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REVIEW ARTICLE

Gender differences in obstructive sleep apnea and the associated public health burden

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Abstract

Obstructive sleep apnea, (OSA) is a sleep disorder traditionally associated with high blood pressure, cardiovascular disease, and/or obesity in which an obstruction of the upper respiratory airflow occurs in patients. This airflow disruption is repeated resulting in a cyclical breathing pattern that leads to frequent arousals during sleep. Epidemiological analyses of OSA have found that the disorder occurs more frequently in men than women. Yet, the severity of OSA-associated comorbidities are worse in women than in men upon initial OSA-diagnosis. The primary reasons for sex differences in OSA are thought to be associated with variations seen in normal sleep between men and women, distinctions in the clinical manifestations of sleep disturbances, and in the prevalence of risk factors for sleep disorders. However, it has also been suggested that this sex difference is due to an under-diagnosis of OSA in women during the early stages of the disease, as initial presentation of female patients with OSA has often been interpreted as depression and/or insomnia. Due to the risk factors associated with OSA, heart disease as the leading cause of death in both men and women in the United States, and the commonality of sex differences in sleep disorders, we examined the literature to determine what may contribute to these sex differences in OSA. This brief review summarizes what may be the causes of sex differences in normal sleep, sex differences that are associated with OSA, and whether this sex difference may be primarily due to an under-diagnosis of OSA in women.

Key words: cardiovascular disease, female, sex differences, sleep, sleep apnea, sleep disorders.

INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic disorder characterized by recurrent episodes of pharyngeal airway collapse during sleep.[1,2] This often results in reduced or total cessation of upper respiratory airflow. OSA is clinically described as having five or more hypopneas or apneas per hour of sleep. These events result in a cyclical breathing pattern that can lead to frequent arousals from sleep as the patient alternates between wakefulness and sleep. Other common symptoms of OSA include loud snoring, witnessed breathing pauses during sleep, fitful sleep quality, and excessive daytime sleepiness. If left untreated, OSA may lead to cognitive dysfunction, diminished work performance, and a diminished health-related quality of life. Current evidence also suggests that OSA may contribute to the development of several comorbidities, such as systematic hypertension, cardiovascular disease, and abnormalities in glucose metabolism.

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Treatment for this disorder depends on the symptom severity and the primary cause, but includes: weight loss in the obese, nasal continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), dental appliances such as an adjustable mandibular advancement device, surgery such as uvulopalatopharyngoplasty (UPPP), laser-assisted uvulopalatropharyngoplasty (LAUP), and maxillomandibular advancement or orthognathic surgery.[3,4] Epidemiological insights into OSA has shed light on the natural history, risk factors, adverse health effects, and to aid in understanding the severity levels of both the clinical and public health significance.[5] Despite the increased awareness and knowledge that OSA is relatively common, population disease prevalence estimates in the United States and abroad were not present until about 21 years ago. Since then, the health burden of OSA has become much more apparent. Studies now exist that use large sample sizes that are representative of the general population. However, making sense of the various studies that are available can be difficult due to methodological limitations. For example, differences in sampling techniques, disparities in the methods used for monitoring sleeping and breathing, and variability in definitions, all have an effect on disease prevalence and potentially impede researchers gathering a comprehensive estimate of the true burden of OSA. Today, moderately consistent estimates of disease prevalence across several population cohorts exist. Based on several population-based studies, it has been concluded that the prevalence of OSA associated with accompanying daytime sleepiness is approximately 3% to 7% for adult men and 2% to 5% for adult women in the U.S. population. Another community-based study by Young and coworkers suggests that up 5% of adults in Western countries are likely to have undiagnosed OSA, which increases prevalence numbers.[6] Disease prevalence is higher in different population subsets, including overweight or obese people, those of a US minority race, older individuals, as well as sex.[1] As reported by Krishnan *et al*. OSA, when defined as an apnea hypopnea index (AHI) of at least five events per hour of sleep, is prevalent in 24% of men and 9% of women in the US adult population.[7] This difference has remained relatively consistent from when data on sleep disordered breathing was collected in a study done by Young and Finn in 1998.[4]

Sex differences have been observed in many sleep disorders, including insomnia, narcolepsy, and restless leg syndrome, among others. The primary reasons for the sex differences that are seen in sleep disorders are associated with the various differences seen in normal sleep, in clinical manifestations of disturbances of sleep, and in risk factors for sleep disorders. Due to these sex differences, there is likely to be an under-diagnosis of OSA in women. This brief review summarizes what may be the cause of these sex differences, as well as, whether an under-diagnosis of OSA in women exists. A summary of the studies used can be found in Table 1.

