Journal of Alzheimer's Disease xx (2022) x–xx
DOI 10.3233/JAD-215417
IOS Press

The Role of Amyloid, Tau, and *APOE* Genotype on the Relationship Between Informant-Reported Sleep Disturbance and Alzheimer's Disease Risks

Hyun Kim[a,b,*], Alina Levine[c], Daniel Cohen[b], Philip Gehrman[d,e], Xi Zhu[a,b], Davangere P. Devanand[a,b,f], Seonjoo Lee[c,g] and Terry E. Goldberg[a,b,h] on behalf of the Alzheimer's Disease Neuroimaging Initiative[1]

[a]*Department of Psychiatry, Columbia University Irving Medical Center, New York, NY, USA*
[b]*Division of Geriatric Psychiatry, New York State Psychiatric Institute, New York, NY, USA*
[c]*Division of Mental Health Data Science, New York State Psychiatric Institute, New York, NY, USA*
[d]*Department of Psychiatry, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA*
[e]*Mental Illness Research, Education, and Clinical Center, Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA*
[f]*Department of Neurology, Columbia University Irving Medical Center, New York, NY, USA*
[g]*Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY, USA*
[h]*Department of Anesthesiology, Columbia University Irving Medical Center, New York, NY, USA*

Accepted 31 March 2022
Pre-press 28 April 2022

Abstract.

Background: The association between sleep and Alzheimer's disease (AD) biomarkers are well-established, but little is known about how they interact to change the course of AD.

Objective: To determine the potential interaction between sleep disturbance and Aβ, tau, and *APOE4* on brain atrophy and cognitive decline.

Methods: Sample included 351 participants (mean age 72.01 ± 6.67, 50.4% female) who were followed for approximately 5 years as part of the Alzheimer's Disease Neuroimaging Initiative. Informant-reported sleep disturbance (IRSD) was measured using the Neuropsychiatric Inventory (NPI). Changes in magnetic resonance imaging (MRI)-measured AD signature brain regions and cognitive performance and IRSD's interaction with cerebrospinal fluid amyloid-β ($A\beta_{42}$) and p-Tau depositions and *APOE4* status were examined using the linear mixed models.

Results: Baseline IRSD was not significantly associated with the rate of atrophy after adjusting for covariates (age, sex, education, total NPI severity score, and sleep medications). However, there was a significant interaction between IRSD and

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

*Correspondence to: Hyun Kim, PhD, T32 Post-doctoral Fellow, Department of Psychiatry, Columbia University Medical Center, 1051 Riverside Drive, Clinic 1501, New York, NY 10032, USA. Tel.: +1 646 774 7202; E-mail: hk3141@cumc.columbia.edu.

AD biomarkers on faster atrophy rates in multiple brain regions, including the cortical and middle temporal volumes. *Post-hoc* analyses indicated that Aβ and p-Tau/Aβ predicted a faster decline in these regions/domains in IRSD, compared with biomarker-negative individuals with IRSD ($ps \leq 0.001$). There was a significant IRSD**APOE4* interaction for brain atrophy rate ($ps \leq 0.02$) but not for cognition.

Conclusion: IRSD may increase the future risk of AD by contributing to faster brain atrophy and cognitive decline when combined with the presence of AD biomarkers and *APOE4*. Early intervention for sleep disturbance could help reduce the risk of developing AD.

Keywords: All sleep disorders, Alzheimer's disease, cognitive aging, insomnia, volumetric MRI

INTRODUCTION

Alzheimer's disease (AD) affects 50 million people suffering from the disease globally and this number is expected to triple by 2050 [1]. It is increasingly important to understand the role of modifiable lifestyle factors that could be targeted for prevention or delay of AD, especially given that currently there is a lack of effective pharmacological treatment for AD [2].

Accumulating evidence suggests that sleep disturbance may be an important modifiable factor. Sleep contributes to brain health through tissue restoration and clearance of neurotoxins [3, 4]. Slow-wave activity (SWA) during non-rapid eye movement (NREM) sleep is particularly crucial for memory formation and consolidation [5, 6]. Furthermore, disruptions in the sleep-wake cycle have been associated with various pathways leading to AD, including accumulation of neurotoxins, such as amyloid-β (Aβ) and tau, as well as brain atrophy and cognitive impairment [7]. Sleep disturbance may be manifested as both short and long sleep duration, which could lead to pathologic brain aging and faster cognitive decline [8, 9]. However, the relationship between sleep and brain structure and functioning are complex, and little is known about how sleep disturbance could interact with AD biomarkers to result in adverse brain and cognitive outcomes.

Amyloid and tau deposition in the cortex and their reduction in the cerebrospinal fluid (CSF) are key AD biomarkers that contribute to the progression of other key markers for AD pathogenesis, such as neurodegeneration and cognitive decline [10, 11]. The potential role of AD biomarkers in sleep-related AD risk can be inferred based on their associations with both sleep and the brain. In animal and human clinical studies, sleep disturbance has been associated with Aβ and tau accumulation [3, 12–14]. Negative changes in sleep over time (shorter or excessive sleep quantity) from mid- to later-life could also predict higher Aβ burden in late life [15]. Sleep and these AD biomarkers potentially have a bidirectional relationship, such that accumulation of Aβ and tau could also modify the impact of poor sleep on the brain [7, 16].

Another AD risk marker that contributes to AD development is apolipoprotein ε4 genotype (*APOE4*). Interestingly, sleep disturbance is more prevalent in *APOE4* carriers compared with noncarriers [17], and recent studies demonstrated that *APOE4* moderates the relationship between sleep and Aβ accumulation in cognitively normal older adults [18]. Conversely, sleep has been shown to modify the relationship between *APOE4* and AD [19], suggesting that consolidated sleep may provide protection against biological mechanisms linking ε4 allele to neurodegenerative pathology. These findings indicate that there is an intricate mechanism linking *APOE4* and sleep that leads to accelerated brain and cognitive changes associated with AD.

Taken together, the mechanisms of how Aβ, tau, and *APOE4* contribute to AD risks appear to have a substantial overlap with how sleep disturbance impacts the brain. While previous studies have focused on AD biomarkers as a cause or a result of sleep disturbance [15, 16, 20, 21], no published studies examined how these AD biomarkers and genetic markers interact with disturbed sleep to impact long-term changes in the brain and cognition. Clarifying the roles of AD risk markers with large-scale datasets would be crucial for future practice of precision medicine for AD that considers one's genetic factors, Aβ/tau status, and lifestyle factors. The current study was designed to investigate the interplay between sleep disturbance and key AD biomarkers in a comprehensive dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We used reduced CSF $A\beta_{42}$ as a marker of Aβ deposition, given its function as an early biomarker of amyloid plaque and

its associations with sleep disruption [7, 22]. CSF p-Tau/Aβ_{42} was used to determine tau burden given that this demonstrates the best performance for prediction of clinical decline in MCI populations, compared with t-Tau or p-Tau alone [23–25]. This p-Tau/Aβ measure reduces measurement error that could arise from individual differences in CSF production and is likely more sensitive in detecting tau-related neurodegeneration and cognitive decline [26, 27]. Here we aim to test two hypotheses: 1) sleep disturbance would predict faster 5-year progression of AD risk, as measured by rates of brain atrophy and cognitive decline; and 2) the presence of *APOE4* and Aβ− and tau deposition would accelerate brain and cognitive changes in the presence of sleep disturbance.

METHODS

Study sample

Analyses for the current study were conducted using data from the ADNI (http://www.adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership and examines the progression of mild cognitive impairment (MCI) and AD through longitudinal assessments of MRI, PET, and other biomarkers, along with clinical and neuropsychological assessments.

