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Perspective

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Sex differences in sleep apnea and Alzheimer's Disease: role of cerebrovascular dysfunction

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Obstructive sleep apnea (OSA) significantly impacts cardiovascular health in post-menopausal females. Given that cardiovascular and cerebrovascular diseases are tightly linked, OSA-mediated impacts on cerebrovascular function and Alzheimer's Disease (AD) risk are also likely more manifest in females. This review will: summarize sex differences in cerebrovascular function, review the vascular hypothesis of AD, characterize sex differences in the OSA phenotype and implications for cerebrovascular control, and highlight OSA-mediated AD risk.

Alzheimer's Disease (AD) is the sixth leading cause of death in the United States and over six million adults aged ≥ 65 years are now diagnosed with this neurodegenerative condition[1]. As the United States population is rapidly aging, the prevalence of AD is expected to reach 13 million by mid-century[2]. Poor vascular health associated with cerebrovascular disease is recognized to increase AD risk by altering cerebrovascular blood flow and interrupting blood-brain-barrier integrity, which thereby may increase the likelihood of cognitive impairment[3–5]. With age, cardiovascular disease (CVD), cognitive decline, vascular dementia, and AD become more common and appear to impact females at a greater rate compared to age-matched males[6,7]. Therefore, cerebrovascular blood flow regulation is an important area of investigation in aging females.

Health consequences of poor sleep and sleep disruption remain under intense investigation[8,9], and investigations continue to suggest a bidirectional between disrupted sleep and AD[10–13]. Sleep disruption is common in patients following a mild cognitive impairment or AD diagnosis[11]. Additionally, inadequate sleep may also proceed and increase risk for AD related dementia[14]. Specifically, it is estimated that sleep impairment may contribute to 15% of all AD diagnoses[11]. Obstructive sleep apnea (OSA) is a common sleep disorder that is related to future AD risk[10,14,15]. In a study examining OSA and AD risk, younger females with OSA exhibited higher risk of mild cognitive impairment compared to age-matched males with OSA[16,17]. The vascular hypothesis of AD states the precursors of mild cognitive impairment and eventual AD diagnosis stem from poor cerebrovascular control[18,19]. Indeed, sleep curtailment via habitual short sleep[20] and clinical OSA[21] are associated with increased risk of hypertension, which is a modifiable risk factor for future cerebrovascular disease. Interestingly, the relationship between short sleep and hypertension risk is strongest in females across the adult lifespan, and is most apparent following the menopausal transition[20]. By extension, OSA-mediated brain injury may also disproportionately impact females via cerebrovascular dysfunction, thereby increasing AD risk[22,23].

This perspective article seeks to characterize female specific relationships between OSA and AD in relation to impairment in cerebrovascular function. We will present sex differences in cerebrovascular function in healthy adults, assess the vascular hypothesis of AD, communicate differences in the female OSA phenotype that may disproportionately increase AD risk, and focus on sleep disruption data supporting an association between OSA and AD. This body of work is warranted as AD is the most common form of dementia, contributing to 60–80% of all cases of dementia. Additionally, several investigations support a sex difference in AD risk impacting females at a disproportionate rate. We encourage future research into the mechanistic underpinnings of cerebrovascular dysfunction that may contribute to sex differences in OSA-mediated AD risk.

Sex differences in cerebrovascular function

Cerebrovascular function is commonly assessed noninvasively via two techniques—magnetic resonance imaging (MRI) or transcranial Doppler ultrasonography (TCD)[24,25]. Each methodology often assess common cerebral vascular health metrics including cerebrovascular reactivity and cerebrovascular autoregulation. Cerebrovascular reactivity is defined as the change in cerebral blood flow from resting measures to vasoreactive stimuli such as alterations in blood gases[26,27]. Cerebrovascular autoregulation is the ability of cerebral blood flow to maintain relatively constant blood flow across changes in arterial pressure and cerebral perfusion pressure[28]. Perturbations to these relationships can be evaluated via manipulations in arterial partial pressure of carbon dioxide ($PaCO_2$). Increases in $PaCO_2$ result in elevations in cerebral blood flow via vasodilation[29]. Given the high metabolic activity of neural tissue, broad cerebral vasodilation protects against brain injury and ischemia. However, alterations in cerebrovascular

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reactivity to CO_2 may offer prognostic evidence for future cerebrovascular disease[26,30,31].

