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SCIENTIFIC INVESTIGATIONS

Relevance of cortical arousals for risk stratification in sleep apnea: a 3 cohort analysis

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Study Objectives: There is uncertainty on best approaches for defining apnea-hypopnea events. To clarify the contributions of desaturation vs arousal to defining hypopneas, we examined the associations of events with desaturation (≥ 3%) but not arousal (apnea-hypopnea index [AHI]$_{\geq 3\%Only}$) vs events with arousals but no desaturation (AHI$_{ArOnly}$) with obstructive sleep apnea-related comorbidities and incident cardiovascular disease across multiple cohorts.

Methods: In the Sleep Heart Health Study (n = 5,473), the Multi-Ethnic Study of Atherosclerosis (n = 1,904), and the Osteoporotic Fractures in Men Study (n = 2,685), we examined the independent associations of AHI$_{\geq 3\%Only}$ and AHI$_{ArOnly}$ with hypertension, diabetes, and daytime sleepiness, and incident cardiovascular disease.

Results: After adjusting for covariates and AHI based on events with electroencephalogram arousal (regardless of desaturation), AHI$_{\geq 3\%Only}$ was associated with hypertension in Sleep Heart Health Study (odds ratio: 1.12; 95% confidence interval: 1.04,1.21), per 1 standard deviation increase). Similar associations were observed in the Multi-Ethnic Study of Atherosclerosis and Osteoporotic Fractures in Men Study, as well as for associations with diabetes (odds ratio: 1.30; 1.09,1.54, and 1.25; 1.07,1.47, respectively), sleepiness (odds ratio: 1.19; 1.00,1.41; and 1.17; 1.01–1.35), and incident cardiovascular disease (hazard ratio: 1.37; 1.05,1.77 and 1.14; 1.00,1.29). In contrast, after adjusting for events with desaturation (regardless of arousal), AHI$_{ArOnly}$ was unassociated with these outcomes. In Sleep Heart Health Study, greater baseline obstructive sleep apnea severity was associated with a reduction in arousal frequency over 5 years ($P < .0001$).

Conclusions: In middle-aged and older individuals, addition of events with arousals does not improve the strength of associations with comorbidities or incident cardiovascular disease. Research is needed to understand generalizability to younger individuals and the mechanistic role of arousals in obstructive sleep apnea.

Keywords: arousal, hypoxemia, desaturation, sleep apnea, cardiovascular disease, prediction

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The apnea-hypopnea index is commonly used for obstructive sleep apnea diagnosis. A hypopnea is included in the apnea-hypopnea index calculation if it was accompanied by either a ≥ 3% oxygen desaturation or an electroencephalogram arousal. The notion of using respiratory arousals to quantify the severity of obstructive sleep apnea assumes that the arousals provide a measure of physiological stress apart from or in addition to the event-related desaturations. However, the independent effect of respiratory arousals has not been adequately addressed.

Study Impact: Our findings suggest that including arousals in the apnea-hypopnea index calculation does not improve cross-sectional or prospective associations with cardiovascular disease and sleepiness. These results support screening and diagnostic approaches for sleep apnea in middle-aged and older adults that rely on recording event-related desaturations.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder[1] associated with cardiometabolic dysfunction,[2] daytime sleepiness, and neurocognitive deficits.[3] OSA is characterized by upper airway obstructions (apneas/hypopneas) during sleep that lead to oxygen desaturations and/or cortical arousals ("respiratory arousals"). A growing body of research implicates OSA-related intermittent hypoxemia, particularly sleep-apnea associated hypoxic burden[4–8] as a key mechanism linking OSA to adverse health outcomes.[4,5,9–13] Sleep fragmentation is another pathway that may mediate adverse outcomes,[14] and its quantification has been suggested to be important in characterizing OSA-related morbidities. However, identification of sleep fragmentation requires electroencephalogram (EEG)-based approaches that are limited through home sleep apnea tests, which are increasingly used for OSA diagnosis. It is therefore important to understand the contributions of desaturation vs arousals (occurring alone or in combination) for risk stratification.

The apnea-hypopnea index (AHI), defined as the number of complete (apnea) or partial (hypopnea) obstructions of the upper airway per hour of sleep, is the most commonly used metric to quantify the severity of OSA. Several different criteria for accompanying features to define a hypopnea for inclusion in the AHI calculation are widely used: a ≥ 4% decrement in oxygen saturation; a ≥ 3% decrement in oxygen saturation; or

either a ≥ 3% decrement in oxygen saturation or an EEG arousal. Use of desaturation and/or arousal to quantify OSA severity reflects the expectation that there are dual effects of OSA on health: (1) intermittent desaturation promotes oxidative stress, systemic inflammation, sympathetic nervous system activation and endothelial dysfunction,[15,16] increasing cardiovascular and metabolic risk; (2) recurrent arousal impairs the restorative function of sleep, increasing risk of daytime sleepiness and cognitive impairment.[17] However, while arousal frequency does predict daytime impairment in OSA, the AHI and degree of hypoxemia have also been shown to predict these outcomes.[18,19] Finally, the notion of using respiratory arousals to quantify the severity of OSA (eg, AHI based on arousals or ≥ 3% desaturation) assumes that the frequency of respiratory arousals is a reliable measure of sleep fragmentation, which is linked experimentally to adverse metabolic[20] and cardiovascular[21] responses and that the arousals provide a measure of physiological stress apart from or in addition to the apnea/hypopnea-related desaturations. However, there may be maladaptation to arousals over time[22] and across the night, and the independent effect of respiratory-related arousals has not been adequately addressed.

