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Original Article

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Sleep architecture and dementia risk in adults: an analysis of 5 cohorts from the Sleep and Dementia Consortium

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Abstract

Study Objectives: Poor sleep may play a role in the risk of dementia. However, few studies have investigated the association between polysomnography (PSG)-derived sleep architecture and dementia incidence. We examined the relationship between sleep architecture and dementia incidence across five US-based cohort studies from the Sleep and Dementia Consortium.

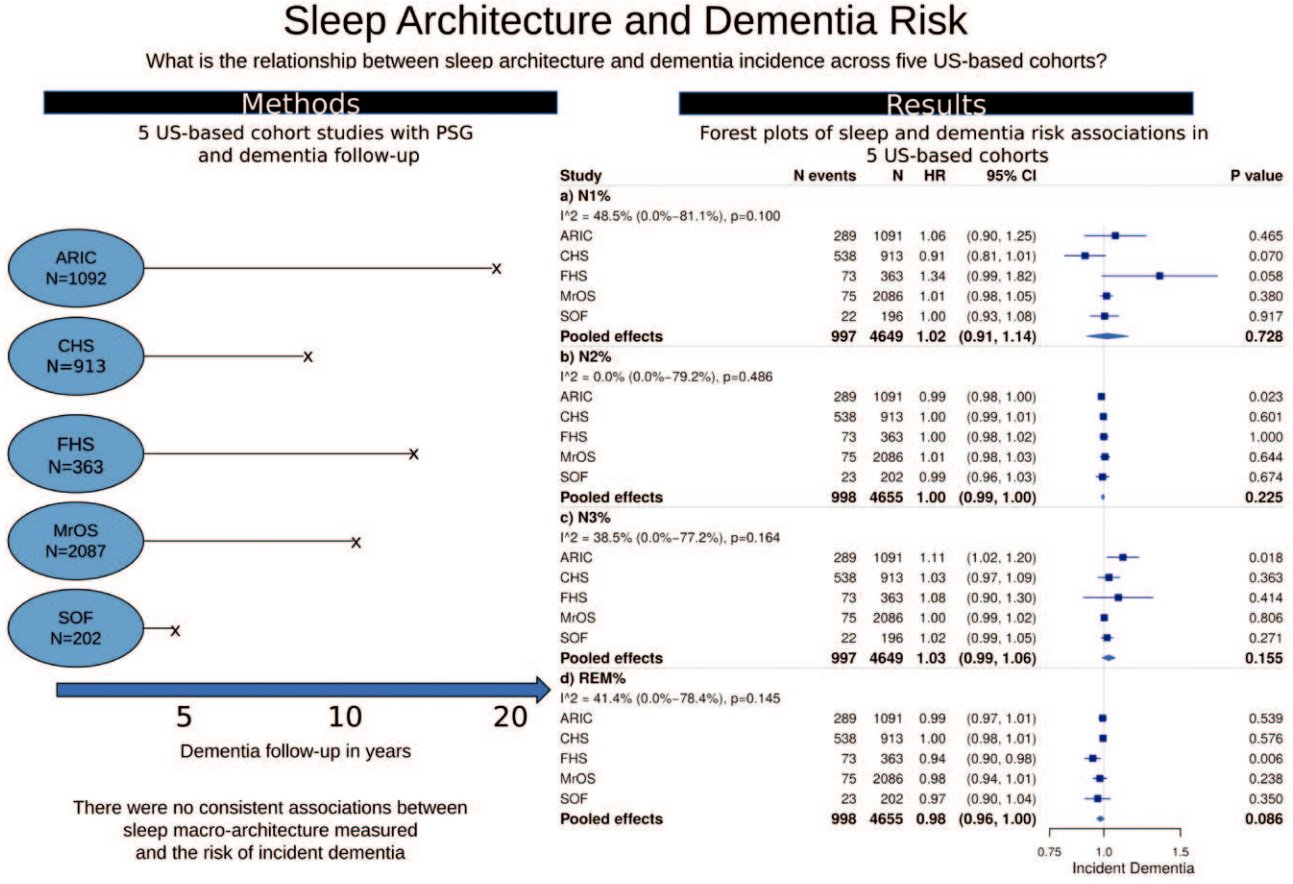
Methods: Percent of time spent in stages of sleep (N1, N2, N3, rapid eye movement sleep), wake after sleep onset, sleep maintenance efficiency, apnea-hypopnea index, and relative delta power were derived from a single night home-based PSG. Dementia was ascertained in each cohort using its cohort-specific criteria. Each cohort performed Cox proportional hazard regressions for each sleep exposure and incident dementia, adjusting for age, sex, body mass index, antidepressant use, sedative use, and *APOE e4* status. Results were then pooled in a random effects model.

Results: The pooled sample comprised 4657 participants (30% women) aged ≥ 60 years (mean age was 74 years at sleep assessment). There were 998 (21.4%) dementia cases (median follow-up time of 5 to 19 years). Pooled effects of the five cohorts showed no association between sleep architecture and incident dementia. When pooled analysis was restricted to the three cohorts which had dementia case ascertainment based on DSM-IV/V criteria (n = 2374), higher N3% was marginally associated with an increased risk of dementia (hazard ratio (HR): 1.06; 95%CI: 1.00-1.12, per percent increase N3, p = .050).

Conclusions: There were no consistent associations between sleep architecture measured and the risk of incident dementia. Implementing more nuanced sleep metrics and examination of associations with dementia subtypes remains an important next step for uncovering more about sleep-dementia associations.

Key words: Alzheimer's disease; dementia; sleep; sleep macro-architecture

Graphical Abstract



Statement of Significance

Poor sleep may represent a potential lifestyle risk factor for dementia. Sleep is thought to be important for the clearance of toxic Alzheimer's disease proteins, but whether sleep is associated with dementia risk remains unclear. In the largest study of its kind, utilizing overnight polysomnographic assessment of sleep and data from 5 large U.S. cohort studies, we examined the association between sleep architecture and dementia risk. There were no clear associations between sleep measures and dementia risk, though there was a suggestion that a higher proportion of N3 sleep may be associated with greater dementia risk. Further exploration of sleep patterns across time, latent sleep traits across metrics, and sleep micro-architecture remains an important next step for understanding sleep-dementia associations.

