Diagnosis, Assessment & Disease Monitoring

The relationship between Alzheimer's-related brain atrophy patterns and sleep macro-architecture

Antoine Weihs[1] | Stefan Frenzel[1] | Linda Garvert[1] | Luise Kühn[1] | Katharina Wittfeld[1,2] | Ralf Ewert[3] | Ingo Fietze[4,5] | Thomas Penzel[4] | Beate Stubbe[3] | András Szentkirályi[6] | Niklas Wulms[6] | Henry Völzke[7,8] | Hans J. Grabe[1,2]

[1]Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany

[2]German Centre for Neurodegenerative Diseases (DZNE), Site Rostock/Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany

[3]Department of Internal Medicine B–Cardiology, Pneumology, Infectious Diseases, Intensive Care Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany

[4]Interdisciplinary Centre of Sleep Medicine, CC 12, University Hospital Charité Berlin, Berlin, Germany

[5]The Fourth People's hospital of Guangyuan, Guangyuan City, Sichuan, China

[6]Institute of Epidemiology and Social Medicine, University of Muenster, Muenster, Nordrhein-Westfalen, Germany

[7]Institute for Community Medicine, Department SHIP/Clinical Epidemiological Research, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany

[8]German Centre for Cardiovascular Research (DZHK), Partner Site Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany

Correspondence
Antoine Weihs, Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Ellernholzstr 1-2, 17475 Greifswald, Germany.
Email: antoine.weihs@uni-greifswald.de

Abstract

Introduction: Sleep is increasingly recognized as a major risk factor for neurodegenerative disorders such as Alzheimer's disease (AD).

Methods: Using an magnetic resonance imaging (MRI)–based AD score based on clinical data from the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI1) case-control cohort, we investigated the associations between polysomnography-based sleep macro-architecture and AD-related brain atrophy patterns in 712 pre-symptomatic, healthy subjects from the population-based Study of Health in Pomerania.

Results: We identified a robust inverse association between slow-wave sleep and the AD marker (estimate: −0.019; 95% confidence interval: −0.03 to −0.0076; false discovery rate [FDR] = 0.0041), as well as with gray matter (GM) thicknesses in typical individual cortical AD-signature regions. No effects were identified regarding rapid eye movement or non–rapid eye movement (NREM) stage 2 sleep, and NREM stage 1 was positively associated with GM thickness, mainly in the prefrontal cortical regions.

Discussion: There is a cross-sectional relationship between AD-related neurodegenerative patterns and the proportion of sleep spent in slow-wave sleep.

1 | BACKGROUND

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders, affecting around 6.5 million individuals in the United States in 2022, a number that is expected to double by 2060.[1] It is characterized by impaired memory and learning in the early stages, eventually leading to language difficulties, disorientation, and behavioral alterations, and finally the loss of bodily functions.[1]

Biological hallmarks of AD include increased amyloid beta (Aβ) plaque depositions and tau protein aggregations in the brain as well as neuronal and synaptic loss and brain atrophy.[2] These neurodegenerative processes precede AD years before its onset, creating tell-tale brain atrophy patterns, which can be accessed via magnetic resonance imaging (MRI).[2,3] The causes of the disorder remain elusive, with increasing evidence pointing to a complex interaction between non-modifiable factors, such as age and genetic predisposition, and modifiable factors, such as obesity, smoking, and hypertension.[1] Another modifiable factor could be sleep, specifically sleep architecture, with a bi-directional relationship being hypothesized between the two.[4]

Subjects with AD or mild cognitive impairment (MCI) exhibited, among others, reduced rapid eye movement (REM) sleep and slow-wave sleep (SWS) as well as longer sleep-onset latencies and lower sleep efficiency as a result of AD-related pathological accumulations and neurodegeneration in sleep-relevant brain areas.[5] On a biological level, animal experiments have observed that the presence of cortical Aβ fragments resulted in shortened non-REM (NREM) sleep and increased wakefulness,[6] and AβPP^{SWE}/PS1$^{\Delta E9}$ mice showed altered sleep architecture and electroencephalography (EEG) profiles, which preceded signs of cognitive deficits and AD neuropathology.[7] In humans, an increased risk of Aβ deposition was associated with reduced night-time sleep in elderly subjects before the onset of MCI or any significant Aβ depositions.[8] In a prospective study, reduced REM sleep and increased REM sleep latency were associated with increased dementia risk,[9] and decreased self-reported sleep latency, efficiency, quality and duration, and reduced slow-wave activity (SWA) were correlated with increased Aβ deposition.[5] SWA in particular was found to be associated with increased cerebral glymphatic clearance of Aβ in mice.[10] Similar observations were also made in humans, with healthy adults artificially deprived of SWS showing acute increases of cerebrospinal fluid (CSF) Aβ concentrations and reduced SWS being recently associated with reduced cortical and subcortical brain volume and increased white matter hyperintensities.[11,12] Furthermore, cognitively healthy elderly subjects with the apolipoprotein E (*APOE*) ε4 allele, the largest known risk factor for AD, exhibited a reduced objective sleep quality compared to noncarriers, as well as reduced total sleep time (TST), with *APOE* ε4 status modulating the association between TST and CSF tau levels.[13,14]

We, therefore, hypothesize that distinct features of polysomnography (PSG)–based sleep macro-architecture are related to MRI-based indicators of early AD-related brain atrophy in pre-symptomatic, healthy subjects from the general population-based Study of Health in Pomerania (SHIP-Trend).[15] But contrary to previous studies analyzing different brain structures individually, we focus primarily on an MRI-based AD marker, which, based on clinical data from the ADNI1 case-control cohort, aggregates subtle but widespread regional AD-related deviations throughout the whole brain.[2,3,16]

