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SCIENTIFIC INVESTIGATIONS

Cardiovascular and somatic comorbidities and sleep measures using three hypopnea criteria in mild obstructive sleep-disordered breathing: sex, age, and body mass index differences in a retrospective sleep clinic cohort

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Study Objectives: To describe sex, age, and body mass index (BMI) differences in comorbidities and polysomnography measures, categorized using 3 different apnea-hypopnea index (AHI) criteria in sleep clinic patients with mild obstructive sleep-disordered breathing.

Methods: A retrospective cohort of 305 (64% female) adult sleep clinic patients who underwent full-night in-laboratory polysomnography having been diagnosed with mild sleep-disordered breathing and prescribed positive airway pressure. Effects of sex, age, and BMI on comorbidities and polysomnography measures, including rates of AHI defined by ≥ 3% desaturations ($AHI_{3\%}$), with arousals ($AHI_{3\%A}$), by ≥ 4% desaturations ($AHI_{4\%}$), and by respiratory disturbance index, were evaluated.

Results: Sixty-nine (23%), 116 (38%), 258 (85%), and 267 (88%) patients had $AHI_{4\%}$, $AHI_{3\%}$, $AHI_{3\%A}$, and respiratory disturbance index ≥ 5 events/h, respectively. Ninety-day positive airway pressure adherence rates were 45.9% overall and higher in women > 50-years-old (51.2%, $P = 0.013$) and men (54.5%, $P = 0.024$) with no difference whether $AHI_{4\%}$ or $AHI_{3\%A}$ was < 5 or ≥ 5 events/h. Men and women had similar rates of daytime sleepiness (43.3%), anxiety (44.9%), and hypertension (44.9%). Women were more likely to have obesity, anemia, asthma, depression, diabetes, fibromyalgia, hypothyroidism, migraine, and lower rates of coronary artery disease. More patients with $AHI_{4\%}$ < 5 events/h had depression, migraines, and anemia, and more patients with $AHI_{4\%}$ ≥ 5 events/h had congestive heart failure. Women were more likely to have higher sleep maintenance and efficiency, shorter average obstructive apnea and hypopnea durations, and less supine-dominant pattern. Average obstructive apnea and hypopnea duration decreased with increasing BMI, and average hypopnea duration increased with age. Obstructive apnea duration and obstructive hypopnea with arousal duration decreased with increasing BMI. More women had $AHI_{4\%}$ < 5 (81.5% vs 69.1%), $AHI_{3\%}$ < 5 (68.7% vs 49.1%), and $AHI_{3\%A}$ < 5 events/h (18.5% vs 10.0%). Greater age and higher BMI were associated with higher AHI.

Conclusions: Current AHI criteria do not predict comorbidities or adherence in mild sleep-disordered breathing patients. In this hypothesis-generating descriptive analysis, sex, BMI, and age may all be factors that should be accounted for in future research of mild sleep-disordered breathing patients. Different sleep study measures may weigh differently in calculations of risk for cardiovascular versus somatic comorbidities.

Keywords: obstructive sleep apnea, mild sleep-disordered breathing, sex, comorbidity, hypopnea

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Mild obstructive sleep-disordered breathing is highly prevalent in the general population and is 50% of sleep-disordered breathing found in women, but the clinical significance is unclear. This study evaluates the sex, age, and body-mass index differences in somatic and cardiovascular comorbidities and sleep study measures in sleep clinic patients with mild sleep-disordered breathing to better understand markers that may be able to risk-stratify patients and predict treatment response.

Study Impact: Sex differences in breathing physiology and somatic arousability may impact the effects of mild breathing obstructive pattern. This work lays a foundation for understanding the phenotypic differences within mild sleep-disordered breathing to inform future research into the impact and treatment of mild obstructive sleep-disordered breathing.

INTRODUCTION

Mild obstructive sleep-disordered breathing (SDB) encompasses several described conditions, including upper airway resistance syndrome (UARS) (now included within the American Academy of Sleep Medicine [AASM] *International Classification of Sleep Disorders* [ICSD-3] definition of obstructive sleep apnea [OSA]), prolonged partial upper airway obstruction (PPO), nonhypoxic OSA, and mild OSA with more severe oxygen desaturations.[1,2] All of these patients have an apnea-hypopnea index defined by hypopneas with ≥ 4% oxygen desaturations ($AHI_{4\%}$) < 15 events/h, but many of these patients have $AHI_{4\%}$ < 5 events/h and yet benefit symptomatically from treatment. UARS is characterized by flow limitation, signifying

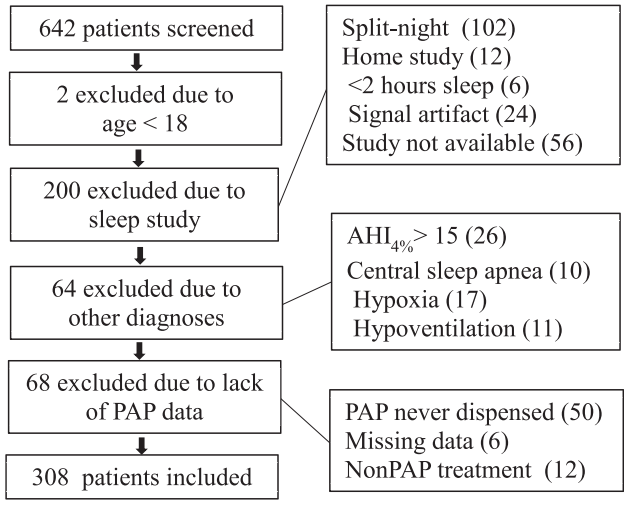
increased respiratory resistance, with arousals but without desaturations, and PPO is characterized by increased respiratory resistance lasting minutes without any clear events, usually in N3 or stable N2, but can be associated with increases in carbon dioxide. These two phenotypes of SDB are more common in women and are associated with symptoms and comorbidities. UARS and PPO tend to present with more somatic symptoms and OSA with more cardiovascular.[1,3] Despite mild SDB being present in up to 35% of the population, there is limited understanding of long-term risks of these findings and the benefits of treatment.[4,5] With increased OSA screening of patients for conditions like stroke, dementia, hypertension, and atrial fibrillation, a better understanding of whether patients in the mild range benefit from treatment is needed and has large health care utilization and cost ramifications.

