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Original Article

Sleep complaints and genetic risk of Alzheimer's disease in older women: associations with memory and tau deposition

Kitty K Lui [a], Xin Wang [b], Melanie A Dratva [b,c], Ella T. Lifset [b], Jordan Stiver [b], Nadine C. Heyworth [b], Qian Shen [b], Michael Thomas [d], Pamela N. DeYoung [e], Atul Malhotra [e], Erin E. Sundermann [f], Sarah J. Banks [b,f,*]

[a] SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA
[b] Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA
[c] Department of Psychology, University of California, Los Angeles, CA, USA
[d] Department of Psychology, Colorado State University, Fort Collins, CO, USA
[e] Department of Medicine, Pulmonary, Critical Care and Sleep Division, University of California, San Diego, La Jolla, CA, USA
[f] Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

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ABSTRACT

Background: Emerging evidence point to a bidirectional relationship between sleep disturbances and Alzheimer's disease (AD). Poor sleep may be an overlooked risk factor for older women, who are disproportionately affected by AD and report worse subjective sleep quality than men. High genetic AD risk—characterized by the polygenic hazard score (PHS), including apolipoprotein *(APOE)* ε4 carriership—may further compound the effects of disrupted sleep on AD, particularly for older women.
Objective: This study examined the moderating effect of genetic AD risk on subjective sleep as it related to memory and tau burden in a sample of older women.
Participants: The sample consisted of older women (≥65 years old) from the Women Inflammation Tau Study.
Measurement: Participants completed the Pittsburgh Sleep Quality Index (PSQI), Rey Auditory Learning Test, and Brief Visuospatial Memory Test-Revised. They also underwent [18]F-MK6240 positron emission tomography. Tau burden was calculated in composite regions across Braak stages. Genetic risk groups were characterized by PHS stratified at the 75th percentile. PSQI global score × PHS group interactions on memory composite scores ($N = 69$) and tau burden ($N = 63$) were examined.
Results: PSQI global score × PHS group interactions were observed on visual memory and pathological tau in Braak regions III/IV ($ps<0.10$). Poorer subjective sleep was associated with worse visual memory and greater limbic tau deposition only among higher genetic risk women ($ps<0.04$). No significant associations were observed for verbal memory or tau in Braak regions I/II or V/VI.
Conclusion: Older women with elevated genetic AD risk and subjective sleep difficulties may be at greater risk for visual memory deficits and tau burden in regions affected in early AD. This suggests that sleep complaints may represent a promising AD risk factor. Improving sleep may be a potential intervention target for AD mitigation and prevention, particularly for older women.

1. Introduction

There is an urgent need to identify modifiable targets that will delay or prevent the onset of cognitive decline in Alzheimer's disease (AD) [1]. Disrupted sleep is a promising modifiable risk factor that often predates expression of hallmark AD pathologies, predicts clinical symptoms, and increases the risk of AD dementia [2,3]. In particular, pathological tau in the form of neurofibrillary tangles (NFTs) is thought to play a key role in the link between sleep and AD. Decades before clinical symptoms of AD and prior to amyloid (Aβ) plaques deposition, phosphorylated tau starts to aggregate in subcortical regions important for regulating sleep-wake cycles—including the locus coeruleus (LC) and basal forebrain—and has been implicated in disrupting sleep and circadian rhythms [4–7]. Tau deposition in these regions occur in the earliest stages of AD, preceding

* Corresponding author at: University of California, San Diego, 9444 Medical Center Drive, La Jolla, CA 92037, USA.
E-mail address: sbanks@health.ucsd.edu (S.J. Banks).

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even the entorhinal cortex [5]. An expanding body of research supports a bidirectional relationship between sleep and AD, such that sleep disturbances have a role in NFT expression and memory dysfunction [4,8–10]. Notably, mice models have shown chronic sleep deprivation increases tau spreading in the LC [8]. Further, poor sleep quality has been associated with more tau deposition in temporal lobe regions affected in early AD [11,12]. Together, this bidirectional relationship creates a vicious cycle in which sleep disruption and AD pathogenesis mutually reinforce each other contributing to progressive cognitive and functional decline [4,8–10,13–15].

Compared to men, women are disproportionately affected by AD, comprising two thirds of AD cases [16,17], and may also experience delayed mild cognitive impairment (MCI) diagnosis because of the female advantage in verbal memory [18,19]. For example, even in the MCI stage, women outperform men in verbal memory measures despite equivalent levels of Aβ pathology, hippocampal volume, and hypometabolism [18,20,21]. Women's verbal memory reserve starts to diminish after MCI onset, with studies showing faster cognitive decline in women with MCI versus men with MCI [22,23]. In contrast, visual memory tests do not show a strong sex bias [24,25] and demonstrate similarly robust, if not stronger associations [26,27] with AD pathology, hippocampal volume, and AD risk [26–30]. The growing body of research suggesting sex differences in early AD detection [31] highlights the importance of incorporating both visual and verbal memory since visual memory may be a sensitive marker of incipient AD-related changes in women.

Emerging evidence point to sleep disturbances as an overlooked AD risk factor that potentially contribute to the sex disparity in AD [2]. First, compared to men, women are more likely to have sleep complaints, including dissatisfaction with sleep quality, yet sleep problems are often both underdiagnosed and undertreated, particularly in women [2,32]. Moreover, Huang et al. [33] reported that poor sleep was more strongly related to cognitive decline, hippocampal atrophy, and AD incidence in women than men. Our own work further showed that comorbid insomnia and sleep apnea (COMISA) attenuated the female advantage in verbal memory [34]. Sleep disturbances in middle age have also been linked to accelerated tau accumulation in later life [14]. This may be especially relevant for women who not only accumulate tau faster than men, but also experience significant changes in sleep patterns and poor sleep quality with the menopause transition [35–40]. Importantly, about 30 % of women continue to experience menopause-related sleep difficulties into older age [35–37]. Collectively, these studies implicate sleep disruption as a potentially relevant AD risk factor for women; although, the sleep and AD relationship remains poorly understood from a sex-specific perspective.

