

Accepted Manuscript

Impact of sex and menopausal status on the prevalence, clinical presentation, and comorbidities of sleep-disordered breathing

Raphael Heinzer, Helena Marti-Soler, Pedro Marques-Vidal, Nadia Tobback, Daniela Andries, Gérard Waeber, Martin Preisig, Peter Vollenweider, José Haba-Rubio



PII: S1389-9457(18)30298-3

DOI: [10.1016/j.sleep.2018.04.016](https://doi.org/10.1016/j.sleep.2018.04.016)

Reference: SLEEP 3736

To appear in: *Sleep Medicine*

Received Date: 8 November 2017

Revised Date: 11 March 2018

Accepted Date: 16 April 2018

Please cite this article as: Heinzer R, Marti-Soler H, Marques-Vidal P, Tobback N, Andries D, Waeber G, Preisig M, Vollenweider P, Haba-Rubio J, Impact of sex and menopausal status on the prevalence, clinical presentation, and comorbidities of sleep-disordered breathing, *Sleep Medicine* (2018), doi: 10.1016/j.sleep.2018.04.016.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Impact of sex and menopausal status on the prevalence, clinical presentation, and comorbidities of sleep-disordered breathing

Raphael Heinzer ^{a,b,*}, Helena Marti-Soler ^c, Pedro Marques-Vidal ^d, Nadia Tobback ^a,
Daniela Andries ^a, Gérard Waeber ^d, Martin Preisig ^e, Peter Vollenweider ^d, José Haba-Rubio
^a

^a *Center for Investigation and Research in Sleep (CIRS), Lausanne, Switzerland*

^b *Pulmonary Department, University Hospital of Lausanne, Lausanne, Switzerland*

^c *Institute of Social and Preventive Medicine, University of Lausanne, Lausanne, Switzerland*

^d *Department of Medicine, Internal Medicine, University Hospital of Lausanne, Lausanne, Switzerland*

^e *Psychiatry Department, University Hospital of Lausanne, Lausanne, Switzerland*

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Published online

Keywords:

Sleep apnea

Menopause

Prevalence

Hypertension

Diabetes

Metabolic syndrome

Depression

* Corresponding author at: Center for Investigation and Research in Sleep and Pulmonary Department, Lausanne University Hospital of Lausanne (CHUV), Lausanne University, Rue du Bugnon 46, 1011 Lausanne, Vaud, Switzerland. Tel.: +41 21 314 67 48; fax: +41 21 314 67 53.

E-mail address: raphael.heinzer@chuv.ch (R. Heinzer).

ABSTRACT

Objective: Sleep-disordered breathing (SDB) is currently considered as a unique condition, but it has been suggested that the prevalence, clinical presentation, and associated conditions may differ by sex or by menopausal status in women. We aimed to assess the prevalence of SDB and associated comorbidities in pre- and postmenopausal women compared with men.

Methods: Participants of the population-based HypnoLaus Sleep Cohort study underwent polysomnography in their home environment and had extensive phenotyping for diabetes, hypertension, metabolic syndrome, and depression.

Results: A total of 2121 subjects (age 40–85 [59 ± 11] years, body mass index 25.6 ± 4.1 kg/m², 1024 men and 1097 women [769 postmenopausal]) were included. SDB prevalence based on an apnea–hypopnea index of $>5/h$, $>15/h$, $>20/h$, and $\geq 30/h$, respectively, was 83.8%, 49.7%, 37.5%, and 22.0% in men; 35.1%, 8.6%, 3.3%, and 1.3% in premenopausal women; and 71.6%, 29.4%, 20.7%, and 10.1% in postmenopausal women. In multivariable models, SDB severity was significantly associated with hypertension in women ($p = 0.007$) (mainly in postmenopausal women) but not in men ($p=0.065$), with diabetes in men ($p = 0.021$) but not in women overall ($p = 0.853$) or in postmenopausal women ($p = 0.725$), with metabolic syndrome in men ($p = 0.002$) and women ($p < 0.001$), and with depression in women ($p = 0.007$) but not in men ($p = 0.853$).

Conclusion: SDB prevalence in this middle-aged to-older population was high, particularly in men and postmenopausal women. SDB was associated with hypertension and depression exclusively in women, whereas an association with diabetes was present only in men. These findings suggest that the SDB definition and management recommendations may need to be adapted to these groups' specificities.

1. Introduction

Obstructive sleep apnea is the most common form of sleep-disordered breathing (SDB) and is characterized by repetitive complete or partial collapses of the upper airway during sleep. The prevalence of SDB has been increasing steadily over time, in part due to the global rise in obesity [1–3]. Although SDB has traditionally been considered a predominantly male disease, with reported prevalence rates up to 49% in middle-aged to older men and up to 23% in middle-aged to older women [4–6], there is increasing interest in female SDB, how this differs from the disease in males, and how these differences might influence approaches to diagnosis and treatment [7,8].

It has been suggested that discrepancies between males and females in the prevalence of SDB could be a result of women being misdiagnosed or underdiagnosed [9]. This may be because women present with different symptoms compared with men [7], because other diagnoses are preferentially considered over SDB in women with excessive daytime sleepiness (eg, depression) [9], because of lifestyle and sociocultural factors [10], or because men might have more severe SDB and are therefore more likely to be diagnosed and referred for specialist care [9]. There are also physiological differences between males and females, including a shorter upper airway [11] and a less collapsible airway [12] in women, and differences in sleep architecture [13,14].

