

Slow-wave sleep across the Alzheimer's disease continuum: cognitive trajectories and sex differences

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Abstract

Background

Sleep disturbances are common in Alzheimer's disease and have been reported in its preclinical stage. A detailed characterization of sleep disruption across the Alzheimer's disease *continuum* is required to clarify its role as a potential therapeutic target and to evaluate the utility of sleep-related biomarkers.

Methods

Sleep architecture was characterized through detailed spectral and temporal analysis of the slow-wave activity using polysomnography across the Alzheimer's disease *continuum*. Participants included: cognitively unimpaired individuals without abnormal Alzheimer's disease biomarkers ($n = 30$), cognitively unimpaired individuals with abnormal Alzheimer's disease biomarkers ($n = 45$), and individuals with mild cognitive impairment or mild dementia due to Alzheimer's disease ($n = 41$). Associations between slow-wave features and longitudinal cognitive performance were tested in cognitively unimpaired participants. Sex differences were also explored.

Results

A stepwise increased wake after sleep onset and latency to rapid eye movement sleep was observed, alongside reduced spectral power of slow-wave activity and a progressive flattening of slow-waves across the Alzheimer's disease *continuum* in both sexes. In cognitively unimpaired individuals, higher slow-wave slope and greater peak-to-peak amplitude were associated with better cognitive trajectories over time.

Conclusions

Sleep macro- and microarchitecture are altered early and progressively deteriorate across the Alzheimer's disease *continuum*. Slow-wave features relate to cognitive trajectories in preclinical Alzheimer's disease, with exploratory analyses suggesting stronger associations in men. These findings support slow-wave morphology as a candidate non-invasive marker for future sleep-based intervention studies.

1. Background

Alzheimer's disease (AD) is the most common cause of dementia[1], affecting over 50 million people globally[2]. It is characterized by the accumulation of amyloid beta ($A\beta$) plaques and phosphorylated tau tangles in the brain[3, 4], which begins decades before the first cognitive symptoms appear[4], during the preclinical phase of the disease[5, 6].

Sleep disturbances, such as insomnia[7], increased daytime sleepiness[8], and sleep-related breathing disorders[8, 9] are highly prevalent in AD patients[10]. Polysomnography (PSG), the gold standard for objective sleep measurement[11], has shown increased nocturnal awakenings, decreased sleep efficiency (SE) and greater sleep fragmentation in AD patients, compared to healthy controls[12, 13]. AD is associated with changes in sleep architecture, including prolonged sleep latency[13] and delayed rapid eye movement (REM) sleep onset [12, 13]. Moreover, patients show reduced time spent in REM sleep and in the deepest non-REM (NREM) sleep stage, also known as slow-wave sleep (SWS)[12, 14, 15].

Slow-wave activity (SWA) is the hallmark of SWS[16]. SWA is defined as the EEG power within the 0.5-4 Hz frequency range during NREM sleep and comprises two main components: slow oscillations (< 1 Hz, SO) and delta activity (1–4 Hz). Slow-waves (SW)[17] are the discrete electrophysiological events underlying SWA, characterized by a high-amplitude negative deflection followed by a positive half-wave[17, 18].

SWS plays a key role in healthy aging[19] and is particularly relevant in the context of AD[20], since it is critically involved in cognitive processes, particularly memory consolidation[21]. During SWS, cortical SO coordinate the reactivation and redistribution of newly acquired memories from the hippocampus to the neocortex[22–24], a mechanism that becomes increasingly vulnerable as AD pathology accumulates[25]. Moreover, glymphatic clearance (i.e., the process of removing waste from the brain, including A β and tau toxic aggregates) is enhanced during SWS[27, 28] and enlarged perivascular spaces in the basal ganglia have been linked to lower SWA[29]. Notably, tau pathology starts to accumulate early in the disease course in sleep-wake regulating regions[30], such as the hypothalamus, locus coeruleus[31], prefrontal cortex[32], or other structures in the brainstem[33–35], and recent evidence has related SWS with the integrity of the locus coeruleus[29].

Alterations in these cortical rhythms have also been reported in patients with amnesic mild cognitive impairment (MCI), considered a prodromal stage of AD[36]. For instance, there is evidence of a reduced power in the SWA frequency range during NREM sleep in central and parietal regions of MCI patients compared to controls[37]. However, few studies have systematically investigated SWA in MCI or AD patients[13, 29, 38–40], and some findings are inconsistent[41]. Moreover, increasing evidence points to the potential role of sleep as a risk factor for AD[8, 42–47], since alterations in sleep physiology are already reported during the preclinical phase of AD[43, 44, 48], and are associated with increased amyloid[25, 49–51] or tau[52] burden and cognitive decline[25, 48, 53, 54]. However, while cross-sectional studies have linked SWS alterations to cognitive impairment in MCI and AD patients[37, 40, 41], longitudinal evidence on how SWS parameters relate to cognitive trajectories during the preclinical phase of AD remains scarce[53]. Understanding whether SWS disruption associates with cognitive decline in cognitively unimpaired (CU) individuals could be particularly valuable, as this window represents the optimal target for early intervention.

An additional layer of complexity in understanding the sleep-AD relationship lies in the well-established sex differences in both sleep architecture and AD epidemiology. Although objective measures reveal that men exhibit poorer sleep, with lower percentage of SWS duration and reduced power in the SO and the delta frequency bands[55, 56], women report worse subjective sleep quality than men[57]. Moreover, sleep disturbances have a higher impact on women compared to men, increasing their risk of depression[58], metabolic disorders[59] or cardiovascular dysfunction[60]. In addition, women are at a higher risk of developing AD than men[61, 62].

Despite advances from previous studies, evidence on SWS alterations across the full AD continuum—including preclinical stages—remains limited[25, 52, 63, 64]. In particular, it remains unclear whether individual slow-wave morphology is progressively altered across preclinical and early symptomatic AD, and whether these alterations relate to longitudinal cognitive trajectories before dementia onset. Ultimately, given the well-documented sex differences in both sleep physiology and AD risk, it remains unclear whether these relationships differ between men and women.

Therefore, in this study, we performed a cross-sectional characterization of PSG-derived SWA expression at different stages of the AD *continuum*, combining a group of CU participants with or without altered AD biomarkers with a group of patients with biomarker-confirmed MCI or mild dementia due to AD. In the CU participants, we further tested associations between SWS parameters and cognitive trajectories. Finally, we explored sex differences to understand how alterations in sleep architecture may affect men and women differently in their cognitive trajectories or throughout the AD continuum.

2. Materials and methods

2.1. Study participants

We included participants from two cohorts. CU (Clinical Dementia Rating (CDR) 0) individuals with and without abnormal amyloid deposition levels were recruited from the ALFASleep study[65]. The ALFASleep study protocol was approved by the Independent Ethics Committee *Parc de Salut Mar Barcelona* and registered at Clinicaltrials.gov (Identifier: NCT04932473). In this study, sleep was extensively characterized in 200 participants by means of actigraphy, sleep diaries and questionnaires, and video-PSG in a subsample of 90 participants.

ALFASleep study is nested in the ALFA+ prospective observational study (Alzheimer and Families), in which 400 CU middle-aged/late middle-aged adults, most of them kindred of patients with AD, with a high prevalence of *APOE-ε4* carriers (55%). Participants are followed every 3 years with a comprehensive set of evaluations including neuropsychological assessment, blood and CSF sampling, and MRI and PET acquisition[66].

