

## SCIENTIFIC INVESTIGATIONS

# The Association Between Obstructive Sleep Apnea Characterized by a Minimum 3 Percent Oxygen Desaturation or Arousal Hypopnea Definition and Hypertension

Rohit Budhiraja, MD<sup>1</sup>; Sogol Javaheri, MA, MD, MPH<sup>1</sup>; Sairam Parthasarathy, MD<sup>2</sup>; Richard B. Berry, MD<sup>3</sup>; Stuart F. Quan, MD<sup>1,2</sup>

<sup>1</sup>Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; <sup>2</sup>Department of Medicine, College of Medicine, University of Arizona, Tucson, Arizona; <sup>3</sup>Division of Pulmonary, Critical Care, and Sleep Medicine, University of Florida, Gainesville, Florida

**Study Objectives:** The association between obstructive sleep apnea (OSA) and hypertension in prior studies has been determined using a definition of hypopnea requiring a 4% O<sub>2</sub> desaturation. However, the American Academy of Sleep Medicine (AASM) recommends using a 3% O<sub>2</sub> desaturation or an arousal. This analysis assesses the relationship between OSA and hypertension utilizing the AASM recommended definition and the 2018 American College of Cardiology/American Heart Association hypertension guidelines.

**Methods:** Data from 6113 participants from the Sleep Heart Health Study were analyzed. The AASM recommended apnea-hypopnea index (AHI) was classified into 4 categories of OSA severity: <5, 5 to <15, 15 to <30 and ≥30 events/h. Three definitions of hypertension were used: elevated (>120/<80 or use of hypertension medications [meds]), stage 1/stage 2 (>130/80 or meds), stage 2 (>140/90 or meds). Data were analyzed using logistic regression controlling for demographics, smoking and body mass index. Multiple linear regression analysis assessed the relationship between natural log AHI, and systolic and diastolic blood pressure controlling for the same covariates.

**Results:** For all definitions of blood pressure elevation, increasing OSA severity was associated with greater likelihood of an elevated or hypertensive status in fully adjusted models (odds ratio [95% confidence interval]): elevated 1.30 (1.09–1.54), 1.39 (1.13–1.70) 1.69 (1.29–2.13); stage 1/2: 1.25 (1.06–1.47), 1.32 (1.10–1.59), 1.53 (1.23–1.91); stage 2: 1.07 (0.91–1.25), 1.21 (1.01–1.44), 1.37 (1.11–1.69) for AHI 5 to <15, 15 to <30 and >30 events/h (<5 events/h reference). Linear regression found that AHI was associated with both systolic and diastolic blood pressure in fully adjusted models.

**Conclusions:** Use of the AASM recommended definition of hypopnea as a component of the AHI is associated with the presence of hypertension.

**Keywords:** obstructive sleep apnea, hypertension, blood pressure, apnea-hypopnea index

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### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Severity of obstructive sleep apnea (OSA) is usually characterized by the apnea-hypopnea index (AHI), which in most studies requires a hypopnea definition utilizing a minimum 4% oxygen desaturation. AASM standards, however, recommend using a hypopnea definition requiring a minimum 3% oxygen desaturation or an arousal. This study analyzes the relationship between the AASM recommended AHI definition and prevalent hypertension.

**Study Impact:** Use of the AASM recommended definition of hypopnea as a component of the AHI is associated with the presence of hypertension. This suggests that use of a 4% O<sub>2</sub> desaturation requirement by several third party payors to define treatable OSA is too stringent and may deny treatment to some patients with OSA.

## INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent disorder characterized by recurrent episodes of either complete upper airway collapse (apneas) or partial collapse (hypopneas) during sleep. In 2012, the American Academy of Sleep Medicine (AASM) recommended that the hypopnea definition include any decrease in airflow by at least 30% from the baseline with an oxyhemoglobin desaturation of at least 3%, or an arousal from sleep.<sup>1</sup> However, several payors including the Centers for Medicare and Medicaid Services (CMS) continue to require a more stringent hypopnea definition necessitating

a 4% or greater decrease in oxygen saturation despite evidence documenting a relationship between the AASM recommended standard and daytime sleepiness. The resistance to universal acceptance of the AASM criteria is based in part on the assertion that 3% desaturations or arousals have not been convincingly demonstrated to have adverse cardiovascular impact. Whether this reluctance to adopt a more inclusive definition of sleep apnea denies appropriate OSA therapy to persons who would be at higher risk of adverse consequences such as hypertension is not clear. Delineating the potential relationship between OSA characterized by lesser degrees of oxyhemoglobin desaturation (3% drop in saturation)

or an arousal from sleep and the putative consequences of OSA in large population studies can help better identify persons at risk for adverse effects and potentially improve health-related outcomes.

Several studies have now firmly established a relationship between OSA and hypertension.<sup>2,3</sup> Diverse physiological derangements, including intermittent hypoxemia, sleep fragmentation, sympathetic activation and endothelial dysfunction may play an integral role in mediating the cardiovascular consequences of OSA. Furthermore, therapy of OSA is associated with a decline in systemic blood pressure.<sup>4-6</sup> In 2017, the American College of Cardiology (ACC) and the American Heart Association (AHA) published updated definitions of hypertension.<sup>7</sup> However, the relationship between OSA and hypertension incorporating the most recent definitions of hypertension has not been determined.

