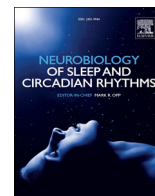




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Research paper

Apnea-hypopnea index, nocturnal arousals, oxygen desaturation and structural brain changes: A population-based study

Lisette A. Zuurbier^a, Meike W. Vernooij^{a,b}, Annemarie I. Luik^{a,c}, Desana Kocevskaja^{a,d,e}, Albert Hofman^a, Harry Whitmore^f, M. Arfan Ikram^{a,b,g}, Henning Tiemeier^{a,e,h,*}

^a Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands

^b Department of Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands

^c Sleep & Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

^d Generation R Study Group, Erasmus University Medical Center, Rotterdam, The Netherlands

^e Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands

^f Section of Endocrinology in the Department of Medicine, University of Chicago, Chicago, IL, USA

^g Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands

^h Department of Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Sleep apnea has been related to brain changes such as atrophy. However, which component of sleep apnea, the apnea-hypopnea index (AHI), nocturnal oxygen desaturation or arousals, can explain this association is unclear. In this large population-based study ($n=681$, mean age 62.1 years), we investigated the associations of AHI, nocturnal oxygen desaturation and arousals with global and regional gray matter and white matter volumes and with white matter lesion volumes. All participants underwent one night of polysomnography and MRI scanning of their brain. Gray matter, white matter and white matter lesion volumes adjusted for intracranial volume were studied as markers of brain atrophy. Nocturnal oxygen desaturation was related to whole brain white matter atrophy independent of covariates (multivariable adjusted $B = -8.3$, 95% CI = $-16.7; -0.02$). This association was most prominently reflected in the association between more oxygen desaturation and a smaller white matter parietal volume ($B = -3.95$ ml, 95% CI = $-6.02; -1.88$). Furthermore, oxygen desaturation was related to a smaller hippocampus ($B = -0.22$ ml, 95% CI = $-0.42; -0.01$). Although a higher AHI was related to smaller parietal gray ($B = -0.05$, 95% CI = $-0.09; -0.004$) and white matter ($B = -0.06$, 95% CI = $-0.12; -0.10$) volumes, these associations disappeared when adding oxygen desaturation to the model. We did not find a relation between arousals and gray and white matter brain atrophy and white matter lesion volumes. This suggests that oxygen desaturation mainly explains the association between sleep apnea and brain damage.

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1. Introduction

Sleep apnea is a common disorder; over 10% of the adult population (30–70 years old) have an apnea-hypopnea index (AHI)

≥ 15 , but the prevalence increases to about 20% in adults aged 60–70 years old (Duran et al., 2001). It is characterized by repetitive respiratory events (apneas and hypopneas) during sleep, leading to sleep fragmentation, nocturnal intermittent hypoxia (or oxygen desaturation), arousals and daytime sleepiness. Sleep apnea has been associated with several clinical outcomes, such as hypertension, cardiovascular disease, cognitive decline and mortality (Marshall et al., 2008; Nieto et al., 2000; Osorio et al., 2015; Parish and Shepard, 1990). Furthermore, in patients with stroke, sleep apnea (AHI ≥ 10) has a much higher prevalence than in the general population (Bassetti et al., 2006; Hui et al., 2002; Wessendorf et al., 2000). These findings suggest that sleep apnea may be related to structural brain changes in adults.

Previous studies of apnea severity and brain changes are

Abbreviations: AHI, apnea-hypopnea index; CI, confidence interval; EEG, electroencephalography; MRI, magnetic resonance imaging; PSG, polysomnography

* Corresponding author at: Department of Epidemiology, Erasmus University Medical Center, P.O. Box 2040, 3000CA Rotterdam, The Netherlands.

E-mail addresses: l.a.zuurbier@erasmusmc.nl (L.A. Zuurbier), m.vernooij@erasmusmc.nl (M.W. Vernooij), annemarie.luik@ndcn.ox.ac.uk (A.I. Luik), d.kocevska@erasmusmc.nl (D. Kocevskaja), a.hofman@erasmusmc.nl (A. Hofman), hwhitmor@medicine.bsd.uchicago.edu (H. Whitmore), m.a.ikram@erasmusmc.nl (M.A. Ikram), h.tiemeier@erasmusmc.nl (H. Tiemeier).

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inconsistent. Whereas several investigators found a relation of moderate to severe sleep apnea and the presence of white matter change and silent cerebrovascular lesions (Harbison et al., 2003; Kim et al., 2013; Nishibayashi et al., 2008), others reported no association (Davies et al., 2001; Ding et al., 2004; Kiernan et al., 2011). The majority of these studies were not conducted in the general population or had a small sample size. Gray matter volumes were smaller in sleep apnea patients compared to controls, mainly in the hippocampus and frontal areas (Canessa et al., 2011; Torelli et al., 2011). However, gray matter volume differences between sleep apnea patients and controls have not been found consistently (Joo et al., 2010). It is yet unclear how several aspects of sleep apnea (the AHI, nocturnal oxygen desaturation and arousals) affects cerebral gray matter, white matter and white matter lesion volumes.

