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Original Research Article

Daytime Sleepiness and Sleep Inadequacy as Risk Factors for Dementia

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Key Words

Dementia · Daytime sleepiness · Sleep adequacy · Elderly · Longitudinal study

Abstract

Background/Aims: To examine the association between self-reported sleep problems and incidence of dementia in community-dwelling elderly people. ***Methods:*** 1,041 nondemented participants over 65 years old were examined longitudinally. Sleep problems were estimated using the RAND Medical Outcomes Study Sleep Scale examining sleep disturbance, snoring, sleep short of breath or with a headache, sleep adequacy, and sleep somnolence. Cox regression analysis was used to examine the association between sleep problems and risk for incident dementia. Age, gender, education, ethnicity, *APOE*-ε4, stroke, heart disease, hypertension, diabetes, and depression were included as covariates. ***Results:*** Over 3 years of follow-up, 966 (92.8%) participants remained nondemented, while 78 (7.2%) developed dementia. In unadjusted models, sleep inadequacy ('Get the amount of sleep you need') at the initial visit was associated with increased risk of incident dementia (HR = 1.20; 95% CI 1.02–1.42; p = 0.027). Adjusting for all the covariates, increased risk of incident dementia was still associated with sleep inadequacy (HR = 1.20; 95% CI 1.01–1.42; p = 0.040), as well as with increased daytime sleepiness ('Have trouble staying awake during the day') (HR = 1.24; 95% CI 1.00–1.54; p = 0.047). ***Conclusion:*** Our results suggest that sleep inadequacy and increased daytime sleepiness are risk factors for dementia in older adults, independent of demographic and clinical factors.

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Introduction

It is of paramount importance to identify early risk factors that may better inform our understanding of neurodegenerative disorders. According to an epidemiologic study, having insomnia is the most common sleep complaint (23–34%) among the elderly, followed by the difficulty feeling rested after waking up in the morning, in 7–15% of the population [1]. Given the evidence that has linked sleep-related disorders to both cognitive decline [2–4] and pathological processes of dementia [5], sleep problems are a significant topic of interest within this field.

The existing literature suggests different types of sleep problems having been linked to incident dementia. Specifically, daytime sleepiness has been shown to be associated with cognitive decline or incident dementia in several longitudinal studies [2, 3, 5–7]. Another study found that daytime sleepiness predicted vascular dementia in a sample of older men [6]. In addition, 'sleep fragmentation' (high activity during sleep) has been linked to incident Alzheimer's disease (AD) [4] in older adults. Prolonged sleep duration has been also associated with an increased risk of dementia in a large population-based study [8].

There are some critical gaps in much of the existing literature, however. The sample sizes of some of these studies were relatively small [9, 10]. The longitudinal study with a great number of participants examining the association between sleep problems and incident dementia used only male participants; thus, the findings cannot be generalized to both genders [3]. Furthermore, existing longitudinal research on this topic typically has not incorporated a comprehensive neurological and neuropsychological interview which would allow for a differential diagnosis and definition of the cognitive status of each participant at each evaluation. There are some great longitudinal studies in the elderly; however, the cognitive measure they used was a simple telephone screening instrument [7, 11]. Lastly, from the existing literature, the study with the greatest sample size examining the relationship between sleep problems and incident dementia, which has also used an extended neurological and neuropsychological evaluation [8], did not include an ethnically diverse sample, thus limiting its ecological validity.

In the present study, we aimed to examine whether daytime sleepiness ('Have trouble staying awake during the day'), as a distinct type of sleep problem, is associated with incidence of dementia in a large, ethnically diverse sample of community-dwelling older adults. We also aimed to examine whether other types of sleep problems would be differentially associated with incident dementia in the same sample of participants.