Using the database from the Sleep Heart Health Study (SHHS), a large well-characterized community based cohort that had undergone polysomnography, the current study aimed to determine the impact of using the AASM recommended standards on the relationship between OSA and prevalent hypertension in middle-aged and older adults. The specific objective was to evaluate the association of hypertension incorporating both new and older AHA definitions of hypertension, with severity of OSA as determined using a definition of hypopnea with at least a 3% desaturation or an arousal from sleep. In addition, the same analyses were performed in which the severity of OSA was assessed using a hypopnea definition requiring at least a 4% oxygen desaturation without the need for an arousal.

## METHODS

The SHHS was a prospective multicenter cohort study designed to investigate the relationship between OSA and cardiovascular diseases in the United States. A detailed description of the study rationale and design have been published elsewhere.<sup>8</sup> Recruitment began in 1995, enrolling 6,441 individuals 40 years of age and older, from several ongoing “parent” cardiovascular and respiratory disease cohorts who were initially assembled between 1976 and 1995.<sup>9</sup> These cohorts included the Offspring Cohort and the Omni Cohort of the Framingham Heart Study in Massachusetts; the Hagerstown, Maryland, and Minneapolis, Minnesota, sites of the Atherosclerosis Risk in Communities Study; the Hagerstown, Maryland, Pittsburgh, Pennsylvania, and Sacramento, California, sites of the Cardiovascular Health Study; 3 hypertension cohorts (Clinic, Worksite, and Menopause) in New York City; the Tucson Epidemiologic Study of Airways Obstructive Diseases and the Health and Environment Study; and the Strong Heart Study of American Indians in Oklahoma, Arizona, North Dakota, and South Dakota. Because of sovereignty issues, 134 participants from the Arizona cohort of the Strong Heart Study withdrew consent. Analyses were performed on the remaining 6,307 participants. Parent cohort data were used for documentation of age, height, sex, ethnicity and smoking status. The SHHS was approved by the respective parent institutional review boards for human research, and

informed written consent was obtained from all participants at the time of their enrollment.

## Polysomnography and Home Visit

Participants underwent overnight in-home polysomnography using the Compumedics Portable PS-2 System (Abbottville, Victoria, Australia) administered by trained technicians.<sup>10</sup> The home visits were performed by two-person, mixed-sex teams in visits that lasted 1.5 to 2 hours. There was emphasis on making the night of the assessment as representative as possible of a usual night of sleep. Participants were asked to schedule the visit so that it would occur approximately 2 hours prior to their usual bedtime. At the time of the home visit, an inventory of each participant’s medications was made. Blood pressure was measured manually in triplicate in a seated position after 5 minutes of rest.<sup>11</sup> The average of the second and third measurements was used for this analysis. Body weight was obtained using a digital scale.

The SHHS recording montage consisted of electroencephalogram (C4/A1 and C3/A2), right and left electrooculogram, a bipolar submental electromyogram, thoracic and abdominal excursions (inductive plethysmography bands), airflow (detected by a nasal-oral thermocouple [Protec, Woodinville, Washington]), oximetry (finger pulse oximetry [Nonin, Minneapolis, Minnesota]), electrocardiogram and heart rate (using a bipolar electrocardiogram lead), body position (using a mercury gauge sensor), and ambient light (on/off, by a light sensor secured to the recording garment). Sensors were placed, and equipment was calibrated during an evening home visit by a certified technician. After technicians retrieved the equipment, the data, stored in real time on PCMCIA cards, were downloaded to the computers of each respective clinical site, locally reviewed, and forwarded to a central reading center (Case Western Reserve University, Cleveland, Ohio). Comprehensive descriptions of polysomnography scoring and quality-assurance procedures have been previously published.<sup>10,12</sup> In brief, sleep was scored according to guidelines developed by Rechtschaffen and Kales.<sup>13</sup> Strict protocols were maintained to ensure comparability among centers and technicians. Intrascorer and interscorer reliabilities were high.<sup>12</sup>

The apnea-hypopnea index (AHI) was calculated for each participant using two definitions of hypopnea, the AASM recommended definition (3%A) and the AASM acceptable (CMS) definition (4% only). For 3%A, hypopneas were identified if the amplitude of a measure of flow or volume (detected by the thermocouple or thorax or abdominal inductance band signals) was reduced discernibly (at least 25% lower than baseline breathing) for at least 10 seconds, did not meet the criteria for apnea and the event was associated with either a 3% oxygen desaturation from baseline or terminated with electroencephalographic evidence of an arousal. For 4% only, hypopneas were identified if the aforementioned reduction in flow or volume occurred and the event was associated with a 4% oxygen desaturation from baseline. In both cases, an apnea was defined as a complete or almost complete cessation of airflow, as measured by the amplitude of the thermocouple signal, lasting at least 10 seconds.

