



Sleep characteristics and brain structure: A systematic review with meta-analysis

Tergel Namsrai ^{a,*}, Joseph M. Northey ^{a,b}, Ananthan Ambikairajah ^{a,c,d,e,f,1}, Oli Ahmed ^a, Khawlah Alateeq ^{a,g}, Daniela Andrea Espinoza Oyarce ^a, Richard Burns ^a, Ben Rattray ^d, Nicolas Cherbuin ^a

^a National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australia

^b Discipline of Sport and Exercise Science, Faculty of Health, University of Canberra, Canberra, Australia

^c Discipline of Psychology, Faculty of Health, University of Canberra, Canberra, Australia

^d Centre for Ageing Research and Translation, Faculty of Health, University of Canberra, Canberra, Australia

^e The University of Sydney, School of Psychology, Sydney, Australia

^f The University of Sydney, Brain and Mind Centre, Sydney, Australia

^g Radiological Science, College of Applied Medical Sciences, King Saud University, Riyadh, 11451, Saudi Arabia

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ABSTRACT

Background: As the global population ages, the prevalence of associated conditions, including neurodegeneration and dementia, will increase. Thus, reducing risk factors is crucial to prevention. Sleep contributes to brain homeostasis and repair, which, if impaired, could lead to neurodegeneration. However, the relationship between sleep characteristics, disorders, and brain morphology is poorly understood in healthy adults. Therefore, we aimed to systematically analyse the literature and clarify how sleep characteristics are associated with brain structures.

Methods: We systematically searched PUBMED, MEDLINE, ProQuest, Web of Science, and Scopus for empirical studies of healthy adults examining the associations between sleep characteristics or disorders and brain structure, adjusting for age, gender, and head size. We conducted a meta-analysis with random effects models for volumetric studies and a seed-based spatial analysis for voxel-based morphometry (VBM) studies.

Results: One hundred and five articles (60 volumetric, 45 VBM) with 106 studies reporting 108,364 participants were included. Most studies (73.1%) found sleep characteristics and disorders to be associated with predominantly lower brain volumes (cross-sectional: 51.9% of all cross-sectional; longitudinal: 45.5% of longitudinal). In VBM studies, REM sleep behaviour disorder was linked to lower grey matter volume in the right frontal gyrus (z -score = -3.617 , 68 voxels, p -value = <0.001).

Conclusion: Sleep characteristics - poor quality, short or long sleep - and sleep disorders are predominantly associated with lower brain volumes, suggesting that inadequate sleep (short, long or poor quality) might contribute to neurodegeneration. This insight highlights the importance of monitoring, managing, and enforcing sleep health to prevent or mitigate potential neurodegenerative processes.

1. Introduction

As the global population ages, the number of individuals over 65 years will reach 1.6 billion by 2050 [1]. This will pose major social, financial, health, and demographic challenges. In particular, cognitive decline and dementia, whose prevalences are projected to double by

2058 [2] will greatly add to the burden of disease. Therefore, preventing and delaying the emergence of these conditions is essential to ensure that limited resources can be adequately distributed. Emerging evidence has suggested sufficient sleep as a potential modifiable risk factor for dementia [3,4]. However, different sleep characteristics show distinct associations with dementia risk. For instance, sleep duration follows a

* Corresponding author. National Centre for Epidemiology and Population Health, Australian National University, 54 Mills Road, Acton ACT (Australian Capital Territory), 2601, Australia.

E-mail address: Tergel.namsrai@anu.edu.au (T. Namsrai).

¹ Co-second author

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U-shaped relationship, with short and long durations associated with an increased risk [4]. In contrast, poor sleep quality and obstructive sleep apnoea (OSA) show a more linear association with an increase in dementia risk. While past research has shown the link between sleep and dementia risk, the extent to which specific sleep characteristics relate to underlying neurodegeneration and ultimately brain structures remain unclear.

Sleep contributes to neurodegeneration and neuronal death through multiple possible mechanisms, many of which converge on pathways involving neuroinflammation and oxidative stress, thus leading to neuronal death. These effects are mediated by sleep's essential roles in maintaining brain homeostasis and regulating immune responses. For example, sleep facilitates the clearance of neurotoxic by-products via the glymphatic system, a paravascular pathway that flushes out debris, misfolded proteins, and cellular waste from the interstitial fluid during sleep [5,6]. When sleep is impaired, the glymphatic waste clearance process could be disrupted, causing the accumulation of amyloid β [7–9] and phosphorylated tau [10–12] (forms neurofibrillary tangles within neurons). Accumulation of amyloid β and phosphorylated tau upregulate the inflammatory response [13,14] and lead to neuronal death and reduced brain volumes [15]. Furthermore, sleep modulates the immune response by interacting with the circadian clock genes [16] and transcription factors [17]. Sleep disruptions, such as short sleep or loss, can dysregulate an immune response by upregulating the production of pro-inflammatory markers [18], including interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and tumour necrosis factor-alpha (TNF-alpha). These cytokines can activate immune response systemically and locally in the brain by passing through the blood-brain barrier. Once in the brain, the pro-inflammatory cytokines may lead to neurodegeneration by priming or activating astrocytes [19] and microglia [20] which exacerbates neuroinflammation, oxidative stress and neuronal death [21]. Interestingly, an increase in pro-inflammatory cytokines, particularly IL-6 may reflect an adaptive physiological process as it increases with physical activity [22] or represent underlying pathogenesis linked to dementia as paradoxically, longer sleep durations have been identified in the clinical progression of dementia [23]. This evidence raises the question of the directionality of effect and reverse causation. Regardless, research findings demonstrate that both short and long-sleepers have lower brain volumes [24,25].

A number of studies have demonstrated an association between sleep disorders and brain changes. For example, insomnia has been linked to lower volumes in the frontal, temporal and cingulate cortices, as well as in the precuneus and thalamus [26,27]. Similarly, OSA has been associated with lower grey matter volume in the cingulate, hippocampus, parahippocampus, orbital frontal cortex and the left cerebellum [28]. However, inconsistent findings on the associations between sleep quality, sleep duration and brain volumes exist. For example, two cross-sectional case-control studies (Winkelman et al.: n = 76; mean age: insomnia = 38.8 (5.3), control = 39.3 (8.7); insomnia duration = unknown; Yu et al.: n = 122; mean age: insomnia = 38.82 (11.4), control = 41.04 (13.77); insomnia duration = 4.9 years) reported that people with insomnia have a larger volume in the rostral anterior cingulate cortex [29] and higher cortical thickness in the left orbital frontal cortex, right rostral anterior cingulate cortex, left middle cingulate cortex, bilateral insula, left superior parietal lobule, and right fusiform area [30]. In contrast, a recent cross-sectional case-control study (n = 113; mean age: insomnia = 39.9 (10.7) control = 39.5 (8.7); insomnia duration = unknown) found lower volume in the right middle cingulate cortex [27] in people with insomnia. The discrepancies observed in the literature could stem from differences in study samples (e.g. sample size, population demographics, sleep disorder severity or duration) or research methods (e.g. sleep disorder severity assessment, brain measure or neuroimaging methods). Furthermore, the complex and multifactorial nature of sleep disorders could stem these inconsistencies in the literature. While insomnia and OSA symptoms are often characterised by short sleep duration or poor quality [31], several demographic (age, sex), medical

(chronic pain, obesity), psychological (anxiety and depression) and socio-demographic factors (noise, living conditions) can contribute to the development of insomnia and OSA in adults. Some of these factors, including depression, anxiety, and obesity, could potentially interact with sleep, amplifying their impact on brain structure and function. This complexity underscores the need to account for such factors when investigating associations between sleep characteristics, disorders, and brain changes.

In addition, differences in widely used brain structure analysis methods, such as volumetric and Voxel-Based Morphometry (VBM) techniques, have been reported. Volumetric techniques segment brain scans to calculate overall or regional volumes without normalising them to a standard space or template. While this method provides relatively precise measurements of brain volume, its focus is on relatively large regions and, therefore, relatively low spatial resolution makes it less sensitive to subtle or diffuse structural differences. In contrast, VBM is a highly standardised technique that allows for voxel-by-voxel comparisons of brain images after normalising them to standardised spatial templates. This enables the detection of subtle, localised differences in brain structure. However, the interpretability of voxel-wise differences in VBM remains limited. Due to these differences in strengths and weaknesses, analysing and interpreting results from these two methods separately but within the same context can help us to draw precise conclusions while ensuring that the unique contributions of each method are kept.

Therefore, while systematically reviewing the associations between sleep characteristics, disorders, and brain volumes, we aimed to address the above-mentioned gaps: 1) the extent to which specific sleep characteristics and disorders contribute to brain volume changes, 2) the directionality of the association, 3) the contribution of demographic factors and 4) the methodological tools.

2. Methods

This systematic review follows the new Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. It is registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42022357562.

2.1. Search strategy and information sources

We formulated the search string based on the PICOS framework and tested its effectiveness through a preliminary search in the PUBMED database (Table S1). This search string was entered into PUBMED, MEDLINE, ProQuest, Web of Science, and Scopus, applying filters for “English” language and “Human” studies on the September 29, 2022.

