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

Lisette A. Zuurbier, Meike W. Vernooij, Annemarie I. Luik, Desana Kocevska, Albert Hofman, Harry Whitmore, M. Arfan Ikram, Henning Tiemeier

Department of Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands
Department of Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands
Sleep & Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom
Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands
Department of Endocrinology in the Department of Medicine, University of Chicago, Chicago, IL, USA
Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands
Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands
Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands

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 et al., 2016). These findings suggest that sleep apnea may be related to structural brain changes in adults.

Previous studies of apnea severity and brain changes are
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 oximeter. Participants were instructed to sleep 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/m²) 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 (≥ 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 ≤ 30) and n=81 had a high AHI (≥ 30). The average oxygen desaturation was 0.3 per minute (range 0–19) 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 (β = -10.4 ml, 95% CI = -18.0; -2.8, Table 3). In the multivariable adjusted model, the effect size was attenuated (β = -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 (β = -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 (β = -2.16, 95% CI = -3.93; -0.39), smaller parietal white matter (β = -3.95, 95% CI = -6.02; -1.88), smaller occipital white matter (β = -1.49, 95% CI = -2.81; -0.18) and smaller hippocampal volume (β = -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 (β = -0.05, 95% CI = -0.09; -0.004) and smaller parietal white matter volumes (β = -0.16, 95% CI = -0.31; -0.01) in the multivariable adjusted model. The AHI was significantly related to hippocampal volume only in the age and sex adjusted model (β = -0.01, 95% CI = -0.01; -0.003), but the association was attenuated in the multivariable adjusted model (β = -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 (β = -5.5 ml per SD, 95% CI = -9.9; -1.0) whereas the AHI and arousals were not (β = 3.4 ml per SD, 95% CI = -1.0; 7.8; β = -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: β = -1.8 ml per SD, 95% CI = -2.9; -0.7, AHI: β = 0.6 ml per SD, 95% CI = -0.6; 1.7, arousals: β = -0.1 ml per SD, 95% CI = -0.8; 0.5) and smaller hippocampal volumes (oxygen desaturation: β = -0.1 ml per SD, 95% CI = -0.2; -0.004, AHI: β = 0.1 ml per SD, 95% CI = -0.07; 0.2; arousals: β = -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 1**

| Category                          | Mean (SD), n (%) |
|-----------------------------------|-----------------|
| Age, years                        | 62.1 (5.4)      |
| Sex, female                       | 380 (55.8%)     |
| Education: Low                    | 53 (7.8%)       |
| Education: Intermediate           | 409 (60.1%)     |
| Education: High                   | 217 (31.9%)     |
| Body mass index, kg/m²            | 27.2 (4.4)      |
| Smoking: Never                    | 199 (29.2%)     |
| Smoking: Current                  | 116 (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 (179.9)   |
| 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 ≤ 30)            | 153 (22.5%)     |
| High AHI (≥ 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.
Table 2  
Associations of AHI and brain structural measurements (n=681).  

|                | Gray matter (ml) | White matter (ml) | White matter lesions (SD) |
|----------------|------------------|-------------------|---------------------------|
|                | B (95% CI), p     | B (95% CI), p     | B (95% CI), p             |
| AHI continuous |                  |                   |                           |
| Age, sex adjusted |                |                   |                           |
| Multivariable adjusted |            |                   |                           |
| Low AHI ( < 15), n=447 |            |                   |                           |
| Moderate AHI (15 ≤ 30), n=153 |              |                   |                           |
| Age, sex adjusted |                |                   |                           |
| Multivariable adjusted |            |                   |                           |
| High AHI (≥ 30), n=81 |               |                   |                           |
| Age, sex adjusted |                |                   |                           |
| Multivariable adjusted |            |                   |                           |

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.

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

|                | Gray matter (ml) | White matter (ml) | White matter lesions (SD) |
|----------------|------------------|-------------------|---------------------------|
|                | B (95% CI), p     | B (95% CI), p     | B (95% CI), p             |
| Oxygen desaturation (n/min) |                  |                   |                           |
| Age, sex adjusted |                |                   |                           |
| Multivariable adjusted |            |                   |                           |
| Mediator model |                  |                   |                           |
| Low oxygen desaturation, n=220 |   |                   |                           |
| Moderate oxygen desaturation, n=221 |       |                   |                           |
| Age, sex adjusted |                |                   |                           |
| Multivariable adjusted |            |                   |                           |
| High oxygen desaturation, n=219 |         |                   |                           |
| Age, sex adjusted |                |                   |                           |
| Multivariable adjusted |            |                   |                           |

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.