In a large population-based sample of middle-aged and elderly persons, we studied the associations of AHI, nocturnal oxygen desaturation and arousals with global and regional white and gray matter brain atrophy and white matter lesion volumes. We hypothesized that the sleep apnea aspects are associated with gray and white matter brain atrophy and with larger white matter lesion volumes. We expected that the AHI would be the best predictive measure, because oxygen desaturation and arousal are included in its definition.

2. Materials and methods

2.1. Study population

This study was conducted within the Rotterdam Study, a population-based cohort of persons aged 45 years and older, living in one district in Rotterdam, the Netherlands. The study targets neurological, psychiatric, cardiovascular and other chronic disorders (Hofman et al., 2015). The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Population Studies Act: Rotterdam Study". All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

From January 2012 until February 2014, 1434 persons were invited for the polysomnographic (PSG) sleep study; 811 participants (56.6%) agreed. Persons who participated in the PSG study did not significantly differ in age or sex from persons who refused participation. Of the 811 persons, we excluded 15 participants because the PSG was of insufficient quality. Of the included persons, 724 persons (91.0%) also had a usable MRI scan of the brain, acquired as part of the Rotterdam Scan Study (Ikram et al., 2011). Participants who used a continuous positive airway pressure mask, or who had a clinical stroke or MRI-defined cortical infarct were excluded ($n=43$). Therefore, the recordings of 681 persons were used in analyses. The time between the PSG and MRI scan was on average 10 months (standard deviation (SD) 17).

2.2. Polysomnography

Ambulant PSG was recorded at the participant's home using the ambulatory Vitaport 4 (Temec Instruments, Kerkrade, the Netherlands). A trained research assistant placed all sensors. The PSG included electroencephalography (EEG: F3, F4, C3, C4, O1, O2, A1 and A2), bilateral electrooculography, electromyography, electrocardiography and respiration measurements (Luik et al., 2015). Respiration was measured with respiratory belts, an oronasal thermocouple, a nasal pressure transducer and oximetry. Participants were instructed to spend the night as normal as possible. There were no restrictions on medication, alcohol and coffee use,

or bedtimes. An experienced registered polysomnogram technologist (RPSGT) scored all recordings for apneas and hypopneas. Apneas were defined as a continuous reduction of airflow of at least 90% from baseline for at least 10 s. Hypopneas were defined as a continuous reduction of airflow of at least 30% from baseline for at least 10 s, together with oxygen desaturation of at least 3% from pre-event baseline, or an arousal (Iber et al., 2007). We calculated the AHI as the total number of apneas and hypopneas per hour of sleep using Prana software (PhiTools, Strasbourg, France). Nocturnal peripheral oxygen desaturation was defined as the number of times per minute the participant's oxygen saturation dropped by at least 3% during sleep, regardless of presence of an apnea or hypopnea (Iber et al., 2007). Arousals were measured in events per minute. Of all participants, 21 persons did not have information on oxygen desaturation and 51 persons did not have information on arousals.

2.3. Magnetic resonance imaging

Brain imaging was performed with a 1.5-Tesla scanner (General Electric Healthcare, Milwaukee, USA, software version 11x) with an eight-channel head coil and included T1-weighted, T2*-weighted, proton-density-weighted and fluid-attenuated inversion recovery sequences (Ikram et al., 2011). Gray matter, white matter and white matter lesion volumes were quantified by a validated automatic tissue classification technique based on a k-nearest neighbor classifying algorithm using T1-weighted, proton density weighted and FLAIR scans (de Boer et al., 2009; Vrooman et al., 2007). Next to global gray and white matter volumes, we also investigated gray and white matter volumes of the frontal, parietal, temporal and occipital lobes separately. Intracranial volume was calculated by summing gray matter, white matter, white matter lesions and cerebrospinal fluid volumes. Segmentation of the amygdala, hippocampus and thalamus was performed by FreeSurfer version 4.5 (<http://surfer.nmr.mgh.harvard.edu/>) (Erpelding et al., 2012). FreeSurfer was used with the default parameters.

2.4. Covariates

Age, sex, educational level, body mass index, smoking, alcohol use, depressive symptoms, diabetes mellitus, myocardial infarction and use of sleep medication were analyzed as possible confounders based on established risk factors for brain changes (Kim et al., 2013). Additionally, systolic blood pressure and total cholesterol were considered as possible intermediates and entered in additional analyses. Information on educational level (low, intermediate, high), smoking (no, previous, current) and depressive symptoms (assessed using the Center for Epidemiologic Studies Depression scale) (Radloff, 1977) was collected during a home interview. During a research center visit, height and weight were measured to calculate the body mass index (kg/m^2) and sitting blood pressure was measured twice using a random-zero sphygmomanometer. Serum total cholesterol was measured in mmol/L using an automated enzymatic procedure. History of myocardial infarction and diabetes were determined by medical records and self-report. Participants were asked whether they used sleep medication on the night of the PSG.