INFLUENCE OF SEX ON SLEEP DISORDERS

Sex differences in normal sleep may contribute to the risk of individuals developing sleep disorders. In order to understand these differences among those with a sleep disorder, one must understand and identify the differences of those who experience "normal sleep." Sex differences are found in normal sleep characteristics such as the stimulus for sleep onset, the durations of sleep and sleep architecture.[7]

According to Krishnan and Collop,[8] sleep can be defined as, "the reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment." Sleep is a diverse state that consists of both rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. REM is characterized by mixed frequency electroencephalogram activity, muscle atonia, and eye movements. The lack of electroencephalogram synchrony with muscle activation potential characterizes NREM.[9]

More specifically, it is due to the ability of biological sex and sex-driven characteristics to alter sleep states that seems to contribute to the various sex disparities that are present among sleep disorders.[10] Clear sex differences in upper airway anatomy, supraglottic and pharyngeal resistances,[11] and genioglossal muscle activity during the awake state, in craniofacial morphology, and pattern of fat deposition have been proposed to account for a higher male risk of OSA. Sex differences in sleep, as well as both hormonal and physical changes in women, put them at a higher risk for developing sleep disorders. Women undergo these changes when they go through puberty, menstruation, pregnancy, and particularly menopause.[7] Pregnancy puts women at a higher prevalence because of the excess weight gained, diffuse pharyngeal edema and the effect of sleep deprivation on the pharyngeal dilator muscle activity.[6] A review conducted by Ralls and Grigg-Damberger,[12] found that these factors, along with pregnancy and polycystic ovarian syndrome, increase the risk of OSA in women, they also found that men tend to need higher pressures when using CPAP, even when the patients had

Table 1 Primary research studies reviewed in this article

Study	Study type	Number of patients (if applicable)	Primary objective(s)	Prevalence		
				Men	Women	Overall
Young and Finn (1998)[4]	Epidemiological research report	N/A	To review and to discuss epidemiological advances and research needs pertaining to sleep disordered breathing	24%	9%	2–4%
Bixler *et al.* (2001)[13]	Primary	Phase I: 12 219 women and 4364 men Phase II: 1000 women and 741 men	To contrast the prevalence of Sleep disordered breathing in a large sample of women compared with men from the general population across a wide range (20–100 years) while controlling for age, obesity, and, in women, menopause and hormone replacement therapy	3.9%	1.2%	
O'Connor *et al.* (2000)[14]	Retrospective	830 patients	To analyze differences in the between men and women in the severity and type of OSA and in the distribution of respiratory events during NREM and REM sleep	24%*	62%*	
Valipour *et al.* (2007)[15]	Primary	782 women and 2739 men	To prospectively assess gender-related differences in presenting symptoms in a clinical sample of patients with suspected sleep disordered breathing			
Shepertycky *et al.* (2004)[16]	Retrospective chart review analysis	130 women and 130 men	To assess differences in clinical presentation between women and men with OSAS	4%	2%	
Larsson *et al.* (2003)[17]	Questionnaire study in a representative sample of the population; a second cohort was investigated	5426 participants; 4648 responses were obtained	To study the prevalence, risk factors, and gender differences in symptoms related to obstructive sleep apnea; to study gender differences in relation to referral to a sleep clinic for sleep investigations			
Young *et al.* (1996)[18]	Community-based	388 women and 551 men	To compare men and women and to match for severity level of sleep apnea in order to investigate whether or not women with sleep apnea have unique symptoms or complaints			
Pillar *et al.* (1998)[19]	Primary	2271 patients (294 women and 1977 men)	To evaluate the association of SAS with psychiatric symptoms as determined by the SCL-90 psychiatric questionnaire.	n/a	n/a	n/a
Koehl *et al.* (2006)[20]	Primary	Adult male and female C57BL/6J mice were used	To examine sex differences in sleep in the mouse, not only under baseline conditions, but also after sleep deprivation and restraint stress	n/a	n/a	n/a
Mohsenin, V. (2003)[22]	Primary	Seventy-one consecutive patients with OSA; 18 women and 53 men	To investigate their hypothesis that – due to differences in tissue linkage women have more stable and less mobile upper airway structures than men, providing protection against severe forms of OSA.	n/a	n/a	n/a
Mohsenin, V. (2001)[23]	Prospective study	52 women and 78 men	To examine the effect of obesity on pharyngeal size in both men and women; to determine the role of upper airway dimensions in the expression of sleep-disordered breathing and its relationship to gender	15%	9%	
Lee *et al.* (2013)[24]	Primary	655 patients (86 women and 569 men)	To investigate gender differences in the effect of comorbid insomnia symptom on depression, anxiety, fatigue, daytime sleepiness, and quality of life in patients with OSA	n/a	n/a	n/a

