Non-sleepy obstructive sleep apnoea: to treat or not to treat?

Sex differences in obstructive sleep apnoea

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Changes accross the lifespan can alter the expression of OSA in females at both symptomatic and physiological levels. OSA in females is different from that in males, and is under-studied. http://bit.ly/2XTnXPK

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ABSTRACT Obstructive sleep apnoea (OSA) and obstructive sleep apnoea/hypopnoea syndrome (OSAHS) have long been considered predominantly male-related conditions. The clinical presentation of sleep disordered breathing in females differs from males and can vary with age and physiological status, *e.g.* menopause and pregnancy. Overall, females appear to be more symptomatic, with lower apnoea–hypopnoea index scores compared to males. Furthermore, they appear to have more prolonged partial upper airway obstruction, and may report insomnia as a symptom of OSAHS more frequently. As a consequence of these differences in clinical presentation, females with sleep disordered breathing are often underdiagnosed and undertreated compared to males. This review is aimed at discussing the epidemiology, clinical presentation, pathophysiology and hormonal and metabolic differences in females who present with OSA/OSAHS in comparison to males.

Epidemiology of obstructive sleep apnoea

The most prevalent form of sleep disordered breathing in industrialised societies is obstructive sleep apnoea (OSA) [1]. OSA is characterised by repetitive collapses (apnoeas) or near collapses (hypopnoeas) of the upper airway during sleep, resulting in intermittent hypoxaemia and increased sympathetic arousal. When symptoms of daytime dysfunction and other neurological impairment are directly attributed to the apnoeas and hypopnoeas in sleep, the disorder is known as obstructive sleep apnoea/hypopnoea syndrome (OSAHS) [1–3].

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The apnoea–hypopnoea index (AHI) can be used to assess severity of the sleep disorder when an electroencephalographic measure of sleep is available. Daytime sleepiness is usually recorded by a thorough clinical history, but is also frequently recorded in both practice and in research studies using the Epworth Sleepiness Scale (ESS) [4]; a score of ⩾11 out of 24 is considered consistent with excessive daytime sleepiness. Unfortunately, the ESS does not correlate well with objective measures of daytime sleepiness [5].

Thus, the epidemiology of OSA and OSAHS can vary significantly in the population depending on definitions used for the nocturnal breathing pauses and any resulting daytime sleepiness/impairment. Additionally, the prevalence of sleep disordered breathing will vary according to age and sex [1–3].

The most frequently cited study in respect of OSA and OSAHS prevalence in a mostly white, mid-American cohort of people demonstrated that 24% of males (n=325) and 9% of females (n=250) had an AHI ⩾5 events·h^{-1} of sleep [6]. However, when sleepiness was factored in as causally related to the AHI, the prevalence fell to 4% in males and 2% in females. Several population prevalence studies since then have quoted mean prevalences of OSA of 27.3% in males (range 9–86%) and 22.5% in females (3.7–63.7%) and mean (range) prevalence of OSAHS of 6% (3–18%) in males and 4% (1–17%) in females [7, 8].

Consequently, and unsurprisingly, OSA/OSAHS has thus been considered a male disease, with male:female ratios ranging from 3:1 to 5:1 in the general population and from 8:1 to 10:1 in selected clinical populations [9]. Despite this, females now represent up to 40–50% of presentations at sleep clinics [10].

Clinical presentation

Failure to recognise the distinct clinical presentation and sex-specific differences in sleep studies may lead to underdiagnosis or misdiagnosis of OSA/OSAHS in females [11, 12].

Females are less likely to report snoring (males have higher snoring intensity by comparison [13]) or witnessed apnoeas. Females are more likely to complain of daytime fatigue, lack of energy, insomnia symptoms, morning headaches, mood disturbances and nightmares compared to males [11, 12]. This "atypical" clinical presentation at least partly explains the fact that female patients are diagnosed with OSA/OSAHS at older ages and with higher body mass index (BMI) than males [11, 12]. Females seem to have greater impairment of quality of life and higher healthcare expenditure compared to males with similar AHI levels [14–19]. In addition, females with OSA report a higher rate of impaired work performance, sick leave and divorce compared to females without OSA, identical in age and visceral fat mass; this kind of association has not been found among males [14–19]. OSA in females is associated with an increased risk of sickness absence compared to males with OSA, even 5 years *versus* 1 year prior to diagnosing OSA [20]. A prospective study of 74 543 cases of OSA from the Swedish Patient Register matched with 371 592 non-cases, demonstrated during a 5-year follow-up period a higher risk for disability pension among females with OSA compared to males with OSA [19].

