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Association of Sleep-Disordered Breathing With Alzheimer Disease Biomarkers in Community-Dwelling Older Adults
A Secondary Analysis of a Randomized Clinical Trial

Claire André, PhD; Stéphane Rehel, MSc; Elizabeth Kuhn, MSc; Brigitte Landeau, MSc; Inès Moulinet, MSc;
Edelweiss Touron, MSc; Valentin Ourry, MSc; Gwendoline Le Du, MSc; Florence Mézenge, BA;
Clémence Tomadesso, PhD; Robin de Flores, PhD; Alexandre Bejanin, PhD; Siya Sherif, PhD; Nicolas Delcroix, PhD;
Alain Manrique, MD, PhD; Ahmed Abbas, PharmD; Natalie L. Marchant, PhD; Antoine Lutz, PhD;
Olga M. Klimecki, PhD; Fabienne Collette, PhD; Eider M. Arenaza-Urquijo, PhD; Géraldine Poisnel, PhD;
Denis Vivien, PhD; Françoise Bertran, MD; Vincent de la Sayette, MD; Gaël Chételat, PhD; Géraldine Rauchs, PhD;
for the Medit-Ageing Research Group

⊞ Supplemental content

IMPORTANCE Increasing evidence suggests that sleep-disordered breathing (SDB) increases the risk of developing Alzheimer clinical syndrome. However, the brain mechanisms underlying the link between SDB and Alzheimer disease are still unclear.

OBJECTIVE To determine which brain changes are associated with the presence of SDB in older individuals who are cognitively unimpaired, including changes in amyloid deposition, gray matter volume, perfusion, and glucose metabolism.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study was conducted using data from the Age-Well randomized clinical trial of the Medit-Ageing European project, acquired between 2016 and 2018 at Cyceron Center in Caen, France. Community-dwelling older adults were assessed for eligibility and were enrolled in the Age-Well clinical trial if they did not meet medical or cognitive exclusion criteria and were willing to participate. Participants who completed a detailed neuropsychological assessment, polysomnography, a magnetic resonance imaging, and florbetapir and fluorodeoxyglucose positron emission tomography scans were included in the analyses.

MAIN OUTCOMES AND MEASURES Based on an apnea-hypopnea index cutoff of 15 events per hour, participants were classified as having SDB or not. Voxelwise between-group comparisons were performed for each neuroimaging modality, and secondary analyses aimed at identifying which SDB parameter (sleep fragmentation, hypoxia severity, or frequency of respiratory disturbances) best explained the observed brain changes and assessing whether SDB severity and/or SDB-associated brain changes are associated with cognitive and behavioral changes.

RESULTS Of 157 participants initially assessed, 137 were enrolled in the Age-Well clinical trial, and 127 were analyzed in this study. The mean (SD) age of the 127 participants was 69.1 (3.9) years, and 80 (63.0%) were women. Participants with SDB showed greater amyloid burden (t_{114} = 4.51; familywise error–corrected P = .04; Cohen d, 0.83), gray matter volume (t_{119} = 4.12; familywise error–corrected P = .04; Cohen d, 0.75), perfusion (t_{116} = 4.62; familywise error–corrected P = .001; Cohen d, 0.86), and metabolism (t_{79} = 4.63; familywise error–corrected P = .001; Cohen d, 1.04), overlapping mainly over the posterior cingulate cortex and precuneus. No association was found with cognition, self-reported cognitive and sleep difficulties, or excessive daytime sleepiness symptoms.

CONCLUSIONS AND RELEVANCE The SDB-associated brain changes in older adults who are cognitively unimpaired include greater amyloid deposition and neuronal activity in Alzheimer disease–sensitive brain regions, notably the posterior cingulate cortex and precuneus. These results support the need to screen and treat for SDB, especially in asymptomatic older populations, to reduce Alzheimer disease risk.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Medit-Ageing Research Group members appear at the end of the article.

Corresponding Author: Gaël Chételat, PhD, Institut National de la Santé et de la Recherche Médicale Unité Mixte de Recherche-S U1237, GIP Cyceron, Blvd Henri Becquerel, BP 5229, 14074 Caen, Cedex 5, France (chetelat@cyceron.fr).

