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Original Research

Sex differences in low arousal threshold in obstructive sleep apnea☆

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A B S T R A C T

Background: Obstructive Sleep Apnea Syndrome (OSAS) is the most common sleep-related breathing disorder, considered more prevalent in males. Recent evidences suggest that prevalence of OSAS in females is underestimated, with a clinical phenotype marked by sleep fragmentation, poor sleep quality, and neurobehavioral symptoms. We hypothesized that a low arousal threshold (low AT) may be more common in females, which may underline these clinical and polysomnographic differences.

Methods: In this retrospective multicentric study, 84 females and 93 males with OSA underwent a Home Sleep Apnea Test (HSAT) reviewed by a sleep expert. Low AT was predicted using the Edwards score criteria.

Results: Out of 177 patients, low AT was identified in 60.7 % of females and 40.9 % of males ($p = 0.008$). Stratifying by OSA severity, low AT was more prevalent in patients with mild disease, both in females and males. Among obese patients (Body Mass Index, BMI $\geq$30 kg/m^2), low AT was present in 60.9 % of females compared to 24.3 % of males ($p = 0.001$).

Conclusion: Our findings indicate that a low AT is significantly more prevalent in OSA females, remembering that our female population mainly corresponds to post-menopausal females. This may explain the more pronounced sleep fragmentation and neurobehavioral symptoms in women.

1. Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is characterized by repeated episodes of upper airway collapse during sleep. Although OSAS is traditionally seen as a predominantly male disorder, with an estimated prevalence of 14% in males and 5% in females in the general population [1] and 24% versus 9% in the 30–60 year age group [2], emerging data indicate that the condition in females is frequently underdiagnosed. OSA is defined by the number of apneas and hypopneas per hours of sleep (Apnea Hypopnea Index, AHI), with a diagnosis requiring an AHI >5 events/h in the presence of associated symptoms or comorbidities, or an AHI >15 events/h irrespective of symptoms [3]. Pathophysiologically, OSA results from a combination of a compromised anatomical factor and variable contributions from three functional factors: ventilatory instability or high Loop Gain (LG) neuromuscular dysfunction of the upper airway (poor muscles responsiveness), and low Arousal Threshold (low AT) [4]. Determining the dominant factor in individual patients can facilitate endotyping and the development of targeted therapies [5].

Loop Gain (LG) describes how the respiratory system reacts to change in breathing. It determines the magnitude and time course of the ventilatory response that follows a ventilatory disturbance [6]. Patients with heightened LG exhibit a more responsive system, potentially leading to exaggerated responses to changes in CO_2 levels [7]. In OSA patients with high LG, an exaggerated post apnea hyperventilation could increase the respiratory effort until generating a suction traction of the upper airway or a reduction of the CO_2 value that decrease the drive activity both responsible of subsequent collapsibility of the upper airway.

The arousal threshold (AT) refers to the neuromuscular-mechanical pressure at the end of a respiratory event, responsible for awakening from sleep (arousal), and it can be quantified invasively by an epiglottic or esophageal pressure catheter [8]. In the recent years, literature has shown that apnea does not necessarily end with an arousal [9]. Indeed, patients can reopen the airways when the negative endothoracic pressure during the apnea reaches the threshold of recruitment (Ter). This is defined as the negative endothoracic pressure in which the mechanical and chemical reflexes reopen the airways with a fixed value for each patient [9]. On the other hand, a patient may have a different AT value depending on sleep stages, sleep deprivation in the previous days, hypnotics, alcohol intake etc., which may be different from the

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recruitment threshold. A patient with low AT, during the event reaches the endothoracic pressure that gives an arousal but not the endothoracic pressure of recruitment (AT > Ter), so after the arousal, the airways are not yet completely reopened and may collapse again [10]. A patient with low AT has more arousals from sleep with a ventilatory instability secondary to an increase in ventilation after arousal and also it is followed by an hyperventilation that gives fluctuation in blood CO_2 levels, and so breathing instability [9]. In addition the sleep fragmentation does not allow reaching slow-wave sleep (deep sleep in which respiratory events are less frequent and breathing more stable) [11,12].

In approximately one-third of patients with OSA [13] respiratory events are terminated early because of a low respiratory arousal threshold (low AT), preventing the opportunity for ventilatory drive to build up and restore pharyngeal patency during sleep.