2 | METHODS

2.1 | Participants in SHIP-Trend

SHIP-Trend is a general population-based cohort based on a sex, age, and city/county of residence stratified sample of $N = 8016$ adults selected randomly from local registries in western Pomerania in 2008, with $N = 4420$ individuals being examined between 2008 and 2011 (response rate: 50.1%).[15] All were invited to participate in an MRI or PSG examination and, after excluding all subjects who refused participation in the whole-body MRI or fulfilled an exclusion criterion (e.g., presence of a pacemaker), MRI scans were performed on $N = 2159$ individuals, and $N = 1264$ SHIP-Trend participants underwent a PSG assessment.[2,17] For the current analysis, all subjects were included who had more than 4 hours of TST during the PSG, did not show any major structural abnormalities (e.g., large cysts or brain tumors), and who did not have multiple-sclerosis, epilepsy, or Parkinson disease, or had a stroke (Figure S1). The SHIP-Trend study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the University Medicine Greifswald Institutional Review Board. All subjects provided written informed consent.

2.2 | Data assessment in SHIP-Trend

Clinical data were collected using computer-assisted face-to-face interviews and medical examinations. Cognition was assessed using the word list recall test (WLR) from the Nuremberg Gerontopsychological Inventory and the inference score from the Stroop test.[15] A full list of the definition of the used variables can be found in Supplementary Methods 1. Genotyping was performed in two batches and missing single nucleotide polymorphisms (SNPs) were imputed using the Haplotype Reference consortium and the Michigan Imputation Server.[18] *APOE* status was defined based on rs7412 and rs429358 (Table S1). For more details see Supplementary Methods 2.
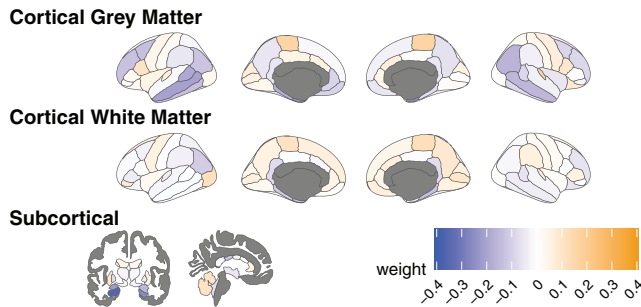
FIGURE 1 Weights/estimates of the 169 features of gray matter (GM), white matter, and the ventricular system used to create the Alzheimer's disease (AD) score

2.3 | Polysomnography

The PSG was carried out as described by Stubbe et al. (2016), with scoring being performed by trained scorers according to American Academy of Sleep Medicine (AASM) 2007 criteria.[19–22] At this stage TST, the apnea-hypopnea index (AHI), as well as the objective sleep quality markers, namely sleep efficiency, sleep latency, REM latency, the arousal index, and wake after sleep onset (WASO) were assessed. To assess subjective sleep quality, subjects participating in the PSG were asked to fill out the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS).[19]

2.4 | MRI acquisition and image processing

We used T1-weighted structural MRI scans of the head (Magnetom Avanto, Siemens, Erlangen, Germany).[15] Cortical reconstruction and volumetric segmentation were performed with FreeSurfer 7.2.[23] (For more details, see Supplementary Methods 3.) At this stage, FreeSurfer also assessed the intracranial volume (ICV), total brain volume, mean cortical gray matter (GM) thickness, and total subcortical volume.

2.5 | The AD score

The AD score was defined as described by Frenzel et al. (2020).[2,3] Briefly, a L2-penalized logistic regression was used to train a binary classifier, which, based on 169 features of GM, white matter, and the ventricular system, optimally separated individuals with AD from cognitively normal subjects in $N = 374$ ($N = 165$ with AD and $N = 209$ cognitively healthy) individuals from the ADNI1 case-control cohort.[16] The resulting classifier was used to predict the log-odds of having AD in SHIP-Trend (Figure 1 and Table S2). As such, a higher score would indicate a higher similarity of the subject's brain to an AD-brain as defined by the ADNI1 sample.

2.6 | Statistical analyses

All statistical analyses were performed with R Version 4.0.[24] Missing covariates were imputed using the "missForest" R package using the whole SHIP-Trend data set.[25]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed. Sleep is increasingly recognized as a major risk factor for Alzheimer's disease (AD). However, although various studies have analyzed the effect of AD and sleep on the brain, most base their results on self-reported sleep data and use markers that either only quantify individual AD-related pathways (e.g., florbetapir-PET [positron emission tomography]) or use nonspecific morphometric magnetic resonance imaging (MRI) markers.

2. **Interpretation**: Using an AD score, based on sample morphometric MRI measures from the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI1) case-control cohort, we found that specifically slow-wave sleep was robustly inversely associated to AD-related brain atrophy in pre-symptomatic, healthy subjects.

3. **Future directions**: Further studies are needed to investigate the long-term dynamics of this relationship and its potential as a target to delay the onset of AD, as well as the specific role of non–rapid eye movement (NREM) stage 1 or 2 or REM sleep-related components in these processes.

