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REVIEW

Advances in the Diagnosis and Treatment of Obstructive Sleep Apnea in Women

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ABSTRACT

Obstructive sleep apnea (OSA) in women is often underdiagnosed due to various and different symptoms, significant delay of referrals, sex-specific polysomnographic patterns that are usually not detected by standard severity indices from the home sleep apnea test, and limitations of current screening tools. Up to 75% of women with OSA remain undiagnosed, with relevant clinical and socioeconomic consequences. Women often report daytime fatigue, insomnia, depression, anxiety, and poor sleep quality rather than excessive daytime sleepiness or snoring, which may lead to fewer sleep clinic referrals. Additionally, the menstrual phase significantly influences symptom expression. Comorbidities also exhibit sex-based differences: OSA in premenopausal women is strongly linked to depression, metabolic syndrome, and polycystic ovary syndrome, while postmenopausal women with OSA reported hypertension and diabetes more frequently, leading to a greater cardiometabolic risk in postmenopausal women with OSA. The screening questionnaires showed numerous limitations in women due to the lack of items concerning symptoms. Women's typical polysomnographic pattern, especially in the premenopause period, is characterized by predominant hypopneas, mild OSA with prevalent rapid eye movement (REM)-OSA, respiratory effort-related arousals (RERAs), and low arousal threshold, highlighting the crucial role of sleep fragmentation evaluation, beyond the apnea–hypopnea index (AHI). New indices such as hypoxic burden, pulse wave amplitude drops index and arousal burden may provide more appropriate OSA severity classification and risk stratification in women.After a review of the literature, we proposed four women phenotypes, highlighting the heterogeneity of OSA in women and the key role of sex-tailored OSA management. From a therapeutic perspective, women differ in apnea–hypopnea index (PAP) compliance, required lower PAP levels for the same disease severity as men, and experience mask-related side effects. However, we have to

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mention that this is suspected to be biased due to significant lower number of women included in cohorts and even lower in randomized controlled trials (RCTs). Mandibular advancement devices (MADs) and endotype-based pharmacotherapy may be beneficial in women with mild OSA and low arousal threshold or low muscle responsiveness. Emerging evidence suggests that a sex-centered approach to screening, diagnosis, and treatment may reduce the clinical and socioeconomic burden of OSA in women in the future.

Keywords: Obstructive sleep apnea; Sex differences; Sleep-disordered breathing; Clinical presentation; Polysomnography; Diagnosis; Risk stratification; Therapy; Outcomes

Key Summary Points

Obstructive sleep apnea (OSA) in women is underdiagnosed due to different clinical presentation with respect to men, low sensitivity of screening questionnaires, and reduced specificity of the home sleep apnea test due to unique polysomnographic features in women. Different menstrual phases further influence all the above.

Women with OSA frequently report symptoms such as daytime fatigue, poor sleep quality, nightmares, features of insomnia, depression, anxiety, and sexual dysfunction.

Women with OSA present a typical polysomnographic pattern characterized by mild OSA (with predominantly rapid eye movement [REM]-OSA), a predominant hypopnoic load, numerous respiratory effort-related arousals (RERAs), and arousals.

The screening questionnaires currently available are not very sensitive or specific for women, so new sex-specific questionnaires are needed.

Although there are limited existing published data on OSA gender-specific treatment differences, for women who have mild OSA and a low cardiometabolic risk, a treatment approach including non-apnea–hypopnea index (PAP) therapies may be attempted first, such as a mandibular advancement device, endotype-targeted pharmacotherapy (although still experimental), and/or combination therapies.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by recurrent upper airway collapse, intermittent hypoxia, and sleep fragmentation [1, 2]. Although OSA has been historically considered more prevalent in men (3:1 ratio) [3], it is now evident that the condition is frequently underdiagnosed in women, with up to 75% of cases remaining unrecognized, mainly due to the different and often underestimated symptoms. [4, 5]. Mild OSA appears more frequent in women, while moderate-to-severe OSA still predominates in men [6–8], however, this ratio seems to change after menopause. Among older adults, the male:female ratio is close to 1:1, suggesting that menopause significantly increases the risk of OSA in women [9].

Currently, women represent 40–50% of sleep clinic referrals, with a higher healthcare use and annual costs than men with OSA, due to a more delayed diagnosis [10, 11]. This phenomenon is observed despite lower average income levels, reduced employment rates, and higher disability pension rates [11]. On the other hand, it is a favorable outcome that healthcare costs decline after 2 years of continuous apnea–hypopnea index (CPAP) therapy in women [12].

In this narrative review, we summarize the recent advances in the diagnosis and treatment of OSA in women, covering sex-related differences in clinical presentation and comorbidities, screening/diagnosis, polysomnographic features/phenotypes, and therapeutic approaches.