### Statistical Analyses

Mean and standard deviation were used to provide an overall description of the data used in the analyses. For both definitions of the AHI, each participant’s AHI was assigned to one of 4 OSA severity categories: normal (AHI < 5 events/h), mild (AHI 5 to ≤ 15 events/h), moderate (AHI 15 to ≤ 30 events/h) and severe (AHI ≥ 30 events/h). Analysis of variance was used for each variable to assess for differences among the OSA severity categories.

Three definitions of hypertension were used in these analyses. For each definition, the threshold for classifying a participant as hypertensive used the new ACC/AHA guidelines.<sup>7</sup> However, participants with blood pressures exceeding the minimum threshold as well as those who were taking antihypertensive medications also were classified as hypertensive. Thus, the following definitions were used:

- Elevated or higher blood pressure: > 120 mmHg systolic and < 80 mmHg diastolic or use of antihypertensive medications
- Stage 1 or 2 hypertension: > 130 mmHg systolic or > 80 mmHg diastolic or use of antihypertensive medications
- Stage 2 hypertension: > 140 mmHg systolic or > 90 mmHg diastolic or use of antihypertensive medications

For each definition of hypertension, the association between AHI severity and the presence of hypertension was modeled using logistic regression. Four progressively complex models were constructed: unadjusted, adjusted for demographic variables (age, ethnicity, and sex), adjusted for demographic variables plus body mass index (BMI, kg/m<sup>2</sup>) and adjusted for demographics, BMI and smoking status. Two sensitivity

analyses were performed. In the first, antihypertensive medications were omitted from the aforementioned definitions. In the second, for elevated blood pressure, models were constructed in which hypertensive cases were limited only to those with blood pressure > 120 mmHg systolic and < 80 mmHg diastolic.

Multiple linear regression was used to determine the relationship between systolic and diastolic BP and AHI controlling for age, sex, ethnicity, smoking and BMI. Inasmuch as the distribution of AHI is heavily skewed leftward and some values are 0, AHI was transformed using the natural log + 0.1 in these analyses.

Analyses were performed using IBM SPSS Statistics version 25 (Armonk, New York). *P* < .05 was considered statistically significant.

### RESULTS

The demographic and anthropometric characteristics of the SHHS cohort, overall and stratified by the 3%A definition of AHI, are shown in **Table 1**. With greater AHI severity, there is an increase in the prevalence of men, age, BMI, blood pressure and American Indian ethnicity. In contrast, the prevalence of African Americans and other ethnicities (primarily Hispanic and Asian) declined. The percentage of Non-Hispanic whites increased at the AHI 5 to < 15 category and was stable thereafter. Current smoking declined with increasing AHI. Of particular note is that the greatest number of participants was in the AHI 5 to < 15 category which represents mild OSA.

**Table 2** depicts the overall demographic and anthropometric characteristics of the SHHS cohort stratified using the 4% only

**Table 1**—Study population demographic and anthropometric characteristics stratified by apnea-hypopnea index (current AASM-recommended hypopnea definition).

Characteristic	Overall (n = 6,131)	Apnea-Hypopnea Index Category (events/h)				P
		< 5 (n = 1,079)	5 to < 15 (n = 2,387)	15 to < 30 (n = 1,662)	≥ 30 (n = 1,003)	
% overall n		17.6	38.9	27.1	16.4	
Sex (% men)	47.2	24.7	40.2	58.9	68.4	< .001
Mean age (years)	62.9	58.6	62.4	64.9	65.2	< .001
Ethnicity (%)						< .001
Non-Hispanic white	n = 4,814	74.8	78.9	80.3	78.6	
African American	n = 481	10.8	7.2	6.9	7.9	
American Indian	n = 467	5.5	7.6	8.1	9.1	
Other	n = 369	8.9	6.3	4.7	4.5	
Smoking (%)						<.001
Never smokers	n = 2,802	48.5	48.2	43.0	43.1	
Ex-smokers	n = 2,607	36.1	40.0	47.9	48.2	
Current smokers	n = 680	15.4	11.8	9.0	8.6	
Mean BMI (kg/m <sup>2</sup> )	28.1	25.8	27.4	28.9	30.6	<.001
Mean SBP (mmHg)	130.2	125.2	129.6	132.2	133.6	<.001
Mean DBP (mmHg)	74.4	73.5	74.2	74.7	75.2	.002

Apnea-hypopnea index calculated defining hypopneas as events with at least at 3% oxygen desaturation from pre-event baseline or the event is associated with an arousal. AASM = American Academy of Sleep Medicine, BMI = body mass index, DBP = diastolic blood pressure, SBP = systolic blood pressure.

**Table 2**—Study population demographic and anthropometric characteristics stratified by apnea-hypopnea index (acceptable AASM/CMS hypopnea definition).