Therefore, in this study, added predictive value of arousals vs desaturation (occurring alone or in combination) were systematically assessed. The frequency of events with desaturation (≥ 3%) but not arousal ($AHI_{\geq 3\%Only}$) vs events with arousals but no desaturation (AHI_{ArOnly}) was obtained from 3 community-based prospective cohort studies comprising more than 10,000 adults. Independent associations of these 2 metrics with prevalent comorbidities, including hypertension, diabetes, and excessive daytime sleepiness (Epworth Sleepiness Scale > 10), and incident cardiovascular disease (CVD) were assessed. Finally, the data from an Epworth Sleepiness Scale 5-year follow-up polysomnogram in a subsample of participants were used to assess whether the longitudinal change in the number of arousals was associated with baseline OSA severity to explore the hypothesis that arousal index decreases as an adaptive phenomenon (ie, maladaptation to arousal stimuli over time).

METHODS

To examine the association of event-related arousals vs desaturations with comorbidities and outcomes, 3 independent prospective cohort studies were used, including the Sleep Heart Health Study (SHHS), the Multi-Ethnic Study of Atherosclerosis (MESA), and the Osteoporotic Fractures in Men Study (MrOS) (see supplemental material for detailed methods).

Study samples

SHHS

The SHHS is a large community-based, prospective cohort study designed to assess the cardiovascular outcomes of sleep-disordered breathing in adults.[23–25] A total of 5,473, ages ≥ 40 years, had sufficient quality EEG for arousal scoring and had complete data on covariates and outcome.

MESA

The MESA is a longitudinal community-based cohort of 6,814 adults enrolled between 2000 and 2002 (Exam 1) from 6 clinical centers when participants were ages 45–85 years and free of known CVD.[26] A total of 2,261 participated in the sleep exam,[27] performed in proximity to the Exam 5 (2010 to 2013), which included sleep questionnaires, actigraphy, and in-home polysomnography (PSG).[28] Of these, 1,904 participants had complete data on covariates and outcomes, had sufficient quality EEG for arousal scoring, and were available for analysis.

MrOS

The MrOS Sleep Study (https://mrosonline.ucsf.edu) was a community-based, prospective cohort study of 5,994 men ≥ 65 years enrolled between 2000 and 2002 from 6 centers across the United States and designed to describe the epidemiology of osteoporosis and fractures in older men.[29,30] A total of 3,135 men from the MrOS parent study participated in the ancillary MrOS Sleep Study (2003–2005). A total of 2,685 participants had complete data and were available for analysis.

In all 3 cohorts, Institutional Review Board approval was obtained at all study sites and all participants provided written informed consent.

Clinical endpoints and outcomes

Definition of hypertension

For this report, hypertension was defined as participant reported use of antihypertensive medications, or an average systolic blood pressure measurement of ≥ 140 mm Hg or a diastolic blood pressure measurement of ≥ 90 mm Hg, obtained during a research clinic examination (based on the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[31]). Systolic blood pressure and diastolic blood pressure were the mean value of 2 measurements in sitting position.

Definition of diabetes

Diabetes was defined based on current treatment of diabetes using hypoglycemic medications or insulin in SHHS and MESA, while in MrOS, diabetes was defined based on a "yes" answer to "Is your diabetes being treated by a doctor?" Those who answered "I don't know" or were unsure were considered nondiabetic.

Definition of sleepiness

Excessive daytime sleepiness (or sleepiness) was defined as an Epworth Sleepiness Scale score of 11 or more.[32]

Definition of incident CVD

SHHS: In SHHS, incident CVD included fatal and nonfatal myocardial infarction (MI), MI-related procedures, fatal and nonfatal stroke, congestive heart failure, coronary heart disease-related death, and other CVD-related deaths not defined in other events as defined by adjudication procedures described before.[10,23] The follow-up time was defined as the time between the sleep study and the first CVD event or the last contact. After excluding

those with preexisting CVD, 3,944 were available for incident analysis.

MESA: CVD-related events included MI, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), stroke, stroke death, coronary heart disease-related death, other CVD- or atherosclerotic-related death not otherwise defined in other categories, ascertained through periodic follow-up contact and adjudicated as described before.[26] After excluding those with preexisting CVD, 1,783 individuals were available for incident CVD analysis.

MrOS: Incident CVD was defined as any type of fatal or nonfatal cardiovascular events, including coronary heart disease, cerebrovascular disease events, peripheral vascular disease, other CVD events, and any heart failure, adjudicated as described in previous studies.[33] After excluding those with preexisting CVD or incomplete data, 1,557 participants were available for incident CVD analysis.

