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Sleep Disturbance and the Risk of Cognitive Decline or Clinical Conversion in the ADNI Cohort

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Abstract

Background: We investigated the relationship between sleep disturbance and cognitive decline or clinical conversion in individuals with normal cognition (CN), as well as those with mild cognitive impairment (MCI) and dementia due to Alzheimer's disease (AD-dementia).

Methods: Secondary analysis of 1,629 adults between 48 and 91 years old with up to 24 months of follow-up from the Alzheimer's Disease Neuroimaging Initiative, a longitudinal cohort study.

Results: Sleep disturbance was not associated with decline in memory, executive function, or global cognition. The presence of sleep disturbance did not significantly increase the risk of diagnostic conversion in CN, early MCI, or late MCI participants.

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Conclusion: This study investigated the effect of sleep disturbance on cognitive decline using several outcomes and does not support the hypothesis that sleep disturbance predicts subsequent cognitive decline.

Keywords

ADNI; Alzheimer's Disease; sleep; sleep disruption; memory; executive function

I. Objective

Sleep disturbances are found at all stages of Alzheimer's disease (AD) and are common in both patients with mild cognitive impairment (MCI) and dementia due to AD [1–4]. Among patients with AD, up to 44% experience either increased daytime sleepiness or difficulty sleeping at night [5]. Furthermore, sleep disturbances are a major contributor to the decision to institutionalize older individuals [6]. Investigating the association between sleep disturbance and cognitive decline may help define the role of sleep disturbance in neurodegenerative disease.

Several biomarker studies have supported the hypothesis that sleep disturbance is related to the pathogenesis of AD [7]. In healthy middle-aged men, a single night of unrestricted sleep has been reported to lead to a 6% decrease in CSF amyloid-β (Aβ) 42, whereas one night of sleep deprivation prevented this decrease [8]. Furthermore, shorter sleep duration and poor sleep quality have been associated with greater Aβ burden in older adults [9]. Together, these studies suggest that sleep may aid in the clearance of Aβ, while disrupted sleep may lead to Aβ accumulation that causes neurodegeneration due to AD.

Speculation that disrupted sleep may be involved in the pathogenesis of AD is also supported by preclinical studies using mouse models in which sleep deprivation has been associated with memory impairment and synaptic loss [10]. Furthermore, Aβ levels in the interstitial fluid of both wild-type and transgenic-AD mice has been observed to fluctuate with diurnal sleep patterns and to increase with sleep deprivation and infusion of orexin, a neuropeptide that regulates wakefulness. A similar pattern has been seen in the CSF of young, cognitively normal (CN) humans [11]. A study of two-photon imaging in mice has suggested that natural sleep or anesthesia induces fluxes of brain interstitial fluid that increases Aβ clearance [12].

The effect of disrupted sleep on cognition in CN adults has been evaluated in several cross-sectional and longitudinal cohort studies. These investigations have used both continuous and dichotomous measures of cognitive decline and have largely indicated that disrupted sleep in CN individuals increases the risk of cognitive decline [13–18]. Sleep disturbance has also been linked with increased risk of cognitive decline in individuals with already existing cognitive impairment. Nighttime behavioral disturbances, either disrupted nighttime sleep or daytime sleeping, increase the risk of progression from MCI to AD [19] and individuals with AD who had nighttime behavioral disturbances had increased mortality [20].

To further investigate the association between sleep disturbance and AD, we utilized data collected as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI is an observational study of aging which enrolls individuals diagnosed as CN, early MCI (EMCI), late MCI (LMCI), or AD-dementia which allowed a robust assessment of risk across various diagnostic groups. We assessed the effect of sleep disturbance symptoms on both the change in cognitive performance over time, as well as the risk of progression to a more advanced stage of disease.