Guilleminault *et al.* (1988)[25]	Primary	27 OSAS women, 16 control women, and 110 OSAS men	To analyze the features presented by OSAS women and to compare the data with that obtained for a control group of non-OSAS women and for OSAS men	n/a	n/a	n/a
Hedner *et al.* (2005)[26]	Case control	161 patients with hypertension; 183 normotensive controls	To explore OSA as a risk factor for HT in two community-based samples; to investigate the influence of sex on this association	47% (25%)#	26% (24%)#	n/a
Kapur *et al.* (1999)[27]	Cross-sectional	238 cases; 476 controls	To investigate the medical costs associated with patients who were found to have clinically significant SDB; to compare those patients to controls in order to obtain an estimate of the magnitude of SDB associated costs; to determine the relationship between severity of SDB and medical costs prior to diagnosis			2–4%
Runyon *et al.* (2001)[60]	Clinical	2757 patients (958 women and 1799 men)	To investigate whether there would be significant differences in the way that men and women reported symptoms of apnea if they were studied using several reliable methods of measurements	n/a	n/a	n/a
Dursunoglu *et al.* (2009)[28]	Clinical	91 Patients (20 women and 71men)	To investigate gender differences in initial symptoms and associated public health diseases of patients admitted to the sleep clinic.	29.1 ± 22.7	17.9 ± 17.7	
Vagiakis *et al.* (2006)[29]	Retrospective study	1010 (166 females and 844 males)	To investigate patients diagnosed with OSAS by polysomnographic (PSG) over a period of three consecutive years, during which clinical findings were compared.	n/a	n/a	n/a
White *et al.* (1985)[11]	Pharyngeal resistance study	35 patients	To investigate the etiology of OSA and focus on the upper airway and pharyngeal resistance and range of supraglottic.	4.6 ± 0.8	2.3 ± 0.8 (pharyngeal resistance)	
Ye *et al.* (2009)[30]	Clinical study	N/A	To discuss gender differences in OSA polysomnographic features, demographic factors, symptom presentation, functional status, comorbidities, health care utilization, and therapeutic management.	n/a	n/a	n/a
Ramachandran *et al.* (2009)[31]	Meta-analysis review to compare clinical screening	N/A	To discuss metaregression, which revealed that clinical models, logarithmic equations, combined techniques, cephalometry, and morphometry are significant characteristics.	n/a	n/a	n/a
Matos *et al.* (2013)[32]	Clinical study on humans and rats	N/A	To investigate the effects of paradoxical sleep deprivation and chronic sleep restriction on cardiovascular parameters and adrenocorticotropic hormone levels in male and female rats.	n/a	n/a	n/a
Ralls *et al.* (2012)[12]	Review of research on the roles of demographics of (OSA) and their treatment	N/A	To review the recent research on the roles of gender, race/ethnicity, residential socioeconomics and age in (OSA) and their treatment.	n/a	n/a	n/a
Kinkead *et al.* (2013)[33]	Respiratory disorders of rats	N/A	To review evidence of early life exposure to neonatal maternal separation stress, which is sufficient to exert sex-specific effects on the respiratory development of rats, thus instability of sleep	n/a	n/a	n/a
Henry *et al.* (2013)[34]	Clinical diagnosis	N/A	To investigate the roles of spouses for the initial diagnosis and push to seek medical care of OSA patients.	n/a	n/a	n/a
Krishnan *et al.* (2006)[7]	Review of clinical studies	N/A	To review gender differences in OSA that become apparent after puberty. Menstrual cycles, pregnancy, and menopause can alter sleep architecture.	n/a	n/a	n/a

Table 1 *Continued*

Study	Study type	Number of patients (if applicable)	Primary objective(s)	Prevalence		
				Men	Women	Overall
Subramanian *et al.* (2012)[35]	Review of influence of gender on OSA patients	1029 (368 women and 661 males)	To investigate the anthropometric measurements of subjects' height, weight, neck size, and waist and hip sizes; waist-hip ratio and neck-to-height ratio and it's relationship to OSA.	n/a	n/a	n/a
Walia *et al.* (2012)[36]	Clinical study	1275 adults	To assess the relationship between shift work (SW) history and symptom severity in a sleep clinic population.	n/a	n/a	n/a
Walker *at al.* (2001)[37]	Non-randomized cross sectional study.	686 (111 women and 575 men)	To evaluate the differences between female and male patients with obstructive sleep apnea syndrome (OSAS) in the preoperative period.	n/a	n/a	n/a
Simpson *et al.* (2010)[38]	Prospective case-series observational study	96 (36 women and 60 men)	To describe sex differences in the associations between severity of obstructive sleep apnea (OSA) and measures of obesity in body regions defined using both dual-energy absorptiometry and traditional anthropometric measures in a sleep-clinic sample	n/a	n/a	n/a
Smith *et al.* (2006)[39]	Analysis of archival clinical data	1779 patients	To investigate the extent to which medications are used in the OSA population or the effects of common prescription medications on the sleep architecture of patients with OSA.	n/a	n/a	n/a
Subramanian *et al.* (2013)[21]	Clinical study	239 patients	To investigate the link of the influence of slow-wave sleep on OSA and identify the differences attributable to gender and/or age if any.	n/a	n/a	n/a
Pellegrino *et al.* (2011)[40]	Clinical study	N/A	To evaluate the influence of polymorphism on sleep parameters on OSA patients.	n/a	n/a	n/a
Eckert *et al.* (2009)[41]	Clinical study	20 (10 women and 10 men)	To compare the genioglossus (GG) activity between OSA patients and control subjects during REM sleep using CPAP to minimize the influences of upper-airway resistance and blood gas disturbances on GG activity.	n/a	n/a	n/a
O'Connor *et al.* (2000)[14]	Clinical study	830 patients	To examine the influence of gender on the PSG features of OSA in a retrospective study of patients diagnosed by overnight PSG.	n/a	n/a	n/a
Ware *et al.* (2000)[42]	Clinical study	430 (215 women and 215 men)	To examine how apnea frequency and duration varied according to age, sex, and sleep stage in a clinical population.	n/a	n/a	n/a
Kapsimalis *et al.* (2002)[43]	Review of clinical studies	N/A	They explored the reasons for the clinical presentation and PSG findings between male and female patients.	n/a	n/a	n/a
Pedrosa *et al.* (2011)[44]	Review of clinical studies	N/A	A review to discuss the recent advances in the pathophysiological mechanisms, clinical presentation, and treatment of OSA, as well as the benefits this treatment can bring on blood pressure.	n/a	n/a	n/a

