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Advances in pathophysiology and neuroimaging: Implications for sleep and dementia

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ABSTRACT

The burden of dementia is increasing globally. In the absence of curative treatment, preventive strategies to delay or reduce progression of dementia are crucial. This relies on the identification of modifiable risk factors. The effects of dementia on sleep are well recognized; however, there is now growing evidence suggesting a bidirectional relationship between sleep pathologies and dementia. SDB, poor quality sleep and extremes of sleep duration are commonly experienced by both middle-aged and older populations. All have been associated with increased risk of dementia and cognitive decline in a number of observational studies, albeit inconsistently. The mechanisms by which these sleep disorders may contribute to neurodegeneration are manifold, and include impacts of fragmented sleep on the clearance of neurotoxins, and in SDB by the additive effects of intermittent hypoxia on beta-amyloid production, hypoxic cell death, neuroinflammation and damage to cerebral vasculature. Untangling the mechanisms by which sleep pathologies may impact risk of dementia is a challenge. Many insights into the pathophysiology of these relationships have been derived from animal- and population-based studies. Neuroimaging modalities offer important opportunities to further understand the link between sleep pathologies and dementia risk in vivo, especially in the critical preclinical phase of AD. In this review, we canvas updates in dementia pathophysiology, the evidence linking sleep pathologies with dementia and outline the advances in determining this potential pathophysiological link that have eventuated from the application of neuroimaging.

Key words: cognitive dysfunction, dementia, neuroimaging, sleep-disordered breathing, sleep–wake disorders.

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INTRODUCTION

Dementia is a leading cause of disability and death worldwide.[1] It frequently adversely affects both subjective and objective indices of sleep[2] including sleep-disordered breathing (SDB).[3] There is growing evidence that sleep pathologies often precede dementia diagnosis,[4] signifying that certain sleep changes may be not only be a marker of increased risk but may directly contribute to dementia pathogenesis, especially dementia attributable to Alzheimer's disease (AD) and vascular dementia (VaD). There are several mechanisms via which abnormalities of sleep may do this. Delineating these pathways is challenging, made more so by the heterogeneity of sleep changes and populations that have been studied, the various pathological causes of dementia as well as the multiple intermediary and confounding factors that need accounting for. Furthermore, the long latency period between the onset of neurodegenerative processes and a diagnosis of dementia occurring poses a further challenge in determining to what extent sleep changes truly predate, and therefore may contribute to, neurodegenerative processes, as opposed to what extent sleep abnormalities reflect preclinical pathological changes in areas of the brain critical for good sleep.

It is in this regard that the neuroimaging modalities are of great value. This narrative review presents an update on the understanding of pathophysiology of the most common types of late-onset dementia due to AD and VaD, the evidence associating common sleep pathologies with dementia and new insights into the potential mechanistic pathways linking sleep changes and dementia as highlighted by the application of neuroimaging.

SEARCH STRATEGY

A search of Medline was undertaken. Keywords of amyloid PET, tau PET, brain magnetic resonance imaging, sleep, insomnia and sleep apnoea as well as MESH words of magnetic resonance imaging, leucoencephalopathies,

dementia, sleep apnoea syndromes, sleep–wake disorders and insomnia were used to identify studies that had evaluated amyloid positron emission technology (PET), tau PET or brain MRI measures of vascular pathology in association with subjective or objectively measured sleep parameters. Reference lists of retrieved publications were also reviewed.

DEMENTIA

Definition and epidemiology

Dementia is a clinical syndrome that is characterized by the development of cognitive impairment of sufficient severity to impact a person's daily function. It is a diagnosis made after exclusion of reversible causes. Most dementias are progressive conditions from which death is inevitable, and for which no curative treatment is available.[1] Mild cognitive impairment (MCI) is a further syndromal diagnosis, in which cognitive function is below that expected for age but is insufficient to impact daily function. Between 22% and 39% of persons with MCI will progress to dementia.[1] The prevalence of dementia is strongly linked to age, with approximately 1 in 10 persons aged over 65 years and 3 in 10 aged 85 years and over affected.[5] Although certain types of dementia occur in middle age, 90% of cases occur in those aged 65 years and over, in what is termed late-onset dementia.[6] With populations ageing, the number of dementia cases globally, estimated to be 47 million in 2015, is predicted to approach nearly 150 million by 2050.[1]

Pathophysiology and neuroimaging in dementia

There are several pathological causes of late-onset dementia. Accurate classification requires neuropathological confirmation (i.e. autopsy); however, in practice, diagnoses are based on syndromal presentations. Approximately two-thirds of late-onset dementia is attributable to AD. Pathologically, this is characterized by the accumulation of cortically based extracellular beta-amyloid plaque and intracellular neurofibrillary tangles.[6] In the 'amyloid cascade' hypothesis of AD, an accumulation of beta-amyloid proteins develops when there is an imbalance in the formation and clearance of the small beta-amyloid peptide, which is itself a fragment of a larger protein, the amyloid precursor protein, that traverses the cell membrane. Beta-amyloid cleavage and metabolism is influenced by a number of factors, including genetics, and is incompletely understood, although sleep and hypoxia may play a role (see discussion below). Excess beta-amyloid accumulation can result in the formation of oligomers, then fibrils, then mats and finally extracellular plaques, which all serve to disrupt neural cell function and connections. In AD, this is then followed by the development of tau neurofibrillary tangles that spread throughout the brain causing intracellular damage, synaptic dysfunction and neuronal cell death, with localized reactive inflammatory processes accelerating damage.[6] Research using biomarkers for the presence of beta-amyloid and tau in vivo, such as by cerebrospinal fluid (CSF) analysis, or use of radiolabelled tracers for amyloid plaques and tau in the brain with PET scans (termed amyloid PET and tau PET), has demonstrated that such pathological processes begin approximately two decades prior to the clinical signs of dementia manifesting. Together with structural neuroimaging measures of neurodegeneration (such as atrophy), these biomarkers underpin the new National Institute of Aging and the Alzheimer's Association (NIA-AA) research framework that classifies the presence and stage of AD in vivo, recognizing that AD may be present in a preclinical stage (with positive amyloid biomarkers as well as tau), prodromal (e.g. with MCI) and then clinical stage.[7] This highlights both a critical window of opportunity for preventative interventions, as well as the potential of molecular neuroimaging in detecting neurodegenerative changes in the preclinical phase of AD.