Increasing evidence suggests that the effect of disrupted sleep on tau pathology may be a function of apolipoprotein *(APOE)* ε4 genotype [41–43]. *APOE* ε4 is posited to promote earlier and faster tau accumulation in sleep-wake regulating regions, thereby increasing vulnerability to dysregulated sleep [5,6,13]. Supporting this, previous work has found *APOE* ε4 carriers exhibiting worse objective and subjective sleep parameters as opposed to non-carriers [44–46]; however, this has not been consistently reported across studies [47–49]. Further, the relationship between sleep difficulties and AD have been found to be more pronounced in *APOE* ε4 carriers [43,50,51]. *APOE* ε4 carriership also contributes to sex differences in AD as female ε4 carriers progress to AD earlier, accumulate tau more rapidly, and exhibit faster memory decline than male ε4 carriers and women non-carriers [42,52–54]. The cumulative effects of poor sleep and *APOE* ε4 may therefore disproportionately affect women. For example, Koo et al. [55] found that female ε4 carriers across the AD continuum were more likely to experience sleep disruptions than female non-carriers. Yet, the interplay between sleep and genetic AD risk remain largely unknown, especially for women with elevated genetic risk who are most vulnerable AD.

Research has primarily focused on *APOE* ε4 as the primary genetic risk factor for AD. More recently, the polygenic hazard score (PHS) have gained recognition as a more sensitive measure to determine genetic AD risk since it accounts not only for the cumulative effects of two *APOE* variants (ε2 and ε4), but also other single nucleotide polymorphisms (SNPs) that been linked to small increases in disease risk [56–58]. For instance, the PHS include SNPs associated with *BIN1, FERMT2*, and others that have been linked to tau deposition [56,57,59,60]. AD PHS has showed to be more sensitive than *APOE* ε4 alone in predicting age of AD onset, Aβ and tau pathogenesis, and cognitive decline [56,57,60,61]. Intriguingly, even in absence of *APOE* ε4, PHS is still predictive of age of AD onset [56]. This unique sensitivity of the PHS in capturing convergence and progression of AD lends support in integrating the PHS in AD research, particularly in the context of how modifiable risk factors relate to AD biomarkers in those with high polygenic risk. To date, no study has leveraged the PHS to characterize the relationship between sleep and AD.

In the Women: Inflammation Tau Study (WITS), we examined the relationship of self-reported sleep to memory and tau burden and the modifying role of AD genetic risk (i.e., PHS and *APOE* ε4 status). We hypothesized that poorer sleep would be reported in women with higher genetic AD risk. Further, worse subjective sleep would be related to higher tau pathology and poorer memory more strongly in women with higher genetic risk than women with lower genetic risk.

2. Methods

2.1. Participants

WITS is an ongoing, prospective study at the University of California San Diego. This study focuses on older women at higher AD risk by way of older age (≥65 years), telephone Montreal Cognitive Assessment (T-MoCA) [62] score of 13–20 out of 22 (suggestive of MCI), and either a PHS≥50th percentile and/or family history of dementia. Other inclusion criteria are ability to complete psychometric and other clinical assessments in English (i.e., adequate English language skills, vision, and hearing) and no major medical incident in the past 4 weeks (e.g., trauma or infection). Exclusion criteria are contraindication to lumbar puncture, chronic major psychiatric or neurodegenerative disorders, unstable or poorly controlled medical problems (e.g., heart failure, diabetes, hypertension, pulmonary disease with hypoxia or hypercapnia, significant liver problems or renal failure, major inflammatory disorders), current use of illegal substances or excessive alcohol use, taking specific medications known to influence our measures of interest (cognition, inflammation, hormones, insulin resistance) including neuroleptics, anti-parkinsonism drugs, central nervous system stimulations, anticonvulsants, insulin, coumadin, sedating antihistamines or hypnotics, and potent anti-inflammatory medications as well as magnetic resonance imaging (MRI) or PET contraindications, including non-MR safe electronic devices or implants (e.g., cochlear implant), claustrophobia, adverse reactions to intravenous (IV)/oral contrasts, and body mass index (BMI) greater than 35 kg/m^2.

Seventy-three women have been enrolled in WITS so far. On average, all study procedures were completed within a 58-day period (SD=86 days, range=7–457 days). Of the 73 participants enrolled in the study, 4 participants had incomplete or invalid Pittsburgh Sleep Quality Index (PSQI) data and thus, were subsequently removed resulting in a final sample of $N = 69$ in analyses between PSQI and memory. Regarding tau PET data, 2 participants withdrew from the study prior to undergoing tau PET, 2 participants had been excluded from the study prior to neuroimaging due to contraindication (but had completed PSQI and neurocognitive testing), and 1 participant had significant MRI artifact and did not complete PSQI, resulting in an $N = 68$. Within that subsample, 3 participants had invalid or incomplete PSQI data and an additional 2 participants had tau standard uptake value ratios (SUVRs) in Braak regions I/II and Braak regions III/IV that were statistical outliers (>3SD). Thus, these participants were removed from analyses, resulting in a final sample of $N = 63$ in analyses between PSQI and tau PET. A visual

depiction of participant exclusion is shown in Fig. 1.

2.2. Polygenic hazard score (PHS)

Saliva samples were collected at-home as part of pre-enrollment to characterize AD risk for study eligibility. The PHS was developed to estimate genetic AD risk and is associated with age of AD onset [56]. Genetic sequencing was performed by Diagnomics Lab (San Diego, CA) and the AD PHS was computed based on 198,424 SNPs from the Illumina Global Screening Array, including two APOE variants (ε2 and ε4) [63]. Ambiguous SNPs were excluded. No additional quality control procedures were applied to assess genotype quality.

Since WITS enriched for participants with already elevated genetic risk (PHS≥50th percentile) and given the sensitivity of the 75th percentile in identifying those with highest risk for AD development—evidenced by earliest age of AD and highest yearly incidence rate of AD [56]—the 75th percentile was used to stratify the sample into higher-risk PHS group (PHS≥75th percentile) and lower-risk PHS group (PHS<75th percentile).

