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Rapid Eye Movement-Related Sleep-Disordered Breathing:

Influence of Age and Gender

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Abstract

Background—Sleep-disordered breathing (SDB) occurring during rapid eye movement (REM) sleep occurs more frequently in women than men. We sought to characterize REM SDB prevalence by gender and age to identify factors that could account for this discrepancy.

Methods—Subjects with REM SDB were identified among 2,486 patients referred to a university sleep laboratory with an apnea-hypopnea index (AHI) ≥ 5 events per hour. REM SDB was defined as non-REM (NREM) AHI ≤ 15/h and REM AHI/NREM AHI ratio ≥ 2. Regression analyses were utilized to determine factors associated with REM SDB.

Results—REM SDB prevalence was 40.8% in women and 21.0% in men. After adjusting for age and obesity, female sex remained a risk factor for REM SDB (odds ratio, 3.0; 95% confidence interval [CI], 1.8 to 4.2). REM SDB prevalence waned with increasing age in both sexes, such that the odds of having REM SDB fell by 26.7% (95% CI, 15.2 to 38.2%) per decade. REM AHI/NREM AHI decreased with age only in women, falling 10.9% (95% CI, 5.5 to 16.3%) per decade. NREM AHI in women increased the most with age (16.0%; 95% CI, 11.1 to 20.9%) per decade, and least with body mass index (BMI) [13.0%; 9.1 to 16.9%] for every 5-unit BMI increase when compared to REM AHI for women and either index for men.

Conclusions—REM SDB prevalence decreases with age in women as does REM AHI/NREM AHI, perhaps secondary to a disproportionate age-dependent rise in NREM vs REM AHI in

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women. Younger women may be protected from SDB during NREM sleep, even in the face of obesity. These patterns may reflect age-related decreases in female hormones.

Keywords

age; gender; obstructive sleep apnea; rapid eye movement; sleep-disordered breathing

Rapid eye movement (REM)-related sleep-disordered breathing (SDB) is a subcategory of obstructive sleep apnea (OSA) in which respiratory events occur predominantly during REM sleep. While OSA is more common in men,[1] the REM SDB population is comprised chiefly of women, with a gender ratio of approximately 3:1.[2,3] REM SDB accounts for 10 to 36% of OSA, with prevalence among male and female apneics ranging broadly from 8 to 24% and 24 to 62%, respectively.[2–4] In part, this variability in prevalence may be secondary to demographic differences in the sampled populations and inconsistent criteria used to define REM SDB.

Despite these differences, criteria assigned to REM SDB have all contained the ratio of the apnea-hypopnea index (AHI) in REM sleep to AHI in non-REM (NREM) sleep,[2–5] requiring a REM AHI/NREM AHI ratio of at least 2. REM AHI/NREM AHI reflects the extent to which respiratory events are confined to REM sleep because of either an increase in REM-related events or a decrease in NREM-related respiratory events. In a prior study,[3] we found that women with REM SDB had significantly higher REM AHI and lower NREM AHI than their male counterparts, suggesting that these women might have a higher REM AHI/NREM AHI; however, REM AHI/NREM AHI was not considered as an independent variable. In this same study, we found the prevalence of REM SDB to be age related, highest in women < 55 years old, intermediate in older women, even less in men < 55 years old, and least in older men.[3]

In the current work, we aimed to more precisely quantify the gender-related predisposition for REM SDB in a large cohort and to further characterize how this gender difference is influenced by two other important risk factors for SDB: age and level of obesity. We expected to see that REM SDB prevalence decreases with age in women but not in men. We also sought to determine whether changes in the prevalence of REM SDB were due to disproportionate changes in REM AHI, NREM AHI, and REM AHI/NREM AHI with age in order to better understand the underlying pathophysiology predisposing to this disorder. We expected that in women, NREM AHI would increase at a faster rate than REM AHI with age, whereas in men the two indexes would increase proportionally with age.

