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Sex differences in sleep apnea and comorbid neurodegenerative diseases

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Abstract

Sleep apnea is a disorder, which increasingly affects people worldwide. Whether the associated hypoxic events during sleep are central or obstructive in origin, the end result is excessive daytime sleepiness and an increased risk for several comorbidities, such as cardiovascular and neurodegenerative disorders. Sleep apnea is diagnosed more frequently in men than women, suggesting a role of sex hormones in the pathology of the disease. Furthermore, there are sex differences in the development and progression of comorbid diseases associated with sleep apnea. Therefore, treatment of sleep apnea may be clinically relevant for prevention of subsequent sex-specific comorbid disorders. While the impact sleep apnea has on cardiovascular events has been the subject of many research studies, the role of sleep apnea in neurodegeneration is less established. Here we review known risk factors for sleep apnea and the implications of the observed sex differences in this disease. We also summarize the evidence and mechanisms for how sleep apnea may contribute to the onset of neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease.

Keywords

Androgens; estrogens; oxidative stress; inflammation; chronic intermittent hypoxia; hypertension

Sleep apnea is estimated to affect 26% of the population in the United States [1], although up to 80% of those with the disorder are undiagnosed [2]. The major outcome of this condition is repetitive reduction in inspired oxygen during sleep [3]. This may be due to either a loss of central control of breathing effort or a physical obstruction of the upper airway [3], leading to apneas and/or hypopneas. One measure of the severity of sleep apnea is the apnea/hypopnea index (AHI), which quantifies the number of times per hour an apnea or hypopnea occurs. Cutoff points for the diagnosis of mild, moderate, and severe sleep apnea are AHI ≥ 5, ≥ 15, and ≥ 30 respectively [4]. Treatment is considered necessary for cases of moderate and severe sleep apnea, but optional for mild sleep apnea [5]. The most

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common therapeutic options include use of an oral apparatus or continuous positive airway pressure (CPAP) to maintain an open airway during sleep [5, 6].

Sleep apnea comorbid disorders include neurodegenerative disorders, such as Alzheimer's disease (AD) or Parkinson's disease (PD). These types of diseases are progressive disorders, which lead to a loss of neurons in specific areas of the central nervous system. Significant loss of neurons results in a functional deficit associated with the affected region. The initial degradation is a slow insidious process, wherein the patient is often unaware of the disorder. Clinical symptoms of AD include loss of working and episodic memory, followed by impaired executive functions and eventual autonomic system deficits [7]. These do not become apparent until approximately 40% damage to neurons in hippocampal structures occurs [8]. PD symptoms of bradykinesia, tremor, rigidity, and postural instability [9] do not manifest until 70–80% of neurons in the substantia nigra are lost [10]. Because diagnosis generally occurs during advanced stages of the disease, therapeutic treatments are generally not efficacious [11–15]. Identification of modifiable risk factors which exacerbate neurodegeneration may prove to be crucial to improving therapeutic options. One of these factors may be sleep apnea.

The association between sleep apnea and neurodegeneration has only recently begun to be explored, but current evidence suggests people with sleep apnea are at higher risk for neurodegenerative diseases [3]. For example, Peng, et al., recorded deficient regional brain activity in men with severe obstructive sleep apnea, connecting this sleep disorder with pathologic neural consequences [16]. Sleep apnea has been associated with deficits in working memory [17] and overnight consolidation of motor skill acquisition [18]. Evidence exists to support the hypothesis sleep apnea can increase the risk of developing AD or PD [17, 19–22]. In a multi-ethnic study, people who carried a genetic predisposition for AD exhibited a significant decline in cognition as hypoxic events increased in severity [23]. Additionally, sleep apnea is linked with increased risk for sporadic PD [22]. Therefore, treatment of sleep apnea may improve cognitive deficits in people with AD and PD [24–27].