Compared to males, OSA/OSAHS typically manifests in females as a lower AHI, shorter apnoeic episodes, lower proportion of supine OSA and clustering of apnoea during rapid eye movement (REM) sleep [11]. However, in females, the longest apnoeas are associated with a more severe oxygen desaturation [21]. Respiratory events during sleep are less frequently associated with complete upper airway collapse in females than in males [11]. However, despite less-severe OSA in terms of AHI, females are not less symptomatic compared to males, but report sleepiness at relatively low levels of AHI [22]. Therefore, especially in females, AHI alone is not a sufficient criterion for clinical severity of OSA. The severity should be specified with objective polysomnography (or cardiorespiratory polygraphy) findings (AHI/respiratory effort index plus flow-limitation) and subjective daytime sleepiness with functional disability. In females with low AHI, a continuous positive airway pressure (CPAP) trial should be symptom-driven [23, 24].

What might explain this apparent discrepancy between AHI and symptoms in females particularly? In females, upper airway obstruction often manifests as subcriterion events (snoring, flow limitation or prolonged partial upper airway obstruction) [25–28]. Arousals induce less ventilatory instability in females, thereby protecting them from OSA. Prolonged episodes of partial upper airway obstruction [25–28] typically appear in slow-wave sleep and are associated with increased carbon dioxide (CO_2) levels [29–31]. Importantly, prolonged partial upper airway obstruction is far more common than "conventional" sleep apnoea in females [32]. Furthermore, hypothyroidism is more prevalent in females than in males, which *per se* may induce OSA. Prolonged partial upper airway obstruction is related to increased respiratory resistance [33], which is characterised by increase in end-tidal CO_2 [34] and transcutaneous CO_2 [29, 30]. Prolonged partial obstruction with increased CO_2 during sleep may contribute to a different symptom profile in females. This is supported by the finding that in females, excessive daytime sleepiness and

daytime fatigue associate with habitual snoring independent of AHI, age, obesity, smoking or sleep parameters [26]. Correction of prolonged flow limitation with CPAP treatment is associated with a higher attentiveness and a higher efficiency in normalising daytime vigilance than when eliminating only apnoea, hypopnoea and snoring [35]. Hypercapnia is associated with electroencephalogram (EEG) slowing and daytime sleepiness in OSA [36], and CPAP treatment corrects the EEG slowing and alleviates daytime sleepiness [37].

Comorbidities

The AHI seems to underestimate systemic inflammation in females [38]. REM predisposition of AHI is associated with increased intima thickness, even in females with no or mild OSA and normal non-REM AHI [39]. In a Finnish longitudinal population-based study with up to 25-year follow-up data on almost 37 000 individuals, OSA independently increased the risk for coronary heart disease and type 2 diabetes mellitus, particularly in females [40]. Of importance, clinical OSA phenotypes with insomnia-like symptoms are more prevalent in females than in males [41], and despite less severe sleep disordered breathing in terms of AHI, those OSA phenotypes have a higher burden of cardiovascular, pulmonary and psychiatric comorbidity and lower CPAP adherence compared to patients with the traditional sleepy phenotype [42]. A high prevalence of particularly cardiovascular comorbidity among patients with insomnia-like symptoms seems to be linked with nocturnal hypoxaemia [41]. However, the data are not consistent, and some studies suggest a higher risk of cardiovascular comorbidity [43] and type 2 diabetes [44] in males with OSA.

Menopause

There is paucity of data regarding possible differences in clinical presentation of OSA/OSAHS between pre- and postmenopausal females. In postmenopausal females, symptoms of OSA may easily be neglected or interpreted as menopausal symptoms. Prevalence of OSA/OSAHS in females doubles after menopause [45–47] independently of age and BMI [46], the peak being at age 65 years, 10 years later than in males [45]. Less hyperpnoea after episodic hypoxia and more stable respiratory effort in non-REM sleep in response to hypercapnia and arousals might protect premenopausal females from OSA [48]. During menopausal transition, respiratory drive decreases [49]. Increased arousals and increased soft tissue collapsibility predispose to respiratory instability and aggravate upper airway obstruction. Recent data suggest that severe vasomotor symptoms may be an independent risk factor for OSA [50]. Premenopausal females and females who use hormone therapy have lower apnoeic thresholds than postmenopausal hormone therapy non-users and males [48] resulting in more stable breathing. Furthermore, in a large follow-up study, the hazard ratio for OSA in females with surgical menopause was 1.27 compared with females with natural menopause, independently of age at menopause [51]. The increased OSA risk due to surgical menopause persisted for over 15 years into the postmenopausal period and was more pronounced in lean females and those who had never used menopausal hormone therapy. Higher physical activity was associated with lower OSA risk.