METHODS

A comprehensive search was conducted on PubMed (from 1995 to 2025) using various keyword combinations, including "obstructive sleep apnea ", "OSA", "gender", "sex", "female" and "women". The search was manually reviewed by two authors to select articles of clinical and methodological relevance, supplemented by relevant reviews and meta-analyses. Finally, the most impactful articles were included based on expert consensus, focusing on the specific influence of sex on the clinical, diagnostic, and therapeutic issues of OSA. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CLINICAL PRESENTATION

Symptom Profile in Women

Women with OSA often experience different symptoms compared to men, contributing to the delayed recognition of OSA in women. Importantly, up to 40% of women with OSA do not report symptoms such as snoring, nocturnal choking, and witnessed apneas, particularly among premenopausal women [13]. On the contrary, the above symptoms are more frequently reported in postmenopausal women [8, 14, 15] (Table 1). Nocturia rates are higher in women with OSA and the risk of nocturia increases after menopause. In this way, nocturia may be more frequently reported by postmenopausal women with OSA, but current cohort data are lacking [16]. Regarding sleep-related symptomatology, features of insomnia, including difficulty initiating or maintaining sleep, non-restorative sleep, and nightmares, are more commonly reported in premenopausal women, contributing to the high burden of comorbid insomnia and sleep apnea (COMISA) [17–22]. After menopause, insomnia symptoms may persist but often coexist with more typical obstructive features and cardiometabolic comorbidities [21, 22]. Different types of insomnia have varying implications for the likelihood of suspecting OSA. In particular, sleep-maintenance insomnia—characterized by recurrent nocturnal awakenings with difficulty returning to sleep—may represent a relevant clinical clue for underlying sleep-disordered breathing [23]. In this context, respiratory events and associated autonomic arousals can trigger nocturnal awakenings, which patients may interpret as primary insomnia rather than a manifestation

Table 1 Differences in symptoms by menopausal status

	Premenopausal women	Postmenopausal women
Snoring	↑↑	↑↑
Witnessed apneas	↑↑	↑
Morning headache	↑↑↑	↑
Nocturia	↑	↑↑
Daytime Fatigue	↑↑↑	↑
Daytime sleepiness	↑↑	↑
Nightmares	↑↑↑	↑
Features of insomnia	↑↑	↑
Features of depression	↑↑↑	↑
Poor sleep quality	↑↑	↑↑

of OSA, leading to delayed diagnosis [23]. In addition, women often report lower Epworth Sleepiness Scale (ESS) scores than men, despite similar disease burden [24, 25]. However, the ESS scoring system has not been validated in women with OSA and may fail to correctly identify sex-specific manifestations of excessive daytime sleepiness (EDS) [10, 24]. Regarding mood-related symptoms, premenopausal women more frequently report features of depression and anxiety, with higher mood disturbance scores, which may further mask the underlying sleep-disordered breathing [17–20].

Table 1 shows the symptom prevalence in premenopausal and postmenopausal women with OSA [8, 14–25]. Premenopausal women exhibited a higher frequency of morning headaches, daytime fatigue, daytime sleepiness, nightmares, insomnia, and depressive symptoms [8, 14–23]. Conversely, postmenopausal women more often reported witnessed apneas and nocturia [16, 17]. Snoring and poor subjective sleep quality occurred at comparable levels across the two groups [8].

Sexual Dysfunction in Women

Women diagnosed with OSA tend to experience female sexual dysfunction (FSD) more often, with rates between 32% and 71%, negatively impacting a couple's harmony [26, 27]. More specifically, OSA leads to a lower Female Sexual Function Index (FSFI), indicating worse sexual functioning and higher Female Sexual Distress Scale (FSDS), indicating greater levels of sex-related distress [28–30]. More specifically, postmenopausal women with OSA report lower FSFI and higher FSDS scores, both due to the higher incidence of anxiety, depression, and insomnia and to the more severe OSA during the menopausal period [27, 30]. Androgen abnormalities and endothelial dysfunction related to menopause may also contribute to FSD pathophysiology in women with OSA [29].

CARDIOMETABOLIC COMORBIDITIES

Cardiovascular

OSA is increasingly recognized to increase the risk for cardiometabolic comorbidities. Compared to men, women with OSA exhibit more endothelial dysfunction and platelet activation, making them more predisposed to atherosclerosis and ischemic events [31, 32]. Furthermore, rapid eye movement (REM)-OSA is associated with higher sympathetic activity and nocturnal ischemic burden [33]. As women more frequently exhibit REM-OSA, these pathophysiological mechanisms may contribute to high cardiovascular risk in women with OSA. In a large Canadian clinical OSA cohort, nocturnal hypoxemia (measured by T90%), EDS, reduced sleep efficiency and periodic leg movements were significantly associated with adverse cardiovascular outcomes in women but not in men [34]. Numerous studies have shown that cardiovascular risk in women with OSA increases in parallel with apnea–hypopnea index (AHI) levels [35, 36]. In the Communities-Sleep Heart Health Study, OSA predicted ventricular hypertrophy, heart failure, and mortality only in women [37]. In a study by Wang et al., women with acute coronary syndrome (ACS) and OSA presented a higher risk of major adverse cardiovascular and cerebrovascular events (MACCE) compared to ACS men with OSA and ACS women without OSA, even after adjustment for anthropometric and cardiovascular risk factors [38]. This evidence has been explained by authors due to ischemic-related unplanned rehospitalization and/or revascularization [38]. Additional evidence from the Women's Health Initiative showed that OSA-related risk factors and symptoms, such as obesity and snoring, were significant predictors of heart failure in women with OSA [39].

