Neurobiology of Aging 154 (2025) 16–24

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

How is self-reported sleep-disordered breathing linked with biomarkers of Alzheimer's disease?

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ARTICLE INFO

Keywords:
Sleep-disordered breathing
Alzheimer's disease
Amyloid-beta
Fluorodeoxyglucose imaging
Grey matter volume

ABSTRACT

Sleep-disordered breathing (SDB) is prevalent in Alzheimer's disease (AD). Here, we assessed how self-reported SDB is linked with AD biomarkers, including amyloid-beta plaque burden (Aβ), regional fluorodeoxyglucose uptake (rFDG-PET), grey matter volume (GMV), cognitive scores, and cerebrospinal fluid (CSF) biomarkers. We selected 757 individuals, including AD, mild cognitive impairment (MCI), and cognitively unimpaired (CU) groups, and divided them according to self-reported SDB condition. Using a stratified subsampling approach, we selected 512 matched subsamples, and effect sizes (ES) of the group-SDB interaction were computed for each biomarker and cognitive score across subsamples. Linear regression assessed associations between the ES of Aβ, rFDG, and GMV with the ES of cognitive scores and CSF biomarkers. The group-SDB interaction had a medium-sized effect on Aβ, rFDG, and GMV biomarkers in several brain areas. Participants with SDB exhibited reduced Aβ burden and increased rFDG uptake in the CU and MCI groups, whereas the AD group showed elevated Aβ burden and decreased rFDG. Additionally, SDB+ individuals demonstrated GMV alterations across all groups. The ES of group-SDB interaction on Aβ in the precuneus, middle temporal gyrus, and fusiform gyrus was associated with the ES of cognitive scores. Taken together, we observed a robust association of SDB with Aβ pathology in PET and CSF relative to rFDG and GMV in the AD group, which was also associated with cognitive decline.

1. Introduction

Alzheimer's Disease (AD) constitutes 60–70 % of all cases of dementia, making it the most common form of neurodegenerative disease worldwide (Leng and Edison, 2021). It has been estimated that the prevalence of AD will be three-fold and affect about 150 million people

Abbreviations: SDB, Sleep Disordered Breathing; AD, Alzheimer's Disease; MCI, Mild Cognitive Disorder; CU, Cognitively Unimpaired; Aβ, Amyloid Beta plaque; RFDG, regional Fluorodeoxyglucose; GMV, Grey Matter Volume; PET, positron emission tomography; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, Apolipoprotein E; BMI, Body Mass Index; MMSE, Mini Mental State Examination; OSA, Obstructive Sleep Apnea.

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

https://doi.org/10.1016/j.neurobiolaging.2025.06.006
Received 11 December 2024; Received in revised form 10 June 2025; Accepted 18 June 2025
Available online 19 June 2025

worldwide by 2050 (Scheltens et al., 2021). Identification of risk factors for AD is critical for its optimal clinical management. The (modifiable) contributing factors for AD include diabetes, obesity, hypertension, vascular disease (Silva et al., 2019), and sleep disorders such as insomnia (Elberse et al., 2024; Osorio et al., 2011) and Sleep-Disordered Breathing (SDB) (Emamian et al., 2016; Ercolano et al., 2024; Liguori et al., 2021). SDB is an umbrella term characterized by abnormal respiration during sleep ranging from heavy and loud snoring to frequent episodes of partial or complete airway obstruction for at least 10 s; so-called Obstructive Sleep Apnea (OSA) (Cowie, 2017; Lévy et al., 2015). OSA is the most common form of SDB, which causes intermittent hypoxemia, arousal, and sleep fragmentation (Cowie, 2017). It is estimated that globally, around 1 billion adults aged 30–69 years could have SDB symptoms, and over 400 million have moderate to severe OSA and require treatment (Benjafield et al., 2019). Lower quality of life, a higher risk of road traffic accidents, cardiovascular and metabolic disorders, and cognitive impairments are often seen in patients with SDB (Lyons et al., 2020). Thus, assessing the neurobiology of SDB and its consequences in the general population is needed.

Several reviews suggest a complex relationship between SDB and AD (Andrade et al., 2018; Ercolano et al., 2024; Liguori et al., 2021). A meta-analysis found that patients with AD have an increased risk of presenting SDB compared to cognitively normal individuals (Emamian et al., 2016). SDB advances cognitive impairment in individuals with Mild Cognitive Impairment (MCI), and such cognitive decline happens earlier in patients with SDB (Osorio et al., 2015). Thus, individuals with SDB symptoms are more likely to develop AD dementia in the future (Ercolano et al., 2024; Liguori et al., 2021; Osorio et al., 2015). Transgenic AD mouse models found that induction of chronic intermittent hypoxia, a characteristic of SDB/OSA in humans, increased brain Amyloid-beta (Aβ) plaque burden (Shiota et al., 2013) and tau phosphorylation (Gao et al., 2013). A longitudinal study found that baseline SDB severity was associated with increased cortical amyloid burden in cognitively normal older adults (Sharma et al., 2018). Increased cortical Aβ accumulation in middle-aged patients with severe SDB has been shown (Yla-Herttuala et al., 2021). Further, in healthy and MCI groups, lower cerebrospinal fluid (CSF) Aβ and higher CSF phosphorylated tau (p-tau) have been reported, primarily in individuals with SDB (Bubu et al., 2019). Therefore, SDB may interact with AD biomarkers in preclinical stages to increase the risk of developing AD and cognitive decline.