II. Methods

Data were obtained from the ADNI database (adni.loni.usc.edu) on 9/28/2014. ADNI was launched in 2003 as a public-private partnership, led by Michael W. Weiner, MD. All participants have given their informed consent and the study protocol has been approved by the committee on human research at each participating institution. At the time of download, the dataset contained 1629 adults (48 to 91 years old) with baseline data: 418 CN, 308 EMCI, 561 LMCI, and 342 AD-dementia. Detailed information describing diagnostic criteria can be found at www.adni-info.org. CN subjects had no memory complaints, normal memory performance, and absence of impairment in cognitive or function. EMCI subjects had a subjective memory concern, mildly abnormal memory performance, and preserved functional performance such that a diagnosis of AD-dementia could not be made. LMCI subjects had a subjective memory concern, memory performance that was abnormal and below that of EMCI subjects [21], and preserved functional performance such that a diagnosis of AD-dementia could not be made. AD-dementia subjects had a subjective memory concern, abnormal memory performance, and functional impairment meeting NINCDS/ADRDA criteria for probable AD [22].

Outcomes

Presence of sleep disturbance was determined by caregiver report on the Neuropsychiatric Inventory (NPI) or a brief questionnaire form of the NPI (NPI-Q). The NPI is a retrospective (up to 1 month) caregiver-informant interview that investigates 12 neuropsychiatric symptom domains: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, nighttime behavioral disturbances, and appetite/eating disturbances [23]. A sleep disturbance symptom prior to conversion was considered to be present if a caregiver-informant reported the symptom during the study prior to conversion from CN to MCI, or MCI to AD-dementia. Since neuropsychiatric symptoms are more common among individuals with MCI and AD-dementia compared to those who are CN, symptoms reported at the conversion visit or the last study visit were excluded to minimize reverse causation. The primary outcomes used in this analysis included the AD Assessment Scale-cognitive sub-scale (ADAS11), a measure of global cognition, as well as a composite score of memory (ADNI-Mem) and a composite score of executive function (ADNI-EF) [24–26]. As an additional, primary outcome visit diagnosis was used to determine if a subject converted from CN to MCI (early or late) or MCI to AD-dementia. MMSE, Clinical Dementia Rating Scale sum of boxes (CDRsb), Geriatric Depression Scale (GDS), apolipoprotein E (*APOE*) genotype, medication use data, and medical comorbidities listed in Table 1 were utilized to

characterize the study cohort. Sedative/hypnotic use was defined as use of a benzodiazepine or non-benzodiazepine GABA agonist for at least 1-month prior to conversion.

Statistical Analyses

Independent analyses were performed for each of the 4 baseline cognitive diagnoses: CN, EMCI, LMCI, or AD-dementia. A dichotomous variable was assigned as either positive for a sleep disturbance symptom prior to conversion (PSD), or negative for a sleep disturbance symptom prior to conversion (NSD). A comparison of baseline characteristics, including sleep disturbance, age, sex, level of education, sedative/hypnotic use, *APOE* genotype, CDR, MMSE, and ADAS11, as well as comorbidities of hypertension, diabetes, hypercholesterolemia, and coronary artery disease, for participants with 24 months of follow up data and those without 24 month follow up data was performed to assess for sources of attrition bias. In addition, a comparison of baseline characteristics between those with sleep disturbance symptoms and those without sleep disturbance symptoms prior to conversion was performed. Analysis of variance was used for continuous outcome variables and χ^2 testing for categorical outcome variables.

To determine if differences in cognitive decline were dependent on presence of sleep disturbance prior to conversion, three repeated measures linear mixed models were used with ADAS11, ADNI-Mem, or ADNI-EF as the outcome variable and the interaction of sleep disturbance and time as the main explanatory variable. Age, sex, *APOE* genotype, education level, and sedative/hypnotic use were included as covariates since these are known risk factors for MCI or dementia that are routinely included in statistical models [27,28].

Survival curves of conversion from CN to MCI or AD-dementia, as well as conversion from MCI to AD-dementia were calculated using the Kaplan-Meier method. A Cox proportional hazards model was used to assess the risk of conversion based on sleep disturbance. The model used the same covariates as described above in addition to baseline ADAS11 score to adjust for disease stage. The confidence level for statistical inference was 95% (p<0.05). When interpreting statistical results, false discover rate (FDR) correction was applied since multiple outcome variables were assessed for each diagnostic group (ADNI-Mem, ADNI-EF, ADAS11, and conversion). Statistical analysis was performed using SPSS Statistics Version 21.0 (IBM Corp, Armonk, NY).