Polysomnography

For all 3 cohorts, unattended type 2 PSG was conducted using Compumedics Ltd., (Abbotsville, AU) equipment. All montages included central EEG, bilateral electrooculography, chin electromyography, electrocardiogram, nasal pressure (only MESA and MrOS) and thermistry (for airflow measurement), chest and thoracic inductance plethysmography, and finger pulse oximetry (Nonin, Minneapolis, MN). Using standardized criteria, a centralized Sleep Reading Center (initially based at Case Western Reserve University, Cleveland, OH, and then at Brigham and Women's Hospital, Boston, MA; both directed by SR) scored all studies. Hypopneas were scored if the reduction in airflow or respiratory inductance effort was 30–90% from baseline for at least 10 seconds, while apneas were defined by a reduction in airflow exceeding 90% for at least 10 seconds. Sleep stages and arousals were scored consistently across the 3 cohorts consistent with published guidelines,[34] with arousals identified as an abrupt increase in EEG frequency of at least 3 seconds in duration, with arousals in rapid eye movement sleep also requiring an increase in chin electromyogram activity. Scoring of respiratory events and arousals was conducted by trained and research-certified PSG technologists who underwent regular assessment of scoring reliability, with retraining as needed. The intra- and interscorer for respiratory event detection ranged from 0.76 to 0.99. For arousal index, the interscorer variability was 0.54 for an early set of SHHS studies, including 500 (7.7% of total sample) PSGs, which had larger amount of technical artifact. Subsequent interscorer reliability in SHHS (kappa statistic ranging 0.70–0.76) reflected a higher reliability that was also consistent with the good to excellent reliability (inter- and intraclass correlations) for scored arousals in MrOS (0.74–0.97) and MESA (0.84–0.94). Moreover, this range is consistent with what is achieved in routine clinical/research studies.[18]

Definitions of AHI metrics and nonrespiratory arousal index

To compare events based on desaturation vs EEG arousal, frequency of events with desaturation (≥ 3%) but not arousal ($AHI_{\geq 3\%Only}$) and frequency of events with arousals but no desaturation (AHI_{ArOnly}) was calculated across 3 cohorts. In this study, both apneas and hypopneas were required to have desaturation or arousal to be included in the experimental AHIs defined above; nonetheless, apneas with neither desaturation nor arousal were rare (SHHS: 0.1[0, 0.6] events/h; MESA: 0.0[0.0, 0.0] events/h; MrOS: 0.0[0.0, 0.1] events/h).

An event was associated with arousal if a scored arousal was identified within a subject-specific search window (see supplemental material for more details) at the end of events. Similarly, the desaturation was calculated as the difference between maximum pre-event SpO_2 and minimum SpO_2 within a subject-specific search window (see supplemental material for more details), described in previous studies.[4,5,35] In addition to these AHIs, the nonrespiratory arousal index was defined as the number of arousals, not linked with respiratory events, per hour of sleep.

Statistical analysis

Distributions of covariates, AHI variables, and cross-sectional outcomes are summarized for each study cohort. All statistical analyses were conducted using the R statistical package (http://www.r-project.org).

Primary analyses (role of desaturation vs arousal)

Multiple logistic or Cox regression models were constructed to assess the independent association of $AHI_{\geq 3\%Only}$ vs AHI_{ArOnly} with hypertension, diabetes, and sleepiness (for every 1 standard deviation increase in each AHI; each AHI variable was log-transformed and then modeled). In the first model, the additional role of $AHI_{\geq 3\%Only}$ was examined after adjusting for age, sex, race and ethnicity, and the AHI based on events with arousal (regardless of desaturation). In the second model, the additional role of AHI_{ArOnly} was examined after adjusting for age, sex, and race and ethnicity and the AHI based on events with ≥ 3% desaturation (regardless of arousal). In sensitivity analyses, these associations were further adjusted for body mass index. Adjustment for additional risk factors or confounders was not performed as we were not attempting to develop a causal model but focused on differences in prediction for AHI based on arousal or desaturation in a demographic-adjusted model as may be used in a clinical setting.

Secondary analyses

In an additional secondary analysis to explore whether associations persisted in those with milder OSA, we examined the associations of AHI_{ArOnly} with health outcomes, described above, in a subgroup of individuals with an AHI < 15 events/h (AHI based on events with ≥ 3% desaturation regardless of arousal). A similar analysis was performed for $AHI_{\geq 3\%Only}$. In a separate secondary analysis, the associations of AHI (based on ≥ 3% desaturation or arousal) with health outcomes, described above, were quantified.

Secondary analyses (longitudinal change in arousal [SHHS])

One hypothesis for why the inclusion of EEG-based arousal as an event-defining metric appears to weaken associations of

these AHIs with outcomes is that arousal frequency decreases over time as a maladaptive mechanism, and thus low arousal frequency may reflect longer duration of disease and higher arousal threshold. We explored this by performing additional analysis in SHHS to evaluate the longitudinal change in the number of arousals and to examine the extent to which baseline OSA severity predicted the change in arousal index.

RESULTS

Baseline characteristics

The baseline characteristics of participants in SHHS, MESA, and MrOS studies are shown in **Table 1**. At the baseline sleep study, MrOS participants were older (76.4 ± 5.6 years) than SHHS (63.0 ± 11.2 years) and MESA (68.3 ± 9.1 years). MESA had the highest proportion of women (53.5%) followed by SHHS (52.5%) and MrOS (only male), respectively. Finally, MESA participants were more diverse by racial and ethnic group (**Table 1**). The prevalence of hypertension and diabetes was higher in MESA (59.2% for hypertension and 15.6% for diabetes; **Table 1**), followed by MrOS and SHHS. However, excessive daytime sleepiness was more prevalent in the SHHS (25.0%) than in MESA (13.4%) or MrOS (13.0%). The incidence of CVD was highest in MrOS (24.9%, follow up: 8.2 ± 3.3 years) followed by the SHHS (19.8%, follow up: 10.3 ± 3.5 years) and MESA (5.4%, follow up: 4.7 ± 1.1 years), reflecting the differences in the age, sex, and duration of follow-up across cohorts.

