Implications of sleep disturbance and inflammation for Alzheimer's disease dementia

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Nearly half of all adults older than 60 years of age report sleep disturbance, as characterised either by reports of insomnia complaints with daytime consequences, dissatisfaction with sleep quality or quantity, or the diagnosis of insomnia disorder. Accumulating evidence shows that sleep disturbance contributes to cognitive decline and might also increase the risk of Alzheimer's disease dementia by increasing β-amyloid burden. That sleep disturbance would be a candidate risk factor for Alzheimer's disease might seem surprising, given that disturbed sleep is usually considered a consequence of Alzheimer's disease. However, a bidirectional relationship between sleep and Alzheimer's disease is supported by advances in our understanding of sleep disturbance-induced increases in systemic inflammation, which can be viewed as an early event in the course of Alzheimer's disease. Inflammation increases β-amyloid burden and is thought to drive Alzheimer's disease pathogenesis. Improved understanding of the mechanisms linking sleep disturbance and Alzheimer's disease risk could facilitate the identification of targets for prevention, given that both sleep disturbance and inflammatory activation might be modifiable risk factors for Alzheimer's disease.

Introduction

More than 47 million people globally were estimated to have dementia in 2015, and the number of dementia cases is projected to triple to nearly 150 million by 2050, due in part to the increasing number of people living more than 65 years.[1] An individual's risk of developing dementia, especially Alzheimer's disease dementia, is related to several genetic factors, but emerging evidence has shown that lifestyle factors, such as sleep disturbance, might also increase an individual's risk.[1]

Sleep benefits the consolidation of memory.[2] However, nearly half of all adults older than 60 years of age have difficulty initiating and maintaining normal sleep patterns.[3] Accumulating evidence shows that such sleep disturbance contributes to cognitive decline,[4–6] and might also heighten the risk of Alzheimer's disease by increasing β-amyloid burden.[7] Although a widely held clinical view is that disturbed sleep is a consequence of Alzheimer's disease,[8] a bidirectional relationship appears to exist between sleep and Alzheimer's disease, in which sleep disturbance is associated with Alzheimer's disease biomarkers, including β-amyloid deposition in the brains of adults older than 60 years of age.[9] The notion that sleep disturbance is a risk factor for Alzheimer's disease is supported by advances in our understanding that sleep disturbance induces increases in systemic inflammation,[10,11] which is increasingly viewed as an early event in the course of Alzheimer's disease.[12,13] Immune system-mediated actions contribute to β-amyloid burden to drive Alzheimer's disease pathogenesis.[12] Better understanding of the mechanisms underlying the effect of sleep disturbance on Alzheimer's disease risk has the potential to optimise efforts for the identification of targets for Alzheimer's disease prevention.[14]

In this Review, we evaluate the association between sleep disturbance and Alzheimer's disease risk, and we discuss the role of inflammation in explaining how sleep disturbance might contribute to Alzheimer's disease. These findings are contextually framed by evidence that activation of the innate immune system alters CNS inflammatory mechanisms and increases amyloid burden, possibly driving onset and progression of Alzheimer's disease.[12] Finally, because sleep disturbances are treatable, they might be targets for the prevention of Alzheimer's disease,[14] especially given findings that such treatment, including low-cost, community-based interventions, might mitigate age-related increases in inflammation.[10,15]

Effects of sleep disturbance

Clinical characteristics and assessment

Insomnia can be classified into four categories: insomnia symptoms, insomnia complaints with daytime consequences, dissatisfaction with sleep quality or quantity, and insomnia disorder; the latter three categories are characterized as sleep disturbance.[16] Insomnia symptoms, such as taking longer to fall asleep and night-time wakefulness, are common occurrences and are not necessarily viewed as bothersome, because the low severity of these symptoms is such that older adults report satisfaction with their sleep and the absence of daytime consequences due to these symptoms.[3] When insomnia symptoms are bothersome, resulting in daytime consequences (ie, fatigue and depressed mood), or when there is dissatisfaction with quality or quantity of sleep, such insomnia complaints are generally termed as sleep disturbance.[16] When sleep disturbance and insomnia complaints become more severe, occurring 3 or more nights a week for at least 3 months with dissatisfaction with sleep and daytime consequences, the diagnosis of insomnia disorder is fulfilled, using Diagnostic and Statistical Manual of Mental Disorders criteria (panel 1).[17] Insomnia disorder is diagnosed using a patient's clinical history and does not require the use of objective measures of sleep, such as polysomnography or actigraphy (ie, wrist-worn motion detector to track rest or activity and to infer sleep or wakefulness over a period of days or weeks).[17] However, these techniques, particularly actigraphy, might be used to identify problematic circadian sleep patterns. In the following sections, the general term sleep disturbance will be used to indicate presence of insomnia complaints, dissatisfaction with quality or quantity of sleep, or insomnia disorder. If studies described the formal diagnosis of insomnia disorder or measures of sleep duration, such specificity will also be provided.