Power Analyses—For repeated measures linear mixed models, power analyses were performed using simulation with MATLAB R2015a and the Statistics Toolbox (The MathWorks, Inc., Natick, MA). Study data parameters were used for baseline mean cognitive scores (ADAS11, ADNI-EF, ADNI-Mem), standard deviation, and standard error of the parameter estimate for change in cognitive score over time. Presence of a sleep disturbance was the main explanatory variable and covariates were not included. For cox proportional hazards models, power analysis was performed using the proportion of subjects with PSD and the event rate for each baseline diagnosis[29]. Power Analyses were performed to assess the likelihood of a Type II error.

III. Results

Participant Characteristics

CN Participants.—Of the 418 CN participants who had a baseline visit, 66 (16%) were categorized as PSD. PSD participants were slightly younger compared to NSD participants (73.4 vs 75.0 years, p=0.040). There were no significant differences between PSD and NSD participants in sex, education, *APOE* genotype, sedative/hypnotic use, CDRsb, ADAS11, geriatric depression scale (GDS) score, or comorbid cardiovascular diagnoses at baseline (Table 1). There was no significant difference in the average follow-up time between PSD (22.6 months) and NSD (21.6 months) groups (p=0.158). Supplemental Table 1 contains a detailed summary of demographics stratified by diagnostic group and attrition.

EMCI Participants.—Of the 308 EMCI participants who had a baseline visit, 118 (38%) were categorized as PSD. PSD subjects were slightly older (72.5 vs 70.4 years, p=0.018) and less educated (15.5 vs 16.2 years, p=0.018) compared to NSD participants. PSD subjects were more likely to have *APOE ε4* alleles (p=0.013). In addition, PSD subjects were more likely to be taking a sedative/hypnotic medication (17.8% vs 10.0%, p=0.048), had a slightly higher CDRsb (1.4 vs 1.2, p=0.024), and slightly higher GDS scores (2.0 vs 1.7, p=0.038). There were no significant differences between PSD and NSD participants in sex, ADAS11, or comorbid cardiovascular diagnoses at baseline (Table 1). There was no significant difference in the average follow-up time between PSD (21.3 months) and NSD (19.6 months) groups (p=0.070).

LMCI Participants.—Of the 561 LMCI participants who had a baseline visit, 190 (34%) were categorized as PSD. PSD subjects were more likely to be taking a sedative/hypnotic medication (10.0% vs 4.0%, p=0.005) and had slightly higher GDS scores (1.0 vs 1.4, p<0.005). There were no significant differences between PSD and NSD participants in age, sex, education, ADAS11, *APOE* genotype, CDRsb, ADAS11, or comorbid cardiovascular diagnoses at baseline (Table 1). There was no significant difference in the average follow-up time between PSD (20.9 months) and NSD (20.1 months) groups (p=0.215).

AD-dementia Participants.—Of the 342 AD participants who had a baseline visit, 153 (45%) were categorized as PSD. There were no significant differences between PSD and NSD participants in age, sex, education, ADAS11, *APOE* genotype, CDRsb, ADAS11, GDS score, sedative/hypnotic use, or comorbid cardiovascular diagnoses at baseline (Table 1). In AD participants, the PSD group had a significantly longer average follow-up time (17.8 months) compared to the NSD group (14.5 months (p=0.002).

Association between Sleep Disturbance and Longitudinal Cognitive Performance: Linear Mixed Models

The association between sleep disturbance and change in memory, executive function, or composite cognitive performance over time was investigated using a linear repeated measures mixed effects model with presence of sleep disturbance (PSD vs NSD) as the main explanatory variable and either change in ADNI-Mem score, change in ADNI-EF score, or change in ADAS11 score over time as the outcome variable (Table 2). Covariates included

sex, *APOE* ε4 allele number, education level and sedative/hypnotic use, as well as all of their interactions with time (Supplemental Table 2).