On the other hand, early AD participants were recruited at the Alzheimer's Disease and other Cognitive Disorders Unit, Hospital Clínic de Barcelona (HCB). This group consisted of 58 individuals with either MCI ($n = 36$, CDR 0.5) or mild dementia ($n = 22$, CDR 1), with a clinical and biomarkers profile consistent with AD in agreement with the Alzheimer's Association Workgroup diagnostic criteria[67]. The HCB Institutional Review Board approved the study, and all participants gave their written, informed consent (HCB/2021/0668, HCB/2024/0319). Participants from the ALFASleep cohort were free from sleep related medication, while nine HCB patients were not (Supplementary Table 1). The final sample (Supplementary Fig. 1) consisted of 116 participants: 75 CU and 41 early AD (including 27 MCI and 14 mild AD).

2.2. Definition of AD continuum groups

To assess AD pathophysiology, CSF and PET measurements of core AD biomarkers were evaluated. In CU participants, CSF A β 40 and A β 42 were measured with Roche NeuroToolKit, and A β PET ($[^{18}\text{F}]$ flutemetamol) was available in 66 CU participants. CU participants were classified as A+ based on either a CSF A β 42/40 ratio below 0.071, or an A β PET showing more than 12 Centiloids in cases where CSF biomarkers were not available ($n = 5$). This cutoff was chosen because it has previously been shown to maximize agreement between A β PET and CSF positivity in the ALFA+ cohort[68], and has been reported to optimally detect moderate-to-frequent neuritic plaques, as defined by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), in a postmortem study[69].

Patients with early AD were diagnosed by a panel of neurologists and neuropsychologists and all of them had a biomarker profile consistent with AD (54 based on CSF, 4 based on PET). Levels of CSF amyloid- β (A β 42), total tau (T-tau), and phosphorylated tau (P-tau) were measured using Lumipulse G ELISAs, following the manufacturer's instructions (Fujirebio, Ghent, Belgium). CSF biomarker cut-off values for abnormality were defined based on in house data: A β 42 ≤ 600 pg/ml, T-tau > 385 pg/ml, and P-tau > 65 pg/ml.

One CU, and one early AD participant were discarded as their amyloid status data was missing (Supplementary Fig. 1).

2.3. PSG and Actigraphy acquisition

All participants underwent one night of PSG with BrainRT™ (OSG, Waarloos, Belgium) at the HCB Sleep Unit. EEG signals were recorded from electrodes placed at F3, F4, C3, C4, O1 and O2 and referenced to combined ears. Electrooculography (EOG), EMG from the mentalis muscle, upper limbs (right and left flexor digitorum superficialis) and lower limbs (right and left anterior tibialis), and ECG were also recorded. Respiration was assessed with nasal and oral thermistors and nasal cannula, thoracic and abdominal strain gauges, and finger pulse oximeter. Time during

lights off was divided in 30-s epochs that were scored into sleep stages (N1, N2, N3 and REM sleep) by neurologists specialized in sleep (A.I. and A.F.A) according to standard criteria[70]. Epochs containing either an arousal or an artifact were manually discarded for SWA micro-architecture analysis. Participants with an apnea-hypopnea index (AHI) > 30 events per hour (nine CU A-, five CU A+ and 16 early AD) were excluded (Supplementary Fig. 1).

Actigraphy measures (Actiwatch2, Philips Respironics) were taken from the non-dominant wrist of CU participants during the PSG night and the week before (seven days in total)[65, 71]. A sleep diary was used to cross-validate sleep-wake periods. Due to undetermined device errors, actigraphy information in three participants was not retrievable, and was only available for two nights in two additional participants. Actigraphy data was analyzed with the validated Actiware-Sleep® software algorithm[72]. In the early AD group of participants, the actigraphy device (Motion Watch 8, CamNtech Ltd, UK) was worn on the non-dominant wrist for two weeks while the patients continued their daily activities and sleep-wake rhythms in their environment. Actigraphy data was analyzed by the Sleep and MotionWare Software (CamNtech Ltd, UK). Considering the actigraphy-derived total sleep time (TST) of the night that preceded the PSG test (Prev. TST), a threshold of less than six hours was used to identify participants that were sleep-deprived at the moment of the PSG test. These data were used in a sensitivity analysis to account for the potential effect of sleep deprivation in PSG recordings. Two CU A-, two CU A+, and two early AD participants were discarded for this sensitivity analysis as their actigraphy data was missing.

2.4. Spectral analysis

PSG frontal electrodes (F3 and F4) were used to compute the averaged power at the slow oscillation (SO, 0.5-1 Hz), delta (1–4 Hz) and SWA (0.5-4 Hz) frequency bands during deep NREM sleep stages N2 and N3. After bandpass filtering the EEG signals in each channel from 0.5 to 35 Hz, the power spectral density of each 30s epoch classified as either N2 or N3 and free from arousals or artifacts was computed for each channel using the Fourier transform. Then, the average of all the epochs across the night was computed for each channel and finally averaged between channels F3 and F4. Last, the area under the curve of the frontal average power spectral density was computed at each frequency range. Final measures showed a non-normal distribution and were log transformed. In six early AD patients (14.6%), the deepest NREM phase (N3) was not reached during the PSG night, while in all CU participants at least one N3 period was detected.

2.5. SW detection

To detect individual SWs, an algorithm based on the methods employed in previous studies[73, 74] from a validated open-source Python toolbox for sleep analysis (Yet Another Spindle Algorithm, YASA)[75] was used. In brief, the EEG signal in the F3 channel was bandpass filtered between 0.3 to 1.5 Hz using a Finite Impulse Response filter with a transition band of 0.2 Hz. Then, all the negative peaks in the filtered signal that had an amplitude between – 40 to -200 μ V and all the positive peaks with an amplitude comprised between 10 to 150 μ V were detected. For each negative peak, the nearest following positive peak was found, and several metrics were computed: the peak-to-peak (PTP) amplitude, durations of the negative and positive phases and total SW duration. A set of thresholds in PTP amplitude (50 to 400 μ V), positive (0.1 to 1 s) and negative (0.3 to 1.5 s) phase durations were applied to determine true SWs. Only the SW detected during N2 or N3 sleep stages were selected. Finally, for each participant, the number of SW, density of SW per minute of NREM sleep (that is, considering N2 and N3 only), SW slope, PTP amplitude and SW duration (Supplementary Fig. 2) were computed.

2.6. Cognitive performance

A modified version of the Preclinical Alzheimer Cognitive Composite (PACC)[76, 77] was used to assess the cognitive performance of all CU participants in each ALFA+ visit. It was computed as the arithmetic mean of four standardized cognitive scores: the Free and Cued Selective Reminding Test (FCSRT) Total Immediate Recall, the Wechsler Memory

Scale (WMS) Logical Memory Total Delayed Recall, the Wechsler Adult Intelligence Scale (WAIS) Coding subtest, and a Semantic Fluency measure (animals named in one minute), the latter included following[78]. Each raw score was converted to a z-score using the mean and standard deviation of a CU, A- reference sample from the ALFA+ cohort at baseline (n = 251, Visit 1), which served as the reference for all visits. PACC scores from visits both preceding and following the PSG were included (see Statistical analysis for more details).