2.2. Eligibility criteria

2.2.1. Inclusion and exclusion criteria

The inclusion and exclusion criteria detailed in Table S2 required articles to be empirical and involve healthy adult human participants equal to or over 18 years without psychiatric, developmental, mental, or neurological disorders that might affect outcomes. Articles were eligible if they explored associations between sleep characteristics and brain structures or if they examined brain volume differences between individuals with sleep disorders and a healthy population. In addition, all articles must have adjusted for head size, sex, and age or featured participants without significant age or sex disparities.

Articles were excluded if they involved participants younger than 18 years or had fewer than 20 participants due to potential homogeneity, low generalisability, low statistical power, unstable estimates and inflated standard errors in neuroimaging practice [32–34]. Single-night polysomnography-based articles were omitted as they may not accurately represent long-term sleep traits. Furthermore, articles comparing sleep disorder groups only with clinical groups and those not adjusting

for significant age, sex, and head size differences were excluded. Finally, post-mortem, non-peer-reviewed, case reports, theses, and non-English articles were not considered.

2.3. Study selection and screening

We screened using Covidence, a specialised online toolkit for systematic reviews (Veritas Health Innovation). The screening process was conducted in three stages as per previous works: 1) title screening by a single reviewer (TN), 2) abstract screening by two reviewers (TN and another team member: AA, RB, JN, BR, or NC), and 3) full-text screening by two reviewers (TN and another team member: AA, RB, JN, BR, or NC) [35]. Any disagreements during the screening process were resolved by consensus or by consulting a third reviewer (NC or RB).

2.4. Data extraction

We performed double data extraction on the included studies using a pre-developed data extraction sheet (TN with DO, KA, or OA). Discrepancies were resolved through discussion among the reviewers. The data extraction sheet's items are detailed in [Table S3](#).

2.5. Data analysis

We conducted a meta-analysis followed by a narrative synthesis of the included studies, categorising them based on the neuroimaging tools used: volumetric and VBM. In the narrative synthesis, for instance, when we address the sleep characteristics and brain structures, we separated the results from healthy individuals and synthesised them to minimise confounding in cases of clinical studies or epidemiological studies with case and control groups.

2.5.1. Volumetric studies

2.5.1.1. Meta-analyses and meta-regression. We employed a random-effects model with restricted maximum likelihood (REML) estimator [36] to address assumed heterogeneity from diverse sampling and methods among volumetric studies while incorporating the variance of heterogeneity (τ^2) and Knapp-Hartung adjustments [37,38]. The analyses for volumetric studies were conducted with “meta” package in R version 4.4.2.

Initially, meta-analyses of brain structures in healthy populations were conducted, where effect sizes were represented by the mean volume of brain structures ([Fig. S1](#)). Subsequently, comparisons of brain structures between healthy and sleep disorders populations were conducted when data were available in at least three studies. Effect sizes were the raw mean differences (RMD) in brain structures between the healthy and sleep disorder populations. This approach aims to provide insight into the included sample's brain structures and determine whether they are comparable to the general population.

Meta-analyses were also performed to examine associations between sleep characteristics and specific brain regions in at least three studies, with effect sizes derived from correlation coefficients and beta estimates. Meta-regression was used to investigate the influence of age on these relationships when ten or more studies were available [39].

Finally, the same meta-analyses in disorder-specific groups, including insomnia, OSA, REM sleep behaviour disorder (RBD), restless legs syndrome (RLS), and narcolepsy, were used to identify distinct associations.

2.5.1.2. Heterogeneity and bias assessment. Heterogeneity in the volumetric studies was quantified with Cochran's Q statistics [40] and I₂ statistics [41]. Publication bias of volumetric studies was assessed with the “meta” package in R using funnel plots and Egger's regression test, where $p \leq 0.05$ indicates a significant asymmetry and evidence of

publication bias [42]. Furthermore, in cases of significant Egger's test, the trim-and-fill method was used to address potential publication bias to identify and impute any missing studies and calculate corrected effect sizes [43].

2.5.2. VBM studies

2.5.2.1. Meta-analyses and meta-regression. Seed-based D Mapping with permutation of subjects' images (SDM-PSI) software (v 6.22) was used for a coordinate-based random effects meta-analysis of VBM studies as the random-effects model integrated in the SDM-PSI software is designed to account for inter-study variability and reduce risk of bias from study specific features [44]. VBM meta-analyses focused on grey matter volume differences between populations with sleep disorders (including insomnia, OSA, RBD, RLS) and healthy controls [44], given that three or more studies reported similar findings in brain structures between the same sleep disorder and healthy populations ([Fig. S2](#)). We adhered to the default settings for kernel size (20 mm) and statistical thresholding in SDM-PSI with an uncorrected peak height threshold of $p < 0.05$, <0.01 , and <0.001 . Threshold-Free Cluster Enhancement (TFCE) correction ($p < 0.001$) was applied as it is well suited for neuroimaging data when the size and the shape of the signals are unknown [45] while still enabling family-wise error rate (FWER) correction [46].

2.5.2.2. Heterogeneity and bias assessment. Heterogeneity in the VBM studies was quantified with Cochran's Q statistics [40] and I₂ statistics [41]. Publication bias of VBM studies was assessed with a funnel plot and Egger's regression test using SDM-PSI software, where $p < 0.05$ indicates a significant asymmetry. This was followed by an excess significance test to evaluate whether the observed results were excessively large relative to the expected distribution of findings ($p < 0.05$) [47].

2.5.3. Quality assessment

Two reviewers (TN and a team member: DO, KA, or OA) independently rated the quality of included studies using an adapted version of the Newcastle-Ottawa Scale ([Table S4](#)) [48]. The Newcastle-Ottawa Scale was adapted to suit the study designs by merging the case-control and cohort studies' scales into one scale with three sub-categories, including selection, comparability, and outcomes or exposures.

2.5.4. Sensitivity analyses

Given the literature suggests varying effects of sleep at different ages, the influence of age was further investigated in two ways in volumetric studies. First, we conducted a meta-regression to examine the influence of age and sex on the effect sizes when ten or more comparable studies were present. Secondly, we stratified studies by the average age of participants into two groups based on the common ages observed in the included studies to ensure that each subgroup contains enough studies to allow for meaningful comparisons [39] and examine the potential effect of age by comparing the effect sizes and heterogeneity with I² and Q-test [49] across groups. Similarly, in VBM studies, we conducted a meta-regression to examine the influence of age and sex on the effect sizes using mean age and percentage of female population with the SDM-PSI software when ten or more comparable studies were present.

3. Results

3.1. Literature search

The systematic review identified 4273 results. After removing duplicates, 2830 articles were screened ([Fig. 1](#)). Of those, 105 articles met the inclusion criteria, with one reporting two separate studies [29]. Thus, 106 studies reporting on 108,364 participants (sample range, $n = 26$ to 37,553; sleep disorder sample = 3279; mean age 54.8 [SD = 18.0];