2.5. Statistical analysis

We studied whether AHI, nocturnal oxygen desaturation and arousals were associated with global gray and white matter brain atrophy and white matter lesion volumes using multivariable linear regression analyses. All analyses were adjusted for intracranial volume to correct for head size. Furthermore, white

matter lesion volumes were normalized by natural logarithmic transformation and standardized. All sleep apnea related determinants were studied continuously and categorically. For these categorical analyses, we defined low AHI (AHI < 15), moderate AHI (15 < 30) and high AHI (\geq 30); oxygen desaturation was transformed into tertiles; and arousals were analyzed dichotomously.

We specified two etiological models and a mediator model. The first model was adjusted for age, sex and intracranial volume. The second model, the multivariable adjusted model, was additionally adjusted for body mass index, education, smoking, alcohol use, diabetes, myocardial infarction and the interval between brain scan and polysomnography study. The mediator model was additionally adjusted for systolic blood pressure and total cholesterol.

In post-hoc analyses, we studied the association between the sleep apnea variable (AHI, nocturnal oxygen desaturation and arousals) that was significantly related to global brain atrophy, with regional brain atrophy (frontal, parietal, temporal and occipital lobes, and the subcortical volumes of amygdala, hippocampus and thalamus). We conducted two sensitivity analyses. First, AHI, oxygen desaturation and arousals were all included in one mutually adjusted model to study their independent effects. In this analysis, parameters were standardized to facilitate interpretation. Second, we tested whether sex-specific differences were present for the associations.

The proportion of missing values of the covariates never exceeded 3%. Missing values in quantitative covariates were replaced by the mean. For missing values in qualitative covariates a separate missing category was used. Analyses were performed using SPSS Statistics (version 21; SPSS, Chicago, IL, USA).

3. Results

Descriptive statistics of the participants ($n=681$) can be found in Table 1. Participants were on average 62.1 (range 51–95) years, 56% was female and the average body mass index was 27.2 (SD 4.4). The average AHI was 13.5 (SD 12.5); $n=447$ had a low AHI (< 15), $n=153$ had a moderate AHI (15 \leq 30) and $n=81$ had a high AHI (\geq 30). The average oxygen desaturation was 0.3 per minute

Table 1
Descriptive statistics ($n=681$).

	Mean (SD), n (%)
Age, years	62.1 (5.4)
Sex, female	380 (55.8%)
Education: Low	53 (7.8%)
Intermediate	409 (60.1%)
High	217 (31.9%)
Body mass index, kg/m ²	27.2 (4.4)
Smoking: Never	199 (29.2%)
Current	113 (16.6%)
Previous	368 (54.0%)
Alcohol use at night of PSG, units	0.5 (1.0)
Depressive symptoms, score	5.4 (6.7)
Systolic blood pressure, mmHg	132.9 (17.9)
Total cholesterol, mmol/l	5.6 (1.1)
Diabetes mellitus, yes	41 (6.0%)
Myocardial infarction, yes	11 (1.6%)
Sleep medication, yes	55 (8.1%)
AHI	13.5 (12.5)
Low AHI (< 15)	447 (65.6%)
Moderate AHI (15 \leq 30)	153 (22.5%)
High AHI (\geq 30)	81 (11.9%)
Nocturnal oxygen desaturation, n/min	0.3 (0.3)
Arousals, n /min	0.05 (0.15)

Abbreviations: AHI, apnea-hypopnea index; PSG, polysomnography; SD, standard deviation.

(range 0–1.9) and the average arousal index was 0.05 per minute (range 0–2.6). The AHI correlated strongly with the number of oxygen desaturations ($r=0.79$, $p < 0.001$), but did not correlate with the number of arousals ($r=-0.001$, $p=0.98$). The number of oxygen desaturations and arousals correlated weakly ($r=-0.17$, $p < 0.001$).

We found no associations of AHI with global gray matter, global white matter and white matter lesion volumes, whether modeled continuously or categorically (Table 2). No sex-specific differences were present in the associations of AHI and brain volumes.

More oxygen desaturations (events/minute) during sleep was related to a smaller white matter volume ($B=-10.4$ ml, 95% CI = -18.0 ; -2.8 , Table 3). In the multivariable adjusted model, the effect size was attenuated ($B=-8.3$ ml, 95% CI = -16.7 ; -0.02). Further adjustment for the possible mediators systolic blood pressure and total cholesterol did not change the effect ($B=-8.4$, 95% CI = -16.7 ; -0.03). Categorical analyses confirmed a dose-dependent effect. No associations were found between oxygen desaturation and global gray matter or white matter lesion volumes.

To test the association between oxygen desaturations and brain atrophy in more detail, we also studied the association of oxygen desaturation with regional brain structures (Table 4). More oxygen desaturations were significantly related to smaller parietal gray matter ($B=-2.16$, 95% CI = -3.93 ; -0.39), smaller parietal white matter ($B=-3.95$, 95% CI = -6.02 ; -1.88), smaller occipital white matter ($B=-1.49$, 95% CI = -2.81 ; -0.18) and smaller hippocampal volume ($B=-0.22$, 95% CI = -0.42 ; -0.01) in the multivariable adjusted model. The consistent associations of oxygen desaturation with the parietal cortex and the hippocampus prompted us to conduct post-hoc analyses testing the association of AHI and arousals with the respective structures. The AHI was related to smaller parietal gray matter ($B=-0.05$, 95% CI = -0.09 ; -0.004) and smaller parietal white matter volumes ($B=-0.06$, 95% CI = -0.12 ; -0.10) in the multivariable adjusted model. The AHI was significantly related to hippocampal volume only in the age and sex adjusted model ($B=-0.01$, 95% CI = -0.01 ; -0.003), but the association was attenuated in the multivariable adjusted model ($B=-0.004$, 95% CI = -0.01 ; 0.001). Arousals were not related to parietal or hippocampal volumes.