As shown in **Table 2**, a total of 1,592,429 events with ≥ 3% desaturation or arousal were identified across the 3 cohorts (n = 10,062 participants), of which 205,598 (12.9%) were linked with an arousal and with no or minimal desaturation (ie < 3%), whereas 49% were associated with ≥ 3% desaturation and with no arousal (**Table 2**). The prevalence of moderate to severe OSA in this sample ranged from 67 to 70% based on a total AHI (≥ 3% or arousal) ≥ 15 events/h. Excluding events with arousal and no desaturation lowered the prevalence of moderate to severe OSA by about 10%, ranging between 58% and 60% of this community sample (**Table 2**).

Contributions of arousals vs desaturations

Primary analyses (role of desaturation vs arousal)

After adjusting for demographic factors and the AHI based on events with arousal (regardless of desaturation), $AHI_{\geq 3\%Only}$ was associated with increased odds of adverse health outcomes (**Table 3**). In contrast, after adjusting for covariates and the AHI based on events with desaturation (regardless of arousal), AHI_{ArOnly} was not associated with increased odds/hazard ratio of these outcomes (**Table 3**). The findings were consistent across 3 cohorts (**Table 3**). For example, in the adjusted model in MESA, the odds [point estimate (95% confidence interval)] of hypertension, diabetes, sleepiness increased by 33 (18–50)%,

Table 1—Baseline characteristics of cohort studies, including the MESA, the MrOS study, and the SHHS.

	SHHS (n = 5,473)	MESA (n = 1,904)	MrOS (n = 2,685)
Age, years	63.0 (11.2)	68.3 (9.1)	76.4 (5.6)
Female sex, n (%)	2871 (52.5%)	1019 (53.5%)	0 (0.0%)
BMI, kg/m^2	28.2 (5.1)	28.7 (5.5)	27.1 (3.8)
Race, n (%)			
White	4647 (84.9%)	694 (36.4%)	2430 (90.5%)
Chinese	0 (0.0%)	230 (12.1%)	0 (0.0%)
Black	458 (8.4%)	527 (27.7%)	0 (0.0%)
Hispanic	0 (0.0%)	453 (23.8%)	53 (2.0%)
Other	368 (6.7%)	0 (0.0%)	29 (1.1%)
African American	0 (0.0%)	0 (0.0%)	90 (3.4%)
Asian	0 (0.0%)	0 (0.0%)	83 (3.1%)
Hypertension, n (%)	2760 (50.4%)	1013 (59.2%)	1518 (56.5%)
Diabetes, n (%)	385 (5.2%)	267 (15.6%)	294 (10.9%)
Sleepiness (ESS > 10), n (%)	1316 (25.0%)	253 (13.4%)	349 (13.0%)
Follow-Up Data	**SHHS (n = 3,944)**	**MESA (n = 1,783)**	**MrOS (n = 1,557)**
Incident CVD, n (%)	779 (19.8%)	96 (5.4%)	388 (24.9%)

In MESA, incident CVD included myocardial infarction (MI), resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), stroke, stroke death, coronary heart disease-related death (CHD), other atherosclerotic death not defined in stroke and CHD-related death, and other CVD-related death not defined in other categories. In MrOS, incident CVD include any type of fatal or nonfatal cardiovascular events, including coronary heart disease, cerebrovascular disease events, peripheral vascular disease, cardiovascular disease events, and any heart failure. In SHHS, incident CVD included fatal and nonfatal MI, MI-related procedures, fatal and nonfatal stroke, congestive heart failure, CHD-related death, and other CVD-related deaths not defined in other events. BMI = body mass index, CVD = cardiovascular disease, ESS = Epworth Sleepiness Scale, MESA = Multi-Ethnic Study of Atherosclerosis, MrOS = Osteoporotic Fractures in Men, SHHS = Sleep Heart Health Study.

Table 2—Indices of obstructive sleep apnea severity in the MESA, the MrOS study, and the SHHS.

	SHHS (n = 5473)	MESA (n = 1904)	MrOS (n = 2685)
Total number of events, n (%)	872,808	315,506	404,115
Events with ≥ 3% desaturation only	474819 (54.4%)	137224 (43.5%)	172034 (42.6%)
Events with arousal only	114215 (13.1%)	47350 (15.0%)	44033 (10.9%)
Total AHI, events/h	27.4 (20.7)	28.4 (20.7)	25.7 (17.1)
$AHI_{\geq 3\%Only}$	14.9 (13.2)	12.1 (11.4)	10.8 (8.8)
AHI_{ArOnly}	3.5 (3.4)	4.2 (4.3)	2.8 (2.8)
Prevalence of moderate to severe OSA, n (%)			
Total AHI ≥ 15 events/h	3,682 (67.3%)	1,340 (70.4%)	1,841 (68.6%)
$AHI_{\geq 3\%}$ ≥ 15 events/h	3,168 (57.9%)	1,110 (58.3%)	1,619 (60.3%)

The numbers are mean (standard deviation) or total number (proportion). Total AHI = total number of apneas and hypopneas associated with ≥ 3% desaturation or arousal, $AHI_{\geq 3\%Only}$ = total number of apneas and hypopneas associated with ≥ 3% desaturation and with no arousal, AHI_{ArOnly} = total number of apneas and hypopneas associated with arousal and with desaturation < 3%, $AHI_{\geq 3\%}$ = total number of apneas and hypopneas associated with ≥ 3% desaturation regardless of arousal, MESA = Multi-Ethnic Study of Atherosclerosis, MrOS = Osteoporotic Fractures in Men, SHHS = Sleep Heart Health Study.