MATERIALS AND METHODS

Patient Population

Patients referred for clinical sleep evaluation at St. Michael’s Hospital (Toronto, ON), a tertiary care facility, who underwent overnight polysomnography between 2004 and 2006 were considered for this analysis. Inclusion criteria were as follows: (1) age ≥ 18 years; (2) AHI ≥ 5/h; and (3) total sleep time ≥ 100 min and REM sleep time ≥ 10 min. Of the 2,643 patients (878 women and 1,765 men), a total of 2,486 subjects were included in the analysis

(817 women and 1,669 men). A total of 157 subjects were excluded from analysis, 154 patients for REM time < 10 min and 3 patients for incomplete data. Height and weight were measured in a standardized fashion, and body mass index (BMI) was computed. Sleepiness was measured using the Epworth sleepiness scale (ESS).[6] This study was approved by the Institutional Review Board of St. Michael's Hospital.

Polysomnography

Attended overnight polysomnography was performed (Sandman; Mallinckrodt/Nellcor Puritan Bennett; Melville, ON, Canada). The recording montage included EEG (C_3-A_2, C_4-A_1); bilateral electrooculography; submental and bilateral anterior tibial electromyography; ECG; thoracic and abdominal respiratory inductance plethysmography (Respitrace; Ambulatory Monitoring; Ardsley, NY); nasal airflow using nasal pressure cannula (dual-pressure sensor model 0585; Braebon Medical Corporation; Ogdensburg, NY); and finger pulse oximetry (model NPB-290; Nellcor Puritan Bennett; Pleasanton, CA).

Sleep was scored manually in 30-s epochs according to the criteria of Rechtschaffen and Kales,[7] while arousal was scored using standard criteria.[8] Respiratory events were scored using standard criteria for hypopnea and apnea.[9] Briefly, an apnea was scored if airflow was absent for at least 10 s, while hypopnea was defined by a ≥ 50% reduction in airflow accompanied by oxygen desaturation ≥ 3% and/or arousal. The AHI was defined as the number of apneas and hypopneas divided by total sleep time. NREM AHI was calculated as the number of apneas and hypopneas during NREM sleep (stages I to IV) divided by total NREM sleep, whereas REM AHI was determined by dividing the number of apneas and hypopneas during REM sleep by total REM time. Criteria for REM SDB included the following: (1) AHI ≥ 5/h, (2) NREM AHI ≤ 15/h, and (3) REM AHI/NREM AHI ≥ 2.

Statistical Analysis

Logistic regression was used to determine the odds ratio (OR) of having REM SDB. Linear regression was utilized to identify predictors of REM AHI/NREM AHI, REM AHI, and NREM AHI. In order to approximate a normal distribution, each of these three variables was transformed logarithmically (after adding a fixed constant of 0.1 for REM AHI/NREM AHI and 1.0 for REM AHI and NREM AHI) prior to analysis. Because several patients had an NREM AHI of zero, REM AHI/NREM AHI was winsorized at the ninth percentile, which corresponded to a value of 15. We employed cubic splines separately in both sexes in order to identify a target age above and below which either the likelihood of having REM SDB or REM AHI/NREM AHI by year changes significantly. Analyses were performed using statistical software (R 2.4; University of Auckland; Auckland, New Zealand; and SPSS 15.0; SPSS; Chicago, IL).

RESULTS

Overall, 2,486 patients (32.9% women) were identified who met the inclusion criteria for the study. Table 1 presents demographic and polysomnographic characteristics of this cohort (mean ± SE). All subjects had the following characteristic means: age, 50.8 ± 0.3 years; BMI, 30.8 ± 0.1 kg/m^2; and AHI, 29.7 ± 0.5/h. Women were significantly older, more obese, and had lower overall and NREM AHI than men; however, they had a higher REM AHI than men, resulting in a greater REM AHI/NREM AHI. The prevalence of REM SDB was 40.8% among women and 21.0% among men ($p < 0.0001$). After adjusting for differences in age and BMI, female gender remained strongly associated with REM SDB (OR, 3.0; 95% confidence interval [CI], 1.8 to 4.2). Among women, those with REM SDB were younger, had lower overall NREM and REM AHI, and had more REM sleep. Similarly among men, those with REM SDB were younger, less obese, had lower respiratory indexes, and spent more time in REM sleep. Women with REM SDB had a higher REM AHI, lower NREM AHI, and thus a higher REM AHI/NREM AHI than their male counterparts.