We found no associations between the numbers of arousals with gray and white matter brain atrophy or white matter lesion volumes, whether modeled continuously or dichotomously (Supplemental Table 1).

In a mutually adjusted analyses, oxygen desaturation remained associated with white matter ($B=-5.5$ ml per SD, 95% CI = -9.9 ; -1.0) whereas the AHI and arousals were not ($B=3.4$ ml per SD, 95% CI = -1.0 ; 7.8 ; $B=-1.0$ ml per SD, 95% CI = -3.7 ; 1.6 respectively). Parameters were standardized to facilitate interpretation). Consistently, oxygen desaturation also remained associated with smaller parietal white matter (oxygen desaturation: $B=-1.8$ ml per SD, 95% CI = -2.9 ; -0.7 , AHI: $B=0.6$ ml per SD, 95% CI = -0.6 ; 1.7 , arousals: $B=-0.1$ ml per SD, 95% CI = -0.8 ; 0.5) and smaller hippocampal volumes (oxygen desaturation: $B=-0.1$ ml per SD, 95% CI = -0.2 ; -0.004 , AHI: $B=0.1$ ml per SD, 95% CI = -0.07 ; 0.2 , arousals: $B=-0.002$ ml per SD, 95% CI = -0.01 ; 0.2) in the mutually adjusted models. In the mutually adjusted analyses with parietal gray matter the associations were attenuated (results not shown).

4. Discussion

In this large population-based study, we assessed whether aspects of sleep apnea were related to brain changes. Nocturnal oxygen desaturation was related to whole brain white matter

Table 2
Associations of AHI and brain structural measurements (n=681).

	Gray matter (ml) B (95% CI), p	White matter (ml) B (95% CI), p	White matter lesions (SD) ^a B (95% CI), p
AHI continuous			
Age, sex adjusted	–0.06 (–0.24; 0.11), 0.48	–0.13 (–0.33; 0.07), 0.19	0.002 (–0.003; 0.01), 0.49
Multivariable adjusted ^b	–0.06 (–0.25; 0.12), 0.49	–0.06 (–0.28; 0.15), 0.55	0.001 (–0.004; 0.01), 0.72
Low AHI (< 15), n=447	0 (reference)	0 (reference)	0 (reference)
Moderate AHI (15 ≤ 30), n=153			
Age, sex adjusted	3.4 (–1.7; 8.6), 0.19	–2.8 (–8.7; 3.2), 0.36	–0.03 (–0.17; 0.11), 0.69
Multivariable adjusted	3.9 (–1.4; 9.2), 0.16	–1.9 (–7.9; 4.2), 0.55	–0.05 (–0.19; 0.10), 0.53
High AHI (≥ 30), n=81			
Age, sex adjusted	–3.5 (–10.1; 3.2), 0.31	–5.6 (–13.3; 2.0), 0.15	0.04 (–0.13; 0.22), 0.62
Multivariable adjusted ^b	–3.4 (–10.3; 3.5), 0.33	–4.0 (–11.9; 3.9), 0.32	0.03 (–0.16; 0.21), 0.78

Abbreviations: AHI, apnea-hypopnea index; CI, confidence interval; SD, standard deviation. Values represent difference in brain tissue volume per unit increase in AHI. Linear regression analyses adjusted for intracranial volume.

^a Normalized and standardized.

^b Additionally adjusted for body mass index, education, smoking, alcohol use, diabetes, myocardial infarction and interval between brain scan and polysomnography study.

Table 3
Associations of nocturnal oxygen desaturation with brain structural measurements (n=660).

	Gray matter (ml) B (95% CI), p	White matter (ml) B (95% CI), p	White matter lesions (SD) ^a B (95% CI), p
Oxygen desaturation (n/min)			
Age, sex adjusted	–4.3 (–11.0; 2.3), 0.20	–10.4 (–18.0; –2.8), 0.01	0.04 (–0.14; 0.21), 0.67
Multivariable adjusted ^b	–4.6 (–11.7; 2.7), 0.22	–8.3 (–16.7; –0.02), 0.049	–0.004 (–0.20; 0.19), 0.97
Mediator model ^c	–4.6 (–11.8; 2.7), 0.22	–8.4 (–16.7; –0.03), 0.049	–0.004 (–0.20; 0.19), 0.97
Low oxygen desaturation, n=220	0 (reference)	0 (reference)	0 (reference)
Moderate oxygen desaturation, n=221			
Age, sex adjusted	–1.4 (–6.6; 3.8), 0.60	–1.5 (–7.5; 4.6), 0.63	–0.09 (–0.23; 0.05), 0.19
Multivariable adjusted	–1.1 (–6.5; 4.2), 0.67	–0.7 (–6.8; 5.4), 0.83	–0.11 (–0.25; 0.04), 0.14
High oxygen desaturation, n=219			
Age, sex adjusted	–2.8 (–8.1; 2.4), 0.29	–6.1 (–12.2; –0.1), 0.047	–0.00 (–0.14; 0.14), 0.99
Multivariable adjusted	–2.6 (–8.2; 3.1), 0.37	–4.2 (–10.7; 2.3), 0.20	–0.03 (–0.18; 0.12), 0.70

Abbreviations: AHI, apnea-hypopnea index; CI, confidence interval; SD, standard deviation. Values represent difference in brain tissue volume per unit increase in oxygen desaturation. Linear regression analyses adjusted for intracranial volume.

