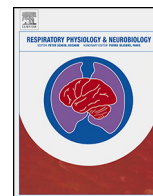




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Sex differences in sleep disordered breathing in adults

Tijana Lozo^{a,b}, Dragana Komnenov^{a,b}, M. Safwan Badr^{a,b,c,d}, Jason H. Mateika^{a,b,c,*}

^a John D. Dingell Veterans Affairs Medical Center, Detroit, MI 48201, United States

^b Department of Physiology, Wayne State University School of Medicine, Detroit, MI 48201, United States

^c Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI 48201, United States

^d Department of Biomedical Engineering, Wayne State University Detroit, MI 48201, United States

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ABSTRACT

The prevalence of sleep disordered breathing is greater in men compared to women. This disparity could be due to sex differences in the diagnosis and presentation of sleep apnea, and the pathophysiological mechanisms that instigate this disorder. Women tend to report more non-typical symptoms of sleep apnea compared to men, and the presentation of apneic events are more prevalent in rapid compared to non-rapid eye movement sleep. In addition, there is evidence of sex differences in upper airway structure and mechanics and in neural mechanisms that impact on the control of breathing. The purpose of this review is to summarize the literature that addresses sex differences in sleep-disordered breathing, and to discuss the influence that upper airway mechanics, chemoreflex properties, and sex hormones have in modulating breathing during sleep in men and women.

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* Corresponding author at: John D. Dingell VA Medical Center, 4646 John R (11R),
Room 4332, Detroit, MI 48201, United States.
E-mail address: jmateika@med.wayne.edu (J.H. Mateika).

1. Sleep-disordered breathing

1.1. Definition of sleep disordered breathing

Sleep disordered breathing refers to a wide spectrum of sleep related breathing abnormalities including upper airway resistance syndrome with and without snoring, obstructive sleep apnea-hypopnea syndrome and central sleep apnea. Alterations in breathing that accompany increased upper airway resistance (i.e. upper airway resistance syndrome) do not meet the criteria that define obstructive apneic events (Pepin et al., 2012). However, upper airway resistance syndrome is accompanied by outcomes similar to those linked to obstructive sleep apnea (Pepin et al., 2012). Obstructive and central sleep apnea are defined by the cessation of airflow. Obstructive events are characterized by collapse of the upper airway in the presence of a continued effort to breathe (Dempsey et al., 2010). In contrast, central sleep apnea is characterized by an absence of airflow and breathing effort because of a brief pause in the generation of the respiratory rhythm (Dempsey et al., 2010). Independent of the type of abnormality the outcomes that have been linked to sleep-disordered breathing include autonomic, cardiovascular, neurocognitive and metabolic dysfunction (Dempsey et al., 2010). In the present review we will address sex differences in the epidemiology of sleep apnea and in the clinical manifestations and polysomnographic features of sleep-disordered breathing. The review will also focus on physiological mechanisms that could be responsible for sex differences in sleep-disordered breathing.

1.2. Sex differences in the prevalence of sleep disordered breathing

Obstructive sleep apnea is more prevalent in men compared to women (Bixler et al., 2001, 1998; Peppard et al., 2013; Quintana-Gallego et al., 2004; Redline et al., 1994; Young et al., 1993). The disparity in the prevalence of obstructive sleep apnea tends to be more pronounced in clinic based studies, which revealed that this disorder is evident in 56% of men and 11% of women (Quintana-Gallego et al., 2004). Nonetheless, findings from community based studies (i.e. Wisconsin Sleep Cohort Study) also reported that the prevalence of sleep-disordered breathing is higher among working men (i.e. 24%) compared to women (i.e. 9%) 30–60 years of age (Young et al., 1993). However, the discrepancy in the prevalence of sleep disordered breathing is dependent in part on the criteria used to define the disorder. The stated prevalence of sleep disordered breathing in men and women that participated in the Wisconsin Sleep Cohort Study was based on a single criterion (i.e. an apnea/hypopnea index ≥ 5 episodes per hour of sleep). However, when symptoms of daytime sleepiness were added to the criteria the prevalence was reduced to 4% and 2% respectively in early reports (Young et al., 1993), and in 14% of men and 5% of women in more recent findings from the Wisconsin Sleep Cohort Study (Peppard et al., 2013).