Pregnancy

Sleep disordered breathing in pregnancy is thought to play a role in maternal and fetal outcomes. The prevalence of OSA/OSAHS in pregnancy, diagnosed by polysomnography or polygraphy is not well defined, and there is a lack of large prospective studies. Potential risk factors for sleep disordered breathing in pregnancy include a reduction in upper airway size due to increased fluid retention and weight gain; nasal obstruction due to increased oedema from high oestrogen levels, nasal congestion or rhinitis; and reduced functional capacity and residual volume due to the lung mechanics in pregnancy [52–54]. Minute ventilation increases, and sleep may be fragmented depending on the level of discomfort and the trimester in which sleep is recorded [52].

Conversely, there are protective factors for OSA in pregnancy, including high progesterone levels, leading to increased upper airway dilator muscle activity; enhanced chemoreceptor responsiveness; and improved delivery of oxygen with a right-shifted Severinghaus curve and increases in heart rate and stroke volume [54]. Females tend to spend less time in the supine position, particularly during the third trimester [52].

Studies that have been conducted in pregnancy report that snoring steadily increases during the three trimesters [55]. The prevalence of snoring has been estimated to be between 10% and 46% [55]. This wide range can be attributed to variability in study design and the use of both objective and self-report measures. Longitudinal studies have shown that habitual snoring (three or more nights per week) increases from 7–11% in the first trimester to 16–25% in the third trimester [55, 56]. In pregnant females, the prevalence of OSA with an AHI $\geqslant$5 events·h^{-1} has been reported to be 3.6% in early pregnancy and 8.3% in mid-pregnancy; however, studies have been limited to small populations [57]. Snoring/OSA during pregnancy has been associated with pregnancy-induced hypertension and intrauterine growth retardation

as well as hypertension and diabetes [58]. Currently, there are no published randomised controlled trials of treatment of OSA/OSAHS in pregnancy, but observational studies have suggested that treatment can reduce blood pressure and improve pregnancy outcomes [52]. In summary, what comprises clinically significant sleep disordered breathing in pregnancy has not been defined. As technology advances rapidly, the ability to identify upper airway flow limitation will improve and the use of other sensors to define what may be clinically impactful sleep disordered breathing for both the mother and the developing fetus will become clearer.

Polycystic ovary syndrome

Females with the polycystic ovary syndrome (PCOS) represent an exception to the general findings of less prevalent/less severe OSA compared to males. PCOS is the most common endocrine disorder in females of reproductive age, and is characterised by hyperandrogenism, obesity, insulin resistance and OSA [59]. Some studies reported a worse metabolic profile in PCOS+OSA than in PCOS without OSA. However, a recent meta-analysis underlined the difficulty in interpretation of available data, since the confounding effect of obesity cannot be ruled out and more studies are needed [60]. A positive effect of CPAP on metabolic variables has been reported in this group of patients [61].

Obesity

Patients with severe obesity, who are candidates for bariatric surgery include more females than males. Large improvements in both OSA and diabetes are common after bariatric surgery [62]. OSA has been associated with worse metabolic profile in patients with morbid obesity, independently of BMI or type 2 diabetes mellitus [63]. In females on a waiting list for bariatric surgery with polysomnographically documented OSA, pharyngeal collapsibility correlated with the degree of insulin resistance [64]. CPAP use in patients with morbid obesity and OSA was associated with unchanged insulin resistance and improved glucose tolerance compared to conservative treatment in a short-term randomised controlled trial (females 72% of the sample, mean BMI 47 $kg{\cdot}m^{-2}$) [65].

The paucity of data on males undergoing bariatric surgery does not allow conclusions to be drawn about the sex-related effects of morbid obesity.

Pathophysiology of OSA in females

The different OSA prevalence between males and females has generated interest in sex-related aspects of OSA pathophysiology. The topic is complex, encompassing anatomical and physiological features of the upper airways, the modulating effects of sex hormones on control of breathing, and sex-dependent features of fat distribution in obesity [66]. Animal models have been developed, allowing to assess sex-related differences in sleep structure [67] and acquisition of phenotypes during early development. Moreover, recent work in animal models focused on the complex action of sex steroids, not only in control of breathing, but also regarding the protective action of oestrogen against oxidative stress [68].

