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**Abstract**

There are suggestions that the loss of female sex hormones following menopause is critical for the development or progression of sleep-disordered breathing (SDB). We conducted a review of the literature on the role of menopause and hormone replacement therapy (HRT) in SDB risk. There is an increase in SDB during the menopausal transition period, but data on an effect beyond that of changes in body habitus and increasing age are weak or absent. Early community-based, observational studies reported a protective effect by HRT on SDB prevalence, but this could possibly be explained as a healthy user effect. Interventional studies of the effect of HRT on SDB are sparse, with only a few randomized placebo-controlled studies, often performed on small samples of women without clinically significant SDB. HRT regimens have varied and all the studies are fairly old. They do not definitely assure the alleviation of SDB and HRT cannot thus be recommended as treatment for SDB. It is concluded that there is no evidence that female sex hormone changes during menopause per se are able to explain the increase in SDB in midlife women and conclusions on the effect of HRT on SDB cannot be drawn from the current literature.



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| **Keywords** | Menopause; Sleep-disordered Breathing; Obstructive sleep apnea; Hormone Replacement Therapy; Estrogen; Woman; Obesity; Metabolism |



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Dear Editor-in-Chief,

We hereby have the privilege to submit the invited review on “Role of Menopause and Hormone Replacement Therapy in Sleep-disordered Breathing”.

The background for this review article has already been discussed by e-mail. In summary; the question whether menopause is a risk factor for sleep-disordered breathing (SDB) is not even controversial as several review articles (for example Jordan AS et al. Lancet. 2014;383:736-47) and text books list menopause as one of the main risk factors for SDB. At a symposia at World Sleep Congress there was a discussion on existing literature within this field and it was concluded that the scientific evidence for menopause causing SDB is very weak or absent. In addition, the effect of hormone replacement therapy on SDB in women has been analyzed in some studies but with conflicting results.
Unfortunately, the general belief that menopause is a risk factor for SDB also have clinical implications as clinicians tend to ignore SDB symptoms in premenopausal women. We therefore believe that there is a need for this review on Menopause, HRT and sleep-disordered breathing.

We also apologize for the delay in this submission. Actually this manuscript was submitted 23rd April 2019 and I got an e-mail informing that the manuscript was successfully received. However, we had used the wrong documents for author agreement and did not notice the information in the system that there was need for resubmission until now. Sorry for that.

We are looking forward to your response.

Sincerely,

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# Role of Menopause and Hormone Replacement Therapy in Sleep-disordered Breathing

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**Summary**

There are suggestions that the loss of female sex hormones following menopause is critical for the development or progression of sleep-disordered breathing (SDB). We conducted a review of the literature on the role of menopause and hormone replacement therapy (HRT) in SDB risk. There is an increase in SDB during the menopausal transition period, but data on an effect beyond that of changes in body habitus and increasing age *are weak or absent*. Early community-based, observational studies reported a protective effect by HRT on SDB prevalence, but this could possibly be explained as a healthy user effect. Interventional studies of the effect of HRT on SDB are sparse, with only a few randomized placebo-controlled studies, often performed on small samples of women without clinically significant SDB. HRT regimens have varied and all the studies are fairly old. They do not definitely assure the alleviation of SDB and HRT cannot thus be recommended as treatment for SDB. It is concluded that there is no evidence that female sex hormone changes during menopause per se are able to explain the increase in SDB in midlife women and conclusions on the effect of HRT on SDB cannot be drawn from the current literature.

Key words: Menopause; Sleep-disordered Breathing; Obstructive sleep apnea; Hormone Replacement Therapy; Estrogen; Woman; Obesity; Metabolism

**List of abbreviations:**

AHI: apnea-hypopnea index

BMI: body mass index

CEE: conjugated equine estrogen

CI: confidence interval

CPAP: continuous positive airway pressure

$etCO_2$: end-tidal carbon dioxide pressure

$E_2$: estradiol

$E_1$: estrone

ER: estrogen receptors

EV: estradiol valerate

FSH: follicle stimulating hormone

HDL: high-density lipoprotein

HVR: hypoxic ventilatory responsiveness

HRT: hormone replacement therapy

LH: luteinizing hormone

MHT: Menopausal Hormone Treatment

MPA: medroxyprogesterone acetate

ODI4: oxygen-desaturation index $\geq$ 4%

OR: odds ratio

OSA: obstructive sleep apnea

P: progestin

PSG: polysomnography

RDI: respiratory distress index

REM: rapid eye movement sleep

$SaO_2$: arterial oxyhemoglobin saturation

SAS: sleep apnea syndrome

SDB: sleep-disordered breathing

SHBG: sex hormone binding globulin

WHI: Women's Health Initiative

## Introduction

Sleep-disordered breathing (SDB) is common in the general population [1]. Knowledge of contributory factors is important in order to identify risk groups that should be referred for clinical investigation and treatment to avoid long-term consequences. While age, male gender and obesity are well-known risk factors for SDB, the role of hormonal changes during menopause in SDB risk is less clear.

Sex hormones are important for sleep across people's life span [2]. Menopause is an important hallmark in a woman's life and it has been suggested that the loss of female sex hormones following menopause is critical for SDB [3-5]. A higher prevalence of SDB in postmenopausal women as compared with premenopausal age groups has been reported in several studies [4-10]. This does not, however, necessarily mean that hormonal changes during menopause are the reason for developing SDB. Studies within the field are complicated by the fact that menopause is very closely related to age. In addition, both ageing and menopause are strongly related to both weight gain and central adiposity [4,8], the strongest risk factors when it comes to sleep apnea. As SDB is associated with significant daytime impairment [11-14], as well as severe morbidity [15-17] and mortality [18], it is important to understand whether menopausal changes in reproductive hormone levels can be a cause of or a contributory factor to the development or progression of SDB in women. The consequences of such a relationship would be twofold; 1) if the depletion of female sex hormones has a causal role, hormone replacement therapy (HRT) could be considered as a possible intervention for SDB in postmenopausal women and 2) the occurrence of menopause should be controlled for in studies designed to analyze the health consequences of SDB in women.

The aim is to review the current literature on menopause as a risk factor for SDB. The key question is whether menopause *per se* is responsible for SDB, or whether the increase in SDB among post-menopausal women is due to the normal aging process or alterations in fat distribution related to menopause.

## Clinical features of sleep-disordered breathing

The term "sleep-disordered breathing (SDB)" is commonly used and includes a wide range of conditions linked by narrow upper airways and the loss of a normal respiration pattern during sleep. At one end of the spectrum, there are subjects with intermittent partial obstruction of the upper airways giving rise to snoring without the fragmentation of sleep ("simple snorers"). In the most severe form of the condition, previously often referred to as the Pickwickian syndrome, frequent apneas during sleep are only separated by short periods of effective ventilation and loud snoring.