Developing AD biomarkers, including amyloid-beta Positron Emission Tomography (Aβ-PET), 18F-Fluorodeoxyglucose PET (FDG-PET), and structural Magnetic Resonance Imaging (sMRI) (Sperling et al., 2011), as well as Aβ and tau in CSF, advanced our understanding of pathophysiological mechanisms, early detection, and monitoring of the progress and management of AD (Marquez and Yassa, 2019). The Amyloid-Tau-Neurodegeneration AT(N)) framework classified biomarkers into Aβ deposition, pathologic tau, and neurodegeneration (Jack et al., 2018). Focusing on these biomarkers may help to understand the underlying neurobiological mechanisms of the association of SDB with AD progression. For example, Andre and colleagues observed that SDB was associated with medial temporal lobe atrophy in cognitively normal older adults, mainly in amyloid-positive individuals (Andre et al., 2023). Higher Grey Matter Volume (GMV), Aβ, brain perfusion, and glucose metabolism, mainly in the posterior cingulate cortex (PCC) and precuneus, have been reported in SDB-positive participants, but those alterations were not linked with cognitive decline (Andre et al., 2020). However, our previous study did not observe any association between SDB and brain aging in AD (Mohajer et al., 2020). A systematic review also highlighted the inconsistent GMV and FDG-PET findings on the association between SDB and AD, highlighting the need for further comprehensive multimodal studies (Liguori et al., 2021).

In the present study, we measured Aβ PET imaging (as a proxy of Aβ plaque burden in the brain), regional uptake of fluorodeoxyglucose metabolism (rFDG) indicating cerebral glucose metabolism (as a surrogate of neural activity), and GMV (as an indicator of brain structure) of cortical and subcortical brain areas among participants in different groups (i.e., cognitively unimpaired (CU), patients with MCI and AD). Our research questions were (a) does the interaction between group (CU, MCI, AD) and SDB condition (SDB+, SDB-) affect AD biomarkers such as Aβ, rFDG, and GMV?; (b) are the brain regions affected by SDB-AD interaction linked with cognitive impairment and also CSF biomarkers? Recently, it has become apparent that neuroimaging research faces a replication crisis (De Boeck and Jeon, 2018). Thus, to increase the generalizability and robustness of results, particularly considering our imbalanced sample size across our groups, we have divided our individuals into 512 covariate-matched subsamples to explore how group-SDB interactions are associated with AD biomarkers.

2. Methods

2.1. Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Diagnoses of MCI and AD were based on the ADNI criteria, which have been documented elsewhere (adni.loni.usc.edu). We selected participants with three imaging modalities (including 18F-AV45 (florbetapir) amyloid-beta PET, FDG-PET, and T1w MRI), and Mini-Mental State Examination (MMSE) as a measure of individuals' cognitive performance, as well as CSF measures of Aβ42 and p-tau. Study participants with a history of stroke, Parkinson's disease, or brain tumors were excluded as they could independently cause cognitive impairment. PET and sMRI scans and MMSE assessment data were collected within two months of each other. From 757 included participants, the 102 "SDB+ " were defined with the self-reported "sleep apnea", and/or history of "obstructive sleep apnea", "OSA", or "sleep-disordered breathing" in the ADNI dataset. Otherwise, participants without any self-reported SDB symptoms are considered "SDB-", which included 655 participants with no other sleep disorders. The SDB+ individuals who had received any treatment like Continuous Positive Airway Pressure (CPAP) or bi-level positive airway pressure (BiPAP or BPAP) were excluded, as it has been shown that CPAP treatment may minimize the effects of SDB on biomarkers of AD and cognitive decline (Osorio et al., 2015), as well as CSF Aβ42 and p-tau (Liguori et al., 2017). Furthermore, MMSE, CSF Aβ42, and p-tau data were obtained from the participants' medical history, and we assembled six distinct categories according to their group (CU, MCI, AD) and SDB condition (SDB+ or SDB-; Table 1).

2.2. Subsampling

To ensure the reliability of our findings, given the imbalanced sample size across groups and to minimize the impact of covariates such as age, sex, APOE ε4, and BMI Farrer et al., 1997), we used a stratified subsampling approach. Out of 10,000 random stratified subsampling, 512 matched subsamples were selected (n = 10 per subsample as the AD+SDB subgroup had limited study participants) (Supplemental information).

2.3. Imaging acquisition and preprocessing

The average of Aβ, rFDG-PET, and GMV was calculated in 116 regions (100 cortical (Schaefer atlas) and 16 subcortical (Melbourne atlas)) (Jack et al., 2008; Schaefer et al., 2018; Tian et al., 2020). A detailed explanation of the image acquisition is available on "adni.loni.usc.edu." All images were preprocessed using the FMRIB software library (FSL) (Woolrich et al., 2009). Then PET and sMRI co-registered nonlinearly into the MNI152 space using the FNIRT pipeline (Andersson et al., 2007). Preprocessed PET images were scaled by normalization of voxel-wise Aβ and rFDG uptake values to the cerebellar

Table 1
Characteristics of the study participants. (*) cerebrospinal fluid. SDB: sleep-disordered breathing.