A key mechanism linking OSA to arterial hypertension (AH) in women is the sympathetic overactivation, which leads to the phenomenon of 'nocturnal non-dipping' pattern. This sympathetic burden may arise both from frequent RERAs, which promote sustained sleep

sympathetic overactivation, and from REM-OSA, characterized by longer obstructive events, deeper oxygen desaturations, and marked sympathetic surges. Together, these mechanisms contribute to the development of a nocturnal non-dipping blood pressure pattern [40, 41]. Although many large cohort studies report a higher risk of AH in men with OSA compared to women, findings are conflicting [42, 43]. Data from the Truven Health MarketScan Research Databases reported that AH was more frequent among women with OSA compared to men [44]. This apparent sex-related discrepancy appears to reflect different recruitment methods, as postmenopausal women display higher systolic and blood pressure levels compared to premenopausal women [45] (Table 2).

Table 2 shows comorbidity prevalence in premenopausal and postmenopausal women with OSA [32–53]. Premenopausal women exhibited a higher frequency of depression and asthma. Conversely, postmenopausal women more often suffer from hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and heart failure. Metabolic syndrome occurred at comparable levels across the two groups.

Metabolic

Metabolic syndrome (MS) is another frequent comorbidity in patients with OSA, with a prevalence rate between 43% and 81% [46]. A study by Chaudhary et al. showed that MS is more prevalent in women compared to men with OSA (88% vs. 68%) and postmenopausal women presented a higher risk compared to premenopausal ones [47]. Data from the National Health and Nutrition Examination Survey confirmed that menopause was associated with increased visceral fat deposition in women with OSA [48]. The endocrine–metabolic axis may also differ by sex: a study by Zi Qian C et al. showed that young women with severe OSA exhibited insulin resistance and greater adrenal axis activation (elevated cortisol levels) compared to age-matched men. Furthermore, only in women were these endocrine–metabolic changes correlated with nocturnal hypoxia [49]. Another interesting study showed that depressed perimenopausal women with low estradiol (E2) levels appear to have a higher risk of OSA [50]. Women with OSA also face a heightened risk of developing diabetes. A nationwide Swedish Hospital Discharge Registry with a 16-year follow-up reported that women with OSA had a markedly higher risk of new-onset diabetes mellitus (DM) compared to men (50% vs. 19%), with OSA conferring an odds ratio (OR) of 11.8 for new-onset DM in women [51].

Finally, polycystic ovary syndrome (PCOS) has been identified as an independent risk factor for OSA. In fact, according to a 2019 British cohort study, PCOS doubles the risk of OSA in women by 2 times, after adjusting for body weight [52]. Importantly, both OSA and PCOS

Table 2 Differences in comorbidities by menopausal state

	Premenopausal women	Postmenopausal women
Hypertension	↑	↑↑↑
Diabetes	↑	↑↑↑
Metabolic syndrome	↑↑	↑↑
Depression	↑↑	↑
Asthma	↑↑↑	↑
COPD	↑	↑↑
Heart failure	↑	↑↑↑

synergistically increase the risk of non-alcoholic fatty liver disease (NAFLD) independently of BMI, due to insulin resistance and hyperandrogenism [53]. Ultimately, current findings point toward a close connection between the severity of OSA in women and its contribution to cardiovascular disease. Early identification of these abnormalities may lead to better management of this cardiometabolic burden in women with OSA.

POLYSOMNOGRAPHIC FEATURES AND PHENOTYPES

Polysomnographic Features

Men typically show higher AHI and oxygen desaturation index (ODI) compared to women [54–57]. Men also exhibit a greater and longer apnea burden while women report a greater and longer hypopnea burden [55, 56]. In mild OSA, women exhibit a larger desaturation area, while men predominate in moderate-to-severe OSA [55].

Regarding sleep architecture, women generally present a higher proportion of N3 sleep and lower wake after sleep onset (WASO) time compared to men [57, 58]. Instead, the higher spontaneous arousal index and more frequent respiratory effort-related arousals (RERAs) compared with men may contribute to insomnia and disturbed sleep in women [57–59]. The higher frequency of low arousal threshold (lowAT) endotype at polysomnography (PSG) in women may also explain the different symptoms of OSA with respect to men [60, 61].

Furthermore, women exhibit a higher rate of REM-OSA, which is known to increase AH, atherosclerosis, and cardiovascular risk [62, 63], which is likely due to greater REM-related hypotonia of upper airway muscles, leading to REM respiratory instability [64]. These features (REM-OSA, RERAs, and arousal-related hypopneas) limit home sleep apnea test (HSAT) applicability in women, supporting the current crucial role of PSG in women [9]. Few studies have addressed menopausal status, with the data presented in Table 3. Premenopausal women are predisposed to greater REM-OSA risk, due to lower arousal threshold [65, 66]. Positional OSA (P-OSA) prevalence increases with age in older women, due to more collapsed upper airways and increased neck fat accumulation [67]. Several studies demonstrated that OSA severity increases in postmenopausal women, even after adjusting for BMI, neck circumference, and other confounders, suggesting that hormonal changes and functional airway changes play a key role [68, 69].

In summary, the findings of the PSG analysis indicate that OSA in women is characterized by sleep fragmentation, hypopneas, and arousals, as opposed to significant nocturnal hypoxemia, potentially resulting in different symptoms. This underscores the significance of incorporating sex-specific diagnostic methodologies.