An increase in sleep disorders has been reported in association with both AD and PD [21–23, 28–36]. In our studies using the Texas Alzheimer's Research Care and Consortium cohort (TARCC, a collaborative Alzheimer's research effort funded by the State of Texas), we found participants with cognitive deficits are more likely to report a significant elevation in sleep disturbances than those who are cognitively intact or have mild cognitive impairment (figure 1, table 1). As dementia severity increases, so do sleep disturbances, which is evidenced by the higher number of sleep disturbances in AD patients versus mild cognitive impairment patients. Similar to our observations, other studies have documented an increased incidence of sleep apnea as the severity of PD progresses [21, 37, 38]. Although a few studies have not found the same association between sleep apnea and neurodegeneration [30, 34, 36], small sample sizes could be a contributing factor to this discrepancy. In general, literature indicates that sleep apnea increases the risk of neurodegeneration. However, it is unknown whether sleep apnea is a causative agent of AD or PD.

SEX DIFFERENCES IN SLEEP APNEA

Men are 2 – 3 times more likely to be diagnosed with sleep apnea than women, and the incidence in both sexes increases dramatically with age [1, 39–41]. This suggests sex hormones play a role in the development of sleep apnea. Estimates of the prevalence of sleep apnea indicate sex differences occur worldwide. In the United States, 24% of men and 9% of women are reported to experience an AHI ≥ 5 [41]. Similar results are observed in investigations conducted in Europe, Asia, and South America [1, 39, 42–44]. Several basic science studies indicate that biological sex differences are involved in the manifestation and progression of sleep apnea.

Sex has an impact on other risk factors, such as age and body weight, which can affect the onset and severity of sleep apnea. Men with sleep apnea are at higher risk for comorbid events than women [40], and have higher risk for sleep apnea during middle age than women [45]. In addition to more frequent incidence with age, men, unlike women, experience increasing AHI severity as they age [1, 39, 46]. Women diagnosed with sleep apnea are not only older at initial diagnosis, they are also diagnosed with less severe AHI than their male counterparts [45]. While the prevalence appears to increase as women enter menopause, the severity of AHI events does not [1, 41]. Interestingly, young women with polycystic ovary syndrome (PCOS), characterized by high testosterone levels, are at higher risk to develop obstructive sleep apnea [47]. This suggests that sex hormones (e.g. androgens and estrogens) may underlie these sex differences in sleep apnea onset, progression, and severity.

Sex-specific anatomical differences in adipose tissue deposition and airway size may account for some of the discrepancies in sleep apnea prevalence and severity. It has been postulated fat deposition around the neck contributes to airway constriction [3, 48, 49]. Sex hormones are crucial in determining the composition and deposition of adipose tissue, as well as the size of airway structures [50]. The result of this is a higher deposition of fat in upper body areas in men, such as around the neck and in the thoracic abdominal region, as opposed to women who are more likely to carry weight in their lower abdomen [40]. Interestingly, obesity and anatomical features contribute to the development and severity of sleep apnea in men, but not women [1, 39]. Men experience a positive correlation between AHI severity and all obesity measures, such as body mass index (BMI), waist-hip ratio, or neck circumference, regardless of age. The severity of AHI can be reduced by weight loss [45]. Neck circumference, narrow airway structure, and loss of muscle tone in a supine position can all be indicators of risk in men [45, 49].

Unlike men, associations between obesity and sleep apnea are not observed in women. Pre-menopausal women with sleep apnea tend to be more obese at lower AHI’s than men, and there is not an association between BMI and AHI severity [45]. Additionally, sleep apnea severity is not dependent on waist-hip ratios or neck circumference in women or affected by weight loss [39]. Although the prevalence of sleep apnea increases in post-menopausal women compared to pre-menopausal women, an association between obesity and sleep apnea is still not present in post-menopausal women, unlike what is observed in men [40, 45]. Pre-menopausal women do not experience the functional loss of airway musculature in a supine position observed in men [49], despite smaller anatomical structure. It is only post-

menopausal women who experience a loss in respiratory function, which may be one contributor to the age-related increase in prevalence observed in women. Women with PCOS exhibit altered fat composition and deposition, which closely resembles patterns observed in men [51]. However, no studies have examined the impact of airway function on sleep apnea in PCOS women. The change in adipose tissue to resemble male characteristics may partially account for the elevated risk of sleep apnea in these women, and is further support for the idea sex hormones are contributing to observed sex differences.

