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SCIENTIFIC INVESTIGATIONS

Varying Hypopnea Definitions Affect Obstructive Sleep Apnea Severity Classification and Association With Cardiovascular Disease

Christine H.J. Won, MD, MS[1,2]; Li Qin, PhD[3]; Bernardo Selim, MD[4]; Henry K. Yaggi, MD, MPH[1,2]

[1]Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University School of Medicine, New Haven, Connecticut; [2]Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut; [3]Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut; [4]Section of Pulmonary, Critical Care, and Sleep Medicine, Mayo Clinic, Rochester, Minnesota

Study Objectives: To compare clinical features and cardiovascular risks in patients with obstructive sleep apnea (OSA) based on ≥ 3% desaturation or arousal, and ≥ 4% desaturation hypopnea criteria.

Methods: This is a cross-sectional analysis of 1,400 veterans who underwent polysomnography for suspected sleep-disordered breathing. Hypopneas were scored using ≥ 4% desaturation criteria per the American Academy of Sleep Medicine (AASM) 2007 guidelines, then re-scored using ≥ 3% desaturation or arousal criteria per AASM 2012 guidelines. The effect on OSA disease categorization by these two different definitions were compared and correlated with symptoms and cardiovascular associations using unadjusted and adjusted logistic regression.

Results: The application of the ≥ 3% desaturation or arousal definition of hypopnea captured an additional 175 OSA diagnoses (12.5%). This newly diagnosed OSA group (OSA_{new}) was symptomatic with daytime sleepiness similarly to those in whom OSA had been diagnosed based on ≥ 4% desaturation criteria ($OSA_{4\%}$). The OSA_{new} group was more obese and more likely to be male than those without OSA based on either criterion (No-OSA). However, the OSA_{new} group was younger, less obese, more likely female, and had a lesser smoking history compared to the $OSA_{4\%}$ group. Those with any severity of $OSA_{4\%}$ had an increased adjusted odds ratio for arrhythmias (odds ratio = 1.95 [95% confidence interval 1.37–2.78], P = .0155). The more inclusive hypopnea definition (ie, ≥ 3% desaturation or arousal) resulted in recategorization of OSA diagnosis and severity, and attenuated the increased odds ratio for arrhythmias observed in mild and moderate $OSA_{4\%}$. However, severe OSA based on ≥ 3% desaturation or arousals ($OSA_{3\%/Ar}$) remained a significant risk factor for arrhythmias. OSA based on any definition was not associated with ischemic heart disease or heart failure.

Conclusions: The most current AASM criteria for hypopnea identify a unique group of patients who are sleepy, but who are not at increased risk for cardiovascular disease. Though the different hypopnea definitions result in recategorization of OSA severity, severe disease whether defined by ≥ 3% desaturation/arousals or ≥ 4% desaturation remains predictive of cardiac arrhythmias.

Commentary: A commentary on this article appears in this issue on page 1971.

Keywords: apnea, arrhythmias, cardiovascular disease, hypopnea, obstructive sleep apnea, sleep-disordered breathing

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BRIEF SUMMARY

Current Knowledge/Study Rationale: This study was performed to assess the clinical effect of changing hypopnea definitions in the diagnosis of obstructive sleep apnea (OSA). It is the first to assess the clinical effect of varying hypopnea definitions in a sleep clinic population.

Study Impact: This study demonstrates how the different hypopnea criteria currently in use modify disease severity classification in patients with OSA, as well as capture a new population of patients with the disorder. It also demonstrates that altering hypopnea criteria can modify cardiovascular risk stratification in patients with OSA.

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive episodes of upper airway obstruction resulting in reduced airflow, nocturnal hypoxemia and hypercapnia, arousals, sympathetic stimulation, and exaggerated intrathoracic pressure swings. The apnea-hypopnea index (AHI) scored on overnight polysomnography is the basis for OSA diagnosis and severity classification, as well as the most commonly used metric to determine associations between OSA and comorbidities. Criteria for scoring apneas on polysomnography are straightforward and have remained consistent since their initial description in 1965 (apneas are defined as ≥ 90% cessation in airflow lasting ≥ 10 seconds).[1] However, the definition of hypopnea has been variable, contributing to variability in disease diagnosis and severity classification among clinicians and researchers. Several studies have emphasized the importance of standardizing the definition of hypopnea to appropriately capture disease and to categorize disease severity. The "best" or most meaningful definition will be determined by which most accurately identifies individuals at risk for adverse health outcomes.