We hypothesized that both the AASM-recommended criteria defined by hypopneas with 3% desaturations or arousals ($AHI_{3\%A}$) and alternative ($AHI_{4\%}$) scoring criteria inadequately diagnose symptomatic patients who could benefit from treatment and inadequately risk-stratify patients at risk of adverse outcomes.[2,5] Depending on the AHI criteria used, the percentage of patients diagnosed with OSA can differ by 20%, and an additional 20% can be diagnosed with more severe disease.[6,7] AHI also fails to differentiate events based on duration, desaturation severity, or autonomic response.[8] UARS and PPO studies demonstrate that some patients with normal AHI have higher risks for comorbidities and symptoms that can be treated with therapy. Since different phenotypes of mild SDB affect the risk of comorbidities and symptoms differently, a scoring system that can better discriminate between these differences is needed[5,9,10] Additionally, untreated mild SDB may cause upper airway changes and autonomic responses and permanent nerve damage that could evolve into more severe disease later in life; so finding sleep measures that can better predict future risks is needed.[2]

Patient characteristics, including age, body mass index (BMI), and sex also likely play a significant role in the phenotypic heterogeneity of mild SDB.[11–13] Anatomical and hormonal factors play large roles in the risk of developing SDB and in its breathing patterns. Premenopausal women are more likely to present with upper airway resistance syndrome,[14] and healthy postmenopausal women are 17 times more likely to have prolonged partial airway limitation than OSA.[1] It is unclear whether different breathing patterns are more significant in certain populations.

In order to create better diagnostic criteria and risk models to determine which patients would most benefit from treatment, a better understanding of the factors which influence mild sleep-disordered breathing are necessary. Our study looked at possible variables, including sex, BMI, age, and sleep study measures and their association with cardiovascular and somatic comorbidities, The goal of this study was to describe the comorbidities and sleep study features in a retrospective cohort of patients with $AHI_{4\%} < 15$ events/h who had been prescribed positive airway pressure (PAP) therapy and to evaluate for differences by sex, BMI, and age to lay a foundation for future research.

Figure 1—Patient selection.



METHODS

Study design

This was a retrospective analysis of adult Baystate Sleep Medicine patients who attended in-laboratory sleep studies between 2010 and 2016 and had been diagnosed with mild SDB and prescribed PAP. Clinical, PAP adherence, and sleep study data were obtained retrospectively from the electronic medical record, sleep study, and PAP adherence databases. The study protocol was approved by the Institutional Review Board of Baystate Medical Center.

Eligibility

Mild SDB was defined as patients with $AHI_{4\%} < 15$ events/h with PAP prescribed. This included both patients with AHI defined by hypopneas with ≥ 3% desaturations or arousals ($AHI_{3\%A}$) > 15 events/h (moderate or severe OSA by American Academy of Sleep Medicine–recommended criteria) and some patients with $AHI_{3\%A} < 5$ events/h and respiratory disturbance index (RDI) ≥ 5 events/h who were prescribed PAP for upper airway resistance syndrome. We also included patients with RDI < 5 events/h who were treated with PAP therapy for a prolonged partial airway limitation pattern.

Our sleep clinic database was queried for patients who had been prescribed PAP with in-laboratory polysomnography (PSG) between 2010 and 2016 with an $AHI_{3\%A} < 15$ events/h and all patients with $AHI_{3\%A} \geq 15$ events/h with lowest saturations ≥ 85%. We excluded patients with age < 18 years, lack of full-night in-laboratory sleep study, $AHI_{4\%} \geq 15$ events/h, inadequate study data, treatment with modality other than PAP, and other sleep diagnoses including central AHI ≥ 5 events/h, baseline hypoxia, or hypoventilation (**Figure 1**). Only patients who received PAP equipment verified with electronic adherence data were included.

Polysomnography

All sleep studies were full-night in-laboratory attended-baseline PSG recordings using electroencephalogram, electrocardiography, electrooculogram, electromyography, thermistor, nasal pressure