Characteristic	Overall (n = 6,307)	Apnea-Hypopnea Index Category (events/h)				P
		< 5 (n = 3,409)	5 to < 15 (n = 1,783)	15 to < 30 (n = 732)	≥ 30 (n = 383)	
% overall n		54.1	28.3	11.6	6.1	
Sex (% men)	47.2	37.0	54.6	63.9	71.3	< .001
Mean age (years)	62.9	61.4	65.0	65.2	64.7	< .001
Ethnicity (%)						< .001
Non-Hispanic white	n = 4,814	78.6	78.5	76.6	77.3	
African American	n = 481	8.4	7.3	8.6	9.7	
American Indian	n = 467	6.4	8.8	10.1	8.1	
Other	n = 369	6.5	5.3	4.6	5.0	
Smoking (%)						< .001
Never smokers	n = 2,802	47.7	43.3	44.4	42.0	
Ex-smokers	n = 2,607	38.7	48.1	45.9	52.0	
Current smokers	n = 680	13.6	8.6	9.6	6.1	
Mean BMI (kg/m <sup>2</sup> )	28.1	26.6	29.1	30.3	31.8	< .001
Mean SBP (mmHg)	130.2	128.3	132.1	133.1	134.1	< .001
Mean DBP (mmHg)	74.4	74.0	74.4	75.3	75.8	.001

Apnea-hypopnea index calculated defining hypopneas as events associated with at least a 4% oxygen desaturation from pre-event baseline. AASM = American Academy of Sleep Medicine, BMI = body mass index, CMS = Centers for Medicare and Medicaid Services, DBP = diastolic blood pressure, SBP = systolic blood pressure.

definition for hypopnea. The findings are similar to those in [Table 1](#) except that the greatest number of participants is now in the AHI < 5 category, and the percentage of African Americans and American Indians increased in the higher AHI categories. Additionally, the prevalence of Non-Hispanic whites remained stable across AHI categories.

Adjusted odds ratios (OR) and their 95% confidence intervals (CI) for the association between AHI using the 3%A hypopnea definition and three definitions of hypertension are shown in [Table 3](#). Irrespective of the definition of hypertension used, the association between hypertension and AHI became stronger as the severity of OSA increased. Adjustment for demographic characteristics and BMI, but not smoking attenuated, but did not eliminate this relationship.

In [Table 4](#) are the OR and 95% CI for the association between AHI using the 4% only hypopnea definition and three definitions of hypertension. Similar to the data shown in [Table 3](#), the association with hypertension increased with greater severity of AHI with all three definitions of hypertension. The strength of these associations appeared similar to that observed in [Table 3](#) using the 3%A definition of hypopnea.

[Table 5](#) shows the association between severity of AHI and hypertension in those participants who were identified as having OSA using the 3%A hypopnea definition, but not the 4% only definition. Because there were only 10 participants with an AHI ≥ 30 events/h, this category was combined with the AHI 15 to < 30 category. Of particular note are the 281 participants with an AHI ≥ 15 events/h (moderate to severe OSA) who did not have OSA using the 4% only definition. For the elevated blood pressure and stage 1 hypertension definitions of hypertension,

both AHI 5 to < 15 and AHI ≥ 15 events/h were associated with a greater likelihood of hypertension with higher risk assigned to AHI ≥ 15 events/h in both unadjusted and adjusted models. For stage 2 hypertension, AHI 5 to < 15 events/h was not associated with risk of hypertension in adjusted models. However, increased risk was observed with AHI ≥ 15 events/h.

In sensitivity analyses, removal of cases defined only by use of antihypertensive medications did not substantially alter the relationships between OSA severity and hypertension. Similarly, limiting cases in models of elevated blood pressure to only those who met the blood pressure criteria did not change these findings.

Linear regression analyses of systolic and diastolic blood pressure in participants not using antihypertensive medications are shown in [Table 6](#) with graphic representations shown in [Figure 1](#). Using either the 3%A definition or the 4% only of hypopnea, there was a significant association between systolic or diastolic blood pressure and the natural log of AHI in models including BMI, age, sex, ethnicity and smoking. When analyses were limited only to those who had an AHI ≥ 5 events/h using 3%A definition of hypopnea, but AHI < 5 events/h using the 4% only definition, the association between systolic or diastolic blood pressure and natural log of AHI persisted.

## DISCUSSION

In this large community-based study, we demonstrated that OSA defined by apneas and hypopneas characterized by 3% desaturation events or arousals is associated with significantly increased odds of prevalent hypertension. The elevated odds seen

**Table 3**—Adjusted odds ratios and 95% confidence intervals of hypertension definitions stratified by AHI severity categories (current AASM-recommended hypopnea definition).

AHI Category	n	Unadjusted	Adjusted Demographics *	Plus BMI	Plus BMI/Smoking
<b>Elevated (n = 4,691/6,113)</b>					
< 5	1,079	1.00	1.00	1.00	1.00
5 to < 15	2,380	1.79 (1.53–2.09)	1.50 (1.27–1.77)	1.30 (1.10–1.54)	1.30 (1.09–1.54)
15 to < 30	1,659	2.55 (2.14–3.04)	1.81 (1.49–2.19)	1.41 (1.15–1.72)	1.39 (1.13–1.70)
≥ 30	995	3.63 (2.92–4.52)	2.46 (1.94–3.11)	1.69 (1.32–2.17)	1.66 (1.29–2.13)
P (overall)		< .001	< .001	< .001	.003
<b>Stage 1 or 2 (n = 4,197/6,112)</b>					
< 5	1,079	1.00	1.00	1.00	1.00
5 to < 15	2,380	1.65 (1.43–1.92)	1.46 (1.25–1.71)	1.27 (1.09–1.49)	1.25 (1.06–1.47)
15 to < 30	1,659	2.19 (1.86–2.57)	1.73 (1.45–2.06)	1.36 (1.13–1.63)	1.32 (1.10–1.59)
≥ 30	994	2.94 (2.42–3.57)	2.25 (1.83–2.77)	1.58 (1.27–1.97)	1.53 (1.23–1.91)
P (overall)		< .001	< .001	< .001	.002
<b>Stage 2 (n = 3,204/6,112)</b>					
< 5	1,079	1.00	1.00	1.00	1.00
5 to < 15	2,380	1.44 (1.25–1.67)	1.19 (1.02–1.40)	1.07 (0.92–1.26)	1.07 (0.91–1.25)
15 to < 30	1,659	2.01 (1.72–2.35)	1.47 (1.24–1.74)	1.22 (1.02–1.45)	1.21 (1.01–1.44)
≥ 30	994	2.55 (2.14–3.05)	1.84 (1.52–2.24)	1.38 (1.12–1.69)	1.37 (1.11–1.69)
P (overall)		< .001	< .001	.008	.01

