Association of Sleep Disturbance With Longitudinal Cognitive Decline Among Cognitively Normal Elders

Wei Feng
Capital Medical University School of Public Health
Mandela William Nzoyoum Kuetche
Capital Medical University Affiliated Tiantan Hospital
Meng Zhang
Capital Medical University School of Public Health
Mengmeng Liu
Capital Medical University School of Public Health
Yue Liu
Capital Medical University School of Public Health
Deginet Aklilu
Capital Medical University School of Public Health
Wei Wang
Edith Cowan University
Xiaonan Wang
Capital Medical University School of Public Health
Xiuhua Guo (statguo@ccmu.edu.cn)
Capital Medical University https://orcid.org/0000-0001-6657-6940

Research

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Abstract

Background: A lot of evidence demonstrated sleep disturbance (SD) gets associated with Alzheimer's disease (AD), but whether or not sleep disturbance could be the preclinical stage of AD is still unknown.

Objective: 463 cognitively normal elders (357 normal and 106 SD) in baseline with cognitive and biomarker data were included in the study. Participants were collected from 2005 to 2020 (16 years follow-up) in the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods: A generalized linear mixed model was used to adjust time variables and other covariates selected by the Akaike Information Criterion (AIC). Besides, the marginal effect estimation method was used to evaluate the interaction between sleep disturbance and time on cognitive decline. Cox regression was used to assess the survival risk of AD in sleep disturbance.

Results: The age range of participants was 73.60±5.71 years old, and the female proportion was 43.63%. Taking time as a continuous variable in longitudinal analyses, it was found that sleep disturbance had a significant long-term negative effect on MMSE, PACC, CSF Aβ, and ventricular volume (P<0.05). Cox regression analysis showed that sleep disturbance is a significant risk factor of AD (HR=1.55, 95% CI=1.08 to 2.22).

Conclusion: Sleep disturbance in baseline was associated with subsequent cognitive decline among cognitively normal elders and is an increased risk of AD, which means sleep disturbance could probably be the pre-symptomatic stage of AD.

1. Introduction

Sleep disturbance (SD) has been defined as difficulty in initiating or maintaining sleep, along with an impairment of daytime functioning[1]. The elderly have been associated with increased night sleep disturbance whose prevalence is estimated to be approximately 50%[2]. Sleep disturbance in this population has adverse effects including an increased risk of dementia, hypertension, diabetes, obesity, depression, heart attack, and stroke[3,4]. Alzheimer's disease (AD) is a dementia syndrome in which cognitive impairment interferes with the performance of daily activities. The daily activities that are affected include sleep (sleep disturbance) which is the most common in patients with AD[5]. Consequently, whether sleep disturbance, which is common in the elderly, is the cause of AD or not should be verified with more evidences.

Accumulating evidence suggests that sleep disturbance precedes the neurobiology of AD and symptoms of cognitive decline by years. Poor sleep quality was associated with Mild Cognitive Impairment (MCI), which often represents a prodromal phase of preclinical dementia[6]. Moreover, it is thought that sleep disturbance starts to occur in the preclinical phases of AD, as they have been found to predict incident dementia[7–9]. However, these studies don't use the people with normal cognition and overlook the variance of cognition from time, and so it is hard to say in this case that the main reason of cognitive

decline is the effect of time or the sleep disturbance. Moreover, there is still no consensus on whether sleep disturbance could cause cognitive decline. Some studies report there is no association between sleep disturbance and cognition[10]. Furthermore, some studies even report slightly better cognitive functioning in those with sleep disturbance[11]. So, there is a conflict about whether sleep disturbance is a pre-symptomatic stage of AD or not.

Preclinical AD is important for the understanding of ageing and AD and drug development because of the hypothesis that disease-modifying interventions will be most effective when initiated early[12]. If we can ensure that sleep disturbance in the preclinical AD has adverse effects on subsequent cognitive change, then we can know the causal relationship between sleep and dementia and whether it's essential to slow the progression of AD by regulating sleep disorder. The purpose of this current study was to compare the differences in subsequent cognitive change between normal sleep and sleep disturbance at baseline among normal cognition or subjective memory concerns individuals.

2. Methods

Study Participants

Data used were collected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was launched in 2005 as a public-private partnership, led by Michael W. Weiner, MD[13]. The primary purpose of ADNI was to investigate whether serial MRI, PET, other biomarkers, also clinical and neuropsychological assessment could be combined to assess the progression of MCI and early dementia. In this current study, we downloaded and merged the data (16 years follow-up, from 2005 to 2020) which was updated at 30th Jun 2020 from the official website of ADNI, including 83 ADNI sites in the Canada and United States.

For the present study, a subset of individuals with Normal Cognition (NC) or subjective memory concerns those who were self-reported or reported by a study partner or clinician and was included in the analyses. Individuals with sleep disturbance were termed as SD based on the medical history diagnosed by clinicians with "insomnia", "sleep disorder", "sleep apnea", and "sleep disturbance". As shown in Figure S1, the participants without the medical history information of sleep disturbance were considered to have normal sleep and were termed as NS. So, we got 1165 individuals: 152 SD, 1013 NS. After that, we excluded the participants without baseline information of CSF Aβ42, CSF tau, CSF phospho-tau (p-tau), medical history, variables of demographic, medication history, and cognition evaluated variables. Lastly, we got 463 individuals: 106 SD, 357 NS. The follow-up time in months for the individuals of this study is shown in Table S1.