Moorish *et al.* (2008)[45]	Review of hospital records	339 (47 women and 292 men)	To compare the mortality risk of men and women diagnosed with OSA and started on treatment with CPAP.	n/a	n/a	n/a
Powers *et al.* (2010)[46]	Review of common surgical techniques	N/A	The work reviews common surgical techniques for clinical management of OSAHS patients in a presentation format for primary care and sleep medicine specialists,	n/a	n/a	n/a
Wali *et al.* (1997)[47]	Clinical study	N/A	The 10 year investigation of retrospective analysis of the clinical features and survival of 60 Saudi children with systemic lupus erythematosus.	n/a	n/a	n/a
Mermigkis *et al.* (2012)[48]	Clinical study	436 (184 females, 252 males)	To investigate possible gender differences in CRP evolution in OSA patients 3 and 6 months after the start of effective CPAP treatment.	n/a	n/a	n/a
Jayaraman *et al.* (2011)[49]	Retrospective review	95 (56 women and 39 men)	To investigate the disparities in pharyngeal collapsibility and, consequently, positive airway pressure requirements of patients with OSA.	n/a	n/a	n/a
Jordan *et al.* (2004)[50]	Clinical study	22 (11 women, 11 men)	An investigation to assess whether elevated sleeping upper airway resistance (R(UA)) alters the ventilatory response to arousal and subsequent breathing on return to sleep in patients with OSA.	n/a	n/a	n/a
Lichstein *et al.* (2013)[51]	Archival analysis study	299 patients	The study used an incomplete factorial design, crossing OSA with INS to more clearly focus on the question, is comorbid INS an epiphenomenon of OSA or an independent disorder?	n/a	n/a	n/a
Krakow *et al.* (2013)[52]	Retrospective chart review	1,035 Patients	This study evaluated treatment-seeking insomnia patients and their self-report of sleep breathing complaints.	n/a	n/a	n/a
Yardim-Akaydin *et al.* (2014)[53]	Clinical study	139 healthy patients	To investigate the role of inflammation by measuring the C-reactive protein and fibrinogen levels, and erythrocyte sedimentation rate in the OSA according to gender.	n/a	n/a	n/a
Björnsdóttir *et al.* (2012)[54]	Clinical questionnaire	824 patients	To compare the prevalence of initial and middle insomnia between OSA patients and controls from the general population as well as to study the influence of insomnia on sleepiness and quality of life in OSA patients.	n/a	n/a	n/a
van Dijk *et al.* (2011)[55]	Clinical study	99(44 women and 55 men)	To assess subjective sleep characteristics in patients with type 1 diabetes, to relate sleep characteristics to long-term glycemic control and to assess possible risk factors for impaired sleep.	n/a	n/a	n/a
Celen *et al.* (2010)[56]	Clinical and questionnaire study	318 (64 women and 254 men)	To address the influence of gender and obstructive sleep apnea (OSA) on development of diabetes mellitus (DM) in a sleep clinic cohort.			

comparable severities. These studies highlight the significant influence of sex hormones estrogen as well as progesterone in the role of OSA, despite conflicting results for hormonal replacement therapy of both men and women.[57] A number of studies suggest that sex may influence factors such as sleep-wake amount, the daily timing of the sleep-wake cycle, and the ability to restore sleep after extended wakefulness.[10] Krishnan and Collop found that healthy women appeared to have better sleep quality than men.[7] However, women were found to report more sleep problems including sleep efficiency, sleep onset latency, REM onset latency, as well as wake time after sleep onset.[29] Additionally, women were found to be less likely to function at their best during the day with less than 7 hours of sleep and reported frequent morning headaches. These findings suggest that women are either more likely to develop clinical symptoms from inadequate sleep, or they are more likely to report symptoms in general.

PATHOPHYSIOLOGY OF OSA

Current data suggest that men have a larger upper airway composition than women. This includes the soft palate, tongue volume, and pharyngeal length. This difference is seen in both normal and OSA patients. Other sex differences appear in the upper airway shape and genioglossal muscle activity during the awake state in craniofacial morphology, which account for a higher male risk of OSA.[41] Upper airway caliber during wakefulness also seems to be greater in men than in women suggesting that characteristics other than upper airway anatomy are causing an obvious predisposition to OSA. Mohsenin,[23] found that, despite displaying similar clinical symptoms of OSA, women tended to have mild OSA (respiratory disturbance index [RDI], 9.2 ± 2.7 events per hour) or increased upper airway resistance syndrome, while men tended to have more severe OSA (RDI, 28.0 ± 3.5 events per hour; $P < 0.0001$). However, Walker[37] and coworkers found that, among the OSAS population studies, the RDI increased as the body mass index (BMI) increased, correlation coefficient [r] = 0.40 $P \leq 0.001$ for men, and [r] = 0.21 $P \leq 0.034$ for women, respectively.