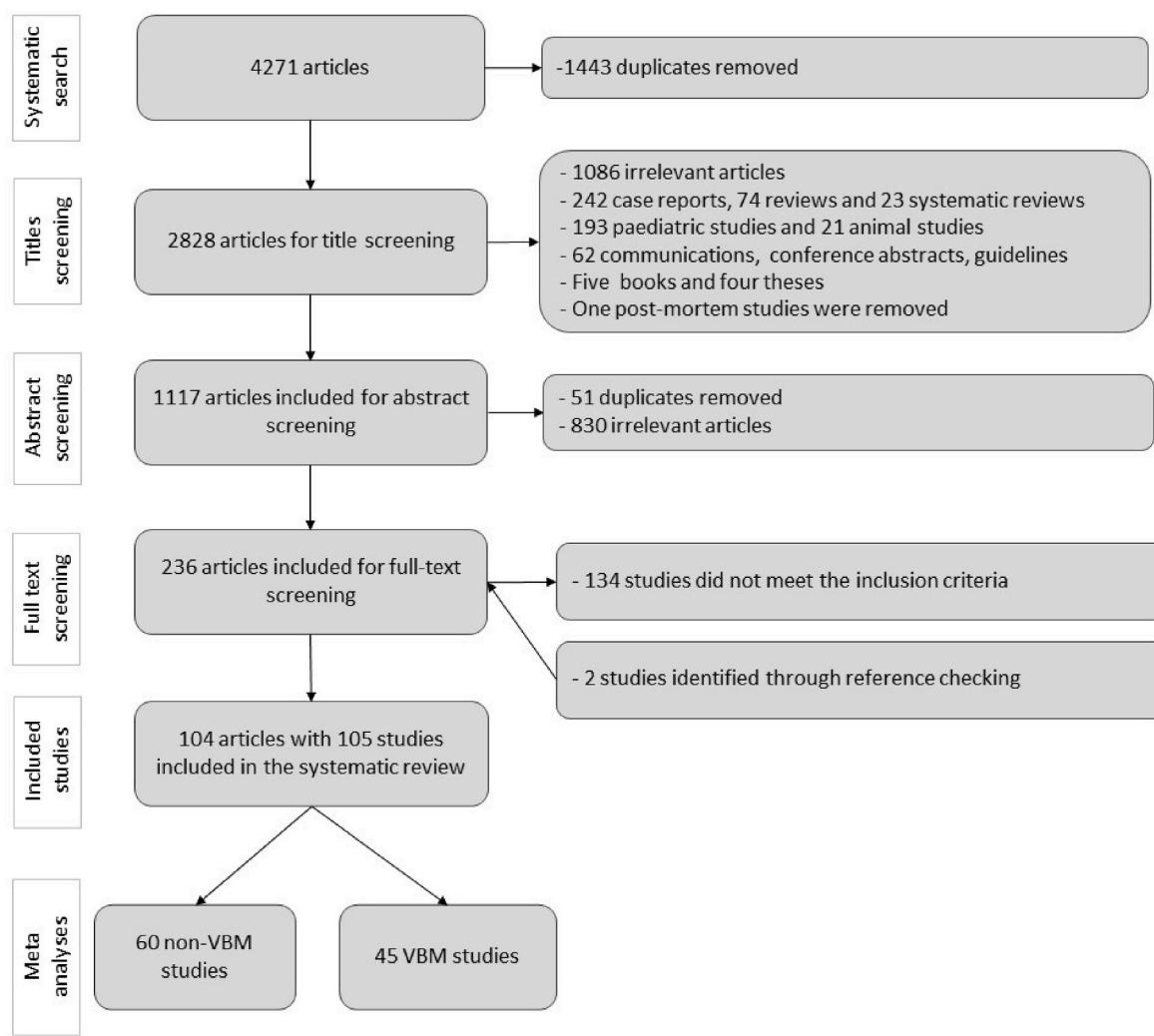


Fig. 1. Study selection flow. This figure shows the study selection flow with the results of the systematic search and excluded studies at each screening stage.

47.7 % male out of 58,454 participants whose sex was known) were included in the review (Table 1).

The included studies used volumetric ($n = 60$) and VBM ($n = 45$)

Table 1
Characteristics of all included studies.

	Volumetric ($n = 60$)	VBM ($n = 45$)	Overall ($n = 105$)
Sleep duration measured			
No	34 (56.7 %)	39 (86.7 %)	73 (69.5 %)
Yes	26 (43.3 %)	6 (13.3 %)	32 (30.5 %)
Sleep quality measured with PSQI			
No	35 (58.3 %)	28 (62.2 %)	63 (60.0 %)
Yes	25 (41.7 %)	17 (37.8 %)	42 (40.0 %)
Sleep disorder status			
No	28 (46.7 %)	10 (22.2 %)	38 (36.2 %)
Yes	32 (53.3 %)	35 (77.8 %)	67 (63.8 %)
Sleep disorders			
Insomnia	14 (23.3 %)	10 (22.2 %)	24 (22.9 %)
RBD	5 (8.3 %)	10 (22.2 %)	15 (14.3 %)
Narcolepsy	2 (3.3 %)	1 (2.2 %)	3 (2.9 %)
RLS	1 (1.7 %)	7 (15.6 %)	8 (7.6 %)
OSA	10 (9.5 %)	7 (6.7 %)	15 (14.3 %)
Newcastle-Ottawa Scale			
Fair	8 (13.3 %)	6 (13.3 %)	14 (13.3 %)
Good	52 (86.7 %)	39 (86.7 %)	91 (86.7 %)
VBM- Voxel-based morphometry studies; PSQI- Pittsburgh Sleep Quality Index; RBD- REM sleep behaviour sleep disorder; RLS- Restless legs syndrome; OSA- obstructive sleep apnoea			

methods (Table S5). Eleven were longitudinal, with a follow-up from 2 months to 9 years (volumetric = 8; VBM = 3). The eight longitudinal volumetric studies focused on sleep characteristics and included epidemiological populations, while the three longitudinal VBM studies included clinical populations with OSA [50], narcolepsy [51] and insomnia [52].

The remaining 94 studies were cross-sectional (volumetric = 52; VBM = 42). Twenty-six cross-sectional volumetric studies focused on epidemiological populations (sleep characteristics = 20; sleep disorders = 6), while the remaining 26 focused on clinical populations with sleep disorders healthy controls. Fourteen cross-sectional VBM studies focused on epidemiological populations (sleep characteristics = 10; sleep disorders = 4), while the remaining 28 focused on clinical populations with sleep disorders and healthy controls.

3.2. Quality assessment

The mean Newcastle-Ottawa Scale score was 5.02 [SD = 0.768] out of 6. Overall, most studies were of good ($n = 91$, 85.8 %) or fair quality ($n = 14$, 14.2 %) (Table S5).

3.3. Overall sleep characteristics and brain structure in the included studies

Fig. 2 shows that most studies ($n = 83$, 73.1 %) found significantly



Fig. 2. Associations between sleep characteristics, disorders, and brain structure include volumetric and VBM studies. As meta-analysis was not feasible. To supplement the current understanding of sleep and brain structures, this figure shows only the significant effect sizes of associations between sleep characteristics, disorders and brain structures for each study grouped by brain regions. The number of studies is on the y-axis, and the brain regions are on the x-axis. The light pink depicts cross-sectional studies with negative associations, while bright pink shows longitudinal negative results. Orange shows mixed results, while green shows positive associations. AV- Amygdala volume, CC- Cingulate cortex and rostral anterior cingulate cortex volume, CTh- any studies with global or regional cortex thickness, Cb- cerebellum, ETC- entorhinal cortex thickness, GMV- any studies with global or regional grey matter volumes, HV- hippocampus volume, Lobes- any studies with lobular volumes, PuV- Putamen volume, WMH- any studies with white matter hyperintensity or lesion volumes, WMV- any studies with global or regional white matter volumes, Others- include regional volumes including pineal gland, olfactory bulb, sulci and gyri. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.) As meta-analysis was not feasible. To supplement the current understanding of sleep and brain structures, this figure shows only the significant effect sizes of associations between sleep characteristics, disorders and brain structures for each study grouped by brain regions. The number of studies is on the y-axis, and the brain regions are on the x-axis. The light pink depicts cross-sectional studies with negative associations, while bright pink shows longitudinal negative results. Orange shows mixed results, while green shows positive associations. AV- Amygdala volume, CC- Cingulate cortex and rostral anterior cingulate cortex volume, CTh- any studies with global or regional cortex thickness, Cb- cerebellum, ETC- entorhinal cortex thickness, GMV- any studies with global or regional grey matter volumes, HV- hippocampus volume, Lobes- any studies with lobular volumes, PuV- Putamen volume, WMH- any studies with white matter hyperintensity or lesion volumes, WMV- any studies with global or regional white matter volumes, Others- include regional volumes including pineal gland, olfactory bulb, sulci and gyri. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

poorer sleep characteristics and disorders linked to lower brain volumes ($n = 55$ or 58.5 % of cross-sectional; $n = 5$ or 45.5 % of longitudinal). Conversely, 13 studies (12.3 %) found poorer sleep characteristics and disorders were associated with higher brain volumes, while 7.6 % reported ($n = 7$) mixed findings dependent on the brain regions.

3.4. Results of the volumetric studies

3.4.1. Meta-analyses and meta-regression of sleep characteristics and brain structures

Volumetric studies reported the volumes of the intracranial (ICV), total brain (TBV), grey matter (GMV), white matter (WMV), hippocampus (total, right and left hippocampus; THC, RHC, and LHC), thalamus (RTV and LTV), putamen (RPV and LPV), pineal gland, and ventricles (Table S6). Meta-analyses of available mean total and regional brain volumes are illustrated in Fig. 3. The pooled mean volume of ICV was 1395.4 [1297.3; 1493.6], and the TBV was 1289.7 [243.5; 2335.8]. The GMV was 616.2 [399.9; 832.6], while the WMV was 499.4 [366.2; 632.6]. The THC was 7.9 [7.2; 8.6], with RHC measuring 3.7 [3.4; 4.1] and the LHC measuring 3.7 [3.3; 4.0]. The RTV was 6.5 [3.9; 9.1], and the LTV was 6.5 [3.6; 9.3]. The RPT was 4.1 [2.9; 5.3], and the LPT was 4.1 [2.7; 5.4].

No significant differences in brain volumes were observed between healthy individuals and those with sleep disorders (Fig. 4). The ICV had an RMD of 80.1 (95 % CI = [-47.8, 208], $p = 0.2$). For hippocampal volumes, the THC had an RMD of 0.09 (95 % CI = [-1.1, 1.3], $p = 0.8$), the LHC had an RMD of 0.08 (95 % CI = [-0.03, 0.19], $p = 0.1$), and the

RHC had an RMD of 0.09 (95 % CI = [-0.01, 0.2], $p = 0.08$). The LTV had an RMD of 0.44 (95 % CI = [-0.5, 1.4], $p = 0.3$), and the RTV had an RMD of 0.50 (95 % CI = [-0.8, 1.8], $p = 0.3$). The LPV had an RMD of 0.04 (95 % CI = [-0.2, 0.3], $p = 0.7$), and the RPT had an RMD of 0.04 (95 % CI = [-0.3, 0.3], $p = 0.7$).