2.3. Pittsburgh sleep quality index (PSQI)

PSQI is a questionnaire that evaluates sleep quality over the past month across seven domains of sleep health: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction [64]. Nineteen items were transformed into seven component scores and treated as ordinal level data (range: 0–3). These component scores were then summed together to calculate a global score (range: 0–21) with higher scores reflecting poorer sleep. A global score >5 distinguished poor sleepers from good sleepers and has been validated as a sensitive measure of sleep quality in older adults [64,65].

2.4. Memory tests

Both visual and verbal memory were assessed in order to have measure of memory with and without a sex bias to account for the well-established female advantage in verbal memory observed across cognitively normal and MCI stages [18,21].

For visual memory, the Brief Visuospatial Memory Test-Revised (BVMT-R) was administered, which required learning six geometric shapes that were presented for 10s each over 3 trials [66]. After each learning trial, participants were asked to draw the geometric shapes. Following a 25-minute delay period, participants were asked to reproduce those shapes again. Each shape was scored with 2 points (one for correct shape, the other for correct location). The maximum score for total learning across the 3 trials was 36 and delayed recall was 12. For verbal memory, the Rey Auditory Verbal Learning Test (RAVLT) was administered, which required learning a 15-word orally presented list read over 5 learning trials [67]. Participants were asked to immediately recall as many words as possible after each learning trial. Short-delayed recall was assessed after an interference list and long-delayed recall was assessed after a 20-minute delay period. The maximum score for total learning across 5 trials was 75 and delayed recall was 15.

Visual and verbal memory composite scores were computed from the total learning and delayed recall raw scores from the BVMT-R and RAVLT, respectively. Each score was transformed to a z-score and then averaged together.

2.5. MRI

MRI was collected in a 3.0T GE 750 with the sequence of inversion recovery fast spoiled gradient-echo sequence (IR-FSPGR; TI = 400 ms, FA = 11°, voxel resolution = 1 × 1 × 1 mm^3) scanner following ADNI protocols [68] at the Altman Clinical Translational Research Institute (San Diego, CA). T1 weighted images were processed with FreeSurfer (v.7.1.1) to derive region of interests (ROIs) in each participant's native

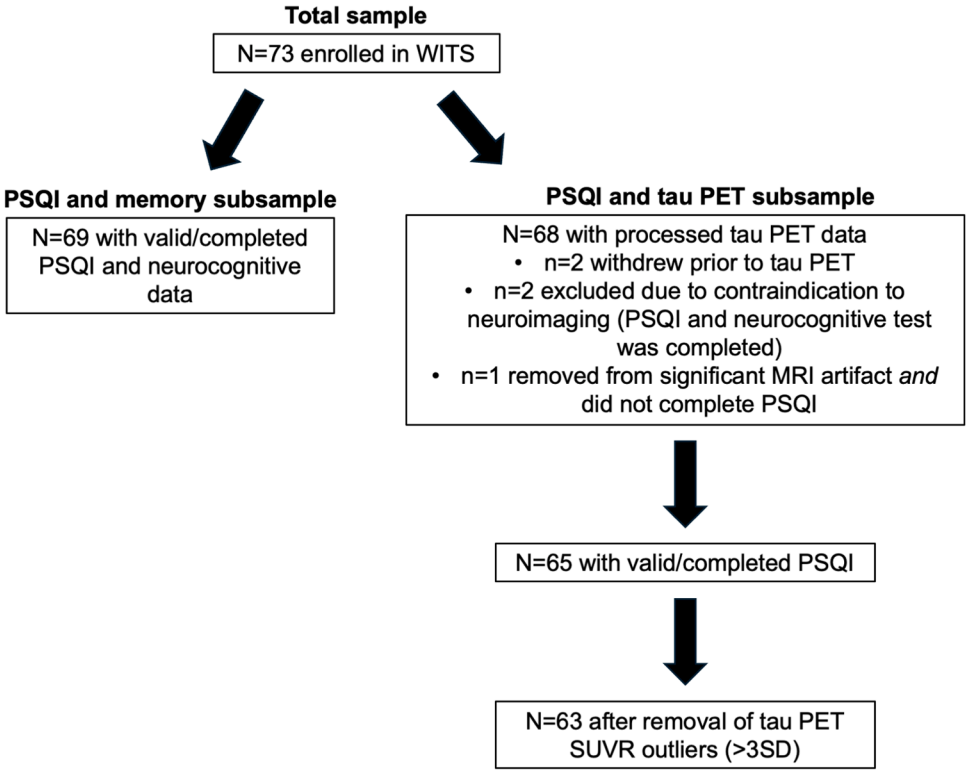

Fig. 1. Flow diagram showing the exclusion/removal of participants and arrival for the final samples for the PSQI and memory analyses and PSQI and tau PET analyses.

space using the Desikan-Killiany atlas. Quality control of FreeSurfer outputs were conducted by trained MRI analysts (coauthors: XW and MAD). Visual inspection was conducted to assess whether the pial and white matter surfaces accurately followed the gray–white matter boundaries, and whether the subcortical segmentation conformed to anatomical intensity boundaries. Manual edits (when deemed necessary) involved removing non-brain voxels from the pial surface and adding white matter control points to correct white matter segmentation errors by improving intensity normalization. Twelve participants had manual edits completed ($n = 6$ with PHS ≥75th percentile).

2.6. Tau PET imaging

[18]F-MK6240 PET imaging was acquired in a GE Discovery 610 PET/computed tomography (CT) scanner at California Protons Cancer Therapy Center (San Diego, CA). The [18]F-MK6240 ligand has demonstrated better signal-to-noise ratio, has stronger affinity to NFTs, and reduced off-targeting binding compared to older generation tracers [69]. Participants were injected with 5 mCI (185 MBq) ±10 % dose of tracer for at least 60 secs. Scans started at 80 min post injection and lasted for 30 min (6 × 5 min frames). Smoothing, interframe realignment, and co-registration of 4D tau PET to T1 weighted MRI was performed using SPM12. The first 4 frames of PET data were then summed to generate SUVRs with the eroded inferior cerebellum grey matter as the reference region [70]. The eroded inferior cerebellum was created in the automated anatomical labeling (AAL) atlas in native T1 space from each individual's segmented MRI [70]. Tau PET processing followed an established pipeline that was described in Betthauser et al. 2019 [70]. Since tau deposition typically follows a predictable temporal pattern [71], SUVRs were calculated in composite regions associated with Braak regions I/II (entorhinal cortex and hippocampus), III/IV (limbic regions), and V/VI (neocortex) [71,72]. The regions used to calculate SUVRs in the Braak regions are shown in Table 1.