Sleep-disordered breathing (SDB) is a respiratory disorder characterized by recurrent upper airway collapse during sleep, associated with intermittent hypoxia and sleep fragmentation.[1,2] It affects 30% to 80% of older adults who are cognitively unimpaired, depending on the SDB definition criteria.[3,4] Patients with a clinical diagnosis of Alzheimer disease (AD) are even more likely to suffer from SDB,[5] and untreated SDB is associated with cognitive decline and conversion to the Alzheimer clinical syndrome at a younger age.[6-8]

To clarify the mechanisms underlying the association between SDB and dementia risk, growing efforts have been deployed to better characterize the brain changes associated with SDB. Yet, previous studies have provided heterogeneous results, showing both SDB-associated decreases[9-11] and increases[12,13] in gray matter (GM) volume or cortical thickness in various brain areas including frontal, temporal, and parietal regions. Similarly, both decreased perfusion[14-16] and increased perfusion[15,17] have been reported in patients with SDB compared with control participants. Finally, SDB has been associated with increased amyloid and tau levels in the blood and cerebrospinal fluid, both cross sectionally and longitudinally.[18-21] However, cross-sectional positron emission tomography (PET) studies have reported inconsistent results, some showing greater amyloid burden in association with SDB,[22,23] while others do not report significant associations.[21,24] These discrepancies may be explained by the characteristics of patients with SDB (eg, recruited from sleep clinics vs from the community, differences in age and disease duration), the scoring criteria of respiratory events, sample sizes, and/or the lack of controls for possibly biasing covariates.

To our knowledge, no previous study has used a multimodal neuroimaging approach to highlight early brain changes associated with the presence of untreated SDB within a large sample of older participants who are cognitively unimpaired and are recruited from the community, with no or few sleep symptoms. Therefore, our main objective was to provide a comprehensive picture of structural, functional, and molecular brain changes associated with untreated SDB in aging, to provide substantial advances in the understanding of early brain mechanisms underlying the associations between SDB and AD. Secondary objectives aimed at identifying which aspect of SDB severity (ie, sleep fragmentation, hypoxia severity, or frequency of respiratory events) is most associated to brain changes. Lastly, we investigated the associations between SDB severity and/or SDB-associated brain changes and cognitive performance, self-reported cognitive and sleep difficulties, or symptoms of sleepiness.

Methods

Participants

We included 127 older adults who were cognitively unimpaired from the baseline visit of the Age-Well randomized clinical trial of the Medit-Ageing European Project[25] (flow diagram in **Figure 1**), sponsored by the French National Institute of Health and Medical Research (INSERM). Participants were recruited from the general population, older than 65 years, na-

Key Points

Question Which brain changes are associated with sleep-disordered breathing in aging?

Findings In this cross-sectional study of 127 community-dwelling older individuals who were cognitively unimpaired, the presence of sleep-disordered breathing was associated with greater amyloid burden, gray matter volume, metabolism, and perfusion in the posterior cingulate cortex and precuneus. There was no association with cognitive performance, self-reported cognitive or sleep difficulties, or excessive daytime sleepiness.

Meaning Sleep-disordered breathing–associated changes include amyloid deposition in brain regions typically involved in Alzheimer disease, which might explain why sleep-disordered breathing is associated with an increased risk for developing Alzheimer clinical syndrome at a younger age.

Figure 1. Flow Diagram of the Inclusion Process
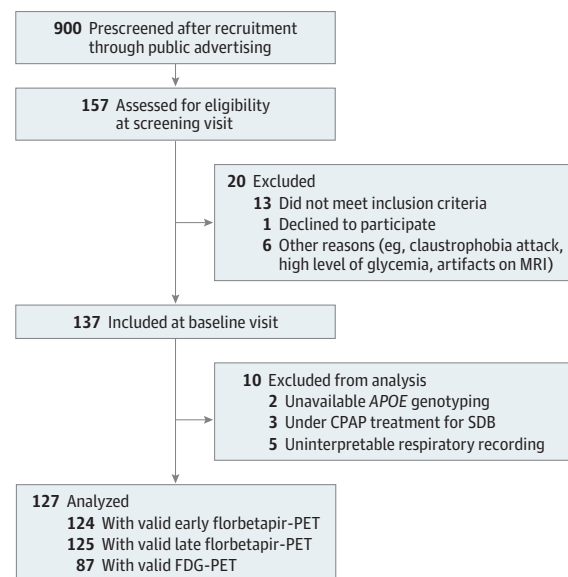
APOE indicates apolipoprotein E; CPAP, continuous positive airway pressure; FDG, 18F-fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; SDB, sleep-disordered breathing.

tive French speakers, retired for at least 1 year, educated for at least 7 years, and able to perform within the normal range on standardized cognitive tests. The main exclusion criteria were safety concerns associated with magnetic resonance image (MRI) or PET scanning, evidence of a major neurological or psychiatric disorder (including alcohol or drug abuse), history of cerebrovascular disease, presence of a chronic disease or acute unstable illness, and current or recent medication usage that may interfere with cognitive functioning.