On the other hand, women had a significantly smaller oropharyngeal junction and pharynx than men ($P < 0.02$). Mohsenin also found a significant correlation between upper airway size and the severity of sleep apnea.[23] This correlation was only found in men. Neither gender displayed a correlation between BMI and pharyngeal size. These findings suggest that upper airway properties in awake men correlate with the severity of OSA. Overall, both structural and functional upper airway characteristics seem to be more favorable in women than in men.[23]

CLINICAL PRESENTATION OF OSA

Snoring, daytime sleepiness, and witnessed apneic events are all typical symptoms of OSA, which can also be expressed as sleep onset, drowsy driving and self-medicated with excessive caffeine intake.[36] Men tend to experience and report the symptoms of snoring or daytime sleepiness, while women are more likely to experience and report atypical symptoms such as headaches, insomnia, tension, fatigue, or have coexistent clinical depression or hypothyroidism.[28] These atypical symptoms can cause a deviation from the diagnosis of OSA. An important clue to the diagnosis of OSA is the occurrence of witnessed apneic events. Witnessed apneas, however, have been found to be reported less often from women than men. These gender differences may lead to a misdiagnosis of disorders such as depression, which share similar symptoms.[7,16,58,59]

According to Valipour *et al*., when using the Sleep Disorders Questionnaire and a polysomnogram to evaluate symptoms of OSA, of the 2739 men and 782 women scored, items related to the worsening of snoring/breathing were scored significantly higher in men with a history of both alcohol ($P < 0.001$) and smoking ($P < 0.01$) than in women.[15] Symptoms such as witnessed apneas ($P < 0.001$) and worsening of snoring in the supine position ($P < 0.05$), were also more frequently reported by men with an AHI < 5/h than AHI-matched women. Women, by contrast, complained significantly more often of insomnia, rest-less legs, depression, nightmares, palpitations at night, and hallucinations than men. This was supported by women scoring significantly higher on the periodic limb movement, psychiatric sleep disorder, and narcolepsy (NAR) scales of the Sleep Disorders Questionnaire ($P < 0.001$, for all). The researchers adjusted for age, BMI, AHI, arousal index, oxygen saturation data, and smoking history by means of multiple analyses of covariances, and the sex differences remained significant ($P < 0.001$, for all scales). Valipour *et al*. suggested that these differences be taken into consideration in the clinical evaluation of women, in particular, with suspected sleep disordered breathing.[15]

A study by Quintana-Gallego *et al*., performed in 2004, found that, of the 1745 patients with suggestive clinical symptoms of OSA included in the study, 1386

were men and only 359 women.[58] The percentage of males and females was similar in patients undergoing an overnight polysomnography (79.5% vs. 20.5%), a nap polysomnography (80.8% vs. 19.2%), and an overnight home polygraphy (78.8% vs. 21.2%). A total of 1166 patients fulfilled polysomnographic or polygraphic criteria of OSA. There were 970 men and 196 women (male/female ratio of 4.9:1).[58]

A review of current literature by Krishnan and Collop, found that women are less likely to come to the clinic accompanied by their bed partner, whose complementary sleep history may assist in the diagnosis of OSA.[7] A review conducted by Henry[34] and coworkers, found several factors that shed some light on the gender roles that are identified in traditional sleep roles. The review described how a patient with sleep apnea comes to understand their illness primarily through how someone else, such as one's spouse, experiences and interprets it. They also concluded that communication within relationships, along with other factors, played an important role in how sleep apnea is recognized and understood by the patient. Gender seemed to play a role in whether, or not a patient was satisfied with the CPAP treatment.[60]

OSA TYPES AND SEVERITY

According to O'Connor *et al*., the prevalence of different types of OSA in men and women varied significantly by sex. Researchers categorized OSA into three different types: mild OSA, which occurred primarily during REM sleep (REM OSA); OSA of any severity, which occurred primarily in the supine position (S OSA); and OSA without a predominance in a particular sleep stage or body position (A OSA). Women with OSA were found to have a higher prevalence of REM OSA than men (62% in women vs 24% in men), while men were found to have a higher prevalence of A OSA (62% in men vs 32% in women), subsequent study of OSA was found to almost exclusively occur in men (14% in men vs 4% in women).[14]

In order to determine whether these differences reflected a higher prevalence of mild OSA among women, researchers exclusively analyzed the patients with mild OSA only (with one group categorizing severe vs non-severe as defined by apnea-hypopnoea index from laboratory-based overnight polysomnography[38]). The overall prevalence of REM OSA was found to be higher when patients with moderate and severe OSA were eliminated; however, male-to-female ratios remained relatively constant. Differences seen in the prevalence of REM OSA and S OSA also remained constant among women.[14] These findings were consistent with the data collected by Mohsenin (2000), who found that, despite displaying similar clinical symptoms of OSA, women were more likely than men to have mild OSA.[23]