52 (29–79)%, and 26 (7–47)% for every 1 standard deviation increase in $AHI_{\geq 3\%Only}$. Similarly, every 1 standard deviation increase in $AHI_{\geq 3\%Only}$ was associated with a 30 (2–65)% increased risk of incident CVD (**Table 3**). In contrast, in the same cohort, AHI_{ArOnly} was associated with decreased odds of hypertension and diabetes, while there was no association with sleepiness or incident CVD (**Table 3**). Further adjustment for body mass index slightly weakened these associations; however, it did not meaningfully change the primary findings of this study (**Table 4**).

Secondary analyses

In a subgroup of individuals with an AHI < 15 events/h (AHI based on all events with arousal regardless of desaturation), the associations of $AHI_{\geq 3\%Only}$ with the health outcomes were similar to the overall sample shown in **Table 4**. The associations with diabetes and incident CVD remained significant in both MESA and MrOS and the hazard ratios for incident CVD increased compared to the overall sample (**Table 5**). These findings indicate that even in those with OSA with low number of arousals, events with desaturation contribute to prediction of health outcomes. In contrast, in a subgroup of individuals with an AHI < 15 events/h (AHI based on all events with ≥ 3% desaturation regardless of arousal), the associations of AHI_{ArOnly} with the health outcomes were null (**Table 5**), indicating that even in those with OSA with less severe desaturation, events with arousals do not appear to contribute to prediction of health outcomes. Finally, **Table S1** in the supplemental material

Table 3—Events with desaturation (≥ 3%) but no arousal are independently associated with increased risk of adverse health outcomes, while events with arousals but no desaturation (< 3%) are not.

AHI	Cohort	Hypertension OR (95% CI)	Diabetes OR (95% CI)	Sleepiness OR (95% CI)	Incident CVD HR (95% CI)
Additional role of events with desaturation (but no arousal)					
$AHI_{\geq 3\%Only}$	SHHS	**1.26 (1.17–1.35)*** **	**1.43 (1.22–1.67)*** **	**1.17 (1.08–1.26)****	**1.10 (1.00–1.21)***
	MESA	**1.33 (1.18–1.50)*** **	**1.52 (1.29–1.79)*** **	**1.26 (1.07–1.47)****	**1.30 (1.02–1.65)***
	MrOS	**1.13 (1.03–1.24)****	**1.43 (1.23–1.67)*** **	**1.21 (1.06–1.39)****	**1.17 (1.04–1.32)***
The models were adjusted for covariates and AHI based on events with arousal (regardless of desaturation)					
Additional role of events with arousal (but no desaturation)					
AHI_{ArOnly}	SHHS	0.89 (0.84–0.94)***	0.93 (0.83–1.05)	0.90 (0.84–0.96)**	1.01 (0.95–1.09)
	MESA	0.85 (0.77–0.95)**	0.81 (0.70–0.93)**	0.88 (0.77–1.01)°	0.94 (0.77–1.41)
	MrOS	0.96 (0.89–1.03)	0.91 (0.80–1.03)	0.94 (0.84–1.05)	0.95 (0.86–1.06)
The models were adjusted for covariates and AHI based on events with desaturation (≥ 3%, regardless of arousal)					

Covariates included age, sex, and race/ethnicity. Bold denotes an association with increased risk. °$P < .1$, *$P < .05$, **$P < .01$, ***$P < .001$. $AHI_{\geq 3\%Only}$ = apnea-hypopnea index based ≥ 3% desaturation and no arousal, AHI_{ArOnly} = apnea-hypopnea index based on arousal and no or minimal desaturation (< 3%), CI = confidence interval, HR = hazard ratio, MESA = the Multi-Ethnic Study of Atherosclerosis, MrOS = the Osteoporotic Fractures in Men study, OR = odds ratio, SHHS = the Sleep Heart Health Study.

Table 4—Events with desaturation (≥ 3%) but no arousal are independently associated with increased risk of adverse health outcomes, while events with arousals but no desaturation (< 3%) are not, after additional adjustment for BMI.