Sleep undergoes significant changes with aging. As adults age, sleep can become less restorative with alterations in sleep architecture. Specifically, there is a shift towards spending more time in lighter sleep stages (N1 and N2), while the duration of slow-wave sleep (N3) and rapid eye movement (REM) sleep diminishes [1]. Slow-wave sleep is thought to affect synaptic plasticity [2]. It also appears to facilitate the clearance of Alzheimer disease proteins [3–5], though recent findings have challenged this notion [6]. Animal studies indicate that glymphatic clearance of amyloid-β, involved in the formation of amyloid-β plaques in Alzheimer disease, is highest during sleep and potentially slow-wave sleep [7]. Due to this and other mechanisms, sleep dysfunction may serve as a potential target to reduce the risk of, or delay the onset of dementia [8]. However, in humans, the relationship between sleep and dementia is complex, as sleep disturbances are a common feature of dementia and the temporal association between sleep architecture and dementia onset remains unclear [9].

Results derived from studies with an objective sleep assessment, including gold standard polysomnography (PSG), accompanied by long-term follow-up of dementia are limited [10, 11]. To address this gap, we recently formed the Sleep and Dementia Consortium (SDC), comprising five US community-based cohort studies with PSG and long-term follow-up of cognitive, brain imaging, and dementia outcomes [12]. Utilizing SDC data ($N = 5946$, mean baseline ages of 58 to 89 years across cohorts), we recently found little evidence of consistent associations between sleep stage percentages and cognitive performance within the next five years; however, sleep disruption measures (poorer sleep efficiency and higher wake after sleep onset, WASO) and the presence of mild to severe obstructive sleep apnea (OSA) were associated with worse global cognition [12]. Other studies have also demonstrated similar associations between sleep disruption and cognition [13–15]. However, whether differences in sleep architecture are associated with dementia incidence remains equivocal, with further studies needed. Accordingly, we aimed to examine the association between sleep architecture, measured with a single overnight PSG, and incident all-cause dementia in five community-based cohort studies from the SDC.

Methods

The SDC has been described previously [12]. Briefly, it consists of five community-based cohorts that have performed methodologically consistent, overnight, home-based PSG, as well as cognitive testing and dementia case ascertainment. The cohorts include the Atherosclerosis Risk in Communities (ARIC) study, Cardiovascular Health Study (CHS), Framingham Heart Study (FHS), Osteoporotic Fractures in Men Study (MrOS), and Study of Osteoporotic Fractures (SOF).

Written informed consent was provided by all participants prior to the commencement of the study. The study was approved by the Monash University Human Research Ethics Committee, and each cohort obtained institutional review board approval at their respective institutions. For CHS and ARIC, analyses were limited to those with available DNA who consented to genetic studies. Study method and results are reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for cross-sectional studies [16].

Participants

A brief description of the participating cohorts is provided in the Supplementary Methods. We included participants at least 60 years old who were free of dementia and other neurological disorders (e.g., stroke, multiple sclerosis, significant head trauma, subdural hematoma, brain tumor) at the time of the sleep study and who had PSG data and information on dementia status available during follow-up. Participants with less than 180 minutes of total sleep time or less than one minute of REM sleep were excluded to avoid potential bias from spurious data. Table S1 shows the sample selection across cohorts.

Sleep metrics

Sleep was measured at baseline. All cohorts used a standardized protocol to complete overnight home-based Type II PSG using Compumedics PSG equipment (Abbotsford, Australia); the model varied by cohort [17–19]). Briefly, EEG (C3-A2 and C4-A1), electrooculogram, electromyogram, thoracic and abdominal displacement (inductive plethysmography bands), airflow (nasal-oral thermocouples and nasal pressure [in MrOS, SOF]), finger pulse oximeter, a single bipolar electrocardiogram, body position by a mercury gauge sensor, and ambient light level were all recorded. Details of the montages for each study are provided at the National Sleep Research Resource (sleepdata.org).

Sleep macro-architecture

All sleep variables were calculated centrally to ensure consistency of analysis and effective harmonization. Respiratory metrics were annotated, and sleep was initially scored in 30-s epochs according to established guidelines (Rechtschaffen and Kales (R&K) & American Sleep Disorders Association arousal criteria) [18, 19]. Given that contemporary AASM criteria combine stages 3 and 4 of the original R&K guidelines, we combined stages 3 and 4 (N3 sleep). The following sleep metrics were calculated: Stage 1 (N1%), Stage 2 (N2%), Stage 3 (N3%), REM sleep (REM%), WASO (total minutes spent awake between sleep onset and offset), sleep maintenance efficiency (SME%) (total sleep time/sleep period time [the time between sleep onset and sleep offset]), total sleep time (minutes), and the apnea-hypopnea index (AHI) (defined as the number of obstructive apneas plus the number of hypopneas accompanied by a greater than 30% reduction in airflow and 4% or greater oxygen desaturation or arousal per hour of sleep). Moderate to severe OSA was defined as an AHI > 15 vs AHI < 5 (reference). Sleep recording in the ARIC, CHS, and FHS cohorts was limited by a maximum battery life to 9 hours, which prevented further examination of sleep duration greater than 9 hours across all cohorts. Therefore, sleep duration was expressed as ≤6 hours vs >6 hours (reference). Sleep stages were expressed as a percentage of total sleep duration. Scoring was performed at the time of data acquisition at a central reading center by a trained and certified polysomnologist with documented high levels of inter- and intrascorer reliability, as described previously [18]. As some sleep metrics were not normally distributed, square root transformation was applied to N1% and N3% and natural log transformation was applied to SME%, WASO, and the AHI.

Delta power

Slow-wave activity (captured in the delta frequency range 1-4Hz) has been associated with glymphatic clearance [7]. Thus, we performed spectral analysis to compute delta (1-4Hz) power to reflect levels of slow-wave activity. Slow-wave activity was analyzed using the Luna C/C++ pipeline, developed by a member of our team (S.M.P., URL: http://zzz.bwh.harvard.edu/luna/). Delta power was derived from both C4/M2 and C3/M1 EEG signals. Power spectral analysis was performed using the

Welch algorithm and fast Fourier transformation applied to 4-s windows, shifted by 2-s increments and tapered with a Tukey window function (taper length = 50%), yielding a frequency resolution of 0.25 Hz. The relative band power was obtained by dividing the absolute band power by the total power, where the total power was based on the band 0.5–30 Hz. The relative spectral power for delta during combined N2 and N3 sleep was computed.