2.7. Statistical analysis

Averages are reported as mean $\pm$ standard deviation unless otherwise stated. One-way ANOVA was used to compare demographics and clinical variables across the three AD *continuum* groups. ANCOVA models adjusted for age and sex were used to test for group differences in each sleep parameter. Pairwise post-hoc comparisons between groups were conducted as linear contrasts extracted directly from each ANCOVA model, such that all comparisons were adjusted for age and sex. For each contrast, the estimated mean difference (β), its 95% confidence interval, and the unadjusted p-value were reported. To control for multiple comparisons across the three pairwise tests (A - vs A+, A - vs early AD, A + vs early AD), p-values were corrected using the Benjamini-Hochberg false discovery rate (FDR) procedure. Both unadjusted and FDR-corrected p-values are reported. Additionally, Kendall's tau-b correlation coefficient was calculated to assess monotonic trends across the ordered AD *continuum* groups (CU A- $\rightarrow$ CU A+ $\rightarrow$ early AD). To test the effect of sleep related medications, sensitivity analyses were performed in the subsample without nine early AD patients taking sleep-related medications. To test the effect of sleep deprivation, sensitivity analyses were performed in a subsample without two CU A-, two CU A+, and eight early AD participants that had slept less than six hours the night before the PSG.

The association between sleep parameters and cognition over time was tested in CU participants (participants from the CU A- and CU A+ groups) using PACC, which was calculated for each ALFA+ visit. Each CU participant had between 2 and 4 PACC visits (average of 3.1 ± 0.4 visits). Assessments were conducted up to 5.3 years before and 4.3 years after PSG (IQR - 2.5 to 2.6 years), with time referenced to the date of PSG. Linear mixed-effects models (LME) were used to test these associations. We included age, sex and education as fixed effects and a random intercept per subject. No random slope for time was included.

To test sex differences, main analyses were performed in stratified subsamples for men and women, with models adjusted for age, or for age and education (when testing associations with cognitive performance).

All analyses except LME were run in Python (version 3.9.18) using the *statsmodels* (0.14.6) and *scipy* (1.17.0) libraries. LME models were fitted in R (version 4.5.2) using the *lme4* package (version 2.0.1).

3. Results

3.1. Demographics

The final sample (Table 1) consisted of 116 participants distributed as 30 CU A-, 45 CU A+ and 41 early AD. Patients classified as early AD were significantly older than CU ($p < 0.001$). The highest percentage of APOE- $\epsilon 4$ carriers was found in CU A+ participants (82.2%) which was significantly higher than in the A- group (40.0%) or in the early AD group (48.8%) ($p < 0.001$). This difference likely reflects the enrichment strategy for AD risk factors applied in the ALFA+ cohort[66]. While nine (22%) of early AD patients were taking some sleep-related medication (Supplementary Table 1), all the CU participants were free from sleep-related medications due to the ALFASleep study exclusion criteria. Early AD patients were significantly less educated ($p = 0.009$, 11.76 years compared to 14.4 and 13.27 years in CU A- and CU A+ groups, respectively) and had significantly lower Mini-Mental State Examination (MMSE) scores ($p < 0.001$, 24.23 compared to 28.87 and 29.27 in CU A- and CU A+ groups, respectively). All groups had a slightly higher

female representation. There were no significant between-group differences in the total time spent asleep during the previous night. Although the arousal index of early AD patients was lower than the other groups ($p = 0.047$), the arousal index during NREM or the AHI were not significantly different across groups. Moreover, participants classified between normal ($AHI \leq 5$), mild obstructive sleep apnea (OSA) ($5 < AHI \leq 15$) or moderate OSA ($15 < AHI \leq 30$) were equally distributed among groups. Finally, there were no significant between-group differences in terms of the periodic limb movements in sleep (PLMS) index or the number of REM sleep behavior disorder (RBD) cases.

Table 1
Demographics across AD *continuum* groups

	Descriptive statistics				ANOVA
	Total (n = 116)	CU A- (n = 30, 25.9%)	CU A+ (n = 45, 38.8%)	Early AD (n = 41, 35.3%)	p
Age (years)	66.42 ± 5.82	63.73 ± 4.73	66.06 ± 4.33	68.78 ± 7.02	< .001
Sex (female)	66 (56.9)	16 (53.3)	28 (62.2)	22 (53.7)	0.653
APOE (ε4 carrier)	69 (59.5)	12 (40.0)	37 (82.2)	20 (48.8)	< .001
Amyloid (positive)	86 (74.1)	0 (0.0)	45 (100.0)	41 (100.0)	< .001
Education (years)	13.03 ± 3.70	14.40 ± 3.39	13.27 ± 3.76	11.76 ± 3.51	0.009
MMSE (score)	27.41 ± 3.19	28.87 ± 1.28	29.27 ± 1.05	24.23 ± 3.35	< .001
Sleep medication (yes)	9 (7.8)	0 (0.0)	0 (0.0)	9 (22.0)	< .001
Prev. TST (minutes)	420.57 ± 55.34	423.68 ± 53.30	424.26 ± 47.78	414.28 ± 64.65	0.680
Arousal index	16.98 ± 6.88	18.97 ± 6.89	17.44 ± 6.79	15.01 ± 6.62	0.047
Arousal index NREM	18.00 ± 7.71	19.66 ± 7.77	18.05 ± 7.81	16.73 ± 7.49	0.288
AHI (events/h)	11.41 ± 8.13	10.64 ± 8.12	11.62 ± 8.27	11.73 ± 8.15	0.837
- normal ($AHI \leq 5$)	33 (28.4)	9 (30.0)	12 (26.7)	12 (29.3)	0.942
- mild OSA ($5 < AHI \leq 15$)	46 (39.7)	13 (43.3)	16 (35.6)	17 (41.5)	0.763
- moderate OSA ($15 < AHI \leq 30$)	37 (31.9)	8 (26.7)	17 (37.8)	12 (29.3)	0.542
PLMS index	19.07 ± 28.90	11.54 ± 20.52	18.42 ± 26.79	25.29 ± 34.98	0.138
RBD (cases)	9 (7.8)	3 (10.0)	2 (4.4)	4 (9.8)	0.544

Continuous measures expressed as mean ± standard deviation. Categorical measures expressed as count (percentage). APOE: Apolipoprotein E, MMSE: Mini-Mental State Examination, Prev. TST: Previous Total Sleep Time (actigraphy), AHI: Apnea-Hypopnea Index, OSA: Obstructive Sleep Apnea, PLMS: Periodic Limb Movements in Sleep, RBD: REM sleep Behaviour Disorder. Bold: $p < 0.05$.

3.2. Macro-, micro-architecture of sleep and SW parameters in the AD continuum

The sleep differences across the AD *continuum* groups were first explored by focusing on the macro-architecture of the PSG night. Significant group differences were found for wake after sleep onset (WASO, $p = 0.002$), sleep efficiency (SE, $p = 0.003$) and REM sleep latency ($p < 0.001$), with early AD group showing higher WASO ($p = 0.004$ and 0.005), lower SE ($p = 0.010$ and 0.005) and higher REM sleep latency ($p < 0.001$ and 0.004) compared to the CU A+ and CU A- groups, respectively. Although there were no significant differences in macro-architecture parameters between CU groups, monotonic increasing trends across AD *continuum* groups were found for WASO ($p = 0.043$), SL ($p = 0.014$) and REM sleep latency ($p = 0.002$) (Table 2, Fig. 1, A-C).