All men and women were stratified by age groups, and the prevalence of REM SDB was determined for each group. As seen in Figure 1, REM SDB prevalence decreases with age in a linear fashion in both men and women, although the decline is steeper in women. For every decade advance in age, ORs follow for women and men, respectively (OR, 0.76; 95% CI, 0.64 to 0.88; and OR, 0.87; 95% CI, 0.72 to 1.02). The formal test of the age-sex interaction yielded a p value of 0.063.

The influence of obesity on REM SDB prevalence is shown in Figure 2. While increasing BMI is associated with a steady decline in REM SDB risk in men, among women no clear decline in risk is identified until a BMI ≥ 35 kg/m^2. For every 5 kg/m^2 increase in BMI, ORs follow for women and men, respectively: OR, 0.92 (95% CI, 0.84 to 1.01); and OR, 0.80 (95% CI, 0.59 to 1.01). Formal testing of the BMI and sex interaction produced a p value of 0.062.

Similar to the effect of age on REM SDB, mean REM AHI/NREM AHI was found to steadily fall with increasing age in women (Fig 3; Table 2) and remain relatively constant in men. These patterns suggest that the fall in REM SDB prevalence with age is due to a generalized increase in both NREM and REM AHI in men and a differential increase in the two indexes for women. As seen in Table 2, the increase in REM AHI and NREM AHI (9.0% per decade vs 11.2% per decade, respectively) with age was of similar magnitude in men. In contrast, among women, NREM AHI increased more than twice the rate with age of the REM AHI, resulting in a nearly 11% fall in REM AHI/NREM AHI with each additional decade.

Also shown in Table 2, increasing BMI had no significant effect on the REM AHI/NREM AHI of either gender, suggesting that the decline in REM SDB with increasing BMI might be due to an overall increase in AHI across sleep stages. Indeed among men, REM and NREM AHI increased identically with BMI severity (24.2% per 5 kg/m^2 BMI). This was not the case for women in whom REM AHI increased to a greater extent than NREM AHI with increasing obesity (17.1% per 5 kg/m^2 vs 13.0% per 5 kg/m^2, respectively).

A greater amount of change in REM AHI was described by 5 kg/m^2 increases in BMI than by decade advances in age for both men and women. Considering NREM AHI, this trend remained for men but not for women in whom age accounted for more change than BMI. Actually in the case of NREM AHI for women, age and BMI accounted for the most and least change, respectively, when compared to REM and NREM AHI for men and REM AHI for women.

Using cubic splines, there was no age for men around which the odds of having REM SDB or the value of REM AHI/NREM AHI by year were different; the same was true for the odds of having REM SDB for women. In women, REM AHI/NREM AHI was found to decrease at a significantly greater rate by year for those > 52 years old when compared to women < 52 years old. ESS score did not differ in any logical fashion in regard to gender and REM SDB, showing that overall, women with OSA score higher on the ESS than male apneics. To demonstrate that gender differences in REM SDB were not due to disparate positional data, a secondary analysis was performed to compare percentage supine sleep in gender-stratified samples of REM SDB and NREM SDB. Percentage of sleep spent in the supine position for women with NREM SDB, women with REM SDB, men with NREM SDB and men with REM SDB did not differ (analysis of variance, $p = 0.06$): 38.2, 41.8, 37.4, and 40.0 min, respectively.

DISCUSSION

Our study affirms previous findings that REM SDB is more prevalent in women than men (40.8% vs 20.1%), while adding new information regarding the relations among REM SDB, gender, age, and obesity. According to our data, the female predilection toward REM SDB occurs irrespective of sleep position across all adult ages and ranges of BMI. There may be a greater discrepancy in the earlier decades because REM SDB prevalence decreases more rapidly with age in women than men (age and sex interaction, $p = 0.063$). REM SDB prevalence is also moderated by obesity and sex (BMI and sex interaction, $p = 0.061$), decreasing with increasing obesity severity more so in men than women. So at any adult age and at any level of BMI, REM SDB is more likely to occur in a woman; however, among respective gender categories, REM SDB expression is more associated with younger age for women and lower BMI for men.

