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Sleep complaints and cerebral white matter: A prospective bidirectional study

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ABSTRACT

Sleep complaints and brain changes co-occur in older adulthood, but the temporal relation between these processes is poorly understood. Poor sleep may destabilize axonal integrity and deteriorate white matter, but white matter pathology can also precede sleep complaints. Our objective was to explore a prospective, possibly bi-directional association between subjective sleep complaints and micro- and macro-structural properties of cerebral white matter. We assessed sleep complaints and brain magnetic resonance imaging at two time-points (2006–2008 and 2011–2014) in a population-based cohort including 2529 participants (56 ± 6 years old, 55% women). Sleep complaints were assessed with the Pittsburgh Sleep Quality Index. White matter lesion (WML) volume was assessed from fluid-attenuated inversion recovery images and global and tract-specific white matter microstructural integrity with diffusion tensor imaging. Sleep complaints at baseline were not associated with changes in WML volume or global white matter microstructure. In tract-specific analyses, however, sleep complaints were associated with reduced microstructural integrity in two white matter tracts projecting to the brainstem, but only when uncorrected for multiple testing. Likewise, we found no evidence for the reverse association; micro- or macro-structural properties of white matter were not related to changes in sleep complaints over time. This study provides evidence against the hypothesis that sleep complaints lead to white matter changes in the aging brain, and shows that white matter properties do not underlie sleep complaints in older persons. As subjective sleep complaints increase in later life, it is important to demonstrate that these are not etiologically related to cerebral white matter pathology.

1. Introduction

Although the exact functions of sleep are unknown, research of multiple disciplines has provided empirical evidence that sleep serves vital functions to the brain (Bubu et al., 2017; Cirelli and Tononi, 2015; Jessen et al., 2015; Scullin and Bliwise, 2015). Older adults often experience sleep complaints that coincide with structural brain changes, but studies exploring associations between these processes have been cross-sectional, thus their temporal relation is poorly understood (Scullin, 2017).

Previous neuroimaging studies have focused on the relation between sleep complaints and functional deficits measured with fMRI, or atrophy of the cerebral cortex (reviewed by Scullin (2017)). However, the microstructural integrity of cerebral white matter might underlie these associations (Bellesi, 2015; Simons and Nave, 2015). Indeed, short sleep duration (Ramos et al., 2014) and reduced sleep quality (Del Brutto et al., 2015; Kanda et al., 2003) have been associated with white matter lesions in older adults. Diffusion tensor imaging (DTI) studies have also shown cross-sectional associations between poor sleep and microstructural alterations of white matter in insomnia patients (Li et al., 2016; Spiegelhalder et al., 2014), and subjects with reduced sleep quality (Khalsa et al., 2017; Sexton et al., 2017).

Next to being relatively small, these studies had a cross-sectional design, thus the direction of the association between changes in sleep and white matter could not be tested. Most authors have inferred that sleep complaints lead to white matter changes, but the direction of this

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association might also be the other way around. White matter properties or pathology could underlie sleep disturbances and lead to sleep complaints. Indeed, white matter damage was prospectively related to increasing sleep disturbances, though only in the context of pre-existing chronic illness, e.g. heart failure (Alosco et al., 2013), stroke (Gudberg and Johansen-Berg, 2015) or vascular dementia (Cheng et al., 2013). It is yet unclear whether these associations exist in the general population.

We explore the bidirectional associations between sleep complaints and macro- and microstructural properties of cerebral white matter in a population-based cohort of middle-aged and older adults. We hypothesized a bidirectional association between sleep complaints and white matter. We posited that sleep complaints are prospectively associated with white matter changes, and also that disturbances in white matter micro- and macrostructural properties are related to increasing sleep complaints.

2. Methods

2.1. Study population

This study was embedded in the Rotterdam Study, an ongoing prospective population-based cohort designed to investigate the causes and consequences of chronic diseases in persons aged ≥45 years (Ikram et al., 2017; Ikram et al., 2015). The study started in 1990 and from 2005 onward MRI scanning was included in the study protocol (Ikram et al., 2015). At the baseline of our study, between 2006 and 2008, 3744 participants (95% of those approached) reported their sleep complaints during a home interview. Two-thousand-six-hundred-ninety-six (72%) participants underwent MRI scanning within one year (Ikram et al., 2015). Twenty-eight participants died before follow-up (between 2010 and 2014). After excluding participants with incident dementia (n = 11), cortical infarcts (n = 43) or stroke (n = 85), 2191 had answered the sleep questionnaire at follow-up, and 2125 were scanned for the second time, of which 1966 had repeated measures of both. The average time interval between questionnaires was 5.5 years (range: 2.9–8.1), and between MRI scans 5.2 years (range: 2.8–8.1).