Regarding the micro-architecture of sleep, the groups differed significantly in delta ($p = 0.008$) and SWA power ($p = 0.014$). Participants from both the CU A+ and the early AD groups showed significantly lower power in the SO ($p = 0.048$, $p = 0.048$) and the SWA ($p = 0.035$, $p = 0.013$) frequency bands than the CU A- group. Moreover, early AD patients showed lower delta power ($p = 0.006$) than the CU A- group.

The groups also differed significantly in the number ($p = 0.036$), slope ($p < 0.001$), PTP amplitude ($p < 0.001$) and duration ($p = 0.002$) of the individual SWs detected during N2 or N3. Slope showed a significant monotonic decrease ($p = 0.013$) from CU A- to early AD patients, such that CU A+ participants had lower slope than CU A- participants ($p = 0.015$), and early AD patients had lower slope than participants in the CU A+ ($p = 0.002$) or the CU A- ($p < 0.001$) groups. Similarly, the PTP amplitude of CU A+ participants was significantly lower than that of the CU A- group ($p = 0.020$), and early AD patients had significantly lower PTP amplitude than participants in the CU A+ ($p = 0.039$) or the CU A- ($p < 0.001$) groups. Finally, SW duration was found to follow a significantly increasing trend from CU A- to early AD groups ($p = 0.006$), with early AD patients showing significantly higher duration than participants in the CU A+ ($p = 0.007$) or the CU A- ($p = 0.003$) groups.

Overall, a progressive flattening of the SW was observed in more advanced AD stages, as depicted qualitatively in the waveform averages of the different groups superposed in Fig. 1J.

Table 2
Sleep parameters across AD *continuum* groups

	Descriptive statistics				ANCOVA	Post-hoc comparisons			Kendall's tau
	Total (n = 116)	CU A- (n = 30)	CU A+ (n = 45)	Early AD (n = 41)	p	β [95% CI] p (p-FDR)			τ (p value)
						CU A + vs CU A-	Early AD vs CU A+	Early AD vs CU A-	
Macro-architecture									
TST (min)	348.07 ± 75.12	372.03 ± 41.72	342.20 ± 62.96	336.98 ± 100.04	0.362	-24.07 [-59.02, 10.87] 0.175 (0.370)	2.21 [-30.08, 34.50] 0.892 (0.892)	-21.86 [-59.09, 15.36] 0.247 (0.370)	0.092 (0.898) ^d
WASO (min)	78.51 ± 57.87	60.75 ± 29.72	63.91 ± 38.56	107.52 ± 77.54	0.002	2.30 [-23.08, 27.67] 0.858 (0.858)	38.97 [15.53, 62.42] 0.001 (0.004)	41.27 [14.24, 68.29] 0.003 (0.005)	0.124 (0.043) ^c
SE (%)	76.66 ± 15.79	83.31 ± 8.12	79.28 ± 12.64	68.90 ± 19.75	0.003	-3.12 [-10.06, 3.82] 0.375 (0.375)	-8.95 [-15.37, -2.54] 0.007 (0.010)	-12.07 [-19.46, -4.68] 0.002 (0.005)	-0.102 (0.079) ^d
SL (min)	15.53 ± 29.85	8.04 ± 7.28	12.16 ± 25.94	24.70 ± 40.52	0.161	1.67 [-12.11, 15.45] 0.811 (0.811)	10.71 [-2.02, 23.44] 0.098 (0.148)	12.38 [-2.30, 27.06] 0.097 (0.148)	0.160 (0.014) ^c
REM latency (min)	119.17 ± 82.61	105.03 ± 65.92	94.59 ± 46.62	156.50 ± 108.72	< .001	-6.77 [-43.81, 30.27] 0.718 (0.718)	68.56 [34.32, 102.79] <.001 (< .001)	61.79 [22.33, 101.24] 0.002 (0.004)	0.210 (0.002) ^c
REM (min)	60.43 ± 25.11	68.53 ± 22.10	59.42 ± 22.63	55.60 ± 28.66	0.204	-8.19 [-20.04, 3.65] 0.173 (0.260)	-2.96 [-13.90, 7.99] 0.593 (0.593)	-11.15 [-23.77, 1.47] 0.083 (0.248)	-0.029 (0.346) ^d
N1 (min)	57.16 ± 31.23	61.43 ± 26.10	51.58 ± 24.04	60.16 ± 40.20	0.388	-7.03 [-21.27, 7.20] 0.330 (0.495)	8.49 [-4.67, 21.65] 0.204 (0.495)	1.45 [-13.71, 16.62] 0.850 (0.850)	0.068 (0.174) ^c
N2 (min)	177.81 ± 54.72	186.15 ± 34.80	174.86 ± 46.83	174.94 ± 72.45	0.775	-9.29 [-35.54, 16.97] 0.485 (0.885)	1.77 [-22.49, 26.03] 0.885 (0.885)	-7.52 [-35.48, 20.45] 0.595 (0.885)	0.023 (0.627) ^d
N3 (min)	52.87 ± 35.10	56.17 ± 28.17	56.49 ± 35.28	46.49 ± 39.16	0.760	0.35 [-15.02, 15.73]	-5.02 [-19.23, 9.19]	-4.67 [-21.05, 11.71]	-0.042 (0.280) ^d

	Descriptive statistics				ANCOVA	Post-hoc comparisons			Kendall's tau
	Total (n = 116)	CU A- (n = 30)	CU A+ (n = 45)	Early AD (n = 41)	p	β [95% CI] p (p-FDR)			τ (p value)
Macro-architecture						0.964 (0.964)	0.485 (0.860)	0.573 (0.860)	
N2 + N3 (min)	230.68 ± 61.18	242.32 ± 41.38	231.35 ± 54.82	221.43 ± 77.61	0.717	-8.93 [-37.36, 19.49] 0.535 (0.802)	-3.25 [-29.52, 23.01] 0.807 (0.807)	-12.19 [-42.47, 18.09] 0.427 (0.802)	0.011 (0.562) ^d
Micro-architecture									
SO power (log10, μV^2)	3.36 ± 0.14	3.41 ± 0.14	3.36 ± 0.14	3.34 ± 0.15	0.051	-0.06 [-0.12, -0.01] 0.032 (0.048)	-0.01 [-0.06, 0.05] 0.805 (0.805)	-0.07 [-0.13, -0.01] 0.026 (0.048)	0.032 (0.672) ^d
Delta power (log10, μV^2)	3.26 ± 0.15	3.32 ± 0.15	3.27 ± 0.14	3.20 ± 0.14	0.008	-0.06 [-0.12, 0.00] 0.060 (0.090)	-0.04 [-0.10, 0.01] 0.115 (0.115)	-0.10 [-0.17, -0.04] 0.002 (0.006)	-0.075 (0.150) ^d
SWA power (log10, μV^2)	3.60 ± 0.14	3.65 ± 0.13	3.59 ± 0.14	3.56 ± 0.15	0.014	-0.07 [-0.13, -0.01] 0.023 (0.035)	-0.02 [-0.08, 0.03] 0.393 (0.393)	-0.09 [-0.15, -0.03] 0.004 (0.013)	-0.007 (0.462) ^d
Slow-wave parameters									
Number (SW)	596.72 ± 499.60	789.80 ± 508.44	601.09 ± 519.86	450.63 ± 427.84	0.036	-201.66 [-406.75, 3.44] 0.054 (0.081)	-81.55 [-271.07, 107.98] 0.396 (0.396)	-283.20 [-501.66, -64.74] 0.012 (0.035)	-0.044 (0.271) ^d
Density (SW/min)	2.55 ± 1.95	3.14 ± 1.76	2.61 ± 2.16	2.04 ± 1.74	0.074	-0.64 [-1.46, 0.18] 0.124 (0.186)	-0.37 [-1.13, 0.38] 0.331 (0.331)	-1.01 [-1.88, -0.14] 0.023 (0.070)	-0.024 (0.369) ^d
Slope ($\mu V/s$)	334.24 ± 57.88	369.70 ± 56.17	341.99 ± 46.79	299.78 ± 52.05	< .001	-27.12 [-48.87, -5.36] 0.015 (0.015)	-33.47 [-53.57, -13.36] 0.001 (0.002)	-60.58 [-83.76, -37.40] <.001 (< .001)	-0.161 (0.013) ^d
PTP amplitude (μV)	94.50 ± 11.08	100.29 ± 11.43	95.20 ± 9.54	89.50 ± 10.34	< .001	-5.41 [-9.67, -1.15] 0.013 (0.020)	-4.15 [-8.09, -0.21] 0.039 (0.039)	-9.56 [-14.10, -5.02] <.001 (< .001)	-0.097 (0.090) ^d