AHI	Cohort	Hypertension OR (95% CI)	Diabetes OR (95% CI)	Sleepiness OR (95% CI)	Incident CVD HR (95% CI)
Additional role of events with desaturation (but no arousal)					
$AHI_{\geq 3\%Only}$	SHHS	**1.12 (1.04–1.21)****	1.15 (0.97–1.36)°	1.09 (1.00–1.18)°	1.05 (0.96–1.16)
	MESA	1.13 (0.99–1.29)°	**1.30 (1.09–1.54)****	**1.19 (1.00–1.41)***	**1.37 (1.05–1.77)***
	MrOS	1.02 (0.93–1.12)	**1.25 (1.07–1.47)****	**1.17 (1.01–1.35)***	**1.14 (1.00–1.29)***
The models were adjusted for covariates and AHI based on events with arousal (regardless of desaturation)					
Additional role of events with arousal (but no desaturation)					
AHI_{ArOnly}	SHHS	0.93 (0.88–0.99)*	1.02 (0.90–1.15)	0.92 (0.86–0.98)*	1.04 (0.97–1.12)
	MESA	0.89 (0.80–0.99)*	0.84 (0.73–0.97)*	0.90 (0.78–1.03)	0.92 (0.75–1.13)
	MrOS	1.01 (0.94–1.10)	0.99 (0.87–1.13)	0.96 (0.85–1.08)	0.97 (0.87–1.07)
The models were adjusted for covariates and AHI based on events with desaturation (≥ 3%, regardless of arousal)					

Covariates included age, sex, race/ethnicity, and body mass index. Bold denotes an association with increased risk. °P < .1, *P < .05, **P < .01, ***P < .001. $AHI_{\geq 3\%Only}$ = apnea-hypopnea index based ≥ 3% desaturation and no arousal, AHI_{ArOnly} = apnea-hypopnea index based on arousal and no or minimal desaturation (< 3%), CI = confidence interval, HR = hazard ratio, MESA = the Multi-Ethnic Study of Atherosclerosis, MrOS = the Osteoporotic Fractures in Men study, OR = odds ratio, SHHS = the Sleep Heart Health Study.

demonstrates the associations of AHI (based on 3% or arousal) and health outcomes that are generally weaker and less consistent than that of $AHI_{\geq 3\%Only}$.

Secondary analyses (longitudinal change in arousal [SHHS])

In the SHHS study, 2,493 participants returned for the second sleep study after approximately 5 years from the initial sleep study visit and had complete data for this analysis. For this analysis, the change in arousal index was regressed on baseline OSA severity. A multiple linear regression analysis in SHHS demonstrated a greater decline in the arousal index in those with more severe baseline OSA over time. On average, after adjusting for age, sex, race, and body mass index, every 1 standard deviation increase in AHI (based on 3% or arousal) at baseline was associated with a decline of ∼3 arousals/h after 5 years (P < .0001). The AHI increased by 1.5 1.5 ± 13.6 events/h after 5 years. Finally, excluding 22 individuals who were treated for sleep apnea (based on a follow-up questionnaire 2 years after baseline) did not meaningfully alter these findings.

DISCUSSION

For over 2 decades there has been considerable uncertainty over how to define the AHI using event-related variations of

Table 5—In individuals with an AHI < 15 events/h (based on events with arousal, regardless of desaturation), events with desaturation (≥ 3%) but no arousal are associated with increased risk of adverse health outcomes.

AHI	Cohort	Hypertension OR (95% CI)	Diabetes OR (95% CI)	Sleepiness OR (95% CI)	Incident CVD HR (95% CI)
Subgroup with an AHI < 15 events/h (based on events with arousal, regardless of desaturation)					
$AHI_{\geq 3\%Only}$	SHHS (n = 3877)	**1.10 (1.02–1.18)***	1.17 (0.97–1.40)°	1.06 (0.98–1.16)	1.07 (0.97–1.18)
	MESA (n = 1,105)	1.13 (0.97–1.33)	**1.25 (1.02–1.53)***	1.16 (0.95–1.43)	**1.49 (1.01–2.19)***
	MrOS (n = 1,630)	0.98 (0.89–1.09)	**1.24 (1.04–1.48)***	1.07 (0.91–1.26)	**1.21 (1.05–1.38)****
Subgroup with an AHI < 15 events/h (based on events with ≥ 3% desaturation, regardless of arousal)					
AHI_{ArOnly}	SHHS (n = 2,305)	0.93 (0.85–1.02)	0.90 (0.70–1.17)	0.91 (0.82–1.02)	0.95 (0.84–1.07)
	MESA (n = 794)	0.85 (0.72–1.01)°	0.86 (0.67–1.11)	0.92 (0.73–1.15)	1.11 (0.77–1.61)
	MrOS (n = 1,066)	1.08 (0.96–1.23)	0.90 (0.72–1.13)	1.00 (0.83–1.22)	0.99 (0.83–1.17)

In contrast, in individuals with an AHI < 15 events/h (based on events with ≥ 3% desaturation, regardless of arousal), events with arousals but no desaturation (< 3%) are not associate with increased risk of adverse health outcomes. Covariates included age, sex, race/ethnicity, and body mass index. Bold denotes an association with increased risk. °P < .1, *P < .05, **P < .01, ***P < .001. $AHI_{\geq 3\%Only}$ = apnea-hypopnea index based ≥ 3% desaturation and no arousal, AHI_{ArOnly} = apnea-hypopnea index based on arousal and no or minimal desaturation (< 3%), CI = confidence interval, HR = hazard ratio, MESA = the Multi-Ethnic Study of Atherosclerosis, MrOS = the Osteoporotic Fractures in Men study, OR = odds ratio, SHHS = the Sleep Heart Health Study.

desaturation thresholds and requirements for associated EEG-based arousal. Our detailed set of analyses that examined the added predictive value of arousals suggest that including EEG-based arousals in the derivation of the AHI does not improve cross-sectional and prospective associations with cardiovascular disease and sleepiness. Specifically, events with arousal (but no desaturation) do not appear to be associated with increased risk of adverse outcomes across 3 community-based cohorts. On the other hand, the AHI based on desaturation is associated with a wide variety of clinical outcomes when events do not also trigger an arousal. These unexpected findings suggested that a low arousal index or low propensity for arousal following a respiratory event may confound assessments of OSA-related cardiovascular, metabolic, and sleepiness-related morbidity, possibly because low arousal propensity may be associated with increased risk for adverse outcomes. Further longitudinal analysis demonstrated that more severe OSA at baseline was associated with a greater decline in arousals over time, suggesting that a low arousal index may be markers of more prolonged and severe OSA, with potential maladaptation over time.