Table 3 demonstrates the polysomnographic differences between pre and postmenopausal women with obstructive sleep apnea [54–69]. Compared with postmenopausal women, premenopausal women exhibited lower overall OSA severity, less prevalent positional OSA, and a greater prevalence of rapid eye movement-related obstructive sleep apnea (REM-OSA).

Women's Phenotypes

Considering the heterogeneous nature of OSA, in recent decades, there have been proposals to classify patients into different phenotypes.

Table 3 Polysomnographic differences between pre and postmenopausal women

	Premenopausal women	Postmenopausal women
OSA severity	Less severe	More severe
Positional OSA	Less prevalent	More prevalent
REM-OSA	More prevalent	Less prevalent

Table 4 Proposed description of the four female OSA phenotypes

	Phenotype 1: Classic sleepy	Phenotype 2: Ischemic heart disease	Phenotype 3: Elderly comorbid paucisymptomatic	Phenotype 4: Insomnia and mild OSA
Age	Middle-aged	Middle-aged	Older	Middle-aged
BMI	Obese	Overweight–obese	Obese	Overweight–obese
CVRF	Mild	Moderate	High	Mild
CVD	AH	Ischemic heart disease	AH, AF, HF	None
Comorbidities	Dyslipidemia, DM	Dyslipidemia	DM, COPD	Depression, anxiety, asthma
Symptoms	EDS, snoring, witnessed apneas	Non-sleepy, paucisymptomatic	Non-sleepy, nocturia, paucisymptomatic	Non-sleepy, insomnia, mood disorders
Sleep efficiency	Normal	Normal	Lower	Lower
AHI severity	Severe	Moderate	Severe	Mild
Hypoxic burden	Mild	Moderate	Severe	Mild
Treatment	First-line: CPAP adjunctive: WL	First-line: CPAP	First-line: CPAP Second-line: MAD	First-line: MAD adjunctive: pharmacotherapy/CBT-I

More recently, considering cluster analysis from two large European cohort studies [70, 71], four main women OSA phenotypes may be distinguished [Table 4]:

- *'Classic' sleepy phenotype*: middle-aged obese women with EDS, severe OSA, and moderate risk of comorbidities. This phenotype responds beneficially to CPAP, which remains the first-line therapy.
- *Ischemic heart disease phenotype*: overweight–obese postmenopausal women, with moderate OSA but with a higher prevalence of ischemic heart disease. This phenotype is often underdiagnosed due to its paucisymptomatic nature but highlights the importance of OSA screening in women with ischemic heart disease.
- *Elderly comorbid paucisymptomatic phenotype*: obese elderly women with severe OSA and high burden of comorbidity such as AH, diabetes, and cardiovascular diseases. In this case, CPAP is crucial for secondary prevention, but therapeutic compliance is low in this phenotype.
- *Insomnia phenotype with mild OSA*: middle-aged overweight–obese women with low comorbidity burden but with insomnia and mild OSA (COMISA). For this particular phenotype, CPAP might not be recommended at the time of diagnosis because patients with COMISA may have difficulty tolerating it. A personalized and multimodal therapeutic approach with mandibular advancement devices (MAD), weight reduction, and cognitive behavioral therapy for insomnia (CCBT-I) could be first attempted.

Recognizing these phenotypes in women with OSA is crucial for the correct characterization and management of OSA in women.

Table 4 shows a description proposed based on the two major cluster analyses by Fontanilles and Pataka [70, 71]. OSA, obstructive sleep apnea; BMI, body mass index; CVRF, cardiovascular risk factors; AH, arterial hypertension; AF, atrial fibrillation; HF, heart failure;

DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; EDS, excessive daytime sleepiness; AHI, apnea–hypopnea index; CPAP, continuous positive airway pressure; WL, weight loss; MAD, mandibular advancement device; CBT-I, cognitive behavioral therapy for insomnia.

SCREENING CHALLENGES

Screening questionnaires remain the most used tool to identify individuals at risk for OSA. However, sex-related limitations have been issued [72]. STOP-BANG (snoring, tiredness, observed apnea, high blood pressure, body mass index (BMI), age, neck circumference, and gender) questionnaire sensitivity shows high sensitivity with ≥ 3 cut-off in men (87%) but only 55% in women; lowering the threshold to ≥ 2 increased sensitivity to 88.5% and specificity to 42.6% in women [73, 74]. Similar sex-related limitations affect the Berlin Questionnaire, whose modified version (BQ-G), which includes gender, improved specificity, and positive and negative predictive values [75].

The NoSAS (neck circumference, obesity, snoring, age, and sex) score performance also improves with a sex-specific cut-off ≥ 6 points in women (sensitivity 87%, specificity 56%) [73]. The multivariable apnea prediction (MAP) index, which includes symptoms, age, BMI, and sex, demonstrated reduced sensitivity in postmenopausal women, highlighting the influence of hormonal status [76]. A key methodological issue of widely adopted questionnaires such as STOP-BANG, NoSAS, and MAP index is the inclusion of male sex as an independent risk factor, together with the use of neck circumference cut-offs primarily derived from male populations. Women may be inherently disadvantaged by this sex-weighted structure, as their smaller neck circumferences and differing symptom profiles could compromise screening sensitivity. Importantly, the assignment of male sex as a risk item in several screening tools may paradoxically lower their diagnostic performance in women.