Obstructive sleep apnea (OSA), the most common form of SDB in the clinical setting, is characterized by recurrent episodes of airway narrowing with airflow reduction (hypopnea) or upper airway collapse with airflow cessation (apnea), despite continued respiratory effort. The repeated respiratory pauses lead to intermittent hypoxia and hypercapnia and sleep fragmentation. The classification of OSA severity is based on whole night sleep recordings and calculated as the mean number of hypopneas and apneas per hour of sleep, the apnea-hypopnea index (AHI). Based on consensus, cut-off values of AHI 5-<15, 15-<30 and ≥ 30 are used to categorize OSA into mild, moderate and severe respectively. Short arousals caused by the respiratory events disturb sleep and cause daytime symptoms. Excessive daytime sleepiness is the key symptom and individuals with OSA often feel fatigued and unrested during the daytime. They may therefore suffer from impairments in vigilance, concentration, cognitive function, social interactions and quality of life [19]. Although sleepiness is a common symptom, the association between the severity of OSA and the severity of sleepiness is weak [1,20]. Moreover, insomnia symptoms with multiple awakenings from sleep during the night are increasingly recognized as a symptom of OSA and occur in over 50% of women with OSA [21,22]. At least in women referred to sleep clinics, the symptoms and signs of SDB are similar in pre- and postmenopausal women [9].

**Pathophysiology of sleep-disordered breathing**

The pharyngeal muscles play an important role in maintaining the patency of the upper airway and counteracting collapsibility. The activity of the pharyngeal muscles is reduced during sleep, but, in healthy individuals, the muscles can respond to respiratory stimuli to prevent airway collapse even during sleep [23]. Although the exact mechanisms underlying the collapsibility of the upper airways in OSA are not completely understood, many patients display an anatomically narrow upper airway [24]. Muscle tone in the pharyngeal muscles is increased by noradrenergic and serotonergic inputs [25]. Estrogen receptors have been identified in the pharyngeal muscles and experimental studies in animals have demonstrated that stimulation with estradiol accentuates the contractility of the genioglossal muscle [26,27]. This raises the hypothesis that premenopausal women may be protected by the effects of female sex hormones on the patency of the upper airway, possibly explaining the differences observed in the prevalence of OSA between genders, especially at young ages.

**Changes in female sex hormones during menopause**

Menopause, the time of the final menstrual period, is an important milestone in a woman's life span. It is a natural process in normal female aging, resulting from the depletion of ovarian follicles. The median age of natural menopause is 51 years , with the menopausal transition usually starting at about 47 years [28]. The Stages of Reproductive Aging Workshop (STRAW +10) standardized the

division of a woman's late reproductive life, broadly grouping women into three categories (reproductive, menopausal transition and postmenopause), further subdivided according to menstrual cycle length and regularity [29]. Perimenopause encompasses the menopausal transition with the first signs of declining ovarian function (irregular menstruation and/or vasomotor symptoms) until 12 months from the final menstruation. Iatrogenic menopause is caused by oophorectomy (surgical menopause) and is also often due to cancer treatments (radiotherapy and cytostatic treatment). Postmenopause begins when menopause is diagnosed (the diagnosis is always retrospective). The term "climacteric" is also used to describe perimenopause and the part of the postmenopausal period in which climacteric symptoms occur.

Ovarian function begins to deteriorate and the function of the hypothalamic-pituitary-ovarian axis begins to change gradually, typically several years before menopause. As a result, the number of oocytes declines and anovulatory cycles increase, leading to irregularity in menstrual cycles. The depletion of functional follicles in the ovaries causes a decrease in estradiol ($E_2$), progesterone, anti-müllerian hormone and inhibin secretion from the ovaries. This leads to the suppression of the negative feedback to control the production of gonadotrophins, resulting in increased follicle stimulating hormone (FSH) and luteinizing hormone (LH) production from the pituitary gland. After menopause, FSH concentrations are 10-15 times higher than in young women during the follicular phase [30] and FSH levels of ≥ 25IU/L are regarded as a mark of the late menopausal transition. After the decline in ovarian estrogen production, the main estrogen is estrone ($E_1$), which is produced primarily via the peripheral aromatization of androstenedione in muscle and adipose tissue. As aromatization mainly takes place in adipose tissue, overweight postmenopausal women have higher $E_1$ concentrations than normal-weight postmenopausal women [30]. Although the production of testosterone from the ovaries remains fairly unchanged, the adrenal production of dehydroepiandrosterone and dehydroepiandrosterone sulfate decreases, following a decrease in overall circulating androgen concentrations. Only a small percentage of testosterone is biologically active, since testosterone is mostly bound to sex hormone-binding globulin (SHBG). The concentration of SHBG increases progressively from late adolescence, accelerating after the age of 70 [31].

The most important climacteric symptoms are vasomotor symptoms (hot flashes and sweating), sleep disturbances and mood symptoms. Other common symptoms include palpitations, headache, myalgia, memory impairment, vaginal dryness and sexual dysfunction [32]. The duration of climacteric symptoms varies considerably. According to a longitudinal study, vasomotor symptoms persisted for 4.5 years after menopause and lasted for more than seven years in half the women [33]. Hormone

replacement treatment (HRT), currently referred to increasingly as menopausal hormone treatment (MHT), comprising estrogen combined with progestin, or unopposed estrogen for women with a history of hysterectomy, is the most effective treatment for climacteric symptoms [34].

**Effects of female sex steroids on breathing and metabolism**

The importance of hormones, including female sex steroids, in SDB is complex. Sex steroids regulate respiration both directly and via central neuromodulatory serotonergic neurons [35], essentially involved in the neural control of breathing. In addition, female sex steroids act peripherally by contributing to upper airway patency [36]. Progesterone in particular is a respiratory stimulant [37,38], acting via central and peripheral chemoreceptors [39,40].

In healthy menstruating women, upper airway resistance has been shown to be lower during the luteal phase (high progesterone levels) than the follicular phase of the menstrual cycle during both wakefulness and sleep [41]. Further, the use of hormonal contraceptives is associated with a lower AHI compared with non-users in both the follicular and luteal phases of the menstrual cycle [42]. Furthermore, in a cross-sectional study of 53 women, a higher AHI was associated with lower levels of estradiol, progesterone and 17-OH progesterone, when adjusted for BMI, age, phase of the menstrual cycle and postmenopausal status, although conclusions on causality could not be drawn [43]. The level of progesterone typically already decreases before menopause because of anovulatory cycles. Popovic and White determined the level of an awake genioglossus electromyogram in 12 premenopausal and 12 postmenopausal women and found that the peak phasic and tonic genioglossus activity was highest in the luteal phase of the menstrual cycle, followed by the follicular phase, and was lowest in postmenopausal women [36]. Eight of the postmenopausal women were re-analyzed after two weeks of HRT and they displayed a significant increase in EMG genioglossus activity, indicating that female sex hormones have a substantial impact on upper airway dilator muscle activity. However, the postmenopausal women were older than the premenopausal women and changes in genioglossus muscle activity were not followed by changes in upper airway resistance [36].

Menopause is associated with weight gain and the loss of muscle and bone mass, as well as increases in fat and the abdominal deposition of fat [44]. Anthropometric variables, including BMI and measurements of central obesity, increase during the age span of menopause [4,8].