In 2001, the American Academy of Sleep Medicine (AASM) supported a definition of hypopnea as a respiratory

event with ≥ 30% reduction in thoracoabdominal movement or airflow lasting at least 10 seconds and associated with ≥ 4% oxygen desaturation.[2] In 2007, the AASM published the first edition of The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications (AASM Scoring Manual) with a recommended definition of hypopnea requiring ≥ 30% reduction in nasal pressure signal accompanied by ≥ 4 % desaturation.[3] These guidelines placed less emphasis on arousal in the scoring criteria compared to the Chicago Criteria from 1999. Several studies argued the 2007 criteria potentially underdiagnoses OSA particularly in low-risk individuals such as those who are lean, women, or children.[4–7] The AASM developed new rules for scoring hypopneas in 2012. Based on these criteria, a hypopnea is scored if airflow decreases ≥ 30% for ≥ 10 seconds and is associated with either ≥ 3% desaturation or an arousal.[8]

OSA is a heterogeneous disease with varying polysomnographic and clinical phenotypes and with a wide potential of disease severity. Therefore, the metrics for any OSA classification should accurately reflect the complex pathology surrounding sleep apnea, and have the greatest predictability for adverse health outcomes. We investigate the effect of the different definitions of hypopnea put forth by the AASM on the AHI, (1) to characterize a newly captured cohort based on a more inclusive definition of AHI, and (2) to determine if a more inclusive versus exclusive definition of hypopnea more accurately identifies risk for cardiovascular outcomes in a high-risk population of United States veterans.

METHODS

The DREAM Study Cohort

The DREAM Study is a multisite, retrospective observational cohort study designed to investigate sleep-disordered breathing and other polysomnographic diagnoses and cardiovascular outcomes. Participants consisted of Veterans Health Administration (VHA) patients from one of three medical centers (West Haven, Connecticut; Indianapolis, Indiana; Cleveland, Ohio). The overall objectives and study design have been reported previously.[9] The Institutional Review Boards at each of the sites approved the conduct of this research (IRB West Haven: #00744; Cleveland: #2007-045; Indianapolis: #0712-57)

At the time of the sleep study, medical, anthropomorphic and demographic characteristics were abstracted from the VHA electronic medical record for visits most recent but proximal to the sleep study. All medical record and polysomnographic abstraction was performed at the central Clinical Epidemiology Research Center (CERC) at the West Haven VHA.

Patients undergoing in-laboratory polysomnography between January 2000 and December 2004 were eligible for inclusion (n = 1,843). Included patients who had a history and physical documented in the electronic medical record prior to the sleep study, and who underwent ≥ 2 hours of attended diagnostic sleep monitoring (924 split-night, 919 full-night diagnostic studies). Patients were excluded if the entire study was performed to evaluate therapy (eg, oral appliance, positive airway pressure, tracheostomy), and if central sleep apnea was a primary sleep breathing disorder (ie, central apnea-hypopnea index [CAHI] ≥ 5 events/h, and CAHI ≥ 50% of respiratory events).

Polysomnography Data Acquisition

Polysomnography acquisition software included: Grass data-acquisition systems (Astro-Med; Warwick, Rhode Island, United States), and CompuMedics PS (Melbourne, Australia). The recording montage included frontal, central, and occipital electrodes referenced to contralateral auricular leads, bilateral electrooculographic channels, two submental electromyographic channels, electrocardiography, nasal pressure transduction, oronasal thermistry, chest/abdomen respiratory inductance plethysmography, finger pulse oximetry, body position (by a mercury gauge sensor) and bilateral anterior tibialis electromyography.

Sleep stages and arousals were scored using 30-second epochs according to Rechtschaffen and Kales criteria. Apnea was defined as ≥ 90% reduction in thermocouple lasting ≥ 10 seconds and was classified as obstructive or central depending on whether respiratory effort was present or absent, respectively. Each polysomnography study was scored twice by blinded sleep technologists, first using the recommended definition of hypopnea from the 2007 AASM Scoring Manual (≥ 30% decrement in amplitude of nasal pressure flow signal for at least 10 seconds associated with a ≥ 4% oxygen desaturation; designated $H_{4\%}$), then using 2012 AASM guidelines (≥ 30% reduction in nasal pressure signal accompanied by ≥ 3% desaturation or an arousal; designated $H_{3\%/ar}$). The $AHI_{4\%}$ and $AHI_{3\%/ar}$ was calculated as the total number of apneas and hypopneas ($H_{4\%}$ or $H_{3\%/ar,}$ respectively) per hour of sleep. The hypopnea index was calculated as the number of hypopneas ($HI_{4\%}$ or $HI_{3\%/ar}$, their respective definitions) per hour of sleep.

Primary Outcomes

Cardiovascular outcomes included self-reported history of arrhythmias (defined as atrial fibrillation, heart block, or history of pacemaker or defibrillator); ischemic heart disease (IHD; including history of coronary artery disease, myocardial infarction, angina, coronary revascularization); congestive heart failure (CHF). All outcomes were adjudicated by an internal medicine trained physician who verified their occurrence by reviewing the medical record.