transducer, chest and abdomen plethysmography, and oxygen saturation with data entered into Natus NeuroWorks software (Pleasanton, CA) in an AASM-accredited laboratory at Baystate Medical Center in Springfield, MA. All studies were rescored by a single registered polysomnography technician (whose AASM interscorer reliability is consistently > 90%) and reviewed by a sleep physician (KJ) to ensure that staging and events were scored accurately and consistently, given AASM changed recommended hypopnea scoring criteria in 2012 in the middle of the study period. Apneas were scored if there was a 90% decrease in thermistor amplitude for at least 10 seconds and scored as either obstructive if effort was present or central if absent. Post-arousal central apneas were not scored. Hypopneas were scored if there was a 30% or more decrease in nasal pressure amplitude for at least 10 seconds and scored as either obstructive hypopnea with arousal or obstructive hypopnea with either ≥ 3% or ≥ 4% desaturations if obstructive features of snoring, flow limitation, or abdominal/thoracic paradox were present. Central hypopneas were scored if obstructive features were absent, but given that patients with central sleep apnea were excluded, there were only 21 patients with central hypopneas and all with less than 10 central hypopneas. Respiratory effort–related arousals were scored if there was at least 10 seconds of evidence of increasing respiratory effort as evidenced by flow limitation or increasing snoring or effort signal followed by an arousal that did not meet criteria for hypopnea. AHI was the sum of the apneas and hypopneas per hour of sleep. RDI was the sum of apneas, hypopneas, and respiratory effort–related arousals per hour of sleep. Prolonged partial airway limitation was considered significant if there were prolonged periods of flow limitation in pressure transducer, but limited arousals with RDI < 5 events/h.

Outcomes and analysis

Presence of comorbidities was determined from self-report on the screening questionnaire prior to the patient's sleep study or sleep clinic visit or documented in the patient's electronic medical record. If a comorbidity was present in our screening questionnaire, it was included in this study if cardiovascular or somatic or could influence the presence of obstructive sleep-disordered breathing. The sleep study measure choice was primarily to focus on obstructive measures that would be available if the patient were tested with either a home sleep apnea test or in-laboratory polysomnography. PAP adherence was defined as ≥ 70% of nights over 4 hours in a 90-day period within the first year of treatment. Excessive daytime sleepiness was defined by Epworth Sleepiness Scale ≥ 10.

Rates of patient characteristics and comorbidities were calculated, including means and standard deviations for continuous measures and frequencies for categorical measures (**Table 1**). Patient characteristics and comorbidities were compared across sleep measures using *t* tests for continuous measures and Pearson's chi-square or Fisher's exact test for categorical measures. Evaluation of trends in proportions across ordered groups were accomplished using nonparametric tests for trends in proportions.[15]

RESULTS

The analysis included 195 females and 110 males. Average age was 48.8 ± 13.7 years. Continuous PAP or AutoCPAP was prescribed for 276 (90.5%) patients, Bilevel PAP or AutoBilevel PAP for 26 (8.5%) patients, and adaptive-servoventilation for 3 (1.0%) patients.

Baseline characteristics and comorbidities by sex

Men and women had similar rates of sleepiness (average Epworth Sleepiness Scale 9.5 ± 5.9) and similar percentages of Epworth Sleepiness Scale ≥ 10. Similar rates of anxiety (45.1%) and hypertension (45.1%) were found in men and women. Women were more likely to have BMI ≥ 30 (average BMI 35.5 ± 8.1 vs 31.3 ± 6.9) with more women with BMI ≥ 40 and more men with BMI < 30. Women were more likely to have anemia, asthma, depression, diabetes, fibromyalgia, hypothyroidism, migraine, and less likely to have coronary artery disease.

Comorbidities by AHI

Similar rates of most comorbidities were present in patients with mild OSA compared with those without by both $AHI_{4\%}$ and $AHI_{3\%A}$ and with mild OSA by $AHI_{4\%}$ compared to $AHI_{3\%A}$. Among all patients, $AHI_{4\%}$ < 5 events/h was associated with higher rates of depression (P = .022), migraine (P = .019), and anemia (P = 0.012). $AHI_{4\%}$ ≥ 5 events/h was associated with higher prevalence of congestive heart failure within all patients (.010), and within males (P = .033), but there were only 6 patients with congestive heart failure so the numbers are too small to understand the effect. Within females (**Table 2**), $AHI_{4\%}$ < 5 events/h was associated with higher rates of anxiety, depression, and borderline significance for migraine than $AHI_{4\%}$ ≥ 5 events/h. Women with lower $AHI_{3\%A}$ were more likely to have anxiety and migraine. There was no significant difference among women for AHI effects on anemia, so the association among all patients may be explained by the increased prevalence of anemia in women, who are more likely to have lower AHI than men.

Sleep study measures by sex, age, and body mass index (Table 3)

Women were more likely to have longer total sleep time, higher sleep maintenance and efficiency, less stage 1 sleep, and more stage 3 sleep. Women had shorter average obstructive apnea duration and hypopnea duration and average hypopnea with arousal duration. Women were less likely to have supine dominant pattern.

Women < 50-years-old were more likely to have higher sleep efficiency, sleep maintenance, average oxygen saturation, and less time with oxygen saturation < 90% than women ≥ 50-years-old. Older women were more likely to have longer average obstructive apnea duration and hypopnea duration

Total sleep time, sleep efficiency, and sleep maintenance decreased with age, with lowest levels in patients ≥ 65 years-old (P = .002, < .001, < .001, respectively). The time with oxygen saturation below 90% increased with increasing age (P = .001) and average oxygen saturation decreased with increasing age (P < .001). Average hypopnea duration increased with age, with durations of 20.1 ± 4.9 seconds for < 40-year-olds to 22.4 ± 4.3 seconds for ≥ 65-year-olds (P = .034).

Table 1—Cohort characteristics and comorbidities.