Examination of REM AHI/NREM AHI by gender and age revealed a very similar pattern, showing higher values for women. However, unlike REM SDB prevalence, REM AHI/NREM AHI ratio was found to decline with age only in women, remaining fairly constant in men. Further, in women REM AHI/NREM AHI declined more quickly in women > 52 years old. We introduce REM AHI/NREM AHI as a new marker identifying the extent to which respiratory events are confined to REM sleep; however, this measure is limited by a lack of specificity in that an elevated value may result from a high REM AHI, low NREM AHI, or a combination of the two scenarios. Indeed, when comparing male and female subjects with and without REM SDB, women had a higher REM AHI/NREM AHI resulting from a combination of a lower NREM AHI and higher REM AHI.

A larger REM AHI, smaller NREM AHI, and greater REM AHI/NREM AHI suggest that women may be protected from disordered breathing during NREM sleep but not REM sleep. That women are resistant to disordered breathing during NREM sleep is implied physiologically because airway resistance from wakefulness to NREM sleep increases less in women than in men.[10] This increased tonicity in women may be mediated by progesterone because genioglossal tone is positively correlated with progesterone levels in female subjects.[11] Additional protection from disordered breathing during NREM sleep may be provided by the stimulatory affects of progesterone on ventilation in part because it sensitizes chemoreceptors to hypoxia and hypercapnia.[12] A mechanistic role for female hormones is further implied by the increase in NREM AHI and decreases in REM AHI/ NREM AHI and REM SDB prevalence observed in women with increasing age that may coincide with age-related changes in sex hormone.

REM sleep may counter some of this protection against disordered breathing. It is characterized by muscle atonia and decreased chemosensitivity,[13] states that may negate the tonic and positive ventilatory effects afforded by female sex hormones, leaving women susceptible to airway collapse and disordered breathing. The end product of this accentuated difference in stage specific susceptibility to disordered breathing may be the expression of REM SDB in women.

Of course, repetitive upper airway obstruction in many individuals is associated with obesity.[14] The presence of progestational hormone in premenopausal women may provide sufficient tonicity to offset the tendency toward collapse in the setting of obesity during NREM but not REM sleep. In this way, the severity of SDB in NREM vs REM sleep for women may be less related to obesity, further favoring the expression of REM SDB. Thus, NREM AHI in women should be least affected by increasing BMI when compared to REM AHI in women and both indexes in men. In fact, this was the case; a 5-unit increase in BMI yielded only a 13.0% increase in NREM AHI for women, compared to a 17.1% increase in REM AHI and 24.2% increase in both indexes for men. Furthermore, REM SDB prevalence was less affected by obesity in women, decreasing only 8.6% with a 5-unit increase in BMI, as opposed to 21.8% in men ($p = 0.061$).

If female sex hormones do offer protection from SDB in NREM sleep, then age should be a stronger predictor of NREM AHI in women than REM AHI in women or either index in men as levels of hormone decrease in women with age.[15] NREM AHI in women did demonstrate the greatest age dependency, increasing by 16.0% for every additional decade in age compared to 11.2% for men and 5.7% and 9.0% for REM AHI in women and men, respectively. Logistic regression also suggested this pattern, demonstrating that with every decade advance in age, REM SDB prevalence decreased 26.7% in women and 13.2% in men ($p = 0.063$).

Observed prevalence patterns by age and sex are likely due to trends in observed changes in NREM and REM AHI by age. The average change in NREM and REM respiratory indexes with age was proportional for men and disproportional for women. In men, every decade advance yielded increases in NREM and REM AHI averaging 11.2% and 9.0%, respectively, while for women these indexes increased by 16.0% and 5.7%. In the end, it may be this disproportionate increase in NREM AHI vs REM AHI with age that accounts for the gender difference in REM SDB prevalence. We suggest that the observed patterns in NREM and REM AHI change by age, sex, and obesity reflect a role for female hormone in protecting women from disturbed breathing during NREM sleep.