1.3. Sex differences in the presentation and diagnosis of symptoms

Sex differences in the prevalence of sleep disordered breathing, particularly in the clinic, may also be a consequence of variations in the reporting of symptoms in men compared to women. Women are more likely to report non-specific symptoms of sleep disordered breathing including headache, fatigue, depression, anxiety, sleep onset insomnia and sleep disruption (Pillar and Lavie, 1998; Wahner-Roedler et al., 2007; Ye et al., 2009). Indeed when body mass index, severity of sleep apnea, age and subjective sleepiness are controlled women report a prior diagnosis of insomnia

and depression more often than men (Sheperdycky et al., 2005). Alternatively, snoring, gasping, snorting and apnea which are primary hallmarks of sleep apnea are reported less frequently by women compared to men experiencing a similar degree of sleep disordered breathing (Redline et al., 1994). Based on these findings, the primary hallmarks of sleep apnea may be deemed less socially acceptable by females and as a result are underreported. Consequently, because of the increased reporting of non-specific symptoms, and the decreased accounting of primary symptoms of sleep apnea, the reported symptoms could be misinterpreted more frequently in women compared to men. This possibility may explain the under-diagnosis of obstructive sleep apnea in women (Kapur et al., 2002; Young et al., 1993). Thus, additional assessment tools, including fatigue (Eliasson et al., 2015), may be necessary to diagnose sleep apnea in women. On the other hand, the under-diagnoses of sleep apnea in women may simply be because the typical symptoms of obstructive sleep apnea tend to be overlooked. Contrary to findings which indicated that women are inclined to report less specific symptoms linked to obstructive sleep apnea, Young et al. (1996) indicated that the frequency of reporting the primary symptoms of sleep apnea (i.e. snoring) was similar in men and women and that no unique symptoms were associated with sleep apnea in women.

Although this latter finding may be the case the manifestation of symptoms related to sleep disordered breathing is sex dependent. For instance, sleep apnea is more severe in men compared to women matched for body mass index (Ware et al., 2000). Consequently, for a given severity of sleep apnea women tend to be more obese than men. In addition, sleep apnea tends to be less severe in pre-menopausal women or women receiving hormone replacement treatment compared to untreated women. Likewise, severe obstructive sleep apnea is more prevalent in middle aged men and elderly women (Bixler et al., 2001; Li et al., 2015). Thus, variations in the physiological mechanisms that impact the manifestation of the symptoms linked to sleep disordered breathing is likely sex dependent. Nevertheless, despite multiple factors that potentially impact on the presentation of sleep apnea there is little doubt that the prevalence of this disorder is greater in men compared to women.

2. Sex differences in polysomnography

The apnea-hypopnea index is greater in men compared to women when body mass index is controlled (O'Connor et al., 2000; Walker et al., 2001; Youn et al., 2015). This difference exists in part because the apnea-hypopnea index, particularly in the supine position, is greater in men during non-rapid eye movement sleep compared to women. The increase is reportedly due to a significant surge in the number of apneic events; consequently the apnea/apnea + hypopnea ratio is greater in men compared to women (Tashkandi et al., 2005). Conversely, disruptive sleep events tend to be more evident in rapid eye movement sleep in women when age and body mass index are controlled (Koo et al., 2008; O'Connor et al., 2000; Ye et al., 2009) (Fig. 1). Thus women tend to be more protected from sleep disordered breathing during non-rapid but not rapid eye movement sleep. However, the sex differences in the apnea/hypopnea index tend to decrease with increasing age. More specifically, the prevalence of sleep disordered breathing during rapid eye relative to non-rapid eye movement sleep decreases with age more rapidly in women compared to men (Koo et al., 2008; Ye et al., 2009). Furthermore, the apnea/hypopnea index during non-rapid eye movement sleep increases more promptly in women with age (Koo et al., 2008). Dissimilarities in the mechanism responsible for the presentation of apneic events in males and females during non-rapid and rapid eye movement sleep is addressed below (see *Sex Differences in Upper Airway Structure and Function*).

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