Ethical Approval and Consent to participate

The data in this study was approved by institutional review boards of all ADNI centers. Additionally, patient informed consent has also been done by ADNI.

CSF biomarkers and cognitive tests

Participants included in this study had baseline Preclinical Alzheimer Cognitive Composite (PACC), Mini-Mental State Examination (MMSE)[14] scores of 24 to 30 (0 to 30, worst to best) and Clinical Dementia Rating (CDR)[15] scores of box (0 to 3, best to worst). PACC[16] is a baseline standardized z score composite of the Alzheimer Disease Assessment Scale—Cognitive Subscale Delayed Word Recall, Logical Memory Delayed Recall[17], MMSE, and (log-transformed) Trail-Making Test B Time to Completion which decreases with worse performance[18]. Logical Memory Delayed Recall scores are based on years of education and were required to be at least 9 for 16 years of education, at least 5 for 8 to 15 years of education, and at least 3 for 0 to 7 years of education (0 to 25, worst to best). Additionally, accumulating studies suggest that increased amyloid protein precedes the cognitive symptoms of AD[19]. So, we required that the participants should have the CSF β-amyloid peptide ($A\beta_{42}$) and the profiles related with $A\beta_{42}$ including CSF tau, p-tau. The above variables needed participants to be followed up at least one time or more.

Confounding variables

Age is associated with the sleep disturbance, so it was treated as the covariate in our model. Additionally, the other variables like APOEε4 carriage, gender, family history of dementia, family history of AD, medication of AD, education level, and ventricular volume at baseline were considered into the model. The intaking of medicine against AD was collected from concurrent medications log. Race and ethnicity were self-reported as required by the National Institutes of Health. ADNI was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all participants at each site.

Statistical Analysis

The profiles of sleep disturbance and normal sleep group were described and the differences between these groups were tested by Pearson χ^2 and two-sample t-test. Progression by sleep disturbance group among individuals with normal cognition was analyzed by generalized linear mixed effects (GLME) models which could control the bias from individual and confounding variables. The interaction of time and sleep disturbance was also included in the model. The Cox regression was also used to investigate if the sleep disturbance could lead to AD to happen in the follow-up years.

The primary GLME model was used to estimate the longitudinal SD over time. Firstly, this analysis used the time as the continuous variable, which could show the long-term effect of SD to cognitive normal individuals in this cohort study. Although time is measured discretely, there are enough numerical values that we could fit a line to it, which could consider the spacing between each time point. Additionally, the time was treated as a categorical variable in the other models of which the design is same as the primary model, which could show the short-term effect of SD in each follow-up. The Akaike Information Criterion (AIC)[20], a model selection tool, was used to decide if quadratic terms for time should be added. The other variables like age, APOEε4 carriage, gender, family history of dementia, family history of AD, medication

of AD, education level, and ventricular volume at baseline were selected into the model by AIC. Moreover, the structure of the model was also chosen by AIC from random intercept, random slope, compound symmetric, and unstructured option.

For the estimation of interaction between the sleep disturbance and time we used the marginal effect estimation method. The marginal effect estimation[21] could evaluate the effect of sleep disturbance on cognitive profiles at each follow-up year. So, we could see how the interaction of sleep disturbance and time influence the cognitive decline.

Sensitivity Analyses

Considering possible reverse causality, sensitivity analyses were used to explore robust associations between sleep disturbance and cognitive decline. People with elevated CSF Aβ42 are more likely to get cognitive decline than those with low level CSF Aβ42. So, we reanalyzed the association between sleep disturbance and cognition function by excluding participants whose CSF Aβ42 less than 985 pg/mL[22].

All of the above analyses and graphs were performed with R software (version 4.0.2, https://www.R-project.org/). All the statistical tests were two-sided and *P* value < 0.05 were considered as statistically significant.

Data Availability

All data are available in the ADNI database (ida.loni.usc.edu). Derived data is available from the corresponding author on request by any qualified investigator.

3. Results

As can be seen from Table 1, all essential characteristics were used to compare between NS (n = 357) and SD (n = 106). The proportion of male SD was significantly lower than that of NS. Whereas, the percentage of family histories of patients with Dementia, family histories of patients with AD, and subjective memory concern in SD was higher than that in NS with statistical significance. The participants in SD had fewer education years than those with normal sleep. Additionally, comparing the profiles of cognition between SD and NS, we found that the people with sleep disturbance have a higher value of PACC, logical memory delayed recall, FDG, and the lower of ADAS13. That indicated people with sleep disturbance have better cognition in the baseline.

Table S2, Table S3, and Table S3 shows that sleep disturbance, time, and the interaction of sleep disturbance and time are significantly associated with PACC, MMSE, and CDR-Sum of Boxes when the model adjusted confounding factors selected by AIC. Although there were protective effects of sleep disturbance for PACC, MMSE, and CDR-Sum of Boxes at baseline, the sleep disturbance could be a risk factor for these cognitive outcomes by the years. As shown in Fig. 1, when the time was treated as a continuous variable, there was a decreased tendency by years on PACC and MMSE, and the CDR-Sum of

Boxes score rose dramatically by time. After first year follow-up, the difference in scores for cognitive variables between sleep disturbance and normal sleep was larger and larger. There was not this kind of relationship in the categorical time models. So, sleep disturbance made the PACC, MMSE, and CDR-Sum of Boxes get worse by years in the continuous time model.