There is increasing awareness of the importance of comorbidities in sleep-disordered breathing. Women with SDB are more likely than their male counterparts to develop a number of comorbid conditions, including mood disturbances (eg, anxiety and depression), hypothyroidism, cognitive impairment, and dementia [15,16]. It is also possible that women with moderate sleep apnea may be more susceptible to the adverse cardiovascular consequences of SDB than men, having been shown to have more marked endothelial

dysfunction [17]. A recent analysis of a large health claims database highlighted sex differences between SDB patients with respect to the occurrence of different comorbidities [18]. Moreover, a prospective epidemiological study with a 13-year follow-up showed that SDB was associated with incident heart failure or death among women only [8]. However, data regarding the prevalence of SDB and its impact on health among women are scarce, as well as the role of menopausal status in women on SDB-related comorbidities.

The HypnoLaus Sleep Cohort study was designed to assess the prevalence of sleep disorders such as SDB using state-of-the-art polysomnographic recording techniques and updated definitions in a general unselected population. This analysis determined the prevalence and characteristics of SDB in women, as well as the differences in SDB-related comorbidities among men, premenopausal women, and postmenopausal women.

2. Patients and methods

2.1. Study population

The HypnoLaus Sleep Cohort study, described previously [6], included a random subset of the population-based CoLaus/PsyCoLaus cohort [19,20], in whom sleep-related complaints and habits were investigated using the Pittsburgh Sleep Quality Index [21], the Epworth Sleepiness Scale (ESS) [22], as well as the Berlin questionnaire [23], the NoSAS score [24], and the STOP-Bang score [25]. The ethics committee of the University of Lausanne approved the CoLaus/PsyCoLaus cohort study and the HypnoLaus Sleep Cohort study. Written informed consent was obtained from all participants.

Within the CoLaus/PsyCoLaus cohort, various clinical tests were performed to investigate the association of SDB with cardiovascular, metabolic, and psychiatric comorbidities. We measured blood pressure three times on the left arm and calculated the average of the last two readings. We defined arterial hypertension as either systolic blood pressure of 140 mm Hg or

higher, diastolic blood pressure of 90 mm Hg or higher, or current use of antihypertensive drugs. We calculated the waist-to-hip ratio as the ratio of the circumference of the waist to that of the hip, as recommended by World Health Organization. We measured neck circumference between the mid-cervical spine and the mid-anterior neck, just below the laryngeal prominence, if palpable. We obtained a fasting blood sample for various analyses, including measurement of glucose concentration and lipids. We defined diabetes as either fasting blood glucose of 126 mg/dL or higher or current drug treatment for diabetes. We defined metabolic syndrome according to the Adult Treatment Panel III (ATP-III) report [26]. Participants self-reported their menopausal status and use of hormonal replacement therapy (for women), and alcohol drinking habits and the number of alcoholic drinks taken during the evening preceding the polysomnographic recording. We used the semistructured Diagnostic Interview for Genetic Studies to diagnose a current major depressive episode, which we defined according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).

2.2. Polysomnography

HypnoLaus participants underwent full polysomnography (PSG) at home between September 2009 and June 2013 in Lausanne, Switzerland. Certified technicians equipped the subjects with a PSG recorder (Titanium, Embla® Flaga, Reykjavik, Iceland) between 17:00 and 20:00 at the Center for Investigation and Research in Sleep (CIRS, University Hospital of Lausanne, Switzerland). All sleep recordings took place in the subjects' home environment and in accordance with the American Academy of Sleep Medicine (AASM) 2007 recommended setup specifications [27]. Breathing was recorded using nasal pressure sensors. Subjects currently being treated for SDB ($n = 38$) were asked to discontinue their treatment 1 week prior to the sleep recording. Two trained sleep technicians who were unaware of the

results of screening questionnaires manually scored the PSG recordings using Somnologica software (Version 5.1.1, Embla® Flaga, Reykjavik, Iceland). Each recording was reviewed by an expert sleep physician, and random checks were performed by a second sleep expert. Quality control for the concordance rate between the two PSG scorers was implemented periodically to ensure that both scorers achieved at least a 90% level of agreement for sleep stages and respiratory events and an 85% level of agreement for arousals [28]. Apnea was defined as a decrease in airflow of at least 90% from baseline, lasting 10 seconds or longer. Hypopneas were scored using the 2012 AASM criteria [29] ($\geq 30\%$ drop in airflow, lasting at least 10 seconds associated with either an arousal or a $\geq 3\%$ fall in oxygen saturation). The average number of apneas and hypopneas per hour of sleep (apnea–hypopnea index [AHI]) was calculated. As in the previously reported analysis of overall SDB prevalence in the HypnoLaus study population [6], this analysis defined significant SDB as an AHI of >20 events per hour.

2.3. Statistical analysis

All statistical analyses were performed using Stata version 11 (Stata Corporation, College Station, TX, USA) and R software. Data were summarized as the number of participants (percentage or 95% confidence interval [CI]), mean (standard deviation [SD]), and median (interquartile range [IQR]). Bivariate analyses were performed using the χ^2 test, Student *t* test, or Wilcoxon rank-sum test. Logistic regression models were used to assess the associations between various demographic and clinical variables and significant SDB (AHI >20 /h). AHI quartiles were defined as follows: quartile 1, 0–4.2 events per hour; quartile 2, 4.3–9.9 events per hour; quartile 3, 10.0–20.6 per hour; quartile 4, >20.6 events per hour). Significant results were considered for a two-sided test with $p < 0.05$.

3. Results

3.1. Study population

A total of 3043 individuals from the CoLaus/PsyCoLaus study cohort were invited to undergo at-home PSG; 2168 (71%) of these individuals accepted the invitation. Of the 2168 PSG recordings, 60 (3%) had technical problems resulting in insufficient data; 54 participants underwent a second recording, and six participants declined. A total of 41 individuals with a total sleep time of less than 4 hours were excluded because of the risk of an unbalanced representation of different sleep stages and body position; therefore, 2121 PSG recordings were included in the analysis. A total of 38 subjects were currently treated with continuous positive airway pressure (CPAP), in whom PSGs were performed after 1 week of CPAP withdrawal. Of the 769 menopausal women, 143 were taking hormone replacement therapy. Demographic and clinical characteristics of the study cohort, by sex and menopausal status, are shown in Table 1.