Participants meeting inclusion criteria performed a detailed cognitive assessment, a polysomnography, structural MRI, fluorine 18–labeled (18F) florbetapir PET and 18F-fluorodeoxyglucose (FDG) PET scans, and apolipoprotein E ε4 (APOE4) genotyping within a maximum period of 3 months. All participants gave their written informed consent prior to the examinations, and the Age-Well randomized clinical trial was

approved by the ethics committee (Comité de Protection des Personnes Nord-Ouest III, Caen, France; trial registration number: EudraCT: 2016-002441-36; IDRCB: 2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819).

Cognitive and Behavioral Assessment

The detailed neuropsychological evaluation encompassed global cognitive functioning, processing speed, attention, working memory, executive functions, and episodic memory.[25] For each cognitive domain, a composite score was computed (eAppendix in the Supplement). In addition, self-reported cognitive difficulties were assessed using the Cognitive Difficulties Scale.[26] Moreover, self-reported sleep quality was assessed using the Pittsburgh Sleep Quality Index,[27] and excessive daytime sleepiness symptoms were measured using the Epworth Sleepiness Scale.[28]

Neuroimaging Examinations

All participants underwent high-resolution T1-weighted anatomical imaging to measure GM volume and a florbetapir-PET scan with a 10-minute early acquisition that began immediately after the intravenous injection and reflected brain perfusion and a 10-minute late acquisition (beginning 50 minutes after injection) that reflected amyloid burden. A subset of participants (n = 87) also underwent an FDG-PET scan to measure brain glucose metabolism. All participants were scanned at Cyceron Center (Caen, France) on the same MRI scanner (Philips Achieva 3.0T) and PET scanner (Discovery RX VCT 64 PET-CT; General Electric Healthcare). The detailed acquisition and preprocessing procedures[25] are available in the eAppendix in the Supplement. The PET analyses were performed on images corrected for partial volume effects (PVE) using the 3-compartmental voxelwise Müller-Gartner method.[29]

SDB Characterization

Participants underwent polysomnography using a portable home device (Siesta; Compumedics). Acquisition parameters are described in the eAppendix in the Supplement. Sixty-eight percent of the participants (86 of 127 individuals) underwent 2 polysomnography recordings, including a habituation night, which was not included in the analyses. The remaining 39 participants only had 1 polysomnography recording. Recordings were visually scored in 30-second epochs following the recommended standard criteria of the American Academy of Sleep Medicine.[1] Sleep apnea was defined by a 90% or greater drop of nasal pressure for at least 10 seconds, whereas sleep hypopnea was characterized by a 30% or greater drop of nasal pressure for a minimum of 10 seconds, associated with an arousal or a 3% or greater oxygen desaturation.

Based on the apnea-hypopnea index (AHI) value (ie, the sum of apnea and hypopnea events per hour of sleep), participants were classified into 2 groups with a cutoff value of 15, independent of clinical symptoms, in accordance with the recommendations of the third edition of the International Classification of Sleep Disorders.[30] Thus, we obtained a group without SDB (AHI <15 events per hour; n = 31) and a group with SDB (AHI ≥15 events per hour; n = 96).[6,20,31,32] The subsample of

87 participants who also had an FDG-PET scan was composed of 69 participants with SDB and 18 participants without SDB, who did not differ from the main sample regarding the proportion of participants with vs without SDB (χ^2_1 = 0.26; P = .61) or demographic, sleep, and cognitive variables (data not shown).

Lastly, to address secondary objectives, we computed 2 composite scores reflecting sleep fragmentation and hypoxia severity. This composite score approach, also used in a previous study,[12] was preferred to a single-item approach, to minimize the issue of multiple statistical testing. The sleep fragmentation composite score corresponded to the mean of the z scores of the respiratory arousal index, the number of shifts to non–rapid eye movement sleep stage 1 per hour, and the number of nocturnal awakenings per hour. The hypoxia composite score corresponded to the mean of the z scores of the oxygen desaturation index, the proportion of total sleep time with oxygen desaturation of 90% or less, and the minimal oxygen saturation.

Statistical Analyses

Between-Group Differences

Between-group differences for demographical, behavioral, sleep, and cognitive variables were assessed using t tests for continuous variables and χ^2 statistics for categorical variables, with statistical significance set to P < .05. Voxelwise group differences in amyloid burden, GM volume, perfusion, and glucose metabolism were explored using analyses of covariance in SPM12 (Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology), controlling for age, sex, education, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), sleep medication use, and *APOE4* status. Voxelwise analyses were performed using MRI and PVE-corrected PET data and considered significant at a voxel-level threshold of P < .005 and a cluster-level threshold of P < .05, corrected for familywise errors (FWE).