Co-variates

Co-variates were chosen based on prior knowledge of confounding variables in the association between sleep and dementia. The following co-variates were assessed at baseline and included in statistical models: age (years), sex (men vs women), body mass index (kg/m2), APOE *e4* status (non-*e4* carrier vs at least one copy of *e4*), antidepressant use (yes vs no), and sedative use (yes vs no). Of note, self-report sleep medication use had a strong overlap with sedative and antidepressant use in each cohort, therefore, adjustment for these medications effectively captured sleeping medication.

Dementia case ascertainment

Dementia case ascertainment is described in detail for each cohort in the Supplementary Methods. Briefly, ARIC, CHS, FHS, and SOF adjudicated dementia diagnosis via varying combinations of neurocognitive data, informant interview, hospitalization records, and based broadly on the Diagnostic and Statistical Manual of Mental Disorders, 4th or 5th edition (DSM-IV/V) criteria. In addition, MrOS investigators adjudicated clinically significant cognitive impairment by a report of physician-diagnosed dementia, use of dementia medication, or a change in modified Mini-Mental State Examination scores ≥ 1.5 standard deviations worse than the mean change from baseline to any follow-up visit. Thus, in MrOS, the outcome includes both dementia with clinically significant cognitive impairment. ARIC, CHS, and FHS all had continuous surveillance of dementia with dementia adjudicated by a committee according to DSM-IV/V criteria (or equivalent). For CHS, continuous surveillance was performed through 1998-99, and dementia cases were identified via multiple data sources thereafter (e.g., medications and ICD-9 codes). Both MrOS and SOF assessed dementia at discrete follow-up time points (e.g., several years), up to approximately 10- and 5-years following sleep assessment, respectively.

Statistical Methods

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). R code for analysis is made available in the Supplementary Methods. Demographic characteristics were examined by study cohort. Cox proportional hazards regression models were used to examine the association between sleep metrics and incident all-cause dementia by estimating hazard ratios (HRs) with 95% confidence intervals (CIs). Follow-up duration ranges for each cohort are provided in the Supplementary Methods, and follow-up median durations are provided in Table 1. For each cohort, dementia follow-up commenced from the date of the PSG study to the event of dementia. Non-events were censored at death or until the last date they were known to be dementia-free, or until administrative censoring. Statistical models were adjusted for co-variates listed above. The proportional hazard assumption was examined by including an interaction term between the sleep exposure and the log of follow-up time. The assumption was confirmed graphically and statistically (*P*-value > 0.05) in all cohorts.

Pooled analysis of 5 U.S. cohorts

Study-level estimates were pooled centrally in random effects models. The Sidik-Jonkman estimator method was used to calculate the heterogeneity variance τ^2 and the classic method was used to calculate the 95% CIs around the pooled effect. The Higgins I^2 test was implemented to test for heterogeneity in effect sizes [20]. Statistical tests were all two-sided. All results were considered significant if $p < .05$.

Exploration of effect modification

Since sex [21, 22] and *APOE* [23] allele carrier status are associated with both sleep and dementia risk, we explored effect modification by *APOE e4* allele carrier status (non-*e4* carrier vs at least one copy of *e4*) and sex (men vs women) by including interaction terms in age and sex adjusted models. In the presence of a significant interaction ($p < .05$), results were stratified at each level of the moderating variable. Interaction results were analyzed within each cohort and not in the pooled analysis. Rather, we interpreted patterns that were evident across studies. Sex was not examined as a moderating variable in MrOS or SOF since these cohorts were exclusively men and women, respectively, and *APOE* genotype was not examined as a moderating variable in SOF (since it was not available on all participants).

Secondary analysis

We performed a secondary pooled analysis using a random effects model restricted to ARIC, CHS, and the FHS based on these three cohorts having PSGs performed at the same time (from 1995-1998) in a methodologically consistent manner as part of the multicenter Sleep Heart Health Study (SHHS) [17]. Moreover, these cohorts had the most similar methods in terms of dementia surveillance and adjudication.

Sensitivity analysis

To account for the potential confounding influence of OSA on sleep macro-architecture measures, the primary analyses were repeated including adjustments with the addition of the AHI.

Results

Sample demographics and sleep architecture measures across cohorts are presented in Tables 1 and 2, respectively. Overall, 4657 participants were included in the analysis (30% were women [owing to the large MrOS study being male only]; mean age (weighted by cohort size) was 74 ± 12 years and ranged from 65-83 years at the time of PSG; 3.9% were Black; 95.6% were White, and 0.5% were categorized as other race or ethnicity. Across cohorts, 10.8% of participants did not have a high school degree and 21.2% of participants reported using sleeping pills regularly. In total, there were 998 (21.4%) incident dementia cases across cohorts, with the highest percentage of cases reported in the CHS (58.9%), one of the oldest cohorts with long follow-up. The lowest percentage of dementia cases was in the MrOS cohort (3.6%), which included only men. The median follow-up time ranged between 4.8 to 19.2 years across cohorts. Sleep characteristics for each cohort are presented in Table 2. Sleep stages were mostly similar between cohorts, with the exception of MrOS which had the highest levels of N1 and N2%

Table 1. Demographic characteristics

Participants, No. (%) (N=4657)*	ARIC N = 1092	CHS N = 913	FHS N = 363	MrOS N = 2087	SOF N = 202
Age, mean (SD), years	65.9 (3.9)	77.3 (4.2)	67.5 (4.9)	76.3 (5.5)	82.8 (3.5)
Women	517 (47.3)	520 (57.0)	181 (49.9)	0 (0.0)	202 (100.0)
Self-reported race and ethnicity					
Black	3 (0.3)	147 (16.1)	31 (8.5)	0 (0.0)	0(0.0)
White	1087 (99.5)	762 (83.5)	314 (86.5)	2087 (100.0)	202 (100.0)
Other	2 (0.2)	4 (0.5)	18 (5.0)	(0.0)	0 (0.0)
Education					
<High school	155 (14.2)	181 (19.8)	37 (10.4)	88 (4.2)	44 (21.8)
High school	398 (36.5)	506 (55.5)	114 (32.0)	344 (16.5)	110 (54.5)
>High school	538 (49.3)	225 (24.7)	205 (57.6)	1655 (79.3)	48 (23.8)
Systolic BP, mean (SD) mmHg	124 (18)	130 (19)	132 (17)	126 (16)	135 (17)
Hypertension treatment	428 (39.2)	523 (57.3)	133 (36.8)	1369 (65.6)	139 (68.8)
Stage I Hypertension	443 (40.6)	538 (58.9)	188 (52.2)	1478 (70.8)	160 (79.2)
Prevalent diabetes	74 (6.8)	118 (12.9)	46 (12.8)	272 (13.0)	24 (11.9)
Prevalent CVD	114 (10.4)	106 (11.6)	41 (11.3)	852 (40.9)	36 (17.8)
Current smoker	97 (8.9)	53 (5.8)	39 (10.7)	40 (1.9)	4 (2.0)
Body mass index, Median (Q1, Q3), kg/m^2	28.3 (25.3, 31.8)	27.3 (24.7, 29.9)	27.3 (24.7, 30.7)	26.8 (24.7, 29.4)	27.3 (24.6, 31.2)
Sleeping pill use	255 (23.4)	214 (23.6)	50 (14.2)	421 (20.2)	46 (22.8)
Antidepressant use	67 (6.1)	48 (5.3)	10 (2.8)	155 (7.4)	11 (5.5)
Sedative use	58 (5.3)	72 (7.9)	13 (3.6)	140 (6.7)	31 (15.4)
APOE e4 carrier	309 (28.3)	218 (23.9)	81 (22.3)	484 (23.2)	22 (10.9)**
Incident all cause Dementia	289 (26.5%)	538 (58.9%)	73 (20.1%)	75 (3.6)	23 (11.4)
Median follow-up time, years (Q1, Q3)	19.2 (13.8, 21.6)	8.5 (4.1, 13.6)	15.7 (9.8, 21.1)	10.5 (7.6, 11.4)	4.8 (4.1, 5.2)