	SDB-	SDB+	Welch's *t*-test (p-value)
Alzheimer's Disease (AD)	**N: 114**	**N: 16**	
Age (mean [SD])	75.1 (8.1)	70.2 (6.5)	0.012*
Age range	[55.7, 90.4]	[60.8, 82.2]	
Sex, female (%)	48 (42 %)	6 (38 %)	
Body-mass index (mean [SD])	25.5 (4.31)	27.3 (4.67)	0.169
CSF* Aβ 42 (mean [SD])	823.38 (476.7)	610.25 (215.6)	0.005*
CSF* p-tau (mean [SD])	37.13 (15.8)	35.59 (14.23)	0.73
Education years (mean [SD])	15.77 (2.64)	15.75 (2.52)	0.974
Aβ-positive (%)	101 (88.6 %)	14 (87.5 %)	
≥ 1 APOEε4 allele presence (%)			
False	37 (33 %)	3 (19 %)	
True	76 (67 %)	13 (81 %)	
missing	1	0	
MMSE (mean [SD])	23.04 (2.11)	22.94 (1.98)	0.843
Mild Cognitive Impairment (MCI)	**N: 276**	**N: 58**	
Age (mean [SD])	72.23 (7.58)	71.24 (7.58)	0.37
Age range	[55.1, 91.5]	[55.1, 88.5]	
Sex, female (%)	130 (47 %)	18 (31 %)	
Body-mass index (mean [SD])	26.67 (5.36)	29.18 (6.22)	0.005*
CSF* Aβ42 (mean [SD])	1101.153 (565.39)	1241.29 (572.41)	0.114
CSF* p-tau (mean [SD])	28.23 (15.09)	24.1 (12.82)	0.04*
Education years (mean [SD])	16.3 (2.6)	16.22 (2.79)	0.855
Aβ-positive (%)	258 (93.5 %)	52 (89.7 %)	
≥ 1 APOEε4 allele (%)			
False	125 (46 %)	35 (64 %)	
True	148 (54 %)	20 (36 %)	
missing	3	3	
MMSE (mean [SD])	27.69 (2.48)	27.93 (1.57)	0.349
Cognitively Unimpaired (CU)	**N: 265**	**N: 28**	
Age (mean [SD])	74.36 (6.41)	72.87 (5.51)	0.19
Age range	[56.3, 93.8]	[65.2, 85.7]	
Sex, female (%)	157 (59 %)	10 (36 %)	
Body-mass index (mean [SD])	27.33 (5.22)	29.19 (5.08)	0.074
CSF* Aβ42 (mean [SD])	1438.58 (639.23)	1755.21 (661.32)	0.058
CSF* p-tau (mean [SD])	22.74 (10.04)	21.58 (9.73)	0.621
Education years (mean [SD])	16.52 (2.48)	16.46 (2.95)	0.928
Aβ-positive (%)	237 (89.4 %)	25 (89.3 %)	
≥ 1 APOEε4 allele (%)			
False	188 (72 %)	22 (88 %)	
True	75 (28 %)	3 (12 %)	
missing	2	3	
MMSE (mean [SD])	29.01 (1.23)	29.07 (1.02)	0.773

vermis Aβ and rFDG uptake, respectively, as applied previously (Tahmasian et al., 2015). For GMV, we used an FSL-VBM protocol (Douaud et al., 2007). More information for image preprocessing is provided in the Supplemental Information.

2.4. Statistical analyses

2.4.1. Analysis of covariance

To evaluate the interaction between the group and SDB condition on neuroimaging biomarkers of AD, a two-way ANCOVA was performed with the diagnostic group and SDB condition as the main factors. Although in the subsampling procedure, the impact of the covariates of no interest was minimized, they might still have some remaining effects. Therefore, we took a strict approach, considering age, gender, APOE ε4 presence, and BMI as covariates of no-interest for ANCOVA (Osorio et al., 2015). Then, the partial Eta-squared method was adopted to calculate the effect size (ES) of group-SDB interaction on Aβ, rFDG, and GMV values across 116 regions (Olejnik and Algina, 2003). Next, a two-way ANCOVA was performed with MMSE-score as the dependent variable, and partial Eta-squared for group-SDB interaction was estimated. Two complementary ANCOVAs were performed to estimate the partial Eta-squared of group-SDB interaction on CSF Aβ42 and CSF p-tau. Moreover, two-way ANCOVA was performed for Aβ, rFDG, and GMV across all subsamples, leading to an average value of 512 estimated ES (using bootstrapping with 10,000 iterations) for each biomarker in each region to select medium effect-size measurements. All statistical analyses were computed in R version 4.2.0. The 95 % confidence intervals and the mean values of calculated ES for all subsamples were estimated for each parcel and biomarker. Further, the designed null model was used to compare the main model, and significant measurements were selected (Bludau et al., 2018; Mordkoff, 2019).

2.4.2. Group comparisons

To explore the nature of the group-SDB interaction, we conducted group comparisons focusing on regions that already showed medium ES (greater than 0.04 and exceeding the null distribution maximum value). We applied a *t*-test on the value of neuroimaging biomarkers (not ES estimated from ANCOVA) within parcels to determine if there were significant differences in neuroimaging biomarkers between the SDB+ and SDB- among the study participants within each group. This analysis further complemented our previous analyses, providing additional insights into the nature of the interaction between the group and the SDB condition.

2.4.3. Linear regression

To reveal a potential association between neuroimaging and cognitive variables, MMSE's ES was considered the "response," and all medium ES of the interaction between group and SDB condition on neuroimaging biomarkers were considered the "explanatory variables." Explanatory variables with $p < 0.05$ were then significantly associated with the response variable. This linear regression approach aimed to estimate how much of the variance in the ES of MMSE was explained by the variance in the ES of neuroimaging biomarkers. Likewise, two linear regressions were applied with CSF Aβ42 and CSF p-tau as dependent (response) variables to investigate whether there is any link between the ES of neuroimaging biomarkers and the ES of CSF biomarkers.