Statistical Analysis

Cross-tabulation of demographics, symptoms, risk factors, and polysomnography was generated with descriptive statistics of mean (standard deviation) or median (interquartile range) for continuous variables, and frequency (percentage) for categorical variables. In addition, *t* test, Wilcoxon-Mann-Whitney test, or Pearson χ^2 test were performed to determine statistically significant difference between groups for which OSA was diagnosed. Logistic regression model was used to determine whether groups in whom OSA was diagnosed were statistically significant predictors of adverse health outcomes with adjustment of age, sex, body mass index (BMI), hyperlipidemia, and diabetes mellitus (DM). The adjusted odds ratio (OR) and its 95% confidence interval (CI) were calculated with No-OSA

group as reference. SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina, United States) was used for all statistical analysis. All of the *P* values were two-sided, with a level of significance of $P < .05$, with Holm-Bonferroni correction for multiple comparisons.

RESULTS

Characteristics of a Newly Defined OSA Group

Among 1,843 eligible individuals, 443 were excluded due to incomplete medical record or polysomnography data. These patients did not differ significantly in demographics as the remaining 1,400 individuals who qualified for the study. Among the 1,400 participants, 932 (66.6%) received a diagnosis of OSA based on criteria of $AHI_{4\%} \geq 5$ events/h. When ≥ 3% desaturation or arousal criteria for hypopnea was applied, it captured another 175 new diagnoses of OSA (OSA_{new}) among the 468 previously negative studies. In other words, 37.4% of participants who were negative for OSA based on ≥ 4% desaturation criteria now had a diagnosis of OSA based on $AHI_{3\%/ar}$ criteria. Participants qualifying for a diagnosis of OSA based on ≥ 4% desaturation scoring guidelines ($OSA_{4\%}$) were more likely to be male, older, more likely to have obesity, and had a greater smoking history than the OSA_{new} group, as well as those who did not qualify for an OSA diagnosis based on either criterion (No-OSA). The OSA_{new} group was in turn more likely to be male and more likely to have obesity than those in the No-OSA group. Most participants in all study groups had hypertension. **Table 1** compares demographic and anthropomorphic data of participants in the various diagnostic categories.

Polysomnography data showed poorer sleep efficiency, greater percentage of stage N1 sleep, and reduced rapid eye movement (REM) sleep in those with $OSA_{4\%}$ compared to the No-OSA group (**Table 1**) As expected, the median arterial oxygen saturation and oxygen saturation nadir in the $OSA_{4\%}$ group were lower than either group. Sleep architecture was more disrupted in the OSA_{new} group, and oxygen saturations were significantly worse than in those in the No-OSA group. Most participants had periodic limb movement index (PLMI) < 5 events/h (n = 969 or 69.6%), compared to 8.6% (n = 120) with PLMI 5 to < 15 events/h, and 21.8% (n = 304) with PLMI ≥ 15 events/h.

Self-reported sleepiness as measured by the Epworth Sleepiness Scale (ESS) was increased in the OSA_{new} group compared to the No-OSA group to a similar degree as the $OSA_{4\%}$ group. ESS score did not correlate with OSA severity (mild, moderate, and severe defined as AHI < 15, 15–29, and ≥ 30 events/h, respectively), whether severity was considered by $AHI_{4\%}$ or by $AHI_{3\%/ar}$. Snoring was more prevalent in more severe OSA (53.7% versus 33.7% in severe versus mild $OSA_{4\%}$ respectively; and 55.6% severe versus 38.7% mild $OSA_{3\%/ar}$; $P < .001$ for both comparisons). There were few occurrences of self-reported insomnia in the cohort (n = 13 participants, 0.93%).

Redistribution of Disease Diagnosis and Disease Severity Based on Varying Definitions of Hypopnea

When the entire cohort was rescored using the arousal and ≥ 3% desaturation hypopnea definition, there was an increase in the frequency of disease diagnosis, as well as an increase in the prevalence of OSA in each disease severity category. The prevalence of mild, moderate, and severe OSA when rescored by $AHI_{3\%/ar}$ increased by 4.2%, 3.9%, and 4.2%, respectively, compared to the $OSA_{4\%}$ groups (**Figure 1**). This represented a relative increase of 21.4% in mild, 21.3% in moderate, and 15.3% in severe OSA. Most of the OSA_{new} category consisted of mild sleep-disordered breathing (ie, $AHI_{3\%/ar} < 15$ events/h) (**Figure 2**). Only one participant was re-categorized from having no OSA ($AHI_{4\%} < 5$ events/h) to having severe OSA ($AHI_{3\%/ar} \geq 30$ events/h), with most scored respiratory events consisting of arousal-related events.