In summary, sex-specific thresholds or sex-specific screening tools are essential to enhance accuracy and to minimize women's underdiagnosis [Fig. 1].

DIAGNOSTIC CHALLENGES

In the Wisconsin Sleep Cohort Study, women with mild OSA were less likely to be diagnosed than men [77]. Furthermore, the higher prevalence of REM-OSA, RERA, arousals, and arousal-related hypopneas [57–64] may explain the greater symptomatology in women with mild OSA. For this reason, PSG testing is suggested for women with a high symptomatologic burden despite a low AHI on HSAT, or when REM-OSA, RERA, or arousal-related hypopneas are suspected. Conversely, in women presenting with a more typical OSA phenotype, characterized by loud snoring, witnessed apneas, or prominent daytime sleepiness, HSAT may represent an appropriate initial diagnostic tool.

The utilization of AHI as a definitive indicator of OSA severity in women has been a topic of extensive discussion, especially when considering the PSG versus HSAT debate, given that women can experience considerable sleep disruption and symptoms despite potentially lower AHI values. Emerging findings support the use of alternative indices that better reflect the pathophysiological burden of OSA. Hypoxic burden (HB), defined as the sum of the areas under the desaturation curve, captures depth, amplitude, and duration of oxygen desaturations and predicts OSA cardiovascular outcomes more precisely than AHI [78]. The pulse wave amplitude drop index (PWAD), which quantifies transient plethysmography signal reductions during sleep, captures sympathetic activation and autonomic arousals, and it may be particularly relevant in women with mild OSA and symptoms such as fatigue, insomnia, anxiety, and depression [79].

Arousal burden, defined as the cumulative percentage of sleep spent in an arousal state, quantifies sleep fragmentation and was

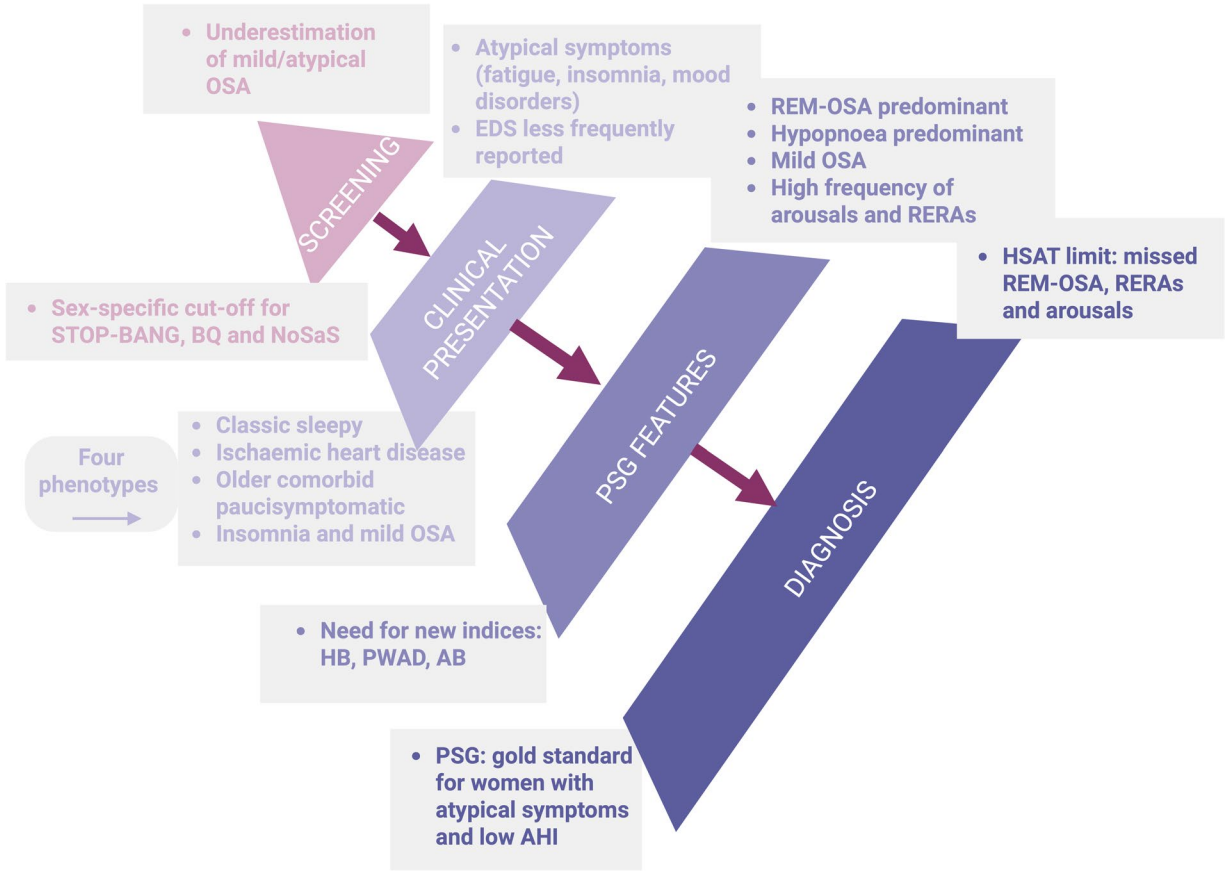

Fig. 1 OSA in women: from presentation to diagnosis. Graphical summary of evidence emerged from this review. *OSA* obstructive sleep apnea, *EDS* excessive daytime sleepiness, *REM-OSA* rapid eye movement-obstructive sleep apnea, *HB* hypoxic burden, *RERAs* respiratory effort-related arousals, *ESS* Epworth Sleepiness Scale, *BQ* Berlin Questionnaire, *NoSaS* neck circumference, obesity, snoring, age, and sex, *HSAT* home sleep apnea test, *PSG* polysomnography, *PWAD* pulse wave amplitude drop, *AB* arousal burden

associated with adverse cardiovascular outcomes [80].