	All Patients	Females Only		*P*-value	All Females	All Males	*P*-value
	(n = 305)	< 50 years (n = 111)	≥ 50 years (n = 84)		(n = 195)	(n = 110)	
Age, mean (SD)	48.8 (13.7)	38.8 (7.8)	60.8 (7.9)	< 0.001	48.3 (13.5)	49.5 (14.0)	0.440
BMI, mean (SD)	34.0 (7.9)	37.8 (7.8)	32.5 (7.5)	< 0.001	35.5 (8.1)	31.3 (6.9)	< 0.001
ESS, mean (SD)	9.5 (5.9)	10.4 (5.6)	8.3 (5.9)	0.013	9.5 (5.8)	9.7 (5.5)	0.721
	n (%)	n (%)	n (%)		n (%)	n (%)	
Age by category							
Age ≥ 50	140 (45.8)	—	—	—	84 (43.1)	55 (50.0)	0.281
Age ≥ 65	47 (15.4)	—	—	—	28 (14.4)	18 (16.4)	0.739
BMI by category				< 0.001			< 0.001
< 25	28 (9.2)	5 (4.5)	10 (11.9)	—	15 (7.7)	13 (11.8)	—
25–-< 30	78 (25.5)	12 (10.8)	24 (28.6)	—	36 (18.5)	42 (38.2)	—
30–-< 35	73 (23.9)	25 (22.5)	24 (28.6)	—	49 (25.1)	23 (20.9)	—
35–-< 40	63 (20.6)	28 (25.2)	14 (16.7)	—	42 (21.5)	21 (19.1)	—
40+	64 (20.6)	41 (36.9)	12 (14.3)	—	53 (27.2)	11 (10.0)	—
Hypersomnia[a]	128 (43.5)	54 (51.4)	28 (34.6)	0.026	82 (44.1)	45 (42.1)	0.807
% Adherent with PAP[b]	141 (46.1)	37 (33.3)	43 (51.2)	0.013	80 (41.0)	60 (54.5)	0.024
Somatic comorbidities							
Anxiety	138 (45.1)	58 (52.3)	37 (44.0)	0.311	95 (48.7)	42 (38.2)	0.093
Depression	151 (49.3)	67 (60.4)	39 (46.4)	0.060	106 (54.4)	44 (40.0)	0.017
Fibromyalgia	31 (10.1)	15 (13.5)	12 (14.3)	1.000	27 (13.8)	4 (3.6)	0.005
Migraine	76 (24.8)	40 (36.0)	18 (21.4)	0.028	58 (29.7)	18 (16.4)	0.009
Cardiovascular comorbidities							
CAD	23 (7.5)	1 (0.9)	2 (2.4)	0.579	3 (1.5)	19 (17.3)	< 0.001
CHF	6 (2.0)	1 (0.9)	3 (3.6)	0.317	4 (2.1)	2 (1.8)	1.000
CKD	14 (4.6)	0 (0.0)	8 (9.5)	0.001	8 (4.1)	6 (5.5)	0.581
Diabetes	68 (22.2)	27 (24.3)	27 (32.1)	0.259	54 (27.7)	13 (11.8)	0.001
High cholesterol	98 (2.0)	24 (21.6)	30 (35.7)	0.036	55 (28.1)	43 (39.1)	0.054
Hypertension	138 (45.1)	36 (32.4)	50 (59.5)	< 0.001	86 (44.1)	51 (46.4)	0.720
Stroke or TIA	12 (3.9)	0 (0.0)	7 (8.3)	0.002	7 (3.6)	4 (3.6)	1.000
Other relevant comorbidities							
Anemia	34 (11.1)	23 (20.7)	6 (7.1)	0.008	29 (14.9)	5 (4.5)	0.007
Asthma	98 (32.0)	44 (39.6)	28 (33.3)	0.374	72 (36.9)	26 (23.6)	0.021
COPD	11 (3.6)	0 (0.0)	6 (7.1)	0.006	6 (3.1)	5 (4.5)	0.534
Hypothyroidism	43 (14.1)	21 (18.9)	14 (16.7)	0.711	35 (17.9)	8 (7.3)	0.010
Tobacco use	33 (10.8)	12 (10.9)	5 (6.0)	0.307	17 (8.8)	16 (14.5)	0.128

[a]Hypersomnia is defined by Epworth Sleepiness Scale ≥ 10.
[b]PAP adherence is defined by ≥ 70% 90-day adherence. BMI = body mass index, ESS = Epworth Sleepiness Scale, CAD = coronary artery disease, CHF = congestive heart failure, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, PAP = positive airway pressure, TIA = transient ischemic attack.

Average obstructive apnea duration decreased with increasing BMI category from 22.3 ± 7.3 seconds for BMI < 25 kg/m^2 to 16.6 ± 4.1 seconds for BMI ≥ 40 kg/m^2 (P = .002). There was no significant change in average hypopnea duration with BMI (P = .148), but average hypopneas with arousal duration decreased from 21.7 ± 4.5 seconds to 18.2 ± 3.8 seconds with increasing BMI (P < .001) Arousal index decreased with increasing BMI (P = .043).

AHI categories by sex, age, and body mass index

By design, all patients had $AHI_{4\%}$ < 15 events/h. Sixty-nine (22.6%), 116 (38.1%), 258 (84.6%), and 267 (87.6%) patients had $AHI_{4\%}$, $AHI_{3\%}$, $AHI_{3\%A}$, and RDI ≥ 5 events/h, respectively. The percentage of patients in the moderate-severe range of $AHI_{3\%A}$ was 28.2%, including 3 severe ($AHI_{3\%A}$ ≥ 30 events/h) and 34 moderate ($AHI_{3\%A}$ 15–30 events/h) patients with $AHI_{4\%}$ < 5 events/h.

Table 2—Among females, effect of AHI on comorbidity prevalence.