A detailed description of the ADNI cohort has been previously published [28]. ADNI has recruited individuals with normal cognition (NC), MCI, and AD throughout its phases but only those with NC and MCI were considered for the present study. Qualifying MCI subjects had memory complaints, but no significant functional impairment, scored between 24 and 30 on the Mini-Mental State Examination (MMSE), had a global Clinical Dementia Rating (CDR) score of 0.5, a CDR memory score of 0.5 or greater and objective memory impairment on the Wechsler Memory Scale – Logical Memory II test [29]. Cognitively normal (CN) participants had MMSE scores between 24 and 30, a global CDR of 0 and did not meet criteria for MCI and AD. Inclusion and diagnostic criteria, as well as procedures and protocols, for the ADNI studies can be found on http://www.adni-info.org/Scientists/ADNIStudyProcedures.html.

For the current study, we included individuals with NC and MCI who had completed sleep measures [Neuropsychiatric Inventory (NPI)/Neuropsychiatric Inventory Questionnaire (NPIQ)], *APOE* genotype data, and CSF data (Aβ_{42} and p-Tau) at baseline and who had one or more follow up assessments three or more years after baseline assessments. Figure 1 describes how the final sample size was derived. The mean number of assessments was 5.2 with a standard deviation of 1.2. No data beyond that collected at five years post baseline was included. In the final sample of 384 participants, 197 (51.3%) were in the NC group and 187 individuals (48.7%) had MCI.

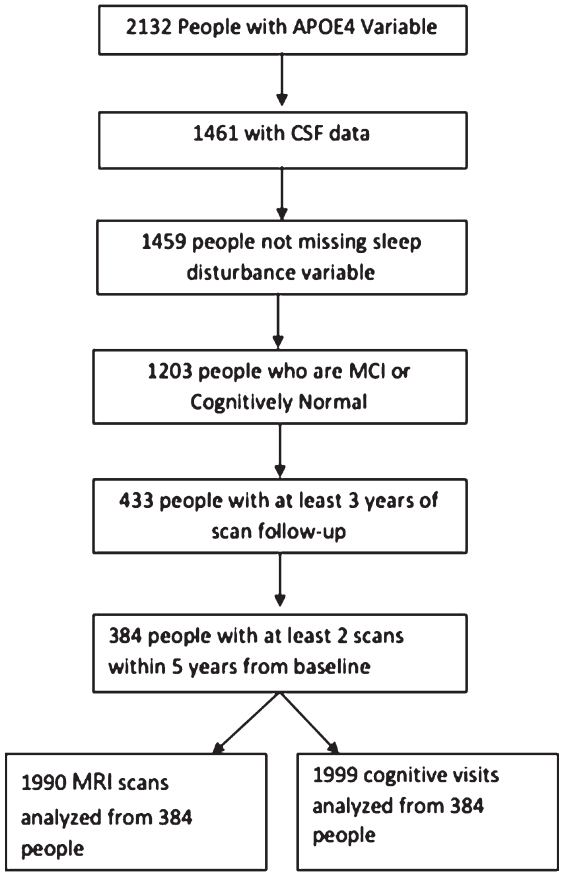

Fig. 1. Flowchart of the Participant Inclusion/Exclusion. Illustration of the inclusion/exclusion criteria for the final sample selection.

Standard protocol approvals, registrations, and patient consents

All procedures were approved by the Institutional Review Boards of all participating institutions. Written informed consent was obtained from every research participant according to the Declaration of Helsinki and the Belmont Report. For more up-to-date information, see http://www.adni-info.org.

Neuropsychiatric inventory/neuropsychiatric inventory questionnaire

The presence of sleep disturbance was assessed using the NPI and the NPI-Q. ADNI-1 used the NPI-Q while ADNI-GO/2 used the NPI. Both versions assess 12 neuropsychiatric symptoms, and the main difference between them is that NPI is conducted as a caregiver/informant interview whereas the NPI-Q is conducted in a questionnaire format. Severity and frequency ratings are highly correlated between NPI and NPI-Q [30].

The 12 symptoms in the NPI/NPI-Q include hallucinations, delusions, agitation/aggression, dysphoric/depression, anxiety, irritability, disinhibition, euphoria, apathy, and aberrant motor behavior. The informant is first asked to rate the presence of each symptom within the past 1 month with "yes" or "no", then if the answer is "yes," is asked to rate severity (range 0–3). For the current study, informant-reported sleep disturbance (IRSD) at baseline was determined to be present if the study partner endorsed having sleep disturbance (e.g., "Does the patient have difficulty sleeping? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?"). It was coded as absent if not endorsed by the partner, and individuals without IRSD were categorized as Good Sleepers. Additionally, the total severity score was calculated for both NPI and NPI-Q by summing up the severity ratings for all domains except for sleep and nighttime behaviors.

NPI or NPI-Q data from the baseline and all annual visits were obtained from the Laboratory of Neuroimaging Image Data Archive (LONI IDA).

CSF AD biomarkers

CSF $A\beta_{42}$ concentrations and p-Tau were measured in picograms per milliliter (pg/mL) by ADNI researchers using the highly automated Roche Elecsys immunoassays on the Cobas e601 automated system following extensive validation studies [31, 32]. The CSF data used in this study were obtained from the ADNI files 'UPENNBIOMK9_04_19_17.csv'. Detailed description of CSF acquisition (including lumbar puncture procedures), measurement, and quality control procedures were presented in http://adni.loni.usc.edu/methods/. We determined amyloid deposition using Aβ-positivity ("*A*β+") which was based on the cut-off value of 880 pg/ml [33]. CSF $A\beta_{42} < 880$ pg/ml was categorized as Aβ-negative ("*A*β−"). CSF p-Tau/$A\beta_{42}$ was examined to assess the interaction between sleep and tau, given that it is a robust biomarker for predicting clinical decline and conversion to AD, more so than tau alone [24]. CSF p-Tau/Aβ threshold was determined using pre-established cutoff of 0.028 to determine "high" versus "low" p-Tau/Aβ ratio [33].

Apolipoprotein E (APOE) genotyping

A detailed description of DNA extraction and processing procedures in ADNI data have been published previously [34]. For *APOE* genotyping, a 10 ml sample of peripheral blood was collected from each subject, and restriction enzyme isoform genotyping was performed on the extracted DNA to test for the presence of the *APOE* ε4 genotype. *APOE4* carriers were defined as participants who had one or more ε4 allele ("*APOE4*+"; ε4/ε4, ε4/ε3, ε4/ε2). Those without any ε4 allele (ε2/ε2, ε2/ε3, ε3/ε3) were categorized as *APOE4* non-carriers ("*APOE4*−").

Neuroimaging data and analysis

All imaging measures were downloaded on August 18, 2020. For internal consistency, T1-weighted MR images from 3T scanners were included for this project. All T1 images went through an automated quality control through MRIQC [35]. For the multiple available T1 images at the same visit, we selected the images with the best quality for further analysis. For all images that passed quality check, cross-sectional image processing was performed using FreeSurfer Version 7.1.1 (https://surfer.nmr.mgh.harvard.edu/). Region of interest (ROI)-specific cortical thickness and volume measures were extracted from the automated anatomical parcellation using the Desikan-Killiany Atlas [36] and Aseg Atlas [37] for cortical and subcortical ROIs. We also extracted the total intracranial volume (TIV) and used it as a covariate in the brain volumetric analyses.

For our focused interest on AD risk factors, we pre-determined AD signature regions from existing literature [38, 39] and selectively examined these areas as regions of interests. These regions included lateral ventricles, middle temporal lobe, hippocampus, posterior cingulate gyrus, temporal pole, entorhinal cortex, perirhinal cortex, parahippocampal gyrus, subcortical gray matter volume and cortex. Volumetric measures were performed for all subcortical regions and cortical regions including the middle temporal lobe and the cortex.

