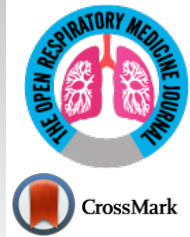




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## PERSPECTIVE ARTICLE

### Is Obesity Hypoventilation Syndrome A Postmenopausal Disorder?

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**Abstract:** Previous studies have assessed the role of gender and menopause in Obstructive Sleep Apnea (OSA). It is well known that menopause is a major risk factor for OSA. However, analogous studies on obesity Hypoventilation Syndrome (OHS) are limited. Recent studies have suggested that OHS is more prevalent in postmenopausal women. Moreover, women with OHS seem to have excess comorbidities, including hypothyroidism, hypertension, pulmonary hypertension, and diabetes mellitus, compared to men. In the present perspective, we discuss recent data on the prevalence and comorbidities associated with OHS in women, as well as the use of noninvasive ventilation in women with OHS, and try to answer the question, “Is OHS a disorder of postmenopausal women?”

**Keywords:** hHpercpania, Obstructive sleep apnea, Hypoxia, Progesterone, Sleep, OHS.

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## 1. INTRODUCTION

Sleep-Disordered Breathing (SDB) is a constellation of disorders characterized by abnormal breathing during sleep. It includes Obstructive Sleep Apnea (OSA), Central Sleep Apnea (CSA), and Obesity Hypoventilation Syndrome (OHS). In general, SDB is under-recognized in women. Studies assessing gender differences in OSA patients have reported differences in its prevalence, clinical presentation, and polysomnographic features [1]. Previous studies have found an impact of gender and menopause on OSA. Specifically, it is well known that menopause is a major risk factor for OSA. OSA is approximately three times more prevalent in men than in women [2]. However, analogous studies on obesity hypoventilation syndrome (OHS) are limited. Other than menopause, which is a well-established risk factor for OSA in women [3], gender differences in the upper airway structure and function and ventilatory control during sleep, including increased sensitivity to carbon dioxide (CO<sub>2</sub>), in men compared to women, have been reported [4]. In this perspective, we discuss recent data on the prevalence and comorbidities associated with OHS in women, as well as the use of noninvasive ventilation in women with OHS, and try to answer the question “Is OHS a disorder of postmenopausal women?”

## 2. OBESITY HYPOVENTILATION SYNDROME IN WOMEN

OHS is the most severe form of SDB. The exact prevalence of OHS in the general population remains unknown; however, a conservative estimate in US adults ranges from 0.15% to 0.3% [5]. The prevalence of OHS among patients referred to sleep disorders clinics has been estimated in multiple studies to range from 8% to 20% [6 - 8].

Unlike OSA, which is a disorder with a well-established predominance in men, OHS is not as commonly prevalent in men [9]. In fact, OHS may be more prevalent in women than in men (15.6% and 4.5%, respectively), even after adjusting for Body Mass Index (BMI) differences. Women may also experience OHS-onset later than men (mean age 61.5 *versus* 49.1 years) [10]. After the comparison of postmenopausal women to age-matched men with OHS, it was observed that the prevalence of OHS remained significantly higher (four times) in postmenopausal women, with no significant differences observed in age, Apnea-Hypopnea Index (AHI), or BMI [10].

Gender differences and the impact of menopause on OHS mentioned previously have not been discussed in detail. However, in a recent review of the literature, Balachandran and his associates [11] carefully examined 11 studies from different countries, including a total of 4,150 patients with OSA, 714 of

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whom also had OHS. The authors concluded that in contrast to OSA, the male gender does not seem to present a significant risk for OHS [7]. However, the mean age of the subjects varied from 43 to 56 years in this study and the menopausal status of the female patients was not reported. The present perspective is the first review that seeks to bridge this gap by addressing the relationship between menopause and OHS.

It was previously reported that, among patients referred to sleep disorder centers for a possible diagnosis of SDB, the prevalence of OHS was 4.5% in men and 5.3% in premenopausal women [10]. However, the prevalence of OHS in postmenopausal women was much higher- *i.e.* 21% [10]. In fact, in King Saud University Sleep Disorders Center database of OHS patients, 89% of women with OHS were found to be postmenopausal [10]. This new finding has not been previously discussed.

### 3. PROPOSED MECHANISMS UNDERLYING THE INCREASED PREVALENCE OF OHS AMONG POSTMENOPAUSAL WOMEN

The underlying cause of the potentially elevated prevalence of OHS among women is not known [9, 10]. However, several potential mechanisms are proposed herein.

Possible explanations for the higher prevalence of OHS among postmenopausal women include the role of female hormones in the course and development of OHS. Progesterone is a known respiratory stimulant that increases alveolar ventilation, lowers the arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>), and augments the hypercapnic and hypoxic ventilatory responses [12, 13]. Moreover, progesterone increases dilator muscle tone in the upper airway [14]. Therefore, it is possible that the withdrawal of progesterone during menopause may, in part, contribute to the increased prevalence of hypoventilation in postmenopausal women *via* reduced respiratory drive and respiratory pathway relaxation. In a placebo-controlled, double-blind trial of postmenopausal women with OSA on Continuous Positive Airway Pressure (CPAP) therapy, women were randomized to Medroxyprogesterone Acetate (MPA) or a placebo for two weeks after discontinuing CPAP therapy [15]. Fourteen days after discontinuing the use of CPAP, nocturnal oxygen saturation remained higher and PaCO<sub>2</sub> remained lower ( $P < 0.001$ ) in the MPA treated group [15]. These results may support the role of progesterone in the development of hypercapnia. Despite these results, a randomized controlled trial is necessary to determine whether treatment with progesterone reverses hypercapnia associated with OHS in postmenopausal women.