3. Results

3.1. The association between group-SDB interaction and Aβ plaque burden

The group-SDB interaction had a medium ES of Aβ plaque burden in the left middle temporal gyrus, left angular gyrus, left inferior frontal gyrus, left cingulate gyrus, right frontal pole, bilateral superior frontal gyrus, right precuneus cortices, left occipital fusiform gyrus, and left lateral occipital cortex. Among subcortical regions, Aβ within both the posterior thalamus and the left nucleus accumbens was associated with the group-SDB interaction (Fig. 1A, SI-Fig. 1). A main effect of SDB condition also had a medium ES of Aβ within the left frontal pole (SI-Fig. 2). In the AD group, in the regions that showed a medium-ES of the group-SDB interaction, Aβ plaque burden was higher in the SDB+ than the SDB- participants. However, the Aβ burden was lower in the SDB+ group than the SDB- group in both CU and MCI groups (Fig. 2A).

3.2. The association between group-SDB interaction and glucose metabolism

The group-SDB interaction was linked with regional glucose metabolism in the left postcentral gyrus, bilateral superior parietal lobule, bilateral lateral occipital cortex, left frontal pole, left inferior temporal

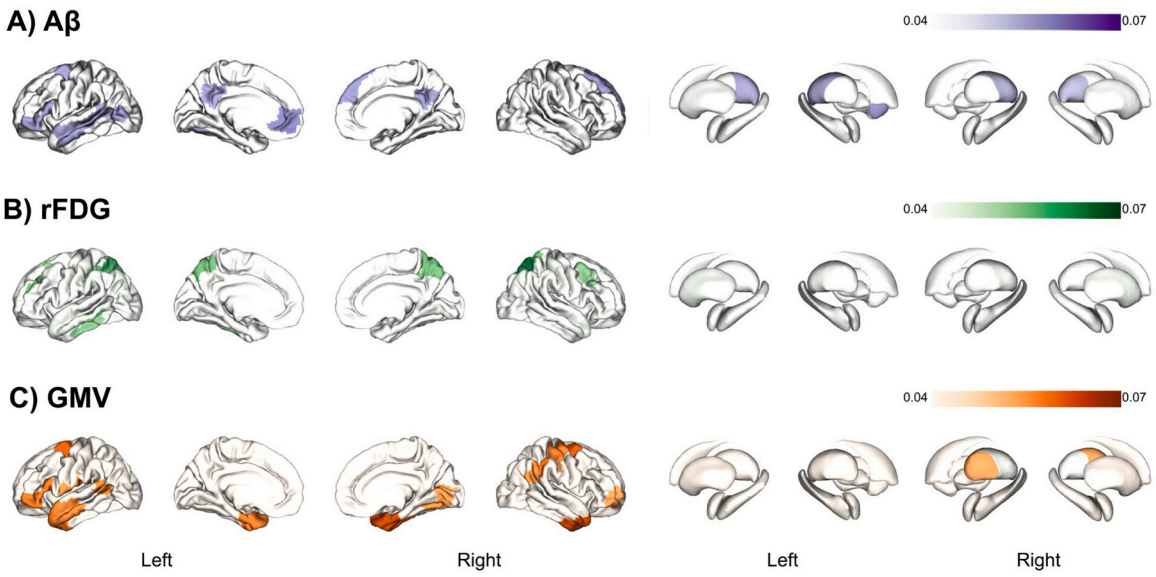

Fig. 1. Group-SDB interaction medium effect sizes of AD biomarkers. The brain regions that have medium effect sizes of the interaction between group (Alzheimer's disease, mild cognitive impairment and cognitively unimpaired) and SDB condition (with and without sleep-disordered breathing) for different biomarkers: A) amyloid-plaque burden (Aβ), B) regional fluorodeoxyglucose (rFDG), C) grey matter volume (GMV).

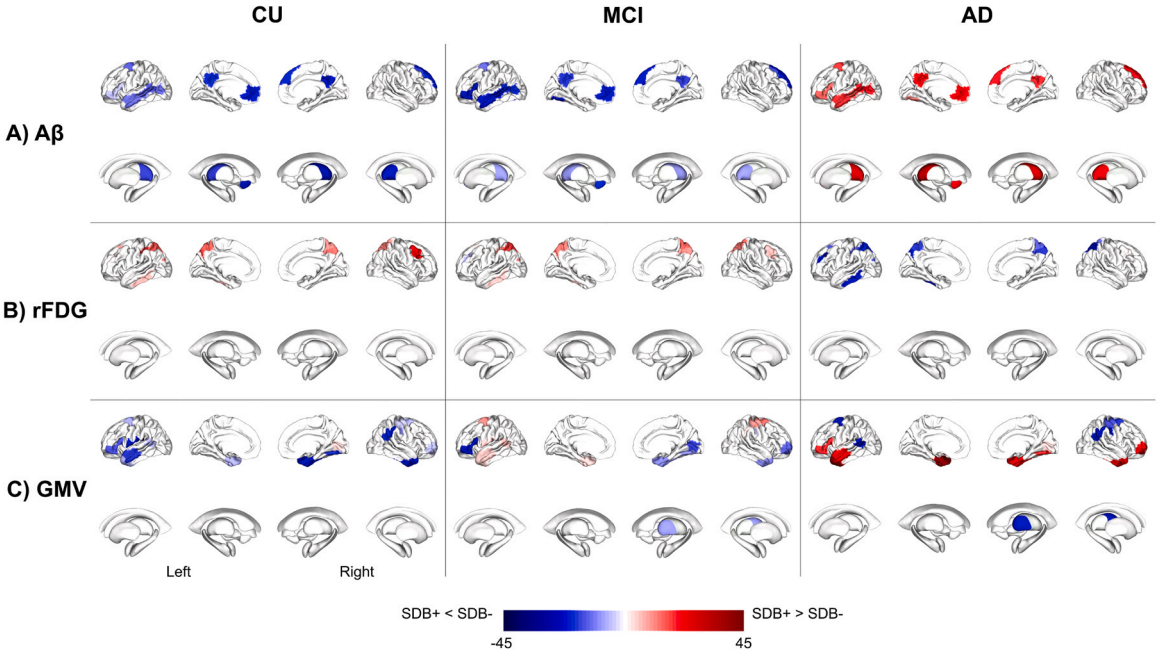

Fig. 2. AD biomarkers alteration in different groups. Differences in each biomarker value in different states of SDB condition (with and without SDB) through different disease groups (Alzheimer's disease, mild cognitive impairment, and cognitively unimpaired).