3.2. Prevalence of SDB

The prevalence of SDB across a range of AHI cut-off values was higher in men than in women, and in postmenopausal versus premenopausal women (Fig. 1). For significant SDB (AHI \geq 20/h), the SDB prevalence was 37.5% in men, 15.6% in women, 3.3% in premenopausal women, and 20.7% in postmenopausal women (Fig. 1). Hypopnea was the most common respiratory event in both men (69% of events) and women (72% of events). Obstructive, central, and mixed apneas comprised 19%, 4%, and 3% of events in men, compared with 16%, 3%, and 1% of events in women, whereas respiratory-related arousals (RERAs) made up 5% of respiratory events in men and 8% in women. None of the participants had central sleep apnea (defined as a central sleep apnea index $>$ 5/h representing

>50% of the respiratory events). Overall, the combined proportion of hypopneas and RERAs was higher, and full apneas lower, in women compared with men (both $p < 0.001$).

Women with significant sleep apnea were older than men and had a slightly lower Epworth Sleepiness Scale score and lower risk of sleeping at the wheel. They had more symptoms of restless legs syndrome and a higher consumption of sleeping pills (Table 2). Menopausal women taking hormone replacement therapy had slightly lower AHI (mean \pm SD adjusted for age and BMI) than the other menopausal women ($12.4 \pm 0.4/h$ vs $10.2 \pm 0.7/h$, $p = 0.006$).

Age, neck circumference, and snoring were significantly associated with SDB in men and postmenopausal women, but not premenopausal women. Body mass index ≥ 25 kg/m² and waist circumference in the highest quartile were only significantly associated with significant SDB in men (Table 3).

3.3. Association with comorbidities

After adjustment for the main confounding variables, increasing AHI (quartiles 2, 3, and 4 compared with quartile 1) was significantly associated with diabetes and metabolic syndrome (but not hypertension and depression) in men, and with depression (especially among premenopausal women), hypertension, and metabolic syndrome (but not diabetes) in women (Fig. 2a, 2b). The association between AHI and metabolic syndrome in postmenopausal women was greater than that in men and premenopausal women (Fig. 2a).

4. Discussion

To the best of our knowledge, this is the first report of the prevalence of SDB and risk of associated comorbidities according to sex and menopausal status from an unselected general population sample using current recording techniques and up-to-date scoring criteria (AASM 2012) [27]. The prevalence of SDB in this middle-aged to older population was higher in men than in women, and in postmenopausal versus premenopausal women, and the clinical presentation and associated comorbidities differed between these groups.

The SDB prevalence rates in our study were higher than previous estimations. In a large, population-based cohort from the United States, the prevalence of SDB (AHI ≥ 10 /h) was 3.9% in men and 1.2% in women [30], much lower than the 49.7% in men and 23.4% in women in our analysis even though we used a higher AHI cutoff of 15/h [6]. The two studies were similar in that the lowest rate of SDB was found in premenopausal women (0.6% in the US cohort and 3.3% in our study). Our prevalence rates were also higher than those reported using data from the Wisconsin Sleep Study and the Episono Study [5,31]. In addition to the different AHI cut-off values used to define SDB, other factors that might have contributed to the different reported prevalence rates include the age of the included subjects and especially the increased sensitivity of the respiratory sensors (nasal pressure rather than a thermistor in previous studies) and the more inclusive scoring criteria currently recommended for respiratory events by the American Academy of Sleep Medicine (AASM 2012) [29], as discussed in a previous report about SDB in the HypnoLaus study [6]. This analysis of data from the HypnoLaus cohort also showed that respiratory events tended to be milder in women versus men, with a greater proportion of hypopneas and respiratory effort-related arousals (RERAs) and a lower proportion of full apnea events. This may be due to differences in the upper airway anatomy between the sexes, with women having a shorter and thus less collapsible pharynx and less central obesity compared to men [11,12,32]. Postmenopausal women using hormonal replacement therapy had slightly lower adjusted mean AHI compared

with those not taking this therapy. Although this difference was statistically significant, the absolute difference of 2.2 events/h in AHI is probably not clinically significant.

Differences between men and women in the prevalence of SDB decrease as age increases, primarily because of a marked increase in the prevalence and severity of SDB in women after menopause [3,5,30,33]. Our findings confirmed a marked difference in the prevalence of SDB in pre- versus postmenopausal women. Comparing anthropometric and demographic characteristics of these two groups of women suggested that postmenopausal women tended to show physical changes that are more similar to those of men, with a higher BMI, neck circumference, and waist-to-hip ratio compared to premenopausal women. It has previously been reported that postmenopausal women have a higher fat mass than prior to menopause, and fat distribution is more likely to be in the upper body and trunk area compared with the lower body [32,34]. Waist circumference has been shown to be associated with SDB in postmenopausal women [35], but we were unable to confirm this in our study. Overall, our data suggest that SDB in premenopausal women may be due to non-obesity-related causes such as upper airway muscle dysfunction, high loop gain, or facial deformities. The pattern of airway obstruction in postmenopausal women has recently been shown to be different from that of premenopausal women [36]. Available evidence showing marked differences in SDB prevalence and manifestations between pre- and postmenopausal women suggest that simply comparing subjects on the basis of sex does not provide an accurate picture, and that menopausal status in women also needs to be taken into account in future studies of SDB.