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). All participants provided written informed consent to participate in the study.

2.2. Sleep assessment

Sleep complaints were assessed using a Dutch version of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989; Zuurbier et al., 2015). PSQI is a self-rated 19-item questionnaire that assesses 7 domains of sleep quality (sleep duration, subjective sleep quality, latency, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) over a 1-month time interval. We operationalized sleep complaints with the global PSQI, which was calculated as the weighted sum of the component scores if a minimum of 6 components was completed. Higher scores represent more sleep complaints. The PSQI showed good test-retest reliability and validity (Buysse et al., 1989). Sleep duration was self-reported by a single question from the PSQI: “How many hours of actual sleep did you get at night?”. Participants sleeping ≤6 h a night were classified as short sleepers (n = 840), whereas those sleeping > 9 h were classified as long sleepers (n = 30). Sleep efficiency (%) was calculated as the percent of sleep within the reported time in bed (hours between reported bedtime and waketime).

2.3. MRI scanning and processing

We performed multi-sequence magnetic resonance imaging (MRI) on a 1.5-T scanner (GE Signa Excite), dedicated to population-based research and maintained without major hardware or software updates during the duration of the study.

An automated tissue segmentation approach (Vrooman et al., 2007) was used to classify scans into gray matter, white matter, cerebrospinal fluid (CSF), and background tissue. Supratentorial intracranial volume (ICV) was estimated by summing total gray and white matter and CSF volumes, and used to correct for head size (Vrooman et al., 2007). White matter lesions (WMLs) were identified using an automated post-processing step based on the fluid-attenuated inversion recovery image and the tissue segmentation (de Boer et al., 2009). The presence of cortical infarcts was visually assessed on structural MRI sequences.

2.4. Diffusion tensor imaging processing and tractography

In the DTI scan, we performed a single shot, diffusion-weighted spin echo planar imaging sequence. Maximum b value was 1000 s/mm^2 in 25 non-collinear directions; 3 volumes were acquired without diffusion weighting (b value 0 s/mm^2). Data were preprocessed using a standardized pipeline (eddy current and head-motion correction) (Koppelmans et al., 2014). Diffusion tensors were fit to the resampled data, and global mean fractional anisotropy (FA), and mean diffusivity (MD) were computed in the normal-appearing white matter. FA describes the directionality of diffusion (lower values reflect reduced microstructural integrity) and MD represents the overall magnitude of water diffusion (higher values reflect reduced microstructural integrity). Using a diffusion tractography approach, the diffusion data were also used to segment white matter tracts (de Groot et al., 2015). For 15 different white matter tracts (12 segmented bilaterally), tract-specific white matter microstructural diffusion-MRI parameters (median FA and MD) were obtained with subsequent combination of left and right measures (de Groot et al., 2015). Tract segmentations were also used to acquire tract-specific white matter volumes (WMV) and WML volumes (natural-log transformed for analyses). The cerebellum could not be fully incorporated in the field of view of the diffusion-MRI scan, resulting in partial coverage of the medial lemniscus. Therefore, alternative seed masks for tractography were selected (de Groot et al., 2015). This was treated as a covariate in models including the medial lemniscus.