Although meta-analyses of correlation coefficients and beta estimates between sleep characteristics and brain structures were not conducted due to insufficient comparable data from at least three studies, a narrative synthesis of descriptive results from individual studies suggests a potential inverted U-shaped or negative association between sleep duration and regional brain volumes, as well as a negative association between sleep quality and brain volumes.

Of the nine volumetric studies performing regression analyses between sleep duration and brain structures [24,25,53–59], four studies consisting of one longitudinal [54] and three cross-sectional [24,25,59] found inverted U-shaped relationships (100 % statistically significant at 0.05 level, effects sizes = 0.4 %–2.5 % lower). Two studies, one longitudinal [55] and one cross-sectional [53], found negative associations (100 % statistically significant at 0.05 level, effect sizes = 0.02 %–0.4 %). Two studies, a longitudinal [56] and a cross-sectional [58], found positive relationships. Still, they indicated increased brain lesions or atrophic changes, including increased ventricles and white matter hyperintensities (100 % statistically significant at 0.05 level, effect sizes = 0.4 % annual to not applicable) [56,58]. The remaining one has reported not significant association without the estimates [57]. The significantly lower volumes with an inverted U-shaped relationship with sleep duration included total grey matter, white matter, right and left

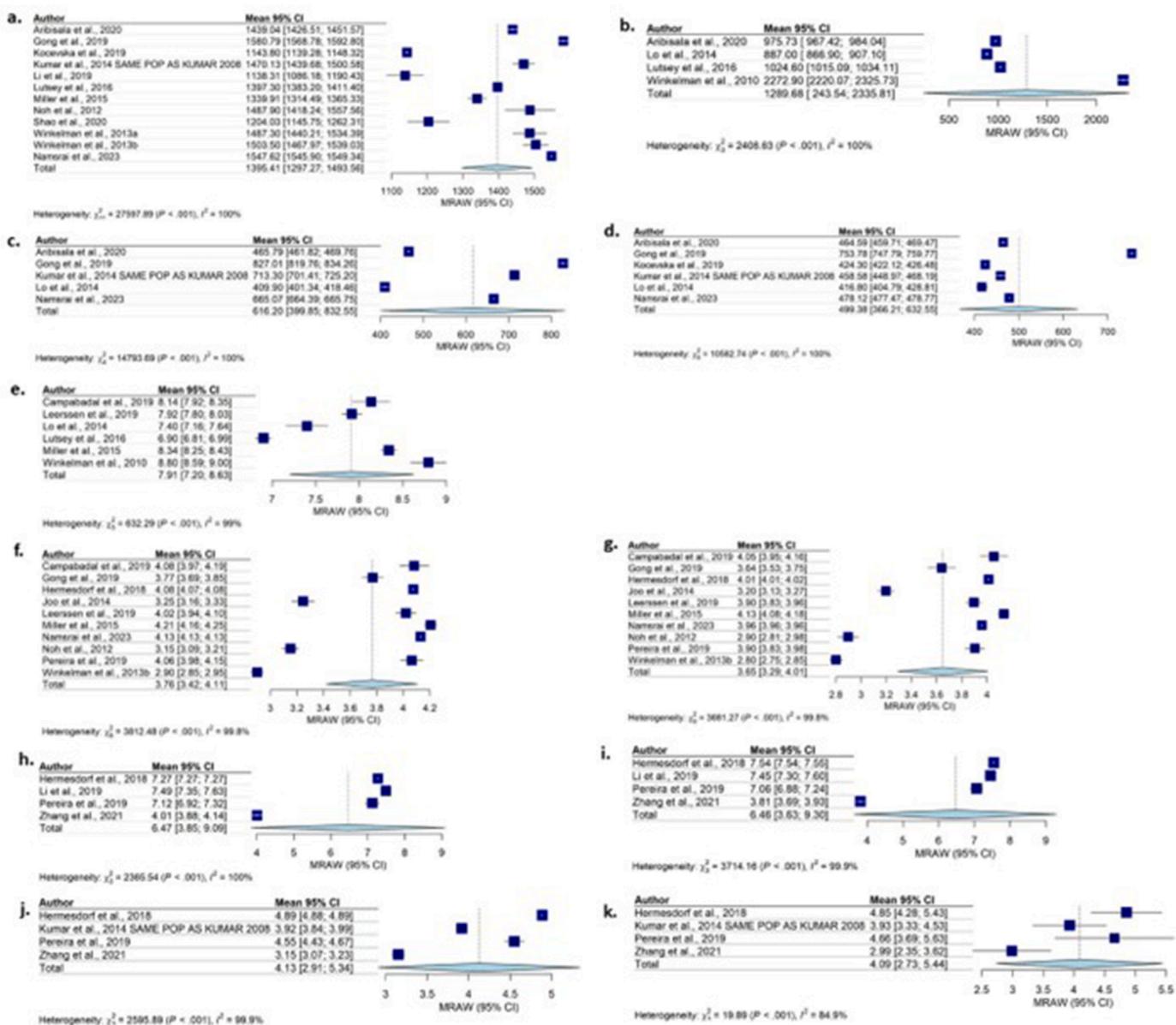


Fig. 3. Meta-analyses of brain structures (effect size is the mean volume in ml) in volumetric studies. a) pooled mean of total mean intracranial volume (ICV), b) pooled mean of total brain volume (TBV), c) pooled mean of total grey matter volume (GMV), d) pooled mean of total white matter volume (WMV), e) pooled mean of total hippocampus volume (THV), f) pooled mean of the right hippocampus volume (RHC), g) pooled mean of the left hippocampus volume (LHC), h) pooled mean of the right thalamus volume (RTV), i) pooled mean of the left thalamus volume (LTV), j) pooled mean of the right putamen volume (RPT), k) pooled mean of the left putamen volume (LPV).

hippocampus and hippocampal subregions, and 46 other regions and increased atrophic changes such as expansion of ventricles and higher volumes of white matter hyperintensities, [24,25,53,54,56,58,59]. Fig. 3 presents the regression estimates from these studies, standardised as a percentage of the relevant brain volumes.

Of the six studies that investigated the association between sleep quality (PSQI) and brain volumes [53,55,56,60–62], three studies reported negative associations (66.6 % significant at 0.05 level, effect sizes = 0.11 % to not applicable) [53,61,62]. Two studies, both longitudinal, found positive associations (0 % significance at 0.05 level) [55, 56]. The remaining study found no significant association without reporting the effect size [60]. The significantly lower brain structure linked to poorer sleep was entorhinal cortex thickness [62]. The regression estimates (beta values) from studies with regressions between sleep quality and brain volumes were standardised relative to the relevant brain volumes and are depicted in Fig. 3 to highlight the trend of

the relationship between sleep quality and brain structure.

All three studies with correlation analyses between sleep quality (PSQI) and brain structures [63–65] reported negative correlations as poor sleep quality (higher PSQI) was linked to lower brain volumes. Of these three, one longitudinal study reported a significant correlation between PSQI right posterior cingulate volumes over two years ($r = -0.5$, p-FDR = 0.02) [64].

Similar to the meta-analyses of associations, the criterion of having ten or more studies for meta-regression analyses was not met. Therefore, it was not conducted.

3.4.2. Sleep disorders and brain structures

3.4.2.1. Insomnia. One clinical [65] and one epidemiological population studies [66] tested the associations between insomnia duration, insomnia severity index (ISI) and several brain regions. Increased