A novel finding of our study was that SDB-related comorbidities differed between men and women. The lack of association between SDB severity and hypertension in men was unexpected. However, it does provide a potential explanation for the results of studies including predominantly male populations in which treatment of SDB has not had dramatic effects on blood pressure [37–41]. In the same line, a 13-year follow-up study on 752 men

and 893 women free of cardiovascular disease showed an association between SDB and incident heart failure or death exclusively in women [8]. Moreover, a recent randomized control study on women with moderate to severe sleep apnea in Spain showed that 12 weeks of CPAP treatment could yield a significant reduction in diastolic blood pressure, especially in sleepy and hypertensive women [42]. This should stimulate further studies focusing on the effect of SDB treatment on blood pressure specifically in women, which could yield better results than the studies currently available in which mostly men were included.

The data from our study could also help inform decisions about whether to treat SDB as part of comorbidity management. Although SDB severity was significantly associated with the metabolic syndrome in all subjects, and particularly postmenopausal women, we found no relationship between SDB severity and depression in men, suggesting that reductions in the AHI during treatment might have only a minor effect on this comorbidity. Conversely, SDB was associated with diabetes exclusively in men, suggesting that SDB treatment could have a greater effect in this group. Similarly, the presence of moderate to severe sleep apnea in women with a history of hypertension or depression, both of which were significantly associated with SDB severity in our study, should trigger a more urgent need for effective SDB therapy. This association between mood disorders and SDB in women was also confirmed in a recent randomized controlled trial showing that treating symptomatic SDB in women with continuous positive airway pressure for 3 months was able to significantly improve depression, mood state, and anxiety, as well as daytime sleepiness and quality of life, compared with conservative treatment [43].

Overall these differences in the prevalence, clinical presentation and comorbidities of SDB may question the current concept of a single definition of the disease for both sexes and all ages, as proposed by the International Classification of Sleep Disorders (ICSD III). The “normal” apnea–hypopnea index may be different and the association with comorbidities will

also vary among men, premenopausal women, and postmenopausal women, suggesting that the management strategy and treatment recommendations for this condition should probably be adapted accordingly.

The main limitations of this study are the cross-sectional setting and the population studied, which was within a prespecified age range (40–80 years), almost exclusively of white European origin, and with a low prevalence of obesity. This limits the generalizability of our findings to other populations, including those with a younger age, a high prevalence of obesity, or higher proportions of subjects from different ethnic backgrounds. Selection bias might have resulted from almost one-third of subjects (29%) declining to undergo PSG. However, this bias would be very limited, as the characteristics of the HypnoLaus population were similar to those included in the wider population-based cohorts from which they were identified, suggesting that our sample was representative of the general population in the Lausanne area [6]. The interval between clinical assessment and PSG varied between subjects. However, given that the comorbidities studied are all chronic conditions, this is unlikely to materially influence the study findings. Finally, menopausal status was self-reported, and women in perimenopausal transition may have misclassified themselves.

5. Conclusion

Our analysis shows that the prevalence of SDB in an unselected cohort of middle-aged to older subjects varied by sex and women's menopausal status. We also report important differences in the relationship between SDB severity and various comorbidities for men and pre- versus postmenopausal women. These findings highlight the importance of taking sex and women's menopausal status into account when investigating and treating SDB.

ACCEPTED MANUSCRIPT

Conflict of interest

None of the authors have any conflicts of interest to declare.

Acknowledgements

Funding: The HypnoLaus and the CoLaus|PsyCoLaus study were and are supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (grants 3200B0-105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468 and 33CS30-148401), Leenaards Foundation, and Vaud Pulmonary League (Ligue Pulmonaire Vaudoise).

Additional contributions: The authors thank Prof Mehdi Tafti and Prof Vincent Mooser for their important contribution to the HypnoLaus and CoLaus Cohorts, the Lausanne population who volunteered to participate in the CoLaus, PsyCoLaus, and HypnoLaus studies, the whole team of CoLaus and Nicola Ryan, BSc for her medical writing assistance.

Role of the sponsors: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Faculty of Biology and Medicine of Lausanne, the Lausanne University Hospital (CHUV), Leenaards Foundation and Ligue Pulmonaire Vaudoise provided funding for salaries of the technicians who performed sleep recordings. The Swiss National Science Foundation provided funding for the statisticians and supported the initial “CoLaus” cohort. GlaxoSmithKline supported the initial “CoLaus” cohort and provided funding for the polysomnography recorders.

Author contributions: RH and JH-R designed the analysis plan. NT and DA recruited the subjects and performed the sleep studies in the HypnoLaus cohort. DA, NT, JH-R, and RH analyzed the sleep studies. PV, PM-V, MP, and GW provided the cardiovascular and metabolic data from the main cohort (CoLaus-PsyCoLaus). PM-V, HMS, and RH performed the statistical analysis. RH and JH-R analyzed and interpreted the sleep, cardiovascular, and metabolic data. All coauthors critically reviewed the manuscript.

Access to data and data analysis: All authors had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Pelone F, Specchia ML, Veneziano MA, et al. Economic impact of childhood obesity on health systems: A systematic review. *Obesity Rev* 2012;13:431–40.
2. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: Systematic review. *Int J Obes* 2011;35:891–8.
3. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population health perspective. *Am J Respir Crit Care Med* 2002;165:1217–39.
4. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230–5.
5. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177:1006–14.
6. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study. *Lancet Respir Med* 2015.
7. Valipour A, Lothaller H, Rauscher H, Zwick H, Burghuber OC, Lavie P. Gender-related differences in symptoms of patients with suspected breathing disorders in sleep: A clinical population study using the sleep disorders questionnaire. *Sleep* 2007;30:312–9.
8. Roca GQ, Redline S, Claggett B, et al. Sex-specific association of sleep apnea severity with subclinical myocardial injury, ventricular hypertrophy, and heart failure risk in a community-dwelling cohort: The Atherosclerosis Risk in Communities–Sleep Heart Health Study. *Circulation* 2015;132:1329–37.
9. Lin CM, Davidson TM, Ancoli-Israel S. Gender differences in obstructive sleep apnea and treatment implications. *Sleep Med Rev* 2008;12:481–96.