	$AHI_{4\%}$, n (%)		*P*-value	$AHI3_{\%A}$, n (%)			*P*-value
	< 5	5–< 15		< 5	5–< 15	≥15	
	(n = 232)	(n = 70)		(n = 36)	(n = 112)	(n = 47)	
Anxiety	84 (52.8)	11 (30.6)	.016	21 (58.3)	60 (53.6)	14 (29.8)	.010
Depression	93 (58.5)	13 (36.1)	.015	21 (58.3)	63 (56.3)	22 (46.8)	.479
Migraine	52 (32.7)	6 (16.7)	.057	12 (33.3)	39 (34.8)	7 (14.9)	.038
Anemia	27 (17.0)	2 (5.6)	.082	5 (13.9)	17 (15.2)	7 (14.9)	.982

$AHI_{4\%}$ = apnea-hypopnea index with hypopneas defined by ≥ 4% desaturations; $AHI_{3\%A}$ = apnea-hypopnea index with hypopneas defined by ≥ 3% desaturations or arousals.

Table 3—Sleep measures.

	Total	Female Only			All Females	All Males	*P*-value
	(n = 305)	<50 years (n = 111)	≥ 50 years (n = 84)	*P*-value	(n = 195)	(n = 110)	
Total sleep time (min)	334.8 (74.1)	343.0 (69.7)	338.6 (75.5)	.676	341.1 (72.1)	323.7 (76.7)	.049
Sleep efficiency (%)	76.5 (14.8)	80.1 (12.9)	75.1 (13.9)	.011	77.9 (13.5)	74.2 (16.6)	.036
Sleep maintenance (%)	83.2 (12.9)	87.0 (10.4)	81.2 (12.8)	.001	84.4 (11.8)	80.9 (14.3)	.017
Sleep latency (min)	29.8 (34.8)	30.4 (35.1)	28.2 (29.5)	.656	29.4 (32.8)	30.3 (38.2)	.830
% Stage 1	11.9 (8.3)	10.7 (7.9)	10.6 (6.4)	.955	10.7 (7.3)	14.2 (9.5)	<.001
% Stage 2	51.5 (15.7)	50.0 (15.2)	51.3 (17.2)	.588	50.6 (16.1)	53.1 (15.0)	.186
% Stage 3	20.6 (15.0)	22.9 (14.4)	22.1 (17.2)	.741	22.5 (15.6)	17.2 (13.3)	.003
% REM	15.9 (7.4)	16.3 (7.5)	16.0 (8.2)	.731	16.2 (7.8)	15.5 (6.6)	.464
Average O_2 saturation (%)	95.4 (1.6)	95.8 (1.5)	95.1 (1.7)	.002	95.5 (1.6)	95.2 (1.5)	.104
Lowest O_2 saturation (%)	85.7 (4.6)	85.9 (4.8)	85.7 (4.2)	.815	85.8 (4.6)	85.4 (4.6)	.424
O_2 below 90% (min)	4.3 (10.4)	2.8 (7.6)	6.8 (14.2)	.014	4.5 (11.1)	3.8 (8.9)	.551
O_2 below 88% (min)	0.9 (1.8)	0.8 (1.7)	1.2 (2.4)	.169	0.9 (2.0)	0.8 (1.5)	.562
Arousal index (/h)	16.9 (10.5)	15.8 (11.5)	16.8 (9.0)	.532	16.2 (10.4)	18.0 (10.5)	.153
Ave OA duration (s)	18.3 (5.7)	15.8 (4.1)	17.9 (5.2)	.036	17.0 (4.8)	20.2 (6.4)	<.001
Ave OH duration (s)	21.1 (4.6)	19.5 (3.9)	20.7 (3.8)	.041	20.0 (3.9)	23.1 (5.2)	<.001
Ave OH/Ar duration (s)	19.2 (4.0)	18.3 (4.1)	18.7 (3.0)	.375	18.5 (3.7)	20.5 (4.3)	<.001
PLM index (/h)	5.4 (12.8)	4.1 (10.6)	6.0 (14.5)	.273	4.9 (12.4)	6.4 (13.4)	.344
	n (%)	n (%)	n (%)		n (%)	n (%)	
REM-dominant pattern	128 (43.1)	48 (44.4)	34 (41.5)	.768	82 (43.2)	46 (43.0)	1.000
Supine-dominant pattern	95 (60.1)	32 (47.8)	20 (50.0)	.844	52 (48.6)	43 (84.3)	<.001

Values are mean (SD), except as noted. OA = obstructive apnea, OH = obstructive hypopnea, OH/Ar = obstructive hypopnea with arousal only, PLM = period limb movement, REM = rapid eye movement.

Women were more likely to be in the normal range with all criteria and were more likely to have lower mean $AHI_{4\%}$, $AHI_{3\%}$, $AHI_{3\%A}$, and RDI than men (**Table 4**). More women had lower $AHI_{4\%}$, $AHI_{3\%}$, and $AHI_{3\%A}$ severities by AHI < 5, ≥ 5 to < 15, and ≥ 15 events/h.

There was no significant difference in percentage of patients with $AHI_{4\%}$ < 5 events/h by age (85.5% < 40 vs 76.1% ≥ 65 events/h, P = .15) or $AHI_{3\%}$ < 5 events/h (73.5% < 40 vs 56.5% ≥ 65 events/h, P = .16). There were more younger patients with $AHI_{3\%A}$ < 5 events/h (27.7% < 40 vs 8.7% ≥ 65 events/h, P = .01). The average $AHI_{4\%}$ (P = .04) and $AHI_{3\%}$ (P = .03) increased with age but not $AHI_{3\%A}$ (P = .18). The percentage of patients with $AHI_{3\%A}$ in moderate or severe ranges increased with age (P = .01) (**Figure 2**).

