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Disturbed Sleep and Diabetes: A Potential Nexus of Dementia Risk

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Abstract

Type 2 diabetes (T2D) and sleep disturbance (e.g., insomnia, sleep-disordered breathing) are prevalent conditions among older adults that are associated with cognitive decline and dementia, including Alzheimer's disease (AD). Importantly, disturbed sleep is associated with alterations in insulin sensitivity and glucose metabolism, and may increase the risk of T2D, and T2D-related complications (e.g., pain, nocturia) can negatively affect sleep. Despite these associations, little is known about how interactions between T2D and sleep disturbance might alter cognitive trajectories or the pathological changes that underlie dementia. Here, we review links among T2D, sleep disturbance, cognitive decline and dementia—including preclinical and clinical AD—and identify gaps in the literature, that if addressed, could have significant implications for the prevention of poor cognitive outcomes.

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Keywords

sleep; diabetes; cognition; Alzheimer's Disease

1. Introduction

Type 2 diabetes (T2D) is a complex chronic disease characterized by the development of insulin resistance and defective insulin secretion from pancreatic beta cells, leading to hyperglycemia[1]. In 2015, about 12.2% of persons in the U.S. over age 18 had diabetes, with age-related increases in prevalence (4% of those aged 18-44 years, 17% aged 45-64, 25.2% aged 65+)[2]. Diabetes incidence varies significantly by race and ethnicity, with Black and Hispanic individuals in the US having about twice the odds of diabetes relative to their White counterparts[3]. This disparity appears to be due to differences in socioeconomic status, access to health care, and other health issues such as obesity and hypertension[3]. Indeed, the influence of socioeconomic factors is influencing the incidence of diabetes worldwide; 80% of diabetes cases live in low and middle-income countries[4].

This high prevalence of T2D will have significant implications for the global prevalence of cognitive impairment and disability in coming years. T2D is associated with an increased risk of cognitive decline and dementia[5] and an accelerated transition from mild cognitive impairment (MCI) to dementia[6]. Alzheimer's Disease (AD) is the most common cause of dementia, affecting 26.6 million people as of 2006, and is expected to quadruple by 2050, at which point 1 in 85 people worldwide will have the disease[7]. There is currently no cure for AD, so preventing or slowing progression of AD is essential to reducing its population burden[8]. Diabetes has been identified as a modifiable risk factor for dementia, including dementia caused by AD[9].

In recent years, disturbed sleep has emerged as a potential risk factor for poor cognitive and neurological outcomes, including cognitive decline and dementia, and AD pathology[10–13], and importantly, may both contribute to and result from T2D[14]. Here, we use “disturbed sleep” or “sleep disturbance” to refer to a range of sleep problems, including abnormal sleep duration, fragmented sleep, poor perceived sleep quality, or sleep-disordered breathing; however, we specify the type of sleep disturbance we are referring to in particular cases. Given the link between sleep and T2D, and the association of each with cognitive outcomes, sleep and T2D may interact in ways that are important to the prevention of dementia in general, and AD in particular. Here, we review the links among sleep disturbance, T2D, and cognitive decline and AD, and discuss how these associations might be leveraged to mitigate poor cognitive outcomes.

2. Normal and Disturbed Sleep, Metabolic Alterations, and Diabetes

Sleep is a complex biological process that is essential for survival. Sleep is comprised of rapid eye movement (REM) and non-REM (NREM) sleep[15], which are differentiated largely by patterns of brain activity, measured by electroencephalogram (EEG), and by other differences in physiological activity[15]. REM sleep is characterized by rapid eye movements, an EEG waveform that resembles wakefulness, and paralysis of the skeletal muscles[15]. In

addition, the majority of dreams occur during REM. NREM sleep is divided into three stages: N1; N2; and N3[15]. N1 is the lightest stage, from which one is most easily aroused, and is characterized by a rapid low-amplitude EEG waveform. N2 is associated with K-complex waveforms and spindles on the EEG and an increased arousal threshold, compared to N1 (i.e., requiring a higher intensity external stimulus to produce an arousal). Finally, N3 is dominated by slow-wave activity (i.e., slow, high-amplitude waveforms) on EEG (which is why it is referred to as slow-wave sleep (SWS)) and is the stage with the highest threshold for arousal[15]. Typically, after sleep onset, healthy adults cycle through NREM sleep stages, followed by REM about 80 minutes later. NREM and REM sleep continue to alternate in roughly 90-minute cycles throughout the night[16]. NREM sleep accounts for the largest proportion of the earlier cycles of the night, with a decreasing amount accounted for by SWS with each cycle; the proportion of REM in each cycle increases toward the latter part of the sleep period. Notably, the distribution of sleep stages varies by age, with SWS showing substantial decreases with older age[16]. This is of particular relevance to diabetes and AD, given SWS is critical in regulating metabolic function and plays an important role in Aβ production and clearance, as discussed below.