10. Quintana-Gallego E, Carmona-Bernal C, Capote F, et al. Gender differences in obstructive sleep apnea syndrome: A clinical study of 1166 patients. *Respir Med.* 2004;98:984–9.
11. Segal Y, Malhotra A, Pillar G. Upper airway length may be associated with the severity of obstructive sleep apnea syndrome. *Sleep Breath* 2008;12:311–6.
12. Jordan AS, Wellman A, Edwards JK, et al. Respiratory control stability and upper airway collapsibility in men and women with obstructive sleep apnea. *J Applied Physiol* 2005;99:2020–7.
13. Valencia-Flores M, Bliwise DL, Guilleminault C, Rhoads NP, Clerk A. Gender differences in sleep architecture in sleep apnoea syndrome. *J Sleep Res* 1992;1:51–3.
14. Yamakoshi S, Kasai T, Tomita Y, et al. Comparison of clinical features and polysomnographic findings between men and women with sleep apnea. *J Thorac Dis* 2016;8:145–51.
15. Greenberg-Dotan S, Reuveni H, Simon-Tuval T, Oksenberg A, Tarasiuk A. Gender differences in morbidity and health care utilization among adult obstructive sleep apnea patients. *Sleep* 2007;30:1173–80.
16. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 2011;306:613–9.
17. Faulx MD, Larkin EK, Hoit BD, Aylor JE, Wright AT, Redline S. Sex influences endothelial function in sleep-disordered breathing. *Sleep* 2004;27:1113–20.
18. Mokhlesi B, Ham SA, Gozal D. The effect of sex and age on the comorbidity burden of OSA: an observational analysis from a large nationwide US health claims database. *Eur Respir J* 2016;47:1162–9.

19. Firmann M, Mayor V, Vidal PM, et al. The CoLaus study: A population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 2008;8:6.
20. Preisig M, Waeber G, Vollenweider P, et al. The PsyCoLaus study: Methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. *BMC Psychiatry*. 2009;9:9.
21. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
22. Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep* 1991;14:540–5.
23. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;131:485–91.
24. Marti-Soler H, Hirotsu C, Marques-Vidal P, et al. The NoSAS score for screening of sleep-disordered breathing: A derivation and validation study. *Lancet Respir Med* 2016;4:742–8.
25. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: A tool to screen patients for obstructive sleep apnea. *Anesthesiology* 2008;108:812–21.
26. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–3421.

27. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications. Westchester, PA: American Academy of Sleep Medicine; 2007.
28. Redline S, Sanders MH, Lind BK, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. *Sleep* 1998;21:759–67.
29. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012;8:597–619.
30. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: Effects of gender. *Am J Respir Crit Care Med* 2001;163:608–13.
31. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Med* 2010;11:441–6.
32. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. *Am J Clin Nutr* 1992;55:950–4.
33. Dancy DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. *Chest* 2001;120:151–5.
34. Tremollieres FA, Pouilles JM, Ribot CA. Relative influence of age and menopause on total and regional body composition changes in postmenopausal women. *Am J Obstet Gynecol* 1996;175:1594–1600.
35. Polesel DN, Hirotsu C, Nozoe KT, et al. Waist circumference and postmenopause stages as the main associated factors for sleep apnea in women: A cross-sectional population-based study. *Menopause* 2015;22:835–44.

36. Koo SK, Ahn GY, Choi JW, et al. Obstructive sleep apnea in postmenopausal women: a comparative study using drug induced sleep endoscopy. *Brazil J Otorhinolaryngol* 2016.
37. Gottlieb DJ, Punjabi NM, Mehra R, et al. CPAP versus oxygen in obstructive sleep apnea. *N Engl J Med* 2014;370:2276–85.
38. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: A randomized controlled trial. *JAMA* 2012;307:2161–8.
39. Barbe F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: A randomized, controlled trial. *Ann Intern Med* 2001;134:1015–23.
40. Robinson GV, Smith DM, Langford BA, Davies RJ, Stradling JR. Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. *Eur Respir J* 2006;27:1229–35.
41. Bratton DJ, Stradling JR, Barbe F, Kohler M. Effect of CPAP on blood pressure in patients with minimally symptomatic obstructive sleep apnoea: A meta-analysis using individual patient data from four randomised controlled trials. *Thorax* 2014;69:1128–35.
42. Campos-Rodriguez F, Gonzalez-Martinez M, Sanchez-Armengol A, et al. Effect of continuous positive airway pressure on blood pressure and metabolic profile in women with sleep apnoea. *Eur Respir J* 2017;50.
43. Campos-Rodriguez F, Queipo-Corona C, Carmona-Bernal C, et al. Continuous positive airway pressure improves quality of life in women with OSA. A randomized-controlled trial. *Am J Respir Crit Care Med* 2016.

ACCEPTED MANUSCRIPT

Fig. 1. Prevalence of sleep-disordered breathing by in men and women, and by menopausal status in women