When looking at severity, women were found to have a higher proportion of mild apnea during total sleep time. This was supported by the increase of the male-to-female ratio from 2:1 for mild OSA to 7:1 for severe OSA due to the higher proportion of mild OSA during NREM sleep in women. Similarly, during NREM sleep, the male-to-female ratio increased from 1:1 for mild OSA to 8:1 for severe OSA. This trend was not seen during REM sleep, for which the male-to-female ratio decreased from 6.3:1 for mild OSA to 3.3:1 for severe OSA.[14]

The current literature suggests that the difference in the prevalence of OSA by sex is amplified in both the clinic and hospital patient population. Krishnan and Collop proposed that this could be due to several reasons, such as atypical presentation of women with OSA making diagnosis and management of the sleep disorder less likely and that the difference in prevalence of OSA by sex may be increased with severity of the disease.[7]

SLEEP PATTERNS – REM AND NREM CHANGES

When healthy men and women are compared under controlled sleep laboratory conditions, baseline sleep patterns appear to be very similar between the two groups. However, real-life settings have shown that sleep patterns and sleep quality contain sex differences[20] and vary according to shift time.[36] A review conducted by Matos[32] and coworkers, found that the rat's sex regulated the outcome of sleep deprivation. It was also found that male rats were more affected by sleep deprivation than female rats.[33]

A study conducted by Jefferson *et al*. found that women with OSA were more likely to experience little (less than 8 min) to no REM sleep throughout the night, compared to men with OSA.[61] Also, the latency to the onset of REM sleep takes about an average of 34% longer in women with OSA than in men with OSA.[21,61] A subsequent study on REM and OSA suggests that sleep disordered breathing may be more commonly isolated to REM sleep in female OSA patients compared to males, and suggests that the full causes are not yet known and must be further explored.[41]

During sleep, women have a lower apnea threshold compared with men. Arousal from sleep induces greater ventilator instability in men compared with women. With inspiratory flow limitation during NREM sleep, women are also less likely to exhibit apneas and hypoventilation compared with men. The differences in response to physical and chemical changes associated with OSA may underlie the sex differences in prevalence and clinical presentation of the disorder.[7,21] Another possibility underlying sex differences is the frequency of which medications are used by patients with untreated OSA to examine the potential associations between medication types and indexes of sleep architecture.[39] The upper airway appears to be less susceptible to OSA during slow wave sleep (SWS), than during REM and other NREM sleep.

The findings of Jefferson *et al*. have also been seen in various studies that use polysomnography. These studies show that sex has an influence on specific polysomnographic features of OSA.[14] A retrospective study of 830 patients with OSA carried out by O'Connor *et al*. found that the severity of sleep apnea was similar in men and women, but only during REM sleep. A study by Subramanian[21] and coworkers, found that women had significantly higher SWS by percentage, and lower NREM AHI ($P < 0.0001$) and SWS AHI ($P = 0.03$), and patients with OSA (AHI ≤ 5), the difference between REM AHI and SWS AHU was greater in women than in men. Ware and coworkers, suggests that relative to stage 2 sleep, REM sleep reduced the differences between men and women in apnea frequency.[42] Pellegrino and coworkers,[40] found that Apolipoprotein E polymorphisms can influence the effects of intermittent hypoxia and sleep fragmentation in the sleep architecture of OSA patients and that the presence of the ε2 allele may serve as a biological marker for the identification of the subgroup of patients whom are more likely to suffer with OSAS negative effects on sleep, impacting day to day life as well as the overall quality.[40] Analysis of the polysomnography of NREM sleep showed that apnea during this type of sleep was less severe in women than in men. Specifically, the polysomnography results showed that women tend to have milder OSA than men, while women tend to have a greater proportion of respiratory events in REM sleep than men, and that the prevalence of OSA is higher in women than in men, and it occurs almost always during REM sleep.[14,61]

As mentioned earlier, current knowledge on sex differences within sleep disorders suggests that both biological sex and sex-driven characteristics have an effect on sleep states, which may be the cause of sex disparities in sleep disorders. Current research has also proposed that in mammals, reproductive hormones play a significant role in sleep and may also have a variety of different influences on sleep regulatory mechanisms. For instance, Paul *et al*. found that sex interacts with various sleep mechanisms, such as sleep timing (morningness versus eveningness) and homeostatic sleep drive (sleep pressure).[61]

BIAS IN REFERRAL AND DIAGNOSIS

A gender bias exists in the referral of women into the sleep clinic. According to Larsson[17] *et al*., women were significantly underrepresented in sleep laboratory referrals, even though women who snored experienced more subjective daytime sleepiness than men. A later study by Kapsilmalis and Kryger, of the general population suggest that about a third of all cases are females.[43] This suggests that there may be clinical under-recognition of OSAS in females. The referral ratio for men and women in this study, after correction for population and prevalence of symptoms, was 1.25:1 ($P = 0.012$).[17] The previous study and a related one by Shepertycky reinstates that the larger sleep-apnea prevalence in men has raised the concern that a selective referral and identification bias is common to favor men.[62]