These findings should be considered with some degree of caution, however. The data are cross-sectional and cannot speak to the natural course of disease. Additionally, that these findings support a role for hormones in the protection of women from SDB in NREM sleep is purely speculative and should be treated as such. Hormone levels were not assessed, nor was there information regarding hormonal status reflected by menstrual history or hormone replacement therapy. It is also unclear how pertinent these findings are clinically. Findings regarding sleepiness were not revealing, consistent with prior research.[16] Additional research needs to be done considering clinical correlates of REM SDB, and more importantly how and when this entity should be treated. Despite these limitations, our study introduces new information regarding REM SDB and its relation to gender, age, and obesity, and may add to the present interest in studying the role of hormones in the expression of obstructive sleep apnea.

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Abbreviations

AHI	apnea-hypopnea index
BMI	body mass index
CI	confidence interval
ESS	Epworth sleepiness scale
NREM	non-rapid eye movement
OR	odds ratio
OSA	obstructive sleep apnea
REM	rapid eye movement
SDB	sleep-disordered breathing

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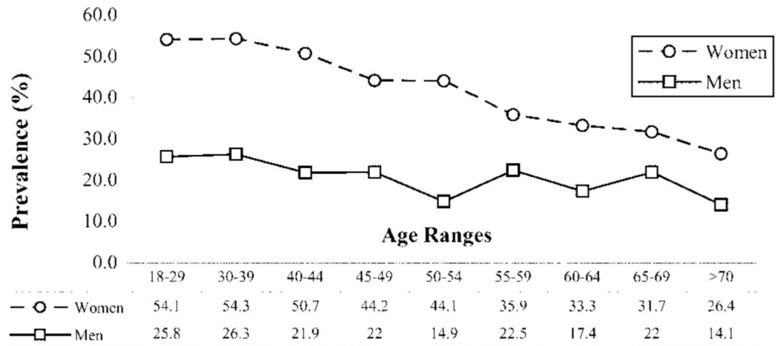


Figure 1.

Prevalence of REM-related SDB by age and sex.

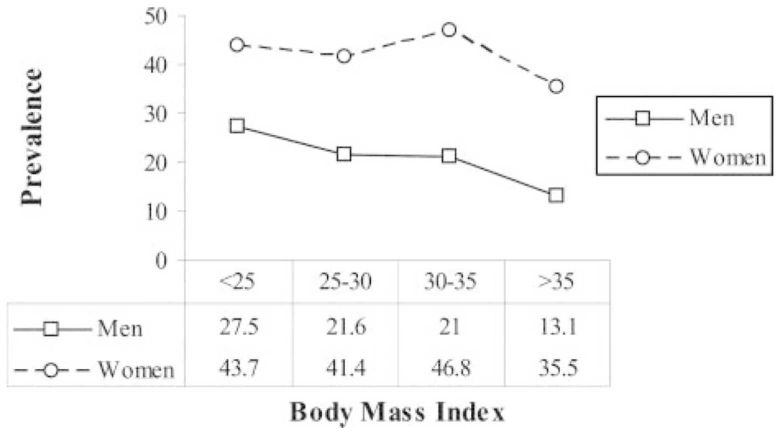
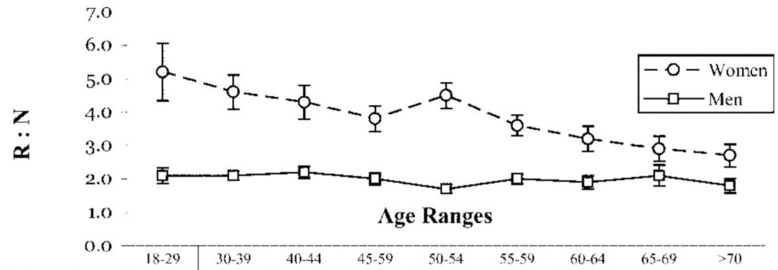


Figure 2.
Prevalence of REM-related SDB by BMI and sex.