Notably, low AT, which can be noninvasively estimated using the Edwards score [8], appears particularly prevalent in non-obese patients and in those with mild OSAS, and may contribute to poor Continuous Positive Airway Pressure (CPAP) adherence [14]. In contrast to males, females with OSAS often present with a distinct clinical phenotype [15–17], characterized by cognitive and emotional symptoms such as insomnia, anxiety, depression, and non-restorative sleep, despite lower overall AHI and shorter respiratory events [18–20]. For this reason, the most used screening questionnaires for OSA symptoms are not accurate in female patients with OSA [21]. In the study by *Edwards* et al. [8], the strongest independent clinical predictors of low AT during both non-REM and REM sleep, were the overall AHI and nadir Sp_{O2}. The Hypopnea fraction was also a significant predictor of low AT only for non-REM sleep, while sex wasn't a significant predictor of low AT overall. In this study, we hypothesize that a low AT may be more common in females and may account for these clinical and polygraphic differences. The aim of this study is to compare the prevalence of low AT between female and male OSA patients, with additional analyses considering obesity and disease severity.

2. Methods

2.1. Study design and population

This retrospective observational study was carried out at the Pulmonology Unit of the University Hospital of Cattinara (Trieste, Italy), and the Pulmonology Department, Policlinico Umberto I (Rome, Italy) between January 2024 and December 2024. All patients aged over 18 years who met the diagnostic criteria for OSAS were included: AHI >5 events per hour with symptoms or comorbidities, or AHI >15 events per hour [22,23]. Exclusion criteria included the presence of other respiratory and/or neuromuscular diseases, a diagnosis of central sleep apnea (CSA) with a central AHI ≥5 events per hour or an OSA with coexisting central sleep apnea with more than 50 % of central events, a non-respiratory sleep disorders or a diagnosis of Obesity Hypoventilation Syndrome (OHS).

2.2. Data collection and assessment

Patients underwent a Home Sleep Apnea Test (HSAT) according to American Academy of Sleep Medicine (AASM) standards [23] using either the Somnolab 2 (Weinmann, Hamburg, Germany) or Domino Light test (Somnomedics, Randersacker, Germany). Data collected included age, sex, menopausal status (for females), BMI, AHI, nadir SpO_2, hypopnea fraction, Oxygen-Desaturation Index (ODI), mean minimum saturation, and mean durations of apneas and hypopneas. Apneas were defined as ≥90 % airflow reduction for ≥10 s, and hypopneas as ≥30 % reduction for ≥10 s accompanied by ≥ 3 % desaturation [23]. Severity of OSAS was defined by AHI, i.e. mild with 5 < AHI ≤15, moderate with 15 <AHI ≤30 and severe with AHI >30.

2.3. Low arousal threshold (AT) assessment

Low AT was estimated using the Edwards score, which assigns one point for each of the following: AHI <30 events/h, nadir SpO_2 > 82.5 %, and hypopnea fraction >58.3 %. A score of ≥2 was indicative of a low AT [8]. We evaluated the difference in the prevalence of low AT between females and males, and subgroup sensitivity analyses has been performed for low AT, stratifying the population according to the presence of obesity and severity of the disease. Furthermore, we evaluated the prevalence of low AT in females before and after menopause, to detect if low AT is more prevalent in females regardless of menopause.

2.4. Statistical analysis

Patient characteristics are presented as medians with interquartile ranges. Comparisons between groups were performed using Pearson's chi-square test for categorical variables and the Mann-Whitney *U* test for continuous variables. Multivariable analysis was performed using ridge logistic regression with bootstrapping to estimate odds ratios (OR) and 95 % confidence intervals for the Edwards criteria. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS Statistics 2019.

3. Results

One hundred and seventy-seven patients were enrolled from January 2024 to December 2024, according to the previous mentioned inclusion and exclusion criteria, and all of them were included in the final analysis. There were 84 females and 93 males. Results are reported as females vs males. Patients' characteristics are summarized in Table 1.

Age distribution at diagnosis did not show a statistically significant difference between the two groups (62.1 ± 15 Vs 59.1 ± 13, p = 0.095). In contrast AHI distribution is statistically significant different between the two groups: (23.2 ± 20.1 Vs 28.2 ± 19.1, p = 0.020).

Fifty-one (60.7 %, IC95 50.0–70.5 %) females *vs* 38 (40.9 %, IC95 31.4–51.0 %) males had low AT according to the Edwards' score, p = 0.008 (Fig. 1.)