Methods

Study Participants

Participants were drawn from the Washington Heights-Inwood Community Aging Project (WHICAP) at Columbia University Medical Center [12, 13]. WHICAP is a community-based research study aimed at identifying risk factors and biomarkers for aging and AD in a multiethnic cohort that includes Caucasian, African-American, and Hispanic participants [14]. Evaluations were conducted in either English or Spanish, based on the preference of the participant. The age of the project participants was over 65 years. Informed consent, as approved by the Internal Review Board (IRB) of the College of Physicians and Surgeons of Columbia University, was obtained prior to study participation. WHICAP has been approved by the IRB of the New York State Psychiatric Institute.

Each participant underwent a structured in-person interview including an assessment of health and function, as well as a neuropsychological assessment. Participants were followed

at intervals of approximately 1.6 years, repeating the baseline examination and consensus diagnosis.

Since 2007, we have been collecting sleep information among the WHICAP II participants. For the current study, the baseline visit was defined as the visit when the sleep questionnaire was first applied in the subjects. The initial sample consisted of 2,358 participants. We excluded 238 subjects who had prevalent dementia at baseline and 5 without data regarding their cognitive status. We made a further exclusion of 1,072 participants because they had no follow-up visit, and 2 had missing follow-up data. Thus, the final sample consisted of 1,041 participants.

Dementia Diagnosis

The diagnosis of mild cognitive impairment (MCI) and dementia was based on standard research criteria using all available information at a consensus conference consisting of physicians, neurologists, neuropsychologists, and psychiatrists. According to the *Diagnostic and Statistical Manual of Mental Disorders*, *Revised Third Edition*, *DSM-III-R*, in order to meet the criteria for a diagnosis of dementia, evidence of cognitive deficit, impairment in social or occupational function, and cognitive and socio-occupational functional decline must have been present in comparison to the past. The type of dementia was subsequently determined. For the diagnosis of probable or possible AD, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [15, 16] were used.

In addition to the neurological evaluation, all participants underwent a full neuropsychological battery which included the following: immediate recall, delayed recall, and delayed recognition from the Selective Reminding Test [17]; the 15-item Boston Naming Test [18]; repetition (total number of correct phrases) and comprehension (total number of correct comprehensive questions), which were assessed with subtests of the Boston Diagnostic Aphasia Examination [19]; total correct on the Mattis Identities and Oddities subtest, raw score on Wechsler Adult Intelligence Scale – Revised Similarities subtest, and mean number of words generated during three 60-second trials for category and letter fluency [20, 21], and finally, the time score on the Color Trails Test parts 1 and 2 [22]. Test scores were evaluated using a fixed paradigm [23]: criterion scores were applied to each test score, and subjects performing below these scores on two of the three aspects of memory testing as well as two other areas (orientation, language, abstract reasoning, or construction) were considered to have sufficient cognitive deficit to meet the criteria for dementia.

Sleep Measures

Sleep quality was assessed using the Sleep Scale from the RAND Medical Outcomes Study. This scale is a self-report 12-item questionnaire which asks the following questions [24]: (1) How long did it usually take for you to fall asleep during the past 4 weeks? (2) On average, how long did you sleep each night during the past 4 weeks? How often during the past 4 weeks did you: (3) Feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc.) while sleeping? (4) Get enough sleep to feel rested upon waking in the morning? (5) Awaken short of breath or with a headache? (6) Feel drowsy or sleepy during the day? (7) Have trouble falling asleep? (8) Awaken during your sleep time and have trouble falling asleep again? (9) Have trouble staying awake during the day? (10) Snore during your sleep? (11) Take naps (5 min or longer) during the day? (12) Get the amount of sleep you needed?

Each of the questions has a possible rating of 0–6, based on the frequency of the sleep problem (Appendix), with a higher score indicating greater sleep dysfunction. Analyses were performed for each of the sleep questions separately.