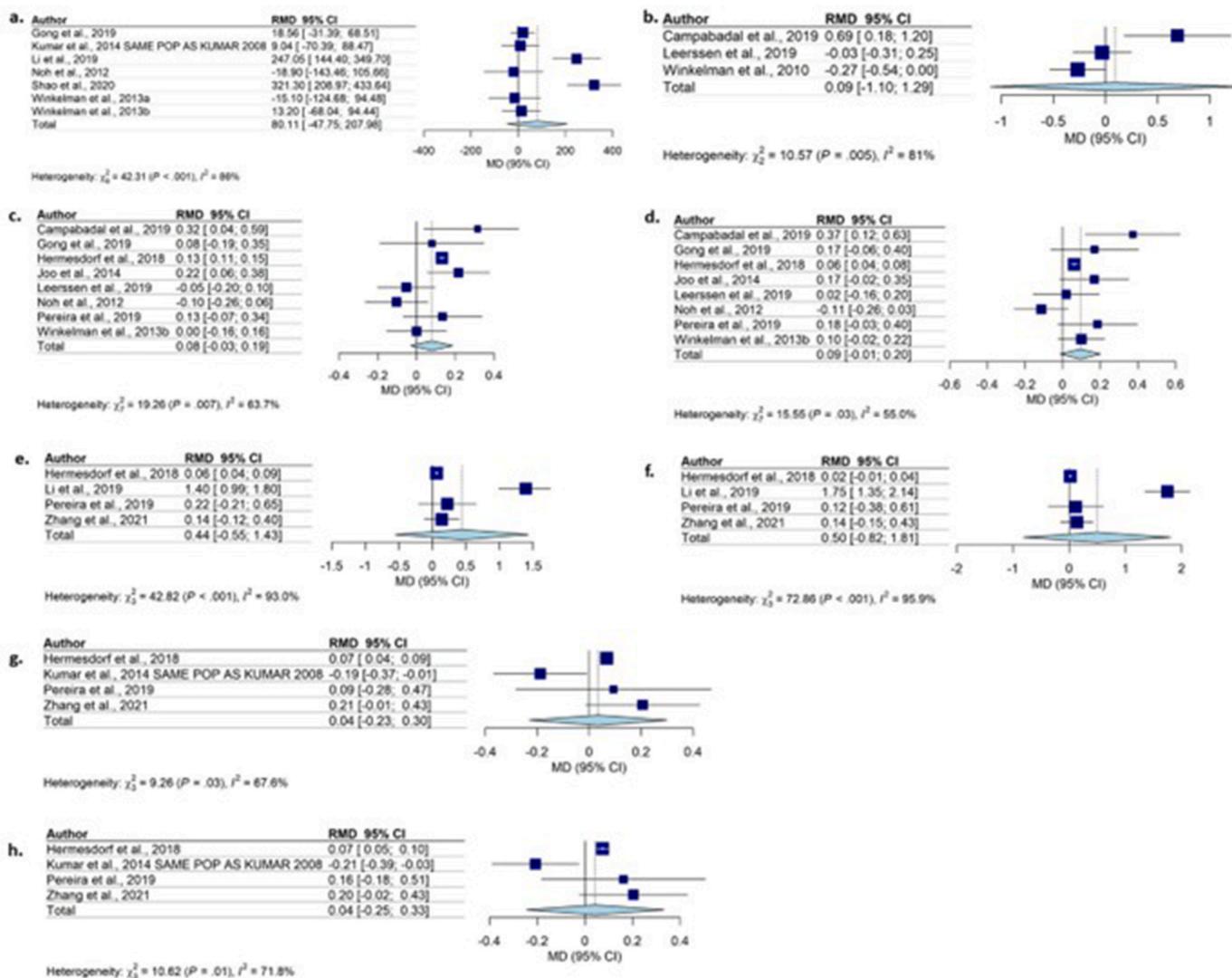


Fig. 4. The meta-analyses of the raw mean difference (RMD) in brain structures (ml) between sleep disorder and healthy population. a) RMD in ICV, b) RMD in THV, c) RMD in LHC, d) RMD in RHC, e) RMD in LTV, f) RMD in RTV, g) RMD in LPV, h) RMD in RPV.

disease duration of insomnia was associated with lower volume in the bilateral hippocampus [65], while greater severity of insomnia correlated with increased volumes in the bilateral putamen among patients with insomnia [66].

Furthermore, eight clinical and one epidemiological volumetric study [66] tested associations between PSQI, insomnia duration, severity, SOL, WASO and brain structures. Six of those found significant correlations between poorer sleep quality, higher insomnia duration and lower hippocampal volumes [65,67]; higher insomnia severity index and cortical thinning in the right orbitofrontal, right superior and caudal middle frontal areas, right temporo-parietal junction and left anterior cingulate cortex [66]; higher WASO and higher SE with increased hippocampus volumes [68]; and higher SOL with higher right anterior cingulate cortex volumes [29]. The correlation values are plotted in Fig. 5.

3.4.2.2. Obstructive sleep apnoea (OSA). Two population [24,69] and seven clinical studies investigated OSA [63,70–75]. Of those, three clinical studies reported ESS [63,71,75]. The OSA population had an 8.2 higher ESS score than controls ($n = 227$; 95 % CI = 0.735; 15.749), indicating higher daytime sleepiness in this population.

Two population [24,69] and one clinical study [63], tested

associations between sleep characteristics and brain structures in people with OSA. Two of them found significant associations between lower oxygen saturation during OSA/sleep characteristics and increased loss of global putamen volume [63]; and negative quadratic relationship between sleep duration and frontal, temporal, cingulate and total grey matter volumes in men with sleep [24]. However, one study found no association between OSA severity and white matter hyperintensity [69].

3.4.2.3. REM sleep behaviour disorder (RBD), restless legs syndrome (RLS) and narcolepsy. Five non-VBM studies investigated RBD in the clinical population [76–80]. Of those, two studies found higher volumes in patients with RBD in the right inferior temporal, the left putamen, the right nucleus caudate and the cerebellum [76,78], while one found lower volumes in the right caudate nucleus than in healthy controls [80]. The other two studies found cortical thinning in the left superior parietal, post-central, fusiform, and occipital regions compared to controls [77,79].

One non-VBM study investigated RLS in the general sample and found no difference [78].

Two non-VBM studies investigated narcolepsy in the clinical population [81,82]. They found increased gyration in the left inferior temporal gyrus, right anterior cingulate cortex [81] and cortical

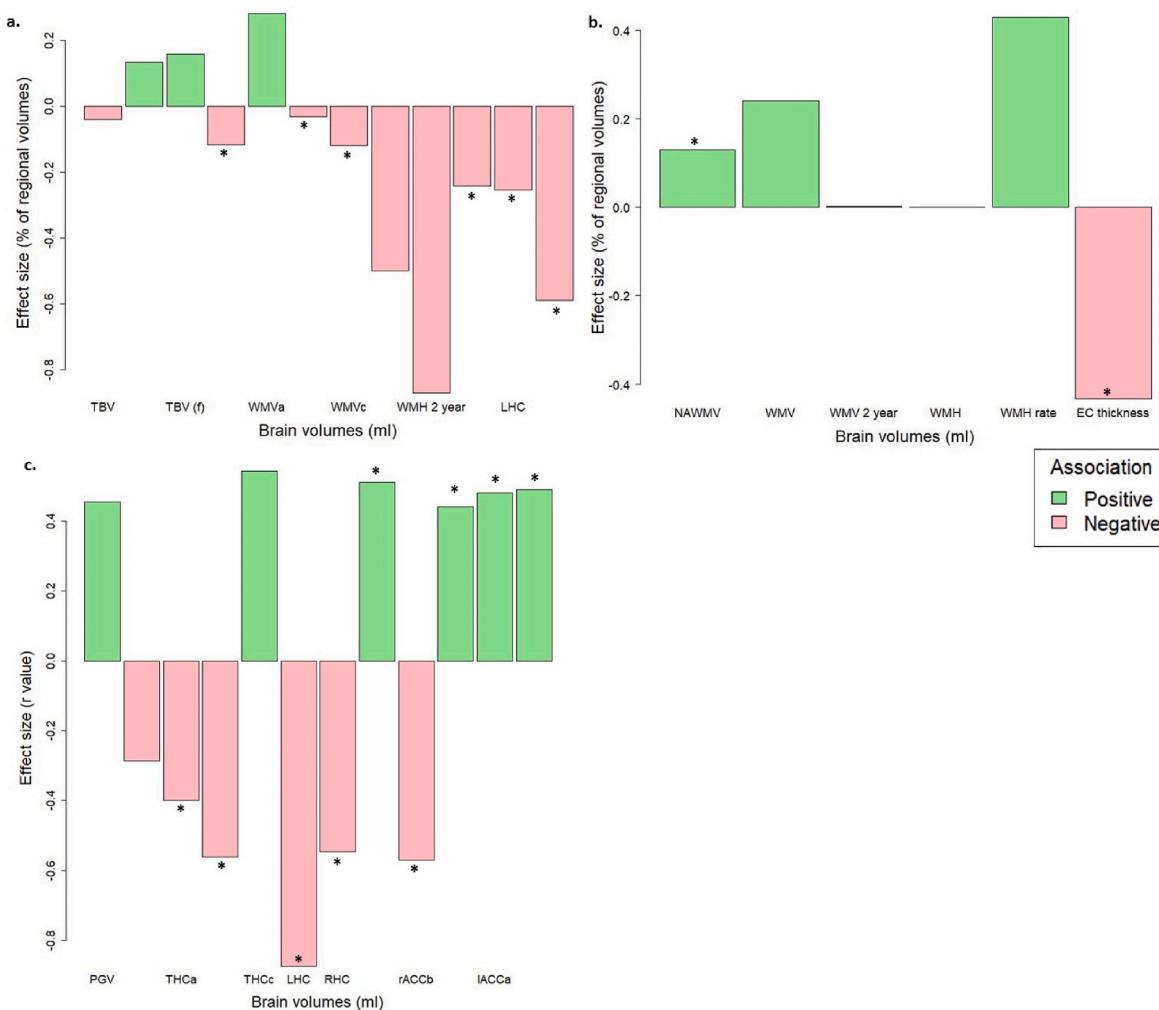


Fig. 5. Individual regression and correlation results of volumetric studies (effect sizes as percent of relevant brain regions) between a) regression sleep duration and brain structures and b) regression sleep quality and brain structures c) correlation between insomnia measures and brain structures; TBV- total brain volume; WMV- white matter volume; m-male; f-female; a-study 1, b-study 2; c-study 3; WMH- white matter hyperintensity volume; RHC- right hippocampus volume; LHC- left hippocampus volume; Vent 2 year – ventricular expansion or atrophic changes at 2 year; NAWMV- normal appearing white matter volume; EC thickness-entorhinal cortex thickness; pineal gland volume; RAmyg-right amygdala volume; THC- total hippocampus volume; rACC-rostral anterior cingulate cortex; IACC-left anterior cingulate cortex; *- p-value <0.05.

thinning in orbitofrontal gyri, dorsolateral and medial prefrontal cortices, insula, cingulate gyri, middle and inferior temporal gyri, and inferior parietal lobule of the right and left hemispheres [82].