gyrus, right middle frontal gyrus, bilateral precuneus cortex, and left superior frontal gyrus (Fig. 1B, SI-Fig. 1). A main effect of SDB condition alone, had a medium ES of rFDG in the left precentral gyrus (SI-Fig. 2). In addition, in patients with AD, rFDG was lower in SDB+ compared to group-SDB but higher in the CU or MCI groups in all regions where rFDG was affected by the group-SDB interaction (Fig. 2B).

3.3. The association between group-SDB interaction and grey matter volume

A medium ES was detected for the group-SDB interaction on GMV measures in the left central opercular cortex, right precentral gyrus, bilateral superior frontal gyrus, right postcentral gyrus, bilateral temporal fusiform cortex, left middle temporal gyrus, bilateral inferior frontal gyrus, bilateral angular gyri, right intracalcarine cortex, right supramarginal gyrus, and right frontal pole, as well as in the right anterior thalamus (Fig. 1C, SI-Fig. 1). Furthermore, a main effect of SDB condition with medium ES was detected in several subcortical and cortical regions, including the bilateral nucleus accumbens, bilateral putamen, right central opercular cortex, bilateral frontal orbital cortex, right lateral occipital cortex, right paracingulate gyrus, right supramarginal gyrus (SI-Fig. 2). Further, the SDB condition did not interact with groups consistently. GMV was decreased in SDB+ relative to SDB- participants in CU and MCI groups in general, but in AD, we observed increased GMV in the right intracalcarine cortex, right occipital fusiform gyrus, and atrophy in left middle temporal gyrus, bilateral temporal

fusiform cortex, bilateral angular gyrus and the left superior frontal gyrus in SDB+ relative to SDB- participants (Fig. 2C).

3.4. The association between group-SDB interaction and cognitive scores

The variation in ES of Aβ burden was linked with the variance in MMSE ES ($p < 0.05$) in three regions: the left middle temporal gyrus, right precuneus cortex, and left occipital fusiform gyrus (SI-Table 1, Fig. 3A). Comparing SDB+ and SDB- conditions, we observed similar rFDG and GMV patterns in the CU and MCI groups in these three regions, but Aβ plaque burden was increased in the AD group, supported by lower CSF measures of Aβ (Fig. 3B, SI-Fig. 4). We found a steeper decline in CSF Aβ42 compared to SDB- individuals along the trajectory of AD. The pattern for CSF p-tau was also different between SDB+ and SDB- i.e., less p-tau increase in SDB+ (SI-Fig. 4).

4. Discussion

The present study assessed the link between the diagnostic groups and the presence of SDB on AD biomarkers, including Aβ, rFDG, GMV, as well as CSF Aβ42, and CSF p-tau, across the preclinical, prodromal, and clinical AD continuum. Individuals with SDB showed lower Aβ burden and higher rFDG in both CU and MCI groups, but higher Aβ burden and lower rFDG in the AD group. We found overall GMV atrophy in SDB+ individuals in CU. However, in the MCI and AD groups, both GMV enlargement and atrophy in different regions in the SDB+ individuals were observed. The group-SDB ES of Aβ in the middle temporal gyrus, precuneus, and fusiform gyrus was linked with the ES of MMSE scores. Patterns of biomarker alterations in these three areas were almost similar in SDB+ vs. SDB- for rFDG and GMV across groups. However, in the AD group, SDB+ participants exhibited a higher Aβ burden in those areas and a decline in CSF Aβ42 compared to SDB- individuals, indicating the particular association of SDB-AD interaction with Aβ burden. Collectively, these findings demonstrate an association between SDB and various AD biomarkers across disease stages, with lower amyloid burden, higher functional hyperactivity, and structural atrophy being greater in earlier stages of AD in SDB+ relative to SDB- individuals, while Aβ burden is particularly increased in SDB+ relative to SDB- individuals in the AD group.

4.1. Interaction between the group and SDB condition

The observed association between SDB and AD biomarkers is consistent with previous findings. For example, higher Aβ burden has been reported in both SDB and AD in the bilateral precuneus (Andre et al., 2020) and temporal cortex (Yun et al., 2017). The previous studies demonstrated reduced rFDG uptake observed in the precuneus and superior parietal lobule in SDB (Andre et al., 2020), which is consistent with the group-SDB interaction that we observed for rFDG in the AD group. Similarly, we found reduced rFDG uptake in regions such as the inferior, middle, and superior temporal gyrus, occipital gyrus, angular gyrus, precuneus, and thalamus, which are known to be AD-related regions (Li et al., 2019). Moreover, AD decoupled the association between regional glucose metabolism (rFDG), functional segregation, and global functional connectivity across various brain regions (Maleki Balajoo et al., 2022). Our findings regarding the interaction between group and SDB in GMV are consistent with reports of decreased GMV in the bilateral middle temporal gyrus in SDB (Shi et al., 2017) and the middle and superior temporal gyrus, parietal lobule, cingulate gyrus, thalamus, and putamen in AD (de Jong et al., 2008; Guo et al., 2010). However, the neural underpinnings of OSA need further exploration (Reimann et al., 2025).