Collectively, these indices indicate the need to look beyond AHI towards a multidimensional diagnostic approach in women, but large-scale prospective cohort studies are needed to validate their use in women.

TREATMENT APPROACHES

CPAP Therapy

Identifying gender differences in CPAP adherence is essential for a sex-centered personalized medicine approach in OSA. In a study by Fujita et al., younger age, insomnia, or lack of deep sleep post-CPAP were independent predictors of poor adherence in women with OSA [81]. Heraganahally et al. also reported that Australian women with OSA and higher ESS and more severe oxyhemoglobin desaturations achieved better CPAP adherence [82].

Importantly, in a randomized trial by May et al., the use of active CPAP was significantly associated with greater CPAP adherence compared to sham CPAP only in women with OSA, but not in men, suggesting that women may be more responsive to early therapeutic benefit [83].

Beyond clinical predictors, patient-reported mask-related side effects (MRSEs) may represent a major limit to long-term CPAP use, especially in women. Women with OSA report higher rates of dry mouth, runny nose, and partner disturbing air leaks, particularly when using nasal masks [84]. These issues may limit comfort and compliance, highlighting the crucial role of mask fitting and side effects management in women with OSA.

Positive airway pressure (PAP) required during CPAP titration is also influenced by sex. Jayaraman et al. demonstrated that women required significantly lower PAP levels during titration than men, despite similar baseline AHI. In multivariate regression (adjusted for sex, AHI, age, BMI, and ESS), sex was the only independent predictor of PAP titration levels [85].

McArdle et al. also developed an automatic apnea–hypopnea index (APAP) device called Autoset for Her (AfH), tailored to women's sleep-disordered breathing patterns [86]. AfH is more sensitive to flow limitations (which are very common in women), has a slower and gentler pressure ramp, and avoids excessive PAP fluctuations. These mechanisms have been shown to be more comfortable and equally effective in reducing AHI (but more effective in reducing flow limitations) than classic APAP. Beyond physiological differences, PAP acceptance in women may also be influenced by cultural, social, and intimacy-related factors, including greater sensitivity to body image, partner-related concerns, and perceived intrusiveness of therapy [87]. In particular, the visibility, noise, and perceived intrusiveness of PAP devices may disproportionately affect women, potentially interfering with sleep-related intimacy and leading to reduced acceptance or early discontinuation of therapy [88]. In this context, devices delivering lower and more stable pressures, such as sex-tailored APAP algorithms, may offer additional advantages in terms of comfort and long-term adherence.

In terms of outcomes, there are data suggesting a positive effect of CPAP on sleep symptoms, mood state, and neurocognitive and cardiovascular outcomes in women with moderate-to-severe OSA [89]. CPAP has shown greater improvement in anxiety, depression, well-being, self-control, and vitality after six months of CPAP therapy in women compared to men with OSA [90]. Moreover, a case study of a woman with severe REM-OSA demonstrated the efficacy of auto-CPAP in alleviating nocturnal symptoms and daytime dreaminess after 3 months of treatment [91]. These findings suggest that CPAP could be important for improving quality of life and symptoms of women with OSA. Furthermore, CPAP significantly reduces FSD in OSA and improves couple dynamics [26]. In fact, partners' International Index of Erectile Function scores improve after women start CPAP [92], although some male partners describe CPAP as less compatible with traditional notions of femininity [93].

Given the underrepresentation of women in RCTs focused on therapeutic outcomes and the lack of RCTs designed to assess sex-specific effects on major cardiovascular endpoints, it is not possible to draw reliable conclusions about potential differences in cardiovascular events and mortality [94–96]. In real-world data, there were no observed sex differences in cardiovascular outcomes when comparing CPAP users and those who discontinued CPAP [95]. Notably, CPAP therapy seems to favorably influence systemic inflammation, leading to decreased levels of cardio-inflammatory biomarkers like myeloperoxidase, paraoxonase, and fibrinogen after 2 months of CPAP in women, whereas these biomarkers increase in men [97]. Conducting adequately powered studies is necessary for a more comprehensive understanding of sex-specific differences in CPAP outcomes.

Taken together, these findings demonstrate that sex-specific factors influence CPAP adherence, efficacy, titration and potentially outcomes. Addressing these differences is crucial to optimize treatment success and to provide a personalized approach to CPAP therapy in women with OSA, such as AfH.

Oral Appliances

Mandibular repositioning devices (MRDs) appear to be a possible alternative to CPAP, especially in non-compliant patients or those with mild OSA without symptoms and comorbidities. Previous research suggests sex differences in MRDs

effectiveness. The ORCADES study showed that female sex was a predictor of MRDs efficacy in mild, moderate, and severe OSA [98].