3.4.3. Heterogeneity and risk of bias

Evidence of between-study heterogeneity was observed in all five analyses investigated, including RMDs of 1) PSQI ($\tau^2 = 5.8$; Q-test = 94, p-value <0.0001; $I^2 = 90.4\%$), 2) ESS between sleep disorder and healthy populations ($\tau^2 = 16.2$; Q-test = 285.4, p-value <0.0001; $I^2 = 98.2\%$), 3) sleep duration ($\tau^2 = 0.5$; Q-test = 32.8, p-value <0.0001; $I^2 = 87.8\%$), 4) PSQI between insomnia and healthy populations ($\tau^2 = 19.8$; Q-test = 1864.1, p-value <0.0001; $I^2 = 99.5\%$), and 5) ESS between OSA and healthy populations ($\tau^2 = 8.5$; Q-test = 30.8, p-value <0.0001; $I^2 = 93.5\%$). Furthermore, in all five analyses, the funnel plots were notably asymmetrical (Fig. S3), and Egger's test revealed a small-study effect bias in two analyses: 1) RMD in PSQI between healthy and sleep disorder populations (t -test = 3, p-value = 0.02) and 2) RMD in PSQI between insomnia and healthy populations (t -test = 27, p-value <0.001). Trim-and-fill method did not impute additional studies in both analyses, possibly due to the small number of studies ($n = 6$ and 5) [83] and high heterogeneity in both analyses [84].

3.5. Results of VBM studies

3.5.1. Sleep characteristics and brain structures

One of the VBM studies investigated and reported a significant association between sleep duration and lower white matter volume in the left precentral gyrus ($t = -3.4$, p-value <0.01) and in the left inferior parietal lobule ($t = -3.8$, p-value <0.01) [85].

Three VBM studies conducted regression between sleep quality (PSQI) and brain structures, and all reported negative associations between poor sleep and the thickness and volume of brain regions [85–87]. Of these three, two reported significant associations between poor sleep and smaller GMV in the right parahippocampus gyrus in women (MNI: 33, -15, -32, $t = 4.9$, p-value = 0.02, whole brain FWE-corrected) [87] and white matter volume in the right middle occipital gyrus, right postcentral gyrus, left inferior parietal lobule and left middle frontal gyrus (t range = -3.33 to -4, p-value <0.01) [85].

Three of the VBM studies investigated the correlation between sleep quality and brain structures, and all reported negative correlations [85, 88, 89]. The two of these studies reported significant correlations between poor sleep and lower white matter volume in the right middle occipital gyrus, the left superior temporal gyrus, the right precentral

gyrus, the left supramarginal gyrus, the left middle frontal gyrus, the left precuneus, and the right superior frontal gyrus (t range = −3.3 to −4.7, p -value <0.01) [85] and lower cortex thickness in the left superior temporal sulcus (r = −0.4, P < 0.001) [89].

3.5.2. Sleep disorders and brain structures

3.5.2.1. Insomnia. Ten studies investigated brain structures via VBM methods between people with insomnia and controls. Of these, eight were derived from clinical [27,30,90–95] and two from epidemiological populations [26,52]. Six of these studies have complete data on VBM results of brain structures' differences between healthy and insomnia populations (n = 824), as shown in Table S7. Thus, they were meta-analysed. The insomnia population showed lower grey matter volume in the right superior frontal gyrus (medial orbital), right inferior frontal gyrus (opercular part), cerebellum (vermis lobule IV/V), temporopolar area, left inferior frontal gyrus (triangular part), right superior frontal gyrus (dorsolateral), right superior temporal gyrus, left inferior frontal gyrus (triangular part), left anterior cingulate/paracingulate gyri, and right insula compared to healthy population at uncorrected p -value <0.05 (Fig. S4a). The right superior frontal gyrus (medial orbital), right inferior frontal gyrus (opercular part), cerebellum (vermis lobule IV/V), temporopolar area and left inferior frontal gyrus

(triangular part) survived at an uncorrected p -value <0.01 (Figure S4b). None of the ten regions survived the correction at uncorrected p -value <0.001 and TFCE correction (Table S8).

3.5.2.2. Obstructive sleep apnoea (OSA). Six VBM studies, five from the clinical [50,96–99] and one from the epidemiological population [100], investigated brain structures via VBM methods between people with OSA and controls. Three of these studies [50,97,99] have complete VBM results in both OSA and healthy populations (n = 55), as shown in Table S9; thus, they were meta-analysed. At uncorrected p -value <0.05, there were no significant differences in grey matter volume between the OSA and healthy population. But two of the VBM studies included in the meta-analyses reported altered brain structures, including lower grey matter volume in the right dorsal lateral prefrontal cortex (DLPFC), the right occipital pole, the vermis [99] and higher grey matter volume in the brainstem regions (Lundblad et al., 2014) while one did not find a difference in grey matter or white matter volume between people with OSA and controls [50].

3.5.2.3. REM sleep behaviour disorder (RBD). Ten VBM studies with clinical populations investigated brain structures in patients with RBD and controls [101–110]. Five of these studies have complete VBM results

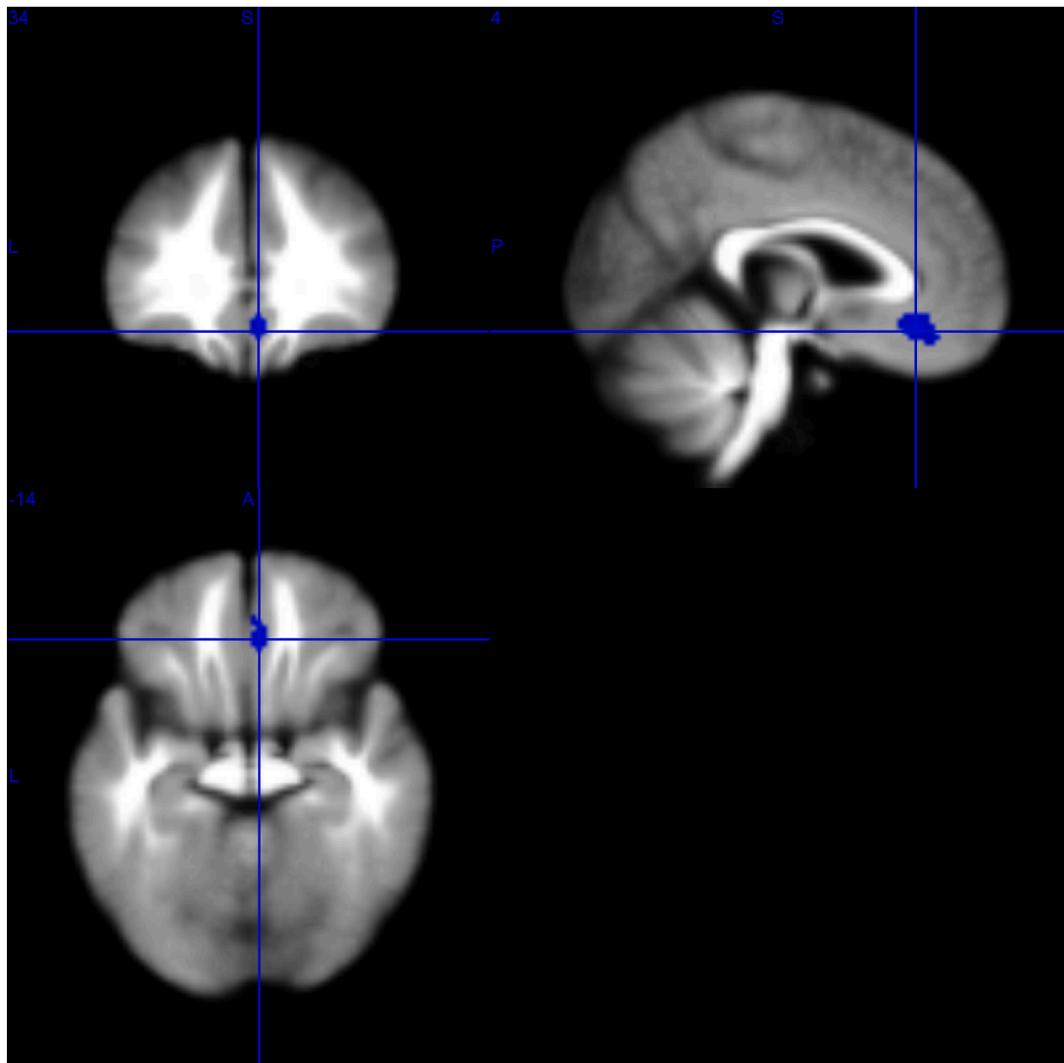


Fig. 6. VBM meta-analysis of GMV difference between RBD and healthy population. XYZ coordinates- 4, 34, −14 showing right superior frontal gyrus (medial orbital); blue-decreased GMV in RBD; TFCE corrected p -value<0.001. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

($n = 286$), shown in Table S10. Thus, they were meta-analysed. The detailed results of the grey matter volume difference between patients with RDB and controls at uncorrected p-values <0.05 , <0.01 and <0.001 are shown in Table S11 and Fig. S5. After correction, the people with RBD had lower grey matter volume in the right superior frontal gyrus (medial orbital) than the controls, as shown in Fig. 6.