Considering that SDB has a differential association with Aβ (low) and rFDG (high) in CU and MCI relative to AD (high Aβ in the brain, low CSF Aβ, and low rFDG), it is possible that SDB leads to neuronal hyperactivity, which may then contribute to cognitive impairment and decline. For example, it has been shown that poor sleep quality, shorter N2 sleep duration, and increased apnea-hypopnea index (often reported in

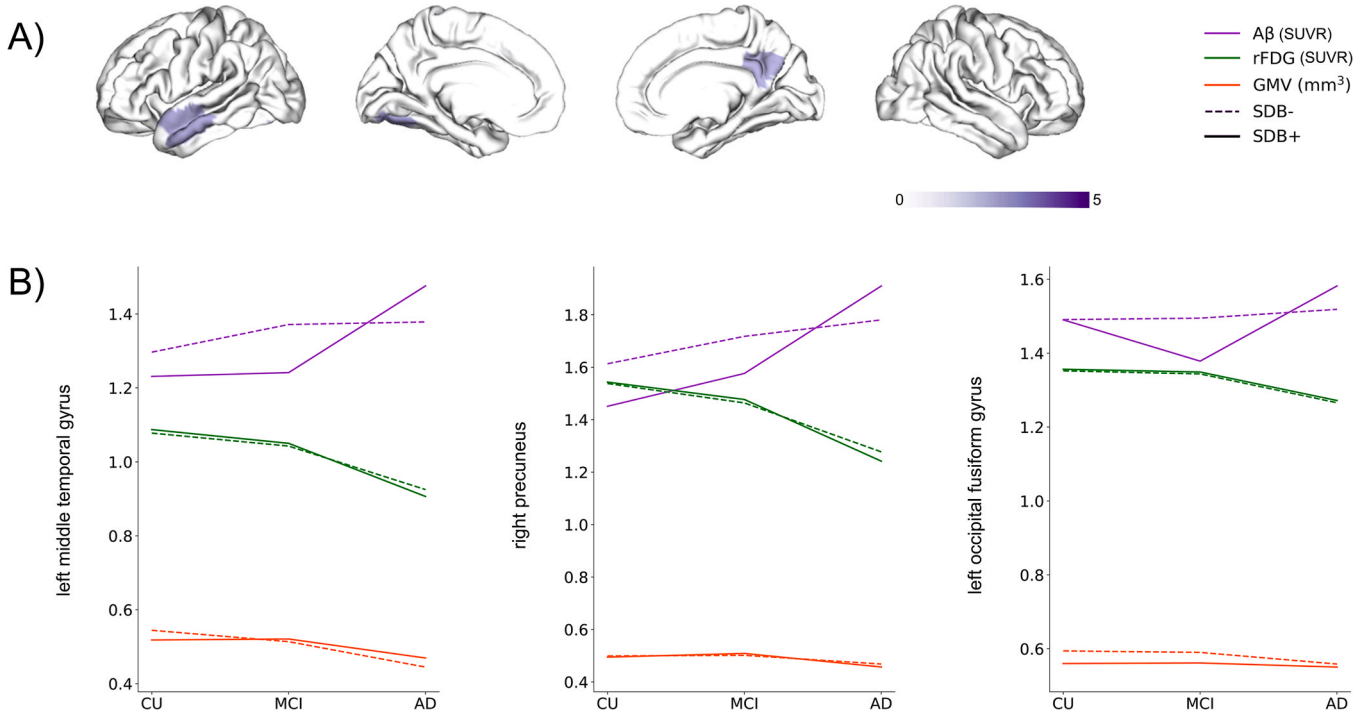

Fig. 3. Association between group-SDB interaction and cognitive score and pattern of biomarker's changes. A) Interaction between group (Alzheimer's disease, mild cognitive impairment, cognitively unimpaired) and sleep-disordered breathing condition (with/without SDB) has a medium effect size on highlighted regions. Furthermore, the highlighted regions are significantly associated with group-SDB interaction effect size on mini-mental state examination (MMSE). B) brain biomarker changes (Aβ, rFDG, and GMV) through the different groups in the highlighted regions from A.

polysomnography results of individuals with SDB) were associated with low Diffusion Tensor Imaging Analysis Along The Perivascular Space (DTI-ALPS) index of glymphatic system, lower GMV, and worse cognitive performance in community-dwelling older adults (Siow et al., 2022). Lower DTI-ALPS is linked with higher Aβ deposition, lower CSF Aβ42, and higher levels of Aβ in AD (Kamagata et al., 2022). Moreover, in AD, cortical accumulation of Aβ in the precuneus and PCC induces functional and structural dysconnectivity at early stages, which leads to hyperexcitability and metabolic changes and higher local tau deposition within the medial temporal lobe, resulting in widespread structural degeneration in later stages (Pasquini et al., 2019; Tahmasian et al., 2015). It has also been suggested that sleep deprivation is associated with both pathological CSF Aβ42 levels and increased Aβ plaque burden, and this relationship could be mainly associated with glymphatic system dysfunction (Liguori et al., 2021). Besides that, intracranial and intrathoracic pressure caused by apneic episodes may act as precipitating factors for neurodegeneration (Liguori et al., 2021).

4.2. The comparison between SDB+ and SDB- groups

We observed an association between the presence of SDB and lower levels of Aβ plaque burden, coupled with higher levels of rFDG uptake in both CU and MCI individuals compared to SDB- participants. The results from our study demonstrated that both CU and MCI individuals had higher levels of CSF Aβ42 in the SDB+ condition compared to the SDB- condition. Furthermore, previous studies suggested that lower CSF Aβ42 levels are linked to higher brain Aβ plaque burden (Ooms et al., 2014). Therefore, our observed low brain Aβ burden in SDB+ might be linked with high levels of CSF Aβ42 in CU and MCI groups. However, it is worth mentioning that even in individuals without SDB, 89.4 % of CU, 93.5 % of MCI, and 88.6 % of AD group were Aβ-positive, which may account for the similarity in Aβ levels between individuals with and without SDB in these two groups.

