

Gender Differences in Obstructive Sleep Apnea

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ABSTRACT

Historically OSA has been regarded as a male disease. Therefore, much of our knowledge comes from studies with largely male populations. Growing evidence suggests that there are significantly different gender aspects of OSA. The symptoms of OSA may manifest differently in female patients, and females tend to be diagnosed and treated less often, despite reporting worse quality of life outcomes. Comparisons of polysomnography data have shown that women appear to have less severe OSA overall with a higher incidence of flow limitation and REM related events. Severe OSA in women appears to be associated with cardiovascular morbidity and mortality, and effective treatment may reduce this risk. Researchers are beginning to understand more about gender differences in OSA, and the optimal treatment for these patients, although more research in this field is still needed.

PREVALENCE

Obstructive sleep apnea (**OSA**) is a condition during which the upper airway closes repetitively during sleep. Airway closures are identified as either apneas (full upper airway closure) or hypopnoe as (partial upper airway closure), where the event is associated with oxygen desaturation and /or arousal from sleep. The count of events per hour; the apnea hypopnea index (**AHI**), indicates the severity of the disorder.

The estimated prevalence of OSA changes depending on which scoring criteria are used. Table 1 displays the estimated population prevalence of OSA in males and females.

Table 1: Estimated population prevalence of OSA.

Study	Mild OSA (AHI ≥ 5)		Moderate to severe OSA (AHI ≥ 15)	
	Males	Females	Males	Females
Young <i>et al</i> (1993) [2]	24%	9%	9%	4%
Redline <i>et al</i> (1994) [5]*	-	-	26%	13%
Bixleret <i>al</i> (1998, 2001) [64,65]	17%	-	7%	2%
Duran <i>et al</i> (2001) [66]	26.2%	28%	14%	7%
Peppard <i>et al</i> (2013) [67]	-	-	13.5%	6%
Franklin <i>et al</i> (2013) [33]^#	-	50%	-	26%
Heinzeret <i>al</i> (2015)*	34%	38%	49.7%	23.4%

*Respiratory Disturbance Index (**RDI**) rather than AHI given.

^ Women aged 20-70 years.

#An updated scoring criteria (AASM 2012) was used.

The prevalence of OSA has been increasingly steadily, in part due to the global rise in obesity, and also due to an update to the recommended OSA scoring rules which were published in 2012 and allow a more liberal scoring of hypopnoeas [1].

CLINICAL FEATURES

While the prevalence of OSA in males is reported to be higher than that of females, there is a much higher discrepancy between the genders in the clinical population. OSA is estimated to have a male to female ratio of between 3:1 and 5:1 in the general population and between 8:1 and 10:1 in some clinical populations [2-5].

It has been hypothesised that the large discrepancy between the population prevalence of OSA, and the clinical populations is due to women being frequently misdiagnosed [4,6]. Women often present with different symptoms than what are considered the “typical” symptoms of sleep apnea [4,7]. The typical symptoms that men with sleep apnea present with are snoring, witnessed apneas and excessive daytime sleepiness. However approximately 40% of women with an AHI ≥ 15 do not report any of the classic OSA [8]. Instead women are likely to complain of insomnia, fatigue, daytime tiredness, headaches, muscle pain and depression [4,9,10]. As a result, women

are frequently misdiagnosed with depression or another illness [4,9]. In addition, women typically have lower scores than men on the Epworth sleepiness scale (**ESS**), a questionnaire designed to evaluate daytime sleepiness which is often used as a screening tool for OSA [11,12]. The ESS has not been validated for use in female OSA patients, and indeed in population based studies OSA has not been strongly associated with daytime sleepiness in female patients [11,12]. It is hypothesized that women may use different words to describe sleepiness, and answer questions on sleepiness differently from men. Or they may have a higher threshold for sleepiness or simply be less inclined to complain about it [4].

Men often attend clinical appointments with their partner, whereas women are more likely to attend on their own [3,4]. This may mean that perhaps apneas in women are less frequently reported [3], or that male partners tend to be less concerned about the events [13]. It has also been hypothesized that women may be reluctant to complain about disturbed sleep and their own snoring, if they consider it unladylike or embarrassing [4].