A gender bias also exists in the diagnosis of OSA. It is estimated that there is a 90% under-diagnosis of OSA in women.[30] In fact, recent evidence suggest that for males, excessive daytime sleepiness and snoring seem not to be good predictors of OSA, and much less effective for women; however, this is a common manner in which professionals diagnose.[44]

Despite all of the evidence, OSA has still been underdiagnosed. Data collected by Jefferson *et al*. found that through previous analysis using rodents as a model an under-diagnosis of OSA in women may be due to sex differences in the sleep response to stress.[61] Another challenge in the under-diagnosis of OSA of women is that an apnea patient's understanding of their illness is critically shaped by their spouses and or partners' direct experience of symptoms, which is usually missing information but is critical to a correct diagnosis.[34]

Quintana-Gallego *et al*.[58] found that the lower diagnosis of OSA that occurs in women may be due to the fact that there are differences in how the disorder is expressed in women could lead women to obtain less and later consultations with a sleep clinic. Another reason could be that the "clinical picture" of OSA that women tend to show could be less recognized by

primary care physicians.[58] Overall, there are various reasons for under-diagnoses, and unfortunately if women aren't diagnosed they are less likely to receive treatment.

TREATMENT OF OSA

A recent study concluded that more effectively powered studies that investigate possible referral and response biases are the next step in examining sex differences in OSA clinical manifestations and response to CPAP treatment.[30] According to Ye *et al*. in 2009, both genders seem to benefit from CPAP treatment.[30] Despite the lack of compliance across the board among genders,[47] while under optimal use, the ventilatory response to arousal is influences by pre-arousal airway resistance and gender.[50] These sex differences were assessed by Campos-Rodríguez *et al*.[60] Researchers found that CPAP treatment for women may decrease cardiovascular mortality and most of the clinical complaints associated with OSA. Another study lead by Mermigkis investigated the effectivity of CPAP on OSA through monitoring the C-reactive protein (indicative of OSA for patients with fatty artery deposits or hypertension) did not continue to decrease after the third month of CPAP use.[48] A subsequent study concluded that the effect of sex on CPAP requirement was found to be significant even when confounding variables were accounted for using linear regression.[35]

Campos-Rodríguez *et al*. also found that the role of non-CPAP therapies such as weight loss, surgery, mandibular advancement devices, and hormone-replacement therapy has not been sufficiently investigated for women.[60] A review conducted by Krishnan and Collop found that weight loss in OSA patients was more successful in men than in women as a treatment.[7] It is clear that the ways in which OSA can be treated are not clear for women. In 2009, a review of the surgical modifications of upper airways was published by Camples and coworkers and concluded that maxiofacial/head and neck surgery, uvulopalatopharyngoplasty, (the removal of throat tissue) with genioglossus advancement can provide a wide range of treatment options for OSA patients that fail non-invasive therapies (such as CPAP compliance) with success rates greater than 85%.[63] These studies were found to work at such levels for both genders.

COMORBIDITIES

Obesity has been identified as a strong risk factor for OSA. Women are more likely than men to be obese. However, it is the distribution of total body fat that is the most significant. In their review, Krishnan and Collop found that men and women with similar BMI and waist circumference had significant differences within the distribution of total body fat, whereas waist-to-hip ratio is more predictive of the severity of OSA in men than in women.[35] Men were found to have greater upper body obesity, which was determined by them having a smaller hip circumference and a greater subscapular skin fold thickness, both of which increase the upper airway resistance[7] and maximizes ventilator pressures.[64] This finding supports previous data collected by Guilleminault *et al*.[25] that found that women with OSA were more likely to be massively obese.[25,65]

Obstructive sleep apnea is a known risk factor for hypertension. A review conducted by Kinkead[33] and coworkers found that male rats that experienced stress due to neonatal maternal separation were hypertensive. Neonatal maternal separation did not have the same effect on female rats.[66] Hedner *et al*.[26] explored this known association between OSA and hypertension in a sex-balanced community-based sample of patients with hypertension. Researchers found that severe OSA was present in about 47% and 25% of hypertensive and normotensive males, respectively. Women belonging to these same groups were found to have severe OSA at rates of 26% and 24%. The odds ratio (OR) for hypertension increased across AHI tertiles from 1.0 to 2.1 (95% confidence interval: 0.9–4.5) and 1.0 to 3.7 (95% CI: 1.7–8.2) in males, but not in females where the OR increased from 1.0 to 1.8 (95% CI: 0.8–3.9) and 1.0 to 1.6 (95% CI: 0.7–3.5). A regression analysis correcting for age, BMI (or waist–hip ratio) and smoking did not eliminate the association between OSA and hypertension in males. These data suggest that OSA is highly prevalent in both the general population and in patients with known hypertension. Researchers in Turkey found that a higher nocturnal mean heart rate and a higher maximum heart rate caused by sympathetic nervous system activation in OSA may explain the link between hypertension and OSA.[67] Ironically, disease related cardiovascular morbidity is also a common comorbidity and has been shown to improve with CPAP use.[48] The contribution of OSA to hypertension risk seems to be higher in males than in females.