Data presented as odds ratio (95% confidence interval). AHI calculated defining hypopneas as events with at least at 3% oxygen desaturation from pre-event baseline or the event is associated with an arousal. Hypertension definitions are: Elevated = blood pressure > 120 mmHg systolic and < 80 mmHg diastolic or use of antihypertensive medications, Stage 1 or 2 = blood pressure > 130 mmHg systolic or > 80 mmHg diastolic or use of antihypertensive medications, Stage 2 = blood pressure > 140 mmHg systolic or > 90 mmHg diastolic or use of antihypertensive medications. \* Adjusted for age, sex and ethnicity. AASM = American Academy of Sleep Medicine, AHI = apnea-hypopnea index, BMI = body mass index.

in the middle aged and older adults with OSA, thus defined, persisted for both older and new definitions of hypertension. Remarkably, the strength of associations using the 3%A definition of hypopnea appeared similar to those observed with the 4% only definition, further reinforcing the clinical relevance of the former. This suggests that the regulatory requirement by the CMS in the United States of using a 4% desaturation definition denies a substantial proportion of people with OSA who are at a meaningfully elevated risk of hypertension a chance at appropriate therapy.

OSA is associated with assorted adverse health-related outcomes, including diverse cardiovascular disorders.<sup>14</sup> Several studies have now established an association between OSA and hypertension.<sup>2</sup> Initially, analyses from the Wisconsin Sleep Cohort Study found elevated odds of prevalent and incident hypertension with increasing severity of OSA.<sup>15,16</sup> Confirmatory results from the SHHS demonstrated a higher prevalence of hypertension in those with OSA.<sup>17</sup> Although there appeared to increased risk of developing hypertension in longitudinal analyses in persons with OSA in SHHS, it was attenuated after controlling for BMI and no longer statistically significant.<sup>11,16</sup> Nevertheless, further support for the robust association between these conditions is provided from other large population based cohorts as well as intervention studies demonstrating an improvement in blood pressure with therapy for OSA.<sup>4–6</sup> Both CPAP and mandibular advancement devices may produce a similar reduction in the blood pressure,<sup>6</sup> and the magnitude

of the reduction in blood pressure may be greater in those with refractory hypertension than those with nonrefractory hypertension.<sup>5</sup> Our analyses extend these previous findings by demonstrating an association between OSA and hypertension as defined by recent criteria irrespective of whether the 4% only or 3%A definition of hypopnea is used.

Hitherto, most studies of the association between OSA and hypertension have employed a minimum 4% desaturation criterion to identify hypopneas for the purpose of calculating the AHI.<sup>18</sup> More recently, a 3% desaturation criterion also has been used.<sup>19,20</sup> However, the impact of using a more inclusive hypopnea definition consisting of a minimum 3% desaturation or arousal (ie, 3%A) as recommended by the AASM has not been thoroughly explored previously. The current study confirms that the 3%A definition is associated with hypertension using both previous and newer definitions of hypertension. Importantly, in the current study, only 17.7% of the participants had moderate to severe sleep apnea using the CMS definition compared to 43.5% using the AASM definition. Therefore, reliance on a more rigorous definition of hypopnea requiring a 4% or greater desaturation in clinical practice will inevitably lead to under-recognition of a significant proportion of patients with OSA. This will potentially deprive some of them the opportunity to have a reversible etiologic factor causing their hypertension treated. Our finding that 1,242 participants, including 281 with moderate to severe OSA were not identified using the 4% only criteria emphasizes this omission.

**Table 4**—Adjusted odds ratios and 95% confidence intervals of hypertension definitions stratified by AHI severity categories (acceptable AASM/CMS hypopnea definition).