The effects of sleep stages (NREM 1, NREM 2, SWS, and REM% of TST) on AD-related brain atrophy patterns were analyzed using ordinary least-squared multivariate linear regression and robust standard errors (HC3).[26] The models were adjusted initially for age, sex, age × sex, ICV, and TST (model 0). To account for the nonlinear dependency between the various outcomes and age as well as TST, restricted cubic splines with four knots were used in all models. Effects were considered significant if the false discovery rate (FDR) was < 0.05 to account for multiple testing.

To assess the robustness of significant associations, the corresponding models were re-analyzed while additionally adjusting for sets of confounders believed to affect either the sleep parameter or the AD score using a one-at-a-time approach. The first set assessed the influence of metabolic factors (model 1, presence of diabetes, diabetes × sex, hypertension, hypertension × sex, waist-height ratio, waist-height ratio × sex, cholesterol ratio, and cholesterol ratio × sex); the second set assessed socioeconomic factors (model 2, partnership status, equivalent income, and number of education years); the third set assessed lifestyle factors (model 3, smoking pack-years and current status, smoking pack-years × current status, physical activity, average daily alcohol consumption, and average daily alcohol consumption × sex); the fourth set assessed sleep disorder-related factors (model 4, AHI, AHI × sex, presence of insomnia and restless legs syndrome, and the intake of sleep medication); the fifth set included total brain volume (model 5) to assess general age-related brain atrophy; and the sixth set (model 6) included the presence of lifetime depression. Next to the AD score, we additionally assessed total brain volume, mean total

cortical GM thickness, and total subcortical volume, as well as regional segmented subcortical volumes (aseg-segmentation) and mean cortical thicknesses (DK-segmentation) using the same method used in the AD scor.[27,28] For the segmented subcortical volumes, instead of analyzing the left and right hemispheres separately, the total bilateral subcortical volumes were used. Similarly, for the cortical thicknesses area, weighted mean thicknesses within the left and right hemispheres were used.

As a side analysis, we investigated associations between the AD score and subjective (PSQI and ESS sum-scores) and objective sleep quality parameters (sleep efficiency and latency, REM latency, arousal index, and WASO) using the same approach described above (model 0) and the association between the sleep stages and cognition (WLR and Stroop scores), where instead of adjusting for the standard covariates, the models were adjusted for age, sex, age × sex, TST, and education years.

Furthermore, to investigate AD-related genetic predisposition, we analysed the relationship between the sleep stages and the *APOE* genotype (additive model) and an AD polygenic risk score (PRS), as well as, for validation, the relationship of the AD score with the *APOE* genotype and the AD-PRS. The AD-PRS was based on a genome-wise association study (GWAS) performed by Kunkel et al. (2019) and was calculated using PRS-CS using the European UKB linkage disequilibrium reference panel.[29,30] The models were adjusted for the base covariates described above (model 0), the first three genetic principal components, and the genotyping batch.

3 | RESULTS

3.1 | Baseline characteristics of the sample population

We included $N = 712$ individuals (47.2% women, mean age ± SD: 52.5 ± 13.4 years) after excluding $N = 3659$ subjects due to missing MRI or PSG measurements; $N = 14$ due to structural MRI abnormalities, ;$N = 10$ due to the presence of multiple sclerosis (MS), Parkinson, epilepsy, or strokes and $N = 25$ because PSG measurements were too short (Figure S1). Compared to the remaining SHIP-Trend sample, the analyzed sample was generally more educated, had a higher income, and exhibited more favorable health parameters (Tables 1 and 2); 93.3% of subjects had a complete set of covariates with equivalent income exhibiting the highest missingness rate of 3.8% (Figure S2). The (locally) optimal imputation had an estimated normalized root mean square error of 0.060 and an estimated proportion of falsely classified of 0.13 (Figures S3 and S4).

3.2 | Sleep macro-architecture and AD-related brain atrophy patterns

After adjusting for multiple testing, SWS was inversely associated with AD-related brain atrophy patterns (estimate −0.02, 95% confidence interval [CI] −0.03, −0.008, FDR 0.004, Table 3). To assess the
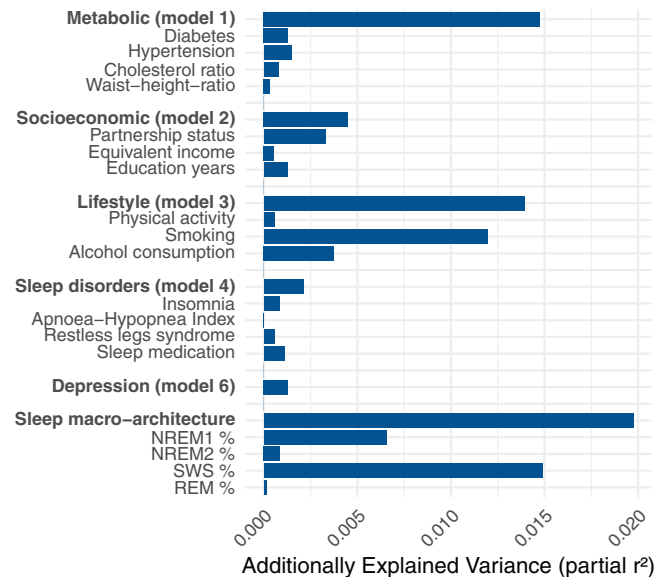
FIGURE 2 Additionally explained variance of the Alzheimer's disease (AD) score by potential confounders. The value represents the percentage of variance that can be explained by the variable set on the y-axis but not by the base model: AD score ~ age (non-linear) + sex + age (non-linear) × sex + intracranial volume (ICV) + total sleep time (TST) (non-linear)

robustness of this effect, we analyzed the impact of various potential confounders suspected to have an impact on the AD marker or sleep, with the effects remaining stable and significant, irrespective of the added extra confounder set (Table 3 and Figure 2). No effects were identified regarding the other sleep stages.