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 a number of factors, 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 (Farra 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 lies 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 desaturation with white matter atrophy.
Values represent difference in brain tissue volume (ml) per unit increase in AHI. Linear regression analyses adjusted for intracranial volume.

Abbreviations: CI, confidence interval. Values represent difference in brain tissue volume (ml) per unit increase in AHI. Linear regression analyses adjusted for intracranial volume.

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

Table 4

|                      | 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* | –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* | –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* | –0.06 (–0.13; 0.02), 0.13 | –0.22 (–0.42; –0.01), 0.04 | –0.05 (–0.30; 0.19), 0.68 |

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 oxygen 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 loss of microstructural integrity of white matter, but in distinct brain regions (Vernooij 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.
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 anaemia 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 Biwealth Ltd. (London, United Kingdom).

Sources of funding

This research was supported by a Netherlands Organization for Scientific Research grant (NWO-VIDI: 017.106.370) awarded to H. Tiemeier. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. M.W. Vernooij is supported by a fellowship grant of Erasmus Medical Center. The work of D. Kocevska was supported by an ERAWEB scholarship grant financed by the European Commission, in accordance with grant agreement 2013-2548/001-001-EMA-2.

Acknowledgments

The authors want to thank Rachel Leproul for analyzing the polysomnography data.

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., Jurkowitz, 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, C., Canstronovo, 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., Lin, C.H., Lin, H.C., Chen, P.C., Chou, K.H., Lin, W.M., Tsai, N.W., Su, Y.J., Canessa, N., Castronovo, V., Cappa, S.F., Aloia, M.S., Marelli, S., Falini, A., Alemanno, L.A. Zuurbier et al. / Neurobiology of Sleep and Circadian Rhythms 1 (2016) 1–7
Durán, J., Esquela, S., Rubio, R., Izuelta, 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.
Erpenberg, 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., Dohansch, 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.P., Gibson, G.J., 2002. Sleep-disordered breathing following acute stroke. QJM 95 (11), 741–747.
Harbison, J., Gibson, G.J., Birchall, D., Zammit-Maempel, L., 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.
Hu, D.S., Choy, D.K., Wong, L.K., Ko, F.W., Li, T.S., Woo, J., Ray, K.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, R.J., Hofman, A., Breteler, M.M., Vernooij, M.W., 2011. The Rotterdam Scan Study: design and update 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 content 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 damage in hypertensive patients: a case series. Neurologist 17 (3), 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) 709–718.
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. Respirology 6 (2), 315–319.
Luik, A.I., Zuurberg, 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., Knutman, 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., Fonniok, T., Tuo, 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., Hiraata, K., 2008. Correlation between severity of obstructive sleep apnea and prevalence of silent cerebral microbleeds. J. Clin. Sleep Med. 4 (3), 242–247.
Osorio, R.S., Cumb, T., Pirraglia, E., Varga, A.W., Lu, S.E., Lim, J., Wohlleber, M.E., Ducua, E.L., Koushyv, V., Glodzik, L., Mosconi, L., Ayappa, I., Rapoort, 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.
Pana, O., Asboe, A., Bechich, S., Garcia-Eroles, L., Montserrat, J.M., Lopez, J.A., Ballester, 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. Countering: Is the AHI the Best Way to Quantify the Severity of Sleep Disordered Breathing? No. Chest.
Radolf, I.L., 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., Santhorn, T., Kraftsk, R., Straubel, J., Darekar, P., Khalili, K., Miklosy, J., 2002. Cerebral hyperperfusion generates cortical watershed microinfarcts in Alzheimer disease. Stroke 33 (8), 1986–1992.
Tian, J., Yang 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. Neurorehabil. Procept. Neurobiol. 30 (1), 46–56.
Torelli, F., Moscino, N., Garrella, G., Placidi, F., Romigi, A., Zannino, S., Bozzali, M., Fasoli, E., Giullietti, G., Dijolagni, L., Malhotra, A., Marciani, M.G., Guttman, C.R., 2015. Cognitive prof®le and brain morphological changes in obstructive sleep apnea. Neuroimaging 54 (2), 787–793.
Tummalra, 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., Nissen, 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., Teschner, 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.