2.7. Statistical analysis

Independent samples *t*-tests (i.e., Student's *t*-test or Mann-Whitney *U* test if normality was not met) or Chi-Square (X^2) tests were used to analyze differences in participant characteristics, PSQI global score, tau SUVR in composite ROIs, and memory scores between PHS groups. Normality of variables were examined with Shapiro-Wilk test and log-transformed variables were used if normality significantly improved.

Linear regression was used to analyze the interaction between PSQI global score and PHS groups on tau SUVR or memory scores while controlling for age and years of education. BMI was included as a covariate in models with tau SUVR as the outcome variable since there are reported associations between tau burden and BMI [73]. Interactions were probed at $p < 0.10$ and was followed by simple slope analyses with significance level set at $p < 0.05$. In models with a non-significant interaction at $p \geq 0.10$, the interaction term was removed to assess the main effect of PSQI global score; significance was set at $p < 0.05$. In addition to p-values, effect sizes were reported as standardized beta-coefficients (β). β values between 0.10–0.29 were considered small, 0.30–0.49 were considered medium, and >0.50 were considered large [74].

Women with preexisting sleep disorders were not excluded from the study ($n = 8$). Two women had a diagnosis of insomnia disorder that was treated with medication (one with an antidepressant and the other with an anticonvulsant), five women had a known sleep apnea diagnosis (with two using continuous positive airway pressure [CPAP]), and one woman reported significant sleep problems that was treated with an antidepressant. Sensitivity analyses were conducted to exclude the 8 women with sleep disorders to examine whether these associations were present independent of clinically significant sleep problems. Further, to compare the results between PHS and *APOE* ε4, we examined the interactive effects of PSQI global score and *APOE* ε4 on memory and tau pathology while controlling for the aforementioned covariates. Lastly, for significant associations with PSQI global score, exploratory analyses were conducted to identify which of the 7 domains of sleep health were contributing to the effects. The statistical approach is described in the **Supplementary Materials**. All statistical analyses were performed using R Studio (V.2023.09.0 + 463).

Table 1
FreeSurfer-defined composite ROIs (bilateral) for each Braak regions.

Braak regions I/II	Entorhinal cortex and hippocampus
Braak regions III/IV	Parahippocampal, fusiform, lingual, amygdala, middle temporal, cingulate, insula, inferior temporal, and temporal pole
Braak regions V/VI	Superior frontal, lateral and medial orbitofrontal, frontal pole, caudal and rostral middle frontal, pars opercularis, pars orbitalis, pars triangularis, superior temporal, parietal superior, precuneus, bank of the superior temporal sulcus, transverse temporal cortex, peri-calcarine, postcentral, cuneus, precentral, and paracentral

3. Results

3.1. Participant characteristics

Participant characteristics by PHS group can be found in Table 2. In this sample of 69 women (age: 72.5 ± 4.5, 93 % White [87 % Non-Hispanic/Latino; 6 % Hispanic/Latino], years of education: 16±2), 26 had a PHS≥75th percentile (higher-risk PHS group) and 43 had a PHS<75th percentile (lower-risk PHS group). Within the lower-risk PHS group, 19 women (34 %) had a PHS<50th percentile. Higher-risk PHS women were more likely to be *APOE* ε4 carriers (100 %) as opposed to those with lower-risk PHS (7 %; $p < 0.001$). Lower-risk PHS women had significantly higher PSQI global scores (more self-reported sleep difficulties) than higher-risk PHS women ($p = 0.04$). There were no significant PHS group differences in age, years of education, t-MoCA scores, BMI, or memory scores.

Table 2
Participant characteristics by PHS groups ($N = 69$).

	Lower-risk PHS group (<75th %ile; $N = 43$)	Higher-risk PHS group (≥75th %ile; $N = 26$)	*p*
Age	72.2 ± 4.4	73.0 ± 4.7	0.46
Primary race (White; n; %)	39 (91 %)	25 (96 %)	0.57
Ethnicity (Non-Hispanic/Latino; n; %)	39 (91 %)	25 (95 %)	0.71
Years of education	16.2 ± 1.9	15.9 ± 1.7	0.71
t-MoCA scores	18.7 ± 1.6	18.7 ± 1.7	0.94
***APOE* ε4+ (n; %)**	3 (7 %)	26 (100 %)	<0.001**
BMI	27.1 ± 5.6	25.4 ± 4.8	0.20
PSQI global score	5.8 ± 3.0	4.3 ± 2.8	0.04*
BVMT-R Total Learning (max=36)	22.1 ± 6.1	21.3 ± 6.4	0.58
BVMT-R Delayed Recall (max=12)	8.6 ± 2.4	8.3 ± 2.5	0.69
RAVLT Total Learning (max=75)	44.2 ± 8.7	44.5 ± 9.0	0.89
RAVLT Delayed Recall (max=15)	8.8 ± 3.0	8.1 ± 4.2	0.40

PHS = polygenic hazard score; t-MoCA = Telephone-Montreal Cognitive Assessment; APOE ε4 = apolipoprotein ε4; BMI = Body Mass Index; PSQI = Pittsburgh Sleep Quality Index; BVMT-*R* = Brief Visuospatial Memory Test-Revised; RAVLT = Rey Auditory Verbal Learning Test.
** $p < 0.01$
* $p < 0.05$

Participant characteristics by PHS group of the subset of 63 women with tau PET data can be found in Table 3, which included 22 participants with PHS≥75th percentile (all *APOE* ε4 carriers) and 43 participants with PHS<75th percentile (3 *APOE* ε4 carriers). Consistent with past findings [60], those in the higher-risk group had higher pathological tau burden than those in the lower-risk group (*ps*=0.003–0.05). There were no significant differences in age, years of education, t-MoCA scores, BMI, PSQI global score, and memory scores between the higher-risk and lower-risk PHS group.