3.3 | Sleep macro-architecture and morphometric brain measurements

Analogous to the AD score, we investigated global morphometric measures as well as individual cortical and subcortical regions of interest (ROIs). Both NREM 1 and SWS were significantly associated with mean cortical GM thickness but not total brain or subcortical GM volume (Table S3). Regarding the subcortical volumetric segmentation, no significant association could be identified after adjusting for multiple testing (Table S4). On a cortical level (Table S5), both SWS and NREM 1 were significantly associated with mean precentral, rostral middle frontal, and superior frontal (all frontal cortex) GM thicknesses. NREM 1 was additionally associated with mean pars orbitalis and pars triangularis (both frontal cortex) GM thicknesses, whereas SWS was also associated with mean caudal middle frontal (frontal cortex), inferior and superior parietal, precuneus (parietal cortex), banks of the superior temporal sulcus, inferior, middle, transverse and superior temporal, fusiform, temporal pole (all temporal cortex), and lateral occipital (occipital cortex) GM thickness. REM was associated with the mean paracentral (frontal cortex) and precuneus (parietal cortex) GM thickness, whereas no association with regard to NREM 2 could be identified. In the sensitivity analysis, the effects remained stable except

TABLE 1 Baseline characteristics of the sample population and the remaining SHIP-Trend population that was not included in the analyses

	Included Mean ± SD or N (%) N = 712	No. Missing (%)	Remaining Mean ± SD or N (%) N = 3708	No. Missing (%)
Age, years	52.5 ± 13.4		52.2 ± 15.8	
Sex, female	336 (47.2%)		1939 (52.3%)	
Waist-height ratio	0.5 ± 0.1	1 (0.1%)	0.5 ± 0.1	15 (0.4%)
Education, years	13.0 ± 2.4	5 (0.7%)	12.1 ± 2.3	64 (1.7%)
Equivalent income	1479.7 ± 774.9	27 (3.8%)	1338.8 ± 685.2	160 (4.3%)
Partner status, yes	564 (79.5%)	2 (0.3%)	2854 (77.2%)	11 (0.3%)
Smoking, pack-years	7.3 ± 15.0		8.8 ± 14.5	
Currently Smoking, yes	131 (18.5%)	2 (0.3%)	1052 (28.5%)	20 (0.5%)
Physical activity, higher value equals more physical activity	3.6 ± 2.1	2 (0.3%)	3.1 ± 2.2	22 (0.6%)
Average alcohol consumption in the last 30 days, g of Ethanol/d	9.1 ± 12.1	7 (1.0%)	8.3 ± 13.7	44 (1.2%)
Lifetime depression, yes	144 (20.5%)	8 (1.1%)	658 (18.3%)	122 (3.3%)
Diabetes, yes	68 (9.6%)	1 (0.1%)	481 (13.0%)	9 (0.2%)
Hypertension, yes	317 (44.6%)	2 (0.3%)	1806 (48.9%)	15 (0.4%)
Cholesterol ratio	4.1 ± 1.2	1 (0.1%)	4.0 ± 1.4	6 (0.2%)
ICV, cm^3	1589.5 ± 167.1		1585.6 ± 155.5	2275 (61.4%)
Total Brain Volume, cm^3	1003.3 ± 108.2		1000.0 ± 105.2	2275 (61.4%)
MRI AD-Score	−4.0 ± 1.2		−4.0 ± 1.3	2275 (61.4%)
WLR sum	11.1 ± 2.5	7 (1.0%)	10.9 ± 2.7	37 (1.0%)
WLR immediate	5.4 ± 1.3	1 (0.1%)	5.2 ± 1.4	14 (0.4%)
WLR delayed	5.7 ± 1.6	7 (1.0%)	5.7 ± 1.7	37 (1.0%)
Stroop interference	19.5 ± 10.1	91 (12.8%)	20.4 ± 13.5	281 (7.6%)
APOE		56 (7.9%)		343 (9.3%)
ε4 homozygotes	14 (2.1%)		73 (2.2%)	
ε4 heterozygotes	149 (22.7%)		733 (21.8%)	

when controlling for lifestyle factors or the AD score (Figures S5, S6, and S7).

3.4 | Sleep quality and cognition

No association between any of the additional subjective or objective sleep quality parameters and the AD score were identified (Table S6). Concerning the cognitive scores, NREM 1 was inversely associated with the WLR immediate sub-score (estimate −0.01, 95% CI −0.02, −0.001; *p*-value: 0.03) and positively with the Stroop interference score (estimate 0.007, 95% CI 0.002, 0.01; *p*-value: 0.007). However, none of the effects remained significant after adjusting for multiple testing (Table S7).

3.5 | Sleep architecture and genetics

Using all available SHIP-Trend subjects, after only excluding those with multiple-sclerosis, Parkinson disease, epilepsy, strokes, or had struc-

tural abnormalities, there was a significant association between the AD score and the AD-PRS (estimate 0.20, 95% CI 0.0016, 0.40; *p*-value: 0.048; N = 1963) but not with *APOE* (estimate 0.10, 95% CI −0.012, 0.21; *p*-value: 0.079; N = 1914), which was not present when analyzing the 712 subject included in this study. Furthermore, no association was present between any of the sleep stages and the two genetic markers (Table S8).