One possible explanation for the counterintuitive Aβ findings across CU/MCI groups is that SDB may affect rFDG and GMV and therefore enhance neuronal vulnerability to Aβ, potentially leading to clinical AD conversion at comparatively lower levels of amyloid accumulation. Consistent with this hypothesis, Aβ burden is lower in SDB+ individuals in preclinical and prodromal stages but higher at the end-stage diagnosis of AD. The fact that rFDG and GMV indicate hyperactivity and greater atrophy in preclinical and prodromal stages in SDB+ relative to SDB- individuals, despite lower levels of Aβ burden, further supports this assumption. These effects were further associated with individual differences in CSF levels of Aβ42 and global cognitive function, with SDB status influencing the associations of Aβ burden, rFDG, and GMV with CSF biomarkers and cognitive function.

Our findings in the AD group align with existing literature suggesting that SDB could modulate a complex relationship between Aβ plaque burden and rFDG metabolism (Andre et al., 2020; Elias et al., 2018). Moreover, the impact of SDB and OSA on brain atrophy has been reported previously, even in children and middle-aged adults (Tahmasian et al., 2016; Yu et al., 2023). We observed a significant reduction of GMV in SDB+ participants compared with SDB- individuals in various brain regions across all diagnostic groups. Nevertheless, higher GMV for SDB+ participants was observed in specific brain regions within all groups. Greater GMV could reflect a higher brain reserve (Stern et al., 2020) and be related to compensatory alterations in response to the progression of cognitive impairment to preserve cognitive performance (Andre et al., 2020).

The biomarker similarities between CU and MCI might be because our MCI group has similar MMSE scores compared to CU, and they were in the early disease stages. Moreover, the pattern of mean MMSE score of our selected CU (SDB+ 29.07, SDB- 29.01), MCI (SDB+ 27.93, SDB- 27.69), and AD patients (SDB+ 22.94, SDB- 23.04) could resemble the pattern of Aβ and rFDG changes in the mentioned three groups. Thus, SDB may have a differential association with neuroimaging biomarkers in CU and MCI individuals compared to AD patients, potentially representing a critical factor that triggers greater cognitive vulnerability to AD pathology.

4.3. The links between group-SDB interaction and cognitive scores

The observed link between the variability of ES of MMSE score and the variability of ES of Aβ plaque burden in our study is consistent with the literature. For instance, visual attention, processing speed, and subtle memory impairments have been reported for study participants with SDB (Elias et al., 2018). SDB is associated with medial temporal lobe atrophy in older adults who are cognitively asymptomatic but on the AD continuum, which potentially heightens the risk of developing memory impairment over time (Andre et al., 2023). Thus, we assume that with the presence of SDB, Aβ and tau contribute to synergistic neurodegenerative mechanisms, and the rate of their accumulation drastically increases (Bubu et al., 2020).

4.4. The neurobiological interaction between SDB and AD

Although this cross-sectional study cannot identify the causal association between SDB and AD, it is unlikely that AD directly affects the upper airways and induces SDB. It has been documented that SDB induces hypoxia, which leads to widespread maladaptive neuroinflammation by activating microglia, triggers hippocampal apoptosis, and impairs synaptic plasticity (Gnoni et al., 2022; Rosenzweig et al., 2015). Intermittent hypoxia in genetically susceptible (familial) AD mice enhances Aβ plaque burden, neuroinflammation, and cognitive impairment. However, inducing chronic *sleep deprivation* impaired working memory but did not lead to neuronal dysfunction or higher Aβ accumulation in mice models (Qian et al., 2022). This suggests that intermittent hypoxia is a key mechanism by which SDB could exacerbate AD pathology. On the other hand, higher sleep fragmentation due to SDB-induced hyperarousal prevents deep, slow-wave sleep. It leads to slower clearance of brain wastes, particularly Aβ, through the glymphatic system, which is highly active during slow-wave sleep. This condition is called glymphatic stasis (Nedergaard and Goldman, 2020).

SDB is associated with age-related cellular and molecular impairments, including stem cell exhaustion, telomere attrition, and epigenetic changes (Gaspar et al., 2017). These changes can also alter synaptic integrity and degenerate neurons even in younger adults, who might not have Aβ in their brains yet. Put differently, these effects enhance brain vulnerability earlier than the accumulation of Aβ. In later stages (i.e., AD), when participants have higher levels of Aβ accumulation, SDB and AD have synergic maladaptive effects. These changes, together with particular genetic, environmental, and lifestyle factors, exacerbate aging effects on the Aβ dysregulation, increase amyloid-beta accumulation in the brain, and raise aggregation and distribution of insoluble tau protein across the brain(Hussain et al., 2023; Rosenzweig et al., 2015). In this study, we observed that SDB is linked with higher Aβ plaque burden, reduced rFDG, and reduced/increased GMV in the AD group, but the association of SDB was prominent with both brain (in the right precuneus, left middle temporal gyrus, and left occipital fusiform gyrus) and CSF measures of Aβ plaque burden. These maladaptive processes collectively result in brain metabolic, functional, and structural alterations, which might increase brain vulnerability to AD pathophysiology and lead to cognitive decline.