Circadian rhythms are closely related to, but distinct from sleep. Humans and other organisms have evolved to anticipate light and dark cycles and adapt their physical activity and physiological processes to occur at the appropriate time in those cycles. The circadian pacemaker, which is housed in the suprachiasmatic nucleus of the anterior hypothalamus, plays an important role in regulating sleep-wake patterns as well as metabolic functions[17–20]. Although an in-depth discussion of links among circadian rhythms, metabolism, and brain health is beyond the scope of this article, future studies of the role of circadian rhythms in the associations under study here could make an important contribution.

Disturbed sleep is highly prevalent, especially among older adults, who are at elevated risk for both diabetes and poor cognitive outcomes[2,21]. Indeed, as many as 50% of older people have a chronic sleep complaint[22,23]. The two most common clinical sleep issues in the older adult population are insomnia symptoms (i.e., complaints of difficulty falling or staying asleep, non-restorative sleep, early awakening), and sleep-disordered breathing (SDB), each affecting over 20% of older adults, respectively[24–27]. Insomnia is based on self-reported sleep complaints (sleep onset and maintenance, waking up too early, poor sleep quality)[28,29]. When it reaches a particular threshold, this can become a clinical disorder[30]. Insomnia is also sometimes quantified in terms of objective markers using actigraphic or polysomnographic data[30]. A chronic insomnia diagnosis requires that one of these sleep complaints occur three or more times a week for 3 months or more, with consequences in daytime functioning[28,29]. In the sections that follow, we clarify the type of insomnia we are referring to when reporting results from studies.

Sleep plays a central role in metabolism, including conservation of energy and recovery from the energy loss incurred during wakefulness[15]. NREM sleep appears especially important for preserving energy, compared to wakefulness[31]. Given these links, it is not surprising that insufficient sleep, sleep fragmentation and SDB are associated with impaired glucose metabolism and the development of T2D[32–35].

The effects of partial sleep deprivation on glucose metabolism have been demonstrated in human research[36,37]. For example, in a study of young, healthy volunteers, sleep restriction decreased glucose tolerance and increased evening cortisol levels[38]. These findings extend to older populations as well. Both short (5 hours or less) and long (9 hours or more) sleep duration have been tied to impaired glucose tolerance and increased risk of diabetes in men and women over age 50, even after adjustment for SDB severity and waist circumference[39]. Apart from the total amount of sleep obtained, the degree to which sleep is fragmented vs. continuous is an important dimension of sleep. Sleep fragmentation (i.e., discontinuous sleep) is common and may be caused by a variety of factors, including poor sleep hygiene (e.g., caffeine consumption or exercise proximal to bedtime)[40], chronic pain[41], sleep-disordered breathing[42], and periodic leg movements[43]. Sleep fragmentation has been shown to affect metabolic function in both human and animal studies[44–46]. For example, in young, healthy adults, selective fragmentation of SWS during the whole night, without reduction in total sleep time, has been shown to decrease insulin sensitivity and reduce glucose tolerance[33,47,48]. In men 65 years or older, those with less slow wave sleep were significantly more likely to develop hypertension 3 to 4 years later, adjusting for BMI[49].

Obstructive sleep apnea (OSA) is the most common subtype of SDB and has also been linked to metabolic dysfunction. OSA is characterized by recurrent complete interruptions in breathing (apneas) or partial reductions in breathing (hypopneas) due to upper airway obstruction during sleep, which often lead to oxygen desaturation and sleep fragmentation[50]. OSA is caused by anatomically compromised or collapsible upper airway due to obesity or craniofacial abnormalities[51,52] in combination with physiological deficits such as inadequate compensatory responses of the pharyngeal muscles during sleep[51], a low arousal threshold[53] and an overly sensitive control of breathing resulting in respiratory instability[52]. OSA is an important predictor of morbidity and mortality in Western society[54–57] and is believed to contribute significantly to the development and progression of metabolic, cardiovascular, and oncologic diseases[58–62].

Investigators first reported that OSA is associated with insulin resistance in the 1990s[63]; however, it was not until 2001 that the association of OSA with insulin resistance was shown to be independent of co-morbid obesity [64,65]. In 2004, this finding was replicated in a community-based sample of nearly 3,000 individuals over the age of 40 from the Sleep Heart Health Study Cohort[62]. However, all of these are cross-sectional, observational studies, so they cannot establish a causal link between OSA and insulin resistance. OSA is very common in persons with T2D, especially those who are obese. Among obese patients with T2D, 86% have been found to have OSA[66], and half had moderate-to-severe OSA[66], diagnosed via unattended polysomnography.

The effect of OSA on glucose metabolism has been studied through clinical trials of continuous positive air pressure (CPAP) therapy, which is the most efficacious prescribed treatment for OSA. Multiple studies have been performed, yielding contradictory results. However, poor CPAP adherence has been a major weakness of the majority of the studies[67]. For example, Babu et al. found that a strong association between improvement in glycated hemoglobin (HbA_{1c}) and the duration of CPAP use, but only among compliant users, defined as those who used their CPAP on average four hours or more per night[68]. A separate

study found that 1 week of effective CPAP treatment significantly improved glycemic control in patients with OSA and T2D[69]. Lastly, an RCT showed that 8 hours of CPAP treatment per night for two weeks led to better glucose metabolism and blood pressure, among individuals with OSA and prediabetes[70].