4 | DISCUSSION

AD is a multifactorial disorder expected to become a major burden on health systems.[1] With no effective cure currently available, the only approach to delay its onset is to target modifiable risk factors such as obesity, smoking, hypertension, or sleep. Although it is commonly accepted that sleep changes with age, such as reduced sleep duration and SWS or REM sleep, increased duration spent in NREM 1 and 2 sleep, and increased sleep fragmentation, the presence of large interpersonal differences might explain why some are at higher

TABLE 2 Characteristics of the sleep-based parameters of the sample population

	Included Mean ± SD OR N (%) N = 712	NO. Missing (%)
Sleep architecture		
NREM stage 1 (% of TST)	14.4 ± 8.6	
NREM stage 2 (% of TST)	52.8 ± 8.0	
SWS (% of TST)	14.2 ± 8.1	
REM (% of TST)	18.6 ± 5.7	
Sleep Disorders		
Insomnia, yes	71 (10.0%)	
AHI	8.8 ± 13.2	
Restless leg syndrome, yes	117 (16.6%)	6 (0.8%)
Sleep medication, yes	43 (6.0%)	
Objective sleep quality		
Total sleep time, hours	6.3 ± 0.9	
Sleep Efficiency, %	82.4 ± 10.2	
Sleep Latency, min	14.4 ± 16.8	
REM Latency, min	115.4 ± 60.4	1 (0.1%)
Arousal index	21.8 ± 10.4	
WASO	59.1 ± 39.5	
Subjective Sleep Quality		
PSQI sum	6.0 ± 3.7	127 (17.8%)
ESS sum	7.0 ± 3.3	17 (2.4%)

Abbreviations: AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; NREM, non–rapid eye movement sleep; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement sleep; SWS, slow wave sleep; TST, total sleep time; WASO, wake after sleep onset.

risk of developing dementias.[31] In the current study, we therefore, investigated the relationship between sleep macro-architecture and an MRI-based AD score, which, unlike most current studies, is based on clinical case-control data and does not rely on individual AD-related markers such as Aβ or tau, or unspecific global MRI morphometric measures, but instead aggregates subtle but widespread and typically AD-related deviations in regional brain structures.

We found that specifically SWS was inversely associated with the AD score independently from potential AD or sleep- related confounders. To further investigate this effect, next to the global AD-MRI score, we analyzed the association between SWS and cortical GM thicknesses and subcortical volumes. Although no subcortical effects could be observed, we found that SWS was associated with total mean cortical GM thickness as well as with typical cortical AD-signature regions.[32,33] Like the AD-score models, the effects remained stable except after the addition of lifestyle factors and the AD score itself.

These results are in line with the currently prevailing theories implicating SWS in AD-related pathological processes. SWS is the deepest NREM sleep phase and characterized by SWA, that is, low-frequency,

high-voltage oscillating waves.[20] During this stage, the brain shows the greatest decrease in neuronal activity compared to the waking state and the stage has been implicated in various restorative functions, thereby providing a counterbalance for the high neurometabolic activity and stress experienced during wakefulness.[34,35] Specifically concerning AD, SWS exhibits a reduced production of the amyloid precursor protein and to promote cellular repair from oxidative damage, both of which were found to promote the pathological accumulation of Aβ.[36] In addition, increased SWS or SWA correlated with a drastic increase of glymphatic clearance of cerebral metabolites among which Aβ and tau.[10,11,37] Conversely, brain atrophy also seems to have an impact on SWS. Cortical GM volume has repeatedly been found to mediate the correlation between age and reductions in SWS or SWA.[38] Furthermore, reduced mean cortical GM thickness in areas involved in the generation and propagation of SWA was associated with reduced slow-wave amplitude and density.[39] The significant associations observed here could, therefore, also represent the increasing inability to generate SWA as a result of brain atrophy, something generally seen in subjects with MCI or AD, or, combining both directions, the vicious circle in which brain atrophy reduces SWS, which disrupts regenerative processes, which in turn leads to more brain atrophy.[4,5]

Contrary to SWS, no associations were observed between the AD score and NREM 1, NREM 2, or REM sleep. The lack of an association with REM sleep is surprising, as reduced time spent in this stage has been linked to an increased dementia risk[9] and declines in executive and general cognitive function and attention.[40] Furthermore, Aβ correlated with reduced REM sleep in both healthy elderly subjects and subjects with AD.[41] A similar observation was made by Baril et al. (2021), who, while identifying significant effects between SWS and reduced cortical and subcortical GM volumes, found no effects regarding REM sleep.[12] The lack of an effect might be due to the participants relatively young age of this and the aforementioned study. Although the proportion of sleep spent in SWS decreases steadily with age and is therefore able to influence AD-related pathology early on, the proportion of REM sleep was found to remain fairly constant from young adulthood to late middle age, starting to show reductions only after 50 to 60 years of age and, therefore, has not affected the brain strongly enough to be observed.[12,31] Another reason might be the presence of a first night effect, with previous studies reporting shorter REM sleep durations during the first night of a PSG measurement compared to subsequent nights.[42,43]