*Values are *n* (%) unless otherwise specified as mean (SD) or median [Q1, Q3] for non-normally distributed variables.
**APOE e4 carrier status was calculated as *the percentage among those for whom their status* was known in SOF. ARIC, Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; MrOS, Osteoporotic Fractures in Men Study; SOF, Study of Osteoporotic Fractures; CVD, cardiovascular disease.

and lowest levels of N3%. SME was similar between ARIC, CHS and FHS (ranging between 85-87%), but lowest in MrOS and SOF (range 78-82%). Similarly, WASO ranged between 54-63 minutes across ARIC, CHS and FHS and was highest in MrOS and SOF (76 to 101 minutes). Across cohorts, the average AHI ranged between 6-8 events/hour. The proportion who experienced short sleep duration of ≤ 6 hours per night ranged from 43-52%.

Sleep and dementia risk

Figure 1 presents the pooled analysis results, summarizing the association between sleep exposures and incident all-cause dementia. In the majority of cohorts, higher N3% (Figure 1c) and lower REM% (Figure 1d) was associated with a non-significant increased risk of dementia. However, pooled estimates revealed no statistically significant associations between these sleep exposures and dementia risk. Higher SME% (Figure 1e) and lower WASO (Figure 1f) were associated with reduced dementia risk in some cohorts (e.g., ARIC, FHS and SOF), though these were largely non-significant; the overall pooled association with dementia risk was not statistically significant. Additionally, heterogeneity in effect estimates between studies was moderate to substantial in these models (SME% I^2 = 50% [95% CI 0.0%, 82%]; WASO I^2 = 72% [95% CI 29%, 89%]).

In the majority of the cohorts, moderate to severe OSA was associated with increased dementia risk (Figure 1h), though these associations were non-significant as was the overall pooled estimate.

Analysis of delta power produced mixed results amongst the cohorts (Figure 1i). Two cohorts showed that higher delta power was associated with reduced dementia risk; however, these same associations were not observed in the other cohorts, and the pooled estimates of the 5 cohorts showed no significant associations. There was, however, moderate to substantial heterogeneity in effect estimates between studies (Delta power I^2 = 78% [95% CI 46%, 91%].

In the secondary analysis limited to CHS, FHS and ARIC from the SHHS, there were 2367 participants and 900 incident dementia cases. Compared to the primary analyses, the age range was slightly younger (range 65 to 77 years; weighted mean age 70.5 years), a higher proportion were women (51.6%), and the average follow-up time was longer (range 8.5 to 19.2 years). In these analyses, restricting to three cohorts, higher N3% was marginally associated with increased dementia risk (HR = 1.06; 95% CI = 1.00 to 1.12, $p < .05$), such that for every percentage increase in N3 sleep there was a 6% increase in dementia risk (Figure 2).

Table 2. Sleep characteristics

Median (Q1, Q3)*	ARIC N = 1092	CHS N = 913	FHS N = 363	MrOS N = 2087	SOF N = 202
N1 (%)	5.1 (3.1, 7.7)	4.7 (2.7, 7.3)	4.8 (3.0, 7.3)	6.0 (4.0, 8.0)	4.1 (2.7, 5.9)
N2 (%)	56.0 (11.5)	57.9 (12.6)	56.75 (12.0)	62.6 (9.5)	55.0 (12.5)
N3 (%)	17.5 (8.3, 25.4)	16.3 (7.3, 25.8)	17.7 (8.8, 26.3)	10.3 (4.1, 17.0)	19.6 (12.6, 29.1)
REM (%)	20.4 (5.9)	18.7 (6.3)	19.5 (5.9)	19.3 (6.5)	18.6 (6.8)
Sleep maintenance efficiency (%)	87.4 (80.6, 91.6)	85.0 (76.7, 90.8)	87.0 (80.0, 92.1)	78.5 (70.4, 85.0)	82.2 (73.4, 88.7)
Wake after sleep onset (min)	54.0 (34.5, 85.0)	63.5 (37.5, 101.3)	55.5 (32.5, 87.5)	101.0 (66.0, 145.0)	76.0 (47.5, 116.5)
Apnea-hypopnea index (no. events/hour)	6.2 (2.3, 13.9)	7.3 (2.8, 15.4)	6.5 (2.2, 14.3)	8.2 (3.2, 17.1)	6.4 (2.5, 13.2)
OSA categories (events/hour)					
Normal: AHI < 5;	437 (44.7%)	313 (39.32%)	155 (44.41%)	920 (35.66)	144 (38.1)
Mild: AHI 5 to < 15	315 (32.2%)	281 (35.30%)	112 (32.09%)	907 (35.16)	146 (38.6)
Moderate: AHI 15 to < 30	148 (15.2%)	133 (16.71%)	61 (17.48%)	501 (19.42)	60 (15.9)
Severe: AHI ≥ 30	77 (7.88%)	69 (8.67%) A	21 (6.02%)	252 (9.77)	28 (7.4)
Total sleep time ≤ 6 hours, *n* (%)	488 (44.7)	471 (51.6)	157 (43.3)	1038 (49.7)	104 (51.4)
Relative Delta power N2 + N3	0.50 (0.05)	0.48 (0.05)	0.49 (0.05)	0.45 (0.05)	0.43 (0.05)

*Values are median (Q1, Q3) for non-normally distributed data or mean (SD) for normally distributed data, unless specified as *n* (%).
N1, stage 1 non-rapid eye movement sleep; N2, stage 2 non-rapid eye movement sleep; N3, stage 3 non-rapid eye movement sleep; REM, rapid eye movement sleep; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index.