Patients often neglect to report symptoms of insomnia, which emphasises the need for clinicians to enquire about the presence of insomnia symptoms and whether they are bothersome and result in daytime problems. When such information is systematically gathered, insomnia symptoms are very common, reported by as many as 50% of adults older than 60 years of age.[3] The prevalence of insomnia complaints or dissatisfaction with sleep (ie, sleep disturbance) occurs in 10–20% of adults, whereas insomnia disorder has a population prevalence of 6–10%, but occurs with considerably higher frequency in adults older than 60 years of age, particularly those with comorbid illnesses.[16] Additionally, women are more likely to report sleep disturbance than men.[16] In two cross-sectional studies[18,19] of sleep duration in the USA (1207 and 6928 participants), ethnic minorities, such as African Americans and Hispanics, were more likely to report sleep disturbance compared with whites. Longitudinal data in 22 252 adults older than 50 years of age in the USA show that the severity of four insomnia symptoms (ie, trouble falling asleep, waking during the night, waking too early, and not feeling rested) increased more in an 8-year period in Hispanic individuals than in non-Hispanic white individuals.[20] Substantial changes in sleep and its underlying circadian rhythm are associated with human ageing.[4] Among the factors that contribute to the high prevalence of insomnia symptoms in older adults are: (1) age-related changes in sleep homoeostatic drive and circadian timing; (2) medical and psychiatric comorbidities and their treatments; (3) primary sleep disorders such as sleep apnoea, restless legs syndrome, and rapid eye movement sleep behaviour disorder; (4) behavioural, environmental, and social factors, often collectively referred to as sleep habits or hygiene, which can maximise or compromise sleep quality; or, most frequently, (5) some combination of these factors.[3]

An individual who is experiencing sleep disturbance or insomnia disorder might also be sleeping for habitually short, normal, or even long sleep durations, indicating the disturbances in the quality or maintenance of sleep during the sleep period might be more salient than the duration of sleep. However, both short (typically <5 h) and long (typically >10 h) self-reported habitual sleep durations were associated with increased morbidity and mortality in a meta-analysis of more than 70 000 adults aged 60 years or more.[21] Insomnia disorder with objective short sleep duration is thought to be a severe biological phenotype, and is associated with significantly increased risk of cardiometabolic and neurocognitive morbidity and mortality.[22] Sleep disturbance and insomnia disorder can also be risk factors for depression and depression recurrence,[23,24] with evidence suggesting that depression is a risk factor for cognitive decline and dementia.[25] However, the relationship between sleep disturbance and depression, as well as between sleep disturbance and dementia, is typically bidirectional.[24] As illustrated in the clinical example (panel 2), this bidirectionality is particularly likely to be the case with insomnia disorder and dementia, because insomnia disorder is the most severe phenotype of sleep disturbance.

Panel 1: Criteria for insomnia disorder

According to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition,[17] each of the following criteria must be fulfilled for diagnosis of insomnia disorder:

- A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
  - Difficulty initiating sleep
  - Difficulty maintaining sleep, characterised by frequent awakenings or problems returning to sleep after awakenings
  - Early-morning awakening with inability to return to sleep
- The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioural, or other important areas of functioning
- The sleep difficulty occurs at least 3 nights per week
- The sleep difficulty is present for at least 3 months
- The sleep difficulty occurs despite adequate opportunity for sleep
- The insomnia is not better explained by and does not occur exclusively during the course of another sleep–wake disorder (eg, narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep–wake disorder, or a parasomnia)
- The insomnia is not attributable to the physiological effects of a substance (eg, a drug of abuse or a medication)
- Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia

Dementia risk

Sleep and its underlying circadian rhythm are disturbed in patients with Alzheimer's disease and these disturbances worsen with disease progression.[8] In advanced stages of Alzheimer's disease, there is an extreme breakdown of the circadian regulation of sleep,[8] in which sleep occurs sporadically across the 24-hour day (ie, irregular sleep wake rhythm disorder). The progressive neuropathological changes caused by Alzheimer's disease in brain centres involved in sleep regulation, such as the suprachiasmatic nucleus, are the likely cause of changes in sleep–wake activity.[8]

Panel 2: **Case study**

A 68-year-old woman who previously had occasionally disturbed sleep was referred to a mental health professional by her primary care physician with a primary complaint of increased disrupted sleep and fatigue over the past 5 months. The patient had difficulty falling asleep, typically remaining awake for 30–50 minutes, and woke several times per night with difficulty falling back to sleep at least four nights per week. The patient reported difficulties with memory and mood during the same 5-month period and noted that poor sleep and forgetfulness affected her mood. She also reported that she no longer enjoyed either her work or her previously active social life, lacked motivation, and also reacted irritably in situations she previously handled easily. To compensate, she increased her caffeine intake over her previous single morning coffee and began to consume diet cola at lunchtime. The patient's medical history indicated hypertension, osteoarthritis, and diabetes (controlled by diet), and a short period of depression in her late 20s following a miscarriage. She had been postmenopausal since the age of 56 years and was on hormone therapy until the age of 62 but discontinued because of breast cancer concerns.

The patient was taking hydrochlorothiazide, nightly acetaminophen-diphenhydramine for sleep and pain, and ibuprofen for pain, which was generalised to muscles, as well as several joints. She reported drinking two glasses of wine most days of the week with dinner and never smoked. She was married with three children and two grandchildren. Mental, neurological, and physical examinations were normal, except for a body-mass index of 31 and blood pressure of 135/92 mm Hg. The patient had a Hamilton Depression Scale score of 14, indicative of mild-to-moderate depression. On the basis of medical history and examination, the patient was diagnosed with insomnia disorder. A glucose tolerance test was ordered to ensure diabetes control. The importance of regular exercise for weight and diabetes control and to improve sleep, pain, and mood was discussed, and the patient was referred to local support programmes. The patient was advised to review her sleep habits, decrease caffeine particularly in the early evening, and discontinue nightly diphenhydramine, replacing it with acetaminophen only, as it was noted that there is unsubstantial evidence for use of chronic diphenhydramine for sleep and it has adverse effects. The patient was prescribed cognitive behavioural therapy for insomnia, either from a local sleep clinic or an on-line treatment programme. It was noted that memory and mood complaints were mild but should be monitored for improvement with improved sleep. Possible referral to the local memory clinic for more in-depth memory testing was discussed if the patient became sufficiently concerned. Follow-up after 3–4 months was recommended to assess exercise, diet, weight loss, sleep improvement, and monitor diabetes, pain, mood, and cognition.