In a subset of participants ($N = 53$), reproductive health information was available. The PHS groups did not significantly differ between age at menopause, type of menopause, sleep changes during the menopausal transition, and hormone replacement therapy use during/after the menopausal transition (*ps>0.20*; **Table S1**).

3.2. Interactions between PSQI global score and PHS on memory

There was an interaction between PSQI global score and PHS group on the visual memory composite score at a trend level, despite a large effect size ($B=-0.17$, $\beta=-0.52$, SE=0.08, $p = 0.05$; Fig. 2). Simple slope analysis revealed that in only higher-risk PHS women, higher PSQI global score (i.e., more self-reported sleep difficulties) related to worse visual memory ($B=-0.16$, $\beta=-0.51$, SE=0.07, $p = 0.02$; Fig. 2**A**). This was not observed in lower-risk PHS women ($p = 0.92$). Results that examined the interactions between each PSQI component score and PHS on the visual memory composite score are presented in the **Supplementary Materials**.

Table 3
Participant characteristics by PHS groups in tau PET sample ($N = 63$).

	Lower-risk PHS group (<75th %ile; $N = 41$)	Higher-risk PHS group (≥75th %ile; $N = 22$)	*p*
Age	72.4 ± 4.3	73.4 ± 4.8	0.43
Primary race (White; n; %)	37 (90 %)	21 (96 %)	0.50
Ethnicity (Non-Hispanic/Latino; n; %)	37 (90 %)	21 (95 %)	0.81
Years of education	16.2 ± 1.9	16.2 ± 1.6	0.97
t-MoCA scores	18.9 ± 1.5	18.7 ± 1.8	0.76
***APOE* ε4+ (n; %)**	3 (7 %)	22 (100 %)	<0.001**
BMI	27.0 ± 5.7	25.4 ± 4.9	0.25
PSQI global score	5.6 ± 3.0	4.4 ± 2.8	0.11
tau in Braak regions I/II SUVR	0.9 ± 0.2	1.1 ± 0.3	0.003**
tau in Braak regions III/IV SUVR	1.0 ± 0.1	1.1 ± 0.1	0.02*
tau in Braak regions V/VI SUVR	0.9 ± 0.1	1.0 ± 0.1	0.05†
tau in meta-temporal ROI SUVR	1.1 ± 0.1	1.2 ± 0.2	0.004**
BVMT-R Total Learning (max=36)	22.0 ± 6.1	21.8 ± 6.5	0.90
BVMT-R Delayed Recall (max=12)	8.5 ± 2.5	8.3 ± 2.7	0.70
RAVLT Total Learning (max=75)	44.5 ± 8.7	45.1 ± 9.2	0.81
RAVLT Delayed Recall (max=15)	8.8 ± 3.1	8.0 ± 4.3	0.38

PHS = polygenic hazard score; PET = positron emission tomography;. t-MoCA = Telephone-Montreal Cognitive Assessment; APOE ε4 = apolipoprotein ε4; BMI = Body Mass Index; PSQI = Pittsburgh Sleep Quality Index; SUVR = standard uptake value ratio; BVMT-*R* = Brief Visuospatial Memory Test-Revised; RAVLT = Rey Auditory Verbal Learning Test.
** $p < 0.01$
* $p < 0.05$
† $p < 0.10$

The interaction between PSQI global score and PHS group on the verbal memory composite score was not significant and effect size was small ($B=-0.08$, $\beta=-0.27$, SE=0.09, $p = 0.33$; Fig. 2**B**). There was also no main effect of PSQI global score on the verbal memory composite score which was further supported with a small effect size ($B=-0.13$, $\beta=-0.14$, SE=0.24, $p = 0.59$).

3.3. Interactions between PSQI global score and PHS on tau burden

PSQI global score interacted with PHS group to predict tau SUVR in Braak regions III/IV at a trend level, although there was a medium effect size ($B = 0.02$, $\beta=0.46$, SE=0.01, $p = 0.098$; Fig. 3). Simple slopes analysis showed that only among those with higher-risk PHS, more subjective sleep difficulties were associated with higher tau deposition in Braak regions III/IV ($B = 0.02$, $\beta=0.53$, SE=0.01, $p = 0.03$). This association was not observed in those with lower-risk PHS ($p = 0.61$). Results that examined the interaction between each PSQI component and PHS on tau burden in Braak regions III/IV are presented in **Supplementary Materials**.

PSQI global score did not interact with PHS to predict tau SUVR in Braak regions I/II, despite a medium effect size (β=0.32, $p = 0.23$). Similarly, no interaction was not observed for Braak regions V/VI and the effect size was small (β=0.17, $p = 0.55$). There was no main effect of PSQI global score on Braak regions I/II or V/VI, and the effect sizes were small (β*s* < 0.23; *ps>0.12)*.

3.4. Sensitivity analyses in women without sleep disorders

We performed sensitivity analyses excluding the 8 women with sleep disorders (3 with PHS≥75th percentile) to account for whether clinical sleep problems (treated or untreated) may have confounded our findings. The PSQI global score and PHS group interaction on visual memory was no longer significant ($B=-0.16$, $\beta=-0.45$, SE=0.09, $p = 0.11$). Although, the medium effect size suggests that we may be underpowered to detect a significant effect given the reduced sample size. Despite the non-significant interaction, simple slopes similarly showed that in higher-risk PHS women, greater PSQI score was related to lower visual memory scores ($B=-0.14$, SE=0.08, $p = 0.08$), and not in lower-risk PHS women ($p = 0.82$).

The PSQI global score × PHS group interaction on tau SUVR in Braak regions III/IV was at trend-level, with a large effect size ($B = 0.02$, $\beta=0.54$, SE=0.01, $p = 0.06$). Simple slope analysis continued to show that in those with higher-risk PHS, more report of sleep difficulties was related to higher tau burden in Braak III/IV ($B = 0.023$, SE=0.01, $p = 0.04$), and not in lower-risk PHS women ($p = 0.71$).