Regardless of the symptoms which patients present with, Young and colleagues found that even when women did report the same classic symptoms of OSA, such as snoring, witnessed apneas and excessive daytime sleepiness, they were still less likely to be referred to sleep clinics than men. They raised the issue that physicians tend to disregard these typical symptoms in women [6]. Similar results were recently reported by Lindberg et al, who found that women were underrepresented at sleep clinics, and despite similar symptoms to males, less likely to be diagnosed or treated with OSA [14].

GENDER DIFFERENCES IN POLYSOMNOGRAPHY

Recent studies have shown that the polysomnography (**PSG**) features of female OSA are different from male OSA. Overall, women have less severe OSA with lower AHIs [15] and shorter apneas [16]. Although overall women have lower AHIs than males, research has shown that women are more symptomatic at lower AHI's than males with a similar diseases severity [6].

One reason women are more symptomatic may be because women have more episodes of upper airway resistance [17]. Obstructive events can be thought of as a continuum of partial to complete upper airway obstruction. Upper airway resistance occurs early in this spectrum, and refers to incidences where there are increases in resistance to airflow in the upper airway during sleep, presenting as flow limitation on a PSG[18]. This upper airway narrowing has the potential to increase work of breathing, cause arousals and disrupted sleep, and effect daytime cognitive function [18]. Upper airway resistance alone, without complete obstructive apnea, has been shown to produce clinical symptoms such as daytime fatigue and depression [19].

As females may have multiple episodes of upper airway resistance without frank apneas, the AHI value may not give the physician a true indication of the degree of sleep fragmentation a patient is experiencing. As a result, episodes during sleep where the flow is reduced; respiratory

effort increases; and the episode is terminated by an arousal have been coined Respiratory Effort Related Arousals (**RERAs**) [18]. The importance of measuring and reporting on RERAs has been emphasised by a task force of the American Academy of Sleep Medicine (**AASM**) in 2007[20]. Updates to the recommended scoring criteria by the AASM in 2012 meant that hypopnoeas could be defined by an arousal only, with no requirement for oxygen desaturation [1]. This broader definition means that less RERAs are scored and more female patients may now be diagnosed with OSA, who previously may not have met the requirements for hypopnoeas. This is likely reflected in the increase in the prevalence of female OSA seen in recent studies.

Women often have events mainly occurring during REM sleep [15]. Body position is far less important for the severity of OSA in women, while with men the severity is more based on position than sleep state [15]. In fact a study by O'Connor and colleagues found that in a group of 830 patients, positional OSA was almost exclusively a male presentation [15].

Sleep architecture is also different in healthy men and women with sleep apnea. A study of 307 patients by Valencia-Flores and colleagues found that women took longer to fall asleep than males. Once women were asleep, they then had fewer awakenings from sleep, and had slower wave (deep) sleep than males [21].

GENDER DIFFERENCES IN PATHOPHYSIOLOGY

In women, the neck and upper airway are smaller in size than in men [4]. MRI imaging has shown that the airway length, the tongue, the soft palate, and the total amount of soft tissue in the throat are all smaller in women than men [22]. Although common sense would dictate that a smaller airway size would collapse more easily than a larger one, this isn't the case. The pharyngeal critical closing pressure, or Pcrit, is lower in women with sleep apnea than men with the same severity of obstructive sleep apnea, meaning that the airway of males is more collapsible than that of females [4,23].

Obstructive sleep apnea has long been associated with obesity, and in both genders increased body mass index indicates a higher severity of the disease [24]. However women with OSA are typically more obese than men who have the same AHI [9]. One possible explanation for this is the differences in fat distributions between the genders. Men tend to put on weight in the upper body and trunk, including the upper airway soft tissue structures – the tongue, soft palate, and lateral pharyngeal walls; whereas when women put on weight it tends to be deposited in the lower body and extremities [4]. Newman and colleagues showed that small weight changes influence sleep disordered breathing in men more than in women as men may reduce fatty tissue in the upper airway more readily [25]. Fat distribution also affects the lungs in different ways between men and women. Women are better able to cope with an increased chest wall load, because with increased obesity women have improved chemosensitivity responses to hypoxia and hypercapnia [22].