CN Participants.—Within the CN sample, there was no significant decline in cognition over time as measured by ADNI-Mem (PE=−0.001, p=0.664), ADNI-EF (PE=0.015, p=0.361), and ADAS11 (PE=−0.038, p=0.634). The PSD and NSD groups did not differ in any measure of longitudinal cognitive performance, including ADNI-Mem, ADNI-EF, or ADAS11 (Figure 1).

EMCI Participants.—Within the EMCI sample, there was no significant decline in cognition over time as measured by ADNI-Mem (PE=0.014, p=0.053), ADNI-EF (PE=0.017, p = 0.146), and ADAS11 (PE=0.002, p=0.765). The PSD and NSD groups did not differ in any measure of longitudinal cognitive performance, including ADNI-Mem, ADNI-EF, or ADAS11 (Figure 1).

LMCI Participants.—Within the LMCI sample, there was no significant decline in cognition over time as measured by ADNI-Mem (PE=−0.006, p=0.722), ADNI-EF (PE=−0.011, p=0.281), and ADAS11 (PE=0.107, p=0.521). The PSD and NSD groups did not differ in longitudinal cognitive performance based on ADNI-Mem or ADNI-EF (Figure1). PSD was associated with a slower rate of ADAS11 increase (worsening) compared to the NSD group (Figure 1I, Table 2), but this was not significant after FDR correction for multiple comparisons (p=0.072).

AD-dementia Participants.—Within the AD-dementia sample, there was a significant decline in cognition over time as measured by ADNI-Mem (PE=−0.079, p<0.001), ADNI-EF (PE=−0.077, p<0.001), and ADAS11 (PE=1.649, p <0.001). The PSD and NSD groups did not differ in any measure of longitudinal cognitive performance, including ADNI-Mem, ADNI-EF, or ADAS11 (Figure 1).

In light of a previous report of non-demented adults [13,14], an additional analysis was performed as above with the exception that CN, EMCI, and LMCI were combined as a non-dementia cohort. PSD and NSD groups did not differ in longitudinal cognitive performance (Supplemental Table 3A).

Association between sleep disturbance and conversion: Cox Hazards Models

The association between sleep disturbance and risk of conversion to a more severe diagnostic group was investigated using Cox proportional hazards models with sleep disturbance as the main explanatory variable. Age, sex, *APOE* genotype, education level, sedative/hypnotic use, and baseline ADAS11 score were included as covariates (Supplemental Table 4).

Twenty-six out of 393 participants (6.6%) with a baseline diagnosis of CN and at least one follow-up visit progressed to a diagnosis of MCI (EMCI or LMCI) over the two-year follow-up period (367 censored). Eighteen out of 281 (6.4%) participants with a baseline diagnosis of EMCI and at least one follow-up visit progressed to a diagnosis of AD-dementia (263

censored). One hundred and ninety-nine participants (36.9%) with a baseline diagnosis of LMCI and at least one follow-up visit progressed to AD-dementia (341 censored).

In the CN participants, PSD did not contribute to the risk of progression to MCI (HR=1.99, p=0.132, 95% CI for HR=0.813–4.918, Figure 2A). Notably, PSD did increase the risk of progression in the EMCI participants (HR 3.70, p=0.024, 95% CI for HR=1.19–11.52), but this finding was not significant after FDR correction for multiple comparisons (p=0.096). Finally, in the LMCI participants, PSD did not contribute to the risk of progression to AD-dementia (HR=0.87, p=0.371, 95% CI for HR=0.64–1.18, Figure 2C).

As with continuous measures, an additional analysis was performed as above with the exception that CN, EMCI, and LMCI were combined as a non-dementia cohort. PSD did not contribute to the risk of progression to either MCI or AD-dementia (Supplemental Table 3B).