According to Table S9, sleep disturbance, time, and the interaction of sleep disturbance and time are significantly associated with CSF Aβ42 in continuous time models. Although time and sleep disturbance alone were not considered risk factors for Aβ42 protein elevation, the interaction of sleep disturbance and time did contribute to Aβ42 protein elevation. The effect of time made all of cognitive profiles get worse significantly. As shown in Fig. 3, the concentration of Aβ42 protein dropped sharply by years and the concentration in sleep disorder group was higher than that in the normal group after 1 year in the continuous time model.

Mean neurodegeneration profiles are depicted in Table S7 and Fig. 3. The percentage of ICV for ventricular volume increased gradually by years and that of sleep disturbance group was higher than the normal one in the continuous time model. As shown in Table S8, S10, and S11, there was not this kind of relationship between sleep disturbance and CSF tau, p-tau, and hippocampal volume in models. The effect of time made neurodegeneration profiles get worse significantly but for hippocampal volume.

Figure 4 shows the hazard ratio of sleep disturbance for the AD in the Cox model adjusting other covariates. The hazard ratio APOEz4 allele was 2.18 (1.54, 3.07), which is the highest one among these variables, followed by sleep disturbance and male. 1.55 (1.08, 2.22) was the second number, belonged to sleep disturbance, and the male was the lowest one with 1.53 (1.05, 2.23). The above results were statistically significant ($P < 0.05$).

In the sensitivity analysis that excluded participants whose CSF Aβ42 more than 985 pg/mL, the results did not change substantially. We found that sleep disturbance can still have a negative effect on the PACC, MMSE, and CDR-Sum of Boxes, CSF Aβ42, and ventricular ICV volume over years. Moreover, we reanalyzed the COX regression for AD, which depict sleep disturbance can still be the risk factor of AD.

4. Discussion

In this longitudinal study of cognitively normal participants, participants with sleep disturbance were easier to develop cognitive decreased symptoms compared participants with normal sleep. The cognitive decreased symptoms included the downward trend of PACC and MMSE, and the upward trend of CDR-Sum of Boxes score, CSF Aβ42, and ventricular volume in 10 to 14 years follow-up. Additionally, people with sleep disturbance who got AD were 1.55 (1.08, 2.22) times more than that of those with normal sleep. That suggests that sleep disturbance probably represent the pre-symptomatic stage of AD.

There were some differences in demographic and cognitive profiles between people with sleep disturbance and normal sleep in the baseline. The sleep disturbance accounted for a higher male percentage than that of those having normal sleep. However, prior studies[23,24] found women to be more

frequent and explain about sleep disturbance saying that women are easier to be influenced by stress and depression which make them difficult to get a good sleep. In this study, the average age of people was around 73 and men got more diseases in this kind of age than women[25], which makes them get difficult to fall in sleep. That's why there were more males with sleep disturbance than females with sleep disturbance. Meanwhile, the proportion of family histories of patients with dementia or AD in sleep disturbance was higher than that in the group with normal sleep, but the percentage of individuals with APOEz4 allele was no significant difference between these two groups. More interesting, the cognitive profiles including PACC, logical memory delayed recall, FDG, and ADAS13 at sleep disturbance group were better than that at normal sleep. So, whether sleep disturbance has adverse effects on cognitive decline or other factors or not needs the longitudinal research part in this study to clarify.

In the longitudinal research part, time was treated as a continuous variable and categorical variable respectively with the generalized linear mixed model to investigate how sleep disturbance influences the subsequent cognitive change. The significant variables in baseline were selected by AIC as covariates into the model to ensure that these variables could influence the cognition. We found that the subsequent cognition outcomes in sleep disturbance group get significantly worse than that in the normal group, such as PACC, MMSE, and CDR-Sum of Boxes, in the continuous time model but not that in the categorical time model. Considering the categorical time model doesn't consider the spacing of the time points compared to the continuous time model[26], sleep disturbance had the adverse effect on cognition with long term effect but not on each time point. A multi-center study about sleep disturbance and later cognitive status also found that sleep disturbance is associated with lower MMSE scores (β=-0.28, 95% CI=-0.49 to -0.07)[27], which is consistent with our results. A research study[28] which evaluates the performance of cognitive questionnaires suggested that the CDR-Sum of Boxes is more precise in measuring the severity of cognitive dysfunction than the MMSE and we also found that sleep disturbance influences that outcome. Consequently, sleep disturbance in baseline probably could make the cognition subsequently decline.

For outcomes of markers of amyloid, sleep disturbance showed the long-term increased effect on the Aβ in CSF. There was not any influence from sleep disturbance on some neurodegeneration markers (CSF tau and p-tau). That is supported by the amyloid hypothesis[29] of Alzheimer's disease which supposes that the concentration of Aβ would increase first and then the high concentration of Aβ induce the amyloid plaques and neurofibrillary tangles. Later, the concentration of tau and p-tau would be at a high level. Our findings are consistent with this hypothesis, when the CSF Aβ rise in individuals with sleep disturbance, the CSF tau and p-tau haven't any significant change. Consequently, sleep disturbance could be a preclinical stage to AD.