Table 1. Demographic and clinical characteristics of the participants

Characteristics	All (n = 1,041)	Nondemented (n = 966)	Demented (n = 75)	p	MCI (n = 185)	p
Age, years	79.30±6.4	79.03±6.3	82.76±5.9	0.000	79.29±6.1	0.961
Females	727 (69.8)	668 (69.2)	59 (78.7)	0.084	129 (69.7)	0.963
Education, years	10.28±5.0	10.50±4.9	7.46±5.0	0.000	9.36±5.0	0.006
Ethnicity						
White	244 (23.4)	237 (24.5)	7 (9.3)		40 (21.6)	
African-American	242 (23.5)	231 (23.9)	11 (14.7)	0.000	34 (18.4)	0.092
Hispanic	544 (52.3)	488 (50.5)	56 (74.7)		111 (60.0)	
Other	11 (1.1)	10 (1.0)	1 (1.3)			
Presence of *APOE*-ε4	256 (24.8)	229 (24.0)	27 (36.0)	0.020	45 (24.6)	0.894
CES-D	175 (17.1)	163 (17.2)	12 (16.2)	0.833	40 (21.7)	0.083
Hypertension	820 (79.5)	761 (79.4)	59 (80.8)	0.765	158 (85.9)	0.022
Diabetes mellitus	288 (27.9)	271 (28.3)	17 (23.3)	0.362	62 (33.7)	0.048
Heart disease	285 (27.6)	271 (28.3)	14 (19.2)	0.095	53 (28.8)	0.686
Stroke	93 (9.0)	85 (8.9)	8 (10.7)	0.597	17 (9.2)	0.993

Data are presented as n (%) or mean ± SD.

Covariates

Age (years) and education (years) were used as continuous variables. Ethnicity was ascertained based on a self-report using the format of the 1990 census [25]. Participants were then assigned to 1 of 4 groups: African-American (non-Hispanic), Hispanic, White (non-Hispanic), and other. Ethnicity was used as a dummy variable with White (non-Hispanic) as the reference. Apolipoprotein E (*APOE*-ε4) genotype was used dichotomously: absence of the ε4 allele versus presence of either 1 or 2 ε4 alleles.

According to the existing literature, depression may be related to sleep [26] and dementia [27, 28], so we included it as a covariate in the analyses. Depressive symptoms at the time of the evaluation were assessed with the 10-item version of the Center for Epidemiologic Studies-Depression (CES-D) scale [29, 30]. The conventional cutoff score of ≥4 was used to indicate the presence of depressive symptoms [31, 32].

Hypertension, diabetes, heart disease, and stroke have also been considered to be strong risk factors for incident dementia [33–35]. A history of these clinical factors was taken based on self-reports during the interview with each participant and/or their informants. The above factors were used in the analyses as dichotomous variables, with no history as the reference.

Statistical Analysis

Analyses were performed using SPSS 22 (SPSS, Chicago, Ill., USA). Baseline characteristics of subjects were compared using the t test or ANOVA models for continuous variables (i.e. age, education), and with the χ^2 test for categorical baseline characteristics (i.e. gender, ethnicity, depression, *APOE*-ε4, hypertension, diabetes, heart disease, and stroke).

In order to examine the association between sleep and dementia, we used the Cox proportional hazards model, with dementia as the dichotomous outcome. The time-to-event variable was the time from recording of baseline sleep to first visit where dementia was diagnosed (for the demented participants), or to the time of the last follow-up (for the nondemented cases).

Adjustments were made for age, gender, education, ethnicity, *APOE*-ε4, stroke, heart disease, hypertension, diabetes, and depression in order to estimate the association between sleep problems and risk for dementia. The main predictor was the sleep question score as a continuous variable.