Stepwise Regression Analyses

As a second step, we aimed at further assessing which aspect of SDB severity (ie, the frequency of respiratory disturbances, associated sleep fragmentation, and/or hypoxia severity) was more specifically involved in the SDB-associated brain changes highlighted in the previous analysis. For this purpose, amyloid burden, GM volume, perfusion, and glucose metabolism signal values were extracted from the significant clusters obtained in the voxelwise group comparisons. Then, stepwise regression analyses were performed on the whole sample of participants, with 9 measures entered in the model as independent variables (ie, the AHI value, sleep fragmentation composite score, hypoxia composite score, age, sex, education, BMI, sleep medication use, and *APOE4* status), while dependent variables were neuroimaging signal values, each modality being tested separately.

Partial Correlation Analyses

Finally, partial correlations were performed on the whole sample of participants to assess potential associations between (1) the

Table 1. Participant Characteristics and Between-Group Differences

Characteristic	Mean (SD)		P value for between-group differences[a]
	Without SDB (n = 31)	With SDB (n = 96)	
Demographic			
Age, y	69.19 (3.53)	69.00 (3.98)	.81
Female, No. (%)	24 (77.4)	56 (58.3)	.06
Education, y	13.45 (2.94)	12.90 (3.12)	.38
Geriatric Depression Scale score	1.55 (1.89)	1.21 (1.70)	.35
State-Trait Inventory form B total score	36.13 (7.35)	34.05 (6.88)	.15
BMI	24.77 (5.07)	26.73 (3.92)	.03
Current sleep medication use, No. (%)[b]	2 (6.45)	10 (10.42)	.51
Florbetapir standard uptake value ratio[c]	0.91 (0.13)	0.99 (0.23)	.07
Amyloid positive, %	10	25	.08
Carrying APOE4, No. (%)	9 (29.03)	26 (27.08)	.83
Sleep			
Pittsburgh Sleep Quality Index score	4.39 (2.67)	5.17 (3.16)	.22
Epworth Sleepiness Scale score	4.77 (3.04)	5.22 (3.45)	.52
Total sleep time, min	358.63 (59.13)	362.81 (67.62)	.76
Sleep efficiency, %	76.39 (10.24)	77.36 (9.89)	.64
Sleep onset latency, min	18.73 (12.41)	21.12 (12.49)	.35
Apnea-hypopnea index events, No. per h	9.63 (3.91)	30.54 (13.26)	<.001
Fragmentation composite score	−0.68 (0.41)	0.22 (0.81)	<.001
Respiratory arousals index, No. per h	7.15 (3.34)	25.28 (11.30)	<.001
Shifts to non-rapid eye movement sleep stage 1, No. per h	5.81 (2.08)	8.39 (3.53)	.001
Awakenings, No. per h	3.29 (1.12)	4.11 (1.72)	.02
Hypoxia composite score[d]	−0.44 (0.39)	0.15 (0.85)	<.001
Oxygen desaturation ≥3% index, No. per h	5.50 (3.96)	16.50 (11.21)	<.001
Total sleep time with oxygen saturation ≤90%, %	0.50 (1.08)	2.88 (9.69)	.18
Minimal oxygen saturation, %	88.27 (3.82)	85.89 (5.05)	.02
Cognition scores			
Mini-Mental State Examination	28.81 (1.08)	29.06 (1.04)	.24
Mattis Dementia Rating Scale	140.61 (2.89)	141.17 (2.64)	.32
Processing speed composite	0.05 (0.85)	−0.02 (0.70)	.66
Attention composite	−0.04 (0.66)	0.04 (0.63)	.58
Executive functioning composite	0.12 (0.70)	−0.04 (0.67)	.26
Working memory composite	0.04 (1.03)	−0.03 (0.85)	.72
Episodic memory composite	0.16 (0.81)	−0.05 (0.69)	.17
Cognitive Difficulties Scale	33.84 (14.27)	34.18 (15.59)	.91

Abbreviations: APOE, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SDB, sleep-disordered breathing.

[a] Between-group differences were assessed using t tests for continuous variables and χ^2 statistics for categorical variables. Statistical significance was set to P < .05.

[b] Use of sleep medication on a regular basis (>1/week), excluding phytotherapy and homeopathy.

[c] Thirty control participants with valid florbetapir–positron emission tomography scan. The threshold for amyloid positivity was defined as more than 0.99 and corresponded to the 99.9th percentile of the neocortical standard uptake value ratio distribution among 45 healthy young individuals younger than 40 years.

[d] Thirty participants without SDB and 88 participants with SDB with valid oxygen saturation data.