3.5. Sensitivity analyses with APOE ε4 status

To compare the results with PHS, *APOE* ε4 stratified analyses were also conducted. PSQI global score interacted with *APOE* ε4 to predict visual memory composite score ($B=-1.63$, $\beta=-0.51$, SE=0.09, $p = 0.06$). Only among *APOE* ε4 carriers, more subjective sleep difficulties were related to worse visual memory performance ($B=-0.16$, $\beta=-0.51$, SE=0.07, $p = 0.02$), but not in non-carriers ($p = 0.99$). There was no interaction between PSQI global score and *APOE* ε4 status on verbal memory composite score ($B=-0.05$, $\beta=-0.16$, SE=0.09, $p = 0.57$).

As for tau pathology, PSQI global score interacted with *APOE* ε4 status to predict tau SUVR in Braak regions III/IV ($B = 0.02$, $\beta=0.57$, SE=0.01, $p = 0.04$). In *APOE* ε4 carriers, more sleep complaints were related to greater tau burden in limbic regions ($b = 0.02$, $\beta=0.61$, SE=0.01, $p = 0.01$); which was not observed in non-carriers ($p = 0.80$). PSQI global score did not interact with *APOE* ε4 status to predict tau deposition in Braak regions I/II, although the effect size was medium ($B = 0.03$, $\beta=0.42$, SE=0.02, $p = 0.13$). There was no significant interaction between PSQI global score and tau burden on Braak regions V/VI and the effect size was small ($B < 0.01$, $\beta=0.22$, SE=0.01, $p = 0.45$).

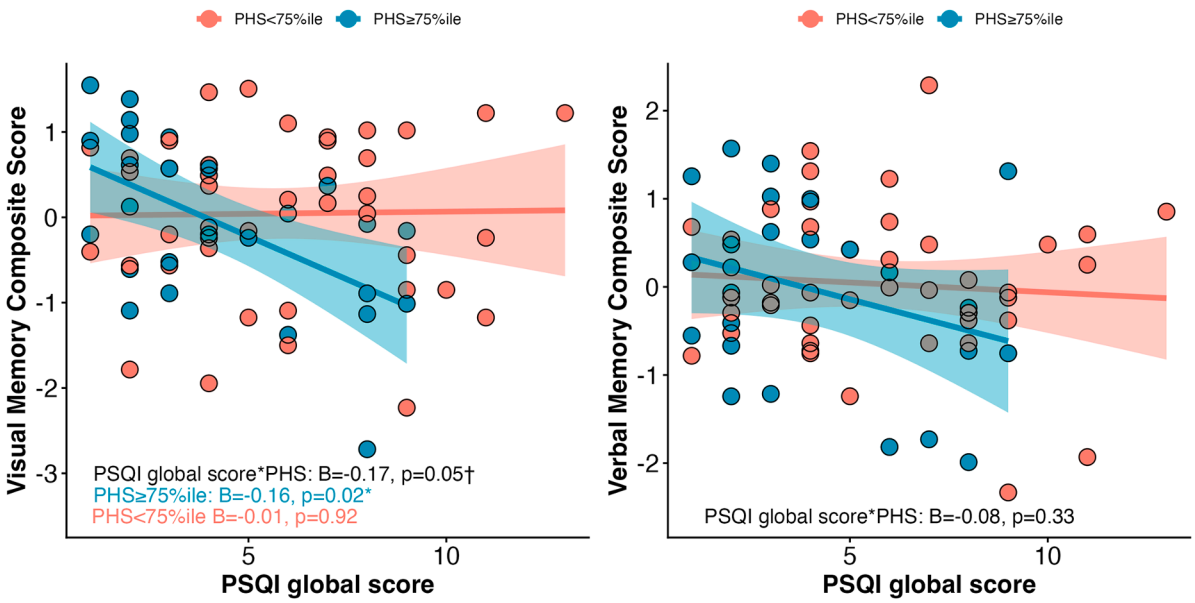

Fig. 2. Scatter plots showing the moderating effect of PHS group (stratified at the 75th percentile) on PSQI global score and memory composite scores. **(A):** PHS significantly modified the association between PSQI global score and visual memory. Higher PSQI global score—reflective of poorer sleep—was related to lower visual memory, specifically in higher-risk PHS women (turquoise) and not in lower-risk PHS women (pink). **(B):** PSQI global score did not significant interact with PHS to predict verbal memory composite score; $^{*}p < 0.05$; $\dagger p < 0.10$.