2.5. Other measures

Prevalent dementia and clinical stroke was ascertained by home interviews and by reviewing medical records (Akoudad et al., 2015; Schrijvers et al., 2012). Education was categorized in line with the international standard classification into primary education, lower education, intermediate education and higher education (UNESCO, 2012). Employment was used as a binary variable (employed/unemployed). Smoking habits were categorized into: current, former and never. Based on weight and height measured at the research center body mass index (BMI) was calculated (kg/m^2). Cardiovascular risk factors were based on information derived from home interviews, medical records or physical examinations. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medication based on medical records. Diabetes mellitus was defined as a fasting serum glucose level ≥7.0 mmol/l, or non-fasting serum glucose level ≥11.1 mmol/l, or use of glucose-lowering medication. Serum glucose, total cholesterol, and high-density lipoprotein-cholesterol (HDL) levels were acquired by an automated enzymatic procedure (Roche Diagnostics GmbH, Mannheim, Germany). Sleep apnea was considered possible when participants reported (1) loud snoring at least two nights per week and at least occasional respiratory pauses, or (2) respiratory pauses during sleep with a frequency of at least 1–2 nights/week (Fogelholm et al., 2007; Luik et al., 2013; Zuurbier et al., 2015). Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression (CES-D) scale,

excluding the question about restless sleep from the total score (Beekman et al., 1997). Mini Mental State Examination was used to assess cognitive status (Folstein et al., 1975). The use of medication affecting the central nervous system (e.g. psycholeptics, psychoanalpetis) was assessed by cabinet check and classified in line with the Anatomical Therapeutic Chemical (ATC)-classification. All covariates were measured at the baseline (2006–2008).

2.6. Statistical analyses

Changes in sleep and white matter across the follow-up were tested using a paired sample *t*-test. First, we explored cross-sectional associations between sleep complaints, sleep duration, and sleep efficiency with white matter properties in linear regression models. Next, we modeled the association between determinants at baseline and change in outcomes using linear regressions. To study white matter changes as a function of sleep complaints, PSQI scores at baseline were entered as predictors for white matter volume, white matter lesion volume or DTI measures at follow-up, while controlling for white matter measures at baseline, and time between baseline and follow-up measures. Vice versa, to study changes in sleep patterns as a function of white matter properties, imaging measures were modeled as predictors of PSQI scores at follow-up, while controlling for baseline PSQI and the time intervals between the assessments. First, global diffusion metrics (FA and MD) were tested. Regional specificity was examined using tract-specific FA and MD. To facilitate comparisons diffusion metrics were z-standardized. In an additional step, we tested the association between self-reported sleep duration (continuous and categorized), and sleep efficiency and changes in white properties. Vice versa, we also explored associations between white matter properties and changes in sleep duration and efficiency over time. We built three models, 1) Model 1: adjusted for age, sex, intracranial volume, and in the DTI models global or tract-specific white matter volume and log transformed white matter lesion volume; 2) Model 2: additionally adjusted for the baseline values of the outcome (WMV, WMLs, DTI or sleep variable) and the time periods between the assessments; and 3) Model 3: additionally adjusted for educational level, employment, smoking habits, total and HDL cholesterol, use of lipid lowering medication, prevalent diabetes, and/or hypertension, depressive symptoms and cognitive score. Confounders were included based on previous literature (Sexton et al., 2017; Yaffe et al., 2016). A Bonferroni-adjusted $p < 0.0016$ was used as threshold for statistical significance in individual tract analyses. Missing covariates (< 1%) were imputed with the mean. All analyses were performed using SPSS v21.

2.7. Posthoc analyses

To investigate whether the statistical approach to model change influenced the results we reanalyzed the data defining change as the difference between baseline and follow-up measure. The delta measure (e.g. $WMV_{follow\text{-}up}$-$WMV_{baseline}$) was then regressed on the baseline values of the determinant (e.g. PSQI). We also tested whether age, sex or depressive symptoms moderated the association between sleep and white matter integrity in either direction. If there was evidence for an interaction ($P_{interaction} < 0.05$), we performed stratified analyses. Finally, we ran additional models adjusting for possible sleep apnea.

3. Results

Mean age of the participants at baseline was 56 ± 6 years (45–87), and 56% were women (Table 1). The volume of white matter lesions increased over the follow-up (3.0 ± 3.8 ml at baseline to 3.7 ± 4.7 ml at follow-up, $p < 0.001$), paralleled by a slight increase in both FA (mean difference = 0.003, $p < 0.001$) and MD (mean difference = 0.01, $p < 0.001$). The average PSQI score, however, did not change significantly during the follow-up. Bivariate correlations between changes in sleep patterns and white matter properties and other demographic characteristics and indices of mental and physical health are shown in Supplementary Table 1. Sleep complaints, and sleep duration were not associated with white matter properties at baseline (Supplementary Table 2). Higher sleep efficiency was associated with more white matter volume at baseline (B = 0.13, 95%CI: 0.000, 0.37, p-value = 0.050), however, this association was explained by education level.