However, sleep disturbance, which is associated with compromised cognitive function in healthy ageing, might also increase risk for development of Alzheimer's disease.[4] The formation of new hippocampal-based memories is dependent on undisturbed sleep both before and after the initial encoding of a potential memory; these processes have been shown to be impaired in older adults.[4] A meta-analysis of self-reported sleep quality, sleep duration, and cognitive function in 97 264 adults aged 55 years or older in the USA, Europe, and Asia reported that both self-reported shorter (≤5 h) and longer (≥9 h) sleep durations were associated with impaired cognitive function.[26] Of note, a meta-analysis of more than 50 000 adults in the USA, Europe, and Asia examining sleep disturbance, sleep duration, and blood and serum concentrations of inflammatory inflammatory markers (C-reactive protein [CRP], interleukin-6 [IL-6], and tumour necrosis factor α [TNFα])[11] found that sleep disturbance and long sleep duration (>8 h) were both associated with increases in markers of systemic inflammation; short sleep duration (<7 h) had only a marginal effect on CRP. In an observational study of 173 community-dwelling adults aged 65–89 years in Australia, objective actigraphic sleep indices, but not subjective reports, were associated with worse memory performance.[27] Finally, in cognitively healthy older adults (mean age 81·7 years), those individuals with greater levels of sleep disturbance (ie, sleep fragmentation in the highest 90th percentile) showed a more rapid rate of cognitive decline and a higher risk of developing Alzheimer's disease over 6 years of follow up, compared with individuals with lower levels of sleep disturbance (ie, sleep fragmentation in the lowest 10th percentile);[28,29] the role of inflammation or other biological pathways in this adverse trajectory is not known.

Additional evidence indicates that sleep disturbance is a risk factor for development of dementia. In a longitudinal study of 124 community-dwelling participants (mean age 60·1 years) in the USA,[30] self-reported measures of excessive daytime sleepiness, a correlate of sleep disturbance, were associated with more than 2·5 times the odds of β-amyloid deposition over an average of 15·7 years follow-up. A meta-analysis of 18 longitudinal studies including 246 786 baseline participants and 25 847 people with dementia in the USA, Europe, and Asia, over an average of 9·5 years of follow-up, reported that participants with sleep disturbances at baseline had a higher risk of incident all-cause dementia, Alzheimer's disease, and vascular dementia compared with those not reporting disturbed sleep.[31] Subgroup analyses found that sleep disturbance increased the risk of incident Alzheimer's disease but not vascular or all-cause dementia. Additionally, sleep disordered breathing also increased the risk of dementia and was associated with a higher incidence of all-cause dementia, Alzheimer's disease, and vascular dementia.[31]

Inflammation

One biologically plausible mechanism that links sleep disturbance and dementia risk is activation of the inflammatory response, which is thought to be an early event associated with the onset and clinical course of Alzheimer's disease.[12,13,32]

In humans, experimental manipulation of sleep duration provides some of the most robust evidence that sleep disturbance leads to increases in inflammation. A number of different experimental methods, including total night sleep deprivation, chronic sleep restriction, or partial night sleep deprivation, appear to induce activation of markers of inflammation, although effects vary due in part to differences in duration of sleep loss, as well as the markers of inflammation being assessed.[10,11,15] Even after a single night of partial sleep deprivation, activation of upstream markers of inflammation occurs, including activation