Power Analyses

Power analyses were performed to aid in interpretation of our results. Depending on baseline diagnosis, the study had 80% power to detect group differences of 0.33–0.68 ADAS11 per year, 0.029–0.048 ADNI-EF per year, and 0.021–0.045 ADNI-Mem per year using repeated measures linear mixed models. Power to detect group differences was estimated by simulation over a range of rates of decline (Supplemental Figure 1, Supplemental Table 5). For the Cox proportional hazards models, the study had 80% power to detect a HR of 4.5 for participants with a baseline diagnosis of CN, 3.9 for participants with a baseline diagnosis of EMCI, and 1.5 for participants with a baseline diagnosis of LMCI.

IV.   Discussion

We investigated the relationship between sleep disturbance and cognitive decline or conversion to a more advanced cognitive diagnosis in individuals who were CN or diagnosed with MCI or AD-dementia as part of the ADNI study. Overall, the presence of sleep disturbance symptoms did not affect the rate of decline in measures of global cognition, executive function, or memory performance. In addition, the presence of sleep disturbance symptoms did not increase the risk of conversion to a more advanced stage of disease. Since our analyses did not show a statistically significant effect of sleep disturbance on any measure, we performed power analyses to investigate the likelihood of a type II error. These analyses indicated that use of continuous measures with linear mixed models should be relatively sensitive compared to conversion (dichotomous) for detecting differences in cognitive decline between groups.

Our results differ from those of several previous prospective [13,15,16,18,19,30,31] or retrospective [32] cohort studies that reported an increased risk of cognitive decline and/or conversion to a more advanced stage of disease in individuals without dementia who have disrupted sleep. These studies have enrolled subjects who were CN [30,31] or not demented [13,15,16,18,19] and examined the risk for conversion to a more advanced diagnostic category [13,15,16,18,19,30–32] and—in one cohort, the Rush Memory and Aging Project —also measured cognitive decline [13,16]. In addition, sleep disturbance had an additive

effect to increase risk in individuals who carried a copy of the *APOE e4* allele [33]. An advantage of our design—and that employed in the Rush Memory and Aging Project [13,16] —is the combined use of disease stage and measured cognitive outcomes. To mitigate the risk of a ceiling effect when measuring cognitive change over time, we utilized multiple cognitive outcomes that together are sensitive to cognitive changes in individuals [24–26].

Another advantage is the separate analyses by stage of disease, since different stages of disease may involve different degrees of diagnostic certainty and different rates of conversion/progression. Lim et al analyzed a single non-demented cohort [13,16], which likely encompassed our CN, EMCI, and LMCI groups. We therefore performed a post-hoc analysis, pooling these groups, but our results still differed. Another strength is our use of data from a multicenter study, which may enhance external validity. However, the ADNI cohort, like many samples recruited for observational studies of AD, is not nationally representative and may contain participants at disproportionate risk of cognitive decline. Because the attrition in ADNI is low over a 2 year follow up period, there is less risk of attrition bias (Figure 1). Finally, we controlled for confounders such as baseline cognitive performance, sedative/hypnotic use, and also used continuous measures of cognition that should be sensitive to changes over time, even prior to conversion to MCI or dementia.

Both questionnaire based sleep scales and actigraphy have been used to measure sleep disruption. Studies using actigraphy may have a strength of being objective measures that are not susceptible to recall bias. However, sleep scales such as the NPI [23] and Pittsburgh Sleep Quality Index [18] are subjective questionnaires that are validated and commonly used to measure sleep characteristics. One disadvantage of the NPI is that it cannot be used to determine the etiology of sleep disturbance (e.g. hypersomnia, insomnia, rapid eye movement sleep behavior disorder).

A major difficulty in the interpretation of studies in this field is the possibility of reverse causation--a common source of confounding in observational research [34]. In this setting, it may be difficult to dissociate whether sleep disruption modifies disease progression or is caused by AD and emerges as an early symptom. I.e., longitudinal studies that report a significant association may simply be identifying a feature of the disease, which is already well-established in cross-sectional studies [35].