^a Normalized and standardized.

^b Additionally adjusted for body mass index, education, smoking, alcohol use, diabetes, myocardial infarction and interval between brain scan and polysomnography study.

^c Additionally adjusted for systolic blood pressure and total cholesterol.

atrophy independent of covariates. This association was most prominently reflected in the association between more oxygen desaturation and a smaller white matter parietal volume. Furthermore, we found an association between more oxygen desaturations and a smaller hippocampus. Although a higher AHI, indicating more breathing pauses, was related to smaller parietal gray and white matter volumes, these associations disappeared when adding oxygen desaturation to the model. We did not find a relation between arousals and gray and white matter brain atrophy and white matter lesion volumes. This suggests that oxygen desaturation mainly explains the association between sleep apnea and brain damage.

Nocturnal intermittent oxygen desaturation is related to an increase in sympathetic vasoconstriction, which can increase blood pressure and change the structure and function of blood vessels, including blood vessels in the brain (Lanfranchi and Somers, 2001). We found a relation between nocturnal oxygen desaturation and white matter atrophy, which was not accounted for by systolic blood pressure or total cholesterol. Furthermore, the association between oxygen desaturation and white matter atrophy was independent of myocardial infarction, another possible cause of oxygen desaturation. This suggests that oxygen desaturation is directly causing white matter atrophy or a different

factor, such as anemia or arteriosclerosis, might underlie this association. Anemia and arteriosclerosis have both been associated with white matter loss and stroke (Abramson et al., 2003; Tian et al., 2004). In contrast, white matter atrophy might also cause oxygen desaturation. Patients with stroke have a higher prevalence of sleep disordered breathing than persons with the same age without stroke (Hui et al., 2002). It has been found that after the acute phase of stroke the AHI decreases in some patients (Bassetti et al., 2006; Harbison et al., 2002). However, it also has been reported that only central respiratory events (not obstructive events) decrease after this acute phase (Parra et al., 2000).

The association between oxygen desaturation and global white matter atrophy was primarily explained by the association with parietal white matter. Acute tissue injury in the parietal cortex of obstructive sleep apnea patients has been found previously (Tummala et al., 2016) and may be related to watershed areas in these regions. Watershed areas are more vulnerable to oxygen decreases, because they lie at the border of the territories of major cerebral arteries and are relatively undersupplied by blood (Wodarz, 1980).

Hypoxia and hypotension have smaller effects on gray matter than on white matter volume (Meng et al., 2005; Suter et al., 2002). This might explain why we found no association of oxygen

Table 4
Associations of oxygen desaturation during sleep with regional brain structural measurements ($n=660$).

	Frontal gray matter ml	Parietal gray matter ml	Occipital gray matter ml	Temporal gray matter ml
Peripheral oxygen desaturation (n/min)	B (95% CI), p	B (95% CI), p	B (95% CI), p	B (95% CI), p
Age, sex adjusted	−0.89 (−3.46; 1.67), 0.50	−2.35 (−3.96; 0.74), 0.004	−0.60 (−1.83; 0.64), 0.34	−1.54 (−3.17; 0.09), 0.06
Multivariable adjusted ^a	−0.94 (−3.75; 1.88), 0.51	−2.16 (−3.93; −0.39), 0.02	−1.28 (−2.63; 0.07), 0.06	−1.08 (−2.86; 0.70), 0.23
	Frontal white matter ml	Parietal white matter ml	Occipital white matter ml	Temporal white matter ml
Peripheral oxygen desaturation (n/min)	B (95% CI), p	B (95% CI), p	B (95% CI), p	B (95% CI), p
Age, sex adjusted	−1.58 (−4.47; 1.31), 0.28	−4.69 (−6.60; −2.78), < 0.001	−0.98 (−2.17; 0.22), 0.11	−1.23 (−2.72; 0.25), 0.10
Multivariable adjusted ^a	−0.68 (−3.83; 2.48), 0.67	−3.95 (−6.02; −1.88), < 0.001	−1.49 (−2.81; −0.18), 0.03	−0.85 (−2.48; 0.78), 0.31
	Amygdala ml	Hippocampus ml	Thalamus ml	
Peripheral oxygen desaturation (n/min), $n=652$	B (95% CI), p	B (95% CI), p	B (95% CI), p	
Age, sex adjusted	−0.07 (−0.13; 0.001), 0.05	−0.37 (−0.56; −0.18), < 0.001	−0.11 (−0.33; 0.12), 0.35	
Multivariable adjusted ^a	−0.06 (−0.13; 0.02), 0.13	−0.22 (−0.42; −0.01), 0.04	−0.05 (−0.30; 0.19), 0.68	

Abbreviations: CI, confidence interval.

