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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 Kocevska [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.

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. Kocevska), 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