3 measures of SDB severity and (2) SDB-associated brain changes with cognitive and behavioral variables. These analyses were controlled for age, sex, education, BMI, sleep medication use, and APOE4 status, and considered significant at a P < .05 threshold, after applying a Bonferroni correction for multiple comparisons. Thus, the threshold for significance was set to $P \leq$ (0.05/number of comparisons).
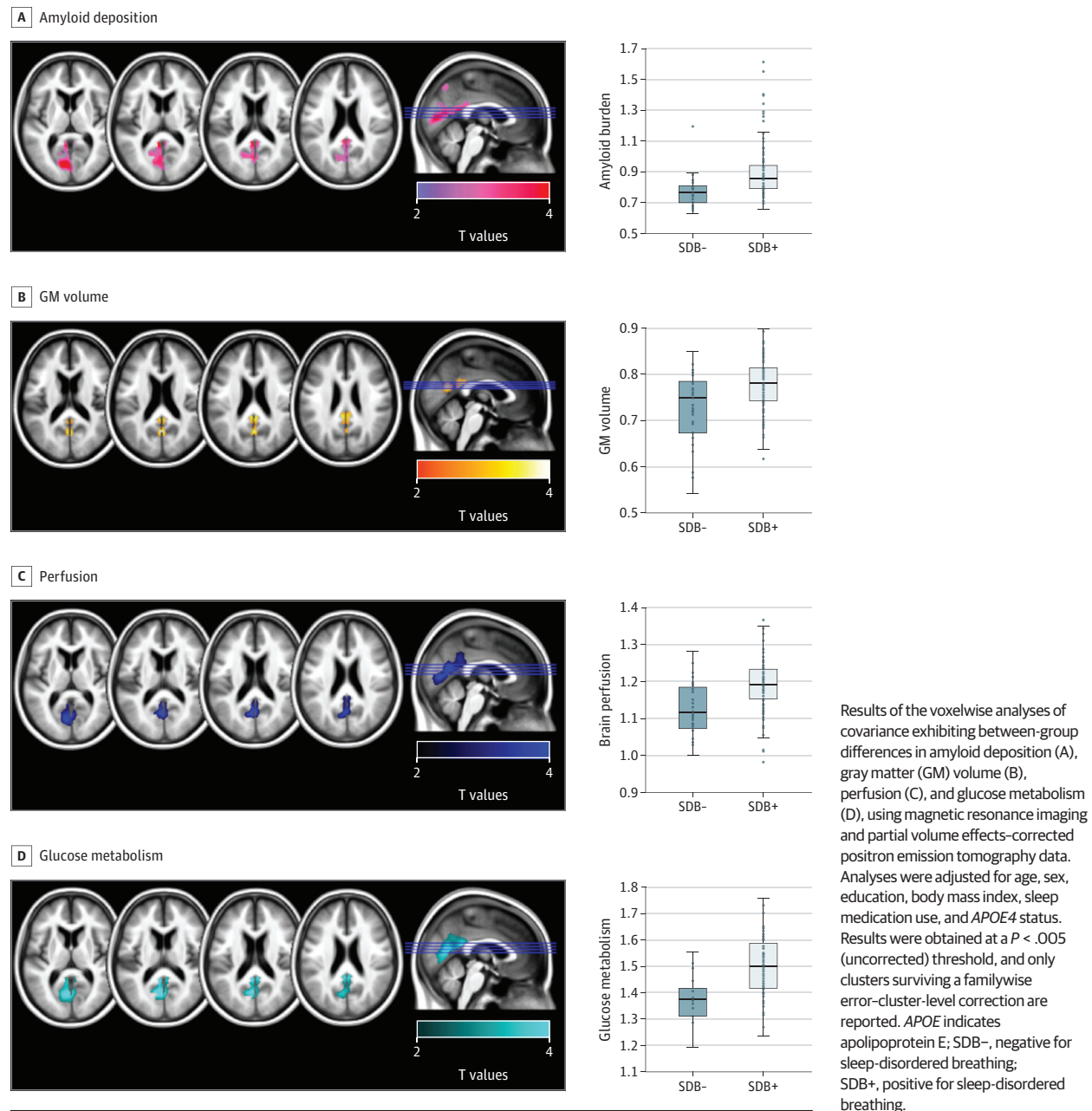
Results

