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GREATER RISK OF ALZHEIMER'S DISEASE IN OLDER ADULTS WITH INSOMNIA

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To the Editor

Physiological changes in the continuity, architecture, and circadian timing of sleep accompany aging, the best-known risk factor for Alzheimer's disease (AD).[1] In older adults, dementia is also typically associated with sleep disorders. Epidemiological evidence shows an association between sleep disorders and AD. In two longitudinal follow-up studies, subjects with insomnia were more likely than those without to have a diagnosis of AD or cognitive decline at follow-up[2,3] (Table 1). Two similar studies reported that prolonged sleep duration[4] and excessive daytime sleepiness[5] were also associated with risk of developing cognitive decline, although negative studies have also been published,[5,6] indicating that the relationship between sleep and risk for later development of AD is unclear. The current study assessed the relationship between insomnia and AD in 346 cognitively normal older adults evaluated during multiple visits over 7.7 years of follow-up.

METHODS

Participants were drawn from a larger pool of 655 normal volunteers (aged 24–96) participating in brain aging studies at New York University's Alzheimer's Disease Research Center. People selected for study had had a minimum of three examinations, with at least two during the normal stages of cognition. All participants were classified into two groups: the normal-AD group (n = 25), who subsequently declined to AD, and the normal-normal group (n = 321) who remained cognitively stable during all the evaluations. Insomnia was collected only during the normal cognition stage and screened using items 4, 5, and 6 from the Hamilton Depression Rating Scale (HAM-D).[7] Number of follow-up visits was different between the normal-AD and the normal-normal groups, so a new average longitudinal score for insomnia was calculated as the sum of all the insomnia HAM-D scores divided by the number of follow-up visits. Subjects were considered to be depressed if they had a score of 10 or greater on the HAM-D or were diagnosed with major depression at any evaluation during the follow-up period. The inflection point of the receiver operating characteristic curve was used to define a cutoff value for the presence or absence of insomnia (with this value, 92.5% of the patients with "insomnia" had a score >1 on the HAM-D insomnia items in more than one follow-up). Odds ratios were obtained using chi-square analysis of the groups with respect to the presence or absence of insomnia. Survival analysis was used to compare risk of faster disease progression in the normal-AD group with insomnia with that in those with normal sleep.

RESULTS

Demographic characteristic are summarized in Table 2. The two groups did not differ in age, sex, Mini-Mental State Examination (MMSE) score at baseline, and apolipoprotein E ε4 (ApoE4) status but were different in education. Presence or absence of insomnia was significantly associated with AD (odds ratio (OR) = 2.39, 95% confidence interval (CI) = 1.03–5.55). Depression did not confound the association, as excluding patients with depression increased the relationship (OR = 3.32, 95% CI = 1.33–8.28). Normal-AD patients with insomnia showed a faster progression to dementia (chi-square = 3.94, $P = .047$).

DISCUSSION

This study documents an association between insomnia assessed during a long follow-up period and incident cases of AD. Depressed mood, age, sex, MMSE score, and Apo E4 did not confound the association. This study had a number of potential limitations. First, the analysis was adjusted for a number of important confounders, but the effect of daytime sleepiness or sleep apnea cannot be excluded as they were not formally analyzed during the evaluation. Second, insomnia was captured through the insomnia HAM-D questions, with a cutoff value that was established post hoc and not validated against clinical criteria. Third, the study did not include sleep examinations or objective methods of measuring sleep such as polysomnography to document the extent of the sleep restriction or to exclude other sleep disorders. Fourth, the study was based on post hoc analysis of a large clinical sample, and the number of patients that developed AD was small. The strengths of this study include uniform assessments, long-term follow-up, strict criteria for defining the outcome groups, and unbiased evaluation of insomnia, as the variable of interest was not the original reason for the data to be collected.