Table 1
Descriptive characteristics (N = 2529).

Sleep	
Baseline	
PSQI score at baseline	4.0 ± 3.3
Sleep duration, hours	6.8 ± 1.1
Follow-up	
PSQI score at follow-up	3.8 ± 3.3
Sleep duration, hours	6.9 ± 1.2
Brain	
Baseline	
Mean FA	0.34 ± 0.01
Mean MD, 10^{-3} mm^2/s	0.73 ± 0.02
ICV, mL	1143.8 ± 116.1
White matter volume, mL	424.3 ± 56.0
White matter lesion volume, mL	2.0 (1.3–3.4)
Follow-up	
Mean FA	0.35 ± 0.01
Mean MD, 10^{-3} mm^2/s	0.74 ± 0.02
ICV, mL	1141.4 ± 116.3
White matter volume, mL	412.1 ± 55.8
White matter lesions volume, mL	2.3 (1.4–4.1)
Socio-demographic characteristics at baseline	
Age, years	55.8 ± 6.0
Sex, No. (%) female	1416 (56)
Educational level, No. (%)	
low	236 (9.3)
medium-low	869 (34.4)
medium-high	729 (28.8)
high	695 (27.5)
Employment, No. (%) yes	1634 (64.6)
Health indicators	
Possible sleep apnea, No. (%) yes	191 (8)
BMI	27.5 ± 4.3
Serum Cholesterol, nmol/L	5.6 ± 1.1
HDL Cholesterol, nmol/L	1.4 ± 0.4
Diabetes, No. (%)	177 (7.0)
Hypertension, No. (%)	1138 (45.0)
Smoking, No. (%)	
never	829 (33.3)
past smoker	1148 (45.4)
yes	541 (21.4)
CNS medication, No. (%) yes	343 (13.6)
MMSE, score	28 ± 1.9
CES-D, score	2 (0–6)

Numbers are mean ± SD or median (interquartile range).
Abbreviations: ICV = intracranial volume, PSQI = Pittsburg Sleep Quality Index, BMI = body mass index, CNS medication = central nervous system (including Psycholeptics, Psychoanaleptic, etc.), MMSE = mini mental state examination (cognitive score), CES-D = center for epidemiologic studies-depression scale. Education: low = primary education, medium-low = lower/intermediate general or lower vocational education, medium-high = intermediate vocational education or higher general education, high = higher vocational education or university.

3.1. Sleep complaints and white matter changes

Sleep complaints at baseline, were not associated with white matter lesions at follow-up or with changes of white matter lesions (Table 2). Likewise, sleep complaints were not associated with global white matter microstructural integrity changes (Table 2). In tract-specific analyses, however, sleep complaints were related to a reduction in FA in two brainstem tracts (Supplementary Table 3): the middle cerebellar peduncle (β = −0.04, 95%CI: −0.07;-0.01, p-value = 0.005) and

Table 2
Associations between sleep complaints and changes in white matter properties across follow-up (n = 2125).

Determinant		Outcomes											
		White matter volume, ml			White matter lesion volume, ml			Fractional Anisotropy			Mean Diffusivity		
		β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
Sleep complaints, PSQI score	Model 1	−0.03	−0.07; 0.014	0.12	0.02	−0.02; 0.06	0.37	0.004	−0.01,0.02	0.56	−0.01	−0.02,0.004	0.19
	Model 2	0.01	−0.01; 0.03	0.18	0.01	−0.01; 0.03	0.30	−0.004	−0.01,0.003	0.31	−0.001	−0.01,0.01	0.72
	Model 3	0.01	−0.01; 0.03	0.17	0.01	−0.01; 0.03	0.37	−0.003	−0.01,0.01	0.44	−0.001	−0.01,0.01	0.71