To determine which Edwards criteria is the most associated with the presence of low AT in the two sexes, a descriptive analysis and penalised logistic regression were conducted. Table 2A shows the frequency of

Table 1
Patient characteristics. Age; BMI Body Mass Index; AHI Apnea Hypopnea Index; Nadir SpO2 %, lowest value; Fraction of Hypopneas, hypopneas frequency compared to total events; Oxygen-Desaturation Index (ODI); Mean of minimum saturation values (%); Mean apnea duration, seconds (s); Mean hypopnea duration, s; Postmenopausal females.

Patients' characteristics and polygraphic indices	Females (n = 84)	Males (n = 93)
Age, years (median, IQR, IC95)	62.1 (15) (58.8–65.4)	59.1 (13) (56.5–60.5)
BMI (median, IQR, IC95)	31 (6.9) (29.0–31.6)	29 (6.8) (27.7–31.0)
AHI, n. (median, IQR, IC95)	23.2 (20.1) (19.8–26.6)	28.2 (19.1) (25.2–31.8)
Nadir SpO2, % (median, IQR, IC95)	81.5 (17.5) (78.0–82.0)	81 (10.5) (78.5–84.0)
Fraction of Hypopneas, % (median, IQR, IC95)	46 (0.4) (37.4–52.0)	32 (0.4) (19.0–40.0)
ODI (median, IQR, IC95)	20.2 (24.5) (18.5–25.5)	24.4 (29.7) (22.0–29.6)
Mean of minimum saturation values, % (median, IQR, IC95)	91 (3) (90.0–92.0)	91 (4) (90.0–92.0)
Mean apnea duration, s. (median, IQR, IC95)	19 (8.5) (17.2–21.5)	22.9 (10) (20.0–25.5)
Mean hypopnea duration, s. (median, IQR, IC95)	24 (10.4) (20.0–26.0)	25 (11) (24.0–26.8)
Postmenopausal females, n (%)	77 (91.7 %)	/

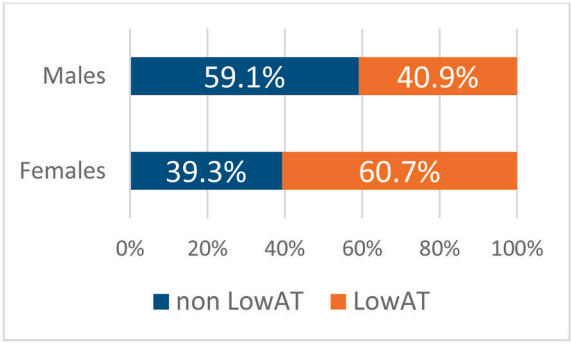

Fig. 1. Prevalence of low AT in females and in males.

Table 2A
Prevalence and predictive role of low AT for each criterion of Edwards score in females.

Edwards criteria	Females(n = 84) (IC95)	Females with low AT (n = 51) (IC95)	OR (IC95 %)
AHI <30, %	76 % (64.8–83.0 %)	98 % (89.8–99.9 %)	6.13 (3–8)
Nadir SpO_2 > 82.5 %, %	52 % (41.0–61.9 %)	80 % (67.0–91.3 %)	1.96 (1–5)
Hypopnea fraction> 58.3 %, %	36 % (26.3 %–46.4 %)	51 % (37.7–64.1 %)	7.63 (4–19)

Edwards' criteria among females with low AT compared to all females included. Among females with low AT, the most common criterion was AHI <30 (98.0 %), followed by nadir of SpO_2 >82.5% (80.4 %) and fraction of hypopneas >58.3 % (51.0 %). However, by ridge logistic regression, the criterion most strongly associated with low AT was fraction of hypopneas >58.3 % (OR 9.72), followed by AHI <30 (OR 3.95) and nadir SpO_2 >82.5 % (OR 2.20).

Table 2B shows that among males the most frequent Edwards criterion was AHI <30 (100 %), followed by nadir of SpO_2 >82.5 % (79 %) and fraction of hypopneas >58.3 % (55 %). The ridge logistic regression showed that the fraction of hypopneas >58.3 % is the most strongly associated with low AT (OR 10), followed by nadir SpO_2 > 82.5 % (OR 8.7) and AHI <30 (OR 5).

We evaluated in each group, females and males, the mean apnea duration in seconds (s), the mean hypopnea duration (s) and the mean of minimum saturation values (%). The mean apnea duration showed a statistically significant difference between the two groups and particularly was shorter in females (19 s ± 8.5 Vs 22.9 s ± 10, p < 0.001). The mean hypopnea duration didn't show a statistically significant difference (24 s ± 10.4 Vs 25 s ± 11, p = 0.148). The mean of minimum saturation values didn't show a statistically significant difference (91 % ± 3 Vs 91 % ± 4, p = 0.691).