AHI Category	n	Unadjusted	Adjusted Demographics *	Plus BMI	Plus BMI/Smoking
<b>Elevated (n = 4,840/6,288)</b>					
< 5	3,403	1.00	1.00	1.00	1.00
5 to < 15	1,779	1.77 (1.48–1.96)	1.36 (1.27–1.57)	1.13 (0.97–1.32)	1.11 (0.95–1.29)
15 to < 30	726	2.33 (1.87–2.90)	1.75 (1.39–2.20)	1.32 (1.04–1.68)	1.30 (1.03–1.65)
≥ 30	380	3.58 (2.54–5.04)	2.79 (1.96–3.98)	1.87 (1.30–2.69)	1.83 (1.27–2.63)
P (overall)		< .001	< .001	.002	.003
<b>Stage 1 or 2 (n = 4,335/6,287)</b>					
< 5	3,403	1.00	1.00	1.00	1.00
5 to < 15	1,779	1.60 (1.41–1.82)	1.36 (1.19–1.56)	1.14 (1.00–1.31)	1.12 (0.97–1.29)
15 to < 30	726	1.90 (1.58–2.28)	1.55 (1.28–1.88)	1.21 (0.99–1.48)	1.19 (0.99–1.45)
≥ 30	380	3.03 (2.29–4.02)	2.55 (1.91–3.40)	1.74 (1.29–2.34)	1.69 (1.25–2.28)
P (overall)		< .001	< .001	.001	.004
<b>Stage 2 (n = 3,324/6,287)</b>					
< 5	3,403	1.00	1.00	1.00	1.00
5 to < 15	1,779	1.59 (1.41–1.78)	1.32 (1.16–1.49)	1.15 (1.01–1.31)	1.14 (1.00–1.30)
15 to < 30	726	1.78 (1.51–2.09)	1.44 (1.21–1.71)	1.19 (0.99–1.42)	1.18 (0.98–1.42)
≥ 30	380	2.41 (1.92–3.02)	2.06 (1.62–2.61)	1.49 (1.16–1.91)	1.48 (1.15–1.89)
P (overall)		< .001	< .001	.006	.008

Data presented as odds ratio (95% confidence interval). AHI calculated defining hypopneas as events associated with at least a 4% oxygen desaturation from pre-event baseline. Hypertension definitions are: Elevated = blood pressure > 120 mmHg systolic and < 80 mmHg diastolic or use of antihypertensive medications, Stage 1 or 2 = blood pressure > 130 mmHg systolic or > 80 mmHg diastolic or use of antihypertensive medications, Stage 2 = blood pressure > 140 mmHg systolic or > 90 mmHg diastolic or use of antihypertensive medications. \* Adjusted for age, sex and ethnicity. AASM = American Academy of Sleep Medicine, AHI = apnea-hypopnea index, BMI = body mass index, CMS = Centers for Medicare and Medicaid Services.

**Table 5**—Adjusted odds ratios and 95% confidence intervals of hypertension definitions stratified by AHI severity categories using the current AASM-recommended hypopnea definition for participants without OSA using the acceptable AASM/CMS hypopnea definition.

AHI Category	n	Unadjusted	Adjusted Demographics *	Plus BMI	Plus BMI/Smoking
<b>Stage 1 or 2 (n = 2,094/3,321)</b>					
< 5	1,079	1.00	1.00	1.00	1.00
5 to < 15	1,961	1.53 (1.32–1.79)	1.32 (1.12–1.55)	1.19 (1.01–1.41)	1.18 (1.00–1.40)
≥ 15 †	281	2.24 (1.68–3.00)	1.70 (1.25–2.31)	1.54 (1.13–2.11)	1.51 (1.11–2.08)
P (overall)		< .001	< .001	.013	.021
<b>Stage 2 (n = 1,537/3,321)</b>					
< 5	1,079	1.00	1.00	1.00	1.00
5 to < 15	1,961	1.34 (1.15–1.55)	1.08 (0.92–1.27)	1.00 (0.85–1.19)	0.99 (0.84–1.18)
≥ 15 †	281	2.12 (1.62–2.77)	1.50 (1.12–2.00)	1.41 (1.05–1.89)	1.40 (1.07–1.08)
P (overall)		< .001	.025	.048	.05

Data presented as odds ratio (95% confidence interval). Hypertension definitions are: Stage 1 or 2 = blood pressure > 130 mmHg systolic or > 80 mmHg diastolic or use of antihypertensive medications, Stage 2 = blood pressure > 140 mmHg systolic or > 90 mmHg diastolic or use of antihypertensive medications. \* Adjusted for age, sex and ethnicity. † 10 participants had AHI ≥ 30 events/h. AASM = American Academy of Sleep Medicine, AHI = apnea-hypopnea index, BMI = body mass index, CMS = Centers for Medicare and Medicaid Services.

There is increasing evidence that intermittent hypoxemia plays an important pathophysiology role in linkage between OSA and hypertension. Some,<sup>21,22</sup> but not all<sup>23,24</sup> studies have demonstrated that administration of supplemental oxygen can mitigate the blood pressure elevation associated with OSA. Intermittent hypoxemia-reoxygenation can result in

inflammation, endothelial dysfunction and activation of the sympathetic nervous system. The damage to the vascular endothelium is associated with imbalance between vasoconstrictors and vasodilators, anomalous cell proliferation, and increased coagulability.<sup>25</sup>

In contrast, whether or not to include arousals in the definition of OSA has been a matter of protracted debate.<sup>26</sup> The

**Table 6**—Linear regression analyses of systolic and diastolic blood pressure in participants not using antihypertensive medications.