In addition to distinctive anatomical differences, men and women with sleep apnea report different symptoms to primary care physicians [2, 40, 45, 52, 53]. Among patients referred for diagnostic sleep studies, men are more likely to report snoring and witnessed accounts of apneas and nocturnal gasping [45]. Women diagnosed with sleep apnea initially present with complaints of daytime sleepiness, fatigue or lack of energy, morning headaches, memory impairments, and enuresis more frequently than men do [45, 52, 53]. During sleep study assessments, men exhibit high AHI events during non-REM sleep phases [49]. Conversely, women are more likely to experience AHI events during both REM and non-REM sleep phases in conjunction with a lower supine AHI overall [49]. This results in more mild diagnoses of sleep apnea for women.

It is intriguing that each of the above risk factors can be modulated by sex hormones. Due to the patterns observed in middle aged men and women, sex hormones may differentially confer protection or exacerbate risk of sleep apnea and associated comorbidities [54, 55]. Sex hormones peak during young adulthood and then decline at different rates in men and women as they age. Testosterone and estrogen levels gradually decline as men age [54, 56, 57]. In contrast, estrogen drops abruptly in women as they enter menopause, while testosterone levels remain stable [58]. In men, the decline in testosterone levels has been associated with adiposity, less efficient sleep, and increased risk for cardiovascular and neurodegenerative events [54, 59, 60]. The role testosterone plays in the mechanisms of sleep apnea is the subject of current discussion and research studies within the aging and endocrinology fields [59, 61, 62]. Further investigation into the role of androgens and estrogens in the mechanisms of this disease are vital to determine how hormone therapy may differentially impact sleep apnea and its associated comorbidities in men and women.

SEX DIFFERENCES IN NEURODEGENERATION

Sex differences exist in the risk and symptoms of neurodegeneration, which parallel the pattern observed in sleep apnea. Aging, which is implicated in elevated incidence and severity of sleep apnea, is the primary risk factor for developing both AD and PD [9, 63]. While the risk for men to develop AD begins during middle age and increases linearly with aging, women appear to be protected from AD until reaching menopause [64]. At this point, the incidence rate in women climbs steeply until it reaches the same level as men. Interestingly, young women with PCOS are at higher risk to develop AD than young women without PCOS [65, 66], and appear to present a similar pattern of developing AD as men, supporting a role for androgens. Following transition from MCI to AD, men appear to have slower cognitive decline than women with AD, suggesting sex hormones impact disease progression [67]. Similarly, men are 1.3 to 2 times more likely to develop PD than women,

are diagnosed at a younger age, and are more likely to experience motor deficits in their face, neck, and arms [9, 68, 69]. Women with PD suffer more often from tremor, postural deficits, and depression [9]. Due to the similarities between men and women with PCOS, it is likely hormones, as opposed to genetics, are major contributors to the patterns observed in sleep apnea and the onset of neurodegeneration.

COMMON MECHANISMS AND INTERACTIONS BETWEEN SLEEP APNEA AND NEURODEGENERTION

Using the Texas Alzheimer's Research Care and Consortium (TARCC) cohort, we found men more frequently report sleep disturbances than their female counterparts (figure 1). This is similar to observations in other studies, in which men with PD report more daytime sleepiness than women with PD [9]. Post-mortem examination of androgens and estrogens in the brains of AD patients show men have a steeper decline in androgens, but not estrogens, than their healthy counterparts [70]. Men with PD also frequently experience a decline in bioavailable testosterone [71]. Women do not exhibit similar effects in either hormone. These observations support the hypothesis androgens may be fundamental to the mechanisms by which sleep apnea heightens the risk of neurodegeneration.