When dividing the population in obese (i.e. BMI ≥30 kg/m^2) and non-obese (i.e. BMI <30 kg/m^2) we observed a higher prevalence of obese patients within the female group [47 (58 %) vs 37 (42 %), p = 0.038].

Stratifying for the presence of obesity, there was no statistically significant difference in the prevalence of low AT between females and males within the non-obese subgroup [20 females (60.6 %, IC95 45.0–76.1 %) vs 26 (52 %, IC95 40.5–66.7 %) males, p = 0.4]. Conversely, low AT was more prevalent in females within the obese subgroup [28 females (60.9 %, IC95 45.3–72.4 %) vs 9 males (24.3 %, IC95 11.7–38.1 %), p = 0.001], Fig. 2.

When stratifying for the OSA severity, although the results did not reach statistical significance, a trend towards a higher prevalence of low AT was noted among females in the mild OSA [27 females (96.4 %, IC95 82.3–99.4 %) vs 17 males (85 %, IC95 64.0–94.8 %), p = 0.158], moderate OSA [22 females (62.9 %, IC95 46.3–76.8 %) vs 20 males (50 %, IC95 35.2–64.8 %), p = 0.263] and severe OSA (2 females (9.5 %, IC95 2.7–28.9 %) vs 1 male (3 %, IC95 0.5–15.3 %), p = 0.310], Fig. 3.

We also divided females in two groups, based on the presence of menopause at diagnosis. 7 females out of 84 (8.3 %) were before menopause and 77 out of 84 (91.7 %) were during menopause. There wasn't statistically significant difference in the prevalence of low AT between female not in menopause ad female in menopause.

Table 2B
Prevalence and predictive role of each criterion of Edwards score in males.

Edwards criteria	Males (n = 93) (IC95)	Males with low AT (n = 38) (IC95)	OR (IC95 %)
AHI <30, %	63 % (53.3–72.5 %)	100 % (90.8–100 %)	5 (3–7.8)
Nadir >82.5 %, %	39 % (29.4–48.9 %)	79 % (63.7–88.9 %)	10 (6.5–16.2)
Hypopnea fraction> 58.3 %, %	23 % (14.7–30.3 %)	55 % (40.9–70.8 %)	8.7 (5–13.3)

4. Discussion

Our findings indicate a significantly higher prevalence of low AT in females as a predominant pathophysiological sex-based mechanism and this could explain clinical, polysomnographic and prognostic features of OSA in females.

4.1. Diagnostic implication

Our findings may explain the distinctive clinical features observed in females—such as sleep fragmentation, unrefreshing sleep, and neurobehavioral symptoms—even when AHI values are relatively low. In literature, it is described that females with OSA have an unrefreshing sleep, more respiratory effort-related arousal (RERA), lower AHI than males and shorter events [19], and it is also described that females report more often insomnia, difficulty falling asleep, more awakenings, anxiety and depression [15,24]. These symptoms, more related to sleep in general than to respiratory disturbance, and the different polysomnographic features support the idea that low AT could be the main functional factor in OSA females. A recent work by *Liang-Wen Hang* et al. confirm a lower AT in females compared to males regardless of OSA severity [25].

These findings may also represent the explanation of OSA underestimation in females: both for RERA and flow limitation arousal not scorable with an HSAT, both for symptoms related to mood changes or cognitive performance often not evaluated by clinicians. Our data support previous reports that low AT is more common in non-obese patients [8,26] and in those with mild OSAS [4]. Our female patients had a low AT regardless of obesity. On the other hand, low AT was prevalent in mild disease in both sexes.

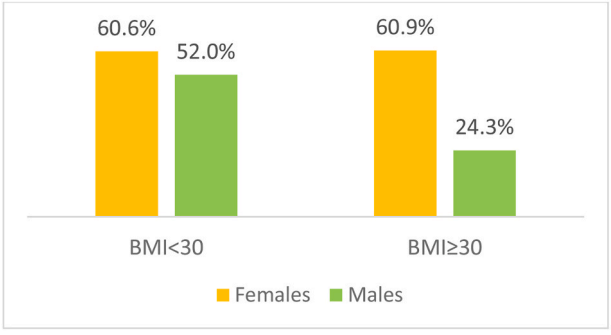

Fig. 2. Prevalence of low AT in females and males in association with obesity (BMI ≥30 kg/m^2).