In recent years, differences in metabolism between men and women have been studied. Men tend to accumulate central fat deposits in the abdomen and upper body and to develop visceral obesity, while women are characterized by peripheral fat accumulation. This difference in the "shape of obesity" is mediated by sex hormones [45] and the role of genetic factors, linked to X and Y chromosomes, has recently been explored [46]. Visceral obesity is associated with an increased cardiovascular risk and can be assessed by a cluster of risk factors, known as the metabolic syndrome. The occurrence of three of five criteria, i.e. increased blood pressure, large waist circumference, increased plasma glucose, increased triglycerides and low high-density lipoprotein (HDL) cholesterol, defines the metabolic syndrome, which is regarded as a pre-diabetic state and is associated with insulin resistance and cardiovascular risk [47]. Conversely, increased subcutaneous fat, typically in peripheral regions of the body, which is commonly found in women, may be protective, as suggested by the low cardiovascular risk in premenopausal women compared with age-matched men [48].

At the onset of the menopause, weight gain often occurs because of a reduction in resting energy expenditure and likely contributes to the increased prevalence of OSA compared with premenopausal women [49]. Moreover, the lack of sex hormones is known to affect metabolism and both estrogen receptors (ER) $\alpha$ and $\beta$ are expressed in adipose tissue. Studies in animal models have clarified the positive role of ER$\alpha$ activation in the regulation of body weight and insulin sensitivity, while ER$\beta$ appears to exert the opposite effects [50]. Although women have more fat mass compared with men, insulin sensitivity is lower in men than in age-matched premenopausal women, possibly reflecting the role of predominantly visceral and subcutaneous adipose tissue compartments respectively [51]. With the onset of menopause, the metabolic profile of women becomes closer to the profile of men and the plasma lipid composition changes with menopause towards a less favorable profile [52].

Via aromatase activation, the adipose tissue is able to convert the relatively weak circulating estrone to estradiol [51]. However, the release of active estrogens by the adipose tissue in postmenopausal women is insufficient to prevent the onset of the metabolic syndrome in many cases and the occurrence of the metabolic syndrome, but not BMI, has been shown to be associated with increased cardiovascular risk in postmenopausal women [53]. In the Study on Women Across the Nation (SWAN), progression from metabolically benign obesity to at-risk obesity in perimenopausal women was associated with high BMI and cardiometabolic abnormalities at baseline. In particular, impaired glucose tolerance played a detrimental role, while habitual physical activity exerted a protective effect [54].

Menopause-associated hormonal changes may interact with changes in the quality and quantity of sleep. Short sleep is associated with worsening insulin resistance and inflammatory activation in postmenopausal women [55]. Moreover, although the amount of slow-wave sleep was similar in post- and premenopausal women, the first peak in growth hormone release during sleep was delayed in postmenopausal women [56]. Other studies underline the fact that oxygen saturation during sleep is slightly lower in healthy postmenopausal women compared with premenopausal women [57].

A complex picture thus results from physiological changes occurring during the menopausal transition. On the one hand, reduced female sex hormone levels may negatively affect the upper airways, sleep architecture and metabolism. On the other hand, increased fat mass may partly counteract the reduction in estrogen levels of ovarian origin. Furthermore, weight gain likely plays a major role in causing clinically significant OSA.

**Epidemiology of sleep disordered breathing**

*Gender*

Previous studies have repeatedly and consistently confirmed that SDB is more common in men than in women. The male-to-female ratio is estimated to be about 2:1 in the general population, with a somewhat larger difference at younger ages, while the effect of gender is smaller among older adults [7,58-60]. Women are, however, often underrepresented at sleep clinics, with only 20% or fewer represented in cohorts from clinical laboratories [60]. In a community-based prospective study, women were less frequently diagnosed and treated for sleep apnea than men, despite similar SDB symptoms [61]. One possible explanation might be that, despite a similar symptom profile in men and women with OSA, the mean AHI is often higher in men [60], while partial upper-airway obstruction appears to be more common in women [62]. Furthermore, women generally have a higher BMI compared with men with SDB of similar severity [60]. The reason for the reduced susceptibility to OSA in females is not entirely clear and many factors, such as upper airway shape, craniofacial morphology, fat deposition and hormonal changes, have been proposed [36,63]. Although the prevalence of OSA in women increases at older ages, the difference in SDB prevalence with respect to gender is also apparent in the elderly population [1,64].

*Age*

For snoring, there is an increase in prevalence in both men and women by age until the age of 50-59 years, followed by a decline [65,66]. Moreover, the prevalence of a clinical diagnosis of OSA reaches a plateau at age 50-59 years [67]. When increased AHI is considered regardless of symptom profile, the

picture becomes less clear, as many studies have only investigated participants until the age of 60 years. Studies including elderly populations have reported somewhat contradictory results, as some have reported a continuous increase in OSA prevalence with age [1], while others have found an increase by age until a plateau is reached, followed by a decline among the elderly [7].

*Life-style factors*

There is no doubt that gender, age and obesity are important risk factors for SDB. Other risk factors that have been identified in some studies include physical inactivity [68] and high alcohol consumption [69]. Smoking has also been reported to be associated with OSA, but the number of studies in this field is limited [70].

*Obesity*

The occurrence of SDB is closely related to obesity which, together with age and gender, is a major risk factor for SDB [10]. Obesity is a common factor responsible for a small caliber in the upper airways and, at least in women, neck circumference is more closely correlated with the severity of OSA as compared to waist circumference [71]. Several studies have assessed the distribution of visceral and subcutaneous fat in overweight men and postmenopausal women with OSA. In a case-control study, OSA was associated with visceral fat in men and with subcutaneous, visceral and total fat in women [72]. According to anthropometric and dual energy absorptiometry (DEXA) measurements, visceral obesity was typical of men with OSA, whereas, in women, the total amount of fat and the percentage of fat in the neck region explained 33% of the variance in AHI [73]. Another study comparing anthropometric, metabolic and sleep variables and visceral and subcutaneous fat assessed by computed tomography in OSA patients concluded that visceral obesity was common in men, while BMI was the only variable associated with fat accumulation in both visceral and subcutaneous compartments in women [74]. Finally, the metabolic syndrome in both genders was associated with waist circumference, a marker of visceral adiposity, whereas, in patients without the metabolic syndrome, anthropometric markers were in agreement with predominant visceral obesity in men and peripheral obesity in women [75]. In middle-aged patients with severe obesity and the metabolic syndrome, no gender-related differences were found and epicardial fat and upper body fat deposition were the best predictors of OSA [76]. Overall, the more favorable obesity pattern in women with OSA would suggest a relatively lower cardiometabolic risk and no metabolic syndrome compared with men, but the higher level of obesity in women with OSA also suggests a word of caution until more data are available. In fact, women with OSA have a higher comorbidity burden and a poorer prognosis compared with men in longitudinal studies [77].

A large body of recent literature has explored the bidirectional relationships between SDB and metabolism, with special regard to glucose and lipids [78,79]. Sleep loss and circadian disorders affect metabolism [80,81]. Additive effects of sleep loss and OSA on metabolic and inflammatory variables have been shown in obese subjects [82] and patients with diabetes [83].