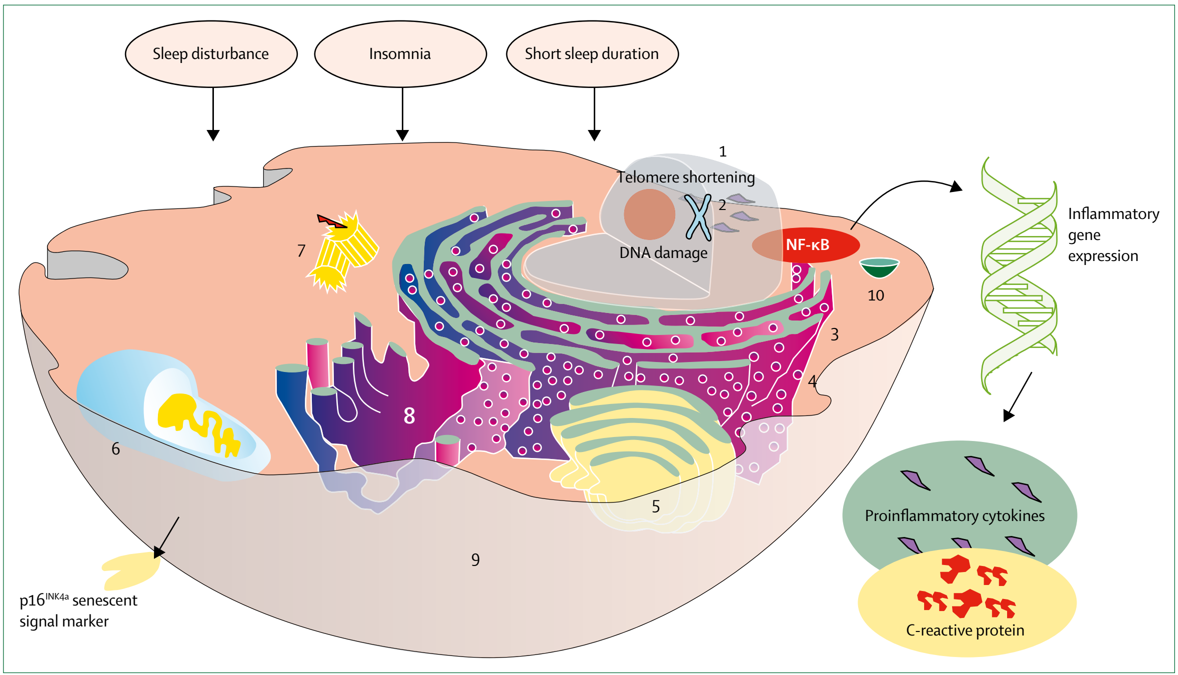

Figure 1: **Potential effects of sleep disturbance on molecular processes of inflammation and biological ageing**
Insomnia, sleep disturbance, and short sleep duration activate cellular and molecular processes of inflammation, including increases in nuclear factor-κ-B (NF-κB) signalling, which leads to inflammatory gene expression, production of proinflammatory cytokines, and systemic inflammation with further increases of proinflammatory cytokines and C-reactive protein. Together, these inflammatory changes can induce cellular ageing, including shortening of the telomeres, increase in the DNA damage response, and expression of the cell surface senescent signal marker $p16^{INK4a}$. This cellular ageing is associated with further increases in inflammation. Expression of $p16^{INK4a}$ cell surface marker indicates the transition of a cell to the senescence-associated secretory phenotype. Depicted within the cell are the following components: (1) nucleus; (2) chromosome; (3) rough endoplasmic reticulum; (4) ribosome (little dots); (5) Golgi apparatus; (6) mitochondrion; (7) centrosome; (8) smooth endoplasmic reticulum; (9) cell membrane; (10) vesicle.

of inflammatory signalling pathways such as nuclear factor-κ-B, activator protein-1, and STAT family proteins,[10,33–35] which together lead to increases in mRNA expression of proinflammatory cytokines (figure 1).[11,35]

Observational studies have also found that sleep disturbance is associated with elevated levels of inflammation, as shown in a meta-analysis of 72 studies comprising more than 50 000 adults.[11] Although sleep disturbance was assessed by a variety of approaches (ie, reporting of items of insomnia complaints, validated questionnaires, or interviews to ascertain insomnia severity or diagnosis) in the studies included in the meta-analysis, the findings were statistically significant. As the quality of the assessment of sleep disturbance improved (ie, from reporting of single items of insomnia complaints to the use of validated questionnaire or diagnostic interviews), the effect sizes linking sleep disturbance to measures of inflammation, such as CRP and IL-6 increased.[11] When pooling data for all assessment approaches, sleep disturbance was associated with increased blood concentrations of CRP and IL-6. Additionally, consistent with experimental findings, shorter sleep duration (≤7 h), as treated continuously or categorically, was associated with increased concentrations of CRP but not IL-6. Long sleep duration (≥8 h), as treated continuously or categorically, was also asssociated with higher concentrations of both CRP and IL-6. Together, these results suggest that reports of sleep disturbance might be more robustly associated with increases in inflammation than can be explained simply by a reduction in sleep duration, although it is not known what aspect of sleep disturbance contributes to increases in inflammation. Additionally, sleep disturbance when combined with short sleep duration is thought to have a particularly negative effect on health outcomes, including hypertension;[22,36] however, most studies of sleep and inflammation have predominantly examined sleep disturbance and sleep duration in separately, or in separate statistical models.[11]

In a 5-year longitudinal study in the USA of 2962 African-American and white adults aged 33–45 years, both sleep disturbance and subjectively reported short sleep duration were significant predictors of increases of CRP and IL-6.[37] Furthermore, objective measures (ie, in home polysomnography, wrist actigraphy) have shown that short sleep duration (<5 h) and sleep fragmentation (awake for ≥90 min during the night) were associated with increases in inflammatory burden in 2531 community dwelling men aged 65 years or older.[38]

A number of modifiable lifestyle factors, including sedentary physical activity and obesity, are reported to be linked to increased risk for dementia,[1] and some have also been found to be associated with increases in inflammation.[39] Importantly, the effect of sleep disturbance on inflammation might be equivalent, or in some cases greater, than that of some demographic (eg, age and race) or biobehavioural (eg, body-mass index and physical activity) factors associated with inflammation.[11,39] In patients with insomnia, treatment of insomnia and its clinical remission lead to decreases in concentrations of CRP.[40–42] A similar magnitude of decrease of CRP was reported in other meta-analyses that examined two other lifestyle factors, namely diet and exercise in healthy adults; one of these studies evaluated the effects of consumption of a healthy dietary pattern in adults on CRP[43] and another examined the effects of exercise on CRP and other inflammatory markers.[44]