Interpreting the NREM 1 and NREM 2 results, on the other hand, is a bit more challenging, as studies analyzing the effect of NREM 1 or NREM 2 on brain atrophy are rare. These two stages are often considered as light sleep, as the chance of an arousal is at its highest.[44] Increased time spent here could, therefore, be a marker for poor sleep quality, which has been linked to increased risk of AD or cognitive decline.[45] This is supported by findings observing that subjects with MCI or AD generally spent a large fraction of TST in both NREM 1 and 2, and that greater time spent in NREM 1 predicts faster cognitive decline.[9,46,47] While not finding any significant associations regarding NREM 2 or subjective and objective sleep quality markers, we have found that reduced NREM 1 was associated with decreased total mean

TABLE 3 Results of the models analyzing the association between AD score and sleep stages (% of TST)

Exposure Outcome	NREM 1 % of TST Estimate (95% CI)	p (FDR)
AD score (model 0, base model)[a]	0.012 (−0.00045, 0.025)	0.059 (0.12)
	NREM 2 % of TST Estimate (95% CI)	p (FDR)
AD score (model 0, base model)[a]	0.0042 (−0.0073, 0.016)	0.47 (0.62)
	SWS % of TST Estimate (95% CI)	p (FDR)
AD score (model 0, base model)[a]	−0.019 (−0.030; −0.0076)	0.0010 (0.0041)
AD score (model 1, Metabolic factors)[b]	−0.018 (−0.029, −0.0066)	0.0076
AD score (model 2, Socioeconomic factors)[c]	−0.019 (−0.030, 0.0077)	0.00097
AD score (model 3, Lifestyle factors)[d]	−0.017 (−0.028, −0.0057)	0.0032
AD score (model 4, Sleep Disorder)[e]	−0.019 (−0.031, −0.0080)	0.00087
AD score (model 5, Total Brain Volume)[f]	−0.018 (−0.029, −0.0068)	0.0016
AD score (model 6, Depression)[g]	−0.019 (−0.030, −0.0077)	0.00095
AD score (all)[h]	−0.017 (−0.028, −0.0051)	0.0047
	REM % of TST Estimate (95% CI)	p (FDR)
AD score (model 0, base model)[a]	0.0025 (−0.014, 0.019)	0.76 (0.76)

[a]Model was adjusted for age (non-linear), sex, age (non-linear) × sex, intracranial volume (ICV), and total sleep time (TST) (non-linear).
[b]Model was adjusted as in model 0 and additionally for the presence of diabetes, diabetes × sex, presence of hypertension, hypertension × sex. cholesterol ratio, cholesterol ratio × sex, waist-height ratio, and waist-height ratio × sex.
[c]Model was adjusted as in model 0 and additionally for the partner status, equivalent income, and education years.
[d]Model was adjusted as in model 0 and additionally for the current smoking status, smoking pack years, current smoking status × smoking pack years, physical activity, average alcohol consumption, and average alcohol consumption × sex.
[e]Model was adjusted as in model 0 and additionally for the presence of insomnia, AHI, AHI × sex, presence of restless leg syndrome, and the intake of sleep medication.
[f]Model was adjusted as in model 0 and additionally for total brain volume.
[g]Model was adjusted as in model 0 and additionally for the presence of lifetime depression.
[h]Model was adjusted as in model 0 and additionally for all of the additional covariates from above.

GM thicknesses as well as mean GM thickness in prefrontal cortical regions, an area found to exhibit some of the earliest pathological Aβ depositions.[36] Of interest, the area is also related to executive function, with, while not surviving FDR-correction, NREM 1 being associated with the Stroop interference score and the verbal memory WLR immediate score, both assessing the cognitive process.[48] As in SWS, the brain effects remained stable except when correcting for lifestyle factors or the AD score. The lack of significant results might, therefore, indicate that the proportion of TST spent in NREM 1 and 2 on their own might not be representative metrics of the AD-related pathological processes and that composite metrics objectively assessing sleep quality or micro-architectural components might be more relevant.

This study has some limitations. (1) PSG examinations were performed in only one quarter of the SHIP-Trend population, possibly leading to a selection bias. A comparison of the study sample with the remaining SHIP-Trend sample showed that the study sample was slightly healthier and more educated, which was also previously observed in the whole PSG data set.[17] However, a closer examination

failed to reveal the presence of any critical selection bias.[17] (2) PSG measurements have been performed for only one night, resulting in a potential first-night effect.[42,43] Studies analyzing this phenomenon reported that subjects tended to have a shorter TST and less REM sleep.[42,43] But while marked differences in spectral NREM-related EEG power were found between the first two nights, no differences in NREM sleep durations were observed.[42] (3) The current study included only cross-sectional and not longitudinal data, thus restricting the analyses to investigate only AD-related atrophy patterns and not the atrophy itself, as well as limiting the causal interpretation of the results. Although longitudinal PSG or MRI data were not yet available, further analyses are planned.

In conclusion, using one of the largest samples of this type to date, the reported results show evidence of a cross-sectional relationship between AD-related neurodegenerative patterns in the brain and the proportion of TST spent in SWS, adding to the growing body of evidence hypothesizing a complex relationship between the two. Supplementary (longitudinal) studies will have to be performed to further

investigate the dynamics of this relationship and its potential as a target to delay the onset of AD, as well as the role of NREM 1, NREM 2, and REM sleep in these processes.