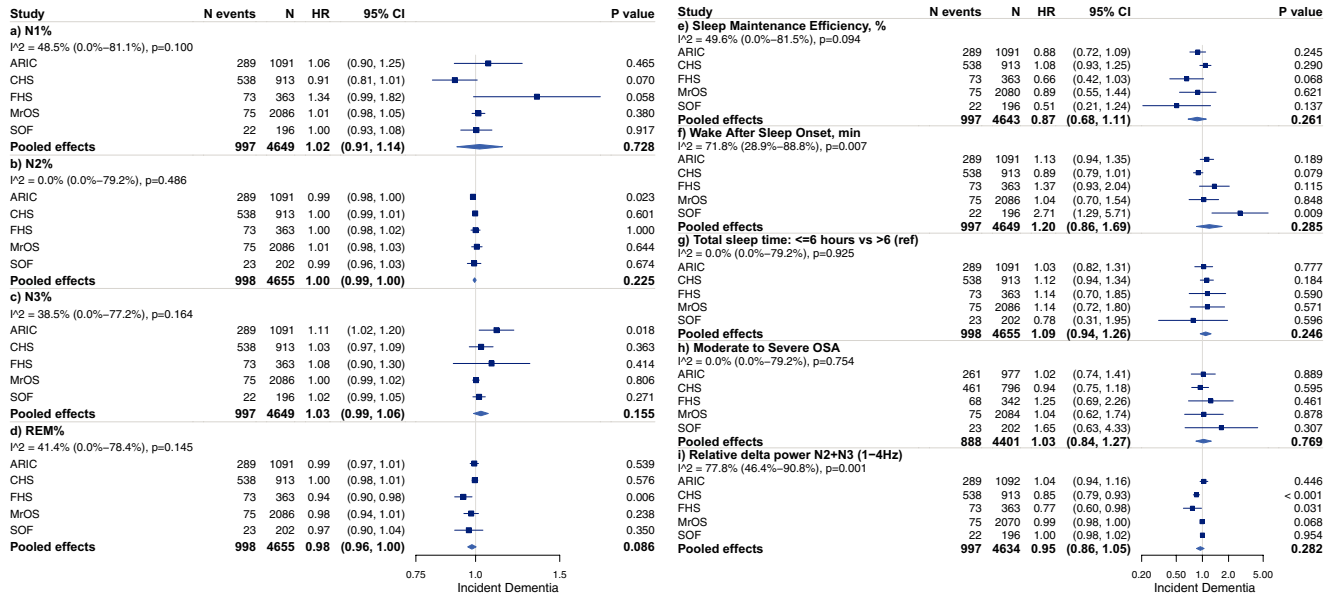


Figure 1. Pooled association between sleep macro-architecture measures and incident dementia. Figure depicts the pooled analysis of 5 U.S. cohorts with forest plot. All results were adjusted for age (years), sex (men vs women), BMI (kg/m^2), antidepressant use (yes vs no), sedative use (yes vs no), and *APOE e4* status (non e4 carrier vs at least one copy of e4). Cohort studies included: ARIC, Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; MrOS, Osteoporotic Fractures in Men Study; SOF, Study of Osteoporotic Fractures. The sleep exposures in each model included: N1, non-rapid eye movement sleep stage 1; N2, non-rapid eye movement sleep stage 2; N3, non-rapid eye movement sleep stage 3; REM, rapid eye movement sleep; WASO, Wake after sleep onset; SME, sleep maintenance efficiency; Moderate to Severe OSA (obstructive sleep apnea; AHI ≥ 15 vs < 15 events/hour); Relative Delta Power N2 + N3 (1-4Hz). Note that, for relative delta power, HRs were re-scaled to reflect a 0.05 (5%) unit change in relative delta power to improve interpretability. Also, square root transformation was applied to N1% and N3% and natural log transformation was applied to SME%, WASO and the AHI due to skewed distributions of these sleep metrics. Dementia case numbers are presented for each cohort with hazard ratio (HR) and 95% confidence intervals (95% CI) for dementia risk. Heterogeneity in effect sizes was determined via the Higgins I^2 test. Statistical significance, $p < .05$.

There were no other associations identified with the other sleep exposure variables.

Moderation analysis

Results for the moderation analysis by *APOE e4* status and sex are presented in Tables S2 to S5. There was no consistent pattern of moderation of *APOE e4* status or sex between any of the sleep measures and dementia incidence across cohorts.

Sensitivity analysis

Additional adjustment for the AHI did not meaningfully alter the results (Table S6).