Cognitive performance

We used ADNI's pre-generated cognitive composite scores that were constructed based on bi-factor confirmatory factor analyses models [40]. Composite scores were used to determine performance on various cognitive domains: memory ("ADNI-MEM", including the Rey Auditory Verbal Learning Test, AD Assessment Schedule-Cognition [ADAS-Cog], MMSE, and Logical Memory), executive function ("ADNI-EF", including Category Fluency-animals, Category Fluency-vegetables, Trails A and B, Digit span backwards, WAIS-R Digit Symbol Substitution, and 5 Clock Drawing items (circle, symbol, numbers, hands, time), language ("ADNI-LAN", including the Boston Naming Test, Category Fluency-animals and vegetables, and language components from the MMSE and ADAS-Cog, and the Montreal Cognitive Assessment), and visuospatial functions ("ADNI-VIS", including 5 Clock Drawing items-Copy and items related to visuoconstruction from the MMSE and ADAS-Cog).

Other covariates

All covariates, including demographic information and clinical diagnoses (hypertension, NC/MCI) were determined during routine ADNI visits. For the current analyses, baseline characteristics were used as covariates except for the TIV, which was a time varying covariate. Use of sleep medication was defined as benzodiazepine and non-benzodiazepine sedatives/hypnotics use for at least 1 month prior to and during the baseline visit. Time from baseline to MRI/neuropsychological performance was calculated in years.

Statistical analyses

All analyses were performed using the LME package for the R software (R Core Team, 2014, Vienna, Austria), and p-values < 0.05 were considered to indicate statistical significance. Residuals diagnoses were made at the end of modeling. To compare sample characteristics between the control group and individuals with sleep disturbance, we examined group differences in continuous variables with 2 sample independent T-tests and categorical variables with chi-square tests.

All models testing interactions were linear mixed effect models with random subject level intercepts and slopes. The mixed effect models are designed to treat unbalanced data in longitudinal repeated measures design under the missing at random assumption [41]. To obtain the associations between IRSD and the rate of brain atrophy, we ran a model which had a time by sleep interaction along with a time and sleep term and we examined the coefficient for the time x sleep interaction term. Age, sex, education, hypertension, sleep medication (hypnotics/sedatives), time from baseline, and total NPI/NPI-Q severity scores were adjusted as covariates. Since we only focused on pre-specified regions of interests to confirm existing theories and find detectable patterns, we primarily focus on reporting the parameter estimates, their 95% confidence intervals and standardized effect sizes (Cohen's f^2) [42]. In addition to reporting p-values, we reported p-values after correcting multiple comparisons controlling false-discovery rate [43] by hypothesis.

The interaction terms between sleep disturbance, AD biomarkers (Aβ and p-Tau/Aβ ratio) and *APOE4*, and brain volumes/thickness outcomes were also measured using a linear mixed effect model. We included the three-way interaction between sleep disturbance, biomarkers and time, lower order interactions between those variables and a term for sleep and time, and examined the coefficient for the three-way interaction. *Post-hoc* analyses were conducted in the event that there was a trend level p-value ($p \leq 0.10$) for the three-way interaction between sleep disturbance, AD biomarkers, and outcome measures. Correction for multiple comparisons was not conducted for *post-hoc* analyses, given that these were performed for the purpose of interpretation.

All codes used for statistical analyses are presented in the Supplementary Material.

Data availability

ADNI datasets are available to the research community upon request at http://www.adni.loni.usc.edu. The processed imaging data are available for the qualified investigators upon request at E-mail: seonjoo.lee@nyspi.columbia.edu.

RESULTS

Characteristics of the study sample

The mean age of the entire study sample ($N = 384$) was 72.00 (SD = 6.66) years, and 51.30% were females. IRSD was reported in 64 individuals (16.67% of the study sample). Comparisons of the

Table 1
Demographic characteristics of the study sample by Control and Sleep Disturbance groups

	Total ($N = 384$)
Age (mean ± SD)	72.00 ± 6.66
Sex (n, %)	
Male	187 (48.7%)
Female	197 (51.3%)
Education (y) (mean ± SD)	16.36 ± 2.58
Hypertension (n, %)	167 (43.5%)
NPI/NPI-Q Total (mean ± SD)	0.98 ± 1.76
Sedative/Hypnotic use (n, %)	42 (10.9%)
Total Intracranial Volume (mean ± SD)	1452554.64 (±179241.45)
Aβ positivity (n, %)	131 (34.1%)
High p-Tau/Aβ (n, %)	123 (32.0%)
Cognitive Status (n, %)	
Normal Cognition	197 (51.3%)
Mild Cognitive Impairment	187(48.7%)

SD, standard deviation; NPI, Neuropsychiatric Inventory; NPI-Q, NPI Questionnaire; Aβ, amyloid-β; p-Tau, phosphorylated tau.

study sample by sleep disturbance groups indicated that there was a significantly greater proportion of MCI in the sleep disturbed group, compared to controls ($p = 0.007$) (Table 1). Additionally, the IRSD group had significantly greater NPI-Q severity score ($ps \leq 0.03$). Other demographic characteristics, including age and education, were not significantly different across groups, and both groups had comparable use of sedative/hypnotic medication use.

Sleep disturbance and brain atrophy/cognitive change over time

All observed brain regions, except for the temporal pole, exhibited significant atrophy over the 5-year follow-up period, along with enlargement of the lateral ventricles (data not shown) ($ps < 0.05$). Reduction in the temporal pole volume was marginally significant across time ($p = 0.07$). Baseline IRSD was not significantly associated with baseline brain volume differences, but baseline executive function (ADNI-EF) performance was significantly lower in the IRSD group ($\beta = -0.26$, $p = 0.01$). In longitudinal analyses, baseline IRSD was not significantly associated with the rate of atrophy in any of the observed regions after adjusting for age, sex, education, hypertension, use of sleep medication, time from baseline, and TIV (Supplementary Table 1).

Additionally, IRSD at baseline was marginally associated with changes in memory performance (ADNI-MEM, $\beta = -0.02$, $p = 0.05$) and language (ADNI-LAN, $\beta = -0.04$, $p = 0.08$) but not with changes in other cognitive domains.

The interaction between sleep disturbance and Aβ burden on brain/cognition

A total of 131 individuals (34.1%) were Aβ+ at baseline. Aβ+ proportions between IRSD and good sleepers were marginally different (45.3% and 31.9%, respectively, $p = 0.054$). Aβ deposition at baseline predicted a faster atrophy rate in the hippocampus, entorhinal cortex, parahippocampal gyrus, middle temporal cortex, and the overall cortex, along with faster enlargement of the lateral ventricles ($ps \leq 0.02$). Aβ deposition was also associated with a steeper decline in all cognitive domains (ADNI-MEM, ADNI-EF, ADNI-LAN, and ADNI-VS, $ps \leq 0.004$).

There was a significant interaction between sleep and Aβ burden on atrophy rate in the middle temporal cortex ($\beta = -0.01$, $p = 0.04$), parahippocampal gyrus ($\beta = -0.02$, $p = 0.04$), and the cortex ($\beta = -2749.22$, $p = 0.02$) (Supplementary Table 2). Further investigation on the effect of Aβ deposition on these regions indicated that being Aβ+ was associated with a greater atrophy in all of these regions when sleep disturbance was present ($ps \leq 0.007$) (Fig. 2).

In analyses with cognitive outcomes, Aβ+ status did not significantly interact with IRSD on any cognitive domains, but its interaction with IRSD was marginally significant in predicting a faster decline in attention/executive function decline (ADNI-EF, $\beta = -0.09$, $p = 0.07$) (Supplementary Table 2). *Post-hoc* analyses indicated that Aβ deposition was significantly associated with greater decline in these domains with the presence of IRSD, compared with the Aβ− group ($\beta = -0.13$, $p = 0.004$ for IRSD X Aβ+ in ADNI-EF) (Fig. 2).