CONFLICTS OF INTEREST

H.J.G. has received travel grants and speaker honoraria from Fresenius Medical Care, Neuraxpharm, Servier, and Janssen Cilag, as well as research funding from Fresenius Medical Care. H.J.G. had personal contracts approved by the university administration for speaker honoraria and one IIT with Fresenius Medical Care. T.P. received travel grants from Jazz Pharma, Löwenstein Medical, and the German Sleep Society, as well as speaker honoraria from Jazz Pharma, Löwenstein Medical, and Neuwirth, and research funding from the European Union, the German Israel Foundation and the Saratov state University. T.P. is on the advisory board of Philips, Crebra, and Nukute (unpaid); an Adcom member of the IEEE Biomedical Engineering Society (unpaid); and the president of the German Sleep Society (unpaid), and received consulting fees from Cerebra, Philips (paid to the institution), NovaResp Technologies (paid to the institution), Sleepimage (paid to the institution), and the National Sleep Foundation; sleep measuring devices from Neurovirtual and Sleepon; and holds shares in Advanced Sleep Research, The Siestagroup GmbH and Nukute. R.E. has received speaker honoraria from Berlin Chemie, AstraZeneca, and Janssen as well as consulting fees from LungPacer and OMT, and is a member of the LungPacer and Janssen advisory board. I.F. received grants from ResMed and Löwenstein Medical as well as consulting fees from ResMed, Stada, Bioproject, and Idorsia, and lecture honoraria from Medice, Henning, Idorsia, Bioprojet, Jazz Pharma, and ResMed. The remaining authors have nothing to declare. Author disclosures are available in the supporting information.

REFERENCES

1. The Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):700-789. https://doi.org/10.1002/alz.12638
2. Frenzel S, Wittfeld K, Habes M, et al. A biomarker for Alzheimer's disease based on patterns of regional brain atrophy. *Front Psychiatry.* 2020;10:953. https://doi.org/10.3389/fpsyt.2019.00953
3. Schwahn C, Frenzel S, Holtfreter B, et al. Effect of periodontal treatment on preclinical Alzheimer's disease – Results of a trial emulation approach. *Alzheimers Dement.* 2021:1-15. https://doi.org/10.1002/alz.12378
4. Lucey BP. It's complicated: the relationship between sleep and Alzheimer's disease in humans. *Neurobiol Dis.* 2020;144:105031. https://doi.org/10.1016/j.nbd.2020.105031
5. Kent BA, Feldman HH, Nygaard HB. Sleep and its regulation: an emerging pathogenic and treatment frontier in Alzheimer's disease. *Prog Neurobiol.* 2021;197:101902. https://doi.org/10.1016/j.pneurobio.2020.101902
6. Roh JH, Huang Y, Bero AW, et al. Disruption of the sleep-wake cycle and diurnal fluctuation of -amyloid in mice with Alzheimer's disease pathology. *Sci Transl Med.* 2012;4:150ra122-150ra122. https://doi.org/10.1126/scitranslmed.3004291
7. Zhang F, Zhong R, Li S, et al. Alteration in sleep architecture and electroencephalogram as an early sign of Alzheimer's disease preceding the disease pathology and cognitive decline. *Alzheimer Dement.* 2019;15:590-597. https://doi.org/10.1016/j.jalz.2018.12.004
8. Insel PS, Mohlenhoff BS, Neylan TC, Krystal AD, Mackin RS. Association of sleep and β-amyloid pathology among older cognitively unimpaired adults. *JAMA Netw Open.* 2021;4:e2117573. https://doi.org/10.1001/jamanetworkopen.2021.17573
9. Pase MP, Himali JJ, Grima NA, et al. Sleep architecture and the risk of incident dementia in the community. *Neurology.* 2017;89:1244-1250. https://doi.org/10.1212/WNL.0000000000004373
10. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science.* 2013;342:373-377. https://doi.org/10.1126/science.1241224
11. Ju YES, Ooms SJ, Sutphen C, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain.* 2017;140:2104-2111. https://doi.org/10.1093/brain/awx148
12. 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:e1462-9. https://doi.org/10.1212/WNL.0000000000011377
13. Drogos LL, Gill SJ, Tyndall AV, et al. Evidence of association between sleep quality and APOE ε4 in healthy older adults: a pilot study. *Neurology.* 2016;87:1836. https://doi.org/10.1212/WNL.0000000000003255
14. López-García S, Lage C, Pozueta A, et al. Sleep time estimated by an actigraphy watch correlates with CSF tau in cognitively unimpaired elders: the modulatory role of APOE. *Front Aging Neurosci.* 2021;13:471. https://doi.org/10.3389/FNAGI.2021.663446
15. Völzke H, Schössow J, Schmidt CO, et al. Cohort profile update: the Study of Health in Pomerania (SHIP). *Int J Epidemiol.* 2022:dyac034. https://doi.org/10.1093/ije/dyac034
16. Weiner MW, Aisen PS, Jack CR, et al. The Alzheimer's disease neuroimaging initiative: progress report and future plans. *Alzheimer Dement.* 2010;6:202. https://doi.org/10.1016/j.jalz.2010.03.007
17. Fietze I, Laharnar N, Obst A, et al. Prevalence and association analysis of obstructive sleep apnea with gender and age differences – Results of SHIP-Trend. *J Sleep Res.* 2019;28:e12770. https://doi.org/10.1111/jsr.12770
18. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet.* 2016;48:1279-1283. https://doi.org/10.1038/ng.3643
19. Stubbe B, Penzel T, Fietze Ingo, et al. Polysomnography in a large population based study-the study of health in Pomerania protocol. *J Sleep Disord Manag.* 2016;2:1-5. https://doi.org/10.23937/2572-4053.1510010
20. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1 st. *Am Acad Sleep Med.* 2007. https://lccn.loc.gov/2007280358