Model 1 is adjusted for age and sex. White matter lesion volume, Fractional Anisotropy and Mean Diffusivity models are also adjusted for intracranial volume and white matter volume. Fractional Anisotropy and Mean Diffusivity models are also adjusted for log transformed white matter lesion volume.
Model 2 is additionally adjusted for white matter properties at baseline and time intervals (between two scans and between scans and questionnaire).
Model 3 is additionally adjusted for educational level, employment, smoking, total and HDL cholesterol, use of lipid lowering medication, prevalent diabetes, prevalent hypertension, cognitive score, depressive symptoms score.

medial lemniscus (β = −0.03, 95%CI: −0.05;-0.002, p-value = 0.035). These associations reached statistical significance only at nominal level. Sleep duration was inversely associated with changes in white matter lesion volume (β = −0.01, 95%CI: −0.02,-0.0001, p-value = 0.047, Supplementary Table 4). This association was driven by persons sleeping less than 6 h per night (beta = 0.02, 95%CI: 0.01,0.04, p-value = 0.038), who had more marked increase in WML load over the follow-up compared to those sleeping between 7 and 9 h (β = 0.02, 95%CI: 0.01,0.04, p-value = 0.038). In addition, higher sleep efficiency was prospectively associated with more white matter volume at follow-up (B = 0.23, 95%CI: 0.03,0.4, p-value = 0.03), but not with changes in white matter volume over time (Model 2, adjusted for baseline WMV: (B = −0.01, 95%CI: −0.09,0.08, p-value = 0.91)).

3.2. White matter properties and changes in sleep complaints

The micro- and macrostructural properties of white matter at baseline were not associated with changes in sleep complaints over time. More white matter volume at baseline was associated with less sleep complaints at follow-up (B = −0.004, 95%CI: −0.01,-0.001, p-value = 0.007), but this relation was accounted for by adjusting for sleep complaints at baseline (B = −0.002, 95%CI: −0.004,0.0001, p-value = 0.112). White matter lesions were not longitudinally related to sleep complaints (Table 3), nor were the global (Table 3) or tract-specific (Supplementary Table 5) microstructural integrity of white matter. The micro- and macrostructural properties of white matter were also not associated with sleep duration or efficiency (Supplementary Table 6).

3.3. Posthoc analyses

Results were very similar when changes in white matter properties were modeled as the difference between baseline and follow-up values. Similarly, the results were essentially unchanged when we used delta measures to model changes in sleep complaints (data not shown).

We found evidence that age modified the associations of sleep complaints with changes in white matter lesions ($P_{interaction} < 0.009$). Supplementary Table 7 shows a trend towards an association between sleep complaints and higher white matter lesion volume in participants in the highest age quartile, aged 57 and older (n = 949) (β = 0.02, 95% CI: −0.002, 0.04, p-value = 0.068). The associations did not differ between the sexes or across levels of depression scores ($P_{interaction} > 0.05$). Adjustment for possible sleep apnea did not influence the null findings (Supplementary Tables 8 and 9).

4. Discussion

We investigated the bidirectional associations between sleep complaints and cerebral white matter properties in middle-aged and older persons. Contrary to our hypothesis, sleep complaints were not associated with an increase in white matter lesions over follow-up of up to 8 years. Consistently, sleep complaints were not related with global microstructural changes of white matter. Persons with more sleep complaints, however, had a reduced microstructural integrity in two white matter tracts projecting to the brainstem, but this finding must be interpreted cautiously given multiple tests performed. We also found no evidence for the reverse association. Global micro- and macrostructural properties of white matter did not underlie sleep complaints in this population.

Previous reports based on cross-sectional data found lower microstructural integrity in frontal-subcortical white matter tracts among older adults with lower sleep quality (Sexton et al., 2017), and among insomnia patients (Li et al., 2016; Spiegelhalder et al., 2014). Del Brutto et al. (2015) also reported that older adults with poor sleep quality have

Table 3
Associations between white matter properties and changes in sleep complaints across follow-up (n = 2191).