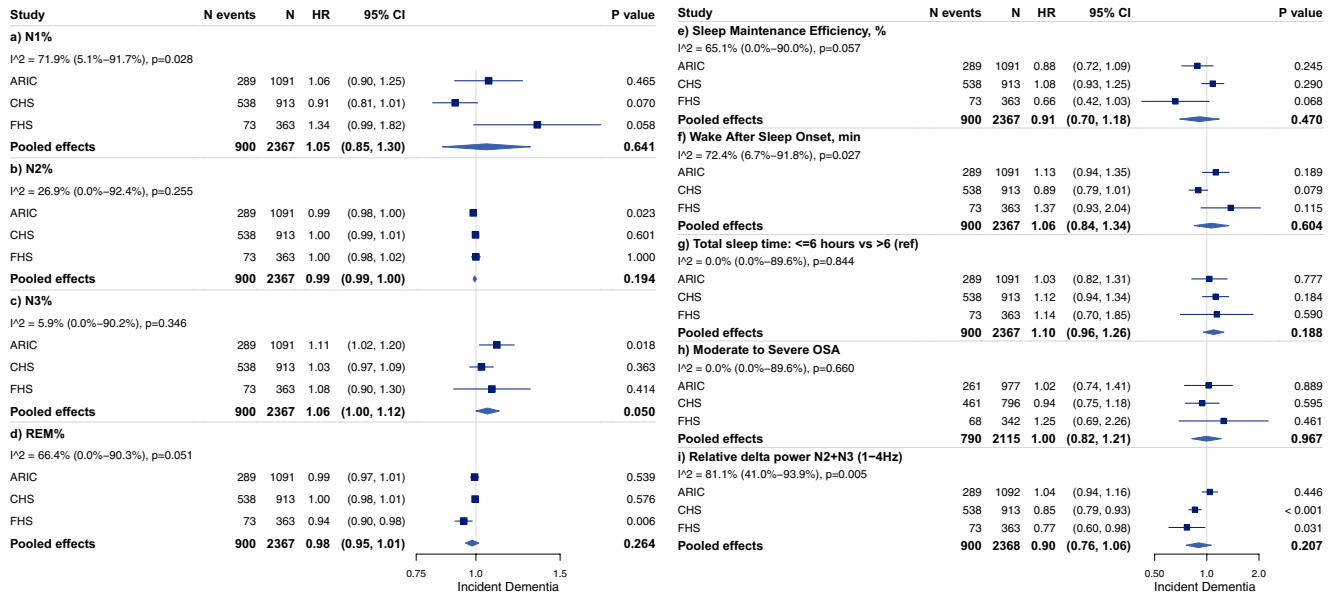


Figure 2. Pooled association between sleep macro-architecture measures and incident dementia—secondary analysis restricted to ARIC, CHS, FHS cohorts. Figure depicts the pooled analysis of 5 U.S. cohorts with forest plot limited to three cohorts. All results were adjusted for age (years), sex (men vs women), BMI (kg/m^2), antidepressant use (yes vs no), sedative use (yes vs no), and *APOE e4* status (non e4 carrier vs at least one copy of e4). Cohort studies included: ARIC, Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study and the FHS, Framingham Heart Study. The sleep exposures in each model included: N1, non-rapid eye movement sleep stage 1; N2, non-rapid eye movement sleep stage 2; N3, non-rapid eye movement sleep stage 3; REM, rapid eye movement sleep; WASO, Wake after sleep onset; SME, sleep maintenance efficiency; Moderate to Severe OSA (obstructive sleep apnea; AHI ≥ 15 vs < 15 events/hour); Relative Delta Power N2 + N3 (1-4Hz). Note that, for relative delta power, HRs were re-scaled to reflect a 0.05 (5%) unit change in relative delta power to improve interpretability. Also, square root transformation was applied to N1% and N3% and natural log transformation was applied to SME%, WASO and the AHI due to skewed distributions of these sleep metrics. Dementia case numbers are presented for each cohort with hazard ratio (HR) and 95% confidence intervals (95% CI) for dementia risk. Heterogeneity in effect sizes was determined via the Higgins I^2 test. Statistical significance, $p < .05$.

Discussion

To our knowledge, this is the largest initiative to investigate the association between PSG-derived sleep architecture measures and risk of dementia. Across five US cohorts, the overall pooled effects showed no association between sleep variables and incident dementia, although some sleep stage percentages and measures of sleep disruption revealed a non-significant association toward increased dementia risk. Higher levels of delta power, reflecting slow-wave activity, also revealed a non-significant reduction in dementia risk. Further, the effect modification analysis showed few and inconsistent interactions of sex and *APOE e4* positivity on associations between sleep and dementia. There was also moderate to large heterogeneity between study effects for some sleep metrics. Of note, when data were restricted to the three SHHS cohorts, there was an unexpected suggestion that higher N3% was associated with greater increased dementia risk but not for other stages.

N3 sleep is important for memory consolidation [24, 25] and animal studies indicate that slow-wave activity (occurring at the delta frequency 0.5-4 Hz), which is dominant during N3 sleep, plays an important role in the glymphatic clearance of amyloid-β [7]. Thus, we hypothesized that lower N3% may be one of the strongest predictors of dementia risk. In contrast to our expectations, our primary results suggest that individual differences in N3 quantity at a discrete time point may not be meaningful for dementia prediction. In line with these findings, the initial analysis of the SDC cohorts also showed no association between sleep stage durations and cognition [12]. To further isolate the contribution of slow-wave activity to dementia risk, we also investigated whether spectral estimates of relative delta power may be associated with dementia risk. However, though some cohorts did show that a higher amount of delta power (CHS and FHS) was associated with a reduction in dementia risk, there were mixed findings among the other cohorts.

There are several explanations for our findings. Importantly, the measure of N3% or delta power may not completely capture the full range and detail of EEG oscillatory activity (e.g., including Up and Down states of increased and quiet activity) reflective of variations in cortical rhythms believed to be important for synaptic plasticity and memory consolidation [26]. That is, within scored N3 sleep, the duration of slow waves, their coupling with spindles and frequency power vary. In this study, we investigated delta power within the frequency range of 1-4Hz. However, studies have shown that within the delta frequency band, slow frequencies (0.5-1 Hz) vs higher frequencies (up to 4 Hz) have inverse associations with cognitive outcomes [14]. Previous studies that utilized spectral analysis have shown that the duration of slow-wave oscillations and the ratio of slow (< 1 Hz) to delta waves (0.5 to 4 Hz), not N3 duration, were associated with cognitive performance [14]. Further, slow delta power has been associated with better brain integrity (assessed by gray matter volume and perfusion measures), while the inverse association for faster delta waves was observed [27]. This suggests the need to characterize multiple aspects of slow-wave activity, as well as EEG features such as spindles and K complexes.

Another explanation for our largely null findings could be the age range at which participants were studied. As N3 sleep declines with age, individual differences at younger ages than studied here may be more relevant to the study of late-life dementia risk (e.g., a lower percentage of N3 sleep or delta power at an earlier age may be indicative of accelerated brain aging). It is also possible

that a loss or gain in N3% over time is more important for determining dementia risk, rather than differences between individuals at a given time point. Recent data from the FHS showed that a 1% decline in N3% per year was associated with a 27% increased risk of dementia [23].