Intermittent hypoxia (IH), or periodic hypoxia, is likely one of the mechanisms linking OSA and T2D. An experimental study demonstrated that daytime exposure to 5 hours of IH caused decreases in insulin sensitivity and glucose effectiveness, among young health adults[71]. Recently, a separate study in young healthy adults showed even just 3 hours of IH led to significant increases in plasma glucose[72]. Hyperglycemia during IH has been attributed to activation of the sympathetic nervous system mediated by the carotid body, an organ of peripheral sensitivity to hypoxia[73]. Results from an animal study demonstrated that denervation of the carotid body prevents glucose intolerance and insulin resistance during IH[73]. Because sleep fragmentation is an important consequence of OSA, OSA-related sleep fragmentation may also link OSA to T2D. Taken together, accumulating experimental and epidemiological evidence links respiratory (OSA) and non-respiratory sleep disturbances to increased risks of T2D. It is important to note that disturbed sleep may not only precipitate T2D, but also result from it. As discussed by Taub et al and others[14,74], T2D-related neuropathic pain, depression, and nocturia can adversely affect sleep.

3. Diabetes, Cognition, and Alzheimer's Disease

T2D is a well-established risk factor for poor cognitive outcomes, including cognitive decline, dementia, and AD pathology[75]. In a cross-sectional population-based cohort study of older adults (median age 80 years), those with a T2D diagnosis in midlife had poorer global cognition and executive function in later life, compared to those without a T2D diagnosis in midlife[76]. Among cognitively normal participants, those with T2D showed substantially greater declines in tasks of memory, reasoning, and global cognition over a period of 10 years compared to those without T2D[77]. Further, there is evidence that the association between duration of T2D and poorer performance on tests of attention, working memory, executive function, verbal fluency, and global cognition is moderated by HbA_{1c} levels[78], such that among those with T2D, higher HbA_{1c} is associated with poorer cognitive outcomes.

Evidence also supports a robust connection between T2D and dementia diagnosis. Results from a meta-analysis of prospective studies indicate that T2D is associated with 1.73 times increased risk of all-cause dementia diagnosis, a 2.27 times increased risk of vascular dementia (VaD) diagnosis, and a 1.56 times increased risk of AD diagnosis[9]. Further, neuroimaging studies demonstrate an association between T2D and dementia pathology. With regard to VaD-related pathology, in a multi-center cohort study, diabetes diagnosis was associated with sulcal widening, incident infarcts, white matter hyperintensities, and increasing ventricular size[79], and higher blood glucose levels, even among those without frank T2D, were associated with decreases in white matter integrity[80]. T2D and glycemic control have additionally been associated with AD-related pathology. In a population-based sample of adults aged 70 and older, midlife T2D diagnosis and poorer glycemic control were associated with reduced cortical thickness in an AD-signature region[81], reduced cerebral

glucose uptake in an AD-signature region[82], cerebrovascular pathology (e.g., infarcts), reduced whole brain volume, and smaller hippocampal volume[76] in later life. T2D was not associated with greater cerebral amyloid deposition as measured on positron emission tomography[82]. However, T2D and insulin resistance have been associated with evidence of greater A β[83] in a study of cognitively healthy middle-aged adults. T2D was associated with greater Tau burden, measured in cerebrospinal fluid (CSF), in a cognitively-diverse sample of older individuals (mean age 75.5 years), when controlling for cognitive status[84]. However, when stratified by cognitive status, this relationship only persisted among individuals with MCI, but not among those with normal cognition or AD diagnosis[84]. Thus, the mechanistic pathways between T2D and development of dementia have yet to be fully elucidated.

Importantly, obesity also appears to be a risk factor for dementia, independent of diabetes. Whitmer et al. report that a 36-year longitudinal analysis reveals that central obesity in midlife increases the risk of dementia, even after controlling for the influence of diabetes[85]. However, findings remain mixed. A longitudinal analysis of 18 years of follow up from the Framingham Heart Study found that obesity only decreased cognitive performance among men, while diabetes decreased cognitive performance for men and women combined, but not alone. Further, obesity and diabetes did not appear to interact to influence cognitive performance[86]. The sex-specific findings were replicated in the Health, Aging and Body Composition study, which found that greater adiposity was associated with greater cognitive decline among older males, but not among older females[87]. It also appears that mid-life, but not late-life obesity may increase the risk of dementia[88].

T2D may either directly contribute to the development of dementia or make individuals more susceptible to dementia pathology[89]. T2D and pre-diabetes, the prodromal stage of T2D, are characterized by prolonged periods of dysregulated glucose and insulin, both of which have been linked with subsequent dementia pathology[89–91]. Hyperinsulinemia, hyporinsulinemia, and hyperglycemia affect levels of insulin-degrading enzyme in the brain, which is linked to Aβ aggregation[92]. Evidence from brain samples of AD patients shows hyperglycemia also promotes generation of advanced glycated end products (AGEs), which additionally promote A β and tau aggregation[93]. Both diabetics and AD patients have an increased number of AGES compared to normal controls, and AGES are at the root of many diabetes-related complications (e.g., neuropathy, vision loss)[94]. Additionally, insulin and insulin-like growth factor 1 (IGF-1) receptors are concentrated in the hippocampus and medial frontal cortex, suggesting that insulin dysregulation might affect memory[89–91]. Findings from murine models show that insulin depletion is associated with long-term cognitive impairment, but that insulin treatment can prevent this[95].