Cardiovascular Risks in the Group With a New Diagnosis of OSA

Hypertension was prevalent in the cohort, with approximately 70% of participants in each OSA category reporting a history of hypertension. There was an increase in prevalence of DM among the OSA_{new} and $OSA_{4\%}$ groups though OR was not significant after adjusting for BMI. High-density lipoprotein levels were decreased in both OSA_{new} and $OSA_{4\%}$ groups compared to the No-OSA group, and these differences remained statistically significant after adjusting for age, sex, and BMI ($P < .01$ for both comparisons) (**Table 1**).

For cardiovascular associations, $OSA_{4\%}$ conferred a statistically significant increase in OR for arrhythmias (defined as those with a history of atrial fibrillation, heart block, or a history of pacemaker or implanted cardiac defibrillator) compared to those without OSA by either criterion (**Table 2**). The OR remained significant after adjusting for age, sex, and BMI. There was a dose-dependent increase in OR of arrhythmia based on $OSA_{4\%}$ severity, with the most severe $OSA_{4\%}$ having the greatest odds. Reclassifying OSA severity based on the 2012 AASM hypopnea definition (ie, $AHI_{3\%/ar}$) resulted in mild and moderate disease losing predictive value, though severe $OSA_{3\%/ar}$ remained a significant predictor of arrhythmias (**Figure 3**). The OR for arrhythmia was not associated with newly diagnosed OSA (OSA_{new}). Among the $OSA_{4\%}$ group, those with moderate to severe, but not mild $OSA_{4\%}$, also had increased odds for left ventricular hypertrophy (OR 2.62, 95% CI 1.43–4.78, $P = .0085$) compared to the No-OSA group. The odds for IHD in the OSA_{new} group were increased similarly to that of the mild and moderate to severe $OSA_{4\%}$ groups, though there was no statistical significance compared to the No-OSA group. Neither $OSA_{4\%}$ nor $OSA_{3\%/ar}$ was associated with CHF.

DISCUSSION

The current study examines the clinical effect of changing hypopnea definitions as they relate to OSA diagnosis and severity classification in a large veteran sleep clinic population. This study is, to the best of our knowledge, the first to describe the unique group of patients who escape OSA diagnosis based on ≥ 4% desaturation hypopnea criteria, but who are captured by the ≥ 3% desaturation or arousal hypopnea definition. This study addresses the question: who are we capturing with the updated 2012 AASM hypopnea criteria, and how clinically

Table 1—Baseline characteristics of DREAM cohort.