The study by Marklund et al. also demonstrated that female sex predicts a better response to MRDs in cases of mild OSA, with an AHI falling below ten events/hour (OR equal to 12 in women and 2.5 in men) [99]. Finally, Rietz et al. demonstrated a reduction in nocturnal blood pressure after 4 months of treatment with MRD only in women with mild OSA [100].

In summary, considering the currently available evidence, we suggest a treatment attempt with MRDs in women with mild OSA and low–moderate cardiovascular risk before moving on to CPAP.

Pharmacotherapy

Pharmacotherapy in OSA remains debated and must be tailored to the underlying endotype. It should not currently be considered a replacement for CPAP, but rather a support to lower PAP levels required to reopen the airways, enhance adherence, or target specific pathophysiological traits.

1. *Low arousal threshold (lowAT):* frequent endotype in comorbid OSA with insomnia (COMISA), which is common in women [101, 102]. In these cases, Z-drugs such as zolpidem raise the arousal threshold and increase sleep efficiency without significant changes in AHI [103, 104]. The combination of APAP with trazodone has shown benefits in women with OSA and with anxiety disorders, a frequent comorbidity [105]. Importantly, hypnotic drugs are not recommended as monotherapy for OSA, and their use, either alone or in combination with CPAP, should be considered experimental, phenotype-driven, and limited to carefully selected patients, pending further evidence from dedicated clinical trials [106]. A crucial therapeutic agent for the COMISA population, CBT-I has been observed to increase the respiratory arousal threshold and decrease the severity of the AHI.
2. *Low muscle responsiveness:* especially after menopause, impaired activity of pharyngeal dilator muscles, especially the genioglossus, may predispose women to upper airway collapse [65, 69]. This endotype of low muscle responsiveness has been linked to reduced endogenous noradrenergic activity during NREM sleep and muscarinic hyperactivity during REM sleep, leading to pharyngeal tone drop [107]. To this purpose, the ato-oxy combination, consisting of atomoxetine, a norepinephrine reuptake inhibitor, and oxybutynin, an antimuscarinic agent, reduced AHI by approximately 63% in patients with OSA compared to placebo by increasing genioglossus responsiveness threefold [108]. Furthermore, this ato-oxy combination achieved maximum effect (complete response) in mild, hypopneas-predominant,

Table 5 Proposed endotype-specific therapeutic strategies for OSA in women

	Endotype 1: Low arousal threshold	Endotype 2: Low muscle responsiveness	Endotype 3: High upper airway collapsibility
Clinical features	Comorbid insomnia, mood disorders	Postmenopausal non-sleepy overweight women	Severely obese and excessively sleepy with high CVRF
PSG features	RERAs, high HI, lower AHI, high arousal burden	REM-OSA, high HI, flow limitations, low HB	High AHI and AI, high HB, p-OSA
First-line therapy	CPAP	CPAP (AfH) with lower PAP	CPAP
Second-line therapy	MAD	ato-oxy combination	MAD
Adjunctive therapy	Z-drugs ± CBT-I	ato-oxy combination	WL