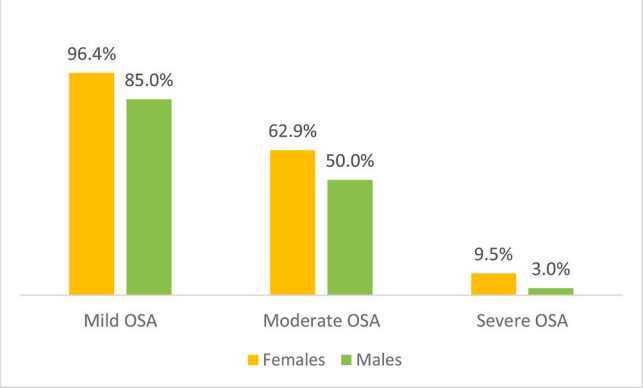

Fig. 3. Prevalence of low AT in females and in males in association with severity.

4.1.1. Hormonal influences

In our study, we also evaluated the prevalence of low AT between females before menopause and females in postmenopausal age, and there wasn't a statistically significant difference between the two groups, maybe due to the poor sample size of premenopausal females. However, it would be useful and appropriate to perform prospective studies to ascertain whether there is a hormonal influence that increases the number of arousals from sleep and decreases the AT in female patients or if the hormonal changes with the menopause could make changes in AT and predispose to OSA. This predisposition could be related to a decrease of estrogen levels in menopause. Indeed, previous studies have demonstrated that estrogen levels were related to good quality of sleep, reduced number of arousal, the increase of deep and REM sleep and also to the increase of the total sleep time [16]. After menopause, the decrease of estrogens, could contribute to sleep fragmentation because of lower AT, and may be associated with poor responsiveness of upper airway muscles related to progesterone decrease.

However, studies regarding the potential role of hormone replacement therapy (HRT) on females patient with OSA are, to date, inconclusive: some epidemiological studies suggest that sleep-disorders breathing is less frequent in HRT users, but interventional studies do not ensure the alleviation of SDB and, as a result, HRT cannot be recommended as treatment for SBD [17,27,28].

4.1.2. Treatment implications

Low AT is responsible not only for a mild disease but also for the low tolerance to CPAP treatment [14,29,30]. The mask and positive pressure in these patients exacerbate micro-fragmentation sleep and unstable breathing [7,12]. Generally, females present more difficulties in coping with CPAP treatment and titration, and maybe it could be due to low AT. Moreover, in the last few years an auto-CPAP machine, with a specific algorithm that varies positive pressure in response to every respiratory event more gradually, has been developed for CPAP titration [31].

Evidences show that preventing arousal with sedatives in appropriately selected patients with a low AT, could yield more stable breathing and less OSA [32]. To date, the more effective drugs able to increase the arousal threshold are triazolam [33] and Z-drugs [34], zolpidem, eszopiclone and zopiclone. Trazodone also could improve arousal threshold [35].

We underlined that in these studies, these drugs have increased the arousal threshold but did not significantly reduce the AHI. However these studies have considered unselected patients [36].

Considering low AT as the main functional trait of OSA in females may lead to important implications in the therapeutic approach to these patients, using drugs alone or in combination with CPAP treatment, or suggesting a greater care of physicians during CPAP titration, with the use of a fixed and lower pressure to start the treatment [31,34], avoiding excessive fluctuation in ventilation [37].

4.1.3. Implications beyond the AHI

Another important finding of our study is the prevalence of shorter events in females. In our sample the median of the mean apnea duration was 19 s in females versus 22.9 s in males ($p < 0.001$) while the hypopnea duration didn't show a significant difference between sexes, although the events in females were shorter. The mean of minimum saturation values didn't show a statistically significant difference (91 % ± 3 Vs 91 % ± 4, $p = 0.691$), but probably because we have missing values in both groups because of the absence of this value in the software Somnolab 2. Shorter events are associated with sleep fragmentation, shorter sleep and excess of sympathetic tone. Shorter events usually are related to low AT (the event ends because the patient wakes up) and it is also related to more sympathetic activation and mortality, as some authors suggest [38].

In a patients with low AT the apnea is shorter because the level of desaturation that triggers arousal is shallow and the arousal comes earlier [20]. Some studies about low AT show that as the respiratory effort increases (mechanical trigger) or a desaturation worsens (chemical trigger), patients with low AT have an arousal and end the event [39,40].

Considering increased symptoms in females with OSA despite low/normal AHI, some authors suggest treatment even if AHI <5 per hour [24].