VaD is another leading contributor to late-onset dementia. This may correlate to large vessel stroke (post-stroke dementia), which may be clinically 'silent' (silent brain infarction, SBI), strategic lacunar infarction and most commonly, disease of small cerebral vessels (SVD) that can be detected on structural brain MRI sequences such as T2-weighted fluid-attenuated inversion recovery (FLAIR) for white matter hyperintensities (WMH) and lacunes, and gradient echo (GRE) and susceptibility-weighted imaging (SWI) to detect cerebral microbleeds (CMB).[8] Similar to AD, VaD may also have a long preclinical phase.[6,8] Newer structural imaging techniques, such as diffusion tensor imaging (DTI), can allow early examination of brain's white matter that may be altered early in both vascular and AD pathologies.[8] In older adults, a mixture of VaD and AD pathologies is common, and these pathologies would appear to be additive phenotypically.[9] Given that there are plausible biological reasons why sleep disorders may impact both AD and VaD, these dementias form the focus of this review.

Risk factors for dementia: A role for sleep?

There has been growing recognition of the role of potentially modifiable risk factors for dementia, such as midlife hypertension, obesity, diabetes, depression and low levels of cognitive and physical activity. Collectively, such risk factors are estimated to contribute to over one-third of all prevalent cases of AD dementia, and have underpinned the rationale for several studies evaluating multipronged interventions in at-risk individuals.[1] It is in this context that the role of sleep pathologies in dementia is highly topical. A growing base of population-based studies suggest that SDB,[11] poor sleep quality, excessively short or long sleep[4] or changes in sleep architecture[12] associate with a higher risk dementia, including dementia due to both AD and VaD. However, these relationships have not been consistently shown. Furthermore, sleep changes may be impacting dementia risk via other relevant intermediaries or associated factors, such as obesity, hypertension or diabetes. It is also difficult to determine to what extent sleep changes are resulting from preclinical neurodegenerative changes, as further described below.

SLEEP AND DEMENTIA

Sleep changes resulting from dementia and MCI

To appreciate how (and if) sleep changes affect dementia pathogenesis, it is prudent to review the impact dementia and MCI have on sleep. Clinicians and carers of persons living with dementia are only too familiar with changes in sleep that occur in dementia, such as difficulty with sleep onset, altered sleep/wake cycles, fragmented sleep at night, excessive daytime sleepiness (EDS) and increased periods of daytime sleep.[2,13] Polysomnographic (PSG) studies show increased sleep latency, reduced efficiency, increased amount of time spent in the lighter stages of sleep and reduced time spent in slow-wave and rapid eye movement (REM) sleep in dementia.[2] Similar changes are also found in MCI, such as in the community-based HypnoLaus study, in which 291 older adults with MCI reported higher scores on the Epworth Sleepiness Scale (ESS), spent longer in the light stages of sleep (N1), less time in deeper slow wave (N3) and REM sleep, and had more wake after sleep onset compared to cognitively normal (CN) older adults.[14]

The mechanisms underlying sleep changes in dementia may relate in part to neurodegenerative change to regions of the brain involved with the circadian rhythm (i.e. the suprachiasmatic nucleus) and those involved in inhibition of cortical arousal pathways (e.g. the ventrolateral preoptic area), leading to disrupted circadian rhythms, altered sleep–wake cycles and multiple night-time arousals.[4] Animal studies have shown that beta-amyloid accumulation itself is associated with a disturbed sleep/wake cycle.[15] Accumulation of tau in AD occurs early in the medial temporal lobe and hippocampus, areas important for generation of non-REM (NREM) sleep spindles and slow-wave sleep.[16] Cortical beta-amyloid accumulation in the medial prefrontal cortex would also seem to impair generation of NREM slow-wave oscillations.[17]

Dementia and MCI are furthermore strongly associated with SDB. A meta-analysis reported that the prevalence of SDB in dementia is fivefold that of healthy older adults.[3] MCI was associated with a significantly higher apnoea–hypopnoea index (AHI) than in CN older adults in the community-dwelling HypnoLaus sample.[14] This may in part be attributable to unstable ventilatory control resulting from fragmented sleep, changes in neuromuscular control of the upper airway due to degenerative changes in the post-central gyrus[18] as well as upper airway muscle weakness, due to sarcopenia/physical frailty that frequently coexists with dementia. Pathological correlates have also found that in AD tau accumulates early in the locus coeruleus, an area of the brain important in breathing regulation and alertness (Fig. 1).[6]