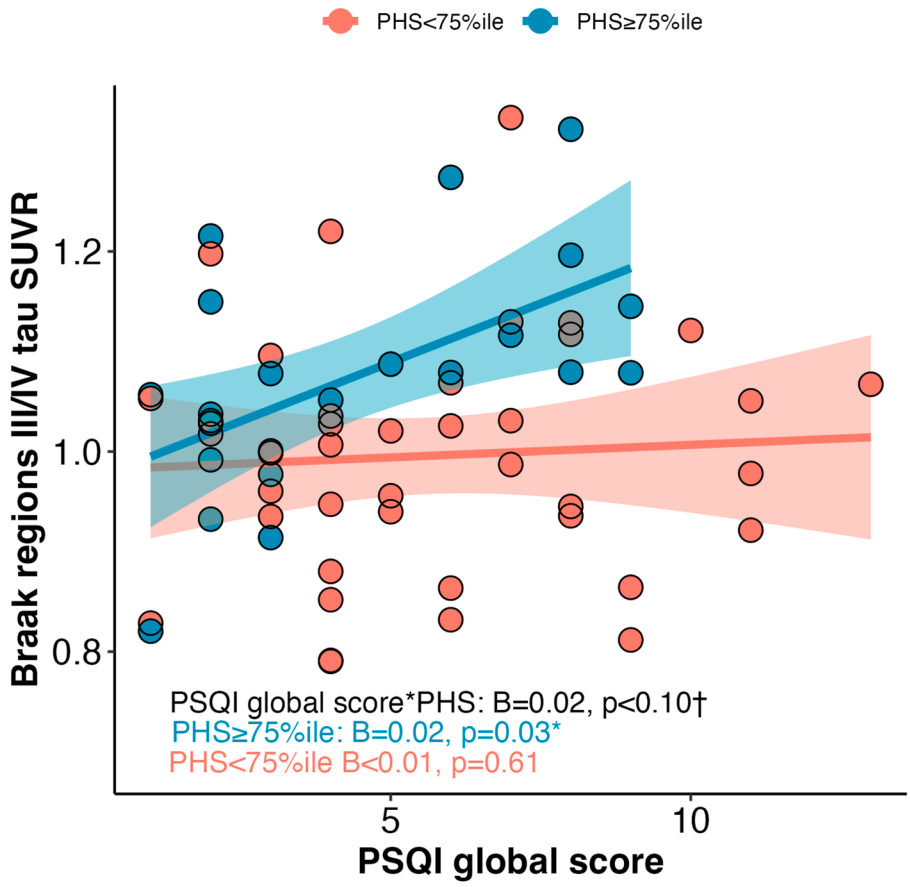

Fig. 3. Scatter plots showing the significant moderating effect of PHS group (stratified at the 75th percentile) on PSQI global score and tau SUVR in Braak regions III/IV. Higher PSQI global score (reflective of poorer sleep) was related to more tau burden, specifically in higher-risk PHS women (turquoise) and not in lower-risk PHS women (pink). $^{*}p < 0.05$; $\dagger p < 0.10$.

4. Discussion

In this study, lower-risk PHS women (PHS<75th percentile) showed higher PSQI global scores, reflecting worse subjective sleep, than higher-risk PHS women (PHS≥75th percentile), which was contrary to our hypotheses. Despite fewer sleep complaints overall, in only women with higher genetic AD risk, more subjective sleep difficulties were related to worse visual memory and greater tau burden in limbic regions. This was not observed in those with lower genetic risk. Self-reported sleep problems were not associated with verbal memory or tau deposition in Braak regions I/II and V/VI in a PHS-dependent manner or across the whole sample.

It remains unclear whether genetic AD risk heightens susceptibility to sleep disturbances. Our results showed that women with lower genetic risk had worse subjective sleep difficulties compared to women with higher genetic risk. A similar finding has been previously reported in the context of *APOE* ε4 carriership, such that non-carriers reported worse sleep [47]. In contrast, other studies have reported that *APOE* ε4 carriers were more likely to report worse sleep measures of shorter duration, longer sleep latency, and more disruptions than non-carriers [44,46,75], or no *APOE* ε4-dependent effects on subjective sleep measures [45,48,49]. Perhaps, in the higher genetic risk group, we may be capturing a discrepancy between self-reported and objective sleep measures, whereby those with MCI tend to overestimate their subjective sleep, possibly reflecting anosognosia or memory recall deficits, early clinical symptoms of AD [76,77]. While our results show that higher genetic risk does not appear to worsen self-reported sleep, it potentially points to an interactive effect between poor subjective sleep and early pathological and cognitive changes among individuals with elevated AD genetic risk.

There are a few proposed mechanisms by which *APOE* ε4 contribute to the bidirectional relationship between sleep and AD. First, *APOE* ε4 accelerates early tau aggregation in the basal forebrain, a region involved in REM sleep-wake regulation, which may explain the marked reduction in REM sleep starting in midlife, particularly in ε4 carriers [5,6,45,78]. This significant change in REM sleep architecture could then lead to acute disruptions in neural functions that support memory consolidation as well as next-day learning and retrieval of new information [10]. Secondly, mice models have demonstrated synergistic effects of *APOE* ε4 and sleep disturbances in accelerating Aβ plaque deposition and subsequently promoting Aβ-related tau seeding and spreading [13]. In line with this, a human observational study reported that worse sleep quality was more strongly associated with worse cognition, greater hippocampal atrophy, and higher AD incidence in *APOE* ε4 carriers [33]. Similarly, older adults with *APOE* ε4 positivity and poor sleep consolidation demonstrated the fastest cognitive decline, highest AD incidence, and greatest post-mortem NFT density; however, good sleep consolidation appeared to attenuate the adverse effect of *APOE* ε4 and those individuals resembled AD-related outcomes similar to non-carriers (irrespective of their sleep pattern) [43]. Together, these findings implicate that poor sleep could accelerate AD pathogenesis and cognitive impairment in those with elevated genetic risk, however, improving sleep may confer some resilience against the disease. Lastly, sleep disturbances could also increase susceptibility to AD through metabolic dysfunction and increased inflammatory response with *APOE* ε4 exacerbating these processes [79–81]. Specifically, Huang et al. (2025) identified GDF15, a marker of cellular stress, mitochondrial dysfunction, and inflammation, as a key protein linking poor sleep and AD in *APOE* ε4 carriers [33].

In prior work, the mechanistic links between sleep and genetic AD risk have largely focused on *APOE* ε4. Leng et al. [82] reported that AD polygenic risk score was associated with higher odds of short sleep duration, with the effects attenuated when removing *APOE* ε4. The results of our study cannot parse out the effect of *APOE* ε4 in the higher genetic risk group since 89 % of the women were *APOE* ε4 carriers. Further, our sensitivity analyses also showed that in only *APOE* ε4 carriers, PSQI global score was related to limbic tau pathology and visual memory. It remains unknown whether SNPs associated with other AD-related genes like *BIN1*, play a prominent role in the sleep and AD relationships, independent of *APOE*. For example, while *BIN1* has been implicated in tau pathogenesis [83], whether *BIN1* disrupts neurobiological mechanisms important for regulating sleep-wake functions have not been examined. Rodent and human studies enriching for higher genetic risk without *APOE* ε4 positivity are warranted to disentangle the strong influence of *APOE* ε4 versus the polygenic component on sleep disruption.