Although AD is less likely to directly cause OSA, degeneration of the brain's respiratory control centers in the late stages of AD can contribute to a specific form of SDB, such as central sleep apnea. Additionally, in patients with advanced AD and severe cognitive decline, reduced physical activity and changes in body composition may lead to higher BMI, further increasing the risk of SDB. Therefore, the relationship between SDB and AD may become bidirectional, particularly in the later stages of AD (Ercolano et al., 2024; Owen et al., 2021).

4.5. Strengths, limitations, and future directions

To address imbalanced sample size across groups, several steps were conducted to ensure the stability and robustness of our results, e.g., dividing our sample into matched subsamples using stratified subsampling and running multiple iterations to calculate ES. Our subsampling approach and Bootstrapping (to estimate mean biomarker values and a null model for comparison) enhanced our result stability and generalizability. Null model estimation was also conducted to establish a reference for comparing and validating observed ES. Comparing the observed ES with the null ES distribution allowed for a better significance assessment against random variations. Nevertheless, our findings should be interpreted with caution because of several limitations. First, our assessment of SDB relied on self-reported questionnaires, which often underestimate the actual prevalence of SDB and OSA compared to objective gold-standard tools such as polysomnography (PSG). Previous epidemiological studies employing objective measures have consistently shown higher SDB rates, particularly in older adults and individuals with cognitive impairment. For instance, a recent study (Lam et al., 2025) highlighted that self-reported questionnaires, like the STOP-Bang questionnaire, have limited accuracy in identifying moderate to severe OSA in memory clinic populations. Also, cognitive impairment can further affect the accuracy of self-reports, possibly because patients may not reliably recall or report their symptoms accurately (Lam et al., 2025). Another limitation of this study is the cross-sectional design, which restricts identifying causality or temporal relationship between SDB and the clinical progression of AD. The number of individuals with all necessary data was limited, mainly in the AD group, to conduct a longitudinal analysis. Studies with larger and more balanced samples with a longitudinal design could provide more insight into dynamic changes in the interrelationship between SDB and AD over time. Further studies should investigate the effect of SDB on tau accumulation, as SDB may accelerate tau deposition through mechanisms like neuroinflammation and disrupted sleep patterns (Rosenzweig et al., 2015). Additionally, SDB has been shown to affect plasma-based biomarkers of Alzheimer's disease, including elevated levels of Aβ42 and tau, potentially due to impaired waste clearance and increased amyloid deposition (Bubu et al., 2020). Finally, sleep fragmentation and intermittent hypoxia due to SDB can impair the glymphatic system, reducing the clearance of amyloid-beta and contributing to neurodegeneration (Nedergaard and Goldman, 2020). The role of neuropsychological and behavioral data on the interplay between sleep disturbance and AD biomarkers should be considered in future studies, as neuropsychiatric symptoms are linked to tau pathology in AD (Macedo et al., 2024). Moreover, altered functional connectivity within and between the main brain networks was associated with increased depressive symptoms and decreased apathy for AD individuals with insomnia symptoms (Elberse et al., 2024).

5. Conclusion

The current study provided evidence that SDB has a medium effect size on AD-related neuroimaging biomarkers, including Aβ, rFDG, and GMV. Individuals with SDB symptoms showed a lower Aβ plaque burden in the CU and MCI groups but a higher Aβ plaque burden in the AD group. This suggests that SDB may increase vulnerability to the cognitive consequences of AD pathology, leading to accelerated conversion at earlier stages, even with lower levels of pathological burden. Hypermetabolism was observed in participants with SDB in the CU and MCI groups, and hypometabolism was observed in the AD group. Furthermore, SDB+ participants in the AD group exhibited altered GMV in several regions. Contrary to rFDG and GMV, the ES of Aβ in the middle temporal gyrus, precuneus, and fusiform gyrus demonstrated a robust association with cognitive scores. We observed that the presence of SDB is linked with higher Aβ plaque burden in the mentioned brain regions and lower CSF Aβ42 in the AD group. We hope that this multimodal study incentivizes clinicians to consider the importance of screening and treating individuals with SDB as potential therapeutic targets to reduce the burden of AD.

CRediT authorship contribution statement

Amir Ebneabbasi: Data curation, Conceptualization. **Hanwen Bi:** Methodology, Formal analysis. **Mohammad Akradi:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Tara Farzane-Daghigh:** Writing – original draft, Visualization, Data curation, Conceptualization. **Simon B. Eickhoff:** Writing – review & editing, Supervision, Conceptualization. **Masoud Tahmasian:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Conceptualization. **Alexander Drzezga:** Writing – review & editing. **Mander Bryce A:** Writing – review & editing, Visualization.

Consent to participate

All research participants provided written informed consent to the ADNI cohort.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The ethics board of the

University Hospital of the Heinrich-Heine University Düsseldorf approved the analysis of this publicly available dataset (No. 4039).

Funding

No funding was received for this particular work to reanalyze the existing dataset.

Statement

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12–2–0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.;Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.;Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Author SBE received Helmholtz Imaging Platform grant (NimRLS, ZT-I-PF-4–010). Author BM currently serves on a scientific advisory board for AstronauTx.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors of this study would like to acknowledge the ADNI for providing the data used in this study. ADNI is a collaborative effort of many institutions and investigators, and we are grateful for their dedication and contribution to the field of Alzheimer's disease research. We also thank the participants and their families for their willingness to participate in the ADNI project. The graphical abstract was created with BioRender.com.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2025.06.006.

Data availability

The ADNI is a multisite initiative to prevent and treat AD. The MRI and CSF biomarkers, as well as the clinical data used in the present study, are available under the ADNI data-sharing policy (https://adni.loni.usc.edu/). The analysis codes are available in (https://github.com/mohammadakradi/ADSDB/tree/main).

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