It is widely accepted that younger females exhibit greater global cerebral blood flow under resting conditions compared to age-matched males[25,32]. Specifically, Aanerud, et al.[32] used positron emission tomography to demonstrate that younger females had greater blood flow to frontal and parietal brain regions compared to younger males. This is supported by other work suggesting there is greater basal cerebral blood flow to white and grey matter in premenopausal females compared to both younger males and post-menopausal females[33,34]. Further, Muer et al.[25] demonstrated that global cerebral blood flow was up to 40% greater in younger females compared to males. These data are supported by TCD methods as younger females exhibit greater middle cerebral artery velocity, compared to younger males[35]. However, the data on sex differences in cerebrovascular reactivity to hypercapnia is somewhat mixed in younger adults[36,37]. Kastrup et al.[36] via TCD methodologies reported higher cerebrovascular reactivity in younger females compared to age-matched males. However, MRI studies by Miller et al.[37] (4D Flow) and Kassner et al.[38] (blood-oxygen level dependent signal intensity) reported greater cerebrovascular reactivity in younger males, perhaps related to a ceiling effect as younger females exhibit greater resting cerebral blood flow. Further research on sex differences in cerebrovascular control in younger adults appears warranted to clarify this discrepancy.

Sex differences in cerebrovascular control become more apparent during mid-life and older age[39,40]. Numerous studies are converging to suggest a global decrease in cerebral blood flow with age[24,32,41]. and that the gradient of this decline is steeper in females[42,43]. This is accompanied by a blunted rise in cerebral blood flow associated with sympathoexcitatory stimuli[24,44] in older females, which increases hypoperfusion risk. Specifically, Kastrup et al.[36] reported that cerebrovascular reactivity to hypercapnia may begin to decline beginning in the fourth decade of life for females; however this pattern is not seen in age-matched males. More recent evidence from Moir et al.[45] suggests that age of menopause transition may also influence the gradient of cerebrovascular reactive decline, suggesting an earlier menopause transition may increase risk for cerebrovascular dysfunction. However, this phenomenon may not simply be related to age at menopause, but also due to lower levels of female sex steroids[46,47]. Further inquiry regarding natural and surgical induced menopause at a younger age (40–45 years) appears warranted to codify this finding. Yet, more sophisticated imaging techniques (4D Flow MRI) suggest similar cerebrovascular reactivity between older healthy males and females underscoring the need for more research in older adults[37]. Collectively, a global decrease in cerebral blood flow[42,43] and blunted cerebrovascular reactivity[36,44] suggest that older females may be at greater risk of brain hypoperfusion with age (compared to males). Thereby, hypoperfusion may disproportionately impact cortical thickness in females[48], and this phenomenon may, in part, explain the higher prevalence of AD in older females[6].

Vascular hypothesis of Alzheimer's Disease

AD is characterized by progressive neuroinflammation, neurodegeneration, and cognitive decline[49,50]. The vascular hypothesis of AD arose out of the observation that conditions associated with vascular dysfunction, such as hypertension, increase future risk of AD development[49]. Specifically, prolonged and untreated hypertension is related to cerebrovascular disruption[51], cerebral small vessel disease[52], and cerebral autoregulation impairment[53]. These conditions may facilitate clinical manifestations of cerebrovascular disease and/or small vessel disease, termed white matter hyperintensities (WMH)[54]. Briefly, WMH volume are quantified from MRI fluid attenuated inversion recovery images and are thought to reflect areas of demyelination and axonal loss[55]. Indeed, WMH presence and increased volume are associated with cognitive impairment[56] and future AD development[57].