Our findings indicated that a PHS-dependent association of poor sleep was specific to visual memory, suggesting that visual memory could potentially be a sensitive marker of sleep-related memory impairment for older women with higher genetic AD risk. The absence of verbal memory findings could reflect the female verbal advantage [21,22], potentially conferring some protection against the effects of poor sleep in preclinical and prodromal AD, even in those with elevated genetic risk. Together, it raises the possibility that poor subjective sleep may act synergistically with genetic risk to increase vulnerability to AD and cognitive decline, with visual memory deficits being more sensitive to this combined influence. These results differ from the scant studies that have examined the modifying role of *APOE* ε4 on the association between subjective sleep measures and memory, particularly with visual memory. Past research have not observed a moderating role of *APOE* ε4 in the relationship of self-reported sleep to either verbal and/or visual memory in samples of both women and men [84,85]. In those studies, the absence of visual memory findings could be attributable to different assessment formats (i.e., incidental encoding of a complex figure as opposed to repeat learning trials of shapes) [84] and combining verbal and visual memory into a memory composite score [85]. While other studies have shown stronger associations between insomnia and verbal memory in *APOE* ε4 carrier than non-carriers, they did not assess for visual memory nor conduct sex-stratified analyses [86,87]. Further, those samples were generally younger (mean ages: mid to late 50s) than this sample (mean age: 72.5 years) [86,87]. Though, a possible explanation is that specific symptoms to insomnia (e.g., troubles with latency and maintenance and early awakenings) could be more closely linked to verbal memory, which somewhat aligns with our past work that found that women with COMISA exhibited an attenuated female verbal memory advantage when compared to women with obstructive sleep apnea only [34]. While this present study showed that poor subjective sleep quality was not related to verbal memory, it does not preclude the possibility that other dimensions of sleep disturbances (e.g., insomnia symptoms, sleep-disordered breathing) may be associated with visual and/or verbal memory deficits across sexes, highlighting the need for further research.

We found that among women with higher genetic risk, more sleep complaints were associated with greater limbic tau pathology. This extends previous work that showed actigraphy-derived measures of less consolidated sleep, less consistent sleep efficiency, and shorter sleep duration were associated with elevated AD pathology, including NFTs and cortical Aβ, in *APOE* ε4 carriers [43,50,51]. Although our findings were limited to tau deposition in Braak III/IV regions, this is consistent with earlier work from our group that demonstrated in Aβ+ older male Veterans, PSQI global scores was associated with tau burden in only Braak regions III/IV [11]. These specific relationships to Braak regions III/IV might reflect that poor self-reported sleep is a risk factor for more widespread tau buildup in limbic regions and adjacent cortical regions, beyond the entorhinal cortex and hippocampus (Braak regions I/II), particularly during the early symptomatic stages of AD.

A few limitations of this study need to be addressed. Generalizability of these results to the wider population are limited due to a sample comprised of mostly White non-Hispanic/Latino and highly educated women and on a genetic marker that was developed in primarily White European cohorts [56]. The sample size also placed some constraints on statistical power, and we did not correct for multiple comparisons. Also,

removing those with sleep disorders ($n = 8$) resulted in nonsignificant and trend-level interactions, despite comparable effect sizes, potentially reflecting reduced power in the subsample. Notably, across interactions with $p < 0.10$, the effect sizes were medium to large, indicating a considerable effect. To address this power issue, we will replicate these analyses once data collection is complete, and also assess longitudinal relationships. Even though the PSQI does not concretely map on to a specific sleep disorder, it is a validated questionnaire that has high sensitivity and specificity in capturing sleep quality. Also, while it could be argued that subjective sleep measurements may be less accurate or reliable compared to objective sleep, there is compelling evidence that self-reported sleep represents a unique dimension of sleep and has also been linked to AD pathology independent of the effects of objective sleep [12]. A comprehensive approach incorporating both objective and self-report measures may better capture the complexity of sleep in order to improve our understanding of its relationship with AD.

In conclusion, our findings suggest a link between poor sleep and AD risk, specifically limbic tau pathology and visual memory, particularly in older women with greater genetic predisposition to AD. Our findings support the use of PHS in combination with *APOE* ε4 status in subsequent work. Notably, self-reported sleep measures, like the PSQI, are cost-effective and low burden, and could be a promising marker to detect early AD changes, offering a practical tool to identify individuals at elevated AD risk in wider populations, although further investigation is warranted. Further, this study highlights sleep as a potential modifiable target to promote healthy brain aging in older women. We acknowledge that we did not test whether these are sex-specific findings and may be observed in older men as well. Thus, replicating these analyses with sex-stratified approaches are necessary in larger, ethnoculturally diverse samples in order to elucidate sleep disturbances as an AD risk factor for each sex.

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Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

AI (i.e., ChatGPT) was only used to improve clarity of certain sentences.

Ethical statement

All study protocols were approved by the Institutional Review Board (IRB) at the University of California, San Diego (under protocol number 200383). All participants provided written informed consent to participate in this study.

Data statement

Please contact PI Dr. Sarah Banks (sbanks@health.ucsd.edu) for data requests.

CRediT authorship contribution statement

Kitty K Lui: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Xin Wang:** Writing – review & editing, Methodology, Data curation. **Melanie A Dratva:** Writing – review & editing, Project administration, Investigation, Formal analysis, Data curation. **Ella T. Lifset:** Writing – review & editing, Data curation. **Jordan Stiver:** Writing – review & editing. **Nadine C. Heyworth:** Project administration, Data curation. **Qian Shen:** Writing – review & editing, Formal analysis. **Michael Thomas:** Writing – review & editing, Formal analysis. **Pamela N. DeYoung:** Writing – review & editing, Data curation. **Atul Malhotra:** Writing – review & editing, Supervision, Conceptualization. **Erin E. Sundermann:** Writing – review & editing, Supervision, Conceptualization. **Sarah J. Banks:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sarah J. Banks reports was provided by National Institute of Aging. Sarah J. Banks reports financial support was provided by Women's Alzheimer's Movement. Sarah J. Banks reports was provided by Alzheimer's Association. Sarah J. Banks reports financial support was provided by UCSD Stein Institute for Research on Aging and Center for Healthy Aging. Sarah J. Banks reports financial support was provided by California Department of Public Health. Dr. Malhotra is funded by NIH. He reports income from Eli Lilly, Livanova, Sunrise, Zoll and Powell Mansfield. He is co-founder of Clairyon, a small startup unrelated to this topic. ResMed provided a philanthropic donation to UCSD. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100581.

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