3.5.2.4. Restless legs syndrome (RLS). Six VBM studies with clinical [111–116] and one with epidemiological populations [117] investigated brain structures in RLS and healthy populations. Three of these studies had complete VBM results in both RLS and healthy populations ($n = 284$), shown in Table S12. Thus, they were meta-analysed. At uncorrected p-value <0.05 , there were no significant differences in grey matter volume between the RLS and healthy population. Despite not finding significant differences, all three studies found altered brain volumes, including higher grey matter volume in the left putamen [116], loss of white matter volume next to the post and precentral gyrus [114], and lower grey matter in the right thalamus, right middle temporal gyrus, right anterior cingulate gyrus, and left insula [115] in the RLS population.

3.5.3. Heterogeneity and risk of bias

Evidence of between-study heterogeneity in studies investigating the RBD was low ($\tau^2 = 0.004$; Q-test = 0.9, p-value = 0.9; $I^2 = 3.2\%$). The funnel plot of VBM studies investigating RBD was asymmetric (Fig. S6). However, Egger's test results did not prove a small study effect ($t = 1.8$; p-value = 0.7) and consistently, the excess significance test indicated that the meta-analysis' result was not too large compared to the expected number (excess significance test p-value = 0.4).

3.6. Sensitivity analyses

Subgroup analyses stratified by age (<50 and ≥ 50 years) could only be conducted for studies investigating the mean difference in RHC and LHC (Table 2). No significant differences in RHC and LHC volumes were detected between healthy and sleep disorder groups in young or middle-aged adults. However, lower heterogeneity was observed in the younger compared to the middle-aged group. In addition, there was no significant difference in age variances between the two groups (F -test = 4.2, $p = 1.85$; 95 % CI = [0.05, 19.74]). An insufficient number of suitable studies were available to conduct stratified analyses in VBM studies.

Table 2

Subgroup analysis in bilateral hippocampus volumes' mean difference between healthy and sleep disorder groups in young and middle-aged adults (<50 and ≥ 50).

ROI	Age group	Number of studies (k), observations (n) (case: control)	Mean difference in volume (ml, 95 % CI)	I^2 (%)	Q-test (df, p-value)
RHC	<50	k = 3; n = 291 (150; 141)	0.09 (-0.06, 0.24)	0.0 %	1.10 (df = 2, p = 0.58)
	≥ 50	k = 5; n = 374 (236; 138)	0.11 (-0.10, 0.33)	71.8 %	14.17 (df = 4, p = 0.007)
LHC	<50	k = 3; n = 291 (150; 141)	-0.01 (-0.15, 0.12)	0.0 %	0.75 (df = 2, p = 0.69)
	≥ 50	k = 5; n = 374 (236; 138)	0.12 (-0.06, 0.30)	63.3 %	10.89 (df = 4, p = 0.03)

ROI- a region of interest; RHC- right hippocampus; LHC- left hippocampus; I^2 - heterogeneity within each subgroup; Q-test - heterogeneity across studies within subgroups; *- p-value significant at < 0.05 .

3.7. Longitudinal studies: volumetric and VBM

Eleven longitudinal studies were included in the review [50–52, 55–57, 118–122]. Five longitudinal studies tested the associations between sleep duration and brain structures [55–57, 121, 122]. Of these, three studies found significant changes in brain lesions and atrophy. These include longer sleepers had decreased white matter lesions [55], shorter sleep predicted increased annual ventricular expansion rate [56], and shorter sleepers had increased cortical thickness in the superior temporal sulcus, superior temporal gyrus, inferior frontal gyrus, middle frontal gyrus, superior frontal sulcus of the left hemisphere, and in the superior frontal gyrus of the right hemisphere while longer sleepers had higher rates of thinning in the superior frontal and middle frontal gyrus of the left hemisphere [122].

Five longitudinal studies examined the relationship between sleep quality and brain structures [55, 56, 118, 120, 121]. Three of these studies found poorer sleep quality to be linked to brain atrophy indices, including faster cortical thinning in the right lateral temporal cortex [118]; faster volume loss in regions in the lateral frontal, temporal, parietal, medial superior frontal cortex, caudal, rostral cingulate, precuneus and isthmus cingulate in the left hemisphere and lateral and medial frontal cortex, extending to the rostral anterior cingulate, temporal cortex in the right hemisphere [121] and faster hippocampal volume loss [120].

Three longitudinal studies investigated the association between sleep disorders (OSA [50], narcolepsy [51] and insomnia [93]) and brain structures. All three studies found significant brain atrophic changes in people with sleep disorders. Healthy controls had higher white matter volume in the right occipital lingual gyrus and the left middle occipital gyrus compared to people with OSA [50]. In people with narcolepsy, there was progressive cortical thinning in superior/middle/inferior frontal, precentral, postcentral, insular, medial orbitofrontal, superior temporal, parietal, parahippocampal, lingual, fusiform, temporal polar, and anterior cingulate cortices compared to healthy controls [51]. There was significant cortical thinning in the left medial frontal cortex, bilateral precentral cortices, prefrontal gyrus, postcentral gyrus, precentral gyrus, middle frontal gyrus, anterior cingulate gyrus, post-central gyrus, and hippocampus in people with primary insomnia compared to healthy controls [52].

4. Discussion

This systematic review presents an important synthesis of the current evidence on the relationship between sleep characteristics, sleep disorders and brain structures. The key findings were that 1) most studies (73%) reported negative associations between characteristics indicative of poor sleep (e.g., short/long, poor, disturbed, lower efficiency sleep or sleepiness) and lower brain volumes/thickness including both volumetric and VBM studies and 2) a lower grey matter volume in the right superior frontal gyrus in individuals with RBD compared to controls in the VBM studies.

A striking finding is that most studies (78%) found that both longer and shorter sleep durations were associated with neurodegenerative changes, including lower volume in several brain structures (total grey and white matter, left and right hippocampi, as well as another 46 regions), expansion of ventricles and higher volume of white matter hyperintensities. Similarly, half of the volumetric studies investigating sleep quality found poor sleep quality to be associated with lower brain volumes in the white matter and entorhinal cortex [53, 62], the right hippocampus and the right posterior cingulate, including a longitudinal study [120].

The findings suggest that the right superior frontal gyrus could be particularly vulnerable to sleep disorders. Consistent findings were identified in other clinical populations, including OSA [123], insomnia [90, 91], and narcolepsy [71, 82]. This converging evidence suggests a shared vulnerability of this region across different sleep disorders. Since

common features of these disorders are poor sleep quality and shorter sleep duration, the underlying mechanisms are likely to include impaired glymphatic function and less effective clearance of neurotoxic substances, such as β -amyloid and tau, resulting in oxidative stress, neuroinflammation, glial activation, and compromised blood-brain barrier. Individually and in combination these mechanisms are known to lead to neuronal body damage, axonal degeneration, dendritic pruning, and synaptic dysfunction, ultimately resulting in neuronal death or Wallerian degeneration (loss of white matter), and reductions in brain volume. The reason for the specific vulnerability of the SFG observed in this study is not completely clear. The SFG is a region implicated in AD amyloid pathway [124], although typically at the more intermediate stages of the disease, and therefore it is possible that sleep disturbances are preferentially associated with increased amyloid plaque deposition. A plausible hypothesis is that the glymphatic system may be less efficient in some cortical regions, such as the SFG, due to differences in vascularisation, or other morphological and physiological features, thus making them more vulnerable to sleep-related neurodegeneration.

Identifying the SFG as a potential region vulnerable to neurodegeneration associated with sleep disorders has important implications for cognitive function. SFG is instrumental in emotional regulation [125, 126], language processing [127], and working memory [128]. Consequently, damage to this region may increase susceptibility to a range of deficits in emotional control, language skills, and memory, as well as a greater risk of mood disorders (e.g., depression, anxiety and bipolar disorders), and cognitive decline. Indeed, the evidence suggests that premature neurodegeneration in SFG is associated with earlier dementia onset and progression [129]. However, further research is required to establish causal relationships and confirm the present findings. Longitudinal studies examining the interplay between sleep quality, brain regions, and cognitive outcomes are particularly needed to develop effective preventive strategies against cognitive decline and dementia.