As mentioned, presence of WMH may also be driven by other peripheral cardiovascular factors including arterial stiffness, defined as the impairment of elastic expansion and recoil of the vasculature associated with systole and diastole. This phenomenon may result in pulsatile flow and facilitate cerebrovascular injury[58]. Specifically, Barnes et al.[58] demonstrated that greater arterial stiffness was associated with a higher middle cerebral artery (MCA) pulsatility index. Although their data were collected in otherwise healthy, post-menopausal females, a greater MCA pulsatility index is characteristic of patients with AD[59] and mild cognitive impairment[60]. This highlights one mechanism by which vascular dysfunction, in the absence of overt CVD, may trigger cognitive impairment.

Another candidate mechanism suggests WMH formation via chronic brain hypoperfusion increases progression to AD[61]. Indeed, this coincides with the established reduction in cerebral blood flow and cerebrovascular reactivity in healthy aging, highlighting pathogenic blood flow alterations may precede AD symptoms and diagnosis[24,62,63]. Specifically, increased WMH volume, in the presence or absence of AD, exhibit reduced cerebrovascular reactivity to CO_2[62], indicating increased hypoperfusion likelihood. Further, longitudinal investigations have demonstrated that lower cerebrovascular reactivity to CO_2 predicts WMH formation at one-year follow-up[64,65], supporting a role for chronic neural hypoperfusion in the etiology of neurodegeneration. This can create a mismatch in oxygen supply and demand in neural tissue, increasing oxidative stress, which triggers a cascade of neuro-immune and -inflammatory responses within the brain[66] to collectively exacerbate AD progression. Collectively, this reduction in cerebral blood flow, resultant hypoperfusion, and greater pulsatility may facilitate blood brain barrier degradation and promote the accumulation of neurotoxic materials. Sleep disturbances, like OSA, are associated with AD, and may therefore be a modifiable risk factor for vascular-derived neurological pathologies. Although sex differences in cerebrovascular control[32] and AD are established[6], sex specific mechanisms linking OSA and neurocognitive decline remain elusive.

Sex differences in obstructive sleep apnea phenotype

Historically, OSA has been, and continues to be, characterized as a male-dominant condition[67]. It is estimated that OSA prevalence among the general population ranged between 15–30% in males, whereas the rate of female OSA diagnosis continues to climb with estimated global prevalence between 10–15%[68]. Further, the hypoxic burden at the surface level may appear lower in females compared to males because: 1) females tend to have more hypopneas (50% reduction in airflow with respiratory effort) vs. apneas ($\geq$ 90% reduction in airflow with respiratory effort)[69], 2) shorter apneic events[69], and 3) greater genioglossus activity during sleep to facilitate greater airway patency compared to males[70]. These underlying phenomena may contribute to underdiagnosis of OSA in females. This is a troublesome issue as we advocate that OSA may be more deleterious to female cardiovascular, cerebrovascular, and neurological health.

We posit that OSA may demonstrate a greater disease burden on females compared to an apnea-hypopnea index (AHI) matched male OSA patient. First, longer female apneic events tend to display a greater oxygen desaturation compared to males. Again, females typically have shorter obstructive apnea events[71], but when longer obstructive events do occur, there appears to be greater hypoxic burden among females[72]. Further, females often present with an overall lower AHI due to high prevalence of partial airway collapse (hypopnea) without 4% oxygen desaturation. Such partial airway collapse, independent of true scored apneic events, can increase nocturnal $PaCO_2$ and explain why many females are symptomatic (daytime sleepiness and morning headaches) with a lower AHI compared to males[73]. This problem highlights the case for scoring female oximetry using the 3% desaturation criterion which would increase AHI values to those typically reported in males[74]. In addition, there is emerging evidence that the cardioneural responses to chemoreflex activation (hypercapnia) are more robust in females, highlighting the apneic burden among females[75]. The American Academy of Sleep Medicine now recommends scoring hypopneas with the 3% desaturation criteria[74], which will likely benefit females with suspected OSA given higher percentage of hypopneas. However, the majority of American health insurance companies and federal plans still use the 4% desaturation criteria for hypopnea scoring, highlighting a potential barrier to effective care in post-menopausal females[76].

