnotics with the same severity of sleep disturbance (or propensity for hypnotic use). However, cognitive outcomes may also vary by hypnotic class,[e93,e107] dosing/half-life,[e92,e93,e107] duration of exposure,[e92] anticholinergic side effects,[e108,e109] psychiatric comorbidities,[e92] polypharmacy,[e93,e107,e108] race,[e110] and treatment efficacy.

Our study has noteworthy limitations akin to other large epidemiologic studies, including lack of objective sleep data, subjective quantitative sleep duration and insomnia severity, detailed hypnotic data (dose, duration of exposure, response to therapy, and side effects), information on CBT-I treatment, OSA severity, and OSA treatment. Although the frequency of chronic insomnia diagnosis reported herein (16.1%) is consistent with the pooled prevalence of insomnia in older adults (19.6%, 95% CI 12.3%–28.3%) in recent meta-analysis,[e111] we suspect some chronic insomnia remains undiagnosed and our study did not address associations with current insomnia symptoms. Although presumed OSA frequency (diagnosed plus high risk for undiagnosed) was 27.2% in subgroup with informant data, approaching pooled prevalence estimates for older adults,[e112] lack of validated systematic assessment of OSA remains a limitation. Last, our community-dwelling cohort is made of predominantly white participants (>90%) due to geographic racial distribution, which may decrease the external validity of our findings to other racial or ethnical groups.

In conclusion, our study provides important evidence supporting an association between insomnia, cognitive decline, and increased risk for CI. Insomnia with reduced sleep was associated with poorer cognitive performance, higher WMH, and global amyloid-PET burden at baseline. Self-reported greater sleep duration was associated with better cerebrovascular health, indicating that treatments targeting sleep improvement could help prevent progression of white matter changes. Further studies should investigate the effects of treatment for insomnia and short sleep duration in the trajectory of cognitive decline and neuroimaging biomarkers, including specific classes of hypnotics and CBT-I.

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Author Contributions

D.Z. Carvalho: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. B.P. Kolla: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. S.J. McCarter: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. E.K. St. Louis: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M.M. Machulda: drafting/revision of the manuscript for content, including medical writing for content. S.A. Przybelski: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. A.J. Fought: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. V.J. Lowe: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. V.K. Somers: drafting/revision of the manuscript for content, including medical writing for content. B.F. Boeve: drafting/revision of the manuscript for content, including medical writing for content. R.C. Petersen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C.R. Jack: drafting/revision of the manuscript for content, including medical writing for content. J. Graff-Radford: drafting/revision of the manuscript for content, including medical writing for content. A.W. Varga: drafting/revision of the manuscript for content, including medical writing for content. P. Vemuri: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data.

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