The Cox regression analysis showed sleep disturbance is a significant risk factor of AD (HR = 1.55, 95% CI = 1.08 to 2.22) considering other covariates, which is supported by previous studies. Similarly, a multi-centre longitudinal study[30] demonstrated that late-life sleep disturbance is associated with an increased dementia risk (HR = 1.94, 95% CI = 1.08 to 3.49). Osorio et al.[31] found that individuals with sleep

disturbance are easier to get AD. Sterniczuk et al.[9] reported that participants who have trouble in sleeping will get dementia or AD within 4 years. The follow-up time of this study cohort was longer than that of previous studies, and the follow-up time was 10 to 14 years. Besides, the confounding factors were fully considered in this research paper, therefore the results were more reliable and credible.

There are some strengths in this study. First of all, the individuals in this longitudinal research study all had a normal cognition, which could rule out the effects of cognitive decline on sleep disturbance. Secondly, we used the marginal effect estimation which quantifies the interaction between sleep disturbance and time on cognitive decline. Additionally, the generalized linear mixed model was used in this research, which could consider the bias of individual-level and use the data which doesn't meet the requirements of the traditional model. Finally, a lot of covariates were included in this study and were selected by AIC, which could exclude the probability that cognitive decline is caused by other factors.

5. Limitations

There are also some limitations to this research. Firstly, the number of participants in our study is limited, therefore the relationship between cognitive decline and sleep disturbance needs a large sample size cohort to verify. Next, the lack of people with clinical imaging indicators in the late follow-up resulted in a short follow-up time and small sample size at each follow-up. Lastly, the research study didn't consider to use biological experiments to verify the results. However, we plan to address these questions in further study.

6. Conclusion

In conclusion, this study confirmed that sleep disturbance in the baseline is associated with subsequent cognitive decline among cognitively normal elders and is an increased risk of AD. Sleep disturbance probably is a pre-symptomatic stage of AD, which will be important for import by the clinical doctor to prevent people to get cognitive decline or AD. Individuals with sleep disturbance should pay more attention to their cognition and be given active treatments. Further studies should explore whether there are some pieces of evidence from the biological mechanism to support the relationship between sleep disturbance and cognitive decline.

Declarations

Consent for publication

All authors approved the final manuscript for submission and gave consent for publication.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Feng Wei designed this research study, did the statistics analyses, and drafted this paper. Mandela William Nzoyoum Kuetche, Meng Zhang, and Mengmeng Liu collected the data from ADNI, revised the manuscripts, and designed the figures in this paper. Yue Liu and Deginet Aklilu gave suggestions to the generalized linear mixed model, revised the method part, and interpretation of data for the work in this research. Wei Wang , Xiaonan Wang, and Xiuhua Guo revised the work of whole manuscript, and offered contributions to the conception of the work from epidemiology and statistics view.

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In this work, we employed the database of the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI was established as a multicenter longitudinal study to identify imaging, clinical, genetic and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). ADNI is the result of a $67 million partnership efforts by both the public and the private sector. Financial support was obtained from the National Institute on Aging, 13 pharmaceutical companies, and two foundations providing funding through the Foundation for the National Institutes of Health. The study can be split into three sub-initiatives - ADNI1, ADNI2, and ADNI GO. The initial phase known as ADNI1 included subjects between 55-90 years of age from approximately 50 sites across the United States (US) and Canada. ADNI2 and ADNI GO add new participants and funding to the study. The database is made available to researchers around the world and has a broad range of collaborators. The principal investigator (PI) of ADNI, who oversees all aspects, is Dr. Michael Weiner, MD, VA Medical Center and the University of California - San Francisco. For up-to-date information, see www.adni-info.org. We sincerely thank those who participated in data management and analysis. In a very particular way, we are grateful for the help from the friends of ours who sacrificed a lot in this study. We are also thankful to Xiaojia Wen of Capital Medical University for her support in helping to point out some mistakes from clinical view. This current study was financially supported by The Program of National Natural Science Foundation of China (Grant Number: 81903408) (XN Wang), The National Key R&D Program of China (Grant Number: 2016YFC1302804) (XH Guo). The funding was neither was used for the study design nor data collection but to cover for the publication fees.

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Tables

Table 1
Participant characteristics by Insomnia disorder Group in baseline

	Normal Sleep n = 357	Insomnia disorder n = 106	Overall n = 463	t/χ^2	*P*
Clinical Characteristics					
Age, (Mean ± SD), y	73.83 ± 5.63	72.81 ± 5.92	73.60 ± 5.71	1.614	0.107
Gender [Male]	178 (49.86)	24 (22.64)	202 (43.63)	24.620	< 0.001
Education, (Mean ± SD), y	16.29 ± 2.56	15.56 ± 2.91	16.12 ± 2.66	2.514	0.012
Family History of Dementia	159 (44.54)	72 (67.92)	231 (49.89)	17.881	< 0.001
Family History of AD	103 (28.85)	50 (47.17)	153 (33.05)	12.400	< 0.001
Medications of AD	16 (4.48)	9 (8.49)	25 (5.40)	2.571	0.109
Ethnicity				1.524	0.467
Not Hispanic/Latino	342 (95.80)	104 (98.11)	446 (96.33)		
Hispanic/Latino	12 (3.36)	2 (1.89)	14 (3.02)		
Race				8.202	0.084
Asian	2 (0.56)	2 (1.89)	4 (0.86)		
Black	27 (7.56)	1 (0.94)	28 (6.05)		
White	323 (90.48)	102 (96.23)	425 (91.79)		
More than 1 race	4 (1.12)	1 (0.94)	5 (1.08)		
Subjective memory concern	89 (24.93)	42 (39.62)	131 (28.29)	8.697	0.003
≥ 1 APOEz4 allele	99 (27.73)	33 (31.13)	132 (28.51)	0.464	0.496
PACC (z score composite), (Mean ± SD)	-0.63 ± 2.64	0.58 ± 2.43	-0.36 ± 2.64	-4.236	< 0.001
MMSE, (Mean ± SD)	29.00 ± 1.22	29.11 ± 0.94	29.03 ± 1.16	-0.881	0.379
Logical Memory Delayed Recall, (Mean ± SD)	13.01 ± 3.23	14.02 ± 3.14	13.24 ± 3.24	-2.844	0.005
ADAS13, (Mean ± SD)	10.10 ± 4.53	7.58 ± 3.61	9.52 ± 4.46	5.254	< 0.001