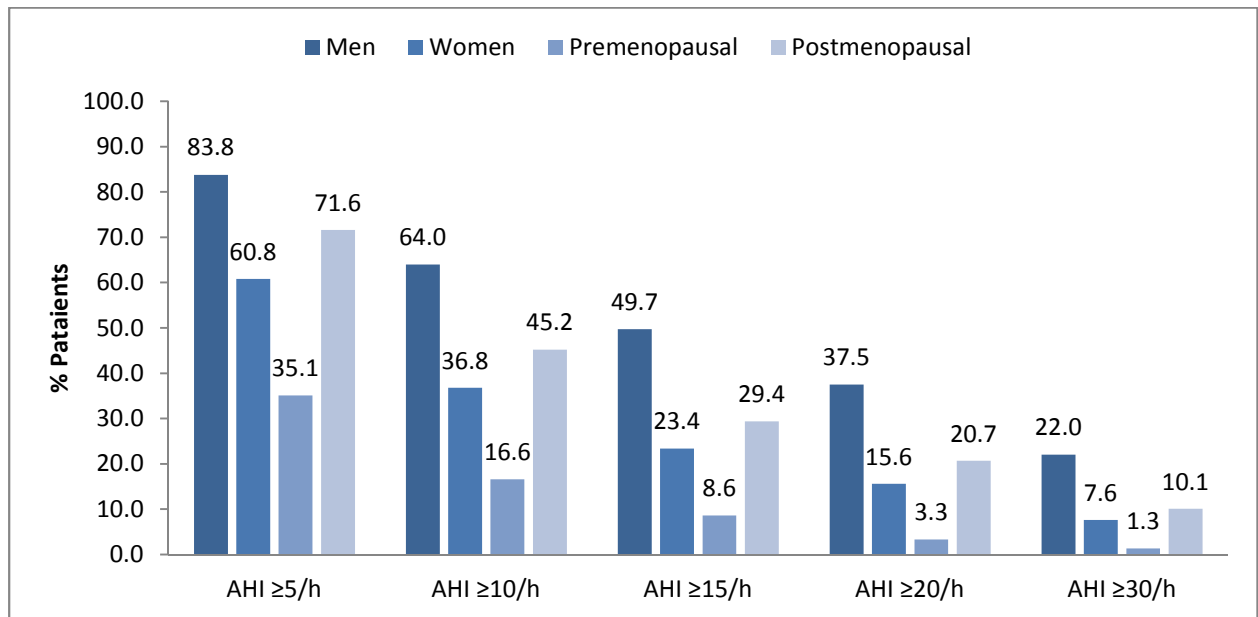
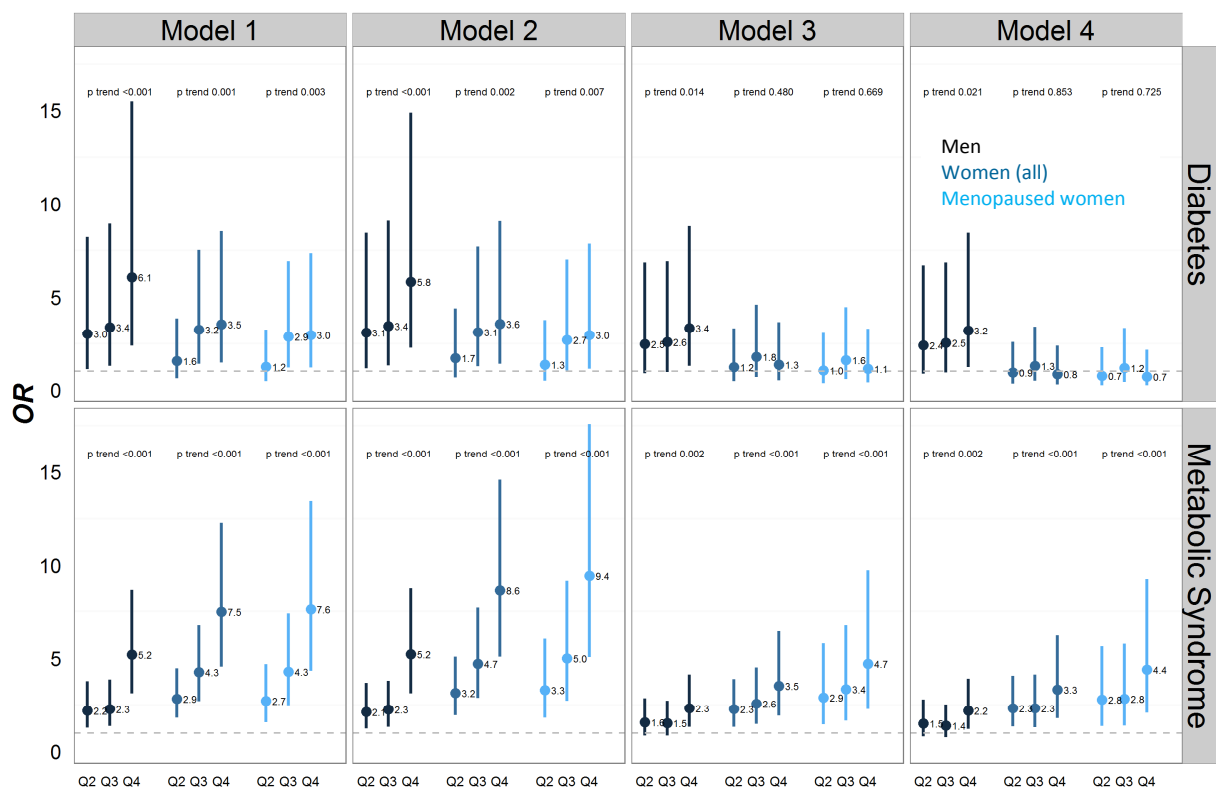
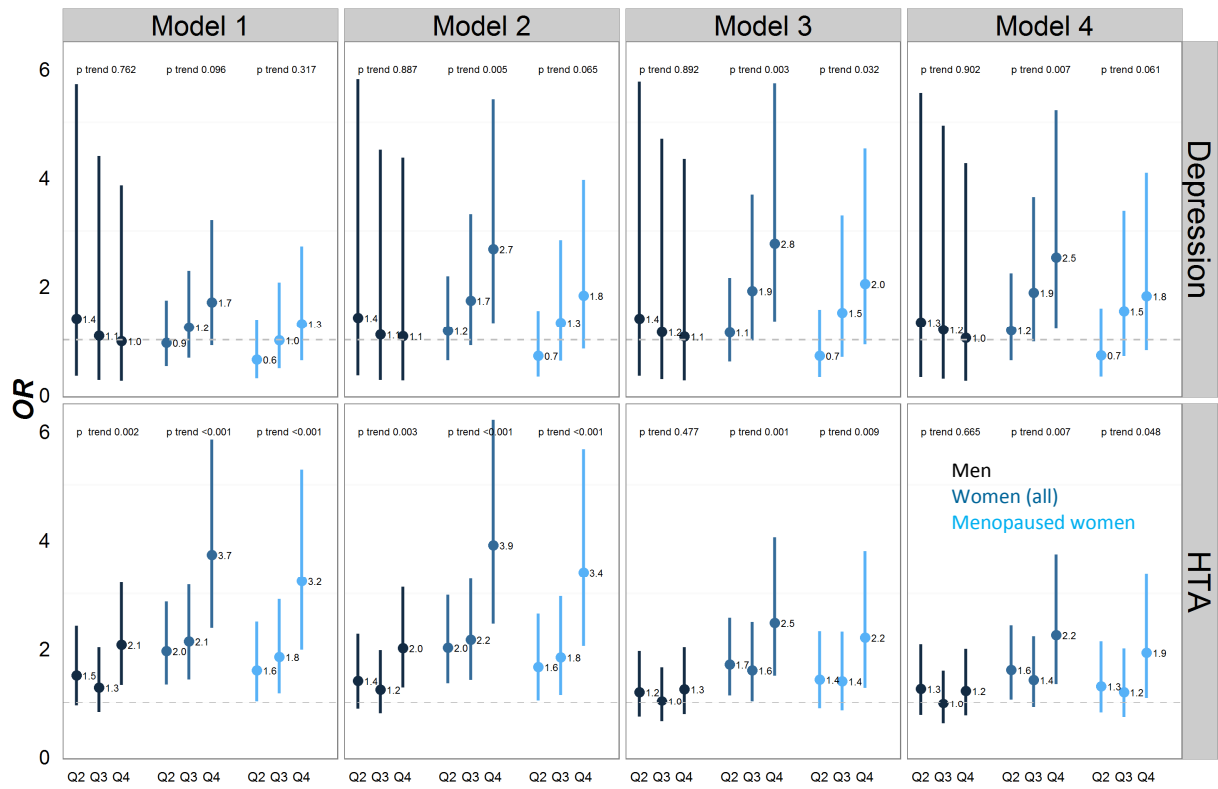