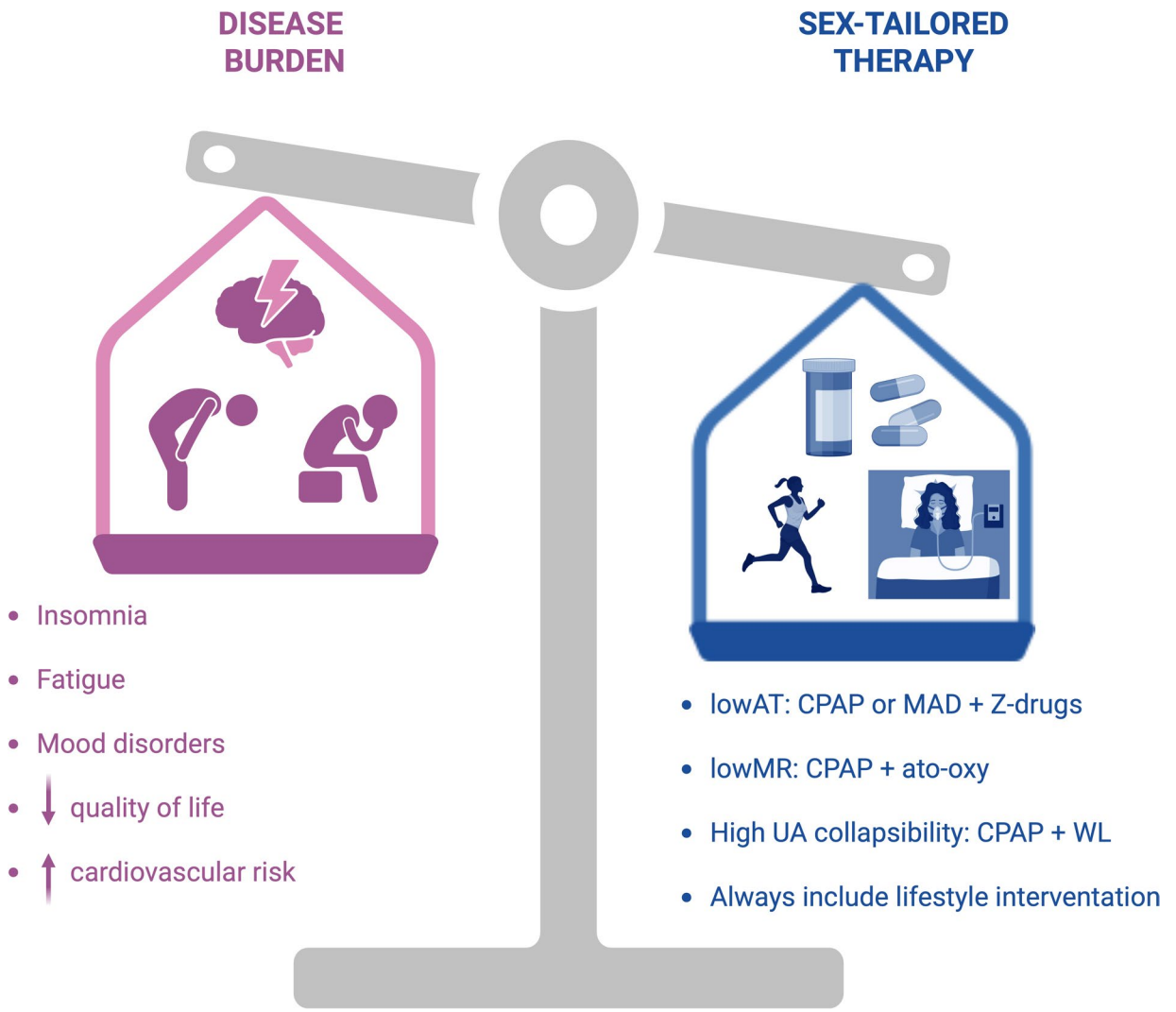

Fig. 2 The interplay between disease burden and sex-tailored therapeutic strategies in women with OSA and a conceptual model illustrating the crucial role of sex-tailored therapy for the management of disease burden in women with OSA. *lowAT* low arousal threshold, *CPAP* continuous positive airway pressure, *MAD* mandibular advancement device, *lowMR* low muscle responsiveness, *ato-oxy* atomoxetine-oxybutynin, *WL* weight loss

low airway collapsibility OSA features, which are typical of women with OSA [9, 109].

In summary, this evidence suggests that endotype-targeted pharmacotherapy, although still experimental and further clinical trials are needed, may be particularly useful for OSA in women (Table 5 and Fig. 2).

Table 5 shows the endotype-specific therapy for women with OSA based on recent clinical trials [65, 101–110]. CVRF, cardiovascular risk factors; PSG, polysomnography; RERAs, respiratory effort-related arousals; HI, hypopnea index; AHI, apnea–hypopnea index; REM-OSA, rapid eye movement-obstructive sleep apnea; HB, hypoxic burden; AI, apnea index; p-OSA, positional OSA; CPAP, continuous positive airway pressure; AfH, autoset for her; PAP, positive airway pressure; MAD, mandibular advancement device; ato-oxy, atomoxetine-oxybutynin; CBT-I, cognitive behavioral therapy for insomnia; WL, weight loss.

Other Therapies

Women seem to predict greater success with upper airway stimulation (UAS) via hypoglossal nerve stimulation (HNS), mainly due to greater adherence to the device rather than anatomical or pathophysiological factors [111]. Respiratory muscle training (RMT) has shown marked improvement in symptoms such as insomnia, irritability, daytime fatigue, psychological distress, and disturbed sleep in patients with mild-to-moderate OSA (a typical pattern in women with OSA) [112]. To date, no consistent sex-related differences have been reported for upper airway surgery for OSA.

CONCLUSIONS

Obstructive sleep apnea in women constitutes a multifactorial clinical challenge, frequently underdiagnosed due to different symptoms, sex-specific polysomnographic features currently unrecognized by severity criteria, and limitations of current screening tools. Growing evidence indicates that OSA in women imposes a significant socioeconomic burden, substantially impacting quality of life and partner relationships. Furthermore, it confers a severe cardiometabolic risk profile, including ischemic heart disease, heart failure, and atrial fibrillation, as demonstrated in large cohorts such as ESADA. This underscores the urgent need for early and sex-specific identification of OSA in women, shifting the clinical focus from symptom-driven diagnosis toward cardiovascular risk prevention. The identification of women-specific phenotypes, such as REM OSA, mild OSA with insomnia, or elderly comorbid paucisymptomatic women, highlights the need for personalized diagnostic and therapeutic approaches. Screening challenges include the limitations of the most commonly used questionnaires in sleep clinics for women and the need to develop women-centered questionnaires. Diagnostic challenges underscore the limitations of AHI alone and the potential key role of newer indices, such as hypoxic burden, PWAD, or arousal burden. From a therapeutic perspective, sex differences in CPAP adherence, titration PAP, and response to oral appliances or experimental pharmacotherapy support the evolution towards personalized, endotype-based management. Ultimately, a sex-tailored approach is needed across all phases of screening, diagnosis, and treatment to improve outcomes and reduce the clinical and socioeconomic impact of OSA in women.

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Declarations

Conflict of Interest. All the authors (Izolde Bouloukaki, Antonio Fabozzi, Esther Irene Schwarz, Sophia E. Schiza) certify that they have no affiliations with or involvement in any organization or entity with any financial interest

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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