Determinant	Outcome: Sleep complaints, PSQI score								
	Model 1			Model 2			Model 3		
	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
White matter volume, ml	−0.21	−0.36;-0.06	0.007	−0.10	−0.23; 0.02	0.11	−0.09	−0.21; 0.04	0.19
White matter lesions volume, ml	−0.01	−0.21; 0.19	0.92	−0.04	−0.21; 0.12	0.61	−0.07	−0.24; 0.10	0.40
Fractional Anisotropy	0.06	−0.09; 0.22	0.42	0.002	−0.12; 0.13	0.97	0.001	−0.13; 0.13	0.99
Mean Diffusivity	−0.01	−0.17; 0.16	0.93	0.06	−0.08; 0.19	0.43	0.05	−0.09; 0.19	0.47

Model 1 is adjusted for age and sex. White matter lesion volume, Fractional Anisotropy and Mean Diffusivity models are also adjusted for intracranial volume and white matter volume. Fractional Anisotropy and Mean Diffusivity models are also adjusted for log transformed white matter lesion volume.
Model 2 is additionally adjusted for sleep complaints (PSQI score) at baseline and time intervals (between two questionnaires and between scan and questionnaires).
Model 3 is additionally adjusted for educational level, employment, smoking, total and HDL cholesterol, use of lipid lowering medication, prevalent diabetes, prevalent hypertension, cognitive score, depressive symptoms score.

more white matter lesions. Based on this research, and supported by evidence linking poor sleep with cognitive decline (Bubu et al., 2017), authors hypothesized that sleep complaints predict white matter changes. However, as disturbed sleep was measured at the same time point with white matter properties (Del Brutto et al., 2015; Kanda et al., 2003; Li et al., 2016; Sexton et al., 2017; Spiegelhalder et al., 2014), none of these studies assessed the temporality of the association (i.e. does the "effect" occur after the "cause"). The only study that evaluated the association between persistency of sleep problems and white matter integrity (Sexton et al., 2017) across a follow-up period of 16 years reported no longitudinal association. The design and analytical approach of our study are likely more suitable for detecting temporal associations. In addition, previous studies often employed analytical approaches that require great statistical power (voxel-wise analyses) (Sexton et al., 2017; Spiegelhalder et al., 2014) in relatively small samples, thus there is a possibility of false positives. Previously reported FA deficits among persons with poor sleep quality (PSQI ≥ 6) have also been small (d = 0.18) (Sexton et al., 2017). Nevertheless, to detect such differences with power of 1-β = 0.9, and an α = 0.05 level, a sample size of n = 499 is required, indicating that our study was sufficiently powered. Therefore, the lack of association, both cross-sectional and longitudinal, in our study challenges the notion that subjective sleep complaints have an impact on white matter. Another important difference between these studies and our study is the age of the participants. Most previous studies have studied older people (> 60 years old (Del Brutto et al., 2015; Kanda et al., 2003; Sexton et al., 2017)). A large study including younger participants (18–98 years) (Gadie et al., 2017) reported an interaction with age, indicating that the relation between sleep and white matter integrity could be specific to older adults. We have included participants aged 45–87 years old, and also found some evidence that sleep complaints were related to an increase in white matter lesions in persons 57 years and older. This indicates that the associations between changes in white matter properties and sleep patterns might be present at a later stage, as changes in both sleep and brain structure are more substantial at a later age. Alternatively, this association could be present in clinical populations that include many participants at the extreme end of the distribution (e.g. severe sleep disorders might be related to white matter damage), but this goes beyond the aims of exploring the bidirectional associations between sleep complaints and white matter properties in the general population of adults without major neurological morbidity (i.e. excluding neurological conditions such as stroke and cortical infarcts). Two previous general population studies (Gadie et al., 2017; Sexton et al., 2017) of white matter integrity and sleep quality, measured with the PSQI, reported attenuation of the cross-sectional associations when controlling indices of physical, mental and cognitive health. We carefully adjusted for potential antecedents and mediators in additional analyses. Thus, it is unlikely that possible over-adjustment due to these covariates masked any indirect associations.