Values represent difference in brain tissue volume (ml) per unit increase in AHI. Linear regression analyses adjusted for intracranial volume.

^a Additionally adjusted for body mass index, education, smoking, alcohol use, diabetes, myocardial infarction and interval between brain scan and polysomnography study.

desaturation and global gray matter atrophy. We observed an association between oxygen desaturation and gray matter atrophy in the parietal lobe. In addition, oxygen desaturation was related to a smaller hippocampal volume. This is in line with studies of [Canessa et al. \(2011\)](#) and [Torelli et al. \(2011\)](#) ([Canessa et al., 2011](#); [Torelli et al., 2011](#)). Rat studies found that intermittent oxygen desaturation (or hypoxia) causes increased apoptosis in the rat hippocampus ([Gozal et al., 2001](#)). Our study confirms the sensitivity of the hippocampus to hypoxic damage. Unexpectedly as white matter atrophy and white matter lesions often co-occur, oxygen desaturation was not associated with more white matter lesions. [Vernooij et al. \(2008\)](#) found that white matter atrophy and white matter lesions are both related to a loss of microstructural integrity of white matter, but in distinct brain regions ([Vernooij et al., 2008](#)). This indicates that these processes are independent, and have a different pathophysiology. The oxygen desaturation measured in this population-based sample might not be severe enough to cause white matter lesions, but can cause subtle white matter atrophy.

Previous studies of the association of apnea severity and white matter change are inconsistent. Several studies found that moderate to severe sleep apnea is associated with the presence of white matter lesions, impaired white matter integrity, silent cerebrovascular lesions and stroke ([Bassetti et al., 2006](#); [Chen et al., 2015](#); [Harbison et al., 2003](#); [Kim et al., 2013](#); [Kumar et al., 2014](#); [Nishibayashi et al., 2008](#)). Also, smaller gray matter volumes have been found in sleep apnea patients, especially in hippocampal and frontal areas ([Canessa et al., 2011](#); [Torelli et al., 2011](#)). However, other studies observed no association of sleep apnea severity with gray matter, white matter or white matter lesion volumes ([Davies et al., 2001](#); [Ding et al., 2004](#); [Joo et al., 2010](#); [Kiernan et al., 2011](#)). We found small associations between a higher AHI and smaller parietal gray and white matter volumes. However, these associations seemed to be mainly driven by oxygen desaturation. In general, previous studies had small sample sizes and were conducted in case-control designs, whereas we assessed sleep apnea components in a large study from the general population. Our results suggest a less prominent association of sleep apnea with brain damage in the general population than in clinical samples.

Many persons with mild or moderate sleep apnea in the general population do not seek treatment. This suggests that some community-dwelling persons suffer less from the consequences of sleep apnea than those seeking treatment with the same degree of apnea. It is also possible that sleep apnea patients with white matter atrophy are more impacted in their daily functioning and more likely to be referred than those without lesions. Therefore the results in clinical samples might be stronger. Another reason for the discrepancies in results is that many studies of sleep apnea assess sleep apnea severity only by the AHI index. The AHI is a crude measure of measuring sleep apnea. First, the AHI ignores the temporal distribution of the apneas and hypopneas, the sleep stage in which these events occur, and it does not take the duration of these events into account. The cumulative effect of apneas and hypopneas might depend on a patient's total sleep time; the longer a person sleeps, the more respiratory events occur with the same AHI index. Furthermore, the AHI does not distinguish between apneas and hypopneas and does not entail snoring or the increased work of breathing. This can result in cardiovascular effects. For example, abrupt increases in blood pressure and heart rate occur immediately after the end of the respiratory event ([Punjabi, 2015](#); [Weiss et al., 1996](#)). Also, the definitions for hypopneas used to calculate the AHI have varied in the field historically, which makes it difficult to compare different studies.

This study has several strengths. First, it is embedded in a population-based cohort. Therefore, results are generalizable and we could assess many different covariates. Furthermore, to our knowledge this is the largest study of sleep apnea and brain changes in the cerebrum in the general population. However, this study also has some limitations. First, it is a cross-sectional study. Therefore we cannot rule out a long-term effect of sleep apnea. Second, brain imaging and PSG were not conducted in the same day.

5. Conclusion

To conclude, this population-based study showed that nocturnal intermittent oxygen desaturation mainly explains the association

between sleep apnea and brain damage. In our study, especially the parietal white matter was vulnerable to oxygen desaturation. Future research is needed to study whether different causes of oxygen desaturation, such as anemia or arteriosclerosis, explain the association of oxygen desaturation and white matter atrophy. In addition, the effect of oxygen desaturation treatment on brain damage will provide more information on this topic.

Conflicts of interest

The authors have no conflict of interest related to this paper. The position of A.I. Luik at the Sleep and Circadian Neuroscience Institute is funded by BigHealth Ltd. (London, United Kingdom).