Longitudinal studies that define sleep disturbance at baseline and then monitor participants for a sufficient follow-up period may be less susceptible to reverse causation. An important limitation of our study is thus the average follow-up period ranging from 16 months in participants with dementia at baseline to 22 months in participants with normal cognition at baseline. Many studies in this field have similar average follow-up periods ranging between 1 and 3.5 years [13,16,18,19,30]. Two studies with longer follow-up periods of 4.9 [15] and 7.3–7.7 years [31] examined conversion to MCI or AD dementia. Studies that utilize outcomes of incident MCI or dementia are likely to be particularly sensitive to reverse causation bias since the use of diagnostic conversion indicating dementia may lag behind the presence of cognitive or functional symptoms [34]. Longer follow up periods can help to minimize this bias and strengthen investigations of causality.

In summary, this study investigated the effect of sleep disturbance on cognitive and clinical outcomes and did not support the hypothesis that sleep disturbance is a risk factor for subsequent cognitive decline. These results raise important methodological questions about the evaluation of risk factors for clinical progression in AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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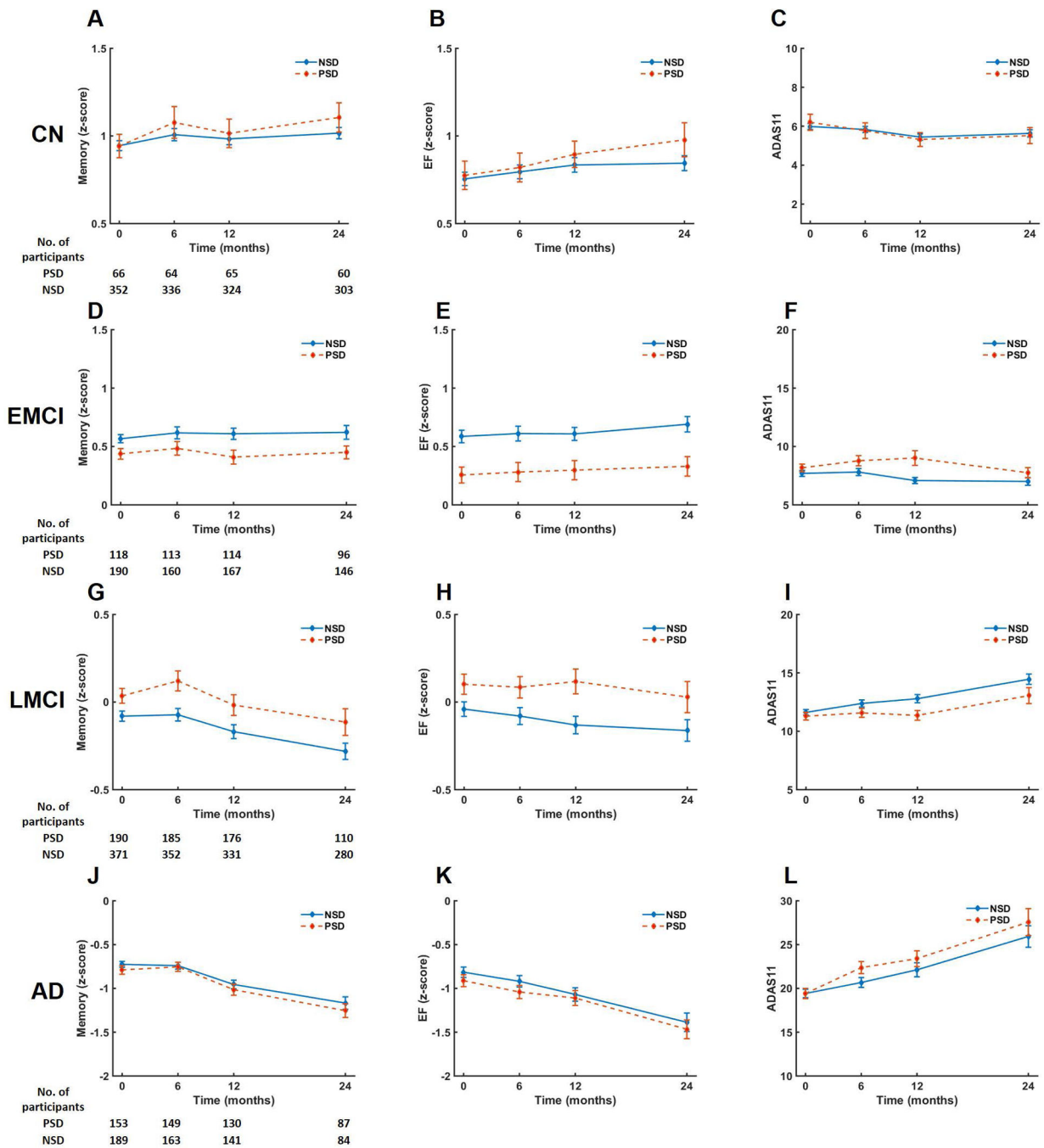
Figure 1: Change in cognition over time for participants with sleep disturbance (PSD) and without sleep disturbance (NSD).