	Descriptive statistics				ANCOVA	Post-hoc comparisons			Kendall's tau
						β [95% CI] p (p-FDR)			
	Total (n = 116)	CU A- (n = 30)	CU A+ (n = 45)	Early AD (n = 41)	p	CU A + vs CU A-	Early AD vs CU A+	Early AD vs CU A-	τ (p value)
Macro-architecture									
Duration (s)	1.26 ± 0.11	1.22 ± 0.10	1.25 ± 0.09	1.32 ± 0.11	0.002	0.02 [-0.02, 0.07] 0.337 (0.337)	0.06 [0.02, 0.10] 0.004 (0.007)	0.08 [0.04, 0.13] <.001 (0.003)	0.181 (0.006) ^c

Measures expressed as mean $\pm$ standard deviation. ANCOVA adjusted for age and sex. Beta: mean difference, CI: confidence interval. p-FDR: FDR-corrected p-value (Benjamini-Hochberg). c: Increasing trend. d: Decreasing trend. TST: Total Sleep Time, WASO: Wake After Sleep Onset, SE: Sleep Efficiency, SL: Sleep Latency, REM: Rapid Eye Movement sleep, N1, N2 and N3: non-REM sleep stages, SO: Slow Oscillation, SWA: Slow Wave Activity, SW: slow-wave, PTP: peak to peak amplitude, min: minute, s: second, μV : micro Volts. Bold: $p < 0.05$.

3.3. Sensitivity analysis

3.3.1. Sleep pressure

The smaller values of SWA power, SW PTP amplitude or slope found in CU A + and early AD patients could be confounded by differences in sleep pressure. To account for this, we inspected the total amount of sleep that each participant had had the night before the PSG test (measured as TST from actigraphy) and found that twelve participants (two CU A-, two CU A+, and eight early AD) had slept less than 6 hours. After excluding these participants, together with six participants for which we did not have actigraphy data (two in each group), the final sample consisted of 98 participants (26 CU A-, 41 CU A + and 31 early AD, Supplementary Table 2). As with the complete sample, participants in the early AD group were older, less educated and presented lower values of MMSE, but the groups did not differ significantly in terms of arousal index, AHI, PLMS index or number of RBD cases.

Supplementary Table 3 shows the ANCOVA analyses of sleep parameters across AD *continuum* groups, excluding participants with less than 6h of TST the previous night. Although slightly attenuated, the same results were observed for WASO, SE and REM latency in this sample. Regarding the SWA power, the differences between CU groups were no longer significant in this subsample. However, early AD participants still showed significantly lower power of delta and SWA frequency bands compared to the CU A- group. Finally, the differences in SW slope, PTP amplitude or duration across AD groups remained as in the complete sample.

3.3.2. Sleep medications

The fact that participants in the CU groups were medication free because of the ALFASleep study exclusion criteria while nine early AD patients were taking sleep-related medication (Supplementary Table 1) could bias the results. To discard this possibility, analyses were repeated in a subsample of 107 individuals (30 CU A-, 45 CU A + and 32 early AD) free from sleep-related medication. As in the original sample, early AD participants were older, less educated and showed lower MMSE values, while no other group differences were found (Supplementary Table 4).

In terms of macro-architecture, the results on WASO, SE and REM latency remained as in the original sample. In this case, REM duration was significantly lower in the early AD group compared to the CU A- group ($p = 0.017$), but this difference did not survive the multiple comparison correction ($p = 0.052$). While the differences in SO power across AD groups were attenuated, the results on delta and SWA power remained as in the original sample. Similarly, results on SW duration were slightly attenuated, while in terms of slope and PTP duration we obtained the same differences across groups as in the original sample (Supplementary Table 5).

3.4. Sex differences

In the original sample there were $n = 50$ men (43.1%) and $n = 66$ women (56.9%). While there were no sex differences in age, *APOE-ε4* status, sleep-related medications or MMSE score, there was a trend towards lower education among women ($p = 0.062$). In contrast, men had a significantly shorter TST the night before the PSG ($p = 0.004$) and a significantly higher AHI compared to women ($p = 0.008$), with more cases of moderate OSA among men ($p = 0.026$). Importantly, the distribution of participants across the AD *continuum* groups did not differ significantly between sexes (Supplementary Table 6).

Adjusting for age, women were found to spend less time awake ($p = 0.048$) or in N1 ($p = 0.001$) than men, while they spent more time in N3 ($p < 0.001$). SWA power was significantly higher in women compared to men ($p < 0.001$) across the three frequency bands studied (SO, delta and SWA). Finally, considering the SW quality parameters, women had significantly greater SW number, density, slope and PTP amplitude compared to men ($p < 0.001$) (Supplementary Table 7).

Although no significant interactions between the AD group and sex were found in any of the sleep parameters studied (Supplementary Table 8), sex-stratified analyses were still performed in order to report any sex difference in sleep across the AD *continuum*.

Regarding the macro-architecture of sleep (Fig. 2, A-C) only men (Supplementary Table 9) showed significantly higher WASO in the early AD group compared to both CU A- or A+ groups and almost significantly lower SE in the early AD group compared to the CU A- group ($p = 0.05$). Moreover, men in the early AD group showed significantly higher REM sleep latency compared to the CU A+ group and the CU A- group while in the women subsample only the difference in REM sleep latency between early AD and CU A+ groups was significant (Supplementary table 10).

Considering the micro-architecture of sleep (Fig. 2, D-F), both men and women in the early AD group had lower SWA power compared to CU A- group, particularly in the delta and SWA frequency bands for women, and only for the delta band for men. However, the statistical significance of these differences did not survive the correction for multiple comparisons.

Despite men showing an overall reduced SW quality compared to women (Supplementary Table 7), both sexes showed a similar decrease in quality of the SW parameters along the AD *continuum* groups (Fig. 2, G-I). Considering slope, both men and women in the early AD group had significantly lower values compared to the CU A+ and CU A- groups. However, some cases remained only as trends when correcting for multiple comparisons. Moreover, the differences between CU groups were no longer significant for any of the two sex subsamples. In terms of PTP amplitude, the early AD group still showed significantly lower values than the CU A- group in both men and women subsamples. Additionally, for the men subsample only, the difference between CU groups was significant but it did not survive the correction for multiple comparisons. Finally, the SW duration parameter showed a similar pattern across AD groups in both sexes, although the only group differences surviving the correction for multiple comparisons were between early AD and CU A- in the men subsample.