	18-29	30-39	40-44	45-59	50-54	55-59	60-64	65-69	>70
Women	5.2	4.6	4.3	3.8	4.5	3.6	3.2	2.9	2.7
Men	2.1	2.1	2.2	2.0	1.7	2.0	1.9	2.1	1.8

Figure 3.
REM AHI/NREM AHI (R:N) by age and sex.

Table 1—

Demographic and Polysomnographic Characteristics*

Variables	All Subjects: Women (n = 817)	All Subjects: Men (n = 1,669)	All Subjects: p Value	Women: REM SDB (n = 333)	Women: NREM SDB (n = 484)	Women: p Value	Men: REM SDB (n = 350)	Men: NREM SDB (n = 1,319)	Men: p Value
Age, yr	53.2 ± 0.5	49.6 ± 0.3	< 0.001†	50.6 ± 0.7	55.0 ± 0.6	< 0.001†	47.7 ± 0.7	50.1 ± 0.4	0.003†
BMI, kg/m^2	32.3 ± 0.3	30.0 ± 0.1	< 0.001†	31.7 ± 0.4	32.7 ± 0.4	< 0.07	29.0 ± 0.3	30.3 ± 0.1	< 0.001†
AHI, events/h	24.6 ± 0.7	32.3 ± 0.6	< 0.001†	11.6 ± 0.3	33.5 ± 1.0	< 0.001†	11.9 ± 0.2	37.7 ± 0.7	< 0.001†
REM AHI, events/h	39.0 ± 0.8	35.4 ± 0.6	< 0.001†	35.7 ± 0.9	41.2 ± 1.3	< 0.001†	32.0 ± 0.7	36.3 ± 0.7	< 0.001†
NREM AHI, events/h	21.4 ± 0.8	31.4 ± 0.6	< 0.001†	6.2 ± 0.2	31.8 ± 1.1	< 0.001†	7.4 ± 0.2	37.8 ± 0.7	< 0.001†
NREM/AHI	3.8 ± 0.1	2.0 ± 0.06	< 0.001†	7.2 ± 0.2	1.5 ± 0.04	< 0.001†	5.3 ± 0.2	1.1 ± 0.02	< 0.001†
REM, min	61.4 ± 0.9	59.2 ± 0.7	0.05	68.3 ± 1.5	56.8 ± 1.1	< 0.001†	67.3 ± 1.4	57.1 ± 0.7	< 0.001†
ESS score	9.2 ± 0.2	8.7 ± 0.1	0.009	9.0 ± 0.3	9.4 ± 0.2	0.27	8.0 ± 0.3	8.8 ± 0.1	0.008

*Data are presented as mean ± SE unless otherwise indicated.

†Significance at $p < 0.003$.

Table 2—

Percentage Change in REM AHI/NREM AHI, REM AHI, and NREM AHI by Sex, Age, and BMI*

	Men		Women	
Variables	Change, %	p Value	Change, %	p Value
REM AHI/NREM AHI				
Age	− 1.9 (− 8.1, 4.3)	0.23	− 10.9 (− 16.3, − 5.5)	< 0.001
BMI	0.5 (− 5.2, 6.2)	0.83	3.1 (− 1.0, 7.2)	0.16
REM AHI				
Age	9.0 (5.9, 12.1)	< 0.001	5.7 (1.7, 9.7)	0.005
BMI	24.2 (20.6, 27.8)	< 0.001	17.1 (13.9, 20.3)	< 0.001
NREM AHI				
Age	11.2 (8.2, 14.2)	< 0.001	16.0 (11.1, 20.9)	< 0.001
BMI	24.2 (20.8, 27.6)	< 0.001	13.0 (9.1, 16.9)	< 0.001

*Data are presented as % (95% CI) unless otherwise indicated. Percentage changes in REM AHI/NREM AHI, REM AHI, and NREM AHI are presented for every 10-yr age increase and 5 kg/m^2 BMI increase.