Systolic Blood Pressure					Diastolic Blood Pressure				
n	Mean ± SD (mmHg)	β	95% CI	P	n	Mean ± SD (mmHg)	β	95% CI	P
<i>Using 3% oxygen desaturation or arousal definition of hypopnea</i>									
3,592	126.2 ± 17.2	1.11	0.45–1.74	.001	3,589	74.2 ± 10.2	0.87	0.50–1.25	< .001
<i>Using 4% oxygen desaturation definition of hypopnea</i>									
3,674	126.2 ± 17.3	0.63	0.22–1.05	.003	3,671	74.2 ± 10.2	0.55	0.32–0.79	< .001
<i>Using 3% oxygen desaturation or arousal definition of hypopnea, analyses restricted to participants with AHI &lt; 5 event/h using 4% desaturation hypopnea definition</i>									
2,122	126.2 ± 16.8	1.31	0.37–2.26	.006	2,121	73.6 ± 9.8	1.04	0.49–1.59	< .001

Independent variables in models include: lnAHI+0.1 (3% desaturation or arousal or 4% desaturation definitions as indicated above), BMI, age, sex, ethnicity (non-Hispanic white/other), smoking (current/other). AHI = apnea-hypopnea index, BMI = body mass index, CI = confidence interval, SD = standard deviation.

controversy stems from an absence of large well conducted trials demonstrating an association between arousals with adverse outcomes such as hypertension. Furthermore, the role of arousals in OSA pathology is not entirely clear. Arousals may precede or follow the upper airway opening after apneic events, and have been suggested by some to even be coincidental.<sup>27</sup> Finally, a relatively lower interscorer reliability for arousals has also been mentioned as a reason to exclude arousals from diagnosis of sleep apnea, but the reliability between experienced scorers appears to be relatively high.<sup>26</sup> From a physiological perspective, the association of arousals with hypertension seems intuitive. The arousals involve an increase in the sympathetic activity and a decrease in the parasympathetic activity.<sup>28</sup> Arousals have been shown in small studies to be associated with a spike in blood pressure during sleep and daytime hypertension even in persons without sleep apnea.<sup>29,30</sup> The increase in blood pressure with apneic events in persons with sleep apnea may also depend on the degree of arousal.<sup>31,32</sup> Analyses from Cleveland Family Study demonstrated a 22% increase in the odds of hypertension with each 5-unit increase in the number of arousals per hour.<sup>33</sup> In fact, in adjusted analyses, arousal index was the only significant predictor of hypertension. The current study incorporates a large number of participants to provide robust evidence that a definition of OSA including cortical arousals significantly increases the odds of associated hypertension. In conjunction with the data revealing the impact of arousals on increasing sleepiness in patients with OSA<sup>34</sup> and other adverse consequences,<sup>26</sup> this now makes a compelling argument for this more inclusive definition to be adopted for consideration of therapy.

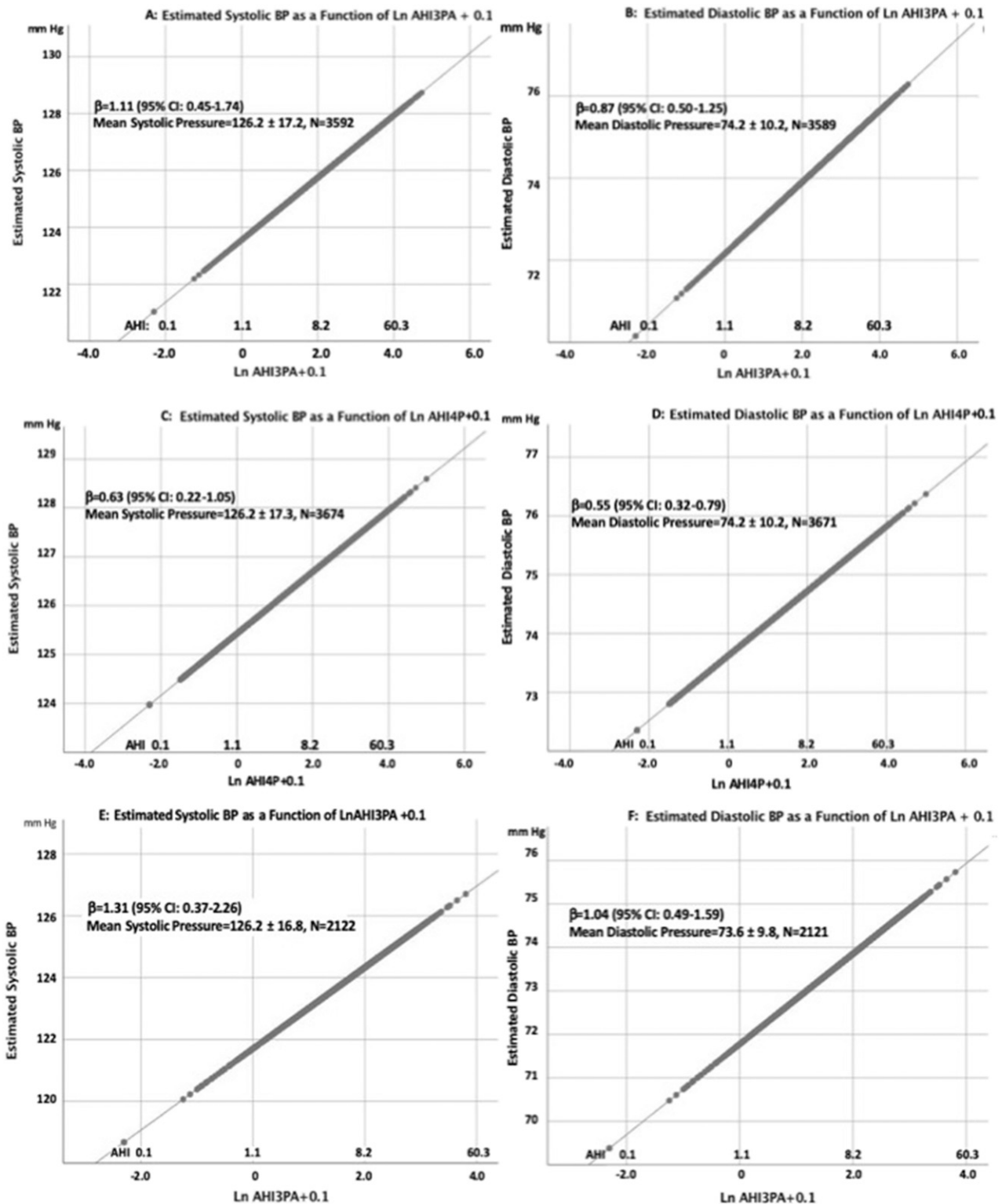
The current study attempts to overcome several of the limitations of the existing literature evaluating the relationship between OSA and hypertension. The large size of the database diminishes the probability of Type I or Type II error. The study participants were derived from the community, hence obviating referral bias. The associations were controlled for multiple confounders including age, BMI and smoking, attesting to an independent association between SDB and hypertension. However, residual confounding and selection bias in participants derived from different