Table 2. Associations of sleep problems with incident dementia

	Unadjusted model		Adjusted model	
	HR (95% CI)	p value	HR (95% CI)	p value
How long did it usually take for you to fall asleep during the past 4 weeks?	1.10 (0.930–1.31)	0.259	1.10 (0.913–1.32)	0.324
On the average, how many hours did you sleep each night during the past 4 weeks?	0.973 (0.836–1.13)	0.722	0.967 (0.840–1.11)	0.645
Feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	0.891 (0.725–1.09)	0.273	0.913 (0.732–1.14)	0.419
Get enough sleep to feel rested upon waking in the morning?	1.06 (0.908–1.25)	0.441	1.09 (0.926–1.28)	0.307
Awaken short of breath or with a headache?	1.09 (0.795–1.50)	0.582	1.06 (0.741–1.52)	0.748
Feel drowsy or sleepy during the day?	1.02 (0.857–1.23)	0.790	1.06 (0.886–1.27)	0.518
Have trouble falling asleep?	1.06 (0.903–1.25)	0.458	1.08 (0.914–1.28)	0.361
Awaken during your sleep time and have trouble falling asleep again?	1.12 (0.956–1.32)	0.158	1.14 0(.965–1.35)	0.123
Have trouble staying awake during the day? (Daytime sleepiness)	1.21 (0.987–1.50)	0.067	**1.24 (1.00–1.54)**	**0.047**
Snore during your sleep?	1.01 (0.860–1.18)	0.916	0.997 (0.843–1.18)	0.976
Take naps (5 min or longer) during the day?	1.09 (0.948–1.26)	0.221	1.04 (0.895–1.22)	0.586
Get the amount of sleep you needed? (Sleep adequacy)	**1.20 (1.02–1.42)**	**0.027**	**1.20 (1.01–1.42)**	**0.040**

Cox proportional HRs for dementia incidence by sleep problems before (first column) and after adjusting for demographics, *APOE*-ε4, depression, stroke, hypertension, diabetes, and heart disease (second column). A p value <0.05 was considered statistically significant, and the corresponding results are shown in bold.

Results

A total of 1,041 participants were included in the analyses, of whom 75 (7.7%) were diagnosed with incident dementia during the follow-up, while 966 (92.3%) remained dementia free. Most of the demented participants were diagnosed with probable AD (n = 72). The mean baseline age (when sleep data were collected) was 79.30 (SD: 6.4) years. In the sample, there was a greater percentage of females than males. There were also more Hispanics than participants in other ethnic groups (table 1). Subjects were followed for an average of 3 (SD: 99; range, 1.14–6.14) years.

In unadjusted models, sleep inadequacy ('Get the amount of sleep you need') was associated with incident dementia (HR = 1.20; 95% CI 1.02–1.42; p = 0.027; table 2). After controlling for age, gender, education, ethnicity, *APOE*-ε4, stroke, heart disease, hypertension, diabetes, and depression, sleep inadequacy remained a significant risk factor for incident dementia (HR = 1.20; 95% CI 1.01–1.42; p = 0.040; table 2; fig. 1). Increased daytime sleepiness ('Have trouble staying awake during the day') was also associated with a higher risk for developing dementia (HR = 1.24; 95% CI 1.00–1.54; p = 0.047; table 2; fig. 2). The other sleep problem indicators were not associated with incidence of dementia (table 2).

We ran further analyses excluding the participants with MCI at baseline (n = 185, 18.2%), and the result remained significant for the daytime sleepiness question (HR = 1.36; 95% CI 1.07–1.72; p = 0.011) unadjusted, as well as after all the adjustments for demographics, clinical factors, *APOE*-ε4, and depression (HR = 1.37; 95% CI 1.06–1.76; p = 0.017).