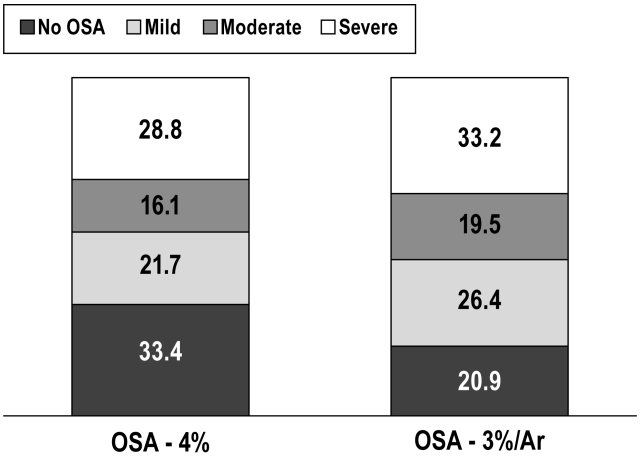
	No-OSA / Control (n = 293, 20.9%)	OSA_{new} (n = 175, 12.5%)	$OSA_{4\%}$ (n = 932, 66.6%)	*P*	
				No-OSA vs OSA_{new}	No-OSA vs $OSA_{4\%}$
Demographics					
Age, years, mean ± SD	54.0 ± 11.9	54.9 ± 10.9	60.0 ± 11.3	.42	< .0001*
BMI, kg/m^2, mean ± SD	32.1 ± 6.0	34.7 ± 8.3	35.3 ± 7.2	.0005*	< .0001*
Male, n (%)	252 (86.0)	164 (93.7)	910 (97.6)	.0103*	< .0001*
Race, n (%)				.60	.40
White	223 (76.1)	139 (79.4)	726 (77.9)		
Black	43 (14.7)	20 (11.4)	110 (11.8)		
Other	27 (9.2)	16 (9.1)	96 (10.3)		
Symptoms					
ESS score, mean ± SD	9.5 ± 5.7	11.9 ± 6.4	10.9 ± 5.8	.0296*	.0200*
Snoring, n (%)	89 (30.4)	26 (14.9)	459 (49.2)	.0002*	< .0001*
Risk Factors					
Hypertension, n (%)	221 (75.4)	122 (69.7)	669 (71.8)	.18	.22
DM, n (%)	90 (31.5)	65 (38.7)	339 (36.8)	.12	.10
HDL, mg/dL, mean ± SD	46.1 ± 13.2	42.6 ± 10.3	43.1 ± 11.0	.0029*	.0010*
Hyperlipidemia, n (%)	197 (67.2)	119 (68.0)	594 (63.7)	.86	.27
Smoking history ≥ 20 pack-year, n (%)	95 (32.4)	55 (31.4)	380 (40.8)	.82	.0105*
Polysomnography					
TST, min, median (IQR)	310.5 (253.5–360.0)	253.0 (140.5–320.5)	119.0 (82.5–223.3)	< .0001*	< .0001*
SE, %, median (IQR)	79.4 (66.8–87.5)	76.2 (65.2–86.0)	74.5 (58.4–85.6)	.12	.0001*
Sleep stages, %TST, median (IQR)					
N1	14.7 (9.7–21.5)	18.0 (11.6–30.1)	20.2 (11.5–35.7)	< .0001*	< .0001*
N2	65.1 (57.2–72.1)	62.0 (49.6–70.6)	66.3 (52.6–76.2)	.0095*	.53
N3	0.9 (0.0–5.5)	1.3 (0.0–6.3)	0.0 (0.0–2.5)	.84	< .0001*
R	12.1 (7.3–18.7)	11.2 (4.1–17.5)	3.4 (0.0–12.7)	.0265*	< .0001*
ArI, median (IQR)	21.1 (14.3–29.0)	31.4 (22.9–43.9)	47.3 (29.1–73.3)	< .0001*	< .0001*
OAI, median (IQR)	0.2 (0.0–0.7)	0.6 (0.0–1.7)	12.3 (5.2–32.2)	< .0001*	< .0001*
CAI, median (IQR)	0.0 (0.0–0.2)	0.0 (0.0–0.4)	0.2 (0.0–1.6)	.22	< .0001*
$HI_{4\%}$, median (IQR)	0.2 (0.0–0.6)	0.8 (0.0–1.7)	3.2 (0.8–9.1)	< .0001*	< .0001*
$AHI_{4\%}$, median (IQR)	0.9 (0.3–1.9)	2.9 (1.6–4.1)	24.5 (11.7–50.4)	< .0001*	< .0001*
$HI_{3\%/ar}$, median (IQR)	1.3 (0.7–2.5)	5.8 (4.1–8.1)	7.4 (3.1–16.1)	< .0001*	< .0001*
$AHI_{3\%/ar}$, median (IQR)	2.5 (1.2–3.4)	7.2 (5.7–9.4)	29.8 (16.6–56.9)	< .0001*	< .0001*
SpO_2, %, median (IQR)	93.9 (92.0–95.3)	92.6 (90.8–94.0)	92.9 (90.7–94.8)	< .0001*	< .0001*
SpO_2 nadir, %, median (IQR)	87.2 (84.0–90.0)	84.2 (81.0- 87.0)	83.0 (78.0–86.4)	< .0001*	< .0001*
PLMI, median (IQR)	0.0 (0.0–11.0)	0.0 (0.0–13.3)	0.0 (0.0–10.4)	.85	.0230*

The $OSA_{4\%}$ group describes participants with $AHI_{4\%}$ ≥ 5 events/h, where $AHI_{4\%}$ is defined by 2007 AASM recommended guidelines for scoring hypopneas (ie, ≥ 30% reduction in nasal pressure signal for ≥ 10 seconds accompanied by ≥ 4% desaturation). The group designated $OSA_{3\%/ar}$ consists of participants with $AHI_{3\%/ar}$ ≥ 5 events/h, whereby hypopneas are scored according to 2012 AASM guidelines (ie, ≥ 30% reduction in nasal pressure signal accompanied by ≥ 3% desaturation or an arousal). OSA_{new} defines the group of participants who have been included in the OSA diagnosis based on $AHI_{3\%/ar}$ criteria, who otherwise did not meet $AHI_{4\%}$ criteria. No-OSA defines the group of participants without OSA based on either criterion. * = Holm-Bonferroni method was used to calculate alpha levels; alpha level of < .025 for first rank *P* value, and alpha level < .05 for second rank *P* value were used for statistical significance (corrected for two group tests). AHI = apnea-hypopnea index (defined according to OSA category), AI = apnea index, ArI = arousal index, BMI = body mass index, CAI = central apnea index, DM = diabetes mellitus, ESS = Epworth Sleepiness Scale, HDL = high-density lipoprotein, HI = hypopnea index (hypopnea defined according to OSA category), IQR = interquartile range, OAI = obstructive apnea index, OSA = obstructive sleep apnea, PLMI = periodic limb movement index, REM = rapid eye movement, SD = standard deviation, SE = sleep efficiency (defined as percentage of bed time spent in sleep), SpO_2 = arterial oxygen saturation, TST = total sleep time.

relevant is the diagnosis for the group? As such, our findings have direct clinical applicability and relevance.