There is increasing evidence that OSA can independently cause metabolic disturbances, through the effects of intermittent hypoxia, sympathetic overactivity, adipose tissue inflammation and sleep fragmentation [84]. Nevertheless, the effects of obesity are far greater than those of OSA and weight loss is much more effective in improving metabolic variables than the treatment of OSA with continuous positive airway pressure (CPAP) [85]. The uncertainty regarding the effects of CPAP on metabolism also depends on the variable adherence by patients to treatment [86]. In this context, differences between men and women are still reported in a minority of studies.

Several meta-analyses of the effects of untreated OSA and of CPAP treatment on metabolic variables included studies with variable and generally low percentages of women (from 0 to around 50%). Gender turned out not to be a significant factor in meta-analyses of the association of OSA with the metabolic syndrome [87] or on the effects of CPAP treatment on glycemic variables [88,89]. Traditionally, menopausal status has been poorly considered as a clinically significant variable. However, a recent population-based study reported an association of sleep-disordered breathing with the risk of diabetes in women but not in men [90].

An interesting, albeit unexplored issue, relates to the role of respiratory events in rapid eye movement sleep (REM) sleep on metabolism in women [91]. In diabetic patients, the derangement of glycemic control was found to be associated with AHI in REM but not with AHI in non-REM sleep, possibly due to the increased sympathetic activity typical of REM sleep [92]. Because REM sleep tends to be concentrated in the second half of the night, CPAP use should be extended beyond four hours, in order to prevent REM-related events and their detrimental metabolic consequences, as confirmed by proof-of-concept studies [93]. The frequency of respiratory events in REM sleep in women decreases with aging, with a relative increase in respiratory events during non-REM sleep [91]. As a result, the metabolic effects of REM-associated respiratory events in menopausal women with OSA remains undefined.

Finally, the possible gender-related differences in leptin in OSA subjects deserves some comment. Leptin is produced by the adipose tissue and its plasma concentration is normally higher in women [94]. Leptin reduces appetite and acts both at the level of the central nervous system and peripherally in several organs. OSA is characterized by leptin resistance and recent data in animal models indicate a possible strong modulatory activity of leptin in controlling ventilation and metabolism at the level of

the carotid body [95]. It is possible that the higher plasma leptin levels in women may contribute to some of the differences in OSA between men and women, but – again – our current state of knowledge prevents any conclusions.

**Menopause and sleep-disordered breathing**

During menopause and beyond, endocrine changes affect several factors that could contribute to the development of SDB: respiratory drive decreases, an increased number of arousals may lead to respiratory instability, increased soft-tissue collapsibility predisposes to upper airway obstruction during sleep and weight gain increases the risk of SDB. In addition, symptoms of SDB may easily be overlooked or interpreted as menopausal symptoms. However, in studies performed to analyze the impact of menopause on SDB risk, the results have diverged.

Back in 1988, Shaver et al. performed a cross-sectional study on healthy, normal-weight midlife women and compared sleep parameters in pre-, peri- and postmenopausal women without HRT. They found few differences between the groups and, although breathing was not recorded, there was no difference in the arousal index as a result of menopausal status [96]. In a similar study where breathing parameters were measured, Sharkey et al. compared polysomnography (PSG) parameters in 13 premenopausal and 12 postmenopausal women. They found that the postmenopausal women displayed a lower sleep stage 1% and shorter slow-wave sleep latency, while there was no difference in AHI between the groups [97].

Carskadon and coworkers compared the susceptibility to SDB in pre-, peri- and postmenopausal women by analyzing their response to nasal occlusion during overnight PSG. All the participants were recruited within the age range of 45-55 years and they were self-reported good sleepers, without HRT and displayed very little sleep apnea at baseline, with a mean AHI of 1.6. Nasal occlusion increased the AHI and arousal index, but the responses did not differ by menopausal status [98]. In contrast, both BMI and waist circumference were higher in responders. Similar results were reported by Millman and coworkers who analyzed the predictors of OSA severity in 25 obese women below 65 years of age who had been diagnosed with OSA, 12 of whom were premenopausal. They found that the AHI was related to the severity of obesity but not to menopausal status [99]. Taken together, the above-mentioned studies of healthy midlife women within a narrow age span found no impact of menopause on SDB, but they were all limited by small sample sizes.

Dancey et al. analyzed the impact of menopause on the prevalence and severity of OSA in a large clinic patient database [3]. A total of 1,315 women were classified as premenopausal (<45 years) or

postmenopausal (>55 years) based on age. BMI and neck circumference were higher in the postmenopausal group. Not surprisingly, a higher prevalence of OSA and a higher mean AHI were found in the postmenopausal – and thereby older – women. The differences between the groups persisted even after adjusting for BMI and neck circumference. It is, however, not possible to draw any conclusion about the role of menopause, as age was not adjusted for.

*Community-based studies*

Community-based studies analyzing the role of menopause in SDB prevalence are summarized in Table 1. In an early study of SDB in women, Gislason et al. investigated women from the general Icelandic population by using a two-stage sampling procedure [6]. In the first phase, women aged 40-59 years responded to the questionnaire and a subgroup of high-risk cases for SDB underwent sleep recordings. Both snoring and daytime sleepiness increased with age and snoring was more common in postmenopausal women. However, when the prevalence of snoring in each five-year age group stratum was compared between pre- and postmenopausal women, no difference emerged. Women selected for sleep recordings were older and generally had a higher BMI. Based on the PSG, 14 were diagnosed with OSA, with a mean age of 55 years, of whom 10 were postmenopausal. The authors did not draw any conclusion about menopause as a risk factor for OSA.

In a prevalence survey of SDB in San Diego adults, Kripke et al. included 190 women aged 40-64 years who all performed sleep recordings with home recording instruments for three consecutive nights [58]. The oxygen-desaturation index $\geq$ 4% (ODI4) was used to define SDB. The median ODI4 for women was 4.3 and 5.3% had an ODI4 of $\geq$ 20. They found that BMI was the most important predictor of ODI4. Waist circumference, waist-to-height ratio and neck circumference were highly intercorrelated and similar to BMI as predictors. Moreover, age and ethnicity were related to ODI4. After controlling for age and BMI, there was no increase in ODI4 following menopause.

Bixler et al. performed a two-way sampling of women from the general population in Pennsylvania in a study with the main aim of contrasting the prevalence of SDB in women compared with men across a wide age range while controlling for age, obesity, menopause and the use of HRT [7]. With an oversampling of women with risk factors for OSA, 1,000 women aged 20-100 years were selected for PSG. The prevalence of SDB was strongly related to BMI and age. Having an AHI of $\geq$ 15 was much more common in postmenopausal women (3.9%) than in premenopausal (0.6%) women, but no comparable data were presented with adjustments for age and BMI.