Additional mechanisms have also been proposed to explain the gender difference in OHS. One such mechanism includes resistance to leptin, a powerful respiratory stimulant [16]. In general, obese individuals have higher leptin resistance than lean individuals, a condition that may affect the respiratory drive in obesity [17]. Moreover, serum leptin levels are an independent predictor of hypercapnia [18, 19]. Obese women have up to four times higher levels of leptin than obese men [20]. In theory, it is possible that obesity in women may lead to more resistance to the central effects of leptin compared to men and hence, a higher risk of hypoventilation and hypercapnia,

which results in an increased prevalence of OHS. However, further research is needed to prove this hypothesis. A previous study that assessed the effects of postmenopausal hormone replacement therapy (pHT) on a large sample of healthy postmenopausal women demonstrated that leptin concentrations were significantly higher in obese postmenopausal women compared to their counterparts of normal weight, and that neither pHT nor serum estradiol concentrations had an effect on leptin concentrations, even after the adjustment for BMI [21]. Moreover, previous studies addressing the relationship between menopausal status and leptin concentration reported conflicting results. While most studies showed no differences in serum leptin concentration between pre- and postmenopausal women, others reported both decreased and increased leptin concentrations [22 - 24].

Another potential but unlikely hypothesis for the gender differences in OHS is the differences in the ventilatory control in men and women. Studies assessing ventilatory responses to hypercapnia and hypoxia in men and women have reported conflicting results [25 - 27]. One such study demonstrated that the hypercapnic ventilatory response in women decreased compared to men; however, after adjusting for the forced expiratory volume in one second (FEV<sub>1</sub>), the gender-difference was not observed [28]. Therefore, ventilatory control may not explain the differences in the prevalence of OHS between men and women. Nevertheless, future studies should examine the physiology of respiratory muscles in men and women with OHS.

Moreover, the prevalence of clinical and subclinical hypothyroidism is significantly higher in women than in men with OHS [10]. Hypothyroidism suppresses the ventilatory response to hypercapnia [29] and hypoxia [30]. Hypothyroidism may impair ventilatory responses, which could predispose patients to hypoventilation due to the increased resistive load of upper airway obstruction [31]. Future research should thus, assess the effects of thyroid replacement therapies on hypoventilation in OHS patients.

### 4. OHS COMORBIDITIES IN WOMEN

Women with OHS have been reported to experience significantly more comorbidities than men, with a higher prevalence of hypertension, pulmonary hypertension, and diabetes, despite similar OSA severity and obesity levels [10, 32, 33]. In a group of age-matched women and men with OHS, the prevalence of hypertension and diabetes was significantly higher in women [10]. A recent study demonstrated that Pulmonary Hypertension (PHTN) was present in 71% of women and 62% of men with OHS [33]. Moreover, severe PHTN (systolic pulmonary artery pressure > 70 mmHg) was diagnosed in 28.6% of women and 14.3% of men with OHS [33].

### 5. NON-INVASIVE VENTILATION IN WOMEN WITH OHS

Approximately 40% of OHS patients initially present with acute decompensation and hypercapnic respiratory failure [34, 35]. This acute presentation is more common in women, indicating that OHS is under-recognized in women as

compared to men till acute decompensation develops [35]. Furthermore, in a study using the data from the national registry in Sweden to assess gender differences in patients undergoing long-term home Non-invasive Ventilation (NIV) treatment for OHS, the five-year survival rate was found to be 68.2% (95% CI, 63.6-72.3%) in men vs. 59.3% (95% CI, 54.2-64.0%) in women [35]. This data collectively indicated increased disease severity in women. It is important to note, however, that after adjusting for age, these survival differences were not observed. [35] Another French study reported that women with OHS had better survival rates than men, though, as shown in the prior work discussed here; however, after adjusting for potential confounders, the gender differences in the survival rate disappeared [36]. Therefore, at present, there is no clear evidence that gender drives differences in the survival rates among patients with OHS treated with long-term NIV.

## CONCLUSION

Recent data from observational studies revealed that OHS is most prevalent among postmenopausal women and that women with OHS more often exhibit cardiometabolic comorbidities, such as hypertension, pulmonary hypertension, and diabetes. Increased knowledge and clinical awareness of the elevated prevalence of OHS among postmenopausal women may lead to earlier diagnosis and more timely and appropriate treatment. Further studies are needed to assess the prevalence of OHS in women and the effect of menopause on the pathophysiology of OHS and the increased risk and comorbidities of OHS.

## DISCLOSURE

The authors report no conflicts of interest in this work.

## AUTHORS' CONTRIBUTION

The authors contributed equally to this manuscript.

## CONSENT FOR PUBLICATION

Not applicable.

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## CONFLICT OF INTEREST

The authors declares no conflict of interest, financial or otherwise.

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