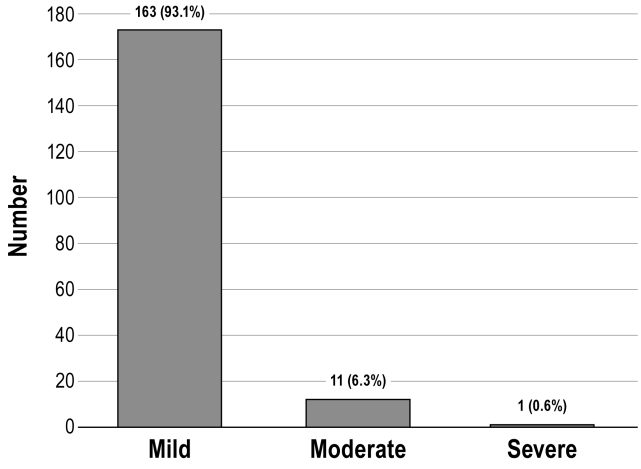
Although previous studies have examined the effect of changing hypopnea definitions on OSA prevalence and severity re-categorization,[10–18] our study compares the currently clinically utilized hypopnea definition and evaluates its significance for clinical associations. Our findings suggest a more inclusive hypopnea definition: (1) alters OSA severity categorization, (2) identifies a new symptomatic group of patients with predominantly mild OSA without increased cardiovascular odds, and (3)

Figure 1—Distribution of OSA severity based on differing hypopnea criteria.



Percentage of participants with different OSA severity among DREAM cohort when OSA is defined by $AHI_{4\%}$ ($OSA_{4\%}$), compared to OSA severity categorized by $AHI_{3\%/ar}$ ($OSA_{3\%/ar}$). Approximately 12.5%, or 175 participants were newly diagnosed with OSA when using the $AHI_{3\%/ar}$. Each severity category increased by approximately 4%. Mild, moderate, and severe OSA defined by 5 ≤ AHI < 15, 15 ≤ AHI < 30, and AHI ≥ 30 events/h, respectively. AHI = apnea-hypopnea index, OSA = obstructive sleep apnea.

Figure 2—Distribution by OSA severity of participants newly captured in OSA diagnosis based on 3% or arousal for hypopnea definition (OSA_{new}).



Most participants with a new diagnosis of OSA were in the mild category (ie, 5 ≤ AHI < 15 events/h); however, 6.5% went from having no OSA to having moderate OSA when polysomnography was scored based on ≥ 3% or arousal definition of hypopnea. AHI = apnea-hypopnea index, OSA = obstructive sleep apnea.

Table 2—Metabolic and cardiovascular adjusted odds ratio in those with new diagnosis of OSA (OSA_{new}) based on ≥ 3% desaturation and arousal-defined hypopneas, and OSA based on ≥ 4% desaturation hypopneas, compared to those without OSA based on either definition.

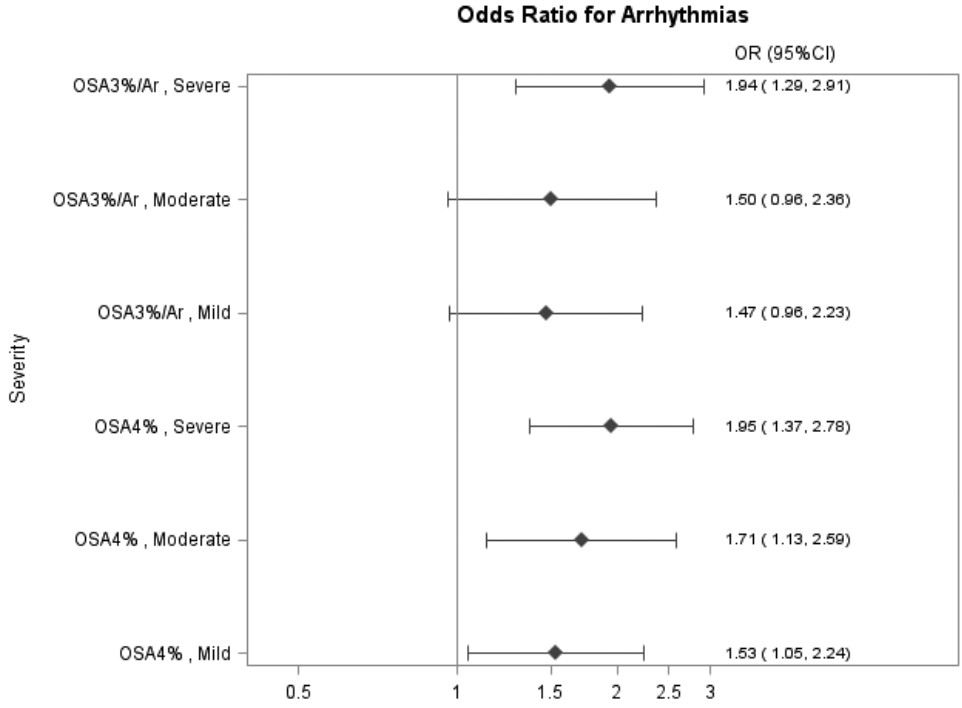
	No-OSA (n = 293, 20.9%)	OSA_{new} (n = 175, 12.5%)	Mild $OSA_{4\%}$ (n = 304, 21.7%)	Mod-Severe $OSA_{4\%}$ (n = 628, 44.9%)
	1.0			
Arrhythmia		1.08 (0.64–1.83)	1.53 (1.05–2.24)*	1.90 (1.28–2.81)*
Ischemic Heart Disease		1.30 (0.82–2.07)	1.22 (0.81–1.83)	1.36 (0.94–1.97)
Heart Failure		1.13 (0.62–2.07)	1.00 (0.58–1.72)	0.96 (0.59–1.57)