BMI had no significant effect on mean AHIs or the percentage of patients with $AHI_{4\%}$, $AHI_{3\%}$, or $AHI_{3\%A}$ < 5 events/h, but there was a trend toward more patients with higher $AHI_{4\%}$, $AHI_{3\%}$, and $AHI_{3\%A}$ severities with increasing BMI (**Figure 3**).

90-day PAP adherence

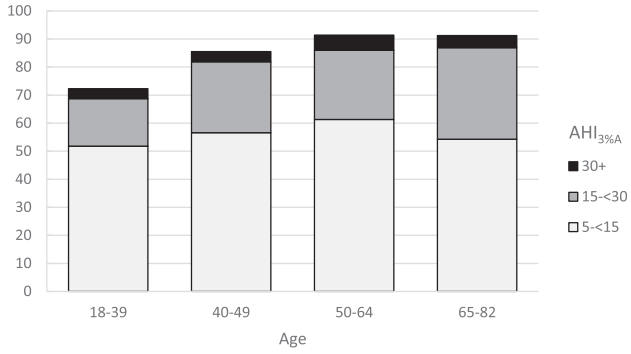
The percentage adherence to PAP was 46.1% of patients. Younger patients were less likely be adherent than older patients (36.3% of < 40-year-olds vs 54% of ≥ 65-year-olds, P = .006). In the 46 patients ≥ 65-years-old, 35 (76%) had $AHI_{4\%}$ < 5 events/h of which 18 (51%) were adherent while 7 (63%) patients with $AHI_{4\%}$ ≥ 5 events/h were adherent. Forty-two (91%) patients ≥ 65-years-old had AHI_{3A} criteria ≥ 5 events/h,

Table 4—Apnea-hypopnea index by sex.

	Female (n = 195)	Male (n = 110)	Total (n = 305)	*P*-value
Average index, mean (SD)				
$AHI_{4\%}$	2.8 (3.0)	3.5 (2.8)	3.0 (3.0)	.024
$AHI_{3\%}$	4.3 (4.4)	5.6 (4.0)	4.8 (4.3)	.017
$AHI_{3\%A}$	11.6 (8.3)	14.1 (8.8)	12.5 (8.6)	.016
RDI	12.7 (8.6)	14.8 (8.8)	13.4 (8.7)	.048
Index by severity	*n* (%)	*n* (%)	*n* (%)	
$AHI_{4\%}$				.023
<5	159 (81.5)	77 (70.0)	236 (77.4)	—
5–15	36 (18.5)	33 (30.0)	69 (22.6)	—
$AHI_{3\%}$				.001
<5	134 (68.7)	55 (50.0)	189 (62.0)	—
5–< 15	54 (27.7)	54 (48.2)	107 (35.1)	—
15–< 30	7 (3.6)	2 (1.8)	9 (3.0)	—
$AHI_{3\%A}$				.039
<5	36 (18.5)	11 (10.0)	47 (15.4)	—
5–< 15	112 (57.4)	60 (54.5)	172 (56.4)	—
15+	47 (24.1)	39 (35.5)	86 (28.2)	—
RDI				.220
<5	29 (14.9)	9 (8.2)	38 (12.5)	—
5–< 15	105 (53.8)	57 (51.8)	162 (53.1)	—
15–< 30	52 (26.7)	36 (32.7)	88 (28.9)	—
30+	9 (4.6)	8 (7.3)	17 (5.6)	—

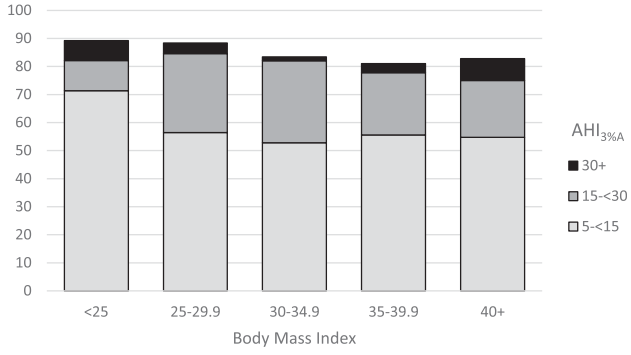
$AHI_{4\%}$ = apnea-hypopnea index with hypopneas defined by ≥ 4% desaturations, $AHI_{3\%}$ = apnea-hypopnea index with hypopneas defined by ≥ 3% desaturations, $AHI_{3\%A}$ = apnea-hypopnea index with hypopneas defined by ≥ 3% desaturations or arousals, RDI = respiratory disturbance index.

Figure 2—Proportion of patients in age category by $AHI_{3\%A}$ cut-off points.



$AHI_{3\%A}$ = apnea-hypopnea index with hypopneas defined by ≥ 3% desaturations or arousals.

Figure 3—Proportion of patients in body mass index category by $AHI_{3\%A}$ cut-off points.



$AHI_{3\%A}$ = apnea-hypopnea index with hypopneas defined by ≥ 3% desaturations or arousal.

of which 24 (57%) were adherent. PAP adherence rates were similar in patients with $AHI_{3\%A}$ and $AHI_{4\%} < 5$ and ≥ 5 events/h.