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.nbscr.2016.04.001>.

References

- Abramson, J.L., Jurkovic, C.T., Vaccarino, V., Weintraub, W.S., McClellan, W., 2003. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. *Kidney Int.* 64 (2), 610–615.
- Bassetti, C.L., Milanova, M., Gugger, M., 2006. Sleep-disordered breathing and acute ischemic stroke: diagnosis, risk factors, treatment, evolution, and long-term clinical outcome. *Stroke* 37 (4), 967–972.
- Canessa, N., Castronovo, V., Cappa, S.F., Aloia, M.S., Marelli, S., Falini, A., Alemanno, F., Ferini-Strambi, L., 2011. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. *Am. J. Respir. Crit. Care Med.* 183 (10), 1419–1426.
- Chen, H.L., Lu, C.H., Lin, H.C., Chen, P.C., Chou, K.H., Lin, W.M., Tsai, N.W., Su, Y.J., Friedman, M., Lin, C.P., Lin, W.C., 2015. White matter damage and systemic inflammation in obstructive sleep apnea. *Sleep* 38 (3), 361–370.
- Davies, C.W., Crosby, J.H., Mullins, R.L., Traill, Z.C., Anslow, P., Davies, R.J., Stradling, J.R., 2001. Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. *Sleep* 24 (6), 715–720.
- de Boer, R., Vrooman, H.A., van der Lijn, F., Vernooij, M.W., Ikram, M.A., van der Lugt, A., Breteler, M.M., Niessen, W.J., 2009. White matter lesion extension to automatic brain tissue segmentation on MRI. *Neuroimage* 45 (4), 1151–1161.
- Ding, J., Nieto, F.J., Beauchamp Jr., N.J., Harris, T.B., Robbins, J.A., Hetmanski, J.B., Fried, L.P., Redline, S., 2004. Sleep-disordered breathing and white matter disease in the brainstem in older adults. *Sleep* 27 (3), 474–479.
- Duran, J., Esnaola, S., Rubio, R., Iztueta, A., 2001. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30–70 yr. *Am. J. Respir. Crit. Care Med.* 163 (3 Pt 1), 685–689.
- Erpelding, N., Moayed, M., Davis, K.D., 2012. Cortical thickness correlates of pain and temperature sensitivity. *Pain* 153 (8), 1602–1609.
- Gozal, D., Daniel, J.M., Dohanich, G.P., 2001. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. *J. Neurosci.* 21 (7), 2442–2450.
- Harbison, J., Ford, G.A., James, O.F., Gibson, G.J., 2002. Sleep-disordered breathing following acute stroke. *QJM* 95 (11), 741–747.
- Harbison, J., Gibson, G.J., Birchall, D., Zammit-Maempel, I., Ford, G.A., 2003. White matter disease and sleep-disordered breathing after acute stroke. *Neurology* 61 (7), 959–963.
- Hofman, A., Brusselle, G.G., Darwish Murad, S., van Duijn, C.M., Franco, O.H., Goedegebure, A., Ikram, M.A., Klaver, C.C., Nijsten, T.E., Peeters, R.P., Stricker, B.H., Tiemeier, H.W., Uitterlinden, A.G., Vernooij, M.W., 2015. The Rotterdam Study: 2016 objectives and design update. *Eur. J. Epidemiol.* 30 (8), 661–708.
- Hui, D.S., Choy, D.K., Wong, L.K., Ko, F.W., Li, T.S., Woo, J., Kay, R., 2002. Prevalence of sleep-disordered breathing and continuous positive airway pressure compliance: results in Chinese patients with first-ever ischemic stroke. *Chest* 122 (3), 852–860.
- Iber, C., Ancoli-Israel, S., Chesson, A.L., Quan, S.F., 2007. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. American Academy of Sleep Medicine, Westchester.
- Ikram, M.A., van der Lugt, A., Niessen, W.J., Krestin, G.P., Koudstaal, P.J., Hofman, A., Breteler, M.M., Vernooij, M.W., 2011. The Rotterdam Scan Study: design and update up to 2012. *Eur. J. Epidemiol.* 26 (10), 811–824.
- Joo, E.Y., Tae, W.S., Lee, M.J., Kang, J.W., Park, H.S., Lee, J.Y., Suh, M., Hong, S.B., 2010. Reduced brain gray matter concentration in patients with obstructive sleep apnea syndrome. *Sleep* 33 (2), 235–241.
- Kiernan, T.E., Capampangan, D.J., Hickey, M.G., Pearce, L.A., Aguilar, M.I., 2011. Sleep apnea and white matter disease in hypertensive patients: a case series. *Neurologist* 17 (5), 289–291.
- Kim, H., Yun, C.H., Thomas, R.J., Lee, S.H., Seo, H.S., Cho, E.R., Lee, S.K., Yoon, D.W., Suh, S., Shin, C., 2013. Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. *Sleep* 36 (5) 709–158.
- Kumar, R., Pham, T.T., Macey, P.M., Woo, M.A., Yan-Go, F.L., Harper, R.M., 2014. Abnormal myelin and axonal integrity in recently diagnosed patients with obstructive sleep apnea. *Sleep* 37 (4), 723–732.
- Lanfranchi, P., Somers, V.K., 2001. Obstructive sleep apnea and vascular disease. *Respir. Res.* 2 (6), 315–319.
- Luik, A.I., Zuurbier, L.A., Whitmore, H., Hofman, A., Tiemeier, H., 2015. REM sleep and depressive symptoms in a population-based study of middle-aged and elderly persons. *J. Sleep Res.* 24 (3), 305–308.
- Marshall, N.S., Wong, K.K., Liu, P.Y., Cullen, S.R., Knuijman, M.W., Grunstein, R.R., 2008. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep* 31 (8), 1079–1085.
- Meng, S., Qiao, M., Foniok, T., Tuor, U.I., 2005. White matter damage precedes that in gray matter despite similar magnetic resonance imaging changes following cerebral hypoxia-ischemia in neonatal rats. *Exp. Brain Res.* 166 (1), 56–60.
- Nieto, F.J., Young, T.B., Lind, B.K., Shahar, E., Samet, J.M., Redline, S., D'Agostino, R.B., Newman, A.B., Lebowitz, M.D., Pickering, T.G., 2000. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 283 (14), 1829–1836.
- Nishibayashi, M., Miyamoto, M., Miyamoto, T., Suzuki, K., Hirata, K., 2008. Correlation between severity of obstructive sleep apnea and prevalence of silent cerebrovascular lesions. *J. Clin. Sleep Med.* 4 (3), 242–247.
- Osorio, R.S., Gumb, T., Pirraglia, E., Varga, A.W., Lu, S.E., Lim, J., Wohlleb, M.E., Ducca, E.L., Koushyk, V., Glodzik, L., Mosconi, L., Ayappa, I., Rapoport, D.M., de Leon, M.J., 2015. Alzheimer's disease neuroimaging. I. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology* 84 (19), 1964–1971.
- Parish, J.M., Shepard Jr., J.W., 1990. Cardiovascular effects of sleep disorders. *Chest* 97 (5), 1220–1226.
- Parra, O., Arboix, A., Bechich, S., Garcia-Eroles, L., Montserrat, J.M., Lopez, J.A., Bal-lesser, E., Guerra, J.M., Sopena, J.J., 2000. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *Am. J. Respir. Crit. Care Med.* 161 (2 Pt 1), 375–380.
- Punjabi, N.M., 2015. Counterpoint: Is the AHI the Best Way to Quantify the Severity of Sleep Disordered Breathing? No. *Chest*.
- Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the general population. *Appl. Psychol. Meas.* 1 (3), 385–401.
- Suter, O.C., Sunthorn, T., Kraftsik, R., Straubel, J., Darekar, P., Khalili, K., Miklossy, J., 2002. Cerebral hypoperfusion generates cortical watershed microinfarcts in Alzheimer disease. *Stroke* 33 (8), 1986–1992.
- Tian, J., Shi, J., Bailey, K., Mann, D.M., 2004. Relationships between arteriosclerosis, cerebral amyloid angiopathy and myelin loss from cerebral cortical white matter in Alzheimer's disease. *Neuropathol. Appl. Neurobiol.* 30 (1), 46–56.
- Torelli, F., Moscufo, N., Garreffa, G., Placidi, F., Romigi, A., Zannino, S., Bozzali, M., Fasano, F., Giulietti, G., Djonlagic, I., Malhotra, A., Marciani, M.G., Guttman, C.R., 2011. Cognitive profile and brain morphological changes in obstructive sleep apnea. *Neuroimage* 54 (2), 787–793.
- Tummala, S., Palomares, J., Kang, D.W., Park, B., Woo, M.A., Harper, R.M., Kumar, R.,