The present study found no significant difference in GMV between individuals with insomnia, OSA, and RLS and those with normal sleep in VBM studies. These no significant findings may be attributable to small sample sizes, which may not have allowed detection of these effects. Indeed, 55 people were included in the VBM meta-analyses of OSA studies, which could be insufficient to detect any significant differences in brain structures. Alternatively, sampling differences could attribute to the negative findings. This is true in insomnia studies utilising VBM methods, as they recruited different cohorts with various age ranges, including people in their mid-thirties, forties, and fifties with either chronic or acute insomnia diagnosed with different clinical criteria, were included, which are known to have an impact on the brain structure. Similarly, the three RLS studies using VBM methods recruited RLS patients at varying disease durations, which may capture brain structural changes at subtle or more severe stages, leading to insufficient data to capture significant brain changes.

It is also important to note that the lack of difference in GMV between individuals with insomnia, OSA, and RLS and those with normal sleep in VBM studies could be due to the brain's predisposition to structural changes. The idea of predisposition was illustrated in the study by Grau-Rivera and colleagues, which indicated that APOE- ϵ 4 carriers with insomnia have lower GMV than people without the APOE gene [26].

Some trends ($p < 0.01$) which did not survive the TFCE correction are also noteworthy as they related to brain region known to be involved in higher cognitive function and sensory processing. In particular, volumes in the right superior frontal gyrus (medial orbital), right inferior frontal gyrus (opercular part), left inferior frontal gyrus (triangular part), cerebellum (vermis lobule IV/V), and temporal pole were found to be lower in individuals with insomnia compared to healthy controls. The superior and inferior frontal gyri support executive function [130], learning, processing and generation of language [131], and inhibition or cognitive control [132]; the cerebellar vermis (lobule IV/V) aids social

cognition or social brain network [133]; and the temporal pole contributes to semantic memory, social cognition, and emotional processing [134]. In addition, these areas have been implicated in Alzheimer's disease and mild cognitive impairment. For instance, recent multi-modal analyses from functional and structural MRI identified the superior frontal gyrus as a key region of structural change in Alzheimer's disease and mild cognitive impairment [135]. Moreover, the temporal poles are particularly affected in frontotemporal dementia and are linked to its semantic symptoms [134]. This evidence underscores the need for further investigation into the possible link between these regions, sleep quality, and cognitive decline.

Although studies examining diurnal variations in brain volume were not included in this review, recent research has identified natural fluctuations in brain volumes occurring over the course of a day. These variations are typically associated with changes in hydration, metabolic activity, and cerebrospinal fluid (CSF) dynamics, often linked to overnight sleep quality [136]. These variations in brain volumes highlight the dynamic nature of brain structures and the importance of considering the timing of neuroimaging assessments concerning sleep. Accounting for diurnal variations in future research could enhance the precision of findings by reducing measurement noise, thereby providing deeper insights into the relationship between sleep quality and brain volume.

Interestingly, sensitivity analyses of volumetric studies stratified in young and middle-aged groups did not identify significant differences between RHC and LHC volumes. However, heterogeneity was lower (low I_2) in younger adults compared to consistent, substantially higher heterogeneity (high I_2) in adults despite similar variance in age among the studies in each group. A possible explanation for this difference is the cumulative effect of risk factors, such as comorbidities, lifestyle changes, or neurobiological factors, which emerge during middle age and progressively influence brain structure. This cumulative impact of unmeasured confounders could potentially obscure the effect of sleep on hippocampal volume as age advances. While the impact of sex could not be investigated in this review, a previous systematic review of sleep characteristics found females tend to sleep longer and have higher sleep efficiency but also experience more sleep complaints and disorders compared to males [137]. These sex and age differences highlight the importance of systematically evaluating the impact of these characteristics on the relationship between sleep and brain health to better inform the development of meaningful, personalised strategies to improve sleep.

4.1. Clinical implications

The findings from the present review may have several clinical implications. First, they underscore the importance of assessing sleep during routine medical follow-ups and addressing sleep complaints proactively to prevent the progression to major sleep disorders. Early intervention is critical, as the development of sleep disorders may coincide with neurodegenerative damage. Intervention styles may involve lifestyle changes or pharmacological treatment. However, caution is warranted, given the potential side effects of sleep medications. Recent research has suggested that certain sleep medications may impair the normal pulsatile function of the glymphatic system during sleep, potentially exacerbating neurodegenerative processes [138]. Secondly, these findings emphasise the need for targeted interventions to improve sleep quality in high-risk populations. Such interventions may play a key role in preventing neurodegeneration, preserving healthy brain structures, and supporting normal cognitive function. These targeted interventions may involve routine screening of sleep problems, integrating sleep professionals in the multidisciplinary care of neurodegenerative diseases, and developing personalised sleep interventions.

4.2. Future directions

In addition, the findings of the present study highlight the need for 1) longitudinal studies to examine the causal relationship between sleep and brain; 2) the use of multi-modal neuroimaging to clarify discrepancies between imaging methods and balance the respective advantages each method brings including spatial resolution, statistical power and structural and functional connectivity; 3) randomised controlled trials of sleep interventions; 4) inclusion of diverse socio-demographic populations covering different age ranges (early adulthood, midlife, late adulthood), professions, and ethnic origins; 5) accounting for comorbidities (e.g., depression, anxiety, obesity, pain) and working arrangements (e.g. shift work) that are linked to poor sleep; 6) investigation of diurnal variations in brain volumes or inclusion of the time of the MRI image acquisition; 7) genetic predispositions to certain sleep patterns and disorders; and 8) investigation of neurodegenerative biomarkers. This further evidence will refine our understanding of the impact of sleep on the brain's structural integrity, inform the development of targeted and personalised interventions, and help maintain brain health across the lifespan.

4.3. Strengths and limitations

A particular strength of the present study is its comprehensive systematic search and detailed inclusion criteria, which account for multiple factors that influence sleep and brain structures. Additionally, this study analysed the available data to provide a comprehensive summary of the current evidence on individual sleep characteristics and disorders. To achieve this, we included studies using different neuroimaging methodologies, such as voxel-based morphometry and volumetric analyses and we reported the outcomes separately to ensure methodological clarity and avoid conflating findings that could be influenced by differing preprocessing and analytical approaches.

Nevertheless, it is important to acknowledge that the variability in findings across the included studies may still stem from the intrinsic differences between these methods. VBM, for example, provides voxel-wise assessments of grey matter density or volume and is sensitive to preprocessing steps such as normalisation and smoothing. In contrast, volumetric analyses typically rely on predefined regions of interest and may miss distributed structural changes. These differences highlight the need for caution when interpreting differences in results across neuroimaging methods. Additionally, this shows the need for future studies to investigate the feasibility of harmonised protocols or multimodal approaches. In fact, a harmonised approach would enable us to tease out from the available evidence whether this variability in findings is attributable to the use of different neuroimaging methods.

Although it may not be addressed as a limitation, it is noteworthy to mention the lack of compatible studies, both longitudinal and cross-sectional, investigating the association between the same sleep characteristics and the same brain region using the same neuroimaging methods, which has prevented the possibility of conducting meta-analyses in this area. Particularly of concern is the insufficient number of compatible longitudinal studies, which are crucial in determining the directionality of sleep's effect on brain structure.

Lastly, it is essential to note that, despite this review being adjusted for head size, age, and gender, other factors that influence sleep including body mass index, smoking, alcohol consumption, and depression were not considered or adjusted for due to lack of data. Future individual studies should incorporate these factors to enable systematic review to perform more comprehensive analyses, including meta-regression and subgroup analyses to tease out the factors that influence the association between sleep and brain structures.

5. Conclusion

The review's findings highlight the possible impact of sleep

characteristics and disorders on the brain structure. This is important because it suggests that poor sleep health, including short and long sleep and poor sleep quality leading to inadequate sleep, might be a modifiable factor in neurodegeneration and, ultimately, be associated with cognitive decline. The implications of these findings are significant for future research in the area as it highlights the importance of monitoring, managing and enforcing sleep health to prevent or mitigate potential neurodegenerative processes.

CRediT authorship contribution statement

Tergel Namsrai: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Joseph M. Northey:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Ananthan Ambikairajah:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Oli Ahmed:** Writing – review & editing, Formal analysis. **Khawlah Alateeq:** Writing – review & editing, Formal analysis. **Daniela Andrea Espinoza Oyarce:** Writing – review & editing, Formal analysis, Conceptualization. **Richard Burns:** Supervision, Methodology, Formal analysis, Conceptualization. **Ben Rattray:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Nicolas Cherbuin:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Data availability statement

Data sharing does not apply to this article as no new data were created or analysed in this study.

Ethics and consent form

Approval from the institutional review board or ethics committee was not needed for this systematic review. This study did not collect individual's data, and participation consent was not required.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2025.02.028>.

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