Second, females with OSA are more likely to present with short sleep OSA via reduced arousal threshold, a phenotype with greatest CVD risk[77]. Briefly, arousal threshold is the propensity to wake from sleep, often driven by respiratory effort[78]. This is likely due to females having a lower respiratory arousal threshold during apneic events[79], which can cause sleep fragmentation and resultant reduced total sleep time. Last, female apneic events often occur more frequently during rapid eye movement (REM) sleep compared to males[80]. From a cardiovascular and cerebrovascular perspective, two unique phenomena occur during REM sleep. Cerebral blood flow is typically at highest levels during REM sleep, when brain activity is near wake levels[81]. Thus, it is plausible that apneic events during REM in females may highly fragment this sleep stage and/or reduce cerebral blood flow during a metabolically active period of sleep, thereby exacerbating the effects of arterial hypoxemia. Another hallmark of REM sleep is marked sympathetic nervous system activation, where sympathetic activity is often higher than wake levels[21]. Obstructive events during REM sleep appear additive and further increase sympathetic nervous system activity[82]. We suggest that REM sleep OSA in females may result in: 1) excessive cerebrovascular vasoconstriction and reduced cerebral blood flow[83], or 2) peripheral vasoconstriction during REM OSA events[9,82], which may trigger cerebrovascular injury from blood pressure excursions, supporting established hypoperfusion seen in AD.

Identifying OSA in mid-life and older females may reduce AD risk. This is important to consider because OSA risk doubles in females following menopause[72], likely amplifying AD risk in older females. It is also important to consider the menopausal transition lies on an age-spectrum, with some females entering menopause earlier than 45[84]. It is estimated that more than 5% of females experience menopause earlier (before age 45)[84] and may have the greatest risk of cerebrovascular impairment and resultant brain hypoperfusion[45]. Additionally, females with OSA may exhibit greater cognitive deficits compared to males with OSA, and this is most evident females younger than 64 years old[16,17]. While sleep quality should be emphasized in all post-menopausal females, we advocate that increased attention be applied to females with early onset menopause who, presumably, have the greatest ability to reduce risk of developing, or delaying, AD. Given that the clinical manifestations of OSA such as lower AHI, more hypopneas, and short apneic events portray a less severe OSA phenotype in females, the underlying cardiovascular, cerebrovascular, and cognitive pathophysiology may go untreated for a longer period compared to male counterparts. To align these discrepancies, it may be advantageous to use the 3% scoring criterion for hypopneas and respiratory event related arousals to define female AHI[74] as it appears that more deleterious effects to CV and neurological disease risk occur at a lower AHI in females compared to males.

Obstructive sleep apnea and Alzheimer's Disease

OSA and AD[85], independently, are respectively male and female dominant conditions[6,86]. At the surface, it may seem incongruous to examine female-dominant AD through a male-dominant OSA lens. Further, OSA is a multifaceted sleep disorder which, on average, shortens total sleep time, alters sleep architecture, and exhibits a range of hypoxic burdens based upon OSA severity[87–90]. In concert with previously outlined impairments in cerebrovascular regulation dominant in females with aging, OSA symptomology characteristics, and OSA pathophysiology, females may be at greatest risk of sleep disruption-related AD risk. However, when the sex differences in cerebrovascular control, symptomatology of OSA, and patterns of nocturnal hypoxemia are considered together, the impact of sleep disruption on AD risk may be more apparent in females than males.

Sleep quality can be assessed subjectively via questionnaire, and objectively via two gold-standard methods: actigraphy and polysomnography. Actigraphy is often employed to characterize habitual total sleep time over a period of one to two weeks. Data from cognitively normal older adults demonstrated that objective poor sleep quality via two-week wrist actigraphy was related to greater beta-amyloid deposition in a predominantly female study sample[91]. Similarly, in a large sample of community dwelling older adults, reduced subjective total sleep time was associated with beta-amyloid presence even prior to onset of overt mild cognitive impairment or AD symptom development[92]. Furthermore, in a large sample of 1165 mid-life to older adults (> 50 years old), worse subjective sleep quality was associated with elevated levels total and phosphorylated tau and lower levels of beta-amyloid in the cerebrospinal fluid, indicative of less time in low neuronal activity state during sleep[93]. While these data clearly show a link between short and irregular sleep duration with risk of AD, disruption of specific and integral sleep stages may also contribute to OSA-mediated AD risk.