Sleep disorders in dementia pathogenesis: Potential mechanisms

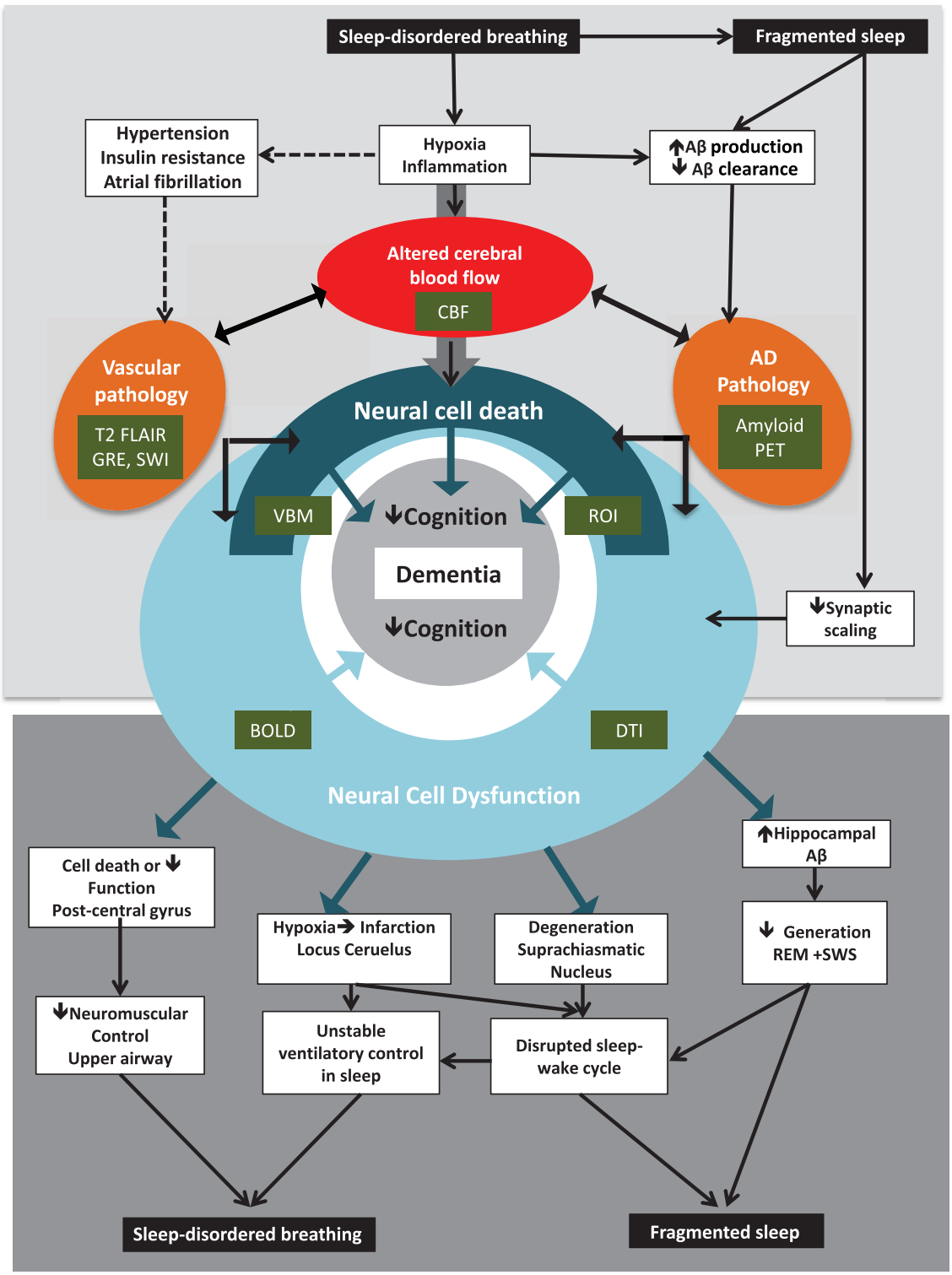
Sleep appears to play both restorative and protective functions in the brain—an imbalance of which could plausibly contribute to neurodegeneration (Fig. 1). The numerous mechanisms underlying this are incompletely understood. However, for restorative functions, sleep seems important for the transcription of genes essential for neural cell membrane and myelin integrity[19] especially in the white matter.[19–21] Certain regions and functions of the brain in particular may be more dependent on sleep for neural health (and conversely, more vulnerable to the deleterious effects of sleep deprivation and fragmentation), for example, for maintenance and restoration of hippocampal synaptic membranes.[22] Sleep also appears crucial for the modulation of synaptic connections (termed synaptic scaling), a process critical for learning and memory.[23] Across the age spectrum, studies have shown the importance of sleep on functional measures of brain health, especially for the cognitive domains of memory and attention, as well as mood and behaviour.[24] Thus, disrupted sleep may have reversible impacts on cognitive function, exacerbating dementia-related cognitive deficits, or contribute to subtle neural cell damage and dysfunction that may be additive to other neurodegenerative processes, reducing the threshold of pathological change required for the diagnosis of dementia to be made.

The protective role of sleep may be critical in AD pathogenesis. The brain has a high metabolic rate relative to its size. Yet, unlike the rest of the body, the brain lacks a lymphatic system to remove metabolic waste, such as toxic beta-amlyoid.[25] Recently, a pseudolymphatic system was described to explain how the brain removes potentially neurotoxic waste.[26] The mechanism was termed the 'glymphatic' system after its lymphatic-like function and its reliance on astroglial aquaporin-4 channels.[25] This glympathic system has been shown to be optimized during sleep.[27] Furthermore, Kang *et al*. showed that beta-amyloid dynamics are tied to the sleep–wake cycle.[28] Specifically, diurnal variation of interstitial fluid beta-amyloid levels was observed in mice; the amount of beta-amyloid correlated with wakefulness. Beta-amyloid levels also increased during sleep deprivation. The findings were confirmed in a small sample of humans, whereby beta-amyloid levels in CSF increased during the day peaking in the evening before decreasing overnight and increasing again the following day.[28] Xie *et al*.[27] showed that sleep was associated with a dramatic increase in the interstitial space. The resultant increase in convective exchange between CSF and interstitial fluid increased the rate of beta-amyloid clearance. Given the role of amyloid accumulation in triggering AD pathology, such findings have lent considerable weight to sleep dysfunction contributing towards AD.