The finding that higher N3% was marginally associated with increased dementia risk in the analysis restricted to the three original SHHS cohorts should not be overinterpreted, given that it was not significant in the primary analyses and the large number of comparisons conducted. Nevertheless, there are a number of mechanisms that could explain this association. N3 sleep is a highly reactive sleep stage [28]. Higher N3 sleep may reflect high homeostatic sleep pressure due to prior night sleep deprivation. That is, higher N3% captured by the single overnight sleep study may serve as a proxy for irregular sleep patterning or chronic sleep deprivation. Alternatively, our findings may reflect the capacity of central mechanisms to make a compensatory increase in the proportion of N3 sleep to protect the brain. It has been proposed that N3 sleep may be responsive to wake-dependent buildup of metabolic and oxidative byproducts, whereby slow-wave activity increases to counterbalance amyloid-β aggregation [29]. Those with higher amounts of N3 sleep may reflect individuals with elevated levels of amyloid. Speculatively, in select people, loss of the ability for N3 sleep to accommodate the accumulation of amyloid could reflect the tipping point at which individuals become vulnerable to neurodegeneration and subsequent dementia. However, further longitudinal studies with sleep assessed at multiple time points are required to confirm this contention.

In contrast to previous studies [11, 30], this study found no association of REM% and OSA with incident dementia. For REM sleep associations, the possible null findings in this pooled analysis of the 5 cohorts may be due to the older age range studied in the overall sample. Unlike N3 sleep, REM sleep sees little decline with older age [1], resulting in a smaller range of REM changes which may be too small to detect a difference. For OSA and dementia associations, although some studies have identified that OSA is associated with higher dementia risk [10, 31], it is important to note that treatment of OSA was part of the exclusion criteria for the Sleep Heart Health Study cohorts (ARIC, CHS, FSH) and MrOS. Further, we did not capture reliable information on OSA treatment during the follow-up period. Thus, some participants with baseline OSA in our study may have been treated, potentially dampening associations between baseline OSA and dementia risk. In these same SDC cohorts, we have previously shown that OSA was associated with poorer cognition within 5-years [12] suggesting that, despite the present findings, OSA may still have more subtle adverse effects on brain health.

Our previous results in the SDC cohort [12], as well as findings from other studies utilizing actigraphy [32], indicate that higher levels of sleep disruption (e.g., lower sleep efficiency and high WASO) are associated with poorer cognition. Although there was a nominal tendency for sleep disruption measures to associate with dementia risk in some cohorts, the pooled effects in this study showed no significant associations. We did observe that higher amounts of WASO were associated with significantly increased dementia risk in the SOF cohort, which was the oldest cohort with the shortest duration of follow-up. Thus, it is possible that reverse causation may underlie this relationship. Measures of sleep disruption at multiple time points across the lifespan would be helpful to further determine the temporal association between WASO and dementia risk.

We also investigated whether any of the study effects were influenced by *APOE* or sex. While *APOE e4* carriage is the most important genetic risk factor for dementia [33], and dementia risk is highest among women [34], evidence to show that these factors (*APOE e4* carriage or sex) moderated any of the sleep-dementia associations was inconsistent between studies. However, these interactions could be dependent on cohort-specific characteristics (e.g., age or sex distributions). Thus, investigating these moderation effects may require a larger sample size (with a higher number of dementia cases) to truly tease out these relationships if they exist.

This study has a number of strengths, including the large sample size, long prospective follow-up duration, representation from five different cohorts and use of methodologically consistent PSG recordings. However, there were several limitations. Firstly, not all studies adjudicated dementia using DSM criteria. To address this in some manner, we performed a sensitivity analysis that contained only the original SHHS cohorts, which had similar dementia adjudication methods. In this analysis, we saw HRs of mostly similar in magnitude and direction for all sleep measures. Secondly, sleep was measured over a single night, which may not fully represent habitual sleep patterns and sleep architecture. Thus, future studies that utilize PSG recordings across several nights and accelerometry may provide a more robust characterization of sleep architecture and its variability. This is particularly relevant given that lower sleep regulatory and circadian rhythmicity have been associated with the risk of dementia [35]. Also, as there could be a critical age where sleep measures more strongly relate to late-life dementia risk, we may not have assessed sleep at the optimal life stage to capture sleep-dementia associations.

Implications and Conclusions

Sleep has been implicated in many mechanisms that are related to dementia, such as memory formation [36], glymphatic clearance [7], and vascular brain health [37]. However, the role of poor sleep as a dementia risk factor remains poorly understood. The current findings suggest that sleep stage quantity, basic sleep disruption and slow wave activity measures obtained at a single time point may not be useful for predicting long-term dementia risk overall. In light of this, research efforts could be directed to explore more precise neurophysiological measures of sleep, including more quantitative measures of oscillations and dynamic changes of the EEG across the sleep period, including distributions of sleep spindles (e.g., slow-wave spindle coupling metrics). Moreover, rather than using individual metrics as exposures, more advanced statistical techniques could be used to derive different sleep phenotypes from combinations of individual metrics. Also, when considering other recent findings [23], understanding the trajectories of sleep with aging, rather than single point measurements, may be more informative for dementia risk. This study also highlights that there is marked variability in sleep-dementia associations between different cohorts. Identification of the drivers of this heterogeneity will be an important next step, as there may be certain factors that protect against dementia in the face of poor sleep. In other words, individual sleep metrics may be more predictive in specific subpopulations.

In conclusion, sleep architecture measures investigated in this study were not consistently associated with dementia risk. Although N3 sleep plays a role in glymphatic clearance [7] and declining N3 sleep has been linked with dementia [23], individual differences in N3 sleep do not have a straightforward association with dementia risk. Future studies stratifying data according to

dementia subtypes is needed, as sleep associations may differ among them. Finally, examining more complex micro-architectural measures of sleep, how sleep metrics change over time, and N3 associations with amyloid and tau burden will be important for further elucidating sleep and dementia relationships.

Supplementary material

Supplementary material is available at *SLEEP* online.