2016. Global and regional brain non-gaussian diffusion changes in newly diagnosed patients with obstructive sleep apnea. *Sleep* 39 (1), 51–57.
- Vernooij, M.W., de Groot, M., van der Lugt, A., Ikram, M.A., Krestin, G.P., Hofman, A., Niessen, W.J., Breteler, M.M., 2008. White matter atrophy and lesion formation explain the loss of structural integrity of white matter in aging. *Neuroimage* 43 (3), 470–477.
- Vrooman, H.A., Cocosco, C.A., van der Lijn, F., Stokking, R., Ikram, M.A., Vernooij, M. W., Breteler, M.M., Niessen, W.J., 2007. Multi-spectral brain tissue segmentation using automatically trained k-Nearest-Neighbor classification. *Neuroimage* 37 (1), 71–81.
- Weiss, J.W., Remsburg, S., Garpestad, E., Ringler, J., Sparrow, D., Parker, J.A., 1996. Hemodynamic consequences of obstructive sleep apnea. *Sleep* 19 (5), 388–397.
- Wessendorf, T.E., Teschler, H., Wang, Y.M., Konietzko, N., Thilmann, A.F., 2000. Sleep-disordered breathing among patients with first-ever stroke. *J. Neurol.* 247 (1), 41–47.
- Wodarz, R., 1980. Watershed infarctions and computed tomography. A topographical study in cases with stenosis or occlusion of the carotid artery. *Neuroradiology* 19 (5), 245–248.