Women are at higher risk for Alzheimer's disease compared with men,[1] more likely to experience sleep complaints,[16] more likely to have higher levels of systemic inflammation,[11] and more likely to have greater increases of inflammation associated with sleep disturbance.[10] In 980 adults in the USA (mean age 66·7 years) with established heart disease, poor sleep quality predicted increases in inflammation, but only in women.[45] In another study of 2553 adults in the Netherlands (mean age 46·9 years), this sex difference in inflammation was especially pronounced for women with extremely long sleep durations.[46] African Americans with short sleep duration (≤ 5 h) were also more likely to show increases of inflammation compared with other ethnic groups in a study of 5587 adults (mean age 45·9 years) in the USA.[47]

Biological ageing

Elevated inflammation contributes to proinflammatory secretory cellular phenotypes and cellular senescence, and such cellular phenotypes are associated with dementia risk and other age-related morbidities.[48] In a study of 29 adults in the USA aged 61–86 years, partial night sleep deprivation induced a shift in transcriptional profiles of leucocytes towards the expression of genes associated with cellular senescence, DNA damage response, and the senescent signal marker $p16^{INK4a}$,[49] a protein that inhibits cell cycle progression (ie, a potent biomarker of human ageing; figure 1).[50–52] In cross-sectional studies, leucocyte telomere length, another robust biological marker of cellular ageing, correlates with sleep disturbance and insomnia.[53–55] Additionally, in the Women's Health Initiative study of 2078 women in the USA (mean age 64·5 years),[56] insomnia symptoms were associated with epigenetic methylation of DNA (ie, epigenetic age), which has predictive utility as an epigenetic clock that is prognostic of age-related morbidity and mortality beyond chronological age.[57,58]

β-amyloid dynamics and stress adrenergic mechanisms

Other fundamental processes that lead to neurodegeneration and possibly contribute to Alzheimer's disease risk are also altered by disturbances in sleep–wake activity. Crucial in the pathogenesis of Alzheimer's disease is the accumulation of β-amyloid peptide,[59] which is in part driven by inflammation.[12] However, decreases in the clearance of β-amyloid might also have a role.[1] In humans, concentrations of β-amyloid in the CSF show a diurnal fluctuation, with increases during the day and decreases in the night.[60] Sleep deprivation can affect this process. In a randomised trial of 26 healthy men in the USA aged 40–60 years, participants deprived of sleep for one night did not have as much of a decrease in CSF concentrations of β-amyloid as participants who had a night of unrestricted sleep.[61] In animal studies, sleep is found to affect glymphatic CSF dynamics with enhanced interstitial solute clearance, including soluble β-amyloid,[62] and disturbances in sleep–wake activity impair the removal of potentially neurotoxic waste products, such as β-amyloid, which have accumulated during the wake period.[62–65] Moreover, when mice are placed in the lateral decubitus position, improved clearance of β-amyloid occurs compared with prone or supine positions.[66] In humans, sleep is known to contribute to β-amyloid clearance from the brain, but it is unknown whether the lateral decubitus position during sleep has an advantage with regard to the removal of waste products, such as β-amyloid, compared with the supine position, for example.[61] In a mouse model of Alzheimer's disease, the accumulation of β-amyloid also has a feedforward effect and further reduces glymphatic clearance of β-amyloid compared with littermate controls.[67]

Sleep disturbance can also activate stress response pathways such as noradrenergic activity,[10] and this sympathetic activation directs the immune system towards upregulation of inflammatory gene transcriptional profiles and increases in systemic inflammation.[68,69] Additionally, animal models indicate that sleep–wake activity regulates central noradrenergic tone in the locus coeruleus, which in turn alters glymphatic clearance mechanisms.[62] In the transition from sleep to wakefulness, central norepinephrine levels increase, whereas mechanisms of glymphatic clearance decrease, suggesting that sleep disturbance in humans, known to increase noradrenergic tone,[10] might also reduce interstitial space volume and thereby reduce glymphatic flow and β-amyloid clearance.[62]

Dementia risk

An increase in systemic inflammation is hypothesised to drive alterations in the microglia which lead to inflammation in the CNS and could result in an increased risk for cognitive ageing and Alzheimer's disease (figure 2).[12,13] Given that inflammation might be a biological risk factor for clinical symptoms, such as the mild cognitive impairment that precedes the onset of Alzheimer's disease,[13,26] and that sleep disturbance has robust effects on inflammatory biology, inflammation is hypothesised to be a biologically plausible pathway linking sleep disturbance and risk of Alzheimer's disease.[6,14]

Several lines of evidence support the idea that inflammation is a risk factor for Alzheimer's disease dementia. First, although changes in a variety of cytokines (ie, IL-6