There are additive effects in SDB. In addition to disrupting sleep, the intermittent reductions (hypopnoeas) and cessations (apnoeas) of respiration characteristic of SDB lead to intermittent drops in oxygenation levels. Hypoxia itself can potentiate neural cell death and dysfunction, especially in the hippocampus,[29] and has also been associated in animal models with increased production and reduced clearance of beta-amyloid.[30] Intermittent hypoxia is furthermore associated with endothelial dysfunction, systemic hypertension, insulin resistance and inflammation, which may all contribute

to VaD and AD pathogenesis by affecting cerebral vasculature.[31]

There is also a growing evidence base on the bidirectional relationships of circadian rhythm dysfunction and neurodegeneration, a detailed discussion of which is beyond the scope of this review, and for a more detailed discussion we refer the reader to Musiek *et al.*[32]



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Sleep disorders in dementia pathogenesis: Population studies

As outlined above, there are several biological underpinnings that support sleep disruptions as potential promoters of neurodegenerative change, and there has been a significant increase in population-based studies assessing these associations. A meta-analysis of 18 longitudinal studies comprising nearly 250 000 participants found that insomnia was associated with an increased risk of AD whilst SDB was associated with increased risks of AD, VaD and all-cause dementia.[33] A meta-analysis on SDB specifically, that included cross-sectional as well as longitudinal studies, reported a 26% increased risk of developing of cognitive decline in those with SDB. The presence of a self-reported diagnosis of SDB was associated with earlier diagnoses of both MCI and AD in the large Alzheimer's Disease Neuroimaging Initiative Study.[34] There is some caution in interpreting these findings. Many have relied on self-report of sleep symptoms and duration. There have been inconsistent adjustments for relevant confounders and possible mediators. Outcome measures of dementia and cognitive impairment have been variable. Most have relied on clinical classification for subtype. Moreover, given the clinical features of dementia lag behind neuropathological changes by up to 20 years, many studies have a relatively short follow-up period, and thus it is likely that to some extent the sleep changes measured are reflecting preclinical disease. In this vein, the interpretation of the finding of an increased risk of either dementia or MCI over 5 years in a cohort of nearly 300 women, aged 82 years, with moderately severe obstructive sleep apnoea (OSA) needs to be tempered by the fact that at age 80 years many persons with incident dementia/MCI on follow-up would have already had AD or VaD pathology at baseline.[35] Two much larger studies, with longer follow-up periods of 8[36] and 15[37] years, respectively, that measured AHI with PSG in community-dwelling older adults at an age in which exposure to SDB might be expected to have a stronger impact on late life dementia (early to mid 60s) found only minor associations with later cognitive function. The use of biomarkers, especially neuroimaging biomarkers, is thus very useful in detecting preclinical change as well as in better characterization of dementia subtype.

Sleep disorders in dementia pathogenesis: Neuroimaging studies

Perhaps, the most significant advance in understanding the link between sleep disorders and in particular AD has been facilitated by the use of amyloid PET, given beta-amyloid burden is predictive of incident dementia.[6] (Table 1). Notable findings include a study of 20 healthy men and women, with a mean age of 40 years, who reported habitual sleep duration and then underwent experimental sleep deprivation. The former was associated with baseline beta-amyloid burden, and the latter with increased overnight beta-amyloid detected in the thalamus and hippocampus.[44] Adverse health outcomes related to short sleep were also reported in an older group of 70 men and women with a median age of 76 years, whereby self-reported short sleep was associated cross-sectionally with higher beta-amyloid in the precuneus and overall cortical load,[38] although three other similarly sized cross-sectional studies evaluating sleep duration in cohorts with a mean age of 62–76 years found no such associations.[40–42] Self-reported sleep quality has also been found to be associated cross-sectionally with global and regional cortical beta-amyloid in several studies older populations,[38,40] especially in association with increased sleep latency,[41,42] as well as correlated with sleep architecture change as captured by PSG[17] and actigraphy.[13] Of course, given these studies are cross-sectional, it is not possible to determine whether these sleep symptoms are resulting from, as opposed to contributing to, beta-amyloid accumulation.

For more robust evidence, longitudinal studies provide more insight. Two studies on older community-dwelling adults, with follow-up periods of 2 and 16 years, respectively, intriguingly reported an association between baseline symptoms of EDS and later beta-amyloid burden on PET imaging.[45,46] This raises the possibility of underlying SDB. Two cross-sectional studies using PSG to evaluate SDB indices found associations between metrics of SDB severity and beta-amyloid burden in older adults, although these were in small samples.[46,47] One longitudinal study of 208 older adults, with a mean age of 68 years, found a trend towards increased beta-amyloid over 2 years that was associated with the AHI, but this was not statistically significant.[49] However, AHI was associated

FIGURE 1 Sleep pathologies that may have a bidirectional relationship with neurodegeneration and neuroimaging can illuminate some of the mechanisms involved. Fragmented sleep may lead to reduced clearance of Aβ, potentiating accumulation of toxic amyloid plaques that trigger AD pathology. Reduced sleep may also reduce restoration of neuronal cell health and connections, for example, by impacting sleep-dependent synaptic scaling. SDB may affect brain health by fragmenting sleep, or by the effects of hypoxia in increasing Aβ production, reducing clearance, by directly damaging cells or by affecting cerebral vasculature directly or by systemic effects of hypoxic on hypertension, metabolic dysfunction and inflammation. Both vascular and Alzheimer's pathologies synergistically cause neuronal dysfunction and cell death (upper half of the figure). Areas of neuronal cell death and dysfunction may be important for sleep—for example, the locus coeruleus for regulation of respiration and alertness, the hippocampus for generation of SWS and REM sleep and the suprachiasmatic nucleus for circadian rhythm. Areas on the cortex important for neuromuscular control of upper airway can similarly be impacted, contributing to SDB. These changes lead to unstable ventilation and/or disrupted sleep/wake cycles, in turn resulting in SDB or fragmented sleep. Neuroimaging modalities (green boxes) such as amyloid PET can be used in vivo to detect evidence of cortical Aβ, T2-weighted MRI sequences of FLAIR, SWI and GRE; can show signs of vascular pathology; CBF can be assessed; subtle neuronal changes in white matter can be detected using DTI; cell death in grey matter can be detected using VBM; and resting state functional connectivity can be measured using BOLD MRI. Aβ, beta-amyloid; AD, Alzheimer's disease; BOLD, blood oxygen-level dependent; CBF, cortical blood flow; DTI, diffusion tensor imaging; FLAIR, fluid-attenuated inversion recovery; GRE, gradient echo; MRI, magnetic resonance imaging; PET, positron emission technology; REM, rapid eye movement; ROI, region of interest; SDB, sleep-disordered breathing; SWI, signal-weighted imaging; SWS, slow-wave sleep; VBM, voxel-based morphology.