Overnight polysomnography offers a more granular assessment of sleep quality via sleep architecture (sleep stages), breathing patterns (airflow and respiratory effort), and blood-oxygen saturation typically on a single night, making it the gold-standard diagnostic assessment for OSA. Indeed, sleep architecture is significantly altered in patients with OSA. Briefly, sleep is broadly classified into REM and non-REM sleep which consists of stages 1, 2, and 3 sleep. The latter is commonly referred to as slow wave or deep sleep while stages 1 and 2 are collectively considered light non-REM sleep. Sleep in a patient with OSA is typically altered and favors a predominantly light non-REM sleep phenotype, where obstructive events during stage 2 sleep often prevent the transition into slow wave sleep and REM sleep[94]. Importantly, slow wave sleep is hypothesized to serve an integral role in AD prevention[95]. Coordinated neural firing producing slow wave activity during deep sleep facilitates glymphatic drainage thus clearing toxins and/or metabolites from neural brain tissue that may accumulate throughout normal wake hours and prevent beta-amyloid plaque deposition[96–98]. Reverse BP dipping (increased BP during sleep compared to wake) during slow wave sleep may also impair glymphatic drainage. Reverse BP dipping was associated with greater dementia risk[99], and chronic hypertension has been shown to limit flow of cerebrospinal fluid through the perivascular spaces[100]. Thus, slow wave sleep disruption from repeated apneic events and OSA-mediated hypertension may impede glymphatic clearing, increase neural activity, and thereby facilitate greater amyloid deposition[95,101]. In addition, REM sleep is shortened and fragmented with OSA[94]. While correlational, reduced REM sleep is associated with greater activation of the orexin system, which increases overall cognitive arousal, and is also related to greater beta-amyloid presence within the brain[102]. However, it remains to be shown whether REM-dominant OSA in females is associated with poor cerebrovascular health, and resultant greater WMH or poor beta-amyloid/tau protein clearance. Last, OSA severity appears to exacerbate AD risk[87]. As previously stated, WMH presence[58] and blunted cerebrovascular reactivity[101] suggest chronic brain hypoperfusion. Indeed, OSA severity is related to both increased WMH presence[103] and blunted cerebrovascular reactivity[104] demonstrating OSA-mediated hypoperfusion, increased likelihood of glymphatic clearance/drainage disruption, and amyloid accumulation. These phenomena appear to be somewhat supported by observational evidence that greater OSA severity and overall hypoxemic burden are related to lower levels of beta-amyloid-42 levels in the cerebral spinal fluid[105], indicative of potential poor glymphatic clearance during sleep. Interestingly, in a mostly female study sample, participants with a greater nocturnal arousal index, respiratory disturbance index, and severe OSA exhibited mild cognitive impairment[106]. Females with OSA also exhibit greater brain damage associated with OSA indexed by reduced white matter structural integrity compared to males with OSA[22]. While evidence is still quite limited, this may indicate a relationship between OSA and AD risk, which may disparately impact females.

Future directions

The relationship between OSA and AD are intertwined[6,86]. This perspective views OSA as a contributing factor to the development of AD. However, it should also be noted that the relationship between OSA, AD, and related dementias are also bidirectional and/or likely a feedforward mechanism, as sleep disruption in early-stage cognitive impairment is highly prevalent and may often exacerbate neurological symptoms[85]. Future work regarding OSA as a causal risk factor for AD development, and identification of relevant sex-specific risks, remain warranted. Additionally, present evidence does