Fig. 2. (a) Estimated risk (odds ratio [OR] with 95% confidence intervals) of diabetes and metabolic syndrome according to sleep-disordered breathing severity, sex, and menopausal status (the models could not be applied to premenopausal women due to the low prevalence of SDB in this group). Model 1, adjusted for age; Model 2, adjusted for age and for alcohol and tobacco consumption; Model 3, adjusted for age, alcohol and tobacco consumption, and body mass index; Model 4, adjusted for age, alcohol and tobacco consumption, body mass index, and neck circumference and waist/hip ratio (diabetes analyses only, because this is part of the metabolic syndrome definition). The *p* value for trend refers to the trend across AHI quartiles (quartile [Q] 1, 0–4.2/h; Q2, 4.2–9.9/h; Q3, 9.9–20.6/h, Q4, >20.6/h).



(b) Estimated risk (odds ratio [OR] with 95% confidence intervals) of hypertension (HTA) and depression according to sleep-disordered breathing severity, sex, and menopausal status (the models could not be applied to premenopausal women due to the low prevalence of SDB in this group). For HTA: Model 1, adjusted for age; Model 2, adjusted for age and for alcohol and tobacco consumption; Model 3, adjusted for age, alcohol and tobacco consumption, and body mass index; Model 4, adjusted for age, alcohol and tobacco consumption, body mass index, and neck circumference and waist/hip ratio. For depression: Model 1, raw data; Model 2, adjusted for age; Model 3, adjusted for age and benzodiazepine use; Model 4, adjusted for age and use of benzodiazepine and antidepressants. Arterial hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or current use of antihypertensive medication. Diabetes was defined as fasting blood glucose level ≥ 7 mmol/L (126 mg/dL) or current use of antidiabetic medication. Metabolic syndrome was defined according to the Adult Treatment Panel III report. Diagnosis of depression was made based on DSM-IV criteria with information collected using the French translation of the semi-structured Diagnostic Interview for Genetic Studies (DIGS). The *p* value for trend refers to the trend across AHI quartiles (quartile [Q] 1, 0–4.2/h; Q2, 4.2–9.9/h; Q3, 9.9–20.6/h, Q4, >20.6/h).



ACCEPTED MANUSCRIPT

Table 1

Subject demographic data and characteristics at baseline.

	Men (n = 1024)	Women	
		Premenopausal (n = 302) ^a	Postmenopausal (n = 769) ^a
Age, years	58 ± 11	47±4 ^{b,c}	64±9 ^b
Body mass index, kg/m ²	26.2 ± 3.7	24.4±4.6 ^{b,c}	25.4±4.6 ^b
Neck circumference, cm	39.8 ± 2.8	33.8±2.4 ^{b,c}	34.2±2.4 ^b
Waist-to-hip ratio	0.96 ± 0.06	0.87±0.06 ^{b,c}	0.89±0.06 ^b
Alcohol use, n (%)	325 (32.2)	66 (22.3) ^b	160 (21.1) ^b
Current smokers, n (%)	192 (18.9)	61 (20.4)	134 (17.6)
Hypertension ^d , n (%)	497 (48.6)	42 (13.9) ^{b,c}	330 (43.0) ^b
Diabetes ^e , n (%)	145 (14.2)	4 (1.3) ^{b,c}	62 (8.1) ^b
Metabolic syndrome ^f , n (%)	366 (35.7)	35 (11.6) ^{b,c}	236 (30.7) ^b
Depression, n (%)	156 (18.5)	103 (42.0) ^{b,c}	186 (28.6) ^b
ESS score	6 (4-9)	7 (4-10)	5 (3-7) ^b
ESS score >10, n (%)	143 (15.2)	55 (19.2) ^c	54 (7.7) ^b
PSQI score	4 (3-6)	4 (3-7) ^b	5 (3-8) ^b
Apnea–hypopnea index	14.9 (7.1-27.1)	2.8 (1.5-7.3) ^c	9.0 (4.2-17.1)
Berlin score ≥2, n (%)	315 (30.9)	43 (15.2) ^{b,c}	160 (20.9) ^b
STOP-Bang ≥3, n (%)	728 (89.7)	46 (20.0) ^{b,c}	292 (58.5) ^b
NoSAS ≥8, n (%)	640 (73.6)	20 (8.2) ^{b,c}	216 (38.3) ^b