An increased number of AGES is also associated with oxidative stress, endothelial and vascular dysfunction, increased inflammation, and protein, DNA, and mitochondrial damage, all of which are associated with neurodegeneration[96,97]. Mitochondrial damage occurs early in the progression of AD, prior to Aβ pathology[98–101]. Because of the brain's high lipid levels and oxygen metabolism, and low antioxidants, it is particularly susceptible to the negative effects of oxidative stress [102]. Aβ and amyloid-precursor protein move to mitochondrial membranes, in turn causing neuronal dysfunction by blocking the passage of nuclear-encoded mitochondrial proteins into mitochondria and causing mitochondrial

damage via disruption of the electron transport chain and increase in reactive oxygen species[103,104].

These pathways and mechanisms may also represent potential therapeutic targets for cognition, among those with and without T2D. For example, insulin treatment has been shown to improve cognition and memory and increase CSF and plasma levels of norepinephrine, which is associated with both better cognition in neurodegenerative disease and sleep-wake cycles[105], in people with AD but no diabetes[106,107]. In a recent trial, individuals without diabetes who were randomized to intranasal insulin treatment showed improved cognition compared to those randomized to placebo[106]. Notably, depending on the trial, results were only significant among APOE ε4 carriers or non-carriers, suggesting more research into insulin therapy is needed and that it may need to be genetically tailored[106,108]. The therapeutic effects of intranasal insulin may be most beneficial among older adults without T2D, because its effectiveness seems to be contingent upon the availability of glucose[109].

Because T2D is highly prevalent—25% of older adults are thought to have T2D and an additional 50% to be pre-diabetic[110]—as well as preventable, treatable, and strongly associated with dementia, interventions aimed at preventing or managing T2D or prediabetes may be particularly beneficial at reducing the prevalence and incidence of cognitive impairment. Indeed, using population attributable risk calculations, it has been estimated that, if T2D prevalence was reduced by 25%, 40,000 cases of AD in the U.S. could be prevented[111]. Targeting T2D alongside other modifiable risk factors could substantially impact the burden of dementia.

4. Sleep, Cognition, and Brain Health

Independent of diabetes, sleep is emerging as critical to the maintenance of brain health and cognition. Disturbed sleep is highly prevalent among persons with neurodegenerative diseases. As many as 40% of caregivers of persons with AD report that patients have difficulty falling asleep (11%), multiple awakenings during sleep (24%), early morning awakenings (8%), and general disruption of the diurnal sleep rhythm (14%)[112]. Importantly, current models hold that disturbed sleep is not just a consequence of neurological changes consistent with AD, but also a potential cause[113].

4.1 Disturbed Sleep and Cognitive Outcomes

Various aspects of disturbed sleep have been linked with cognitive outcomes, though findings are mixed, and appear to depend on the particular cognitive domain and test as well as the type of disturbed sleep. Below we highlight evidence tying sleep deprivation, duration, insomnia symptoms, daytime sleepiness, and OSA to poorer cognitive outcomes.

Experimental sleep-deprivation research demonstrates that sleep loss negatively affects cognition. In cognitively healthy adults, total sleep deprivation has been shown to slow response time for working memory tasks[114], and worsen temporal memory of faces[115] and verbal free-recall[116]. Chronic partial sleep deprivation also impacts cognitive performance. In an experimental study in which healthy adults were randomized to 4 hours, 6 hours, or 8

hours of bed time per night for 14 days, sleep deprivation led to changes in performance over time on a psychomotor vigilance task, digit symbol substitution task, and serial addition/subtraction task[117].

Mixed findings have emerged regarding sleep duration, with some studies linking shorter sleep to cognitive impairment/decline, some linking longer sleep to these outcomes, and others reporting that intermediate sleep duration is associated with better cognitive outcomes relative to both shorter or longer sleep duration[118–125]. A recent meta-analysis of 22,187 participants found that both short and long sleep duration were associated with higher risk of cognitive disorders[126]. Studies using wrist actigraphy, in which an accelerometer is applied to the wrist to measure sleep, typically with a PSG-validated algorithm[127,128], have shown links between various aspects of disturbed sleep and cognitive outcomes[13,121,129–131], providing evidence using an objective sleep measure (rather than self-report measures) that poor sleep may increase the risk of cognitive decline and dementia. Importantly, prospective epidemiologic studies have found that poor sleep is linked to risk of poor cognitive outcomes years later. For example, sleep fragmentation has been linked with increased risk of clinical AD up to six years later, among older adults[13].