Table 1 Studies evaluating sleep with neuroimaging biomarkers of AD

Study	Population	Design	Sleep measure	Confounders	Results
Sleep quality (including fragmentation, disturbance and insomnia)					
Spira (2013)[38]	*n* = 70, F = 47% Age = 76 CN + MCI + D	Cross-sectional	Self-Report WHIRS	Age/sex/race/BMI CVD/lung dis/depression Sleep meds/ APOE4	↓ Sleep quality → ↑ Aβ in precuneus Trend with DIS
Spira (2014)[39]	*n* = 8 CN, age 69 *n* = 5 MCI, age 75	Cross-sectional	PSG TST, AI, WASO	—	No assoc
Mander (2015)[17]	*n* = 26, F = 69% Age = 75, CN	Cross-sectional	PSG EEG NREM and SWS	Age, sex Grey matter volume	↑ Aβ prefrontal cortex→ ↓ NREM + SWS
Sprecher (2015)[40]	*n* = 98, F = 67% Age = 62, CN	Cross-sectional	Self-report (MOS)	Age/sex/BMI/ Fam Hx AD/APOE4	↓ Sleep quality → ↑ Aβ
Brown (2016)[41]	*n* = 184, F = 59% Age = 76, CN	Cross-sectional	Self-report (PSQI)	Age/BMI/CVD/ depression	↑ Sleep latency → ↑ Aβ
Branger (2016)[42]	*n* = 51, F = 55% Age = 64, CN	Cross-sectional	Self-report (PSQI)	Age/depression/ anxiety/BMI/ APOE4	↑ Sleep latency → ↑ Aβ
Musiek (2018)[13]	*n* = 189, F = 64% Age = 67, CN	Cross-sectional	Actigraphy→ Circadian rhythm	Age/sex/APOE4 (unrelated)	Aβ → rest activity rhythm fragmentation
Lucey (2019)[43]	*n* = 38, F = 53% Age = 74, CN + MCI	Cross-sectional	Actigraphy + EEG	Age/sex/cognition/ race/APOE4/AHI/ sleep meds	↓ NREM SWS→ ↑ Aβ and tau
Sleep duration					
Spira (2013)[38]	*n* = 70, F = 47% Age = 76 CN + MCI + D	Cross-sectional	Self-reported	Age/sex/race/BMI CVD/lung dis/depression Sleep med use/APOE4	Short sleep → ↑ Aβ in precunues and global cortex
Sprecher (2015)[40]	*n* = 98, F = 67% Age = 62, CN	Cross-sectional	Self-report (MOS)	Age/sex/BMI/ Fam Hx AD/APOE4	No assoc
Brown (2016)[41]	*n* = 184, F = 59% Age = 76, CN	Cross-sectional	Self-reported	Age/BMI/CVD/ depression APOE4	No assoc
Branger (2016)[42]	*n* = 51, F = 55% Age = 64, CN	Cross-sectional	Self-report (PSQI)	Age/depression/ anxiety/BMI/ APOE4	No assoc
Shokri-Kojori (2018)[44]	*n* = 20, F = 50% Age = 40, CN	Cross-sectional	Experimental SD + self-report	Age/sex/APOE4	SD → ↑ Aβ right hippocampus + thalamus
Daytime sleepiness					
Sprecher (2015)[40]	*n* = 98, F = 67% Age = 62, CN	Cross-sectional	Self-report (MOS and ESS)	Age/sex/BMI/ Fam Hx AD/APOE4	Sleepiness on MOS (but not ESS) → ↑ Aβ
Carvalho (2018)[45]	*n* = 283, F = 28% Age = 77, CN + MCI	Longitudinal 2 years	Self-report (ESS)	Age/sex/Educ/PA/ obesity/HT/DM/ Chol/depression/ APOE4	EDS→ ↑ accumulation of Aβ
Spira (2018)[46]	*n* = 124, F = 51% Age = 60, CN	Longitudinal 16 years	Self-report (one question)	Age/sex/Educ/BMI	EDS→ ↑ accumulation of Aβ
Sleep-disordered breathing					
Spira (2014)[39]	*n* = 8 CN, age 69 *n* = 5 MCI, age 75	Cross-sectional	PSG: AHI, TST AI, WASO	—	In MCI, ↑ AHI → ↑ Aβ global, precuneus
Sprecher (2015)[40]	*n* = 98, F = 67%	Cross-sectional	Self-report	Age/sex/BMI/	No assoc

Continued

Table 1 Continued

Study	Population	Design	Sleep measure	Confounders	Results
	Age = 62, CN		(MOS)	Fam Hx AD/APOE4	
Yun (2017)[47]	*n* = 19 w OSA, CN F = 53% Age = 59 and 19 controls	Cross-sectional	PSG: AHI	Sleep duration/HT/DM/BMI/PA/depression/smoking/ETOH	OSA → ↑ Aβ R posterior cingulate + temporal cortex
Elias (2018)[48]	*n* = 42 w OSA, CN 77 controls Age = 68	Cross-sectional	OSA + CPAP use/PSG	Age/Educ/vascular risk APOE4/BMI	No assoc of Aβ or tau in adjusted models with OSA or CPAP
Sharma (2018)[49]	*n* = 208, F = 62% Age = 68, CN	Longitudinal 2 years	PSG: AHI, AHIall, AHI4%	Age/sex/BMI/APOE4	↑AHI: trend to ↑ Aβ on PET over 2 years (not statistically significant)
Bubu (2019)[50]	*n* = 1639, F = 42% Age = 74, CN + MCI + AD	Longitudinal 2 years	Self-report of OSA diagnosis	Age/sex/BMI/Educ/HT/DM/CVD/CPAP/lung dis	In CN and MCI (not AD): OSA→ ↑ Aβ on PET