DISCUSSION

This retrospective study is the first to evaluate somatic and cardiovascular comorbidities and sleep study measures in a cohort of patients with multiple types of mild SDB defined by $AHI_{4\%} < 15$ events/h who were treated with PAP therapy. As expected from the higher rates of mild SBD in women, our population was 64% female. Depending on AHI criteria used, rates of OSA diagnosis in this population of patients with mild SDB ranged from 23% with $AHI_{4\%}$ to 85% with $AHI_{3\%A}$. As expected, mild SDB patients had more variation between different AHI criteria than patients with all degrees of OSA[6] and were more susceptible to under-diagnosis even when $AHI_{3\%A}$ was in the moderate-severe range. Women were more likely to be in the normal range with all criteria. We only included patients with full-night in-laboratory PSG. Higher rates of under-diagnosis and mild OSA would be expected with home sleep apnea testing without electroencephalogram since only $AHI_{3\%}$ or $AHI_{4\%}$ criteria could be used.

The differing diagnosis rates have significant effects on insurance coverage of treatment. Medicare guidelines use an $AHI_{4\%} \geq 5$ events/h cut-off point, which 76% of patients over 65 in this study were beneath. The AASM-recommended $AHI_{3\%A} \geq 5$ events/h criteria diagnosed 91% of patients over 65-years-old with OSA in this study. Fifteen percent of patients who were normal by $AHI_{4\%}$ and almost 15% more with mild OSA by $AHI_{4\%}$ had moderate-severe OSA by $AHI_{3\%A}$ criteria. Because our screening technique excluded patients with $AHI_{3\%A} \geq 15$ events/h with lowest saturations < 85%, we likely missed many patients with $AHI_{4\%} < 15$ events/h who had $AHI_{3\%A} \geq 15$ events/h and desaturations < 85%, underestimating the number of patients with moderate-severe disease using $AHI_{3\%A}$, but mild or normal by $AHI_{4\%}$. Evaluating more patients with mild OSA with more profound hypoxia could lead to a higher prevalence of cardiovascular comorbidities.

Our study found 90-day PAP adherence of 46%, which was lower than adherence rates in studies in mild SDB patients in Switzerland, Finland, and Denmark, but higher than rates found in the United States.[11,16–18] We chose 90-day adherence because

in our experience, most patients with mild SDB choose to discontinue PAP if they are not benefitting from treatment. Adherence levels were similar in patients with mild OSA and in patients with $AHI_{3\%A} < 5$ events/h suggesting that significant disease that responds to continuous PAP is present in some patients with $AHI_{3\%A} < 5$ events/h as seen in upper airway resistance syndrome and prolonged partial flow limitation literature.[19] We chose to include patients with $AHI_{3\%A}$ and RDI < 5 events/h in this analysis since, in our clinical experience, we see positive clinical response to PAP therapy, suggesting clinically significant obstructive sleep-disordered breathing as suggested by studies of prolonged partial flow limitation and upper airway resistance syndrome.[1] Further evaluation of clinical and sleep study factors associated with PAP adherence in mild SDB patients is warranted.

We found significant differences in comorbidities between men and women, which can be partly explained by known sex differences in comorbidities. We also found significantly higher rates of most comorbidities than population rates, which may be due to the presence of SDB but also to referral and selection bias in patients who are sent for sleep study evaluation and prescribed PAP therapy. For example, 2015–2016 Centers for Disease Control and Prevention data found 29% of Massachusetts residents with hypertension (30.2% of men and 27.7% of women)[20] compared to 44.9% in our cohort. Depression in the United States in 2013–2016 is present in 10.5% of women and 5.5% of men[21] compared to the 54.4% in women and 40.0% in men in our cohort. Given that our study focused only on mild SDB with many not meeting OSA criteria, these disparities suggest that even mildest forms of sleep-disordered breathing may contribute to comorbidities, although screening a general population would be needed to confirm this. It would be expected that even higher rates of comorbidities would be found in patients with more severe OSA, especially cardiovascular comorbidities.

Similar to a recent study by Won et al, we found that women have less stage N1 sleep and more stage N3 sleep and higher sleep efficiency than men.[8] Men were much more likely to have a supine-dominant pattern, but we did not find other differences, including a REM-dominant pattern or significant differences in oxygen saturations, which is likely due to the exclusion of most patients with significant hypoxia.

Duration of obstructive apneas and hypopneas were the primary difference seen in PSG respiratory markers in males and females. Short respiratory events are a sign of low arousal threshold or high loop gain and are felt to represent either increased ventilatory instability and/or augmented autonomic responses. Despite similar arousal index and higher sleep efficiency in women, we found shorter apnea and hypopnea durations in women than in men. High loop gain is more prevalent in men than women, thus arousal threshold may be the explanation of our finding. In the Sleep Heart Health Study, shorter apnea-hypopnea duration was associated with an increase in all-cause mortality, while correlation was not found with AHI.[22] This analysis found shorter event duration associated with higher BMI, lower AHI and high minimum blood oxygen saturation, and younger age and female sex. We similarly found a shorter obstructive hypopnea duration in women < 50-years-old and shorter duration with increasing BMI. We did not find a significantly higher percentage of patients with $AHI_{4\%}$ and $AHI_{3\%A} \geq 5$ events/h with increasing age or $AHI_{4\%} \geq 5$ events/h with higher BMI, but this may be due to limiting the population to mild SDB, so there may have been more patients with higher AHI who were excluded.