The interaction between sleep disturbance and p-Tau/Aβ ratio on brain/cognition

A total of 123 individuals (32.0%) had high p-Tau/Aβ values according to the pre-defined cutoff. There was no significant difference between IRSD and good sleepers on the proportion of high p-Tau/Aβ ($p = 0.66$). High p-Tau/Aβ at baseline significantly predicted atrophy in all ROIs except for the temporal pole (which was marginally significant, $p = 0.05$) and posterior cingulate cortex ($p = 0.87$).

There was a significant interaction between IRSD and p-Tau/Aβ on the cortical volume ($\beta = 2271.67$, $p = 0.01$) (Supplementary Table 3). This interaction was marginally significant for the entorhinal cortex ($\beta = 55.17$, $p = 0.08$). Comparing IRSD and good

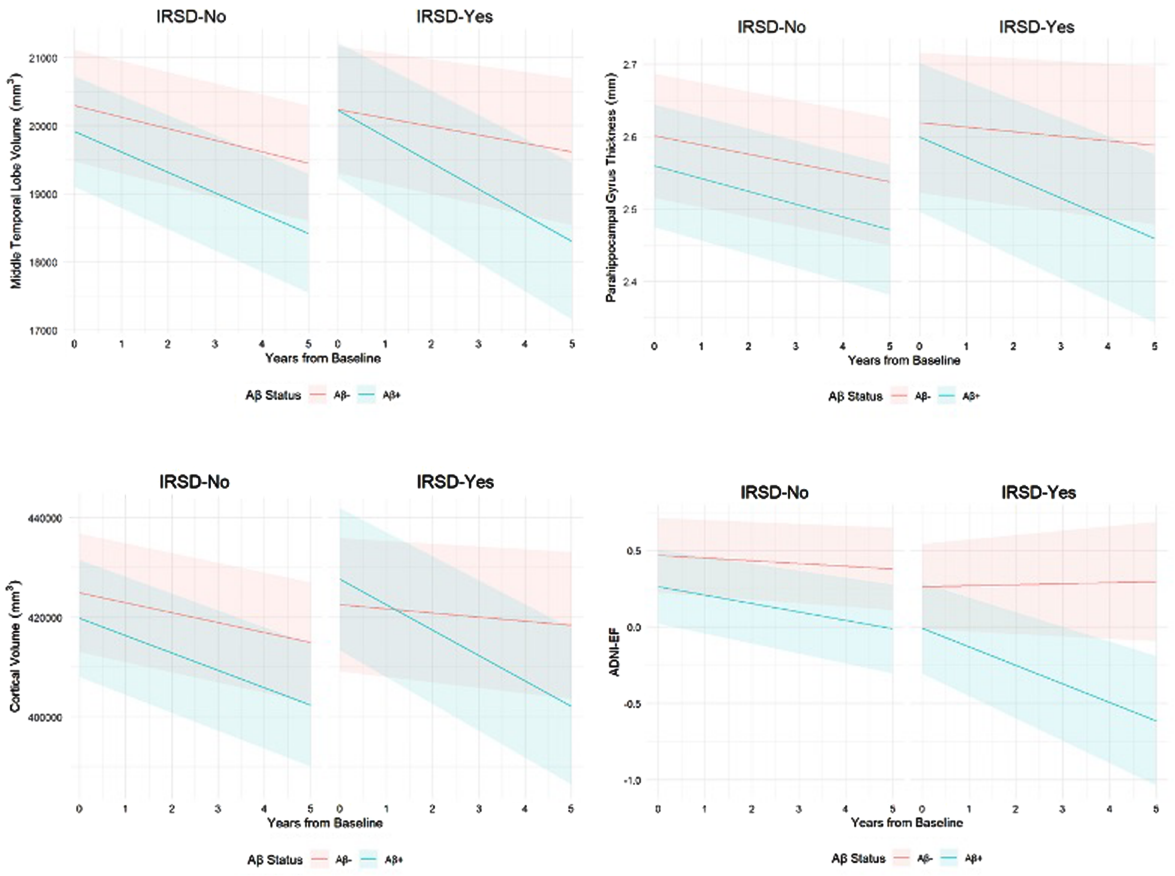

Fig. 2. Interactions between sleep disturbance and Aβ+ on cognitive changes. Amyloid deposition at baseline was associated with a greater atrophy in the cortex, parahippocampal gyrus, hippocampus, and middle temporal cortex when sleep disturbance was present ($ps \leq 0.007$).

sleepers separately, we found that there was a significant difference by p-Tau/Aβ ratio in both brain regions ($ps \leq 0.004$), with high p-Tau/Aβ predicting greater atrophy in IRSD (Fig. 3). IRSD and p-Tau/Aβ also interacted significantly on attention/executive functions (ADNI EF $\beta = 0.12$, $p = 0.02$), but not on any other domains (Supplementary Table 3, Fig. 3).

The interaction between sleep disturbance and APOE4 on brain/cognition

The *APOE4* allele was present in 117 good sleepers (36.6%) and 30 individuals with IRSD (46.9%). The effect of *APOE4*+ on brain atrophy was significant across most brain regions, including the hippocampus, middle temporal lobe, entorhinal cortex, parahippocampal gyrus, and the cortex, with positive status associated with more rapid atrophy ($ps \leq 0.046$) (data not shown). *APOE4*+ was also associated with faster declines in ADNI-EF, ADNI-MEM, and ADNI-LAN ($ps \leq 0.03$).

The interaction between IRSD and *APOE4*+ did not have a significant effect on brain atrophy ($ps \geq 0.10$) (Supplementary Table 4). Although the interactions between IRSD and *APOE4*+ were at the threshold for statistical significance on the middle temporal and total cortical volumes ($ps = 0.10$ for both), *post-hoc* analyses were performed to explore the potential *APOE4* effect in IRSD. Results showed that, within the IRSD group, *APOE4*+ had a significantly steeper atrophy rate in both middle temporal ($\beta = -217.78$, $p = 0.002$) and the cortical volumes ($\beta = -2412.31$, $p = 0.02$), compared to *APOE4*- (Fig. 4). The three-way interactions between sleep disturbance, *APOE*, and cognition were not significant ($p \geq 0.49$) (Supplementary Table 4).