Aβ, beta-amyloid; AD, Alzheimer's disease; AHI, apnoea–hypopnea index; AI, arousal index; APOE4, apolipoprotein E4; assoc, association; BMI, body mass index; Chol, cholesterol; CN, cognitively normal; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; D, dementia; DIS, difficulty initiating sleep; DM, diabetes mellitus; EDS, excessive daytime sleepiness; Educ, education; EEG, electroencephalogram; ESS, Epworth Sleepiness Scale; ETOH, alcohol use; F, female; Fam Hx AD, family history of AD; HT, hypertension; lung dis, lung disease; MCI, mild cognitive impairment; MOS, Medical Outcomes Sleep Scale; *n*, number; NREM, non-rapid eye movement; OSA, obstructive sleep apnoea; PA, physical activity; PET, positron emission technology; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; SD, sleep deprivation; SWS, slow-wave sleep; TST, total sleep time; WASO, wake after sleep onset; WHIRS, Women's Health Initiative Insomnia Rating Scale.

with decreases in CSF levels of beta-amyloid (consistent with increased deposition) in this group suggesting CSF measures may be more sensitive. Finally, a longitudinal evaluation of self-reported diagnosis of OSA has been associated with increased rate of accumulation of beta-amyloid over 2 years in a large cohort of older adults with either normal cognition or MCI at baseline.[50] This is telling, as the majority of SDB in older adults is asymptomatic, and often undetected.[51] Those with a clinical diagnosis may thus have been expected to be more symptomatic (e.g. with EDS), which may also suggest an increased risk in those who have symptomatic disease.

Tau PET, the other neuroimaging biomarker of AD, is a relatively newer modality and as such has only been employed in a small number of studies to date. As discussed in AD pathogenesis, tau accumulation is a downstream phenomenon in the development of AD. A cross-sectional study of 119 older men found no association of a self-reported diagnosis of OSA and tau tracer uptake, although a cross-sectional association with beta-amyloid was found in the same cohort.[48] A newer study of 38 older men and women found an inverse relationship between duration of NREM slow wave activity (SWA) and tau and beta-amyloid uptake, with this relationship more pronounced for tau than amyloid.[43]

There are caveats in interpreting this evidence. Most studies of amyloid and tau PET and sleep have been cross-sectional, several have relied on self-report of sleep symptoms, and moreover each study has applied different thresholds for the measures of amyloid PET on neuroimaging, whilst Tau imaging has only been employed by few studies and techniques are evolving. Furthermore, whilst the presence of amyloid PET is a recognized risk factor for incident dementia, there are certainly many adults with a high burden of brain amyloid on PET imaging (and amyloid pathology) who remain CN throughout their lifespan.[6] Shokri-Kojori *et al.*'s impressive demonstration of acute accumulation of amyloid on PET imaging following one night of sleep deprivation[44] also raises the question as to what extent these observed measures represent permanent, as opposed to reversible, brain changes, as the scan measures tracer retention as opposed to plaque burden.

The other main contributor to late-onset dementia is vascular pathology. Thus, in the preclinical phase of dementia, if sleep pathologies potentiate neurodegeneration via effects on cerebral vasculature we might expect to see associations of sleep indices (objective and or subjective) with neuroimaging measures of vascular disease. Furthermore, given the well-documented associations between SDB and cardiovascular disease, including stroke,[52] it might be expected a relationship would be most robust in those with SDB.

Studies evaluating these associations are shown in Table 2. Several of these investigations were cross-sectional studies of middle-aged, clinic-based cohorts, some of which found associations of SDB indices with WMH or SBI, but not lacunar infarcts.[64,65,72–74] Notably all, bar one,[72] were conducted in Asian populations in which the incidence of cerebrovascular disease is high. In three studies conducted in non-Asian countries, no such associations were found.[61,66,68] This pattern was also observed for community-based cohorts of older adults, where indices of SDB were found to correlate with neuroimaging vascular measures in Asian,[62,67,69] but not in non-Asian[54,63] populations, except for two smaller

Table 2 Studies evaluating sleep with measures of vascular disease

Study	Population	Design	Sleep measure	Confounders	Results
Sleep quality (including fragmentation, disturbance and insomnia)					
Kanda (2003)[53]	*n* = 136, F = 49% Age = 69, CN	Community Cross-sectional	Self-report of DIS, EMA, AB-5	Age/sex	AB-5 → ↑ WMH (not DIS or EMA)
Ding (2004)[54]	*n* = 789, F = 56% Age = 78, CN	Community Cross-sectional	In home PSG	HT/weight/smoking/ DM ETOH/CHD	↑ AI → ↑WMH
Cheng (2013)[55]	*n* = 72, F = 57% D (vascular)	Clinic-based Cross-sectional	Self-report: SDSQ	Sex/age/depression/ DM HT/smoking/lipids/ hypnotics	↑ Sleep disturbance→ ↑ WMH severity
Del Brutto (2015)[56]	*n* = 237, F = 59% Age = 70, CN	Community Cross-sectional	PSQI	Age/sex/education Cardiovascular risk factors	↓ Sleep quality → ↑ WMH prev and severity
Sexton (2017)[20]	*n* = 448, F = 20% Age = 69, CN	Community Longitudinal 16 years	PSQI	Age/sex/BMI/HT/PA Depression/ pyschotropics	No assoc of sleep quality over 16 years with WMH
Sleep duration					
Lutsey (2016)[57]	*n* = 312, F = 54% Age = 62, CN	Community Longitudinal 15 years	Self-report	Age/sex/education/PA/ CHD ETOH/BMI//DM/HT/ APOE4	No assoc of WMH, CMB and SBI with sleep duration
Ramos (2014)[58]	*n* = 1244, F = 61% Age = 70, CN	Community Cross-sectional	Self-report	Age/race/education/ obesity DM/ETOH/HT/CVD/ EDS	Sleep duration ≥9 h → ↑ WMH severity
Yaffe (2016)[59]	*n* = 613, F = 53% Age = 45, CN	Community Longitudinal 5 years	Self-report	Age/sex/race/ education/HT/ Stroke/TIA/ depression/ Smoking/PA	Sleep duration ≤6 h→ ↑ WMH in parietal lobe
Sexton (2017)[20]	*n* = 448, F = 20% Age = 69, CN	Community Cross-sectional	Self-report	Age/sex/BMI/HT/PA Depression/ pyschotropics	No assoc of sleep duration and WMH
Kocevska (2019)[60]	*n* = 2529, F = 55% Age = 56, CN	Community Cross-sectional and longitudinal 5 years	Self-report	Age/sex/ICV/ education/ Employment/ smoking/DM/HT statins/depression/ cognition	Sleep ≤6 h → ↑ WML over time
Sleep-disordered breathing					
Davies (2001)[61]	*n* = 45, F = NS Age = 52, CN Controls = 45	Clinic-based Cross-sectional	In lab PSG	BP	No difference in prev WMH or lacunes between OSA and controls
Ding (2004)[54]	*n* = 789, F = 56% Age = 78, CN	Community Cross-sectional	In home PSG	BP/weight/smoking/ DM ETOH/CHD	No assoc of AHI with WMH
Eguchi (2005)[62]	*n* = 146, F = 74% Age = 67, CN	Community Cross-sectional	Pulse oximetry-ODI 3%	Age/sex/BMI/Chol/BP/ haemoglobin A1c/serum creatinine/nocturnal hypoxia	Higher ODI → ↑ prev SBI
Robbins (2005)[63]	*n* = 843, F = 58% Age = 77	Community Cross-sectional and longitudinal	In home PSG	Age/baseline WMH	CSA and Cheyne–stoke respiration (not OSA)→ ↑