Abbreviations: Intracranial Volume (ICV)

	Normal Sleep n = 357	Insomnia disorder n = 106	Overall n = 463	t/χ^2	*P*
CDR-Sum of Boxes, (Mean ± SD)	0.04 ± 0.14	0.05 ± 0.15	0.04 ± 0.14	-0.704	0.482
CSF Aβ42, (Mean ± SD), pg/mL	1194.64 ± 436.21	1200.13 ± 432.45	1195.90 ± 434.89	-0.114	0.909
CSF t-Tau, (Mean ± SD), pg/mL	240.20 ± 91.20	257.00 ± 108.18	244.05 ± 95.50	-1.594	0.112
CSF p-Tau, (Mean ± SD), pg/mL	22.15 ± 9.30	23.91 ± 11.83	22.55 ± 9.95	-1.601	0.110
MRI Characteristics	**n = 298**	**n = 94**	**n = 392**	t	P
Ventricular Volume, (Mean ± SD), %ICV	3.23 ± 1.63	2.88 ± 1.67	3.14 ± 1.65	1.767	0.078
Hippocampal Volume, (Mean ± SD), %ICV	0.72 ± 0.07	0.73 ± 0.06	0.72 ± 0.07	-1.233	0.218
PET Characteristics	**n = 241**	**n = 73**	**n = 314**	t	P
FDG	1.31 ± 0.11	1.35 ± 0.10	1.32 ± 0.11	-3.260	0.001
Amyloid PET SUVR, [Mean ± SD]	1.13 ± 0.18	1.19 ± 0.23	1.14 ± 0.19	-2.115	0.035
Abbreviations: Intracranial Volume (ICV)					

Table 2
Relationship of cognitive profiles to Sleep Disturbance in the Continuous time Models and Categorical time Models

Continuous time Models	**Sleep Disturbance**		**Time**		**Sleep Disturbance*Time**	
Cognitive Profiles	Beta (95%CI)	P-Value	Beta (95%CI)	P-Value	Beta (95%CI)	P-Value
PACC (z score composite)	1.73 (1.12, 2.34)	<0.001	-0.17 (-0.18, -0.15)	<0.001	-0.15 (-0.18, -0.13)	<0.001
MMSE	0.92 (0.61, 1.22)	<0.001	-0.05 (-0.06, -0.05)	<0.001	-0.10 (-0.12, -0.09)	<0.001
Logical Memory Delayed Recall	0.55 (-0.05, 1.15)	0.071	-0.10 (-0.11, -0.08)	<0.001	0.00 (-0.02, 0.02)	0.861
CDR-Sum of Boxes	-0.81 (-1.06, -0.55)	<0.001	0.05 (0.04, 0.05)	<0.001	0.11 (0.10, 0.12)	<0.001
Categorical time Models	**Sleep Disturbance**					
Cognitive Profiles	Beta (95%CI)	P-Value				
PACC (z score composite)	-0.37 (-1.16, 0.42)	0.363				
MMSE	-0.40 (-0.82, 0.03)	0.069				
Logical Memory Delayed Recall	0.28 (-0.51, 1.07)	0.492				
CDR-Sum of Boxes	0.04 (-0.29, 0.37)	0.805				