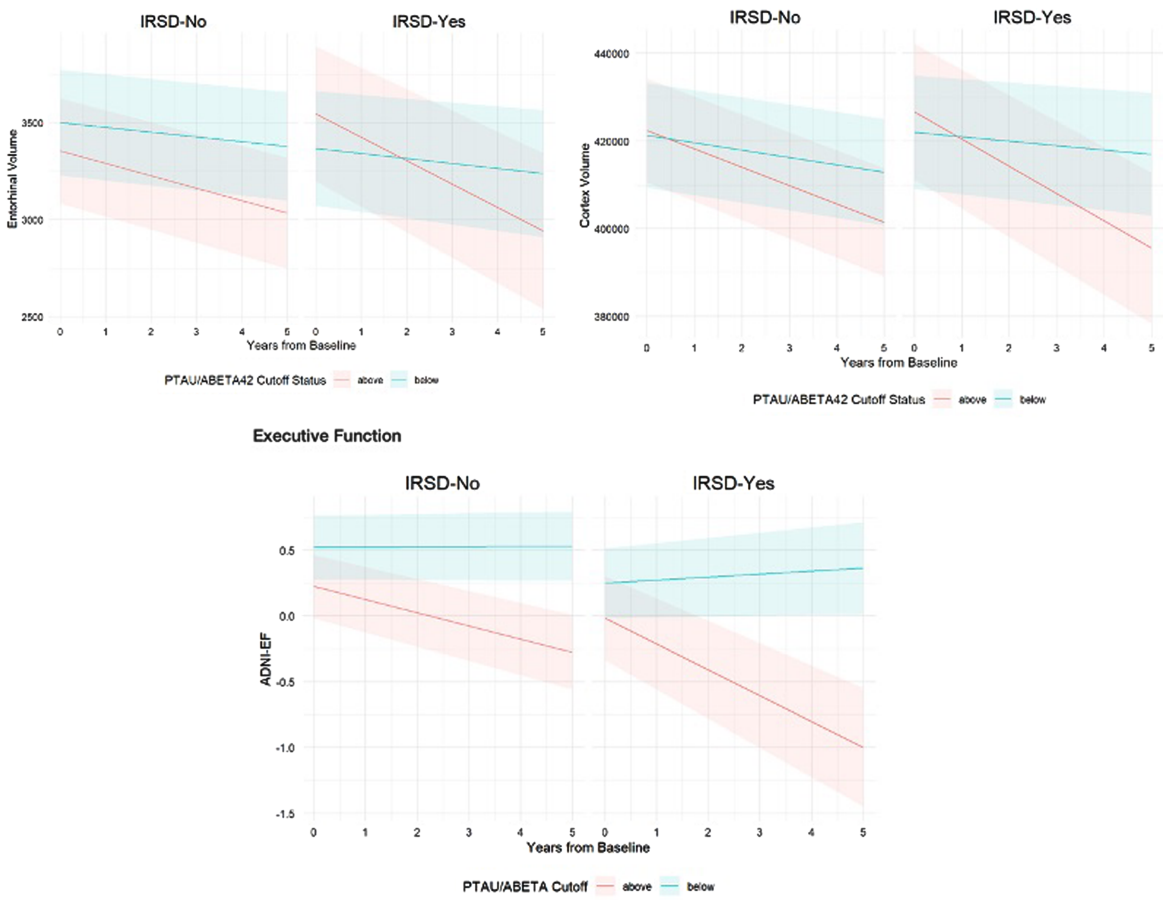

Fig. 3. Interactions between sleep disturbance and Aβ+ on cognitive changes. Amyloid deposition at baseline was associated with a greater decline in executive functions (ADNI-EF) and memory (ADNI-MEM) with the presence of sleep disturbance, compared with the Aβ− group ($ps \leq 0.0004$).

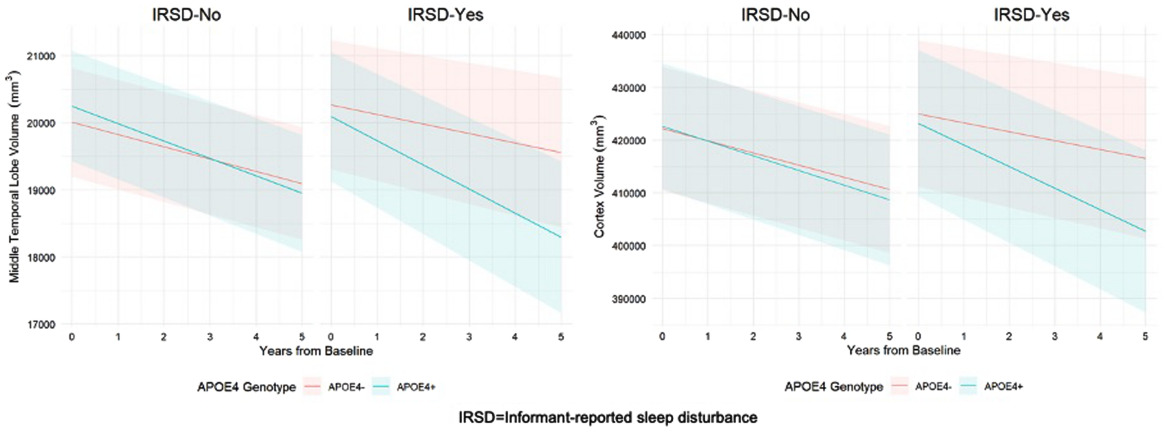

Fig. 4. Interactions between sleep disturbance and *APOE4* on brain changes. Within individuals with sleep disturbance, *APOE4+* had a significantly steeper atrophy rate in both middle temporal ($\beta = 215.04$, $p = 0.005$) and the cortical volumes ($\beta = 2479.57$, $p = 0.02$), compared to *APOE4-*.

DISCUSSION

The current study examined the effect of sleep disturbance on the rate of atrophy and cognitive changes after approximately 5 years of follow-up in a combined sample of cognitively healthy older adults and those with MCI. Although our results were not indicative of a significant association between informant-based sleep disturbance and greater brain atrophy or cognitive performance, further investigation with Aβ deposition, p-Tau/Aβ ratio indicated that these AD biomarkers interacted significantly with IRSD and led to accelerated changes in brain morphometry and cognition. *APOE4* also exhibited a significant interaction with IRSD and led to faster brain atrophy. While the brain regions impacted by the interaction of AD risk markers and IRSD differed slightly for each marker (e.g., the middle temporal volume with Aβ and the entorhinal cortex with p-Tau/Aβ interactions), global cortical atrophy stood out as a variable that was significantly impacted by all Aβ, tau, and *APOE* interactions. These findings provide evidence that AD risk markers may have significant roles in how sleep disturbance may impact cortical thinning as a whole, along with decline in cognitive performance. To the best of our knowledge, this is the first study to examine the interaction between sleep disturbance and key AD risk markers on longitudinal brain and cognitive changes. These results further suggest that good sleep may be protective even in the presence of Aβ or tau deposition and *APOE4* genotype.

The relationship between subjectively reported sleep disturbance and lower brain volume has been noted in healthy older adults [44–47] and older adults with MCI [48], and also longitudinally (i.e., sleep disturbance impacting increased cortical thinning rate) [9, 49, 50]. While the buildup of neurotoxic waste products and subsequent chronic inflammation are suggested as underlying mechanism, little is known about the role of Aβ and tau on sleep-related brain atrophy. Furthermore, brain regions impacted by sleep disturbance were inconsistent (frontal versus medial temporal regions) and neuroimaging findings were not transferrable to findings on cognitive functioning. Previous studies have produced inconsistent findings on how sleep impacts cognitive performance. Some studies [46, 51] found that individuals with sleep disturbance perform worse than controls on tasks measuring domains such as executive functioning, attention, and episodic memory while others have found null findings [52, 53]. Aside from heterogeneity in methodologies, we postulated that mechanisms underlying the sleep-brain and sleep-cognition relationships may be impacted by the contributions of biomarkers that are strongly associated with AD pathology. In that sense, understanding genetic or fluid biomarkers were critical for clarifying the complex associations between sleep and AD related outcomes.

The association of sleep disturbance with Aβ deposition is well established from animal studies [22] and in human younger adults and older adults in pre-clinical and clinical AD stages [15, 54]. One study by Molano and colleagues [55] found in their cross-sectional model that sleep efficiency and Aβ positivity significantly interacted to predict cognitive performance; however, these findings were circumscribed to Aβ, sleep, and cognitive performance. While Aβ-mediated tau progression could be the underlying mechanisms and tau is a stronger predictor of clinical symptoms of AD [4, 10], we further examined this topic using the p-Tau/Aβ ratio and found that high p-Tau/Aβ ratio also predicted faster progression of AD-like brain and cognitive changes. These findings indicate that the presence of Aβ and tau could modify sleep's impact on brain volume and cognitive functioning.

One possible mechanism underlying this phenomenon may be that sleep disturbance modifies the effects of Aβ and tau on the brain. Studies in cognitively normal older adults showed that sleep disturbance modulated the association between Aβ and cognition [56, 57], which may be linked with disruption in the NREM slow wave sleep. Disruption of the NREM could also increase Aβ accumulation [4], and cortical Aβ deposition has been associated with impairment in memory consolidation not directly, but through impairment in SWA [58]. Similarly, NREM slow-wave activity is known to have an inverse relationship with CSF tauopathy [59, 60]. This indicates that sleep disturbance may be associated with decreased SWA, leading to worse cognitive performance in those with amyloid and tau deposition. There is a need for large scale studies with in-depth sleep measures to fully disentangle these relationships.