Hypertension, elevated inflammation, and oxidative stress are all common characteristics of sleep apnea and neurodegeneration, as well as risk factors for subsequent neurodegeneration [63, 72–76]. Clinical and basic science studies have reported sleep apnea contributes to the elevation of hypertension, inflammation, and oxidative stress [29, 77–82]. Indeed, hypertension, itself, is a primary risk factor for AD and PD and can exacerbate inflammation and oxidative stress through vascular dysfunction [63, 74, 76, 82–85]. In patients with PD, men are more likely than women to suffer from hypertension [69]. While the incidence of hypertension in AD does not appear to be different between men and women, women with mid-life hypertension are more likely to be diagnosed with dementia later in life than men with the same condition [86]. As women age, their risk of developing cognitive impairments increases if they have uncontrolled hypertension [87]. Therefore, the association of hypertension with sleep apnea may not only increase a person's risk of subsequent neurodegeneration, it also appears to be a determining factor in the type of neurodegeneration experienced in a sex-dependent fashion.

Men with sleep apnea are more frequently diagnosed with hypertension than women with sleep apnea [88]. Typically, the hypertension is more severe in men than women, and their hypertension severity is positively associated with the severity of AHI [89]. Alternatively, women with sleep apnea experience milder hypertension, which is sustained independent of AHI severity and often resistant to pharmacological therapeutics [89]. In chronic intermittent hypoxia, an animal model of the hypoxic events experienced by patients with sleep apnea, sex differences in the manifestation of hypertension persist. Male rats are observed to experience an elevation in mean arterial pressure, similar to men with sleep apnea [77]. However, in a study comparing male and female responses to chronic intermittent hypoxia, gonadally intact female rats did not experience the sustained hypertension observed in male rats. In fact, only estrogen-deficient ovariectomized female rats exhibited an elevation in

mean arterial pressure [90]. This indicates hormones play a crucial role in the impact of repetitive hypoxic events during sleep on vascular reactivity.

In addition to hypertension, the peripheral elevation in oxidative stress and inflammation documented in people with sleep apnea is integral to the mechanisms by which sleep apnea may preclude neurodegeneration. Children with sleep apnea have higher circulating inflammatory markers as well as elevated beta-amyloid expression, a marker often associated with cognitive impairment, than children without sleep apnea [91–93]. Treatment of sleep apnea in those children appears to improve these conditions. In adults with sleep apnea (in the absence of other comorbid conditions), an increase in inflammatory biomarkers was observed in both men and women [94]. Once again, sex differences were observed in the identity of which biomarkers were more highly expressed. In another study that investigated only men, Kaczmarek, et al. reported an increase in endothelial nitric oxide synthase, hypoxia-inducible factor 1 alpha, and vascular endothelial growth factor, indicative of elevated oxidative stress within endothelial cells with sleep apnea [82]. While anecdotal evidence exists to suggest a difference between men and women in sleep apnea induced vascular dysfunction and oxidative stress, that relationship remains to be definitively answered.

To further examine the impact of sleep apnea on physiology, investigators have used different animal models. A common animal model to examine the hypoxia associated with sleep apnea is chronic intermittent hypoxia, wherein room air is repetitively decreased to 8 – 10% of normal oxygen levels while the animal sleeps. Using this animal model, an increase in inflammation and oxidative stress markers in male rats exposed to chronic intermittent hypoxia has been observed [20, 29, 80, 95–98]. In our lab, increased oxidative stress and inflammatory dysregulation was observed in the periphery and the central nervous system, specifically within the entorhinal cortex and substantia nigra of male rats after only seven days exposure [29]. Damage to these areas is implicated in the onset of AD and PD, respectively [10, 11]. Chronic intermittent hypoxia models of longer duration and more severe hypoxic conditions induce inflammation and neuronal loss in the hippocampus of male rodents, which is indicative of advanced stage AD [97–101]. This suggests the hypoxic events experienced during sleep apnea may be responsible for triggering oxidative and inflammatory events within brain regions responsible for cognition and motor control. Studies investigating the mechanisms of sleep apnea in female rodents are scarce and represent a need for further research. Interestingly, treatment of sleep apnea is correlated with a reduction of inflammatory biomarkers associated with AD [79, 92]. In addition, treatment with anti-inflammatory agents appear to reduce the risk for neurodegeneration compared to the general population [9, 68, 92, 102]. It appears that addressing the underlying pathology of all stages of sleep apnea may be protective against the accumulation of neurodegenerative-inducing inflammation and oxidative stress.