Values are presented as adjusted odds ratio (95% confidence interval). Odds ratio was adjusted for age, sex, body mass index, hyperlipidemia and diabetes mellitus. Mild $OSA_{4\%}$ defined as 5 ≤ $AHI_{4\%}$ < 15, moderate-severe (mod-severe) $OSA_{4\%}$ defined as $AHI_{4\%}$ ≥ 15 events/h. * = P < .001 compared to No-OSA group. AHI = apnea-hypopnea index, OSA = obstructive sleep apnea.

does not ameliorate the increased odds predicted by severe OSA for arrhythmias. The more inclusive hypopnea definition does not affect the odds that a severe OSA diagnosis (ie, $AHI_{3\%/ar} \geq 30$ events/h) confers likely because of the preponderance of ≥ 4% desaturating hypopneas in our high-risk clinic population. The re-categorization of disease severity based on either hypopnea definition persistently predicted greater OR for arrhythmia at greater OSA disease severity. We also noted that among the OSA_{new} group, only 36.6% (n = 64) had AHI ≥ 5 events/h based on a hypopnea definition of 3% desaturations only (ie, without arousal criteria). This means that if type III home testing were used, 63.4% of these participants would have been excluded from diagnosis even though they shared similar demographic and clinical features as the rest of the group, implying hypopnea definitions also affect results for home sleep testing.

Outcome-based definitions of sleep-disordered breathing are important for many reasons, including their implications on disease identification, severity classification, treatment decisions, and public health, as well as for research purposes. However, as our study demonstrates, a clinical outcome-based hypopnea definition may not be easily characterized by a single criterion. A hypopnea is a complex multivariable event involving simultaneous changes in several physiological parameters such as ventilation, oxygenation, and/or arousal, all of which likely differentially contribute to symptoms or development of cardiovascular disease. Other polysomnographic features not captured by a summary AHI may also be important in risk stratification, such as load responsiveness, central breathing stability, positional disease, sleep stage-dependent disease, event-related hypoxemic burden or event-related autonomic burden. For example, several studies have shown that nocturnal hypoxemia rather than AHI or arousal index predicted occurrence of atrial fibrillation,[19–23] with this association being stronger in women and in middle-aged persons with

Figure 3—Adjusted odds ratio for arrhythmias.



Adjusted for age, sex, and body mass index. $OSA_{3\%/ar}$ met OSA diagnosis based on hypopnea definition of desaturation ≥ 3% or arousal, with $AHI_{3\%/ar}$ ≥ 5 events/h. $OSA_{4\%}$ met OSA diagnosis based on hypopnea definition of desaturation ≥ 4%, with $AHI_{4\%}$ ≥ 5 events/h. Reference group was No-OSA group (those who did not meet AHI criteria of ≥ 5 events/h based on either definitions of hypopnea). Mild OSA defined as 5 ≤ AHI < 15 events/h, moderate OSA defined as 15 ≤ AHI < 30 events/h, and severe OSA defined as AHI ≥ 30 events/h. AHI = apnea-hypopnea index, OSA = obstructive sleep apnea.

obesity.[24] Similarly, REM-related OSA has been independently associated with hypertension in the Wisconsin Sleep Cohort Study (WSCS),[25] and with all-cause mortality in the Sleep Heart Health Study (SHHS) but only in men age 70 years or younger.[26] Therefore, a simple comparison of the AHI based on a ≥ 3% versus a ≥ 4% desaturation threshold as a predictor of multiple clinical outcomes may be insufficient. Rather, the clinical value of different respiratory event definitions may need to be individually determined for at-risk populations.