Anatomy of the upper airways

Upper airway dimensions are normally larger in males than in females, but similar when normalised for body size [69]. Smaller dimensions should promote collapsibility of the airways in females compared to males, but this is not the case [70]. Upper airway length was found to be higher in males than in females, and associated with higher airway collapsibility [70]. Differences between sexes in airway length are not present in the prepubertal period, but become evident in post-pubertal girls and boys, suggesting a major effect of sex hormones [71]. Upper airway length correlates with OSA severity assessed as AHI [72], and is modified by ageing, with lengthening of upper airways especially in females [73], possibly secondary to increased laxity of soft tissues [74].

Physiology of the upper airways

In OSA patients, upper airway collapsibility under passive conditions (critical closing pressure, P_{crit}) was consistently shown to be lower in females than in males [75, 76], while no sex-related difference was found in respiratory stability during sleep, evaluated as loop gain [75]. However, data on the relationship between adiposity, assessed as BMI ($kg{\cdot}m^{-2}$), and P_{crit} differed between studies, since the slope of the relationship was similar in males and females in one study [75], and was markedly lower in females compared to males in another study of a larger sample [76]. The higher P_{crit} in males is believed to be secondary to anatomical factors, *i.e.* longer upper airways as previously discussed, and differences in fat distribution, since females, especially in the pre-menopausal phase, show a peripheral rather than the central pattern distribution typical of males, with lower fat deposition around the upper airways and a smaller neck circumference for a similar BMI [77].

Ventilation during sleep is similarly regulated in healthy males and females [78, 79]. However, ventilation and upper airway function in females are physiologically modulated by sex hormones. Progesterone stimulates ventilation especially when associated with oestrogen [80]. Upper airway dilator muscle function at baseline and during application of an inspiratory load during wakefulness increased in normal females during the luteal compared to the follicular phase [81]. In females without OSA, upper airway resistance during sleep was lower in the luteal compared to the follicular phase, in agreement with a "protective" effect of progesterone [82]. However, the response to inspiratory muscle loading during sleep was not accompanied by increased upper airway dilator muscle activity in normal females compared to normal males [83]. More recent data showed that compensatory responses to prolonged upper airway obstruction during non-REM sleep were more effective in obese females than in obese males [84]. Several factors may account for such differences, including a lower airflow demand secondary to lower metabolic rate in females, differences in ventilatory timing responses to obstructed upper airways [85], lower chemoresponsiveness [86] or ventilatory response to arousal [87, 88]. In addition, experimental studies in rodents suggest that females are more resistant to the detrimental effects of chronic intermittent hypoxia, an effect possibly mediated by oestrogens [89, 90]. Although some controversies still exist due to species-dependent differences [91], recent human studies suggested a role of leptin in the modulation of neural compensatory mechanisms at the upper airway level [92]. Since plasma levels of leptin are higher in females, leptin represents a potential protective factor in obese females against upper airway obstruction, possibly acting at multiple levels. The therapeutic use of intranasal leptin has been successfully tested in obese animals [93].

Recent data indicate that expression of oestrogen receptor-α is decreased in the upper airway muscles of males with OSA compared to controls, possibly contributing to changes in muscle fibre types in OSA. However, no similar data in females have been collected thus far [94].

In summary, upper airways in females are less collapsible and more stable during sleep than in males, through a variety of mechanisms which involve sex hormones but are not limited to them. More efficient active responses of upper airways during respiratory events, different body fat distribution and lower instability of respiratory drive after arousals probably contribute to the lower susceptibility to respiratory events during non-REM sleep in females. Currently, there are large efforts to physiologically phenotype OSA patients in order to personalise treatment [95]. To date, the question whether specific physiological phenotypes occur in females with OSA remains unanswered, and deserves further study.

The role of hormone replacement therapy

Approximately 25 years ago, sex steroid-based hormone replacement therapy (HRT) was no longer prescribed worldwide because of the negative results of randomised controlled trials showing that oestrogen did not confer protection against cardiovascular disease and might increase the risk of breast cancer [96]. More recently, a protective effect of oestrogen-based HRT has emerged, especially in females starting treatment early in the perimenopausal period, whereas treatment initiation at a later time did not confer any benefit [96].