parent cohorts cannot be excluded. The study utilized polysomnograms, the gold standard test for measuring sleep disordered breathing. Finally, the large database permitted analyses utilizing diverse definitions of hypertension, including the most recent hypertension classifications per the AHA guidelines.

While the study provides strong evidence for the relationship between OSA and prevalent hypertension, the cross-sectional nature of the study prevents drawing any conclusions regarding causal association between hypopneas associated with lower degrees of desaturation or arousals, and hypertension. Assessment of a longitudinal association between such hypopneas and incident hypertension would help corroborate such an inference. We also recognize that the polysomnography montage in SHHS did not include nasal pressure monitoring. Thus, it is likely that some participants classified as having an AHI < 5 events/h may have had OSA. However, this does not mitigate our conclusions because of the “dose relationship” association between OSA severity and hypertension, and that such cases would have been considered as not having OSA with the 4% only criteria. Furthermore, the participants in the study were middle aged and older and the findings may not be generalizable to younger persons with OSA. Measurement of blood pressure was performed only in the evening. Inasmuch as there is a normal decline of blood pressure at night, ascertainment over a 24 hour period might have resulted in a more precise assessment of the association between OSA severity and hypertension. Finally, the pathogenesis of hypertension may involve a complex and multifactorial process. It is possible that other factors not assessed in the study including diet and exercise may contribute to the increased odds of hypertension seen in those with OSA.

In summary, this large cross sectional study provides robust support for an association between OSA defined by a more inclusive definition than previously utilized in several other studies and CMS, and hypertension. Specifically, the odds of the presence of hypertension, regardless of how it was defined, were higher in those with 3% desaturation events or arousals, even in absence of more severe desaturation. Contemplating the morbidity associated with hypertension, universal adoption of a less restrictive definition of OSA appears to be a prudent

**Figure 1**—Graphic representations of the association of LnAHI + 0.1 and either systolic or diastolic blood pressure for each of the models shown in Table 6.



Values for BMI, sex, smoking, race/ethnicity and age were fixed at their respective means in order to generate an illustrative 2-dimensional plot. The values for LnAHI + 0.1 were converted to the AHI and shown as an alternative x-axis to facilitate visualization. (A) Estimated systolic blood pressure as a function of Ln AHI defined by a 3% desaturation or arousal for hypopneas. (B) Estimated diastolic blood pressure as a function of Ln AHI defined by a 3% desaturation or arousal for hypopneas. (C) Estimated systolic blood pressure as a function of Ln AHI defined by a 4% desaturation for hypopneas. (D) Estimated diastolic blood pressure as a function of Ln AHI defined by a 4% desaturation for hypopneas. (E) Estimated systolic blood pressure as a function of Ln AHI defined by a 3% desaturation or arousal for hypopneas in participants who had an AHI < 5 events/h using an AHI definition defined by a 4% desaturation for hypopneas. (F) Estimated diastolic blood pressure as a function of Ln AHI defined by a 3% desaturation or arousal for hypopneas in participants who had an AHI < 5 events/h using an AHI definition defined by a 4% desaturation for hypopneas.



step toward ensuring appropriate diagnosis and adequate therapy, thus mitigating associated adverse outcomes and higher health care costs.

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Address correspondence to: Stuart F. Quan, MD, Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115; Email: Stuart\_Quan@hms.harvard.edu

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