Young and colleagues analyzed the role of menopause in SDB in 589 women who participated in the Wisconsin Sleep Cohort Study [100]. The participants were carefully categorized as pre-, peri- or postmenopause and investigated with full PSG with up to two follow-up studies at four-year intervals, giving a total of 1,035 observations. In the cross-sectional analyses, postmenopausal stage was related to SDB defined as an AHI of $\geq$ 5 or an AHI of $\geq$ 15 with crude odds ratios of 3.22 and 2.59 respectively, when compared with premenopausal stage. The association remained significant after adjusting for confounders. However, when adjusting for both age and menopause in the same model, the association between age and SDB was no longer significant. This clearly shows the difficulties from an epidemiological point of view involved in analyzing menopause, which was also commented on by the authors of the actual paper. In addition, there was also a significant linear trend for years since the last menstrual period and having an AHI of $\geq$ 5, with increasing crude odds ratios with an increasing duration of menopause up to five years, followed by a decline. Whether this could be an effect of aging is not clear, as no adjustment for age was presented for this analysis.

From a cross-sectional study, Polesel et al. reported a strong association between both early and late postmenopause and having an AHI of $\geq$ 5 (adjusted OR 5.92 and 7.53 respectively) [5]. The associations were independent of waist circumference but despite a great difference in age between the groups (mean ages: premenopausal women/control group 34.8, early postmenopausal women 52.6, late postmenopausal women 62.8 years), age was not adjusted for. In addition, perimenopausal women were excluded from the analyses.

The most comprehensive study of menopause and SDB to date is from the Sleep in Midlife Women Study and it was recently published by Mirer and co-workers [101]. In this longitudinal study, no fewer than 1,667 observations were gathered from 219 women aged 38 to 62 years who were recruited from participants in the Wisconsin Sleep Cohort Study. Each participant underwent in-home PSG every six months to measure the AHI. Menopausal status was determined from daily diaries in which the participants reported menstrual flow, hot flashes and the use of hormonal medications. Despite this careful investigation, the results were not entirely convincing. Compared with premenopausal women, postmenopausal women had a higher AHI when analyzed with multivariable linear regression but not with logistic regression. However, although premenopausal women were used as a control group, only 14 of the participants were premenopausal at baseline. Furthermore, the strongest association between menopausal stage and OSA was found in the group with undetermined menopause status.

The interpretation of the effect of menopausal stage on SDB is further challenged by the fact that, in some previous studies, the menopause was only determined by questionnaires [7,58,101] or age [3], without measurements of FSH, an objective marker of menopause. Furthermore, the type of menopause (natural or surgical) or the time since menopause was not assessed. This may also be crucial, since women with surgical menopause are more often diagnosed with OSA [102]. The risk of OSA diagnosis is increased, especially in non-obese women and in those never using HRT, independently of age. However, studies with sleep registration before and after surgical menopause are lacking, leaving the increased awareness among doctors of SDB in postmenopausal women as one possible explanation. In addition, the intervening effect of menopausal symptoms, especially vasomotor symptoms, on SDB are of interest, although few studies have addressed this question [103,104]. In a small study of 65 postmenopausal women, of whom 32% had some degree of SDB and 17% had partial upper airway obstruction measured by PSG, self-reported vasomotor symptoms, recorded daily for 14 days, were not associated with SDB findings [103]. In contrast, in a recent large questionnaire study of 1,691 women attending a menopause clinic, self-reported severe vasomotor symptoms were associated with an intermediate/high risk of OSA, as defined by a self-report in an eight-item questionnaire developed to distinguish OSA [104].
To summarize, the majority of studies do not make it possible to distinguish between the role of age and menopausal status on the occurrence of sleep-disordered breathing.

**Effect of hormone replacement therapy on sleep disordered breathing**

*Cohort studies*

In the study designed to assess the association between menopause and SDB from the Wisconsin Sleep Cohort, the authors also investigated the role of HRT and found no significant effect on SDB [100]. This is in contrast to two other large observational studies that both reported that midlife women using HRT had less SDB than non-users [7,105].

In the previously cited large community-based study by Bixler et al., the authors compared the odds of prevalent OSA, defined as an AHI of $\geq$ 15, in postmenopausal women with and without HRT [7]. Compared with the premenopausal women, those who were postmenopausal without HRT had adjusted odds of 4.3 for OSA after adjusting for age and BMI, while, in postmenopausal women using HRT, the odds did not differ from those in premenopausal women. However, although a large number of women were included in the study, the estimates of HRT were based on fewer than 30 women with SDB and the age span was wide, including women up to 100 years of age. Although age

was adjusted for, it was based on the assumption that the aging effect is linear over the entire age range or that there was no age difference between postmenopausal women with and without HRT.

Moreover, in the Sleep Heart Study, the authors identified an inverse association between HRT use and SDB [105] in their analyses comprising 2,852 women aged ≥ 50 years. Compared with the non-users, HRT users were younger, more often of white descent and healthier and their mean BMI was lower. The odds of having OSA, defined as an AHI of ≥ 15, was 0.55 (95% CI 0.41-0.75) for HRT users after adjustment for age, BMI, waist-to-hip ratio, neck circumference and race. Despite the lower risk of laboratory-defined OSA, HRT users generally reported more daytime sleepiness and were more likely to use sleep medication, indicating poorer sleep quality overall. As in all the community-based studies mentioned here, the use of HRT was self-chosen. It is therefore possible that poorer sleep quality had been one reason for initiating the use of HRT among these women.

In July 2002, the Women's Health Initiative (WHI) study published its data claiming that combined HRT increases the risk of heart disease [106] and, as a result, many women discontinued HRT. Mirer and coworkers subsequently investigated healthy user bias in the association of HRT with SDB in the Sleep in Midlife Women Study, comprising women aged 38 to 62 years [107]. HRT use was recorded monthly and there was an extreme decline in the number of women using HRT after the WHI report. As the women underwent PSG to measure AHI at home semiannually from 1997 to 2006, they were also able to measure the impact of HRT. They found that HRT was only negatively associated with SDB until the WHI results were publicized. HRT may therefore have been a reflection of healthiness in the early period, creating a spurious association with SDB.

*Interventional studies*

Interventional studies of the effect of HRT on SDB are presented in Table 2. In a small prospective randomized, placebo-controlled, cross-over study comprising nine healthy postmenopausal women [108], combined oral HRT for seven days reduced the total number of SDB episodes, the number of both hypopneas and apneas. In addition, the duration of hypopneas decreased and minimal arterial $O_2$ saturation during SDB tended to be higher during HRT use. According to another prospective, randomized, placebo-controlled study with 55 postmenopausal insomniacs treated with unopposed estrogen or combined HRT for two months, the total number of hypopneas and apneas, as well as the AHI, were lower during combined HRT compared with baseline and placebo, with no such effect with unopposed estrogen [109]. In a third prospective, randomized, placebo-controlled, cross-over study of 62 healthy postmenopausal women without a previous history of SDB, unopposed transdermal estrogen for three months [110] showed a borderline improvement in breathing, which was, however, considered clinically non-significant. The results of these three studies are difficult to

compare, since they varied considerably in terms of HRT regimens, duration of treatment and number of women. In addition, the washout period for possible previous use of HRT varied, from seven days and six weeks to six months and five months respectively. Furthermore, the studies were conducted in women with no or very mild SDB at baseline. Nevertheless, estrogen therapy was shown to have favorable respiratory effects in a subsequent five-year follow-up of the latter study, where Saaresranta et al. [111] found a higher mean arterial oxyhemoglobin saturation in unopposed estrogen users compared with non-users when adjusted for age and BMI. In addition, at follow-up, the change in mean $SaO_2$ was associated with estradiol concentration and women with a higher serum estradiol concentration also had a higher mean nocturnal $SaO_2$ and lower AHI. The present estrogen users spent proportionally less time with $SaO_2$ below 90% than non-users.