Participants' Characteristics

Participants' characteristics, including demographical and behavioral variables, neuropsychological scores, and sleep parameters, as well as corresponding between-group differ-

ences, are provided in **Table 1**. Participants with vs without SDB did not differ in age, sex, education, depression and anxiety scores, current use of sleep medication, and the proportion of individuals carrying APOE4. As expected, participants with SDB had significantly higher BMI values (t_{125} = 2.25; mean difference, 1.96 [95% CI, 0.23-3.69]; P = .03), AHI values (t_{125} = 8.64; mean difference, 20.91 [95% CI, 16.12-25.70]; P < .001), levels of sleep fragmentation (t_{125} = 5.96; mean difference, 0.90 [95% CI, 0.60-1.20]; P < .001), and hypoxia (t_{116} = 3.68; mean difference, 0.59 [95% CI, 0.27-0.91]; P < .001). Interestingly, no between-group difference was observed for subjective sleep quality, daytime sleepiness symptoms, objectively measured total sleep time, sleep efficiency, and sleep onset latency on the polysomnography night. Moreover, cognitive performance

Figure 2. Neuroimaging Pattern of the Significant Differences Between Participants With vs Without Sleep-Disordered Breathing in Amyloid Deposition, Gray Matter Volume, Perfusion, and Glucose Metabolism

Results of the voxelwise analyses of covariance exhibiting between-group differences in amyloid deposition (A), gray matter (GM) volume (B), perfusion (C), and glucose metabolism (D), using magnetic resonance imaging and partial volume effects–corrected positron emission tomography data. Analyses were adjusted for age, sex, education, body mass index, sleep medication use, and *APOE4* status. Results were obtained at a *P* < .005 (uncorrected) threshold, and only clusters surviving a familywise error–cluster-level correction are reported. *APOE* indicates apolipoprotein E; SDB−, negative for sleep-disordered breathing; SDB+, positive for sleep-disordered breathing.

and self-reported cognitive difficulties were comparable between the 2 groups.

Brain Changes Associated With the Presence of SDB

Results of between-group comparisons for MRI and PVE-corrected PET data are presented in **Figure 2**. Cluster peak statistics and coordinates are detailed in eTable 1 in the Supplement.

Participants with SDB presented greater amyloid burden in the left precuneus, posterior cingulate, calcarine, and cuneus regions (Figure 2A; t_{117} = 4.51; FWE-corrected *P* = .04; Cohen *d*, 0.83), compared with participants without SDB. They

also showed greater GM volume in the precuneus and posterior cingulate cortex, bilaterally (Figure 2B; t_{119} = 4.12; FWE-corrected *P* = .04; Cohen *d*, 0.75), and greater perfusion in parietooccipital regions, including the precuneus, posterior cingulate, calcarine, and lingual areas (Figure 2C; t_{116} = 4.62; FWE-corrected *P* = .001; Cohen *d*, 0.86). Finally, participants with SDB presented greater glucose metabolism in the precuneus, posterior cingulate, and lingual areas, bilaterally (Figure 2D; t_{79} = 4.63; FWE-corrected *P* = .001; Cohen *d*, 1.04). Additionally, we compared brain changes between participants with moderate SDB (ie, 15≤ AHI values <30) vs severe SDB (AHI values ≥30) and found no significant differences at the

Figure 3. Overlap of Sleep-Disordered Breathing–Associated Brain Changes Across Neuroimaging Modalities

| ■ Brain perfusion | ■ Amyloid burden |
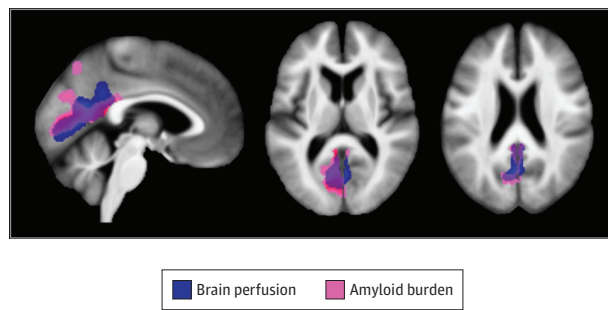
Representation of the overlap between sleep-disordered breathing–associated patterns of greater perfusion (blue) and amyloid deposition (pink), obtained at a $P < .005$ (uncorrected) threshold combined with a familywise error–cluster-level correction.

$P < .005$ level, combined with an FWE cluster-level correction (data not shown). This suggests that brain changes associated with SDB are detectable from the moderate stage and are not exacerbated in participants with severe SDB.

Interestingly, there was an overlap between brain changes observed in all 4 neuroimaging modalities over the posterior cingulate cortex, the precuneus, and the cuneus (**Figure 3**). Perfusion, metabolism, and GM volume signal values extracted from significant clusters showed strong intercorrelations (brain perfusion and glucose metabolism: Pearson r, 0.70 [95% CI, 0.58-0.80]; $P < .001$; brain perfusion and GM volume: Pearson r, 0.59 [95% CI, 0.46-0.69]; $P < .001$; metabolism and GM volume: Pearson r, 0.40 [95% CI, 0.21-0.56]; $P < .001$), and amyloid deposition was significantly correlated with GM volume (Pearson r, 0.21 [95% CI, 0.03-0.37]; $P = .02$) and perfusion (Pearson r, 0.34 [95% CI, 0.18-0.49]; $P < .001$; eTable 2 in the Supplement).