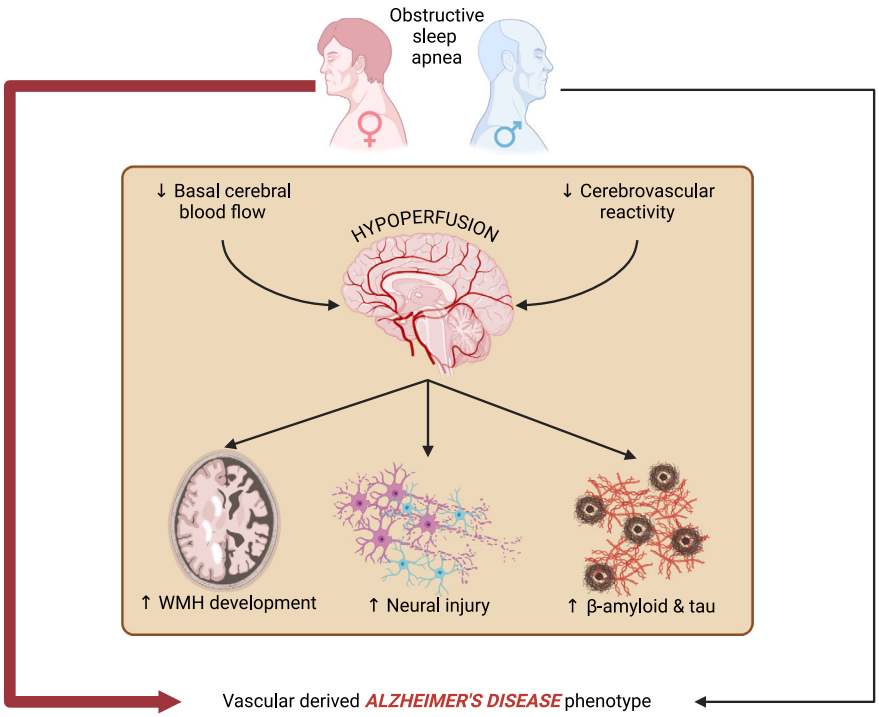

Fig. 1 | Conceptual framework of review. Aging females are at greater risk of reduced cerebral blood flow and blunted reactivity to CO_2. This cerebral hypoperfusion phenomenon supports the vascular hypothesis of Alzheimer's Disease and may initiate white matter hyperintensity development, neural injury, and plaque deposition. The female obstructive sleep apnea (OSA) phenotype is characterized by rapid eye movement (REM) sleep dominant apneic events, whose hypercapnic burden may be exacerbate cerebrovascular health and Alzheimer's Disease risk in older females compared to age-matched males. Created in BioRender. Greenlund, I. (2025) https://BioRender.com/d65j777.

not support a sex difference or impact of OSA on vascular dementia risk, which is in opposition of this review. However, elevated BP at midlife is related to increased risk of both AD and vascular dementia in females, but not males. Such discrepancies warrant future attention on sleep loss, cardiovascular regulation, and vascular dementia.

Summary

Sleep serves a critical role in cerebrovascular and cardiovascular health. Figure 1 outlines proposed mechanisms by which OSA may increase AD risk in females via cerebral blood flow impairments. Cerebral blood flow deteriorates at a faster rate in females with age[24,42], and post-menopausal females exhibit impaired cerebrovascular reactivity[44] suggesting hypoperfusion of brain neural tissue may occur at a higher rate in older females. In conjunction with sleep disorders like OSA, hypoperfusion during apneic events exhibits potential to exacerbate WMH formation, neural injury, and plaque deposition. Future studies seeking to investigate cerebrovascular control in OSA should include sufficient a priori power to examine proposed sex differences. Prior research studies have confirmed a positive effect of OSA treatment on cardiovascular and cerebrovascular health[107]. However, it remains unknown whether effective countermeasures of such as positional therapy, mandibular devices or continuous positive airway pressure can restore/improve OSA-related cerebrovascular dysfunction with long-term treatment in post-menopausal females.

Data availability

No datasets were generated or analysed during the current study.

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Competing interests

V.K.S. has consulted for Lilly, Zoll, Jazz Pharma, Axsome, and ApniMed and is on the Sleep Number Scientific Advisory Board. All other authors have no relevant conflicts to disclose.

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