There are potential explanations why events with EEG arousals may be weaker predictors of OSA-related cardiometabolic and sleepiness outcomes than events with desaturation but without concomitant arousals. The most plausible one—and supported by our longitudinal analysis—is that maladaptation to the arousal stimuli may develop after chronic exposure to untreated OSA.[36] Indeed, untreated OSA has been shown to be associated with impaired arousal responses and increased arousal threshold,[37,38] while CPAP treatment tends to reduce arousal threshold.[39,40] Extended exposure to untreated OSA may lead to maladaptation by requiring stronger arousal stimuli [lowered O_2/increased CO_2] to terminate the respiratory events. Whether this reflects a positive adaptive response—to preserve sleep continuity—or is secondary to impairment of brainstem ventilatory responses due to chronic ischemic or other damage associated with OSA is unclear. However, the latter mechanism is supported by a prior study from the SHHS that showed that brainstem white matter disease was associated with a lowered arousal index.[41] Another alternative explanation may be related to the effect of chronic exposure to sleep fragmentation and deprivation on arousals in OSA. For example, an experimental study demonstrated that sleep deprivation (120 hours) was accompanied by a decrease in both fraction and absolute EEG alpha wave intensity, while after 117 hours of sleep loss, eye closure failed to generate alpha activity.[42] Another study demonstrated that administration of a periodic (once per minute) auditory stimuli for 2 consecutive nights resulted in an increase in auditory arousal threshold both within and between nights.[43] Therefore, severe sleep fragmentation (equivalent to an arousal index of 60 events/h) resulted in changes in EEG, subjective, and behavioral similar to those observed after equal period of total sleep loss.

Previous studies have examined the contribution of arousals to adverse outcomes, including hypertension in human[44] and animal[22,45] studies. For example, Budhiraja et al[44] reported that the AHI (based on 3% desaturation or arousal) was significantly associated with incident hypertension in the SHHS study. Similarly, using the data from the Cleveland Family Study, Sulit et al[46] reported that overall arousal index was significantly associated with hypertension. However, in Budhiraja et al, events based on desaturations and arousals (or arousal index) were examined in combination and not in isolation, and the 3% desaturation was the minimal threshold but also included events that were ≥ 4%. Based on our findings, it is the desaturations and not arousals that appear to explain the association with increased risk of adverse outcomes. Indeed, the association of more severe events (desaturation ≥ 4%) with outcomes appeared to be less affected by inclusion of arousals (**Figure S1** and **Figure S2**). The Cleveland Family Study included younger individuals (mean age 43 years) who were potentially less exposed to untreated OSA (ie, less likely to have an impaired arousal response) compared to older individuals included in this study. Finally, comparing to the $AHI_{\geq 3\%Only}$, the associations of AHI (based on ≥ 3% desaturation or arousal) with health outcomes were weaker and less consistent, suggesting that the inclusion of additional events with arousals appear to dilute the effect for the desaturation-based AHI metrics (**Table S1**, **Figure S1,** and **Figure S2**).

Evidence is accumulating that better characterization of OSA leads to improved risk stratification for adverse outcomes.[4–6,35,47] While cortical arousals are a promising biomarker of risk, EEG-based arousals are scored less reliably than respiratory events,[48] are influenced by sleep stage,[49] and have not been clearly shown to reflect sympathetic activation,[50,51] indicating the need for alternative measures of "arousal" from sleep. For example, addition of "arousal intensity"[52] to arousal frequency may provide additional predictive value. "Autonomic cardiac arousals" may also be a better prognostic marker of OSA than the cortical arousals. Previous studies from our group have shown a dose-response relationship between severity of events (measured by reduction in ventilatory volume) and the postevent increase in heart rate.[53] The dose-response relationship was observed regardless of the presence or absence of cortical arousals.[53] In addition, the heart rate response was associated with intensity of cortical arousals.[52] Finally, heart rate response was associated with increased risk of cardiovascular morbidity and mortality in the MESA and SHHS cohorts[35] and predicted treatment benefit in individuals with nonsleepy OSA and coronary artery disease.[54] Thus, autonomic arousals rather than cortical arousals seem to play an important role in OSA characterization and risk stratification and their incorporation into new AHI definitions warrants further consideration.