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References

1. Edwards BA, O'Driscoll DM, Ali A, Jordan AS, Trinder J, Malhotra A. Aging and sleep: physiology and pathophysiology. *Semin Respir Crit Care Med*. 2010;**31**(5):618–633. doi:10.1055/s-0030-1265902
2. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull*. 2003;**62**(2):143–150. doi:10.1016/j.brainresbull.2003.09.004

3. Wunderlin M, Zust MA, Feher KD, Kloppel S, Nissen C. The role of slow wave sleep in the development of dementia and its potential for preventative interventions. *Psychiatry Res Neuroimaging*. 2020;**306**:111178. doi:10.1016/j.pscychresns.2020.111178
4. Lucey BP, McCullough A, Landsness EC, *et al*. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med*. 2019;**11**(474):eaau6550. doi:10.1126/scitranslmed.aau6550
5. Winer JR, Mander BA, Helfrich RF, *et al*. Sleep as a potential biomarker of tau and beta-amyloid burden in the human brain. *J Neurosci*. 2019;**39**(32):6315–6324. doi:10.1523/JNEUROSCI.0503-19.2019
6. Miao A, Luo T, Hsieh B, *et al*. Brain clearance is reduced during sleep and anesthesia. *Nat Neurosci*. 2024;**27**(6):1046–1050. doi:10.1038/s41593-024-01638-y
7. Xie L, Kang H, Xu Q, *et al*. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;**342**(6156):373–377. doi:10.1126/science.1241224
8. Sprecher KE, Koscik RL, Carlsson CM, *et al*. Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. *Neurology*. 2017;**89**(5):445–453. doi:10.1212/WNL.0000000000004171
9. Ju YE, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology--a bidirectional relationship. *Nat Rev Neurol*. 2014;**10**(2):115–119. doi:10.1038/nrneurol.2013.269
10. Yaffe K, Laffan AM, Harrison SL, *et al*. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA*. 2011;**306**(6):613–619. doi:10.1001/jama.2011.1115
11. Pase MP, Himali JJ, Grima NA, *et al*. Sleep architecture and the risk of incident dementia in the community. *Neurology*. 2017;**89**(12):1244–1250. doi:10.1212/WNL.0000000000004373
12. Pase MP, Harrison S, Misialek JR, *et al*. Sleep architecture, obstructive sleep apnea, and cognitive function in adults. *JAMA Netw Open*. 2023;**6**(7):e2325152. doi:10.1001/jamanetworkopen.2023.25152
13. Cavuoto MG, Ong B, Pike KE, Nicholas CL, Bei B, Kinsella GJ. Objective but not subjective sleep predicts memory in community-dwelling older adults. *J Sleep Res*. 2016;**25**(4):475–485. doi:10.1111/jsr.12391
14. Djonlagic I, Mariani S, Fitzpatrick AL, *et al*. Macro and micro sleep architecture and cognitive performance in older adults. *Nat Hum Behav*. 2021;**5**(1):123–145. doi:10.1038/s41562-020-00964-y
15. Swanson LM, Hood MM, Hall MH, *et al*. Associations between sleep and cognitive performance in a racially/ethnically diverse cohort: the Study of Women's Health Across the Nation. *Sleep*. 2021;**44**(2):zsaa182. doi:10.1093/sleep/zsaa182
16. von EE, Altman DG, Egger M, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;**335**(7624):806–808. doi:10.1136/bmj.39335.541782.AD
17. Quan SF, Howard BV, Iber C, *et al*. The sleep heart health study: design, rationale, and methods. *Sleep*. 1997;**20**(12):1077–1085.
18. Whitney CW, Gottlieb DJ, Redline S, *et al*. Reliability of scoring respiratory disturbance indices and sleep staging. *Sleep*. 1998;**21**(7):749–757. doi:10.1093/sleep/21.7.749
19. Redline S, Sanders MH, Lind BK, *et al*. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. *Sleep*. 1998;**21**(7):759–767.
20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;**21**(11):1539–1558. doi:10.1002/sim.1186
21. Gong J, Harris K, Lipnicki DM, *et al*.; Cohort Studies of Memory in an International Consortium (COSMIC). Sex differences in dementia risk and risk factors: individual-participant data analysis using 21 cohorts across six continents from the COSMIC consortium. *Alzheimers Dement*. 2023;**19**(8):3365–3378. doi:10.1002/alz.12962
22. Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med*. 2004;**164**(4):406–418. doi:10.1001/archinte.164.4.406
23. Himali JJ, Baril AA, Cavuoto MG, *et al*. Association between slow-wave sleep loss and incident dementia. *JAMA Neurol*. 2023;**80**:1326. doi:10.1001/jamaneurol.2023.3889
24. Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci*. 2010;**11**(2):114–126. doi:10.1038/nrn2762
25. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev*. 2006;**10**(1):49–62. doi:10.1016/j.smrv.2005.05.002
26. Torao-Angosto M, Manasanch A, Mattia M, Sanchez-Vives MV. Up and down states during slow oscillations in slow-wave sleep and different levels of anesthesia. *Front Syst Neurosci*. 2021;**15**:609645. doi:10.3389/fnsys.2021.609645
27. Champetier P, Andre C, Rehel S, *et al*.; Medit-Ageing Research Group . Multimodal neuroimaging correlates of spectral power in NREM sleep delta sub-bands in cognitively unimpaired older adults. *Sleep*. 2024;**47**(4):zsae012. doi:10.1093/sleep/zsae012
28. Borbely A. The two-process model of sleep regulation: beginnings and outlook. *J Sleep Res*. 2022;**31**(4):e13598. doi:10.1111/jsr.13598
29. Mander BA, Winer JR, Jagust WJ, Walker MP. Sleep: a novel mechanistic pathway, biomarker, and treatment target in the pathology of Alzheimer's disease? *Trends Neurosci*. 2016;**39**(8):552–566. doi:10.1016/j.tins.2016.05.002
30. Song Y, Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Stone KL; Osteoporotic Fractures in Men (MrOS) Study Group. Relationships between sleep stages and changes in cognitive function in older men: the MrOS Sleep Study. *Sleep*. 2015;**38**(3):411–421. doi:10.5665/sleep.4500
31. Bubu OM, Brannick M, Mortimer J, *et al*. Sleep, cognitive impairment, and Alzheimer's disease: a systematic review and meta-analysis. *Sleep*. 2017;**40**(1):zsw032. doi:10.1093/sleep/zsw032
32. Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol*. 2014;**13**(10):1017–1028. doi:10.1016/S1474-4422(14)70172-3
33. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol*. 2013;**9**(2):106–118. doi:10.1038/nrneurol.2012.263
34. G. B. D. 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;**7**(2):e105–e125. doi:10.1016/S2468-2667(21)00249-8
35. Yiallourou SR, Cribb L, Cavuoto MG, *et al*. Association of the sleep regularity index with incident dementia and brain volume. *Neurology*. 2024;**102**(2):e208029. doi:10.1212/WNL.0000000000208029
36. Rasch B, Born J. About sleep's role in memory. *Physiol Rev*. 2013;**93**:681–766. doi:10.1152/physrev.00032.2012
37. Baril A-A, Beiser AS, Mysliwiec V, *et al*. Slow-wave sleep and MRI markers of brain aging in a community-based sample. *Neurology*. 2021;**96**(10):e1462–e1469. doi:10.1212/WNL.0000000000011377