Continued

Table 2 Continued

Study	Population	Design	Sleep measure	Confounders	Results
					progression WMH
Minoguchi (2007)[64]	*n* = 50 (15 controls), F = 0% Age = 49, CN	Sleep clinic and controls Cross-sectional	In lab PSG	—	AHI ≥15 → ↑ prev SBI
Nishibayashi (2008)[65]	*n* = 192, F = 12% Age = 51, CN	Clinic-based Cross-sectional	In lab PSG	Age/sex/smoking/ ETOH HT/DM/lipids	↑ AHI → ↑ SBI and ↑ WMH
Kiernan (2011)[66]	*n* = 62, F = 32% Age = 67, CN	Clinic-based Cross sectional	In lab PSG	Age (all were hypertensive)	No assoc of AHI with WMH
Kim (2013)[67]	*n* = 503, F = 71% Age = 60, CN	Community Cross-sectional	In home or lab PSG	CVD/DM/HT/lipids Smoking/ETOH	AHI ≥15 → ↑ WMH
Schulz (2013)[68]	*n* = 183, F = 15% Age = 58, CN	Clinic-based Cross-sectional	In lab PSG	Age/HT	No assoc of ODI with WMH
Baik (2015)[69]	*n* = 1763, F = 42% Age = 61	Community Cross-sectional	In home or lab PSG	Age/sex/smoking/ ETOH	AHI ≥15 → ↑ WMH
Lutsey (2016)[57]	*n* = 312, F = 54% Age = 62, CN	Community Longitudinal 15 years	In home PSG	Age/sex/education/PA/ CHD/ETOH/BMI/DM/ HT/APOE4	No assoc of AHI with WMH, CMB, SBI
Rostanski (2016)[70]	*n* = 483, F = 73% Age = 80, CN + D	Community Cross-sectional	Self-reported risks for OSA	Race/age/sex/HT/ APOE4 Intracranial volume	Snoring and higher risk of OSA→ ↑ WMH
Del Brutto (2017)[71]	*n* = 97, F = 65% Age = 72, CN	Community Cross-sectional	In lab PSG	Age/sex/BMI/HT/ glucose/ Chol/PA	AHI ≥15 → ↑ WMH, not deep CMB or lacunes
Yilmaz Avci (2017)[72]	*n* = 297, F = 32% Age = 52, CN	Clinic-based Cross-sectional	In lab PSG	Age/sex/BMI/HT/DM/ lipids/ CVD/CRP/MPV	OSA and ↑ ST Sats < 90%→ ↑ prev WMH
Song (2017)[73]	*n* = 170, F = 43% Age = 58, CN	Clinic-based Cross-sectional	In lab PSG	Age/sex/HT/DM/ stroke/ Minimal O_2/AI	AHI ≥15 → ↑ WMH ↑ CMB, PVS, not lacunes
Koo (2017)[74]	*n* = 75, F = 40% Age = 61, CN	Clinic-based Cross-sectional	In lab PSG	Age/HT/DM/CVD	AHI ≥15 → ↑ CMB

AB-5, awake before 5 am; AHI, apnoea–hypopnoea index; AI, arousal index; APOE4, apolipoprotein E4; assoc, association; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; Chol, cholesterol; CMB, cerebral microbleed; CN, cognitively normal; CRP, C-reactive protein; CSA, central sleep apnoea; CVD, cardiovascular disease; D, dementia; DIS, difficulty initiating sleep; DM, diabetes mellitus; EDS, excessive daytime sleepiness; EMA, early morning awakening; ETOH, alcohol use; F, female; HT, hypertension; ICV, intracranial volume; MPV, mean platelet volume; *n*, number; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; PA, physical activity; Prev, prevalence; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; PVS, perivascular space; SBI, silent brain infarction; SDSQ, Sleep Disturbance Symptom Questionnaire; ST Sats < 90%, sleep time with oxygen saturation <90%; TIA, transient ischaemic attack; WMH, white matter hyperintensity; WML, white matter lesion.

studies, one of which relied on self-report of OSA symptoms.[70] In fact, in one of the only longitudinal studies, no association was found between baseline AHI and WMH, SBI, CMB or lacunes in 312 older adults, aged 62 years at baseline, and imaged 16 years later.[57] It would thus seem that, at least in non-Asian populations, the observed association between SDB and incident cognitive decline and dementia may not be mediated via an effect on cerebral vascular pathology.