In a small placebo-controlled pilot study with unopposed estrogen and combined HRT given subsequently to six postmenopausal patients with mild-to-moderate SDB, unopposed estrogen was associated with a reduction in AHI compared with baseline, whereas a reduction in the AHI during combination HRT did not reach statistical significance, suggesting that no additional effect was achieved with progesterone [112]. In another pilot study of four postmenopausal and one perimenopausal SDB patients, combined HRT reduced the severity of the sleep apnea by 75%, as measured by the AHI [113]. Furthermore, in two earlier small studies of postmenopausal SDB patients using either unopposed estrogen or combination HRT with no control groups, Keefe et al. [114] found a decrease in the overall AHI with HRT and Cistulli et al. [115] found a decrease in the AHI in REM sleep with HRT. In Keefe's study [114], the effect of combined HRT was superior to that of unopposed estrogen. This confirmed the importance of the effect of progesterone on respiration and, in fact, several studies have verified the beneficial effect of progesterone in different populations [116]. In a single-blind placebo-controlled study with 60mg MPA daily for 14 days, MPA increased the partial pressure of arterial oxygen ($PaO_2$) and reduced the partial end-tidal carbon dioxide pressure ($etCO_2$), where the effect could still be seen even after a three-week wash-out period [117]. In a placebo-controlled, randomized, double-blind, parallel-group study of 34 postmenopausal women with previously treated SDB (CPAP), short-term progestogen (MPA 60mg daily) induced a long-lasting stimulatory effect [118]. CPAP treatment was stopped before the exposure to MPA/placebo. The nightly oxygen saturation was sustained at a higher level and the arterial carbon dioxide tension at a lower level with MPA compared with placebo. The $EtCO_2$ was also lower than during CPAP and this effect was sustained beyond three weeks after the cessation of MPA. However, the AHI increased and sleep deteriorated similarly on MPA and placebo after the withdrawal of CPAP therapy.

Taken together, the previous interventional studies of the effect of HRT on SDB are sparse, with only a few randomized placebo-controlled studies. Furthermore, the number of the women was small, the studies were often conducted on women without clinically significant SDB, the HRT regimens varied and all the studies are fairly old, making their application to the present practice for HRT use challenging. New, well-planned studies are therefore warranted. Although it is evident that the prevalence of SDB increases by the time of menopause and some epidemiological studies suggest that SDB is less frequent in HRT users, interventional studies using HRT do not definitely ensure the alleviation of SDB and, as a result, HRT cannot be recommended as a treatment for SDB.

**Discussion**

There is a marked increase in the prevalence of SDB in women during the age period corresponding to menopausal transition, but, despite several studies focusing on SDB prevalence in women during this time span, the role of menopause as an independent risk factor for SDB can be considered weak or even absent.

Less is known about changes in SDB prevalence in men during the corresponding age span and data were therefore retrieved from the Swedish national registry, Swedevox (http://www.ucr.uu.se/swedevox/), to which 37 centers across Sweden have reported data on patients starting treatment with CPAP since 2010, with a geographical coverage estimated at 90% [119]. As shown in Figure 1, there is a clear overrepresentation of men starting CPAP treatment, as expected. Furthemore, the age of starting treatment is normally distributed in both men and women and the prevalence of older women approaches that of men. There is a marked increase in the number of women starting CPAP treatment at about the age of menopause. Interestingly, in the corresponding age group, a similar or even greater increase is seen in men. Although these data should be interpreted with caution, as clinical data, as mentioned above, are often biased compared with population-based data, with an underrepresentation of women, as well as a delay from the debut of SDB to diagnosis. With this in mind, it could be noted that there is a clear increase in the number of midlife women starting CPAP treatment, but this finding may simply capture an aging process similar to that in men.

The hypothesis of a protective effect by female sex hormones on SDB is most probably based on the fact that the occurrence of SDB increases after menopause. The available data do not clearly support the hypothesis that sex hormone changes during menopause are an independent cause of SDB and, in peri- and postmenopausal women, HRT has not been unambiguously proven to alleviate OSA.

There is therefore no evidence that menopause has a direct effect on SDB. Accelerated reproductive aging during menopause in midlife women is closely intertwined with chronologic aging. Due to the strong association between age and SDB prevalence, it is a real challenge to further investigate the role of menopause, as the age range for premenopausal women is biologically limited. Furthermore, although the time of menopause is often defined as the time of the final menstrual period, the hormonal changes actually occur during a period of several years. There is no doubt that SDB increases after menopause, but the scientific evidence that this is due to female sex hormone changes during menopause *per se* is insufficient.

**Conclusions:**

It can be concluded that, although menopause is often referred to as being an independent risk factor for SDB, the previous studies do not consistently support a role for menopause in SDB. The available data provide no evidence that the female sex hormone changes that occur during menopause have a significant impact on SDB prevalence beyond that of the changes in body habitus and increasing age (Figure 2). The challenge within this research field is the strong relationship between age and SDB prevalence, together with a narrow age span for menopause. The seeming protective effect of HRT on SDB in early observational studies can be explained by a healthy user effect and interventional RCT studies within this field are exceptionally few and of poor quality. The true effect of HRT cannot therefore be estimated until well-designed trials are available.

**Practice points**

There is good evidence that, in women, SDB increases with aging across the menopausal transition and clinicians should be aware of OSA symptoms in this age group, as the symptoms could easily be overlooked or interpreted as menopausal symptoms.

This increasing prevalence of SDB during the menopausal transition period can be explained by aging and changes in body habitus.

There is no evidence that female sex hormone changes during menopause *per se* can explain the increase in SDB in midlife women.

Studies evaluating the effect of HRT on SDB are too few, with a small number of participants, and so, based on the present literature, no conclusions relating to the effect of HRT on SDB can be drawn.

**Conflicts of interest**

The authors do not have any conflicts of interest to disclose.