It is important to recognize that our data should not be interpreted as evidence that arousal-related mechanisms do not contribute to OSA-related morbidity, and we caution against the interpretation that the presence of arousals in OSA may be beneficial. In fact, experimental studies suggest that interactions among arousal, hypercapnia, and intrathoracic pressure swings contribute to 24-hour blood pressure profile.[55,56] Indeed, our findings do not negate prior evidence that arousals have deleterious effects,[2,17] however, the absence of an arousal in response to a respiratory disturbance may indicate deleterious maladaptation that portends OSA sequalae and/or may be a marker of underlying disease. For example, prior research has implicated a low arousal index as a risk factor for atrial fibrillation[57] and stroke in women[58] as well as a marker of white matter disease in the brainstem.[41] Therefore, while arousals may be harmful, our data show that the measurement of arousal may not provide added predictive value for risk prediction in sleep apnea over

indices that reflect associated desaturation. Future studies are needed to examine the mechanistic relationship between blunted brain response to respiratory stimuli and adverse health outcomes.

The associations of $AHI_{\geq 3\%Only}$ with diabetes, sleepiness, or incident CVD in the SHHS cohort were slightly weaker than those observed in the MESA and MrOS cohorts; nevertheless, there were statistical trends toward increased risk of diabetes and sleepiness for the $AHI_{\geq 3\%Only}$ in the SHHS (**Table 4**). This could potentially be explained by differences in the sample characteristics and PSG measurements. On average the SHHS participants are 5 and 11 years younger than those in the MESA and MrOS cohorts. Additionally, the MESA sample was more racially/ethnically diverse than the SHHS (and MrOS). Finally, in the SHHS cohort, airflow was recorded using a thermistor while in the MESA/MrOS cohorts, nasal cannula was used. It is possible that some of the hypopneas have been missed in the SHHS cohort due to lower sensitivity of thermistors to detect hypopneas.

Strengths and limitations

This study has several strengths, including (1) the use of large and diverse samples, including 3 well-defined population studies across the United States (total sample size = 10,062), suggesting likely generalizability of the results; (2) use of cross-sectional and longitudinal outcomes to assess the importance of arousals alone or in combination with respiratory events; (3) use of automated subject-specific search windows to link the arousals and desaturations with apneas/hypopneas. However, the study also has several limitations, including the under-representation of younger individuals (age range was 40–90 years) and lack of long-term longitudinal data needed to fully describe factors that influence arousal generation over time. We caution against extending these findings to younger individuals who may have less severe desaturations and higher arousal index and report daytime symptoms. Although we did not observe evidence of sex-specific differences (data not shown) or in persons of color, it is possible that arousals may improve characterization of events that do not lead to a measurable > 3% desaturation. However, the decline in cortical arousal frequency over time in untreated individuals in the SHHS raises the concern that alternatives to cortical arousals may be needed to identify physiologically significant events. The use of symptom-based metrics to inform sleep-disordered breathing disease management approaches that depend less on absolute AHI levels also requires consideration and investigation.

Arousals were scored in these 3 cohorts using standardized definitions from EEG data collected in unattended studies, future attended studies may be needed to confirm these findings. In this study, the disease-defining criteria (desaturation, arousal) were applied equally to both hypopneas and apneas; however, apneas with neither desaturation nor arousal (per American Academy of Sleep Medicine criteria) were rare (SHHS: 0.1[0, 0.6] events/h; MESA: 0.0[0.0, 0.0] events/h; MrOS: 0.0[0.0, 0.1] events/h). Although, the proportion of apneas was low in these community-based cohorts, future research may evaluate whether different criteria should apply for apneas or hypopneas. Desaturations were automatically derived, removing scorer-related sources of error. Therefore, it is plausible that more objective approaches for identifying arousals might improve the value of including arousals in event definitions. Another limitation of this analysis is that it only used a single-channel EEG to score arousals and lack of nasal pressure recording (in the SHHS only). An additional limitation of this study is that the respiratory effort-related arousals were not scored and, therefore, their contributions to health outcomes tested in this study remain unknown. Future studies are needed to assess the clinical utility of respiratory effort-related arousals. Finally, most associations were modest and adjusted for a limited set of covariates to facilitate their comparison. Use of these metrics for risk stratification will require further assessment of the extent to which they predict differential responses to interventions.

CONCLUSIONS

This study systematically assessed the association of arousals with several prevalent comorbidities and risk of long-term CVD outcomes in a large and diverse sample of middle-aged or older adults and provides novel evidence that higher numbers of nonrespiratory or respiratory cortical arousals from sleep do not predict increased risk of adverse OSA-related outcomes in individuals studied in community settings. Rather, we provide new data that a low arousal index may be a marker of maladaptation to severe OSA over time—and that low- vs high-arousal frequencies may be markers for OSA disease duration—which, due to limited longitudinal data, is difficult to assess. Our results do not support the use of AHIs based on linked arousals for predicting health-related outcomes in older adults, although do not exclude their role as mechanisms for disease or for predicting treatment responses.

ABBREVIATIONS

AHI, apnea-hypopnea index
AHI_{ArOnly}, frequency of events with arousals but no desaturation
$AHI_{\geq 3\%Only}$, frequency of events with desaturation (≥3%) but not arousal
CPAP, continuous positive airway pressure
CVD, cardiovascular disease
EEG, electroencephalogram
MESA, Multi-Ethnic Study of Atherosclerosis
MI, myocardial infarction
MrOS, Outcomes of Sleep Disorders in Older Men
OSA, obstructive sleep apnea
PSG, polysomnography
SHHS, Sleep Heart Health Study
SpO_2, oxyhemoglobin saturation

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