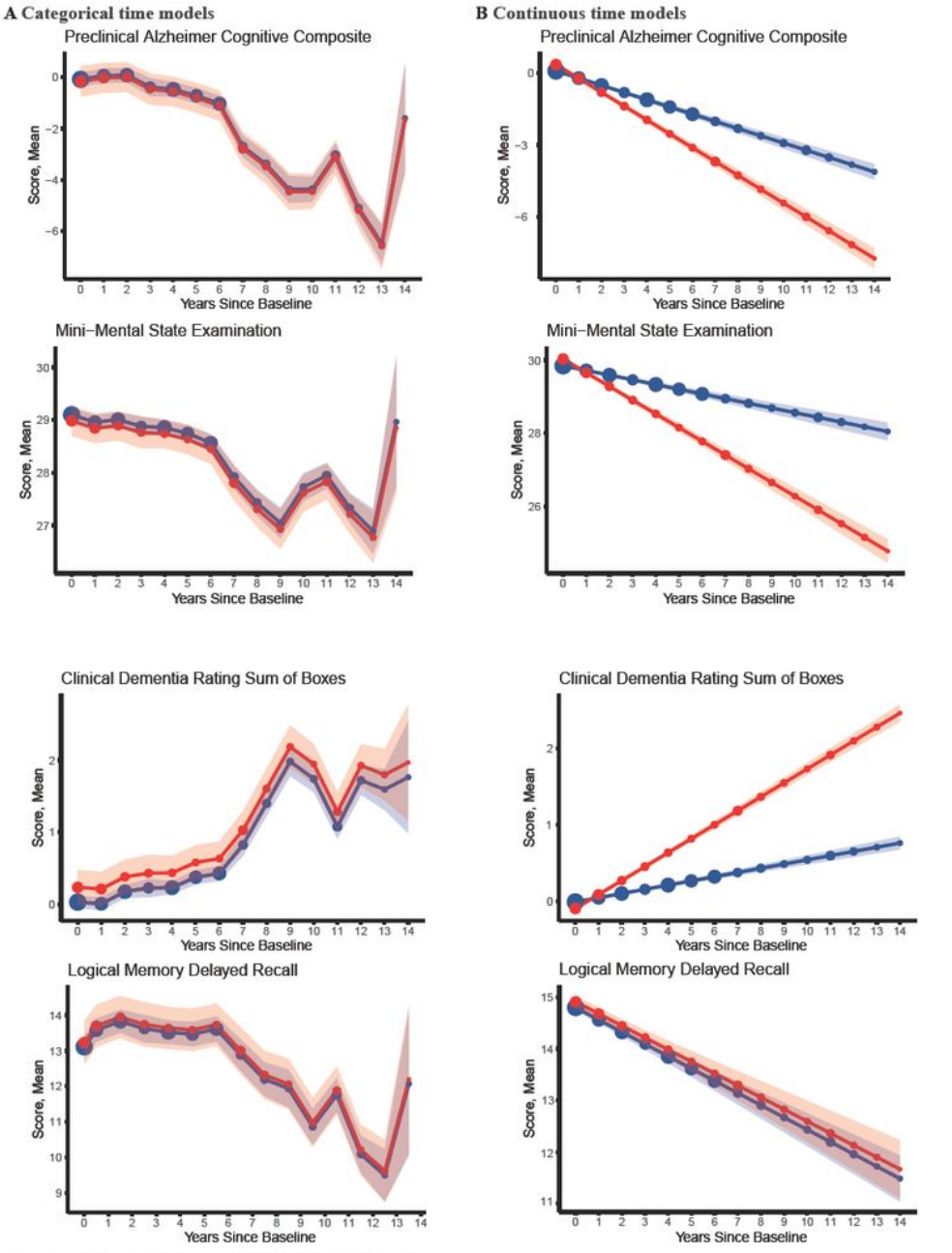
Table 3
Relationship of amyloid markers Profiles and FDG to Sleep Disturbance in the Continuous time Models and Categorical time Models

Continuous time Models	**Sleep Disturbance**		**Time**		**Sleep Disturbance*Time**	
Amyloid markers and FDG	Beta (95%CI)	P-Value	Beta (95%CI)	P-Value	Beta (95%CI)	P-Value
CSF Aβ42	-31.40 (-81.12, 18.32)	0.216	-9.54 (-11.51, -7.56)	<0.001	6.50 (2.96, 10.03)	<0.001
Amyloid PET SUVR	0.00 (-0.02, 0.02)	0.809	0.00 (0.00, 0.00)	<0.001	0.00 (0.00, 0.00)	0.305
FDG	0.00 (-0.02, 0.02)	0.974	-0.01 (-0.01, 0.00)	<0.001	0.00 (0.00, 0.00)	0.091
Categorical time Models	**Sleep Disturbance**					
Amyloid markers and FDG	Beta (95%CI)	P-Value				
CSF Aβ42	26.66 (-36.68, 90.00)	0.409				
Amyloid PET SUVR	0.02 (0.00, 0.05)	0.105				
FDG	-0.01 (-0.04, 0.01)	0.298				

Table 4
Relationship of Neurodegeneration Profiles to Sleep Disturbance in the Continuous time Models and Categorical time Models

Continuous time Models	**Sleep Disturbance**		**Time**		**Sleep Disturbance*Time**	
Neurodegeneration Profiles	Beta (95%CI)	P-Value	Beta (95%CI)	P-Value	Beta (95%CI)	P-Value
CSF t-Tau	2.05 (-9.82, 13.93)	0.735	2.53 (2.22, 2.84)	<0.001	0.52 (-0.05, 1.09)	0.076
CSF p-Tau	0.34 (-0.95, 1.63)	0.609	0.30 (0.27, 0.33)	<0.001	0.00 (-0.06, 0.06)	0.999
Hippocampal Volume	-0.01 (-0.01, 0.00)	0.090	0.00 (0.00, 0.00)	<0.001	0.00 (0.00, 0.00)	0.129
Ventricular Volume	-0.06 (-0.19, 0.07)	0.342	0.09 (0.09, 0.09)	<0.001	0.01 (0.01, 0.02)	<0.001
Categorical time Models	**Sleep Disturbance**					
Neurodegeneration Profiles	Beta (95%CI)	P-Value				
CSF t-Tau	8.66 (-4.59, 21.92)	0.200				
CSF p-Tau	0.89 (-0.52, 2.30)	0.216				
Hippocampal Volume	-0.01 (-0.02, 0.00)	0.034				
Ventricular Volume	0.07 (-0.08, 0.22)	0.345				

Figures



No of participants, by Insomnia Disorder (0-14 Years)

Year	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
SD	106	93	54	42	37	27	26	67	31	22	14	37	19	17	2
NS	357	186	219	97	236	169	193	56	48	23	27	59	32	10	6

Profiles are from linear mixed-effects models controlling for age and other baseline covariates selected by Akaike Information Criterion. Shaded regions indicate 95% CI. Dot sizes are proportional to the number of observations. Continuous time models include a quadratic term.