CONCLUSION

Sleep apnea is a common disorder, which is underdiagnosed in most of the population. The observed sex differences in sleep apnea may be due to the actions of androgens and estrogens. The effects of sleep apnea go well beyond a lack of restfulness during the day to

exacerbate the risk of cardiovascular and neurodegenerative diseases. It is possible sleep apnea contributes to neurodegeneration by inducing vascular dysfunction, resulting in elevation of oxidative stress and inflammation in a regional specific manner within the central nervous system. Preservation of vascular function may be influenced by sex-hormones. While the mechanisms of sleep apnea in cardiovascular disease have been highly investigated, its contributions to neurodegeneration are only recently beginning to be appreciated. Understanding how sleep apnea contributes to oxidative stress and inflammation within the central nervous system will provide valuable information in the search to treat neurodegeneration. Furthermore, investigation is needed into the contribution of sex and sex hormones to provide protection or exacerbation of risk for sleep apnea and its comorbidities.

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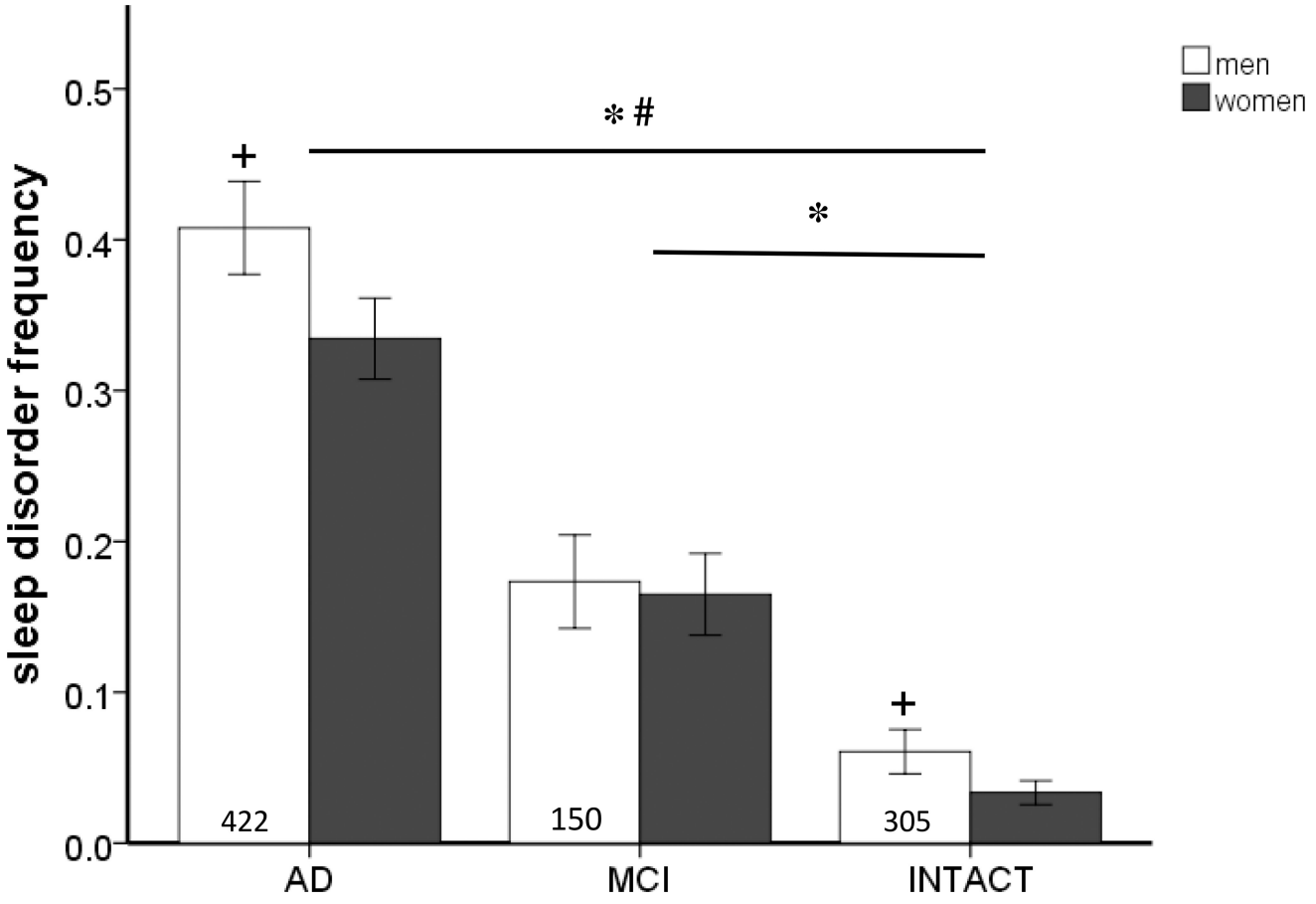