As far as sleep disordered breathing is concerned, the possible protective role of HRT in post-menopausal females with OSA was assessed in studies involving small numbers of subjects. In females without symptoms of sleep disordered breathing, respiratory events during sleep were few and unaffected by oestrogen replacement therapy [97], while treatment with medroxyprogesterone acetate (MPA) improved the inspiratory flow pattern in females with airflow limitation during sleep [49, 98]. In females with OSA, the effects of HRT have been controversial. One study found no effect of MPA 30 mg·day^{-1} [99]. Another study reported improved breathing during sleep after progestin and oestrogen HRT in females with mild OSAS in post-surgical menopause [100]. Cistulli *et al.* [101] found a decrease in AHI in REM sleep after HRT, while another study reported decreased AHI after treatment with oestrogens in post-menopausal females with moderate OSAS [102]. More recently, a randomised controlled trial in post-menopausal females with OSA treated with MPA after discontinuing CPAP for a few weeks showed no protective effects of MPA against respiratory events during sleep [103].

Metabolic changes

Females have a different fat distribution pattern compared to males [104]. Adipose tissue tends to be peripherally distributed in females, and centrally distributed in males, with a higher percentage of visceral fat in males compared to females with a similar BMI. Such differences reflect a role of sex hormones during the fertile age [105], tending to disappear after the menopause, and may influence the prevalence and severity of OSA in females. It has long been known that females are usually more obese than males for a similar level of OSA severity and OSA can be predicted by visceral abdominal fat in males, and by peripheral and total fat in females [106–109]. The metabolic syndrome (MetS), a cluster of risk factors for

visceral obesity and insulin resistance, is often associated with OSA in both sexes [110]. In patients with MetS and OSA, the anthropometric markers of obesity appear to be similar in males and females [111]. Finally, a recent study in young morbidly obese females awaiting bariatric surgery found that the waist-to-hip ratio was the best single predictor of AHI, even though it accounted for only 20% of total variance [112]. Therefore, menopausal status and degree of obesity interact variably in determining adipose tissue distribution and metabolic variables in females, and probably affect OSA prevalence.

The literature on OSA-associated metabolic changes does not provide satisfactory data to explore whether females show particular metabolic changes compared to males. This reflects the predominance of males in patient cohorts, and the fact that data analysis is usually adjusted for age, sex and BMI, which are the variables of interest in studies on OSA according to sex. Conversely, studies in females indicate a similar relationship between altered glucose metabolism and OSA severity as in males [113]. Females show a high frequency of respiratory events exclusively in REM sleep [114]. In diabetic patients, derangement in glycaemic control was associated only with AHI in REM, possibly due to the increased sympathetic activity typical of this sleep phase [115]. According to these data, females may be at relatively higher risk of OSA-associated glucose disturbances compared to males, despite an overall AHI which is lower than in males. To date, no study has tested such a hypothesis. In relatively young (mean age 37 years), overweight/obese subjects without comorbidities other than well-controlled hypertension or hypothyroidism, insulin resistance was documented in males, but not in females with OSA [44], in agreement with the more favourable metabolic pattern associated with peripheral distribution of adipose tissue.

In summary, knowledge on whether metabolic aspects of OSA show differences between males and females is still rather limited. Sex-related differences in adipose tissue distribution are well known, and are probably involved in both upper airway function and metabolism. Such differences tend to disappear after menopause.

Treatment of OSA/OSAHS

To date, there are few studies primarily aimed at investigating sex differences in treatment response in patients with OSA/OSAHS [8]. The "gold standard" treatment for moderate to severe OSAHS continues to be CPAP, which is applied to both sexes equally [3]. Average adherence rates do not appear to differ significantly between males and females [116, 117]. Differences in type of interface chosen, pressures required to eliminate apnoeas/hypopnoeas, humidifier use and overall treatment satisfaction do not appear to differ between the sexes when controlled for BMI, age, AHI and usage [116, 117].

With the pathophysiology of OSA in females so different from males as discussed above, it is interesting to note that very little research has been undertaken in assessing treatment algorithms in CPAP machines. Bench testing has found significant differences between commercially available CPAP devices respond to flow limitation in female patients [118] and one commercially available CPAP device addressing female-specific OSA pathophysiology was found to be as effective as standard CPAP in reducing residual flow limitation using lower mean pressures in a double-blind randomised controlled trial [119].

With exciting new work being undertaken to phenotype OSA according to the predominant physiological abnormality, it is surprising that little effort has been made to examine the prevalence of these differences and their potential impact on personalising treatment between the sexes [95, 120].