21. Weihs A, Frenzel S, Wittfeld K, et al. Associations between sleep apnea and advanced brain aging in a large-scale population study. *Sleep.* 2021;44:1-15. https://doi.org/10.1093/sleep/zsaa204

22. Zacharias HU, Weihs A, Habes M, et al. Association between obstructive sleep apnea and brain white matter hyperintensities in a population-based cohort in Germany. *JAMA Network Open.* 2021;4:e2128225. https://doi.org/10.1001/jamanetworkopen.2021.28225

23. Fischl B. FreeSurfer. *Neuroimage.* 2012;62:774-781. https://doi.org/10.1016/j.neuroimage.2012.01.021

24. R Core Team. R: The R Project for Statistical Computing n.d. Accessed September 2, 2022. https://www.r-project.org/

25. Stekhoven DJ, Bühlmann P. Missforest-Non-parametric missing value imputation for mixed-type data. *Bioinformatics.* 2012;28:112-118. https://doi.org/10.1093/bioinformatics/btr597

26. Long JS, Ervin LH. Using heteroscedasticity consistent standard errors in the linear regression model. *Am Stat.* 2000;54:217-224. https://doi.org/10.1080/00031305.2000.10474549

27. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation. *Neuron.* 2002;33:341-355. https://doi.org/10.1016/S0896-6273(02)00569-X

28. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage.* 2006;31:968-980. https://doi.org/10.1016/j.neuroimage.2006.01.021

29. Ge T, Chen CY, Ni Y, Feng YCA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat Commun.* 2019;10:1-10. https://doi.org/10.1038/s41467-019-09718-5

30. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet.* 2019;51:414-430. https://doi.org/10.1038/s41588-019-0358-2

31. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep.* 2004;27:1255-1273. https://doi.org/10.1093/SLEEP/27.7.1255

32. Bakkour A, Morris JC, Wolk DA, Dickerson BC. The effects of aging and Alzheimer's disease on cerebral cortical anatomy: specificity and differential relationships with cognition. *Neuroimage.* 2013;76:332-344. https://doi.org/10.1016/j.neuroimage.2013.02.059

33. Guo T, Landau SM, Jagust WJ. Detecting earlier stages of amyloid deposition using PET in cognitively normal elderly adults. *Neurology.* 2020;94:E1512-24. https://doi.org/10.1212/WNL.0000000000009216

34. Alger SE, Pardilla-Delgado E, Mattingly SM, Cunningham TJ, Payne JD. 2.31 - The cognitive psychology of sleep and memory. In: Byrne JH, ed. *Learning and Memory: A Comprehensive Reference.* Second Edition, Oxford: Academic Press; 2017:571-596. https://doi.org/10.1016/B978-0-12-809324-5.21062-6

35. Léger D, Debellemaniere E, Rabat A, Bayon V, Benchenane K, Chennaoui M. Slow-wave sleep: from the cell to the clinic. *Sleep Med Rev.* 2018;41:113-132. https://doi.org/10.1016/j.smrv.2018.01.008

36. 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;39:552-566. https://doi.org/10.1016/j.tins.2016.05.002

37. Iliff JJ, Chen MJ, Plog BA, et al. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J Neurosci.* 2014;34:16180-16193. https://doi.org/10.1523/JNEUROSCI.3020-14.2014

38. Wunderlin M, Züst MA, Fehér KD, Klöppel 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. https://doi.org/10.1016/j.pscychresns.2020.111178

39. Dubé J, Lafortune M, Bedetti C, et al. Cortical thinning explains changes in sleep slow waves during adulthood. *J Neurosci.* 2015;35:7795. https://doi.org/10.1523/JNEUROSCI.3956-14.2015

40. Scullin MK, Gao C. Dynamic contributions of slow wave sleep and REM sleep to cognitive longevity. *Curr Sleep Med Rep.* 2018;4:284-293. https://doi.org/10.1007/S40675-018-0131-6

41. Mander BA, Marks SM, Vogel JW, et al. β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci.* 2015;18:1051. https://doi.org/10.1038/NN.4035

42. Bon OL, Staner L, Hoffmann G, et al. The first-night effect may last more than one night. *J Psychiatr Res.* 2001;35:165-172. https://doi.org/10.1016/S0022-3956(01)00019-X

43. Agnew HW, Webb WB, Williams RL. The first night effect: an EEG study of sleep. *Psychophysiology.* 1966;2:263-266. https://doi.org/10.1111/j.1469-8986.1966.tb02650.x

44. Malhotra RK, Avidan AY. *Chapter 3 – Sleep Stages and Scoring Technique. Atlas of Sleep Medicine.* 2nd ed. Saunders; 2014:77-99.

45. Bubu OM, Brannick M, Mortimer J, et al. Sleep, Cognitive impairment, and Alzheimer's disease: a systematic review and meta-analysis. *Sleep.* 2017;40. https://doi.org/10.1093/SLEEP/ZSW032

46. Song Y, Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Stone KL. Relationships between sleep stages and changes in cognitive function in older men: the MrOS sleep study. *Sleep.* 2015;38:411-421. https://doi.org/10.5665/SLEEP.4500

47. Haba-Rubio J, Marti-Soler H, Tobback N, et al. Sleep characteristics and cognitive impairment in the general population. *Neurology.* 2017;88:463-469. https://doi.org/10.1212/WNL.0000000000003557

48. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev.* 2006;16:17-42. https://doi.org/10.1007/S11065-006-9002-X

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.