Additionally, given that the relationship between sleep disturbance and AD biomarkers are bidirectional, it is also plausible that accumulation of Aβ and tau could negatively impact sleep and further advance pathologic brain aging [14, 59]. We cannot determine the direction of causality between AD biomarkers and IRSD from the current study design,

but we hypothesize that sleep disturbance could lead to Aβ and tau accumulation, which in turn, could negatively influence the sleep-wake cycle and disrupt NREM slow-wave activity that is important for cognitive functioning. Regardless of the sequential order of the events, our data suggest that the combination of sleep disturbance and Aβ/tau could accelerate AD-related brain and cognitive changes.

We also found a significant interaction between IRSD and *APOE* genotype on brain and cognitive changes. *APOE4* is believed to increase the risk of AD by increasing cellular vulnerability to oxidative damage, promoting the production of Aβ and phosphorylated tau protein, as well as facilitating neuroinflammatory processes [61]. Notably, recent studies indicated that healthy sleep could moderate the impact of *APOE4* on cognition and neuropathology [19, 62]. Other studies have also supported the moderating effect of *APOE4* on AD risk factors (Aβ and cognitive impairment) in sleep disturbance, which were defined as either actigraphy-based poor sleep quality or apnea-induced oxygen desaturation [63]. Our data demonstrated that individuals with *APOE4* genotype are more prone to greater brain atrophy in the cortex globally and in the middle temporal cortex when sleep disruption is apparent, though its impact on cognitive performance was not detected. Given that cognitive symptoms appear in the later stages of AD pathology, the role of *APOE4* may be clarified with a longer follow-up.

There is a significant overlap between the presence of *APOE4* and Aβ/tau deposition [61], but the current data were not adequately powered to conduct the three-way interaction between sleep, *APOE*, and AD biomarkers on neuroimaging/cognitive outcomes. Therefore, our statistical models do not take into account how the two biomarkers would interact to impact the relationship between sleep and AD pathology. There are also some methodological limitations, particularly with using the NPI/NPI-Q, that warrant careful interpretation of the study results. First, the timeframe of study visits and neuropsychiatric symptoms captured by the NPI/NPI-Q (i.e., the past month) may not adequately capture the intermittent symptoms that could be present during baseline and follow-up. This time frame also limits the assessment of how long sleep disturbance lasted from baseline. The use of NPI/NPI-Q also makes it difficult to identify what specific aspect of sleep disturbance (e.g., nighttime awakening, daytime sleepiness, sleep-disordered breathing) may forecast brain atrophy and cognitive decline. It is also possible that sleep disturbance represented by NPI/NPI-Q could indicate REM sleep disturbance presented in Lewy body disease, which is not investigated thoroughly in the current study. Despite the limitations of the NPI/NPI-Q, these measures have been widely used in epidemiologic studies (ADNI and NACC) due to their simple format and have represented sleep problems in large community-based samples [52, 64]. ADNI's rigorous exclusion criteria (i.e., depression, low education level), lack of racially/ethnically diverse samples, and drop-out rates also limit the generalization of our findings to a broader older adult population.

Despite these limitations, the major strengths of this study, including the use of comprehensive datasets of ADNI and long-term follow-up duration, allowed for a rigorous investigation of the relationship between sleep, AD biomarkers, and AD-related brain and cognitive changes, which is an understudied area in sleep and aging research. While we acknowledge that the causative relationship between sleep disturbance and AD outcomes cannot be determined with this study design, we hypothesize that sleep is a modifiable risk factor for the development of AD based on previous longitudinal studies examining adverse sleep characteristics and incident dementia with long term follow-up spanning midlife and later life (10 + years) [65]. Reverse causation has been also minimized through recent large-scale studies with Mendelian randomization analyses, which indicated causal effect of disturbed/short sleep on dementia and common medical comorbidities associated with dementia risk [66, 67]. Therefore, our findings suggest that sleep may be a powerful intervention tool for delaying or preventing the onset of AD, which has been a consistent and firm message in many sleep and aging research studies. The potential therapeutic implications of sleep treatments for AD are becoming especially important to consider given the failures of anti-amyloid immunotherapy in cognitive disorders [2]. It is notable that the effect sizes for our findings are small (e.g., IRSD x Aβ interaction explained 3% variance in the cortical atrophy). However, our sample is adequately powered to answer our research questions, and the heterogeneity and big proportion of unexplained variance in brain morphometric and cognitive changes are expected in multi-site, large-scale datasets as those in ADNI. Future studies with polysomnography and larger sample sizes that comprise a bigger MCI population may unveil potential associations between sleep, AD biomarkers, and the brain that are not observed in the current findings.

Longer follow-up duration spanning larger adult lifespan may also allow for detection of long-term effects of sleep on AD-related brain and cognitive changes, potentially beginning as early as midlife.

Conclusion

In summary, findings from this study imply that even a simple informant-based screening question to determine sleep disturbance in the primary care setting could imply the potential risk of accelerated brain morphometric and cognitive changes related to AD, particularly in the presence of Aβ deposition, tau accumulation, and *APOE4*. Older adults who report poor sleep and are at genetic/neuropathologic risk may be able to slow the progression of AD risks from targeted intervention approaches that include systemic treatment and monitoring of sleep symptoms.

ACKNOWLEDGMENTS

The authors thank all ADNI participants. This study is supported by the National Institute of Health (Grants 5T32MH020004, R01-AG062578-01A1).

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research &Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-5417r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-215417.

REFERENCES

[1] Alzheimer's Europe (2020) Dementia in Europe Yearbook 2019: Estimating the prevalence of dementia in Europe. https://www.alzheimereurope.org/content/download/195515/1457520/file/FINAL%2005707%20Alzheimer%20Europe%20yearbook%202019.pdf, Accessed January 24, 2021.

[2] Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H, Mohs R, Alzheimer's Disease Cooperative Study Steering Committee, Solanezumab Study Group (2014) Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* **370**, 311-321.

[3] Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, Fujiki N, Nishino S, Holtzman DM (2009) Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science* **326**, 1005-1007.

[4] Winer JR, Mander BA, Helfrich RF, Maass A, Harrison TM, Baker SL, Knight RT, Jagust WJ, Walker MP (2019) Sleep as a potential biomarker of tau and beta-amyloid burden in the human brain. *J Neurosci* **39**, 6315-6324.

[5] Mander BA, Rao V, Lu B, Saletin JM, Lindquist JR, Ancoli-Israel S, Jagust W, Walker MP (2013) Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat Neurosci* **16**, 357-364.

[6] Wunderlin M, Zust MA, Feher KD, Kloppel S, Nissen C (2020) The role of slow wave sleep in the development of dementia and its potential for preventative interventions. *Psychiatry Res Neuroimaging* **306**, 111178.

[7] Ju YE, Lucey BP, Holtzman DM (2014) Sleep and Alzheimer disease pathology–a bidirectional relationship. *Nat Rev Neurol* **10**, 115-119.

[8] Winer JR, Deters KD, Kennedy G, Jim M, Goldstein-Piekarski A, Poston KL, Mormino EC (2021) Association of short and long sleep during with amyloid-β burden and cognition in aging. *JAMA Neurol* **78**, 1187-1196.

[9] Spira AP, Gonzalez CE, Venkatraman VK, Wu MN, Pacheco J, Simonsick EM, Ferrucci L, Resnick SM (2016) Sleep duration and subsequent cortical thinning in cognitively normal older adults. *Sleep* **39**, 1121-1138.

[10] Jack CR, Jr., Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ,

Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol* **12**, 207-216.