Lastly, for the sake of completeness, region of interest–based complementary analyses were performed. The signal was extracted from PVE-corrected and uncorrected FDG, early and late florbetapir PET images, in regions of interest from the Automated Anatomical Labeling Atlas[33] overlapping with the significant clusters obtained in the voxelwise analyses. The results are summarized in eTable 3 in the Supplement and are consistent overall with the findings from the voxelwise analyses. Only results obtained with PVE-uncorrected amyloid PET images were less significant, with between-group comparisons being significant for 3 regions of interest when using uncorrected PET images (right cuneus, F, 4.21; $P = .04$; partial η^2, 0.04; left precuneus, F, 4.03; $P = .05$, partial η^2, 0.03; left lingual, F, 4.26; $P = .04$; partial η^2, 0.04), compared with 9 regions of interest with corrected PET images (eTable 3 in the Supplement), which likely reflect the between-group differences in GM volume highlighted in the main analyses.

Links Between SDB-Associated Brain Changes and Measures of SDB Severity

Forward stepwise regressions were then performed to determine which aspect of SDB severity is the most closely associated with SDB-associated brain changes (**Table 2**). The factors

most strongly associated with amyloid burden were the hypoxia composite score, explaining 8% of the variance (unstandardized β, 0.06 [95% CI, 0.02-0.10]; $P = .002$), followed by *APOE4* status, explaining 4% of the variance (unstandardized β, 0.07 [95% CI, 0.001-0.14]; $P = .05$). No other variable entered the model. The AHI value was the only variable associated with GM volume, explaining 4% of the variance (unstandardized β, 0.01; $P = .04$). No variable was significantly associated with brain perfusion or metabolism.

To ensure that these findings were not biased by a possible circularity issue, we replicated stepwise regression analyses with neuroimaging values that were independent from the previous between-group comparison. For this purpose, amyloid deposition was more globally measured through the global neocortical standardized uptake value ratio, and GM volume was extracted from the composite regions of interest of posterior regions of the Automated Anatomical Labeling Atlas described above (eTable 4 in the Supplement). Briefly, results were similar for amyloid burden, with hypoxia severity being the variable most strongly associated with the global neocortical amyloid standardized uptake value ratio (unstandardized β, 0.06 [95% CI, 0.01-0.11]; $P = .01$), followed by *APOE4* status (unstandardized β, 0.09 [95% CI, 0.01-0.17]; $P = .04$). Moreover, the AHI value remained the SDB-associated variable most strongly associated with GM volume, although it was preceded by the BMI, sex, and age.

Links With Cognition, Self-reported Cognitive Difficulties, and Sleep Difficulties

Lastly, we aimed at exploring the cognitive and behavioral correlates of SDB severity and associated brain changes. No association survived the Bonferroni correction for multiple comparisons (eTable 5 in the Supplement). Neither measures of SDB severity nor measures of SDB-associated brain changes were associated with cognitive performance, self-reported cognitive and sleep difficulties, or symptoms of sleepiness.

Discussion

The main goal of the present study was to provide a comprehensive overview of brain changes associated with untreated SDB in community-dwelling older participants who had few self-reported sleep difficulties. Our results show that participants with SDB presented greater amyloid burden, GM volume, metabolism, and perfusion in parietooccipital regions, including the precuneus and posterior cingulate cortex. Interestingly, greater amyloid burden was robustly associated with the severity of hypoxia. Neither SDB severity nor SDB-associated brain changes were associated with cognitive performance, self-reported cognitive and sleep difficulties, and symptoms of sleepiness.

The association between SDB and greater amyloid deposition is in line with previous studies showing that SDB is associated with lower serum and cerebrospinal fluid amyloid levels.[18,20] Furthermore, these results characterize the regional pattern of amyloid deposition in individuals with SDB who are cognitively unimpaired, extending the findings of

Table 2. Results of Forward Stepwise Regressions Showing the Variables Most Strongly
Associated With SDB-Associated Brain Changes

Factor	Unstandardized coefficient (95% CI)	Standardized coefficient	R^2	P value
Amyloid burden				
Step 1				
Intercept	0.88 (0.85-0.91)	NA	NA	<.001
Hypoxia composite	0.06 (0.02-0.10)	0.28	0.08	.002
Step 2				
Intercept	0.86 (0.82-0.90)	NA	NA	<.001
Hypoxia composite	0.06 (0.02-0.10)	0.26	NA	.004
APOE4 status	0.07 (0.001-0.14)	0.18	0.11	.05
Full model	NA	NA	0.16	.02
Gray matter volume				
Step 1				
Intercept	0.77 (0.76-0.78)	NA	NA	<.001
Apnea-hypopnea index	0.01 (5.718×10^{-4}-0.02)	0.19	0.04	.04
Full model	NA	NA	0.11	.20

Abbreviations:
APOE4, apolipoprotein E; NA, not
applicable.