Memory (ADNI-Mem), executive function (ADNI-EF), and global cognitive (ADAS-11) performance over time for PSD and NSD groups stratified by baseline diagnosis of cognitively normal (CN), early MCI (EMCI), late MCI (LMCI), or AD-dementia (AD). Repeated measures linear mixed models were used to compare the effect of sleep group (NSD or PSD) on change in cognitive outcome over time. The model was adjusted for age, sex, *APOE* genotype, education level, and sedative/hypnotic use. The confidence level for

statistical inference was 95% ($p < 0.05$). Plotted values are mean with error bars for standard error of the mean. FDR correction was performed for multiple comparisons.
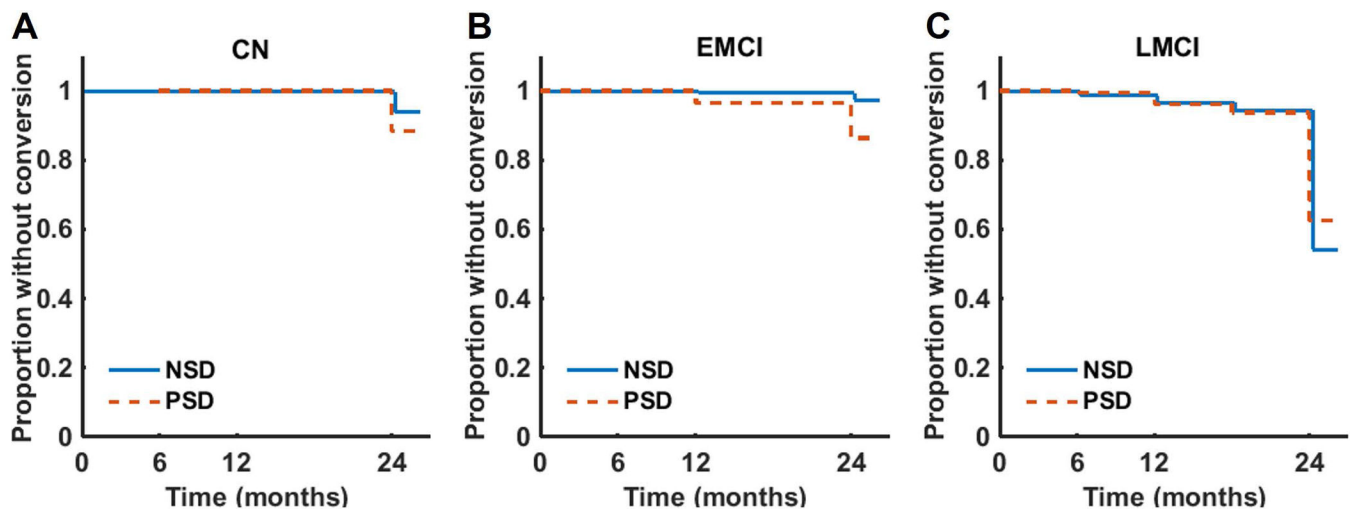
Figure 2: Conversion to a more impaired diagnostic group.
Survival curves were constructed using the Kaplan-Meier method. A Cox proportional hazards model was used to assess the time to conversion for individuals with a sleep disturbance (PSD) versus those without a sleep disturbance (NSD) prior to conversion. The model was adjusted for age, sex, *APOE* genotype, education level, and sedative/hypnotic use, as well as baseline ADAS-11 score to account for baseline disease stage. The confidence level for statistical inference was 95% ($p < 0.05$) and FDR correction was performed for multiple comparisons.