Less intuitively, a stronger association with WMH and other white matter lesions seems to exist between self-reported short sleep, as found in two large, community-based cohorts of middle-aged adults followed up for 5[59] and 16[60] years, respectively, whilst a cross-sectional analysis conducted in an older age group reported an association for longer sleep.[58] These studies all employed robust adjustment for relevant confounders and potential mediators, including vascular risk factors and depression. It should be noted that whilst changes of WMH may indicate SVD, they are not specific for vascular disease and are also associated with AD pathology, and so it is possible that their relationship with sleep duration reflects AD rather than vascular processes.

Other neuroimaging modalities may shed further light. DTI is an MRI technique sensitive to microstructural changes in white matter and tissue density in different parts of the brain. It may thus be more sensitive to very early changes pertaining to either impaired restorative processes or early vascular damage. For example, changes in DTI metrics can be detected in young adults, acutely

after only one night of sleep deprivation[19] and in association with habitual poor sleep quality and long sleep duration.[21] In the two prospective cohorts in whom short sleep associated with increased white matter lesions, changes in DTI were found in one,[59] but not the other.[60] Changes in DTI metrics have also been observed in association with SDB,[75] especially in women on sex-specific analyses.[76]

Structural MRI studies using technologies such as Freesurfer and voxel-based morphometry have been employed to test associations of sleep pathologies with cortical/grey matter volume. SDB in middle-aged adults has been associated with cortical thinning in the pre- and post-central as well as superior temporal gyrus[77] suggesting cell death. In 83 older adults with MCI (and thus at high risk of dementia), measures of oxygen desaturation negatively associated with left temporal cortical thickness.[78] However, in an older cohort of 71 adults, measures of OSA, especially desaturation, were associated with grey matter thickening in certain regions, suggesting underlying inflammation.[79] Resting state functional MRI studies have been conducted in middle-aged subjects and demonstrate altered connectivity in association with OSA and insomnia.[80] Studies investigating cerebral blood flow have also found changes in the setting of SDB, such as a study of 50 older adults with OSA, in which severe OSA was associated with hypoperfusion in several cortical regions and increased medical cortical and subcortical perfusion.[81]

A further application of neuroimaging is in the determining the effects of sleep interventions on neural health. Continuous positive airway pressure (CPAP) therapy has been shown to alter DTI metrics on treatment-naïve subjects when acquired before and after treatment, as well as on measures of cortical blood flow and blood volume.[82] DTI studies have also now been employed to understand why some treatment-compliant patients remain symptomatic with daytime sleepiness, with such studies revealing persistent white matter changes on DTI which may explain ongoing symptoms, as well as potentially highlight a subgroup at higher risk of future cognitive decline.[83,84] A longer term study that evaluated brain morphology after 18 months of CPAP therapy in OSA patients found longer treatment correlated with volume increases in the hippocampal dentate gyrus and cerebellar dentate nucleus, and in those with severe OSA, with volume increases in the pre-frontal cortex.[85] A study led by the first author is utilizing measures of cerebral SVD to determine the effects of low-dose aspirin in older adults with SDB.[31] Studies utilizing amyloid PET following CPAP are eagerly anticipated.[86]

CONCLUSION: FUTURE DIRECTIONS

Significant advances in understanding the role of sleep have taken place in the past two decades, especially with respect to the role sleep plays in the clearance of neurotoxins and in the regulation of beta-amyloid levels. Such findings have mirrored population studies that increasingly report associations between poor sleep quality, excessively short or long sleep, or SDB, with incident cognitive decline and dementia. Meanwhile, the use of neuroimaging and CSF biomarkers has demonstrated that a critical preclinical phase of AD exists, spanning nearly two decades. Thus, the use of structural neuroimaging techniques, which are sensitive to preclinical dementia changes in vascular pathology, white matter integrity, cell death and dysfunction and especially radiolabelled tracers for binding beta-amyloid and tau in vivo, has further bridged the link between laboratory- and population-based studies on sleep and dementia.

Studies investigating sleep and amyloid and tau PET have only emerged in the past 6 years, and have mostly been cross-sectional. Further longitudinal studies, particularly in middle-aged subjects, utilizing objective measures of sleep, and studies that also measure concomitant vascular changes and robustly adjust for confounders will further help to resolve whether these associations between sleep and AD are truly bidirectional. The 2018 NIA-AA framework for defining the presence and staging of AD (in the preclinical and prodromal phases),[7] which is heavily dependent on imaging biomarkers, is now being used in clinical trials and offers a standardized framework upon which to systematically evaluate the associations of sleep changes in the long prodromal phase of AD, and perhaps more importantly, can better guide the development and evaluation of preventive interventions aimed at addressing sleep changes.

Lastly, whilst interest remains strong in the role of sleep changes as risk factors for dementia, the impact of dementia on sleep quality should not be overlooked. Sleep changes in dementia are difficult to manage and can have devastating impacts on patients and carers alike. Neuroimaging studies that help guide development of treatments for sleep disorders in the setting of dementia would be a welcome future direction.

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Abbreviations: Aβ, beta-amyloid; AB-5, awake before 5 am; AD, Alzheimer's disease; AHI, apnoea–hypopnoea index; AI, arousal index; APOE4, apolipoprotein E4; BP, blood pressure; CHD, coronary heart disease; CMB, cerebral microbleed; CN, cognitively normal; CPAP, continuous positive airway pressure; CSF, cerebrospinal fluid; CVD, cardiovascular disease; DIS, difficulty initiating sleep; DM, diabetes mellitus; DTI, diffusion tensor imaging; EEG, electroencephalogram; EMA, early morning awakening; ESS, Epworth Sleepiness Scale; ETOH, alcohol use; HT, hypertension; MCI, mild cognitive impairment;

MOS, Medical Outcomes Sleep Scale; NIA-AA, National Institute of Aging and the Alzheimer's Association; NREM, non-REM; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; PA, physical activity; PET, positron emission tomography; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; SBI, silent brain infarction; SD, sleep deprivation; SDB, sleep-disordered breathing; SVD, disease of small cerebral vessel; SWS, slow-wave sleep; TST, total sleep time; VaD, vascular dementia; WASO, wake after sleep onset; WMH, white matter hyperintensity.

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