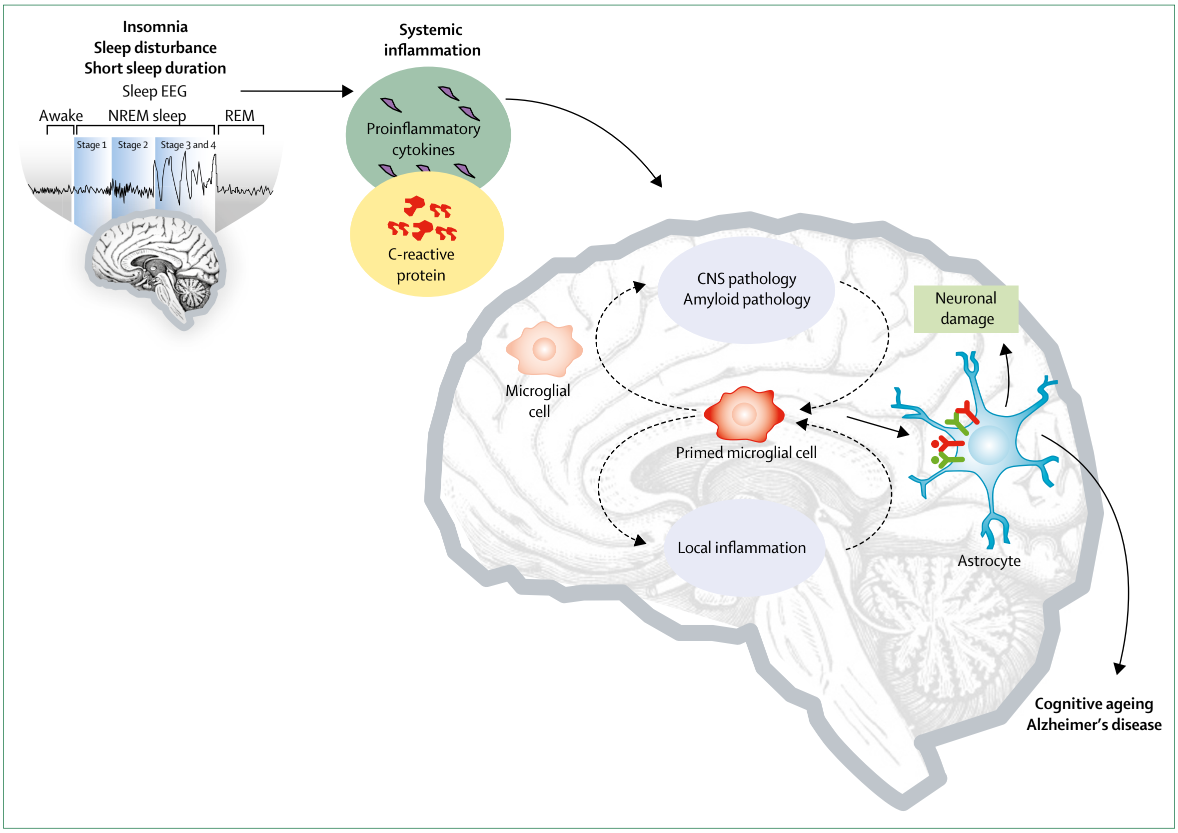

Figure 2: **Hypothetical model linking sleep disturbance, inflammation, and risk of Alzheimer's disease dementia**
Among the several pathways that might explain how sleep disturbance leads to the development of Alzheimer's disease dementia is the activation of inflammatory mechanisms in response to sleep disturbance. Sleep disturbance leads to increases in systemic inflammation (as measured by proinflammatory cytokines and C-reactive protein), which in turn is hypothesised to contribute to the transition of the microglial cell to the primed microglial cell. The primed microglial cell displays an amoeboid morphology and is dysfunctional, resulting in reduced clearance of amyloid, increases in the production of proinflammatory cytokines, and local inflammation within the CNS; all of which are thought to occur during Alzheimer's disease dementia progression. Together these changes in the microglial cell to the primed microglial cell lead to a feedback loop, in which greater increases in local inflammation in the CNS lead to the development of more microglial cells that are activated and primed, with greater accumulation of Alzheimer's disease neuropathology. Furthermore, such accumulation of amyloid leads to the expression of interleukin-12 (IL-12) and IL-23, which are not expressed by microglia in healthy brains. In turn, expression of both of these cytokines by primed microglia is accompanied by astrocyte expression of receptors for IL-12 (green receptor) and IL-23 (red receptor), as reviewed elsewhere.[12] The rise in inflammatory cytokines, including IL-12 and IL-23, and their receptors, further leads to increased deposition of amyloid and presumably neuronal damage, which contributes to cognitive ageing and Alzheimer's disease dementia. Further detail regarding these mechanisms, including neuronal damage, are provided in the appendix.

and TNFα) in relation to mild cognitive impairment and Alzheimer's disease were mixed in a review of 118 studies,[70] concentrations of proinflammatory cytokines in plasma and CSF appeared to increase over the course of Alzheimer's disease. Several studies in animal models[71] and clinical studies of patients with Alzheimer's disease[72–75] also suggested that systemic inflammation accelerated cognitive decline. For example, in a prospective study of 300 community-dwelling participants in the USA (mean age 82·7 years) with mild to severe Alzheimer's disease,[72] events that induce acute systemic inflammation due to an infection or trauma not directly related to the central nervous system were linked to a doubling in the rate of cognitive decline over a 6-month period following the event. Additionally, those with high plasma concentrations of TNFα (eg, >4·2 pg/ml) showed an increase in the rate of cognitive decline of 4 times over 6 months, compared with those with low concentrations (eg, <2·4 pg/mL), who showed no change in cognitive function.[72] Second, in a study of 41 patients with psoriasis in the USA,[73] their levels of inflammation were elevated and they had impairment of long-term verbal memory, executive functions, and attention compared with 37 healthy controls. Finally, traumatic brain injury was shown to lead to short-term and long-term CNS inflammation in a post-mortem analysis of 99 cases (aged 1·5–89 years at time of injury) compared with 20 controls (aged 18–71 years) with no substantial neurological impairment.[74] This association between traumatic brain injury and inflammation is relevant since a registry-based study of 2794852 adults aged 50 years or older in Denmark, found that the risk of all-cause dementia in people with a history of traumatic brain injury was higher than in those without a history,[75] consistent with animal models.[76]