Respiratory stability refers to efficacy of gas exchange, blood circulation and the functioning of central and peripheral chemoreceptors. There are distinctive differences between the efficacy of respiratory stability in men and women [4]. The response to low oxygen in the blood (hypoxia) declines in men during sleep compared with their awake values, whereas in women the hypoxia response is similar between sleep and wake [26]. Men have been shown to have a more significant ventilatory response to high levels of carbon dioxide in the blood (hypercapnia) [27]. Zhou and colleagues showed that men and women require different levels of carbon dioxide in the blood to cause respiratory instability, and that men are more susceptible to hypocapnic dysfunction during NREM sleep than women. This may be due to the notion that women preserve ventilation output during hypocapnia more efficiently than men [28]. Taken together, this may mean that women are better able to stabilise their breathing during sleep, leading to less severe apneas with minimal desaturation.

There may also be gender differences in the arousal response patients have to apneas. Jordan and colleagues found that during NREM men had a higher ventilatory response to apneas, but then they developed a greater hypoventilation when they went back to sleep, especially in the supine position. This prolonged hypoventilation often leads to ventilatory instability upon returning to sleep. The result can be a cycle of respiratory instability leading to consecutive apneas during sleep. Jordan and colleagues hypothesised that this may play a role in explaining why sleep apnea is more severe in men [29]. However the same authors also found that loop gain was not different in males and females matched for AHI and BMI, and therefore respiratory control stability may be less significant than reduced upper airway collapsibility in female patients [30].

The prevalence of sleep apnea increases in post-menopausal women [9]. One reason for this increase may be that menstrual hormones play a role in the distribution of body fat. Post menopausal women have more body fat than menstruating women, and that body fat is distributed in similar areas to males, which is the upper body, specifically the trunk and neck [31]. A second reason that post menopausal women have increased incidence of sleep apnea may be due to the hormone progesterone. Progesterone is a known respiratory stimulant which increases chemoreceptor responses to hypercapnia and hypoxia and has also been shown to increase upper airway muscle tone [32].

HEALTH CONSEQUENCES OF OSA IN FEMALES

In the past, obstructive sleep apnoea (**OSA**) has been primarily considered a male disorder, and as a result clinical trial populations were comprised almost entirely of males [33]. Recently studies have focused more specifically on the unique consequences of OSA in female patients.

Several comparisons of women and men with untreated OSA have found that women experience a worsened quality of life. Women experience more mood disturbances such as anxiety and depression, report lower quality of life scores on a range of questionnaires, display increased

daytime fatigue, reduced sleep quality and worsened neurobehavioral symptoms [34-37]. This worsened quality of life found in female patients may well be a reflection of the more severe flow limitation and sleep fragmentation seen in many women patients. Basically sleep physiology tells us that constant arousals during sleep in healthy subjects severely impacts daytime cognitive performance [38]. And indeed arousals from sleep without corresponding oxygen desaturation have been associated with a range of consequences including tiredness, fatigue and sleepiness [39]; significant daytime impairment, difficulty completing tasks, depressed mood and insomnia [40].

Women with OSA were also found to be more likely to develop hypothyroidism and arthropathy, as well as experience lower perceived health status, overuse psychoactive drugs, and experience increased healthcare costs of 1.3 times compared with men with OSA [36].

Yaffe et al. studied a group of women with sleep disordered breathing (**SDB**) and found that they were more likely to develop cognitive impairment or dementia than those without the condition. They found that cognitive issues were more likely to develop in those with increased oxygen desaturation and higher periods of time spent in apnea or hypopnoea [41]. Further research undertaken by Macey and colleagues discovered that female OSA patients experienced more brain white matter injury than their male counterparts [35]. It is hypothesised, although not yet known, that this change in white matter structure may be responsible for the worsened quality of life reported by women.

Endothelial function, peak blood flow, systemic inflammation, and digital vascular function have been found to be more impaired in females than males with OSA [42-44]. These blunted responses may mean that women with OSA are more susceptible to the adverse cardiovascular consequences of OSA than males [44]. The association between OSA and hypertension in females is not conclusive, with some studies showing no association [45,46], and some studies finding an association in peri-menopausal and older females [47,48]. The largest dataset published to date included 1 704 905 patients with OSA and 1 704 417 matched controls. The authors reported that hypertension was more prevalent in women with OSA than males with OSA, with an overall odds ratio of developing hypertension of 2.14 in the OSA group compared with controls [49].