3.5. SWS and cognitive trajectories among CU individuals

To examine whether SWS parameters were associated with cognitive trajectories over time during the preclinical phase of AD, LME models tested associations between SWS metrics (power of SO, delta, and SWA frequency ranges and SW number, slope and PTP amplitude) and cognitive performance (PACC, mean 3.1 visits, range 6.60 ± 0.87 years). Models were adjusted for age, sex, and education. Higher slope ($p = 0.015$) and higher PTP amplitude ($p = 0.010$) of the SWs were significantly associated with better PACC trajectories over time (Table 3). However, no significant associations were found for the power of SO, delta and SWA frequency ranges nor for the number of SW detected during N2 and N3.

Interaction and stratified analyses were performed to test sex differences in the associations between SWS and PACC over time. Interaction with sex was only significant in the association with delta and SWA power and SW PTP amplitude. Stratified analysis showed that every SWS parameter was positively and significantly associated with better PACC trajectories only in the men subsample, and none in the women subsample (Table 3).

Table 3
Association between sleep measures and cognitive trajectories among CU individuals and across sex.

	All CU (n = 76)	Sex interaction	Men (n = 32)	Women (n = 44)
Micro-architecture				
SO power	0.008 (-0.010, 0.027) 0.366	$p = 0.061$	0.043 (0.011, 0.075) 0.011	-0.001 (-0.028, 0.026) 0.946
Delta power	0.004 (-0.014, 0.023) 0.661	$p = 0.038$	0.040 (0.008, 0.071) 0.016	-0.009 (-0.036, 0.019) 0.529
SWA power	0.007 (-0.011, 0.025) 0.456	$p = 0.038$	0.044 (0.013, 0.076) 0.008	-0.005 (-0.033, 0.024) 0.736
Slow-wave parameters				
Number	0.014 (-0.004, 0.031) 0.140	$p = 0.173$	0.048 (0.007, 0.089) 0.025	0.011 (-0.012, 0.034) 0.361
Slope	0.022 (0.005, 0.040) 0.015	$p = 0.102$	0.047 (0.021, 0.073) < 0.001	0.014 (-0.012, 0.040) 0.296
PTP	0.024 (0.006, 0.042) 0.010	$p = 0.028$	0.065 (0.036, 0.095) < 0.001	0.016 (-0.010, 0.042) 0.222
<i>CU: cognitively unimpaired. LME fixed effects expressed as beta (lower CI, higher CI) p value. Adjusted for age, sex and education. Bold: $p < 0.05$</i>				

4. Discussion

In this study, we found that sleep differences across the AD *continuum* involved both sleep macro-architecture and SW physiology. Macro-architectural alterations were mainly driven by early symptomatic AD, whereas SW activity power was already reduced in CU individuals with abnormal AD biomarkers. SW morphology showed the most evident continuum-related pattern, with flatter waves in more advanced disease stages. In CU participants, SW morphology, particularly slope and PTP amplitude, was associated with longitudinal cognitive trajectories. Exploratory sex-stratified analyses suggested that associations between SWS parameters and cognition were more robust in men.

Consistent with previous literature[2, 12, 13, 40] early AD patients showed distinct alterations in sleep macro-architecture, including higher WASO, lower SE and longer REM latency compared to CU A+ or A- participants. Although the differences between CU A- and CU A+ were not significant, we observed monotonic increasing trends in WASO, SL, and REM sleep latency, suggesting that the macro-architecture of sleep progressively worsens along the AD *continuum*, reflecting early pathophysiological changes happening during the preclinical phase of the disease[40, 79]. Although shorter N3 stage or NREM sleep was not specifically found in early AD patients compared to CU participants, higher values of WASO and lower SE found in patients are consistent with studies finding a link between sleep deprivation and AD pathogenesis[50, 52, 80].

Regarding sleep micro-architecture, spectral power in the SO (0.5-1Hz), delta (1-4Hz) and SWA (0.5-4Hz) frequency bands during N2 or N3 sleep stages in frontal electrodes was lower in early AD patients compared to the CU A- individuals. This finding suggests that power reductions in these frequency bands during NREM sleep may constitute a potential marker – and possibly a contributing factor- for cognitive impairment[37, 41] in the early phases of AD, although causal relationships cannot be claimed due to the cross-sectional study design. Notably, the CU A+ group already showed lower SO and SWA power than the A- group, suggesting that the alterations in the spectral power of the lower frequencies during NREM sleep may be linked to early A β or tau accumulation, as previously proposed[25, 29, 51, 52].

A closer look at the SW morphology revealed a progressive flattening of SWs across AD stages. All the SW parameters studied (number, density, slope, PTP amplitude and duration) showed significantly worse values in the early AD group compared to the CU A-, with differences remaining significant after multiple comparisons correction, except for SW density ($p = 0.070$). Notably, SW slope and PTP amplitude were significantly higher in CU A- compared to the other groups, while SW duration showed a significant progressive increase across the AD continuum – together reflecting an early deterioration in SO quality already at preclinical stages. Importantly, our findings suggest that it is not simply a reduction in the number of SW detected during NREM sleep, but rather changes in the morphology of these oscillations that mark the earliest signs of sleep-related deterioration in AD. This contrasts with Mander et al.[25], who, working exclusively with cognitively unimpaired participants, reported that the association between NREM SWA and beta-amyloid pathology was primarily driven by a reduction in the incidence of SW, with morphological parameters such as slope, amplitude, and period remaining largely unchanged. However, the discrepancy may reflect the narrower disease spectrum in that sample, as the morphological differences we observe emerge most clearly when comparing across the full AD continuum. In line with our results, Sharon et al.[40], using the same YASA-based detection algorithm in a sample spanning cognitively unimpaired individuals through MCI and AD patients, found that the amplitude of the negative peak of the SW was smaller in healthy controls relative to those with MCI or AD, further supporting the notion that SW morphology, and amplitude in particular, is sensitive to disease stage in ways that may not be apparent when restricting analyses to CU individuals alone.

The important findings regarding SW slope, amplitude and duration reported in this study suggest that a decline in neuronal synchrony [40] may already occur in the preclinical stage of the disease, leading to slower recruitment of the local neural network during the transition to the active phase of the SW[81], also called “Up State”[18], which becomes more evident as the disease progresses. This lack of synchrony during the Up State onset may reflect a reduction in the strength of cortical synapses or an increase in cortical excitability during the silent phase of the SW, or “Down State”, as has been observed in computational[82] or murine[83] models of AD.

According to the synaptic homeostasis hypothesis[84], sleep pressure, which is measured with the spectral power of SWA, increases with time awake and decreases during sleep. During wakefulness, learning is produced through the long-term potentiation of synapses, while the synchronization of cortical networks into SWA during sleep downregulates synaptic strength, allowing new memories to be stored in synapses in the following waking period.

Therefore, the reduction in SWA power and flattening of the SWs observed in the early AD group may suggest impaired synaptic downregulation, potentially interfering with memory consolidation during sleep and learning during wakefulness.