Our study has several strengths that allow it to have direct applicability to the current clinic population. In this study, we were able to measure the effect of differing clinically utilized hypopnea definitions on symptoms and clinical associations, rather than simply on the re-distribution of AHI as many studies have previously done. Other strengths that allow this study to have real-world applicability include the fact that (1) we were able to detect hypopneas by current standards of nasal pressure monitoring; (2) we employed currently utilized hypopnea definitions put forth by the AASM; and finally, (3) our study sample was large and consisted of clinic-based participants. Very few large observational studies with outcomes data have incorporated nasal pressure transducer and oronasal thermistor-derived hypopnea definitions, as recommended by the most current AASM guidelines.[3] Data from the two largest sleep cohort studies, the SHHS and WSCS, used definitions of hypopneas based on inductance plethysmography signals with associated desaturation and showed that the derived AHIs using these hypopnea measurements correlated with various indices of morbidity. Likewise, other studies have used thermistors to define hypopneas, with varying desaturation indices or airflow reduction requirements,[11,12] which has shown to be far inferior in validity and reliability of hypopnea detection compared with a nasal pressure device.[27] A recent population study from Switzerland revisited the prevalence of sleep-disordered breathing using nasal pressure transducer signals and the most recent AASM scoring guidelines to find a much higher prevalence of disease in their population, and a continued independent association between sleep apnea and cardiovascular and metabolic disease.[28] These findings reinforce that the identification of disease is highly dependent on technical factors.

Several limitations are noted, including the fact that the cohort consisted entirely of patients from the VHA who were predominantly middle-aged and older Caucasian men, with a high prevalence of obesity, smoking, hypertension, and other important cardiovascular risk factors. The results therefore have limited generalizability, including among other VHA systems that have greater representation of African-American, female, or younger veterans. Because this cohort had significant disease burden, it is possible that the clinical effect of sleep-disordered breathing on cardiovascular risk by either hypopnea criteria may have been underdetected, unlike the findings from the SHHS which found a ≥ 4% desaturation threshold for increased risk of self-reported coronary artery disease, heart failure, or cerebrovascular events in a general population cohort.[29] There may be inaccuracies with self-reported symptoms. For example, fewer than 1% of our cohort reported

insomnia. Insomnia is a very common complaint affecting 10% to 20% of the general adult population,[30] yet the prevalence of diagnosed insomnia in United States veterans is much lower at 0.4% to 3.4%[31,32] likely reflecting underreporting, underrecognition, or underdiagnosis. The fact that the prevalence was so low in this study reflects the methodological limitations of self-reporting a complaint or a diagnosis of "insomnia." Validated assessment tools for insomnia would have potentially captured a more accurate prevalence. Because our participants consisted of a sleep clinic population, there was high clinical suspicion for sleep-disordered breathing, and patients were generally symptomatic or there was enough concern for health implications to warrant sleep study referral. It should also be noted that 46.6% of participants had split-night studies due to the severity of their sleep apnea. Although a truncated diagnostic study may underestimate AHI severity, it is unlikely to have changed our analysis because groups were compared categorically by AHI cutoffs, and the mean $AHI_{4\%}$ for split-night studies was 39.3 per hour (standard deviation 3.2). In addition, the analysis was cross-sectional; therefore, a temporal relationship between sleep apnea and cardiovascular disease could not be established. A causative or temporal relationship is better demonstrated by a prospective longitudinal study design to compare incidences of cardiovascular disease in the different study groups. Finally, as in any observational study, confounding by unmeasured variables cannot be excluded, although there was statistical adjustment for potential confounders.

The results of this study have important clinical implications because they show the most current 2012 AASM criteria for hypopnea identifies a unique group of patients with significant complaints of daytime sleepiness without significant cardiovascular risk. In practice, clinicians generally do not rely solely on AHI for OSA diagnosis and for determining treatment plans, but also base decisions on symptoms, sleep disruptions, degree of hypoxemia, and a host of other polysomnographic and clinical data. Further investigation would be useful to examine how other polysomnographic features may better characterize cardiovascular or other health risks or symptoms in those with sleep-disordered breathing. It would also be important to assess whether treatment in any of these groups leads to improved cardiovascular health, or whether treatment of the OSA_{new} group leads to improved daytime sleepiness or quality of life. The AHI is likely an oversimplified measure of sleep-disordered breathing, and alone does not explain all health risks that affect these patients. Nonetheless, the AHI currently remains a widely used metric for OSA diagnosis, severity classification, treatment determination, and research, emphasizing the importance of this analysis.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
AHI, apnea-hypopnea index
BMI, body mass index
DM, diabetes mellitus
ESS, Epworth Sleepiness Scale
OR, odds ratio
OSA, obstructive sleep apnea
PLMI, periodic limb movement index
REM, rapid eye movement
VHA, Veterans Heath Administration

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Address correspondence to: Christine Won, MD, MS, 333 Cedar Street, New Haven, CT 06520; Email: christine.won@yale.edu

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