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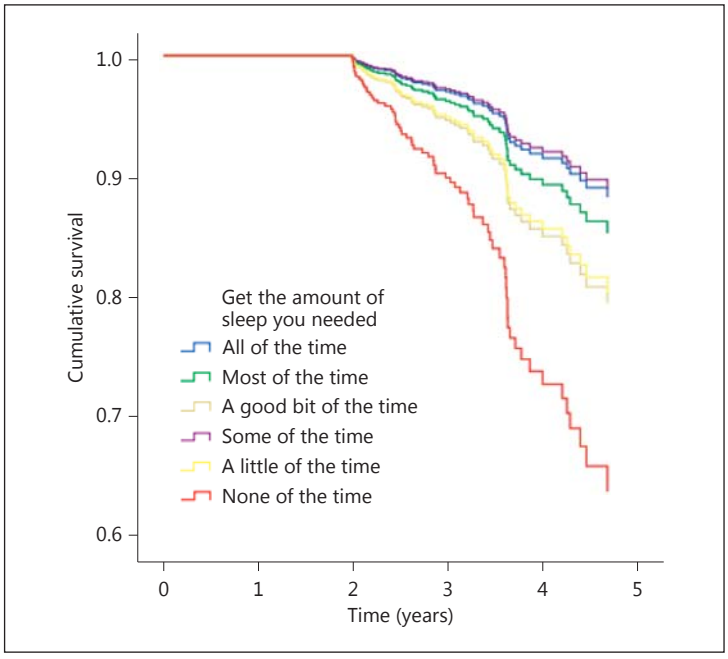

Fig. 1. Survival plot for incident dementia, with sleep inadequacy as the predictor.

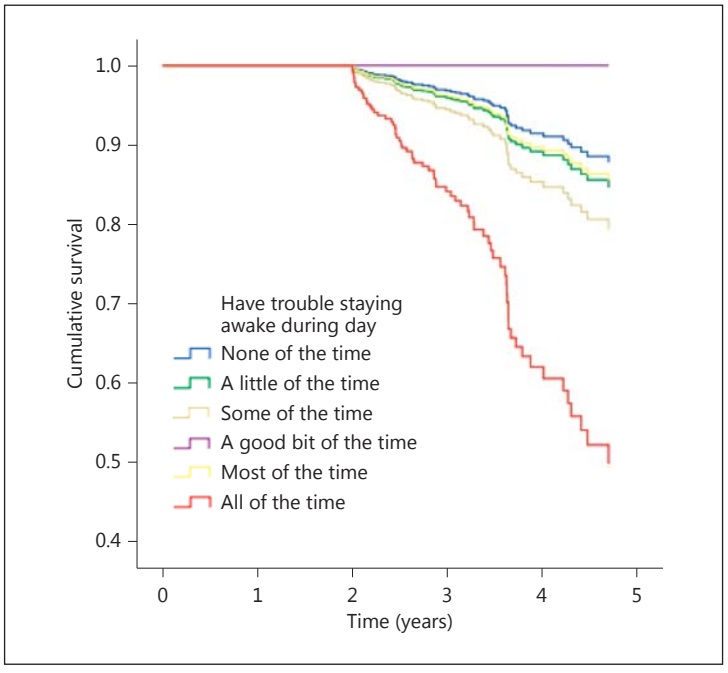

Fig. 2. Survival plot for incident dementia, with daytime sleepiness as the predictor.

Discussion

In the present study, we examined the relationship between self-reported sleep problems and incidence of dementia in a large sample of ethnically diverse older adults. Increased daytime sleepiness and sleep inadequacy were associated with an increased risk for incident dementia.

Several possible explanations for the association between sleep problems and incident dementia have been proposed. It has been suggested that poor sleep may cause neurodegeneration by promoting neuroinflammation and disrupting neurogenesis, especially in areas

such as the hippocampus, a region that plays a crucial role in memory [36–38]. Such degeneration in regions associated with learning [39] could explain why sleep inadequacy and increased daytime sleepiness are associated with incident dementia.

There is also a potential relationship between sleep, β-amyloid (Aβ), and dementia. A recent study in older adults found that both self-reported short sleep duration and increased difficulty falling asleep were associated with greater Aβ levels in cortical areas and the precuneus, an area associated with cognition and dementia [40]. Poor sleep quality was also reported to be associated with greater Aβ deposition in the precuneus [41]. Another study suggested that a steady increase in Aβ levels may be caused by disrupted sleep and increased stress as well [42]. Thus, our results may be explained by the hypothesis that sleep problems lead to an increase in the Aβ deposition, which plays a corroborative role in the development of dementia.