Moreover, SWs also serve as temporal pacemakers for other frequency oscillations (spindles and ripples) that are nested hierarchically, allowing for the replay and long-term storage of memories[22, 85, 86]. Previous literature has shown that SWs-spindle coupling is disrupted in older individuals [87], and further impaired in AD patients[88]. Therefore, alterations in SW slope and PTP amplitude, and the more general reduction of SWA, are expected to be associated with lower cognitive outcomes[40], particularly in the memory domain[25]. This study provides evidence of the longitudinal relationship between SW morphology (SW slope and PTP amplitude) and better AD-specific cognitive (PACC) trajectories over time. Furthermore, associations between slow-wave sleep parameters and cognitive trajectories were more consistently observed in men, possibly because women had an overall better quality of SWS than men (as discussed below).

Consistent with previous literature[55, 56], women showed overall better sleep quality than men. The men and women subsamples were well balanced in terms of basic demographics such as age, APOE status or level of education and in their distribution among the AD *continuum* groups. Although men had a higher AHI and a higher prevalence of moderate OSA than women, these differences did not result in a significantly higher arousal index for men. Women were found to spend more time in N3, having higher SWA power and an overall better quality of SWs. Despite this, both sexes exhibited similar patterns of sleep disturbance progression along the AD *continuum*, with men showing more pronounced between-group differences.

One strength of this study is that all participants underwent one week of actigraphy prior the PSG assessment, allowing estimation of their sleep duration and potential sleep deprivation on the night of recording. Interestingly, excluding participants with reduced TST (less than 6h of sleep) the night before the PSG did not affect the main results of the study, confirming their robustness.

Moreover, although participants were drawn from different cohorts, all underwent an identical protocol for PSG acquisition, evaluation, and processing, ensuring methodological uniformity, cross-cohort comparability, and minimization of inter-site bias.

While participants with severe apneas (AHI > 30) were removed from the analysis to prevent potential confounding effects, early AD patients taking sleep-related medications were retained in the study. However, the small number of participants on sleep medications (all of whom were in the early AD group) limited our ability to properly analyze how these medications affect sleep parameters across the AD *continuum*. Importantly, excluding these participants did not change the main findings.

The changes in SW morphology found in early AD patients underscore a degeneration in sleep architecture that may require the reconsideration of the PSG staging criteria for patients with AD, as it has been suggested for other neurodegenerative pathologies[89, 90].

In conclusion, this study provides new evidence implicating SWS in the early pathophysiology of AD, emphasizing the importance of analyzing not only the sleep macro-architecture, but also micro-architecture and, more precisely, the SWs morphology. These SWS features may represent non-invasive markers for early AD detection and may also inform new therapeutic strategies aimed at preserving memory by improving sleep quality.

Future longitudinal studies should investigate causal links between early amyloid and tau accumulation and the disruption of low-frequency rhythms associated with SWS. In parallel, intervention studies enhancing SWA

(pharmacologically or via auditory or electrical stimulation) should be further evaluated to slow disease progression.

5. Conclusions

This study shows a progressive disruption of the macro- and micro-architecture of sleep along the AD *continuum*, in both sexes. Disruptions of slow wave sleep are not only detectable in preclinical stages but also associated with worse cognitive trajectories, suggesting a role of sleep as both a biomarker of the disease as well as a potential therapeutic target.

Abbreviations

A-

Amyloid negative

A+

Amyloid positive

AD

Alzheimer's disease

AHI

Apnea-Hypopnea Index

ALFA

Alzheimer and Families

APOE

Apolipoprotein E

A β

Amyloid Beta

CDR

Clinical Dementia Rating

CERAD

Consortium to Establish a Registry for Alzheimer's Disease

CSF

Cerebrospinal Fluid

CU

Cognitively Unimpaired

EEG

Electroencephalography

EMG

Electromyogram

EOG

Electrooculography

FCSRT

Free and Cued Selective Reminding Test

FDR

False Discovery Rate

HCB

Hospital Clinic de Barcelona

IQR

Interquartile Range
LME
Linear Mixed Effects
MCI
Mild Cognitive Impairment
MMSE
Mini-Mental State Examination
MRI
Magnetic Resonance Imaging
N1, N2, N3
non-REM sleep stages
NREM
non-REM
OSA
Obstructive Sleep Apnea
PACC
Preclinical Alzheimer's Cognitive Composite
PET
Positron Emission Tomography
PLMS
Periodic Limb Movements in Sleep
Prev. TST
previous TST (from actigraphy)
PSG
Polysomnography
PTP
Peak To Peak amplitude
RBD
REM sleep Behaviour Disorder
REM
Rapid Eye Movement
SE
Sleep Efficiency
SL
Sleep Latency
SO
Slow Oscillation
SW
Slow Wave
SWA
Slow Wave Activity
SWS
Slow Wave Sleep
TST
Total Sleep Time

WAIS
Wechsler Adult Intelligence Scale
WASO
Wake After Sleep Onset
WMS
Wechsler Memory Scale
YASA
Yet Another Spindle Algorithm

Declarations

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7.1. Ethics approval and consent to participate

The ALFASleep study protocol was approved by the Independent Ethics Committee *Parc de Salut Mar Barcelona* and registered at Clinicaltrials.gov (Identifier: NCT04932473). The HCB Institutional Review Board approved the study, and all participants gave their written, informed consent (HCB/2021/0668, HCB/2024/0319).

Consent for publication

Not applicable.

Competing Interests

JDG is now a full-time employee of AstraZeneca, has received research support and/or speaker/consulting fees from GE HealthCare, Roche Diagnostics, Hoffmann—La Roche, Life-Molecular Imaging, Biogen, Philips Netherlands, and Esteve, served in the Molecular Neuroimaging Advisory Board of Prothena Biosciences and is the founder and co-owner of Betascreen SL. MS-C has received in the past 36mo consultancy/speaker fees (paid to the institution) from by Almirall, Biogen, Beckman Coulter, Eli Lilly, Quanterix, Novo Nordisk, and Roche Diagnostics. He has received consultancy fees or served on advisory boards (paid to the institution) of Eli Lilly, Grifols, Novo Nordisk, and Roche Diagnostics. He was granted a project and is a site investigator of a clinical trial (funded to the institution) by Roche Diagnostics. In-kind support for research (to the institution) was received from ADx Neurosciences, Alamar Biosciences, ALZpath, Avid Radiopharmaceuticals, Eli Lilly, Fujirebio, Janssen Research & Development, Meso Scale Discovery, and Roche Diagnostics; MS-C did not receive any personal compensation from these organizations or any other for-profit organization. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a shareholder of CERimmune Therapeutics (outside submitted work). SCH is a full-time employee of F. Hoffmann-La Roche Ltd. KB has during 2023-2025 served as a consultant, at advisory boards, and has given lectures, produced

educational materials and participated in educational programs for AC Immune, ALZPath, AriBio, Beckman-Coulter, BioArctic, Eisai, Lilly, Neurimmune, Novartis, Roche Diagnostics, Sunbird Bio, and Siemens Healthineers; all before Sept 2026, and is since Sept 2026 an employee of Lilly. KB is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. OG-R also receives funding from F. Hoffmann-La Roche Ltd, and has given lectures in symposia sponsored by Roche Diagnostics, S.L.U. NT-C, AF-A, GM, LS, CM, LH, IK, NS-D, GS-B, MK, LTG, AM-L, IM-S, AA, AM, CG, AL, RS-V, GP-R, AV-G, AI, JLM, and NF declare no competing interests.