Both genetic and animal model approaches have provided evidence for an association between Alzheimer's

See Online for appendix

disease mechanisms and activation of the immune system, in which increases in inflammation serve to perpetuate and possibly accelerate the disease course by a feedback loop involving the microglia (appendix).[77–82] In brief, the activated or primed microglial phenotype found in Alzheimer's disease, driven in part by systemic inflammation, represents a dysfunctional phenotype that is characterised by an amoeboid morphology with production of inflammatory factors (figure 2). This amoeboid morphology is tied to marked impairment in phagocytosis, diminished capacity to extend microglial processes toward a tissue lesion, and inefficient clearing of amyloid.[12] Moreover, this dysfunctional microglial phenotype appears to be sustained by inflammatory cytokines, suggesting the presence of a feed-forward feedback loop between the amoeboid microglial phenotype and inflammation, which acts to accelerate accumulation of Alzheimer's disease pathology.[12]

Despite advances in the understanding of the biological mechanisms linking the innate immune system to Alzheimer's disease, effective strategies that target these inflammatory pathways to prevent and treat Alzheimer's disease remain elusive. For example, given the robust associations between innate immunity risk alleles, microglial activation, increases in the inflammatory response, and formation of amyloid plaques and Alzheimer's disease progression,[12] nonsteroidal anti-inflammatory drugs (NSAIDs) were hypothesised to have therapeutic potential.[83,84] However, after a number of large-scale clinical trials with different compounds, little evidence supports the use of NSAIDs for Alzheimer's disease treatment based on neuroinflammation as a target.[85,86] However, some evidence suggests that NSAIDs might be beneficial. In a trial of 2528 adults older than 70 years without Alzheimer's disease in the USA,[87] treatment with a conventional NSAID, such as naproxen, resulted in reduced Alzheimer's disease incidence compared with those receiving placebo, but only in analyses done after 2–3 years of follow-up. In contrast, when NSAIDs were given to adults with Alzheimer's disease dementia, worsening of Alzheimer's disease pathology was reported. Together, these findings have led to the hypothesis that the effects of NSAID treatment might differ at various stages of disease. NSAID COX-1 suppression might protect neurons against inflammatory mediated damage in the early stages of Alzheimer's disease, whereas inhibition of COX-2, through its interactions with NMDA receptor signalling on dendrites, might stress neurons that are already dysfunctional in the later stages.[85,86] However, even in the event of future development of disease-modifying treatments, effective Alzheimer's disease prevention is needed;[88,89] hence, there is growing interest in modifiable risk factors, such as sleep disturbance, and whether improvements in sleep disturbance might mitigate activation of the inflammatory processes that are thought to contribute to Alzheimer's disease.

An alternative to the hypothesised temporal sequence linking sleep disturbance, inflammation, and Alzheimer's disease risk is that β-amyloid deposition causes disturbed sleep as well as inflammation. In humans, cortical β-amyloid burden and CSF measures of β-amyloid correlate with both subjective and objective measures of sleep disturbance.[90–92] Furthermore, in cognitively healthy older adults, β-amyloid deposition is present in sleep-regulating areas, such as the locus coeruleus and basal forebrain.[4] In a PET imaging study of 26 cognitively healthy adults (mean age 75·1 years), β-amyloid burden was selectively associated with loss of slow wave sleep, which in turn contributed to worse performance on a word-pair memory test.[90] Hence, a currently untested hypothesis is whether such β-amyloid deposition triggers sleep disturbance or inflammation (ie, at the CNS level, via direct effects of β-amyloid, or at the systemic level, via sleep disturbance), contributing to Alzheimer's disease risk.

Conclusions and future directions

In their landmark Commission, Livingston and colleagues[1] indicated that about 35% of dementia is attributable to a combination of nine modifiable risk factors: education, midlife hypertension, midlife obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, and social isolation. However, sleep disturbance was not included in their models evaluating the percentage of preventable cases of Alzheimer's disease dementia. In those individuals with sleep disturbance, the relative risk of 1·5 of developing Alzheimer's disease[31] is comparable with the relative risks of the other nine risk factors, which range from 1·4 to 1·9.[1] Additionally, because sleep disturbance contributes to the occurrence of hypertension and diabetes and is associated with sedentary physical activity and social isolation,[15] targeting sleep disturbance might have benefits on several non-independent factors, providing combinatorial gains in reducing the Alzheimer's disease risk profile.