Another possible explanation for the connection between sleep problems and dementia could be that both daytime sleepiness and sleep adequacy are connected to circadian rhythms. This is supported by previous research which has shown that overall sleep problems are linked to disturbed circadian rhythms [43]. Decreased circadian activity rhythm amplitude and robustness have been suggested to be linked to incident dementia [44]. Thus, there might be a biological mechanism connecting sleep problems with dementia.

Although sleep problems may be a risk factor for dementia, the possibility of reverse causality cannot be excluded. Existing literature supports this association between AD and sleep disturbances, especially disruption of nocturnal sleep and impairment of the basic circadian sleep/wake rhythm [45]. Some consider AD not only as a disease of aging, but also as a disease developing throughout lifetime [46]. Despite the longitudinal design of our study that includes clinically nondemented subjects at baseline, it is conceivable that early subclinical pathological changes might have led to sleep problems. Thus, it is possible that sleep problems may be an early sign of the ongoing neurodegeneration instead of a risk factor. Further investigation among nondemented, cognitively healthy, and even biologically brain-healthy participants with much longer follow-up intervals is needed to shed more light on the probable underlying mechanisms.

The present study has some limitations. Firstly, we did not use an objective measure of sleep problems. For example, in clinical practice, the measurement of actigraphy as a diagnostic tool for sleep disturbances appears to have a high specificity [47]. Thus, such a measurement could provide us with more precise information about the sleep problems. Moreover, the answers in the sleep questionnaire refer to the previous 4 weeks and may not accurately represent a chronic sleep pattern of the participant. Finally, the study had a relatively short follow-up period. A longer follow-up period would provide us with more accurate information about the progression to dementia and would allow us to apply more stringent analyses.

Despite these limitations, the present study has some significant strengths. To our knowledge, this is the first longitudinal study to use an extended, validated questionnaire that includes questions regarding different types of sleep disturbances, rather than a unique sleep question or a general category of 'sleep problems' [48] to examine self-reported sleep problems. Furthermore, the sample was large in size, included both men and women, and was multiethnic, including a large number of African-Americans and Hispanics, thus, expanding in this way the ecological validity of the study. Moreover, the present study used an extensive clinical evaluation including a combination of neurological examinations by physicians and a detailed neuropsychological interview in order to define the cognitive status of each participant at each visit.

In conclusion, our study suggests that sleep inadequacy and increased daytime sleepiness are risk factors for dementia, specifically AD type, in the elderly population, independent

of demographics, clinical factors, and depression. Our findings may have significant public health implications and expand upon previous findings. However, further investigation is needed in order to replicate these findings and further examine the possible biological mechanisms underlying the observed associations. Investigation of such mechanisms could allow future interventional studies to provide us with more convincing evidence for the importance of good sleep quality in relation to the risk of dementia.

Appendix

Sleep Scale from the Medical Outcomes Study [49].

1. How long did it usually take for you to fall asleep during the past 4 weeks? (Circle one)	
0–15 min	1
16–30 min	2
31–45 min	3
46–60 min	4
More than 60 min	5
2. On the average, how many hours did you sleep each night during the past 4 weeks? Write in number of hours per night:	
How often during the past 4 weeks did you…	
3. Feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	
4. Get enough sleep to feel rested upon waking in the morning?	
5. Awaken short of breath or with a headache?	
6. Feel drowsy or sleepy during the day?	
7. Have trouble falling asleep?	
8. Awaken during your sleep time and have trouble falling asleep again?	
9. Have trouble staying awake during the day?	
10. Snore during your sleep?	
11. Take naps (5 min or longer) during the day?	
12. Get the amount of sleep you needed?	

Possible answers: 1 = All of the time; 2 = most of the time; 3 = a good bit of the time; 4 = some of the time; 5 = a little of the time; 6 = none of the time; –1 = not asked, –2 = too impaired to respond, –3 = refused.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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