Other treatment options apart from CPAP, such as mandibular repositioning splints (MRS) and therapies applied to a minority of patients such as hypoglossal nerve stimulation and surgery for OSA/OSAHS have been trialled in both males and females, although the percentage of females is generally low in published studies [121, 122]. Two studies have suggested that MRS use is higher in females compared to males, particularly in mild OSA/OSAHS [123, 124]. Weight loss, which ideally should comprise part of the treatment of every overweight and obese person with OSA/OSAHS, can differ between the sexes. One study has shown that intensive lifestyle modifications can result in greater weight loss in females in both the short- and long-term [125], but the drop in AHI is smaller compared to that in males [126]. As discussed earlier, in post-menopausal females, early studies suggested that HRT led to a reduction in OSA severity [49, 98–102], but a more recent randomised controlled study has failed to show such an effect [103], rendering this form of treatment unlikely to be specifically recommended for treating OSA at present. Future studies will have to consider variables such as age, time from beginning of menopause and type of HRT used, as well as occurrence of overweight/obesity, sleepiness and depression, as all these factors may affect the response.

Discussion

Table 1 summarises the unique characteristics of females with OSA/OSAHS. Even when using very broad definitions, OSA/OSAHS is less prevalent in females than in males in all countries. The clinical

TABLE 1 Characteristics unique to females with obstructive sleep apnoea (OSA) or OSA/hypopnoea syndrome (OSAHS) in their clinical presentation, pathophysiology, comorbidities and treatment response compared to males with OSA/OSAHS

Pathophysiology of OSA/OSAHS	Upper airway less collapsible Shorter airway length, which increases with age Lower critical closing pressure Subcutaneous and peripheral fat distribution Prolonged partial upper airway obstruction leading to increased respiratory resistance, increased end-tidal CO_2 Lower chemoresponsiveness Lower metabolic rate Less respiratory drive instability Progesterone stimulates ventilation Higher CO_2 sensitivity and lower upper airway resistance during the luteal phase of menstrual cycle (high progesterone levels) Premenopausal females have lower apnoeic thresholds
In pregnancy	Reduction in airway size, fluid retention, weight gain, nasal obstruction Reduced functional respiratory capacity and residual volume Increased minute ventilation High progesterone leading to increased upper airway dilator muscle activity Enhanced chemoreceptor responsiveness Right-shifted oxygen dissociation curve Increased maternal heart rate and stroke volume Less time in the supine position
Clinical presentation	
Overall	More likely to present with insomnia, mood disturbances, nightmares, fatigue, lack of energy Greater impairment of quality of life Higher healthcare expenditure Higher rate of sick leave, impaired work performance, divorce Hypothyroidism more common Less intense snoring
Pregnancy	Increased snoring as pregnancy progresses Snoring/OSA associated with pregnancy-induced hypertension, intra-uterine growth retardation, hypertension and diabetes mellitus
Menopause	Clinical presentation attributed to menopause Doubling of OSA/OSAHS prevalence in menopause
Findings on sleep studies (polysomnography/polygraphy)	Lower AHI overall Shorter apnoeic episodes More frequent subcriterion events Lower proportion of supine OSA Higher frequency of REM-related OSA Longest apnoeas associated with more severe arterial oxygen desaturation Increased sleep fragmentation in pregnancy
Comorbidities	More systemic inflammation for given AHI More peripheral and subcutaneous fat distribution premenopausally Pharyngeal collapsibility in females awaiting bariatric surgery correlates with degree of insulin resistance
Responses to treatment	CPAP trial should be symptom-driven (AHI lower for given clinical symptoms) Lower CPAP pressures more common MRS use may be higher in mild OSA/OSAHS Greater voluntary weight loss sustained, but smaller relative drop in AHI

CO_2: carbon dioxide; AHI: apnoea–hypopnoea index; REM: rapid eye movement; MRS: mandibular repositioning splints.

presentation of OSA/OSAHS in females also differs from that of males, with females being more symptomatic and having a lower AHI even when controlled for age and BMI. As a consequence of the differences in clinical presentation, females with OSA/OSAHS are often underdiagnosed and undertreated compared to males. Females with OSA/OSAHS appear to have more prolonged partial upper airway obstruction as a pathophysiological hallmark of their disorder, but little work has been undertaken in modifying therapies or investigating how these differences may affect physiological phenotypes.

In summary, there are real differences between males and females in the presentation, pathophysiology, comorbidities and responses to treatment of OSA/OSAHS. These differences have not been fully elucidated and can hinder appropriate investigation and treatment due to conscious and unconscious clinical bias. In an era where personalised medicine is increasingly coming to the fore, sex differences should play the most important initial role in phenotyping patients with a view to developing new management strategies.

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