Yun and colleagues[23] to a larger sample of older individuals. The association between amyloid deposition and hypoxia severity is also consistent with animal studies, showing that hypoxia promotes the cleavage of the amyloid precursor protein by the β-secretase and γ-secretase, leading to increased β-amyloid levels.[34-36] Moreover, it may partly explain why this specific aspect of SDB, rather than the AHI value or sleep fragmentation, is significantly associated with cognitive decline and conversion to Alzheimer clinical syndrome in older adults.[6,37]

Interestingly, participants with SDB also presented greater GM volume, perfusion, and metabolism, in line with the findings of several other studies.[12,15,17,38,39] Nevertheless, other groups have also reported GM atrophy, hypoperfusion, and hypometabolism in participants with SDB.[9-11,14,16] Discrepancies across studies may be attributable, at least in part, to methodological differences, because most studies have been performed on smaller samples of young and middle-aged participants with severe SDB (AHI >30 events per hour). Alternatively, it is possible that studies including participants with less severe SDB (ie, from the moderate stage, corresponding to an AHI >15 events per hour) and few symptoms, as in the present study and in others,[12,15] may be more able to capture earlier brain changes associated with the presence of SDB.

Importantly, to the best of our knowledge, our results show in vivo for the first time that greater amyloid burden colocalizes with greater GM volume, perfusion, and metabolism in older participants with SDB who are cognitively unimpaired.[38,40-42] We believe that these overlapping patterns reinforce the likelihood of common underlying mechanisms. Indeed, it has been demonstrated that higher neuronal activity is associated with increased β-amyloid production.[43-46] In addition, several studies[47] have shown that neuroinflammatory processes play a central role in AD progression and are associated with higher levels of amyloid deposition. Thus, SDB-associated neuroinflammatory processes and associated neuronal hyperactivity are likely to promote amyloid deposition in the same area. Furthermore, greater GM volume, perfusion, and metabolism colocalizing

with amyloid deposition may precede the development of neuronal injury, such as hypometabolism and atrophy.[48,49] Alternatively, greater GM volume, perfusion, and metabolism could also reflect higher brain reserve,[50] helping to cope with amyloid pathology and maintain cognitive performance.

In our study, SDB-associated brain changes were not associated with cognitive performance, self-reported cognitive and sleep difficulties, or symptoms of excessive daytime sleepiness. We believe that this finding indicates that greater amyloid deposition, GM volume, perfusion, and metabolism may represent early and asymptomatic brain changes associated with SDB. Studies exploring the associations between SDB and cognitive performance using cross-sectional designs have provided mixed results,[7,51-53] but longitudinal studies showed that SDB is associated with conversion to Alzheimer clinical syndrome and cognitive decline over time.[6-8] Therefore, older adults with SDB may exhibit silent brain changes, including increased amyloid deposition, which may propagate with time and explain why they are more at risk of developing Alzheimer clinical syndrome. The main strengths of the present study are, first, the multimodal assessment of bain integrity, which allowed us to reveal the overlap of brain changes, and second, the detailed cognitive assessment, on a large sample of older individuals who are cognitively unimpaired.

Limitations
However, the cross-sectional design of the analyses does not allow for the assessment of the causal associations between SDB and brain changes. Longitudinal studies are needed to investigate whether these early SDB-associated brain changes will progress to neurodegeneration and cognitive deficits.

Conclusions

Taken together, community-dwelling older individuals with untreated SDB presented greater amyloid deposition, GM volume, perfusion, and metabolism mainly over the posterior

cingulate, cuneus, and precuneus areas, which are typically altered in AD. However, no association with cognitive performance, self-reported cognitive or sleep difficulties, or sleepiness symptoms was observed. Early neuroinflammatory and neuronal hyperactivity processes promoting amyloid deposition could represent the underlying mechanisms increasing the susceptibility to AD at an asymptomatic stage of SDB. Our findings highlight the need to treat sleep disorders in the older population, even in the absence of cognitive or behavioral manifestations.

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