Figure 1

Mean Cognitive Profiles by marginal effect estimation in linear mixed models.

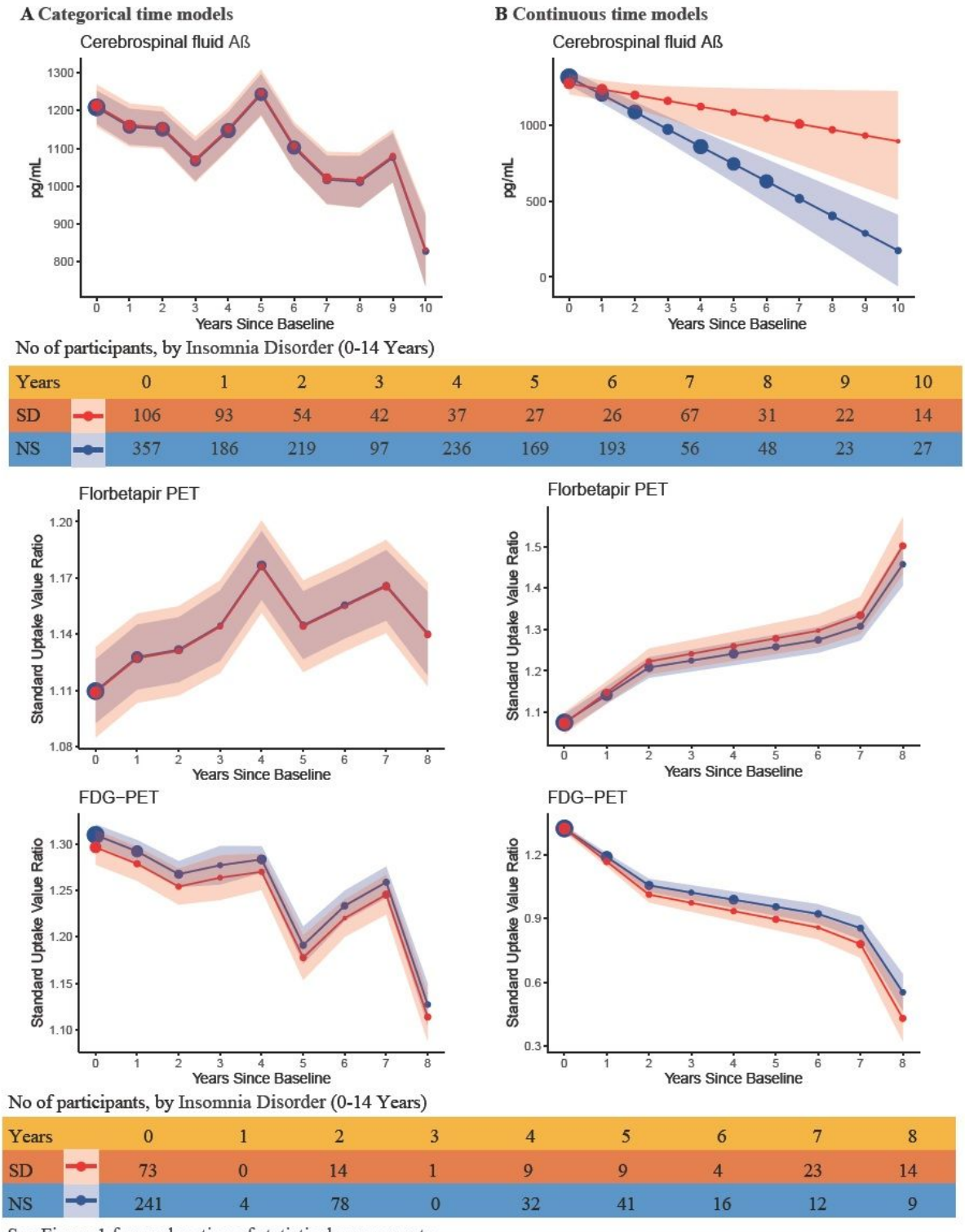


Figure 2

Mean Profiles of Markers of Amyloid (Cerebrospinal Fluid Aβ and Florbetapir PET) and Glucose Metabolism (FDG-PET) by marginal effect estimation in linear mixed models.