Observational studies in relatively healthy samples of older adults link poor sleep quality to poorer cognitive performance, and both cognitive decline and dementia. For example, self-reported insomnia symptoms (e.g., difficulty falling, staying asleep) have been tied to greater decline on measures of global cognitive function, in both cognitively healthy older adults[10], and adults across the life course with varying degrees of cognitive function[11]. Daytime sleepiness also appears to be related to cognitive performance. Most recently, research from the Multi-Ethnic Study of Atherosclerosis showed that in elderly individuals (mean age 68 years, with about 10% of participants with sleep apnea syndrome), excessive daytime sleepiness (measured by the Epworth Sleepiness Scale score was associated with poorer attention, memory, and processing speed[132].

OSA has also been linked to poor cognitive outcomes. Individuals with OSA are more likely to have difficulties with attention[133–135], executive function[133–137], visuospatial learning[133], motor function[133,135], and immediate and delayed recall[136]. In addition, OSA (diagnosed by polysomnography) has been linked to smaller volumes of key brain regions involved in cognitive tasks, such as cortical gray matter, hippocampus, and caudate[136]. It is possible that the link between OSA and cognitive function differs by APOE genotype, with stronger associations between SDB severity and cognitive impairment among APOE ε4 allele carriers[138–140]. This possibility was strengthened further in the recent study from the Multi-Ethnic Study of Atherosclerosis (older adults with median AHI of 9 and mean ESS of 6); individuals who spent more sleep time in less than 90% oxyhemoglobin saturation performed worse on tests of attention and memory, and having sleep apnea syndrome was associated with worse attention and slower processing speed[132]. However, individuals with an APOE-ε4 allele had a stronger link between %Sat < 90% and attention[132].

OSA is also associated with a higher risk of mild cognitive impairment and dementia. In a sample of community-dwelling older women, an apnea-hypopnea index (AHI; number of apneas + hypopneas per hour of sleep) ≥15 was associated with 1.9 times the odds of

developing MCI or dementia 3-6 years later[12]. Importantly, the authors found that hypoxia, but not sleep fragmentation or sleep duration, was significantly associated with MCI or dementia, suggesting that hypoxia, rather than sleep fragmentation or duration, is driving the association between SDB and poor cognitive outcomes[12]. In a separate study, individuals aged 55-90 years who reported having OSA developed MCI and AD at a significantly younger age. Interestingly, the authors found that CPAP use seemed to delay the onset of MCI, among individuals with OSA[141].

Moreover, the potential for a causal link between OSA and cognitive impairment and decline is strengthened by some evidence that treatment of OSA with CPAP seems to improve cognitive trajectories. Ferini-Strambi et al. found that after 15 days of CPAP treatment, patients 45 to 65 years of age with severe OSA (diagnosed by polysomnography) and MMSE scores ≥24 performed similarly to age- and education-matched control individuals on tests of sustained attention, visuospatial learning, and motor performance; there were no effect on tests of executive function or constructional abilities however, and these did not improve even after 4 months of treatment[142]. The literature is mixed, however. The APPLES study, a 6-month multi-center RCT among individuals older than 18 (mean 51-52 years) with OSA (diagnosed by polysomnography), showed that CPAP (relative to sham CPAP) improved executive and frontal-lobe function at 2 months, but only among those with severe OSA at baseline, suggesting that OSA severity may moderate the effect of CPAP on improvement in cognitive function[143].

Further, persons with dementia may also show CPAP-related improvements in cognition. A study by Ancoli-Israel et al. found that among individuals with both AD and polysomnograph-diagnosed OSA, 3-week treatment with CPAP was associated with an improvement in global cognition[144]. In the same study sample, treatment with CPAP for a single night was associated with significantly more deep sleep, fewer arousals, and less time awake after sleep onset (WASO)[145]. Thus, treatment of OSA may hold promise as a means of improving cognitive performance and perhaps preventing cognitive decline. Importantly, we are unaware of investigate the effects of treating non-respiratory sleep disturbances (e.g., insomnia) or improving sleep duration or consolidation on cognitive outcomes. Such studies are needed to rigorously evaluate the extent to which sleep disturbances increase the risk of poor cognitive outcomes.

4.2 Disturbed Sleep and AD Biomarkers

The above findings raise questions about the neurological changes that might link disturbed sleep to cognitive impairment. Recent studies tying poor sleep to AD biomarkers suggest that sleep disturbance may alter cognitive trajectories by promoting the development of AD pathology. For example, self-report of poorer sleep quality and shorter sleep duration[146] and longer sleep onset[147] have been linked to greater amyloid burden on PET scans among older adults with a mean MMSE of about 29.

Moreover, in a cognitively normal sample, lower sleep efficiency (i.e., spending a smaller proportion of time in bed asleep) and greater sleep fragmentation, measured by wrist actigraphy, were tied to amyloid deposition measured in CSF[148]. Further, in another

cognitively normal cohort, poorer subjective sleep quality and greater sleepiness were significantly associated with markers of AD pathology in CSF[149].