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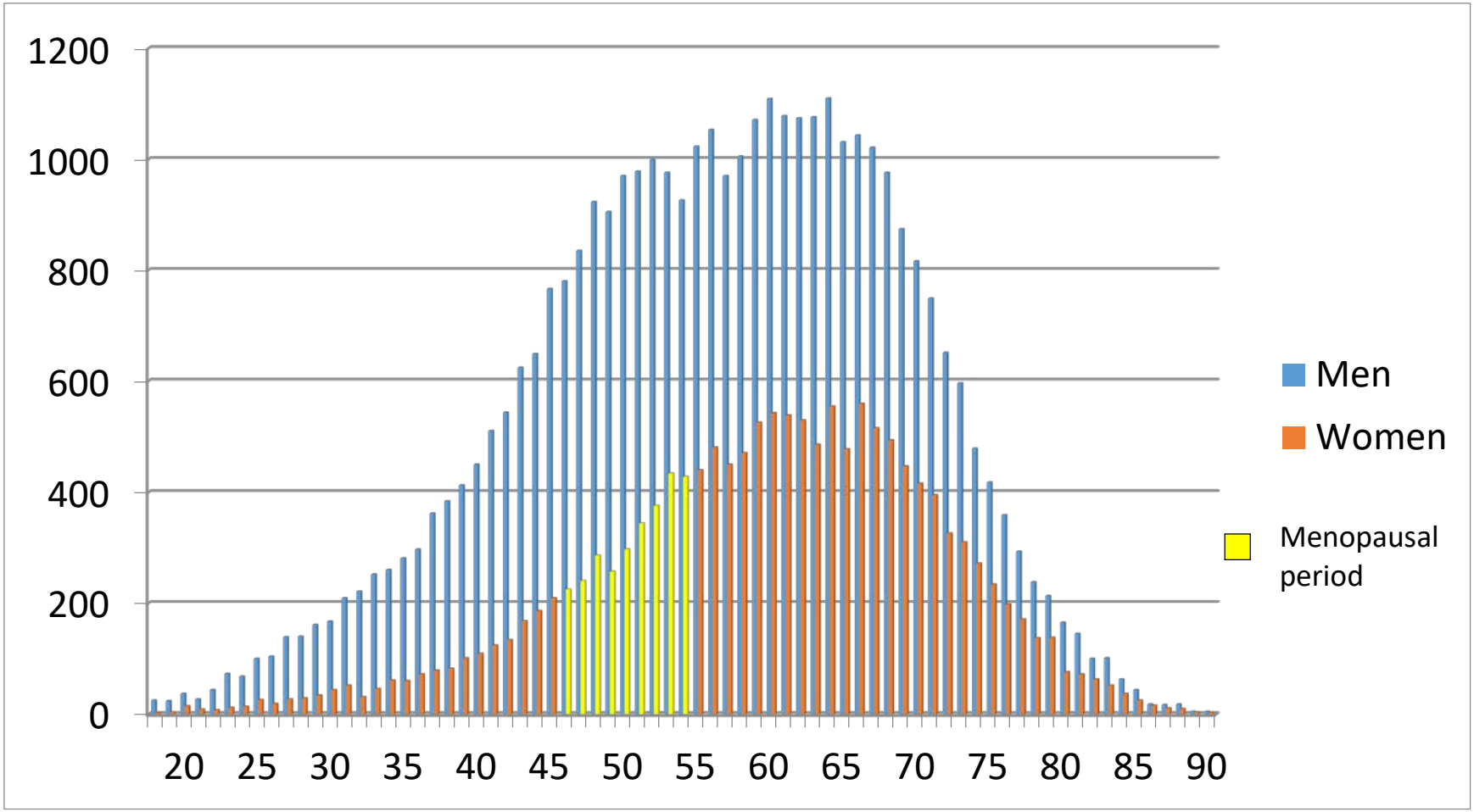
**Figure legends:**

Figure 1.

Number of men and women starting CPAP treatment by age. The data are based on 51,767 patients reported to the Swedish National Register, Swedevox.

Figure 2.

Summary of changes in risk of sleep-disordered breathing associated with menopausal transition. During premenopause, hormones produced in the ovaries exert multiple effects on several organs and may protect women from SDB. In perimenopausal lean women, estrogens exert some local effects, but the risk of developing SDB remains low. Conversely, the perimenopausal period may increase the risk of SDB in overweight/obese women through negative effects on metabolism and the risk of weight gain. Aging can also play a role in women, similar to that observed in men (see Figure 1).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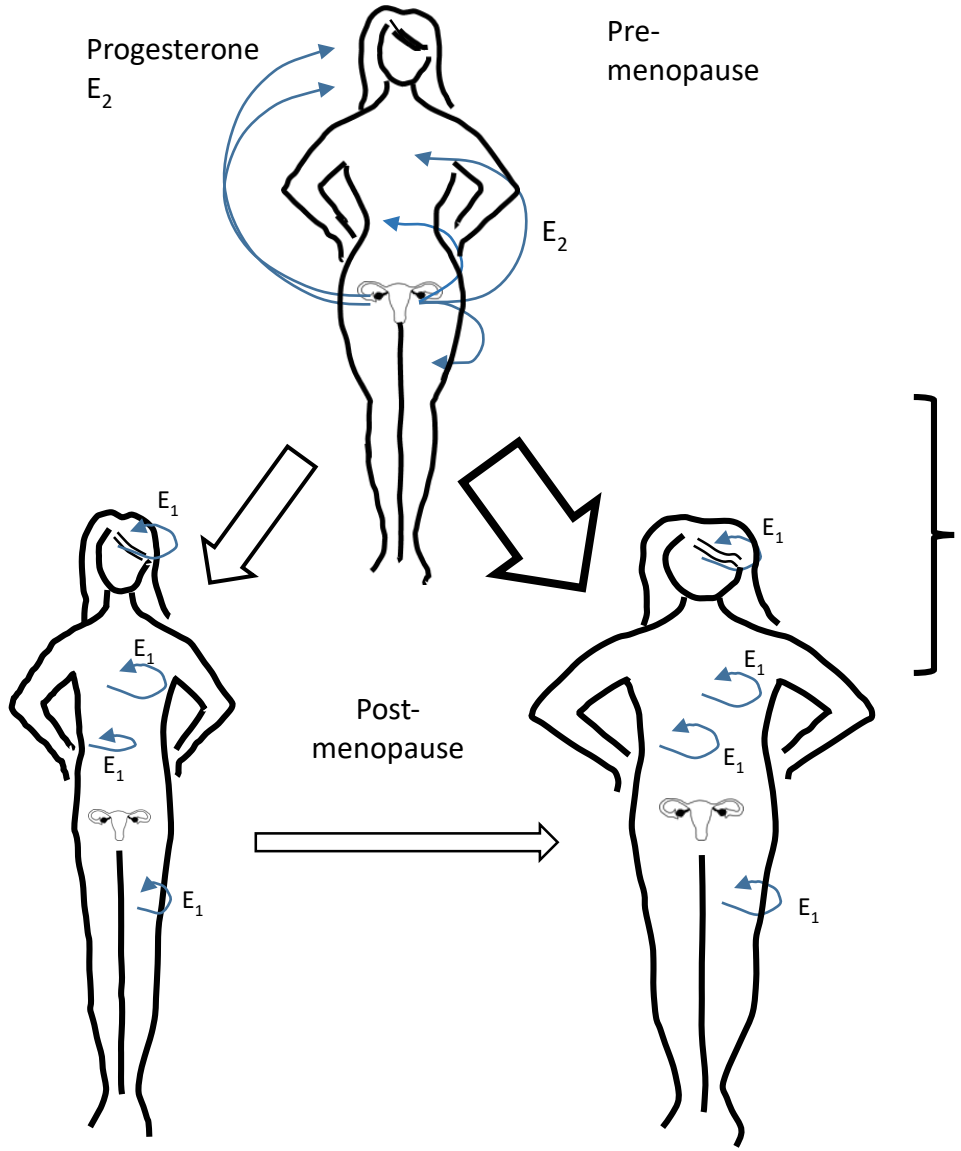