Values are mean ± standard deviation, number of subjects (%), or median (25th to 75th percentile). ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.

- ^a Menopausal status was unknown for 26 women.
- ^b Comparison of women (premenopausal or postmenopausal) versus men.
- ^c Comparison premenopausal women versus postmenopausal women.
- ^d Arterial hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mm Hg and/or a diastolic blood pressure (DBP) ≥ 90 mm Hg, or current use of antihypertensive medication.
- ^e Diabetes was defined as a fasting blood glucose level ≥ 7 mmol/L (126 mg/dL), or current use of antidiabetic medication.
- ^f Metabolic syndrome was defined according to the Adult Treatment Panel III report (ATP-III).

Table 2

Characteristics and symptoms of subjects with an AHI > 20/h.

	Men (n = 382)	Women (n = 167)	
		Premenopausal (n = 10) ^a	Postmenopausal (n = 157) ^a
Age, y	62(11)	47(3) ^{b,c}	68(9) ^b
Snoring, n (%)	277 (83.2)	8 (88.9)	95 (86.4)
ESS score	6 (4-9)	8 (6-10) ^c	5 (2-8)
ESS score >10, n (%)	53 (15.3)	2 (20.0)	12 (9.0)
PSQI score	4 (3-6)	4 (2-13) ^c	6 (3-8)
Depression, n (%)	53 (16.9)	5 (71.4) ^{b,c}	40 (30.1) ^b
Insomnia, n (%)	111 (28.8)	4 (40.0)	50 (31.8)
Nocturia, n (%)	166 (43.5)	4 (40.0)	76 (48.4)
Nightmares, n (%)	43 (11.3)	4 (40.0) ^{b,c}	20 (12.7)
Poor sleep quality, n (%)	54 (14.1)	3 (30.0)	27 (17.2)
Sleeping pill use, n (%)	42 (11.0)	3 (30.0) ^b	39 (24.8) ^b
Witnessed apnea, n (%)	54 (14.1)	2 (20.0) ^b	11 (7.0) ^b
Morning fatigue, n (%)	60 (15.7)	4 (40.0) ^b	31 (19.7)
Sleep at the wheel, n (%)	62 (12.6)	1 (10.0)	8 (5.1) ^b
RLS, n (%)	37 (12.0)	2 (22.2)	37 (28.9) ^b

Values are number of subjects (%) or median (25th to 75th percentile). ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome.

^a Menopausal status was unknown for 26 women.

^b Comparison of women (premenopausal or postmenopausal) versus men ($p < 0.05$).

^c Comparison of premenopausal women versus postmenopausal women ($p < 0.05$).

ACCEPTED MANUSCRIPT

Table 3

Risk of significant sleep-disordered breathing (apnea–hypopnea index >20/h) according to related factors.

	Men		Women			
			Premenopausal		Postmenopausal	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Age, 1 y	1.05 (1.04– 1.07)	<0.001	1.00 (0.83– 1.20)	0.986	1.06 (1.03– 1.09)	<0.001
BMI						
≤25 kg/m ²	1		1		1	
25–30 kg/m ²	1.60 (1.04– 2.46)	0.032	4.30 (0.41– 44.98)	0.223	1.31 (0.70– 2.47)	0.397
>30 kg/m ²	3.11 (1.65– 5.85)	<0.001	2.83 (0.11– 73.67)	0.532	1.90 (0.82– 4.40)	0.136
Neck circumference	1.10 (1.02– 1.19)	0.012	1.22 (0.77– 1.93)	0.394	1.13 (1.00– 1.28)	0.053
Waist-to-hip						

ratio					
Q1	1		1		1
Q2	1.43 (0.90– 2.27)	0.128	0.41 (0.05– 3.15)	0.391	1.12 (0.48– 2.62) 0.800
Q3	1.38 (0.85– 2.26)	0.197	0.39 (0.05– 2.75)	0.345	2.02 (0.95– 4.27) 0.066
Q4	1.88 (1.15– 3.08)	0.013	NA		1.63 (0.72– 3.68) 0.239
Alcohol use	1.04 (0.74– 1.45)	0.818	1.30 (0.20– 8.46)	0.784	1.36 (0.75– 2.47) 0.307
ESS	1.01 (0.97– 1.05)	0.639	1.01 (0.81– 1.26)	0.912	0.98 (0.91– 1.05) 0.588
Snoring	2.15 (1.41– 3.28)	0.000	5.08 (0.53– 48.35)	0.157	3.98 (2.03– 7.83) <0.001

BMI, body mass index; CI, confidence interval; ESS, Epworth Sleepiness Scale; NA, not available; OR, odds ratio; Q, quartile.

Highlights

- Sleep disordered breathing (SDB) is currently considered as a unique condition.
- SDB prevalence was highly different among men, premenopausal women, and postmenopausal women.
- SDB was associated with hypertension and depression only in women and not in men.
- SDB was associated with diabetes exclusively in men and not in women.
- Definition and management of SDB may need to be adapted to these groups' specificities.