Although it may be argued that associations in the above observational studies may reflect sleep disturbances that result from AD pathology[113,150], important animal studies provide evidence that sleep deprivation actually promotes amyloid deposition. The first of these was a seminal paper by Kang et al., which found that the amount of A β in the interstitial spinal fluid (ISF) of an AD mice model increased with wakefulness and decreased with sleep, that sleep deprivation increased these levels and enhanced brain amyloid deposition[151]. Further, Tabuchi et al., in a study of a *Drosophila* model of AD, showed that sleep deprivation increased amyloid deposition it the fly brain[152]. On the other hand, Roh et al. demonstrated in an AD mouse, that amyloid deposition leads to alterations in sleep/wake cycles[153]. Taken together, these studies suggest a relentless cycle in which disturbed sleep enhances AD pathology, which in turn disturbs sleep[113]. Experimental work in humans also supports a causal link between sleep/wake patterns and amyloid levels. Ooms et al. showed that individuals randomized to a night of normal, unrestricted sleep experienced a 6% decrease in the level of A β 42 in their CSF between evening and morning, while those randomized to one night of restricted sleep experienced only a 0.6% decrease[154]. In addition, a recent experimental study demonstrated that selective disruption of slow-wave activity during a single night of sleep led to an increase in A β 40 in the CSF collected the next morning.[155] We further discuss the importance of SWS to A β clearance and deposition below.

OSA has also been linked to AD biomarkers. A recent study of persons with cognitive impairment found that those with OSA, measured by polysomnography, who were not on CPAP had lower levels of CSF $A\beta_{42}$, and higher levels of t-tau/$A\beta_{42}$ ratio, reflecting greater AD pathology, relative to controls and OSA patients with CPAP[156] Moreover, among OSA patients, higher levels of CSF $A\beta_{42}$ were associated with greater nighttime oxygen saturation,[156] suggesting that hypoxemia may enhance Aβ burden. Similarly, Spira et al. found that greater SDB severity, measured by the AHI and oxygen desaturation index, was significantly associated with greater brain Aβ deposition on PET scans in persons with MCI, but not among those with normal cognition[150]. Interestingly, the relationship between OSA and AD biomarkers may depend on APOE genotype. Osorio et al. examined the links between self-reported SDB diagnosis, CSF biomarkers of AD, and APOE genotype, in a sample of cognitively healthy elderly adults, and found that the relationship between SDB and AD-biomarkers differs by APOE status[157], complementing findings that the association between SDB severity and cognitive performance differs be APOE ε4 carrier status[138–140].

Two primary mechanisms have been put forward to explain how insufficient sleep and sleep fragmentation might promote AD pathology. First, according to the synaptic homeostasis hypothesis, wakefulness is associated with an increase in synaptic strength, while sleep is associated with a decrease[151,158–160]. Further, increases in synaptic strength during wakefulness are thought to be downregulated by SWS[161]. Critically, higher levels of synaptic activity increase production of A β peptides[162,163]. Therefore, SWS may play an important role in minimizing A β aggregation resulting from wake-associated increases in synaptic activity[113]. Importantly, OSA may also lead to A β aggregation through its effects on sleep fragmentation and related decreases in sleep duration. In addition, however,

hypoxia due to OSA can lead to cleavage of the B and γ sites of β-amyloid precursor protein via increases in the expression of the Beta-secretase 1 (BACE1) and Alph-1 homolog A, gamma-secretase subunit (APH-1a) genes[164–166]. These changes, can in turn lead to Aβ generation and plaque formation[166].

The second mechanism believed to link disturbed sleep to amyloid levels and deposition involves the "glymphatic" system, elaborated by Iliff et al. as an exchange of CSF and ISF around the cerebrovascular system, which clears metabolites, including A β[167]. Following on this work, Xie at al. found that in mice, SWS markedly increased interstitial space, which resulted in a substantial increase in the exchange between CSF and interstitial fluid and an increased rate of exogenous A β clearance during sleep[168]. This work further implicates SWS as playing an important role in mediating potential effects of disturbed sleep on AD and dementia risk.

5. Links Among Sleep, Type 2 Diabetes, and Brain Health

Despite the established links of diabetes with cognitive decline and dementia, of disturbed sleep with diabetes, and known associations among disturbed sleep, dementia and AD, little is known about how disturbed sleep and diabetes interact to alter cognitive outcomes, including those due to AD[169]. McEwen et al. suggested that disturbed sleep and dysregulated circadian rhythms can contribute to "wear and tear" on the body (i.e., allostatic load), that disrupts the balance of the sympathetic and parasympathetic systems and increases insulin and blood glucose, leaving the brain susceptible to the effects of diabetes and to dementia[170,171]. Nonetheless, the most closely related work of which we are aware has focused on hypoglycemia during sleep among persons with type-1 diabetes. One such study found that hypoglycemia during sleep was associated with impaired memory consolidation in persons with type-1 diabetes and in healthy individuals[172], but another did not[173]. In addition, an observational study of persons with T2D examined whether insulin therapy (oral antidiabetic medication + insulin versus oral antidiabetic medication alone) was associated with better cognitive outcomes in patients with both AD and T2D at baseline[174]. Individuals who received oral antidiabetic medication plus insulin had a smaller decline in cognitive performance and better sleep patterns, relative to those not receiving insulin therapy[174]. Thus, little is known and striking knowledge gaps exist concerning the interplay of sleep, T2D, and cognitive outcomes. Further, much of the research that has been carried out in this domain is cross-sectional or retrospective in design. Longitudinal studies examining the longer-term associations between these factors are needed, as are studies incorporating laboratory measurements of sleep, T2D and AD, to elucidate the biological mechanisms connecting them.