Figure 1.

The frequency of sleep disorders was obtained by TARCC participant or caregiver answers on the Neuropsychiatric Inventory Questionnaire [105] (Table 1). Participants with cognitive impairment reported more sleep disturbances than cognitively intact participants (Intact). Additionally, participants with Alzheimer's disease (AD) reported more sleep disturbances than participants diagnosed with mild cognitive impairment (MCI) ($F(2,1667) = 130.172$, $p < 0.05$). Men reported more sleep disturbances than women ($F(1,1667) = 3.805$, $p < 0.05$). Analysis by ANOVA with Tukey post hoc testing. ; * versus INTACT; # versus MCI; + versus women ($p = 0.07$).

TABLE 1

Characteristics of sample population used to determine frequency of sleep disturbances. Blood samples were provided by Caucasian men and women enrolled in the longitudinal research cohort of the Texas Alzheimer's Research Care and Consortium (TARCC). Normal controls performed within normal limits on all cognitive testing. MCI was defined using Petersen's criteria [103] and AD patients met consensus-based diagnosis for probable AD based on NINCDS-ADRDA criteria [104]. Institutional Review Board approval was obtained at each TARCC site and written informed consent was obtained from participants and/or caregivers.

	Men			**Women**		
Variable	**N**	**Mean**	**St. Dev.**	**N**	**Mean**	**St. Dev.**
Age (years)	**877**	**72.79**	**8.88**	**1312**	**72.21**	**9.67**
	min. age		***max. age***	***min. age***		***max. age***
	50		**94**	**50**		**102**
	N	**%**		**N**	**%**	
hyperlipidemia	557	*63.51*		725	*55.26*	
hypertension	559	*63.74*		814	*62.39*	
obese	192	*21.89*		355	*24.92*	
Alzheimer's disease	422	*48.12*		553	*42.69*	
mild cognitive impairment	150	*17.10*		189	*12.42*	
cognitively intact	305	*34.78*		570	*44.65*	
< high school diploma	105	*11.97*		224	*12.05*	
high school diploma	131	*14.94*		364	*26.21*	
≤ 4 yrs. college	403	*45.95*		525	*43.00*	
> college	238	*27.14*		199	*18.75*	