Other studies have suggested that long hypopnea/apnea duration may be associated with more severe desaturations[23,24] and more symptoms of snoring, witnessed apnea, morning tiredness, and hypertension.[25] They also found longer duration in patients with more severe OSA and more hypoxia. These studies suggest that shorter duration may have more significance in distinguishing risks among patients with mild nonhypoxic OSA. This also concurs with more atypical symptoms of insomnia and absence of daytime sleepiness that is more common in mild OSA.[4] Further evaluation is recommended to determine whether these features can help with diagnosis and risk stratification of patients who are at risk for OSA and who would benefit from treatment.

This study included many patients with very mild sleep-disordered breathing, including 19% percent of women and 10% of men with $AHI_{3\%A} < 5$ events/h. Treatment was suggested in most of these patients for a diagnosis of UARS based on an RDI ≥ 5 events/h. A small number of patients had RDI < 5 events/h but with chronic flow limitation that was felt to possibly contribute to the patient's symptoms and warrant a trial of PAP therapy. Most patients in this time period with AHI < 5 events/h, including Medicare patients with $AHI_{4\%} < 5$ events/h, were able to receive PAP therapy covered by insurance for the indication of UARS. Because the studies were rescored to meet current criteria and ensure consistency in scoring, some patients may have had AHI > 5 events/h based on scoring criteria utilized at the time of the study. Many of these patients would be ineligible to receive insurance coverage now.

Prior research suggests that different subtypes of mild OSA are at risk for different comorbidities[1,26] One example is that patients with upper airway resistance patterns have enhanced parasympathetic drive and more hypotension and more somatic comorbidities (eg, depression and headaches), while patients with more hypopneas with desaturations have increased sympathetic drive and more hypertension[3,27] Our findings that in females anxiety, depression, and migraine were present at higher rates with AHI < 5 events/h support the hypothesis that mild sleep-disordered breathing phenotypes with only arousals or prolonged partial flow limitation without distinct obstructive events are associated with somatic comorbidities.[2,28] Given the exclusion of patients with lower oxygen levels, our study was not able to assess whether more hypoxic mild OSA would increase the prevalence of cardiovascular comorbidities. There is increasing recognition of different phenotypes of SDB and the inadequacy of AHI to differentiate patient risks. Lumping of patients with different types of disease may negate the ability to discern risks and benefits in treatment trials.[29] Further treatment studies evaluating different treatment outcomes in populations of patients with particular sleep study findings are needed to clarify which patients will benefit and in which ways.

This study found relatively high rates of comorbidities and equivalent PAP adherence in a cohort of sleep clinic patients with mild SDB irrespective of AHI cut-off points, confirming the need to develop better measures to define and differentiate

this population. Different AHI criteria led to large differences in rates of OSA diagnosis and severities. This suggests that the term "mild," suggesting that the disease is less worthy of treatment or clinical consideration, can be misleading especially when $AHI_{4\%}$ criteria is used. One real-life conundrum caused by the different AHI criteria is that we now regularly see patients benefitting from PAP therapy who are denied coverage for their treatment or require unnecessary retesting as they switch from private insurance to Medicare. Additionally, home sleep apnea testing (HSAT), the current diagnostic method for most patients, increases the number of patients diagnosed as normal or with mild OSA, since the lack of arousal data and sleep times underestimates the AHI. Finding risk-stratifying sleep study measures that are available with HSAT will be critical, which is why we chose to focus primarily on measures that can be used with either PSG or HSAT. AASM currently recommends that all PSGs report arousal-based scoring and that PSG should be performed if HSAT is normal and OSA is suspected.[30]

Limitations of this study include the retrospective nature of the study and the inclusion of only sleep clinic patients, which could have led to referral bias in the presence of comorbidities. One night of polysomnography may not capture true severity in the milder group, where relatively small changes in body position and sleep stage distribution can move an individual above or below a threshold. This is less likely with severe disease. Our selection criteria excluded some patients with $AHI_{3\%A}$ >15 events/h with desaturations < 85%, which may have reduced the number of patients with increased cardiovascular risk. It is unlikely that the exclusion of patients undergoing HSAT affected the patients prior to the end of 2013, when our lab started to perform HSAT, but may have introduced a selection bias that enhanced certain comorbidities after that point. Similarly, a selection bias may be caused by the exclusion of a small number of patients who used alternative treatments, including mandibular advancement devices. Insurance coverage is also a factor that could have affected the selection of patients in our sample.

Sex, age, and BMI differences were present in comorbidity rates and AHI levels. Sex differences were present in mean obstructive apnea and hypopnea duration. This study supports the finding that somatic comorbidities are more common in patients with arousal events and cardiovascular comorbidities with desaturation events. Further studies are needed to determine whether apnea and hypopnea length influence symptoms and comorbidities in males and females with SDB and predicts treatment response. This study lays the groundwork for future studies on mild SDB, including mild OSA, UARS, and PPO, by expanding the understanding of sex, age, and BMI effects as well as scoring criteria effects. Further studies into the effects of PAP therapy on comorbidities and sleep-related symptoms in mild SDB and risk prediction models with novel sleep measures are planned on this cohort.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
AHI, apnea-hypopnea index
$AHI_{4\%}$, AHI defined by hypopneas with 4% desaturations
$AHI_{3\%}$, AHI defined by hypopneas with 3% desaturations
$AHI_{3\%A}$, AHI defined by hypopneas with 3% desaturations or arousals
BMI, body mass index
HSAT, home sleep apnea testing
OSA, obstructive sleep apnea
PAP, positive airway pressure
PPO, prolonged partial airway obstruction
PSG, polysomnography
RDI, respiratory disturbance index
SDB, sleep-disordered breathing
UARS, upper airway resistance syndrome

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