As a risk factor for Alzheimer's disease, sleep disturbance activates innate immunity relevant in Alzheimer's disease pathogenesis (figure 2). However, it is not known when sleep disturbance initiates its effects—ie, in early or mid-life, similar to hypertension,[93] or in late-life, similar to depression.[1] If the latter is true, sleep disturbance might only be a prodromal symptom, given that dementia induces robust disturbances in sleep-wake activity.[6] However, if sleep disturbance acts early, mitigation of this risk factor might have cumulative and downstream effects on other factors, which might include reserve-enhancing factors such as physical activity, intellectual stimulation, or leisure activities, to reduce risk of Alzheimer's disease. Additionally, there is an absence of information about what aspect of sleep disturbance (ie, sleep maintenance, duration, or both) drives Alzheimer's disease risk. Relevant to this concern, the vast majority of prospective evidence has relied on self-report,[31] which does not necessarily reflect how well people are actually sleeping. Objective sleep measures, such as actigraphy, using algorithms of scoring that have been validated by polysomnography, might address this issue. Moreover, inclusion of inflammatory biomarkers would advance understanding of how sleep disturbance might contribute to Alzheimer's disease, and whether the biological heterogeneity in inflammatory responses can be used to refine identification of those individuals with sleep disturbance who are at greatest risk for Alzheimer's disease.

Little data exist on how various genetic variants that contribute to Alzheimer's disease risk, such as *APOE* gene variants,[88] might be related to sleep disturbance, and whether sleep disturbance (or other modifiable risk factors) interact with these genetic variants to strengthen risk model predictions of Alzheimer's disease. Furthermore, if sleep disturbance and *APOE* gene variants do interact to predict Alzheimer's disease risk, the efficacy of prevention trials could be augmented by targeting the most vulnerable individuals. The latter issue is especially relevant for innate immunity genetic variants, given the effects of sleep disturbance on inflammation. However, in one study of 1264 cognitively healthy adults (mean age 57·5 years) in the USA,[94] *APOE* ε4 carriers 50 years of age or older were more likely to self-report trouble falling or staying asleep, suggesting that APOE might promote Alzheimer's disease by degrading sleep.

No randomised trials are available that show that treatment of sleep disturbance prevents cognitive decline or dementia. Nevertheless, clinical guidelines support the treatment of insomnia disorder in clinical conditions associated with dementia risk (ie, hypertension and diabetes).[95] Additionally, treatment of sleep disturbance might be integrated into combination strategies to prevent dementia, similar to the design of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) that provided four intensive lifestyle-based strategies (diet, exercise, cognitive training, and vascular management) to 1260 adults (mean age 69·3 years) at high risk of dementia, and which was found to improve cognition.[96]

If sleep disturbance is a modifiable risk factor that can be targeted in Alzheimer's disease prevention, several issues should be considered in the selection of a treatment approach to improve sleep disturbance, namely safety, efficacy, cost, and community-level access for broad, population level exposure. Of the large number of available treatments for insomnia disorder, the American College of Physicians recommends cognitive behavioural therapy for insomnia (CBT-I), which combines cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation to improve sleep outcomes.[95] However, despite its efficacy, delivery of CBT-I is expensive and requires a qualified provider, which makes it inadequate for the treatment of insomnia at the population level required for dementia prevention. To address this issue, we have pioneered the development of innovative, community-based interventions that use mindfulness-based approaches to target stress arousal mechanisms and treat sleep disturbance and insomnia disorder.[40,41,97–99] For example, in a study of 90 survivors of breast cancer (aged 42–83 years) in the USA,[98] a form of movement meditation, tai chi, was non-inferior to CBT-I in the treatment of insomnia disorder, and the benefits of both were maintained over 1 year. Similarly, in a study of 49 adults older than 55 years (mean age 63·3 years) in the USA,[99] a mindfulness based treatment was found to improve sleep disturbance (ie, sleep quality) with effect sizes similar to CBT-I. Both tai chi and mindfulness have other broad benefits on several health outcomes, including depression, hypertension, and inflammation,[100–102] and evidence suggests that both interventions reverse sleep disturbance related inflammation,[42,103] with effects maintained over 1 year.[40]

To sum up, sleep disturbance might be a risk factor for late-life Alzheimer's disease. Inflammation is a biologically plausible mechanism for Alzheimer's disease pathogenesis, and the effects of sleep disturbance on inflammatory pathways provide a molecular framework with which to understand how sleep disturbance might contribute to the early, and possibly the later, course of Alzheimer's disease. Treatment of sleep disturbance, using community-accessible and effective interventions that can be disseminated at a population level, has the potential to effectively promote sleep health and reverse insomnia-related inflammatory risk profiles. Given the evidence that sleep disturbance is linked to inflammation, as well as several other modifiable risk factors for Alzheimer's disease, research is needed to evaluate whether the targeting of sleep disturbance might represent a novel treatment opportunity or even preventive strategy in Alzheimer's disease.

Search strategy and selection criteria

We performed a systematic search of the PubMed, ISI Web of Science, and PsycINFO databases to identify studies that reported associations between sleep disturbances, insomnia, inflammation, and dementia. Searches were conducted using the following search terms: (sleep OR sleep disorder OR sleep problems OR sleep disturbances OR sleep quality OR insomnia AND dementia OR Alzheimer's disease); (above named sleep terms AND inflammation OR inflammatory); (above named inflammation terms AND dementia OR Alzheimer's disease). The literature search was limited to the English language and limited to the dates up to Oct 15, 2018, with a primary focus on dates between September, 2013 and October, 2018. We also searched reference lists and review articles for additional studies that met the inclusion criteria. This Review is not exhaustive or a meta-analysis. The final reference list was generated based on relevance to the topics covered in this Review.

Contributors

Both authors contributed to the conception and design of this Review, including acquisition of reference material and interpretation of the findings for publication, contributed to drafting of the Review and revising it critically, and approved the final version of the work to be published. Both authors agree to be accountable for all aspects of the work and in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

We declare no competing interests.

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