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Author Contribution

NTC, NF and OGR designed the study. NTC analyzed the data and drafted the manuscript. AFA contributed to polysomnographic data scoring and data interpretation. NF and OGR contributed equally to this study. All authors read and approved the final manuscript.

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Data Availability

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

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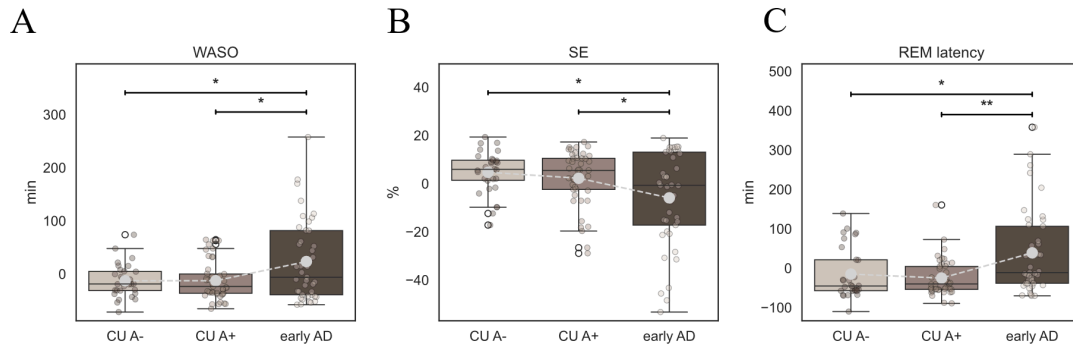
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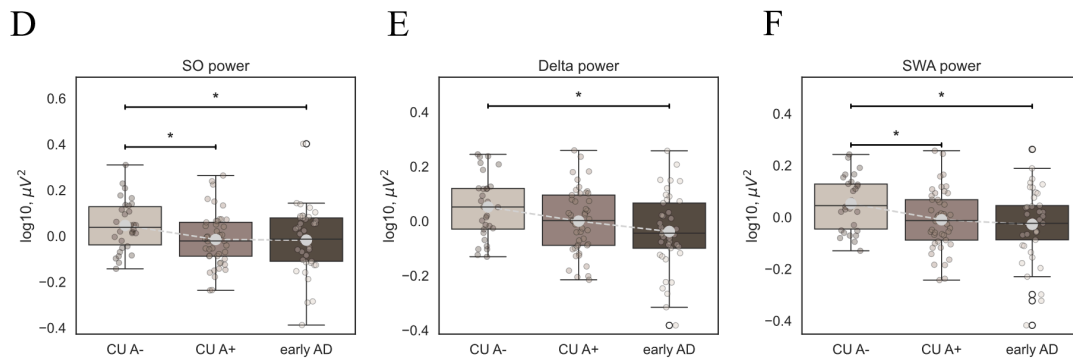
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Figures

Macro-architecture



Micro-architecture



Slow-wave parameters

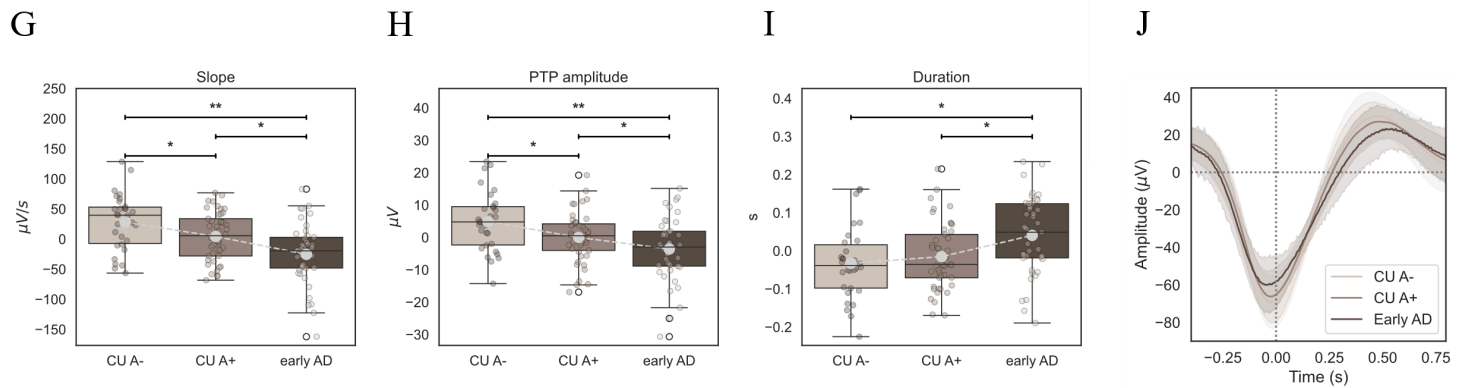
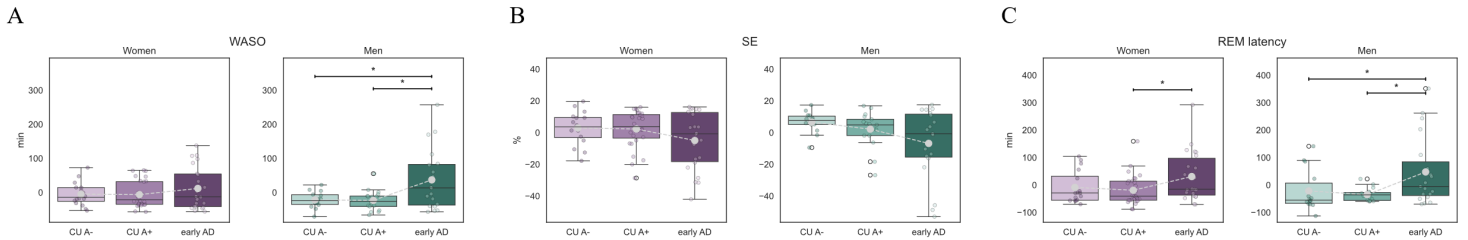


Figure 1

Sleep parameters across the AD continuum groups. Boxplots of the macro- (A-C), micro-architecture (D-F), and slow-wave (G-I), parameters of sleep (adjusted for age and sex). Boxplots display the median (central line), interquartile range (IQR, box edges), and whiskers extending to 1.5×IQR; points beyond whiskers indicate outliers. Grey dots connected by dashed lines represent the mean. * $p < 0.050$, ** $p < 0.001$ (after multiple comparisons correction). (J) Waveform averages of the slow-waves detected during N2 or N3 in CU A- participants (green), CU A+ participants (grey) and early AD patients (magenta), showing qualitatively the differences in SW amplitude and slope for the different stages of the AD continuum. Lines and shadows represent each group's mean and standard deviation, respectively.

Macro-architecture



Micro-architecture

Slow-wave parameters

Figure 2

Sleep parameters across the AD continuum groups, splitted by sex. Left: women, right: men. Boxplots of the macro- (A-C), micro-architecture (D-F), and slow-wave (G-I) parameters of sleep (adjusted for age). Boxplots display the median (central line), interquartile range (IQR, box edges), and whiskers extending to 1.5×IQR; points beyond whiskers indicate outliers. Grey dots connected by dashed lines represent the mean. * $p < 0.050$, ** $p < 0.001$ (after multiple comparisons correction).

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