The same data set found that congestive heart failure was strongly associated with OSA in both sexes compared with controls ($p < 0.000$) with no clear sex differences [49]. A prospective study by Campos-Rodriguez et al. evaluated the long term outcomes of OSA in a group of treated and non-treated female patients. They found that severe OSA was associated with increased cardiovascular mortality risk (adjusted HR 3.50, 95% CI 1.23-9.98), and that adequate CPAP treatment may reduce this risk [10].

THE ROLE OF PREGNANCY

Pregnancy may also increase the risk of developing OSA. During a typical pregnancy, elevation of the diaphragm leads to reduced functional residual capacity, the upper airway narrows, neck circumference enlarges, nasal patency is reduced, and there is substantial weight gain. All of these factors suggest pregnancy may induce or exacerbate OSA [4]. Conversely, pregnant women may be more protected from OSA, with increased levels of female sexual hormones stimulating respiration [50].

While the effect of OSA on pregnancy outcome is not completely understood, some studies have found that OSA is associated with higher rates of pre-eclampsia and intra-uterine growth retardation [51]. An ongoing study in this area will enrol 3702 women to understand the prevalence and outcomes of OSA during pregnancy [52]. Preliminary data from this group found that OSA affects 8.1% of pregnant women by the second trimester, and that there was an association between OSA and hypertension and diabetes in this group [53].

TREATMENT OF OSA IN FEMALES

The treatment of choice for OSA is continuous positive airway pressure (**CPAP**). CPAP attaches to the user with a mask and tubing, and circulates air to increase pressure in the upper airway. The result is a pneumatic splint which holds the airway open and prevents collapse. Effective treatment with CPAP has been shown to improve symptoms and reduce health risks in OSA patients [54].

Personalized medicine has not yet made major inroads into OSA treatments. However due to the different structures and pathologies involved in the disease, personalized diagnostic methods and treatments should be introduced as a way to improve patient care [55]. Sex differences in the use and response to CPAP devices are one example of personalized treatment which has not been extensively studied to date. A review of a database of 4281 patients found that average daily CPAP usage in males patients was slightly higher than in female patients, however usage in both genders was high (377 ± 94 vs. 370 ± 96) [56]. A similar analysis followed a group of 708 women for a median of 6.2 (4.2-7.7) years. Overall long term compliance to treatment was good in female patients, with a median daily usage of 6 (IQR 4-7) hours per day. 82.8% were still using CPAP after 5 years, and 79.9% were still on CPAP at 10 years [57].

The first study to investigate the role of CPAP therapy on quality of life in only female patients has recently been published. The authors studied 307 women with moderate to severe OSA and found that three months CPAP use improved quality of life, anxiety, depression, mood and daytime symptoms compared with controls [58].

Few studies have focused on the physiological differences in women when considering treatments. Clinical trial data suggest that men require higher pressures during CPAP therapy than females, after adjusting for baseline OSA severity or BMI [56,59,60]. One recent bench

test has found that there are significant differences in the way commercially available CPAP devices respond to flow limitation common in female patients [61]. One CPAP device contains an algorithm which aims to address female specific OSA characteristics. This device was tested in a randomised, double-blind, cross-over clinical trial and was found to be as efficacious as a standard CPAP with a significant reduction in residual flow limitation and lower mean pressures [62]. An on-going clinical study is investigating the use of this device on quality of life in women, with outcome measures including daily functioning; sleepiness; depression; sexual function and sleep quality (clinicaltrials.gov registration: NCT02400073).

Non CPAP treatments have rarely been studied for gender specific effects. Weight loss is a common recommendation for mild patients; however this may be more beneficial to males than females based on the fat distribution in the upper airway of males [25]. Mandibular Advancement Devices (**MADs**) are a treatment option for those with mild-moderate OSA or those who have rejected CPAP. One large study found female gender was a predictor of treatment success, particularly in the mild group [63]. However more research is needed in this area.

CONCLUSION

Historically, our understandings of OSA and its treatments have been largely focused on male patients. There are clear gender differences in all aspects of OSA, including prevalence; symptoms; clinical recognition; anatomy (Including the upper airway, as well as obesity and fat distribution); physiology & pathophysiology (Including sleep architecture & respiratory stability) and the influence of hormones.

Knowledge is coming to light that there may also be differences in long term consequences and cardiovascular outcomes of female OSA. Additionally, there may be requirements for gender specific treatment options. More research is required to complete our understanding of the gender differences in OSA and the optimal treatment for patients.

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