We propose three models of how sleep, T2D, and cognition/brain health might interact. Research addressing these models could help identify persons at elevated risk for poor cognitive outcomes, including AD, and perhaps point to opportunities to intervene to slow or even prevent them.

1. Disturbed sleep may modify the association of T2D with cognitive impairment and AD biomarkers, and vice versa (Figure 1)

Although evidence from neuroimaging and other biomarker studies demonstrates links between T2D and both cognitive impairment and markers of AD[76–78,81–84], and between disturbed sleep and both cognitive outcomes and AD pathology [10,11,13,114–125,129–137,139,147–152,154–156,175], little is known about how disturbed sleep and T2D—or related factors, such as insulin resistance or blood glucose levels—interact to affect cognitive trajectories, Aβ deposition and tau aggregation. If the association between T2D and cognitive outcomes or AD biomarkers is stronger among those with disturbed sleep, this could have implications for the prioritization of treating sleep disturbances among those with T2D (Figure 1a). It would also be important to know whether links of disturbed sleep with cognitive outcomes and AD biomarkers are stronger among those with T2D (Figure 1b). In addition, understanding how disturbed sleep may alter insulin resistance, blood glucose levels, and vascular pathology in persons without frank T2D would help clarify the extent to which clinical attention to these variables may help maintain cognitive health in the general population.

2. Metabolic factors, including DM, may mediate the association of disturbed sleep with cognitive impairment and AD biomarkers (Figure 2)

As described above, disturbed sleep may contribute to decreased clearance of Aβ through decreased glymphatic system function[176]. In addition, it may promote the development of T2D through multiple pathways, including alterations in ghrelin, cortisol, orexin and leptin levels[177], as well as increased insulin resistance[64,65,71], decreased growth hormone secretion[178], poorer glycemic control and glucose metabolism[38,69,70], and vascular factors such as hypertension[179,180], Prolonged hyperglycemia and hyperinsulinemia are associated with increased tau phosphorylation[181]. Therefore, poor sleep may affect cognitive outcomes at least in part through its effects on these metabolic factors (Figure 2). If future research supports such mediation, targeting both the primary exposure and the mediator might enhance the outcomes of preventive interventions.

3. AD-related pathology may drive links from disturbed sleep to T2D, and this may further increase AD pathology, beginning the cycle anew (Figure 3)

As described above, the link between sleep and AD pathology likely share a bidirectional relationship[113]. AD-related pathology begins to develop approximately 15 years before the onset of cognitive symptoms, and this period has been termed preclinical AD[182]. Evidence from studies in transgenic mouse models show that amyloid and tau pathology lead to decreased sleep, greater sleep fragmentation, and attenuated circadian rhythms[153,183–186]. Studies conducted in humans have shown similar patterns. For example, in Down's syndrome, which is characterized by early amyloid and tau deposition due to the trisomy of chromosome 21, in which APP is located, patients exhibit substantial sleep disruption[187]. Further, patients with tauopathies (e.g., progressive supranuclear palsy, frontotemporal dementia) also exhibit sleep disruption[183]. Therefore, development of the AD pathology during this preclinical stage could lead to sleep disruption, in turn leading to further amyloid deposition directly, or could promote AD pathology indirectly by promoting hyperglycemia,

hyperinsulinemia, and T2D[188]. Importantly, in addition to increasing the risk of AD, T2D may in turn increase the probability of developing vascular dementia[189,190]. It is believed that a focus on these upstream factors during preclinical AD could prevent the cognitive and functional decline in the future[8].

6. Conclusion

With the incidence of dementia rising in our aging population in the absence of a cure for its most common cause—AD—it is critical that we develop strategies to prevent or slow its onset. The links between T2D, sleep disturbance, and cognitive impairment and dementia suggest the potential for important interactions of T2D and disturbed sleep with respect to neurological changes, including AD pathology, and downstream cognitive outcomes. Significant gaps exist in this research area. Prospective, observational studies are needed to investigate how disturbed sleep might increase T2D-related dementia risk, and *vice versa*, and to elucidate whether these exposures have synergistic effects on AD biomarker trajectories. Results could inform the development of interventions aimed at preventing AD and dementia more broadly.

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Highlights

- Type 2 diabetes (T2D) and sleep disturbances are prevalent in older adults.
- T2D and sleep disturbances are associated with cognitive decline and dementia.
- Sleep disturbances are linked with T2D and related metabolic processes.
- Targeting type 2 diabetes and sleep disturbance may prevent cognitive decline.