This is the second report about insomnia associated with incident AD. Sleep and wake changes that occur during normal aging could increase the risk of cognitive decline after a certain age by increasing Aβ production,[8] and this risk could be greater in older subjects with chronic insomnia.[9] Excessive daytime sleepiness has also been related to AD.[4] This could portray hypersomnia as an early symptom of AD in a similar way that some depressive symptoms may be early manifestations of dementia. Alternatively, insomnia could be a risk factor for AD similar to lifetime recurrent major depression.

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Table 1

Longitudinal Studies (Including Demographic Characteristics) that Have Analyzed the Presence of Sleep Complaints as Predictors of Cognitive Decline or Alzheimer's Disease

Study	Participants	N	Age	Female, %	Education, Years	Symptoms	Sleep Measure	Follow-Up, Years*	Risk
Lobo, 2008	Spanish community-dwelling older adults	4,803	73.5 ± 9.8	57.7	7.9 ± 3.6	Early-, middle-, and late-onset insomnia	Geriatric Mental State— Automated Geriatric Examination for Computer-Assisted Taxonomy	2	Greater risk of mild cognitive impairment (OR = 2.67, 95% CI = 1.92–3.70), Greater risk of Alzheimer's disease (OR = 2.81, 95% CI = 1.30–6.08)
Cricco, 2001	Icelandic community-dwelling older adults	6,444	72	62	81.8% <12	Early-, middle-, and late-onset insomnia. Chronic and incident cases.	Ad hoc insomnia questionnaire	3	Greater risk of cognitive decline in patients with chronic insomnia (OR = 1.78, 95% CI = 1.03–2.14)
Benito-Leon, 2009	Spanish community-dwelling older adults	3,286	79.1 ± 6.9	57	—	Longer sleep duration	Total hours of sleep in a 24-hour period	3	Greater risk of dementia (OR = 2.07, 95% CI = 1.04–4.14)†
Foley, 2001	Japanese-American community-dwelling older adults	2,346	76.6 ± 3.9	—	—	EDS and insomnia	Ad hoc questionnaire	3	Greater risk of dementia with EDS (OR = 2.19, 95% CI = 1.37–3.50). No association with insomnia
Tworoger, 2006	U.S. community-dwelling women	1,844	70–81	100	—	Sleep duration, difficulty sleeping, and snoring	Ad hoc questionnaire	2	No association with cognitive decline

* $P<.05$.

† Results were reported as relative risk, so an odds ratio (OR) was calculated for patients who slept for more than 8 hours a day.

OR = odds ratio; CI = confidence interval; EDS = excessive daytime sleepiness.

Table 2

Baseline Demographic Characteristics

Group	N	Age, Mean ± SD	Female, %	Mean ± SD		ApoE4 Carrier, n/N (%)*	Mean ± SD		Depression During Follow-Up, n (%)
				Education, Years	Number of Visits		Follow-Up, Years†	Baseline Mini-Mental State Examination Score	
NL-NL									
Total	321	75.9 ± 6.6	64.4	16.1 ± 2.2	3.7 ± 1.0	65/215 (30)	7.9 ± 6.8	29.2 ± 1.1	—
Insomnia	70	77.4 ± 6.3	72.9	15.9 ± 2.1	3.3 ± 1.7	15/54 (28)	7.7 ± 5.1	29.1 ± 1	18/70 (26)
NL-AD									
Total	25	76.0 ± 5.4	62.5	14.8 ± 2.9	2.7 ± 1.0	7/21 (33)	5.7 ± 3.8	28.8 ± 1.1	—
Insomnia	10	77.9 ± 4.7	80.0	14.7 ± 2.8	2.9 ± 1.4	1/6 (17)	5.2 ± 3.1	28.8 ± 0.8	1/10 (10)

*Missing values in 110 participants; n = ApoE4 carriers, N = total number of participants for whom ApoE4 information was available.

†$P<.05$.

SD = standard deviation; NL = normal; AD = Alzheimer's disease.