Finally, among the Edwards criteria, an AHI <30 events/hour is present also in OSA females without a low AT. This evidence highlights that females with OSA usually have a lower AHI than males, with the difference tending to be statistically significant and reflecting that the underdiagnosis of the disease is more common in females. An AHI <30 events/hour does not rule out the presence of greater cortical arousal and increased upper airway resistance typical of female patients. However, AHI <30 events/hour does not consider the frequency, duration and intensity of the event during the night. Females with OSA, compared to males, have a lower overall AHI despite being more symptomatic, and have shorter apneas, lower proportion of supine OSA and less severe oxygen desaturations [19]. Females with OSA present more episodes of airflow limitation although not accompanied by significant obstruction and are responsible for nocturnal hypercapnia due to increased respiratory work and airway resistance, sleep fragmentation with arousal and cognitive impairments, asthenia, depression and insomnia [19]. We performed ridge logistic regression analysis to assess the weight of each Edwards criterion. This analysis showed that, although our population of females with low AT is represented by patients with mild disease (AHI <30 events/hour is the most prevalent criterion), the criterion most associated with low AT is the prevalence of hypopneas in females. This finding may be explained for the negative epiglottal pressure reached which causes arousal before airway collapse. This confirms the prevalence of fragmented sleep in females, but also supports the idea that: 'Females with OSA would rather stay awake than experience apnoea'. This explains the mild disease in terms of AHI and the prevalence of symptoms more related to fragmented sleep than to respiratory disturbances, such as mood disorders, insomnia and memory deficits. The ridge logistic regression analysis produced similar results for each criterion associated with low AT in males because arousal prevents complete upper airway collapse (fraction of hypopneas >58.3 %), severe desaturation does not occur (nadir of SpO_2 >82.5 %) and also severe OSA (AHI> 30) does not occur in patients for whom anatomical factors are less important, such as non-obese OSA patients [8,26]. In the study by Edwards et al. [8], female sex was not a predictor for low AT, however, in the supplementary data of the study, the authors underlined that their findings should be interpreted cautiously as a possible reflection of the small sample size of women compared to men. Furthermore, considering that the AT was measured in only 60 % of the women, and that gender AT difference was not the main end point of Edwards study, we do not consider our results in contrast with the previous studies.

4.1.4. Limitations of the study and future research

A limitation of our study is the use of HSAT, which does not capture EEG data necessary to fully assess arousal and respiratory effort-related arousal (RERA). However, the re-analysis of the cardiorespiratory monitoring pattern performed on each patient in the two different sleep centres to confirm the presence of the polygraphic features of low AT described by Bosi et al., [41] supports our results. In this study, authors underlined as the presence of flow limitation arousal followed by a deep breath as well as a constant and progressive increase of upper airway resistance followed by a deep breath, could be suggestive of a low AT. The use of HSAT to characterize the endotype is extremely important for clinicians, because for economical and practical reasons is the most frequently used diagnostic test for Obstructive Sleep Apnea.

Future studies should evaluate prospectively the prevalence of low AT in males and in females using complete polysomnography, giving strength to the causative role of low AT, avoiding bias related to retrospective studies, in particular selection bias. It would be also useful compare the differences between the Respiratory Disturbance Index (RDI) [23] and AHI in males and females. A higher difference between RDI and AHI in females could support the greater prevalence of low AT.

Future studies should also consider a larger sample of premenopausal women to have a reliable comparison between the two groups (premenopausal and postmenopausal) and so the real differentiation between prevalence of low AT.

5. Conclusion

Our study demonstrates that low AT is significantly more prevalent in OSA females compared to males, remembering that our female population mainly corresponds to post-menopausal females. This finding offers a pathophysiological explanation for the unique clinical and polysomnographic features seen in females and highlights the need for personalized treatment strategies based on a sex-approach. Recognizing low AT as a key pathophysiological trait in females may have important diagnostic, prognostic, and therapeutic implications.

CRediT authorship contribution statement

Gloria Maria Citton: Writing – original draft. **Caterina Antonaglia:** Writing – original draft. **Antonio Fabozzi:** Writing – original draft. **Alessia Steffanina:** Writing – review & editing. **Silvia Giannone:** Visualization. **Mattia Manna:** Data curation. **Giulia Prezioso:** Visualization. **Chiara Torregiani:** Writing – review & editing. **Paola Confalonieri:** Visualization. **Francesco Salton:** Formal analysis. **Barbara Ruaro:** Methodology. **Paolo Palange:** Writing – review & editing. **Marco Confalonieri:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appared to influence the work reported in this paper.

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