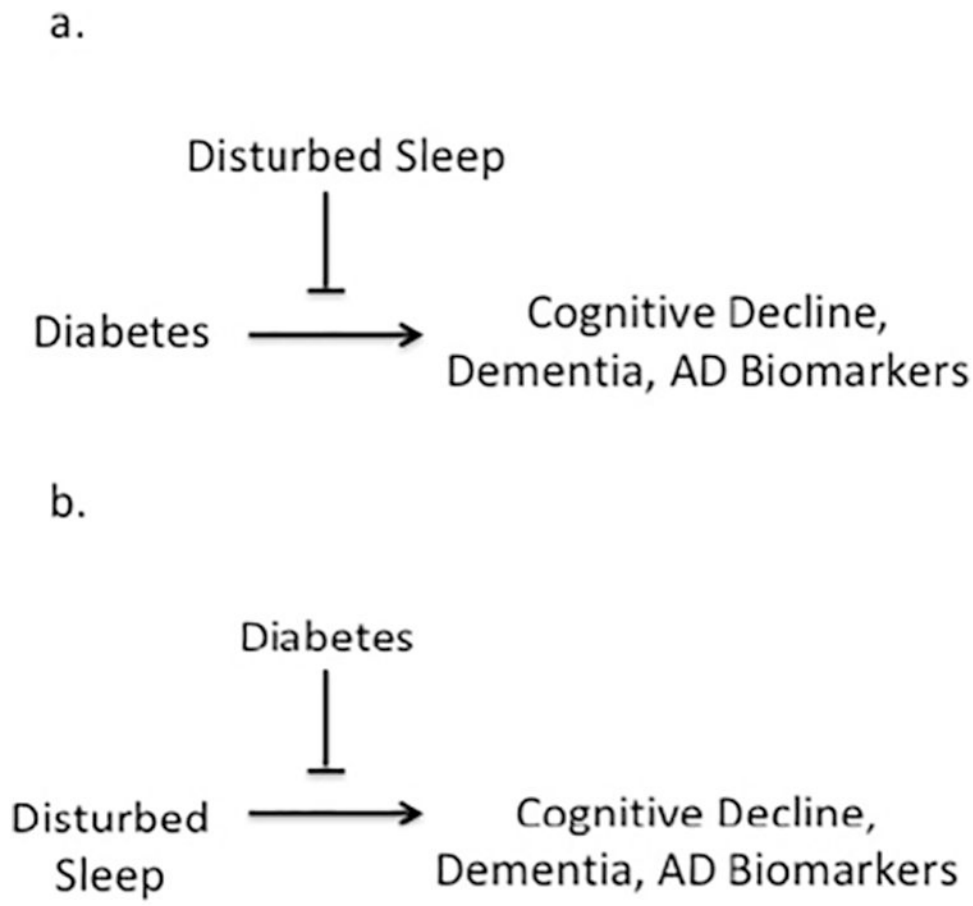

Figure 1. Interactions between Diabetes, Disturbed Sleep, and Cognitive Impairment/AD Biomarkers

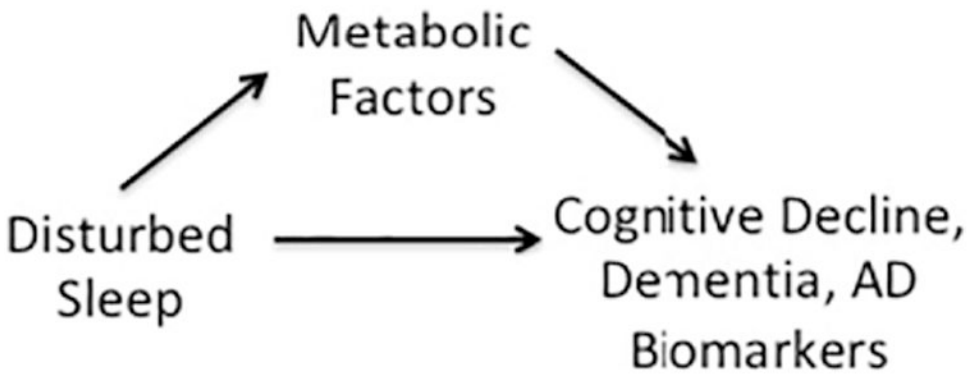

Figure 2. Metabolic Factors as Mediators of the Association between Disturbed Sleep and Cognitive Impairment/AD Biomarkers

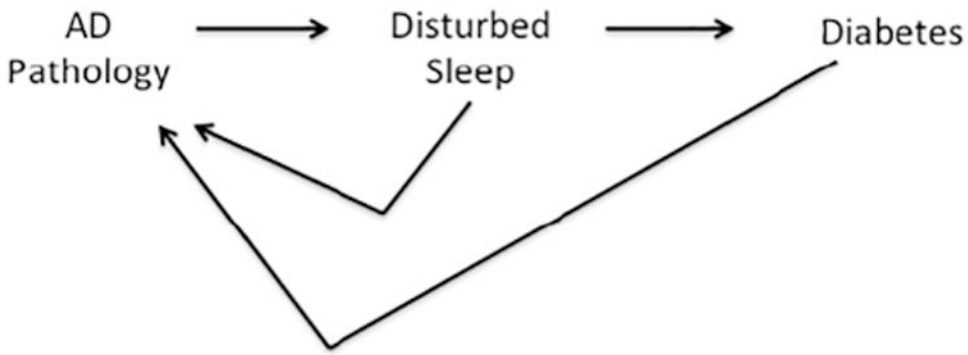

Figure 3. AD-related pathology may drive links from disturbed sleep to T2D, and this may further increase AD pathology