In tract-specific analyses, sleep complaints were related to reduced microstructural integrity in the middle cerebellar peduncle (projecting from the pons to the cerebellum) and the medial lemniscus (part of a larger ascending bundle carrying sensory information to the thalamus) (Ford et al., 2013). Despite the multiple tests performed the regional findings seem plausible given the known neuroanatomical basis of sleep. Multiple areas in the brainstem, in the pons in particular (Pollak et al., 2010), are involved in the generation of, and transitions between, sleep-wake states (Ford et al., 2013). Moreover, the thalamus provides a state-dependent gate of sensory information (Coulon et al., 2012). Thus, it is plausible that inappropriate sleep intrinsically contributes to a dysfunctional arousal system, including cells of the upper brain stem, which is crucial for cortical and thalamic activation during waking. This could result in injury to nuclei cells that would in turn lead to axonal degeneration, as fiber integrity, especially myelin integrity, depends on maintained cellular activity (Bellesi, 2015). However, reduced microstructural integrity in these brainstem tracts (Macey et al., 2008) has also been reported in patients with sleep apnea. We assessed possible sleep apnea by two self-reported questions, so it could be that our results are explained by altered coordination of breathing musculature related to compromised integrity in the middle cerebellar peduncle (Macey et al., 2008).

The reversed relation, a relation between white matter properties and changes in sleep disturbances, has previously been observed in clinical populations. In the context of Alzheimer's disease, white matter damage from amyloid plaques has been hypothesized to underlie disruptions in sleep-wake rhythms (Ju et al., 2014). Previous studies also suggested that white matter damage underlies sleep disturbances in patients with heart failure (Alosco et al., 2013) and vascular dementia (Cheng et al., 2013). In addition, using structural equation modelling on cross-sectional data of older adults, Del Brutto et al. (2018) have shown that white matter lesions might mediate the effect of disturbed kidney function on sleep complaints in older adults, and not vice versa. In our non-demented sample from the general population, we did not observe a temporal relation between white matter integrity and subsequent sleep complaints.

PSQI is the most commonly used questionnaire to measure sleep complaints in large samples, but it relies on the cognitive capacity to reflect on the past month. Subjective experiences of poor sleep can differ substantially from objective sleep parameters, in particular for people with sleep disorders (Landry et al., 2015). Future studies might find that changes in objective sleep parameters play a role in the etiology of structural brain changes. Indeed, two small, cross-sectional actigraphy studies have reported sleep-related microstructural alterations (Baillet et al., 2017; Khalsa et al., 2017). Baillet et al. (2017) reported that sleep fragmentation in elderly subjects (n = 58) is associated with lower white matter integrity in the corpus callosum and the external and internal capsule. Alternatively, it could be that sleep duration rather than sleep quality is more important for white matter properties. Previous studies have shown that both short (Khalsa et al., 2017; Yaffe et al., 2016) and long (Ramos et al., 2014) self-reported sleep duration are associated with white matter alterations. In our study, shorter sleep duration was related with an increase in white matter lesions, but was not related to the microstructural properties of cerebral white matter.

Important strengths of this study are the longitudinal design with repeated measures, which allowed us to study both directions of the association between sleep complaints and white matter properties. We also took many potentially confounding factors into account. Importantly, given the large sample, this study likely had sufficient power to detect a meaningful temporal association, despite the fact that the PSQI might not be ideal in discriminating poor from good sleepers (estimates of sensitivity 89.6% and specificity 86.5% (Buysse et al., 1989)). However, several limitations should also be discussed. We did not have an objective measure of sleep-disordered breathing which might be an important mediator to be considered in the relation between sleep and white matter damage. In addition, intra-individual changes in PSQI scores across the follow-up were small, which might have limited the possibility to detect an association between clinically significant changes in both sleep patterns and white matter properties. Although an important strength of the study is the long follow-up, changes in sleep and brain likely occur at different pace (i.e. changes in white matter properties rarely occur short-term, whereas sleep patterns are more likely to vary), which could account for the null findings. In particular, the average time period of 5 years between the two scans might have been too short for sleep dependent brain changes to be captured. However, we would be more likely to detect the reverse association during the follow-up as sleep patterns have been shown to be variable within such an interval (Tang et al., 2017). Future studies should use repeated measures sampled at shorter intervals across a long follow-up.

This study provides evidence against the hypothesis that subjective sleep complaints are associated with increasing white matter lesions,

and a reduction in white matter microstructural integrity in the aging brain. We also found no evidence that cerebral white matter properties on a micro- and macrostructural level underlie sleep complaints in the general population of middle-aged and older persons. As subjective sleep complaints increase in later life, it is important to show that these are not etiologically related to cerebral white matter pathology. Future studies should however investigate longitudinal relations between objective sleep parameters and cerebral white matter properties.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.02.002.

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