## Menopausal transition:

Several years = Aging process

Reduction in resting energy expenditure; weight gain

Increase in central adiposity

SDB risk: Low → High

**Table 1.**

Community-based cohort studies that have analyzed the effect of menopause on sleep-disordered breathing risk.

| Author, cohort | n | Age | Menopause based on | Main result | Comment |
|---|---|---|---|---|---|
| *Gislason et al.* [6] General population, Iceland | 35 | 40-50 | Questionnaire | No difference in snoring prevalence in pre- and postmenapausals at same age. Women with sleep apnea were older, heavier and more often post-menopausal. | |
| *Kripke et al.* [58] General population, San Diego | 190 | 40-64 | Interview | No association between menopause and ODI4 after adjusting for age and BMI | Cross-sectional |
| *Bixler et al.* [7] General population, southern Pennsylvania | 1,000 | 20-100 | | Premenopausal: 0.6%, postmenopausal 3.9% | Not adjusted for age and BMI |
| *Young et al.* [100] Wisconsin Sleep Cohort Study | 589 (1,025 sleep studies) | 30-60 | Questionnaire and follicle-stimulating hormone (FSH) | Age- and BMI-adj. OR (95% CI)<br>AHI≥5 / AHI≥15<br>Pre-menopause 1 / 1<br>Peri-menop. 1.23 (0.68-2.22) / 1.07 (0.52-2.20)<br>Peri/postmenop. 1.80 (0.79-4.12) / 3.13 (1.06-9.20)<br>Postmenopause 2.60 (1.41-4.81) / 3.49 (1.38-8.78) | Longitudinal. Association between age and SDB non-significant when adjusting for menopause |
| *Polesel et al.* [5] General population, Sao Paulo | 407 | 20-80 | Questionnaire, FSH and luteinizing hormone | Adjusted OR (95% CI) for AHI≥5<br>Pre-menopause 1<br>Early postmenopause 5.92 (2.70-12.97)<br>Late postmenopause 7.53 (4.08-13.92) | Cross-sectional<br>Adjusted for waist circumference b not for age |
| *Mirer et al.* [101] Sleep in Midlife Women Study | N=219 (1,667 observations) | 38-62 | Daily diaries | Multivariable linear (AHI ratio, 95% CI) and logistic (OR, 95% CI) regression:<br>AHI ratio / OR for AHI≥15<br>Premenopause 1 / 1<br>Perimenopause 1.21 (0.96-1.94) / 1.13 (0.31-4.13)<br>Postmenopause 1.31 (1.02-1.68) / 1.31 (0.33-5.15)<br>Undetermined 1.41 (1.08-1.82) / 1.52 (0.39-5.87) | Longitudinal |

ODI4: oxygen-desaturation index ≥4%, AHI: apnea-hypopnea index, SDB: sleep-disordered breathing, OR: odds ratio, CI: confidence interval

**Table 2.** The effect of hormone replacement therapy on nocturnal breathing, interventional studies

| Author | Study design | Subjects | | | | Treatment Type and duration | Findings |
|---|---|---|---|---|---|---|---|
| | | Menopausal state | n | Age range/mean | SDB | | |
| Pickett et al. [108] | Prospective, randomized, placebo-controlled, single-blind, cross-over | Postmenopausal | 9 | 46-57/50 | Mean AHI: 2.5 | Oral CEE 1.25 mg/day + MPA 20 mg/day 7 days | Total number of SDB episodes ↓<br>Number of both hypopneas and apneas ↓<br>Duration of hypopneas ↓<br>Minimal SaO2 during SDB ↑ (tendency) |
| Cistulli et al. [115] | Prospective, open | Postmenopausal | 15 (10) | 60 | Mean AHI:43 | Unopposed estrogen (n=6) or estrogen + progestin (n=9) 50 days. Oral CEE 0.625 mg/day or EV 1mg/day or transdermal E2 8mg/week. Oral MPA 2.5-10 mg/day | No effect on AHI or $MinSO_2$<br>AHI during REM sleep↓<br>HVR ↑ |
| Keefe et al. [114] | Prospective, open | Postmenopausal | 5 | 48-62/56 | Mean RDI: 34 | Oral E2 for 3-4 weeks, thereafter oral E2 + MPA for 12 days | RDI ↓, E2 + MPA superior to E2<br>E2: lowest SaO2 associated with apneic episodes ↑ |
| Saletu-Zyhlarz et al. [109] | Prospective, randomized, placebo-controlled, double-blind, three-arm trial | Postmenopausal insomniacs | 49 | 46-67/57 | Mean AHI: 7 | Oral EV 2mg/day + dienogest 3mg/day or unopposed EV 2mg/day 2 months, then open-label phase with EV 2mg/day + dienogest 2mg/day 2 months | EV+P3mg vs placebo: AHI ↓<br>EV+P3mg vs baseline: AHI ↓<br>Unopposed EV: no effect |
| Polo-Kantola et.al. [110] | Prospective, randomized, placebo-controlled, double-blind, cross-over | Postmenopausal | 62 | 47-65/56 | Mild/No SDB | Transdermal E2 50 µg/24h or 2.5 g/day (patch or gel) 3 months + 1 month wash-out and cross-over | Occurrence and frequency of sleep apnea ↓ (rare condition)<br>No effect on other SDB parameters<br>No effect on SaO2 |
| Manber et al. [112] | Prospective, placebo-controlled, open | Postmenopausal | 6 | 47-63/56 | Mean AHI: 22 | Transdermal E2 + placebo 7-12 days followed by transdermal E2 + micronized progesterone 7-13 days | E2: AHI ↓<br>E2 + progesterone: AHI ↓ (ns) |
| Wesström et al. [113] | Prospective, open | Peri- and postmenopausal | 5 | 50-59/56 | Mean AHI: 14.9 | Oral E2 2mg + trimegeston 0.5mg 5-6 weeks | AHI ↓ |
| Saaresranta et al. [111] | Prospective, open, five-year follow-up | Postmenopausal | 64 | 62 | Mean AHI: 7.6 | Various estrogen formulas (tablet, gel, patch). Four groups: 1) continuous use, 2) present short-term use, 3) previous use, 4) no use | Present E2 users had a higher mean SaO2 and spent less time with an SaO2 below 90% than non-users. At follow-up, a higher E2 concentration was associated with a higher mean SaO2 and a lower AHI. |

AHI = apnea-hypopnea index, CEE = conjugated equine estrogen, E2 = estradiol = 17β-estradiol, EV = estradiol valerate, HVR = hypoxic ventilatory responsiveness, MPA = medroxyprogesterone acetate, ns = non-significant, OSAS = obstructive sleep apnea syndrome, P = progestin, RDI = respiratory distress index, REM = rapid eye movement sleep, SAS = sleep apnea syndrome, SaO2 = arterial oxyhemoglobin saturation, SDB = sleep-disordered breathing