Table 1:

Participant Demographics

	CN			EMCI			LMCI			AD		
	PSD	NSD	p-value	PSD	NSD	p-value	PSD	NSD	p-value	PSD	NSD	p-value
n (%)	66 (16%)	352	-	118 (38%)	190	-	190 (34%)	371	-	153 (45%)	189	-
Age	73.4±5.3	75.0±5.8	0.04*	72.5±7.6	70.4±7.3	0.018*	73.1±8.2	74.4±7.2	0.057	75.7±7.6	74.4±7.9	0.115
Sex (% male)	51.5	49.7	0.788	56.8	54.7	0.726	63.7	59.8	0.376	58.2	52.9	0.331
Education	16.6±2.3	16.2±2.8	0.314	15.5±2.7	16.2±2.6	0.018*	16.0±2.8	15.8±3.0	0.656	15.5±3.0	15.0±3.0	0.110
APOE Genotype (%)												
e3e3	71.2	72.8	0.956	47.9	62.4	0.013*	48.7	44.1	0.472	36.6	31.4	0.418
e3e4	25.8	24.6	-	41.0	33.3	-	40.2	41.9	-	43.1	50.3	-
e4e4	3.0	2.6	-	11.1	4.3	-	11.1	14.1	-	20.3	18.4	-
Sedative/Hypnotic (%)	12.1	6.8	0.137	17.8	10.0	0.048*	10.0	4.0	0.005*	7.2	5.3	0.467
CDRsb	0.0±0.1	0.0±0.1	0.470	1.4±0.8	1.2±0.7	0.024*	1.7±1.0	1.6±0.9	0.485	4.6±1.7	4.3±1.7	0.079
ADAS-11	6.2±3.4	6.0±2.9	0.591	8.1±3.5	7.7±3.5	0.252	11.3±4.6	11.6±4.6	0.420	19.4±7.2	19.4±6.6	0.991
Comorbid Diagnoses (%)												
HTN	51.5	44.3	0.281	54.2	44.7	0.105	48.4	48.8	0.935	54.2	47.1	0.188
DM	7.6	7.4	0.957	11.9	10.0	0.607	8.9	7.8	0.644	8.5	10.6	0.516
CAD	3.0	3.1	0.968	3.4	3.2	0.911	4.2	3.8	0.801	3.9	1.6	0.180
GDS	0.9±1.2	0.7±1.1	0.218	2.0±1.6	1.7±1.5	0.038*	2.0±1.5	1.4±1.3	<0.0005*	1.7±1.4	1.6±1.5	0.436

PSD = positive for sleep disturbance symptoms, NSD = negative for sleep disturbance symptoms, CDRsb = Clinical Dementia Rating Scale - Sum of Boxes Score, ADAS-11 = Alzheimer's Disease Assessment Scale-Cognitive Subscale, HTN = Hypertension, DM = Diabetes CAD = Coronary Artery Disease, GDS = Geriatric Depression Scale, ANOVA for continuous outcomes presented as mean ±standard deviation, chi-square test for categorical outcomes,

*
p < .05

Table 2:

Effect of Sleep Disturbance on Change in Cognition over Time

	CN		EMCI		LMCI		AD-dementia	
	Parameter Estimate	*p-*value	Parameter Estimate	*p-*value	Parameter Estimate	*p-*value	Parameter Estimate	*p-*value
Memory	0.003	0.169	−0.001	0.542	0.000	0.799	0.002	0.335
EF	0.005	0.067	0.000	0.997	−0.001	0.440	−0.002	0.431
ADAS-11	−0.012	0.467	0.010	0.636	−0.047	0.018[*]	0.027	0.558

ADAS-11 = Alzheimer's Disease Assessment Scale-Cognitive Subscale, EF = Executive Function, Parameter Estimates and p-values are for a repeated measures linear mixed effects model, PE = parameter estimate,

[*] $p < .05$ prior to correction for multiple comparisons