[11] Bloom GS (2014) Amyloid-beta and tau: The trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol* **71**, 505-508.

[12] Shokri-Kojori E, Wang GJ, Wiers CE, Demiral SB, Guo M, Kim SW, Lindgren E, Ramirez V, Zehra A, Freeman C, Miller G, Manza P, Srivastava T, De Santi S, Tomasi D, Benveniste H, Volkow ND (2018) beta-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A* **115**, 4483-4488.

[13] Bubu OM, Brannick M, Mortimer J, Umasabor-Bubu O, Sebastião YV, Wen Y, Schwartz S, Borenstein AR, Wu Y, Morgan D, Anderson WM (2017) Sleep, cognitive impairment, and Alzheimer's disease: A systematic review and meta-analysis. *Sleep* **40**, doi: 10.1093/sleep/zsw032

[14] Holth JK, Fritschi SK, Wang C, Pedersen NP, Cirrito JR, Mahan TE, Finn MB, Manis M, Geerling JC, Fuller PM, Lucey BP, Holtzman DM (2019) The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* **363**, 880-884.

[15] Winer JR, Mander BA, Kumar S, Reed M, Baker SL, Jagust WJ, Walker MP (2020) Sleep disturbance forecasts beta-amyloid accumulation across subsequent years. *Curr Biol* **30**, 4291-4298.

[16] Fjell AM, Idland A, Sala-Llonch R, Watne LO, Borza T, Brækhus A, Lona T, Zetterberg H, Blennow K, Wyller TB, Walhovd KB (2018) Neuroinflammation and tau interact with amyloid in predicting sleep problems in aging independent of atrophy. *Cereb Cortex* **28**, 2775-2785.

[17] Koo KYG, Schweizer TA, Fischer CE, Munoz DG (2019) Abnormal sleep behaviours across the spectrum of Alzheimer's disease severity: Influence of APOE genotypes and Lewy bodies. *Curr Alzheimer Res* **16**, 243-250.

[18] Hwang JY, Byun MS, Choe YM, Lee JH, Yi D, Choi JW, Hwang SH, Lee YJ, Lee DY, Group KR (2018) Moderating effect of APOE ε4 on the relationship between sleep-wake cycle and brain beta-amyloid. *Neurology* **90**, e1167-e1173.

[19] Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA (2013) Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep* **36**, 1027-1032.

[20] Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, Wohlleber, M, Miller MD, Andrade A, Lewis C, Tweardy S, Buj M, Yau PL, Sadda R, Mosconi L, Li Y, Butler T, Glodzik L, Fieremans E, Babb JS, Blennow K, Zetterberg H, Lu SE, Badia SG, Romero S, Rosenzweig I, Gosselin N, Jean-Louis G, Rapoport DM, de Leon MJ, Ayappa I, Osorio RS (2018) Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly. A longitudinal study. *Am J Respir Crit Care Med* **197**, 933-943.

[21] Spira AP, An Y, Wu MN, Owusu JT, Simonsick EM, Bilgel M, Ferrucci L, Wong DF, Resnick SM (2018) Excessive daytime sleepiness and napping in cognitively normal adults: Associations with subsequent amyloid deposition measured by PiB PET. *Sleep* **41**, zsy152.

[22] Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M (2013) Sleep drives metabolite clearance from the adult brain. *Science* **342**, 373-377.

[23] Ferreira D, Rivero-Santana A, Perestelo-Pérez L, Westman E, Wahlund L, Sarría A, Serrano-Aguilar P (2014) Improving CSF biomarkers' performance for predicting progression from mild cognitive impairment to Alzheimer's disease by considering different confounding factors: A meta-analysis. *Front Aging Neurosci* **6**, 287.

[24] Blennow K, Shaw LM, Stomrud E, Mattsson N, Toledo JB, Buck K, Wahl S, Eichenlaub U, Lifke V, Simon M, Trojanowski JQ, Hansson O (2019) Predicting clinical decline and conversion to Alzheimer's disease or dementia using novel Elecsys Aβ(1-42), pTau and tTau CSF immunoassays. *Sci Rep* **9**, 19024.

[25] Santangelo R, Masserini F, Agosta F, Sala A, Caminiti SP, Cecchetti G, Caso F, Martinelli V, Pinto P, Passerini G, Perani D, Magnani G, Filippi M (2020) CSF p-tau/Aβ42 ratio and brain FDG-PET may reliably detect MCI "imminent" converters to AD. *Eur J Nucl Med Mol Imaging* **47**, 3152-3164.

[26] Guo T, Landau SM, Jagust WJ, Alzheimer's Disease Neuroimaging Initiative (2021) Age, vascular disease, and Alzheimer's disease pathologies in amyloid negative elderly adults. *Alzheimers Res Ther* **13**, 174.

[27] Guo T, Korman D, La Joie R, Shaw LM, Trojanowski JQ, Jagust WJ, Landau SM, Alzheimer's Disease Neuroimaging Initiative (2020) Normalization of CSF pTau measurment by $A\beta_{40}$ improves its performance as a biomarkers of Alzheimer's disease. *Alzheimers Res Ther* **12**, 97.

[28] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR, Jr., Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW (2010) Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. *Neurology* **74**, 201-209.

[29] Wechsler D (1987) *Wechsler Memory Scale-Revised Manual*, Psychological Corporation: Harcourt Brace Jovanovich, San Antonio.

[30] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology* **44**, 2308-2314.

[31] Bittner T, Zetterberg H, Teunissen CE, Ostlund RE, Jr., Militello M, Andreasson U, Hubeek I, Gibson D, Chu DC, Eichenlaub U, Heiss P, Kobold U, Leinenbach A, Madin K, Manuilova E, Rabe C, Blennow K (2016) Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement* **12**, 517-526.

[32] Shaw LM, Fields L, Korecka M, Waligórska T, Trojanowski JQ, Allegranza D (2016) Method comparison of AB(1–42) measured in human cerebrospinal fluid samples by liquid chromatography-tandem mass spectrometry, the Inno-Bia ALZBIO3 assay, and the Elecsys® B-amyloid(1–42) assay. *Alzheimers Dement* **12**, P668.

[33] Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, Lifke V, Corradini V, Eichenlaub U, Batrla R, Buck K, Zink K, Rabe C, Blennow K, Shaw LM, Swedish BioFINDER Study Group; Alzheimer's Disease Neuroimaging Initiative (2018) CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimers Dement* **14**, 1470-1481.

[34] Saykin AJ, Shen L, Yao X, Kim S, Nho K, Risacher SL, Ramanan VK, Foroud TM, Faber KM, Sarwar N, Munsie LM, Hu X, Soares HD, Potkin SG, Thompson PM, Kauwe JS, Kaddurah-Daouk R, Green RC, Toga AW, Weiner MW, Alzheimer's Disease Neuroimaging Initiative (2015) Genetic studies of quantitative MCI and AD phenotypes

in ADNI: Progress, opportunities, and plans. *Alzheimers Dement* **11**, 792-814.

[35] Esteban O, Birman D, Schaer M, Koyejo OO, Poldrack RA, Gorgolewski KJ (2017) MRIQC: Advancing the automatic prediction of image quality in MRI from unseen sites. *PLoS One* **12**, e0184661.

[36] Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* **31**, 968-980.

[37] Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002) Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron* **33**, 341-355.

[38] Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, Grodstein F, Wright CI, Blacker D, Rosas HD, Sperling RA, Atri A, Growdon JH, Hyman BT, Morris JC, Fischl B, Buckner RL (2009) The cortical signature of Alzheimer's disease: Regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex* **19**, 497-510.

[39] Wu A, Sharrett AR, Gottesman RF, Power MC, Mosley TH, Jr., Jack CR, Jr., Knopman DS, Windham BG, Gross AL, Coresh J (2019) Association of brain magnetic resonance imaging signs with cognitive outcomes in persons with non-impaired cognition and mild cognitive impairment. *JAMA Netw Open* **2**, e193359.