Insomnia and other ailments are common among adults with OSA. A study done by Lee *et al*. in 2013, found that of the 655 adult patients with OSA were enrolled, 233 (35.5 %) reported comorbid insomnia symptoms with OSA.[24] The severity of OSA did not have

an effect on comorbid insomnia symptoms. Researchers from the University of Alabama found a link between OSA severity and co-occurring insomnia, supporting the view that the disorders co-exist in an independent, self-sustaining manner.[51] Comorbidities among OSA, insomnia and sleep breathing disorder were reported by 42% of patients in a 2013 study by Krakow and Ulibarri.[52] Women diagnosed with OSA and treated with CPAP demonstrated a 3.44 greater mortality risk than men, mostly due to greater comorbidity with a history of heart failure or cerebrovascular accident, heart failure, diabetes mellitus and chronic obstructive pulmonary disease.[45] Another study lead by van Dijk, found a higher proportion of patients with type 1 diabetes mellitus had an increased risk for OSA (17.2% vs 5.1%, $P = 0.012$). A study by Celen and coworkers predict an odds ratio of 11.8 of women with type 1 diabetes mellitus also having OSA.[68] Difficulties initiating sleep, was found to be more common in women in a 2012 study lead by Björnsdóttir.[54] Yardim-Akaykin and coworkers, suggested a strong correlation between inflammation (by tracing markers including C-reactive protein, fibrinogen and erythrocyte sedimentation rate) of OSA female patients.[53] Researchers found that women had higher depression, fatigue, and daytime sleepiness and lower health-related quality of life than men (all, $P < 0.05$). The presence of insomnia symptom had negative effects on fatigue ($P = 0.005$) and quality of life only ($P = 0.015$) in men but not in women when taking gender-by-insomnia interaction into consideration. Researchers also found that there were significant differences in polysomnography-based sleep architecture between the OSA-only and OSA-insomnia groups, but only in the subgroup of men.[22]

Since women are more likely to report symptoms of fatigue, insomnia, tension, and the use of sedatives, women who have sleep apnea may be diagnosed with depression, a disorder that shares many of the same symptoms. Anxiety is also frequently reported with OSA[69] According to Shepertycky and Banno,[43] at the time of OSA diagnosis, women with OSA are more likely to be treated for depression, to have insomnia, and to have hyperthyroidism than are men with the same degree of OSA,[16] as well as report an overall lower quality of life.[70] A dangerous self-medication technique that many women use is to use alcohol for sleep, however it is strongly associated with hazardous drinking which prompts physicians concerns for excessive alcohol use.[71] Therefore, it is pertinent that women are appropriately diagnosed.

CONCLUSION

Is there an under-diagnosis of OSA in women? Several studies mentioned within this review have investigated the ways in which gender differences affect sleep, symptoms of OSA, diagnosis of OSA, and treatment of OSA. Recent research has studied whether or not men and women exhibit different symptoms of sleep apnea. For instance, Runyon *et al*.[59] found that men and women do indeed display particular symptoms of apnea differently than men. Other studies investigated gender differences and uncovered various forms of bias that seem to affect diagnosis rates of OSA in both women and among the general population. Despite new technologies for diagnosing OSA, such as radiological imaging techniques, gender differences are still not able to be diagnosed.[72] Due to these aforementioned factors, it is likely that an under-diagnosis of OSA in women exists. This is supported by both the Wisconsin sleep cohort study as well as Jefferson *et al*.,[61] who concluded that OSA is underdiagnosed in approximately 90% of women.

What does all of this mean to public health? In 1999, a study was conducted by Kapur *et al*. that estimated the medical cost of undiagnosed sleep apnea. Cost data from the year prior to the diagnosis of sleep-disordered breathing in a consecutive series of 238 cases were used to estimate the potential medical cost of undiagnosed sleep apnea and to determine the relationship between the severity of sleep-disordered breathing and the magnitude of medical costs. Among cases, mean annual medical cost prior to diagnosis was $US2720 versus $1384 for age and gender matched controls ($P < 0.01$). Regression analysis showed that the reciprocal of the AHI among cases was significantly related to log-transformed annual medical costs after adjusting for age, gender, and BMI ($P < 0.05$). The study concluded that patients with undiagnosed sleep apnea had considerably higher medical costs than age and sex matched individuals and that the severity of sleep-disordered breathing was associated with the magnitude of medical costs. Using available data on the prevalence of undiagnosed moderate to severe sleep apnea in middle-aged adults, it is estimated that untreated sleep apnea may cause $3.4 billion in additional medical costs in the US.[27]

Although it has been 15 years since the Kapur *et al*. study there is still a significant economic burden that stems from the medical costs associated with undiagnosed OSA.[27] Tarasiuk and Reuven investigated these costs, concluding that the cost of untreated OSA doubles the medical cost, primarily because of the increased morbidity from cardiovascular disease that

sufferers of OSA are at risk of.[73] When patients do not properly follow CPAP protocol, this also has increased medical costs.

Based on the above findings and the studies reviewed, healthcare providers should become aware that various gender differences in the presentation of OSA exist. They should also use more caution and keep a more open mind when evaluating the symptoms of women with possible OSA. Future studies should investigate methods that may be more helpful and accurate in the diagnosis of this disorder in women.

DISCLOSURE

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