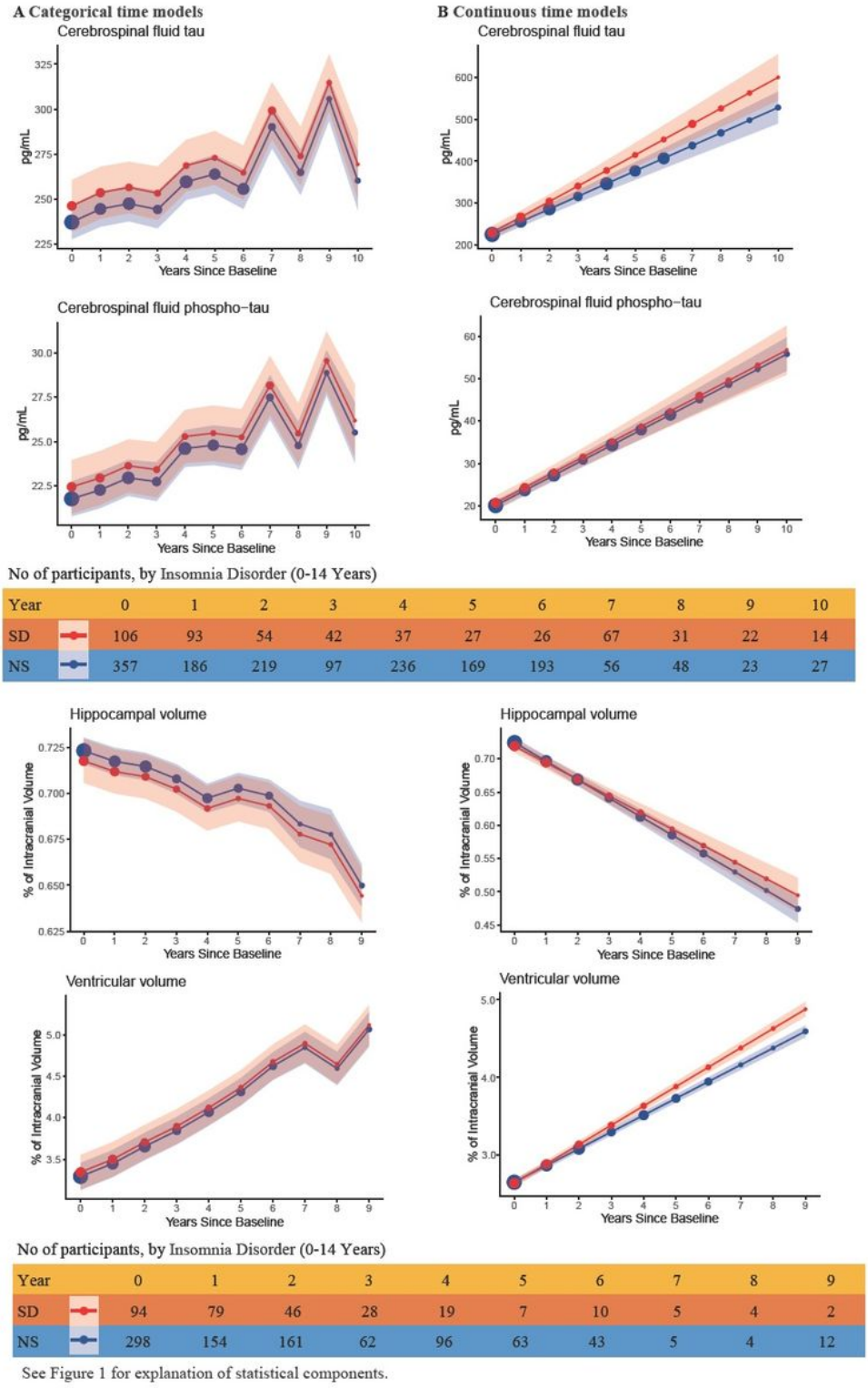


Figure 3

Mean Profiles of Neurodegeneration Markers by marginal effect estimation in linear mixed models.

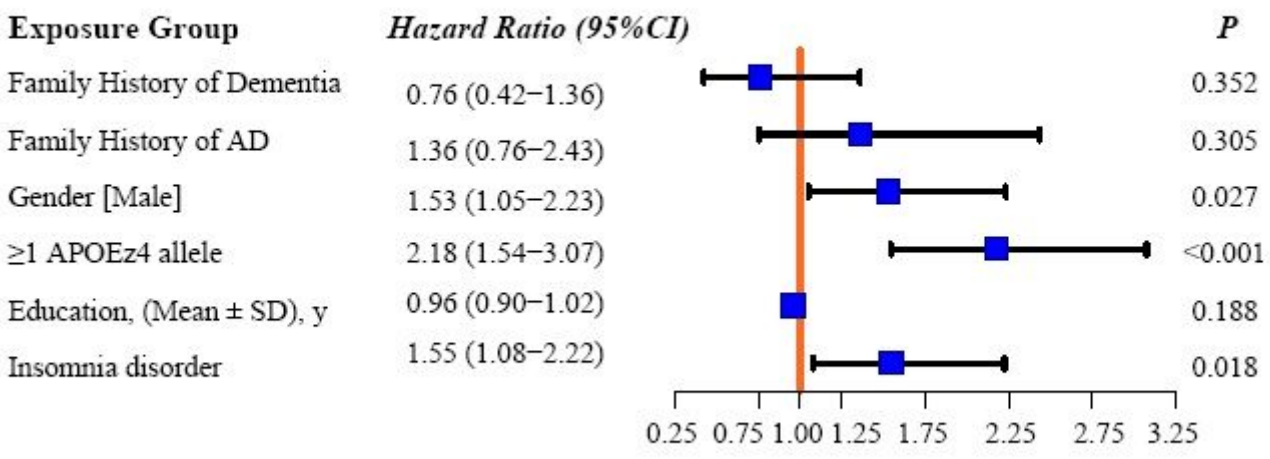


Figure 4

The hazard ratio of insomnia disorder for the AD in the Cox regression model.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.docx