[40] Crane PK, Carle A, Gibbons LE, Insel P, Mackin RS, Gross A, Jones RN, Mukherjee S, Curtis SM, Harvey D, Weiner M, Mungas D, Alzheimer's Disease Neuroimaging Initiative (2012) Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav* **6**, 502-516.

[41] Ibrahim JG, Molenberghs G (2009) Missing data methods in longitudinal studies: A review. *Test (Madr)* **18**, 1-43.

[42] Selya AS, Rose JS, Dierker LC, Hedeker D, Mermelstein RJ (2012) A practical guide to calculating Cohen's f(2), a measure of local effect size, from PROC MIXED. *Front Psychol* **3**, 111.

[43] Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat* **57**, 289-300.

[44] Liu YR, Fan DQ, Gui WJ, Long ZL, Lei X, Yu J (2018) Sleep-related brain atrophy and disrupted functional connectivity in older adults. *Behav Brain Res* **347**, 292-299.

[45] Amorim L, Magalhaes R, Coelho A, Moreira PS, Portugal-Nunes C, Castanho TC, Marques P, Sousa N, Santos NC (2018) Poor sleep quality associates with decreased functional and structural brain connectivity in normative aging: A MRI multimodal approach. *Front Aging Neurosci* **10**, 375.

[46] Grau-Rivera O, Operto G, Falcon C, Sanchez-Benavides G, Cacciaglia R, Brugulat-Serrat A, Gramunt N, Salvado G, Suarez-Calvet M, Minguillon C, Iranzo A, Gispert JD, Molinuevo JL, Alfa Study (2020) Association between insomnia and cognitive performance, gray matter volume, and white matter microstructure in cognitively unimpaired adults. *Alzheimers Res Ther* **12**, 4.

[47] Lim AS, Fleischman DA, Dawe RJ, Yu L, Arfanakis K, Buchman AS, Bennett DA (2016) Regional neocortical gray matter structure and sleep fragmentation in older adults. *Sleep* **39**, 227-235.

[48] Yuen K, Rashidi-Ranjbar N, Verhoeff N, Kumar S, Gallagher D, Flint AJ, Herrmann N, Pollock BG, Mulsant BH, Rajji TK, Voineskos AN, Fischer CE, Mah L, Group PA-MS (2019) Association between sleep disturbances and medial temporal lobe volume in older adults with mild cognitive impairment free of lifetime history of depression. *J Alzheimers Dis* **69**, 413-421.

[49] Sexton CE, Storsve AB, Walhovd KB, Johansen-Berg H, Fjell AM (2014) Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults. *Neurology* **83**, 967-973.

[50] Tahmasian M, Samea F, Khazaie H, Zarei M, Kharabian Masouleh S, Hoffstaedter F, Camilleri J, Kochunov P, Yeo BTT, Eickhoff SB, Valk SL (2020) The interrelation of sleep and mental and physical health is anchored in grey-matter neuroanatomy and under genetic control. *Commun Biol* **3**, 171.

[51] Fortier-Brochu E, Morin CM (2014) Cognitive impairment in individuals with insomnia: Clinical significance and correlates. *Sleep* **37**, 1787-1798.

[52] Mecca AP, Michalak HR, McDonald JW, Kemp EC, Pugh EA, Becker ML, Mecca MC, van Dyck CH, The Alzheimer's Disease Neuroimaging I (2018) Sleep disturbance and the risk of cognitive decline or clinical conversion in the ADNI cohort. *Dement Geriatr Cogn Disord* **45**, 232-242.

[53] Lovato N, Lack L, Wright H, Cant M, Humphreys J (2013) Working memory performance of older adults with insomnia. *J Sleep Res* **22**, 251-257.

[54] Ettore E, Bakardjian H, Sole M, Levy Nogueira M, Habert MO, Gabelle A, Dubois B, Robert P, David R (2019) Relationships between objectives sleep parameters and brain amyloid load in subjects at risk for Alzheimer's disease: The INSIGHT-preAD Study. *Sleep* **42**, zsz137.

[55] Molano JRV, Roe CM, Ju YS (2017) The interaction of sleep and amyloid deposition on cognitive performance. *J Sleep Res* **26**, 288-292.

[56] Wilckens KA, Tudorascu DL, Snitz BE, Price JC, Aizenstein HJ, Lopez OL, Erickson KI, Lopresti BJ, Laymon CM, Minhas D, Mathis CA, Buysse DJ, Klunk WE, Cohen AD (2018) Sleep moderates the relationship between amyloid beta and memory recall. *Neurobiol Aging* **71**, 142-148.

[57] You JC, Jones E, Cross DE, Lyon AC, Kang H, Newberg AB, Lippa CF (2019) Association of β-amyloid burden with sleep dysfunction and cognitive impairment in elderly individuals with cognitive disorders. *JAMA Netw Open* **2**, e1913383.

[58] Mander BA, Marks SM, Vogel JW, Rao V, Lu B, Saletin JM, Ancoli-Israel S, Jagust WJ, Walker MP (2015) β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci* **18**, 1051-1057.

[59] Lucey BP, McCullough A, Landsness EC, Toedebusch CD, McLeland JS, Zaza AM, Fagan AM, McCue L, Xiong C, Morris JC, Benzinger TLS, Holtzman DM (2019) Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med* **11**, eaau6550.

[60] Kam K, Parekh A, Sharma RA, Andrade A, Lewin M, Castillo B, Babu OM, Chua NJ, Miller MD, Mullins AE, Glodzik L, Mosconi L, Gosselin N, Kulkarni P, Chen Z, Blennow K, Zetterberg H, Bagchi N, Cavadoni B, Rapoport DM, Ayappa I, de Leon MJ, Petkova E, Varga AW,

Osorio RS (2019) Sleep oscillation-specific associations with Alzheimer's disease CSF biomarkers: Novel roles for sleep spindles and tau. *Mol Neurodegener* **45**, 104-120.

[61] Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE (2007) Systematic meta-analyses of Alzheimer disease genetic association studies: The AlzGene database. *Nat Genet* **39**, 17-23.

[62] Burke SL, Hu T, Spadola CE, Burgess A, Li T, Cadet T (2019) Treatment of sleep disturbance may reduce the risk of future probable Alzheimer's disease. *J Aging Health* **31**, 322-342.

[63] O'Hara R, Schroder CM, Kraemer HC, Kryla N, Cao C, Miller E, Schatzberg AF, Yesavage JA, Murphy GM, Jr. (2005) Nocturnal sleep apnea/hypopnea is associated with lower memory performance in APOE epsilon4 carriers. *Neurology* **65**, 642-644.

[64] Goukasian N, Hwang KS, Romero T, Grotts J, Do TM, Groh JR, Bateman DR, Apostolova LG (2019) Association of brain amyloidosis with the incidence and frequency of neuropsychiatric symptoms in ADNI: A multisite observational cohort study. *BMJ Open* **9**, e031947.

[65] Pase MP, Himali JJ, Grima NA, Beiser AS, Satizabal CL, Aparicio HJ, Thomas RJ, Gottlieb DJ, Auerbach SH, Seshadri S (2017) Sleep architecture and the risk of incident dementia in the community. *Neurology* **89**, 1244-1250.

[66] Henry A, Katsoulis M, Masi S, Fatemifar G, Denaxas S, Acosta D, Garfield V, Dale CE (2019) The relationship between sleep duration, cognition and dementia: A Mendelian randomization study. *Int J Epidemiol* **48**, 849-860.

[67] Lu H, Wu PF, Li RZ, Zhang W, Huang GX (2020) Sleep duration and stroke: A Mendelian randomization study. *Front Neurol* **11**, 976.