Sleep-disordered Breathing and Cardiovascular Disease
An Outcome-based Definition of Hypopneas

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***Rationale*: Epidemiologic studies on the consequences of sleep-disordered breathing invariably use the apnea–hypopnea index as the primary measure of disease severity. Although hypopneas constitute a majority of disordered breathing events, significant controversy remains about the best criteria used to define these events.**

***Objectives*: The current investigation sought to assess the most appropriate definition for hypopneas that would be best correlated with cardiovascular disease.**

***Methods*: A community sample of middle-aged and older adults was recruited as part of the Sleep Heart Health Study. Full-montage polysomnography was conducted and hypopneas were defined using different thresholds of oxyhemoglobin desaturation with and without arousals. Prevalent cardiovascular disease was assessed based on self-report. Logistic regression analysis was used to characterize the independent association between the hypopnea index and prevalent cardiovascular disease.**

***Measurements and Main Results*: Using a sample of 6,106 adults with complete data on cardiovascular disease status and polysomnography, the current study found that hypopneas associated with an oxyhemoglobin desaturation of 4% or more were associated with prevalent cardiovascular disease independent of confounding covariates. The adjusted prevalent odds ratios for quartiles of the hypopnea index using a 4% desaturation criterion were as follows: 1.00 (<1.10 events/h), 1.10 (1.01–3.20 events/h), 1.33 (3.21–7.69 events/h), and 1.41 (>7.69 events/h). Hypopnea measures based on less than 4% oxyhemoglobin desaturation or presence of arousals showed no association with cardiovascular disease.**

***Conclusions*: Hypopneas comprise a significant component of sleep-disordered breathing in the general community. By varying the criteria for defining hypopneas, this study demonstrates that hypopneas with a desaturation of at least 4% are independently associated with cardiovascular disease. In contrast, no association was observed between cardiovascular disease and hypopneas associated with milder desaturations or arousals.**

Keywords: sleep-disordered breathing; cardiovascular disease; Sleep Heart Health Study

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Sleep-disordered breathing has been associated with numerous health consequences. However, empirical data on an outcome-based definition of hypopneas are lacking.

What This Study Adds to the Field

Hypopneas with a 4% or more decrease in oxyhemoglobin saturation are associated with prevalent cardiovascular disease. Hypopneas with less than a 4% desaturation or those with an arousal are not associated with prevalent cardiovascular disease.

Epidemiologic studies have shown that sleep-disordered breathing (SDB) is associated with hypertension and cardiovascular disease (1–4). If left untreated, SDB increases the risk of fatal and nonfatal cardiovascular events that can be averted with continuous positive-pressure therapy (5). Across most of the published literature on the clinical implications of SDB, the magnitude of disease risk has been independent of confounding covariates and related to the aggregate frequency of apneas and hypopneas. Despite the wealth of empirical data linking SDB with adverse neurobehavioral and cardiovascular endpoints, the independent contribution of hypopneas to these outcomes remains to be determined. Properly addressing this issue begs the question of the most relevant definition of hypopnea that best correlates with one or more clinical consequences. In the absence of empirical evidence, there remains considerable controversy regarding the appropriate criteria for defining hypopneas. In the clinical and research arena, hypopneas are defined on the basis of several physiologic signals, including airflow, respiratory effort, oxyhemoglobin saturation, and the electroencephalogram (EEG). Although a reduction in airflow that is associated with oxyhemoglobin desaturation of at least 4% has become the recommended criterion (6), there are no studies that have systematically explored the possibility of whether hypopneas based on an alternative oxyhemoglobin desaturation threshold (e.g., 2 or 3%) or those with an EEG arousal are also be associated with adverse cardiovascular effects. Information resulting from such exploration could result in an evidence-based definition of a hypopnea with enhanced ability to define the prevalence of SDB, optimize case finding, and stratify disease severity. Thus, the primary objective of this study was to examine the significance of varying levels of hypopnea-related oxyhemoglobin desaturation in the association between SDB and prevalent cardiovascular disease in a community cohort of middle-aged and older adults. It was hypothesized that increasing frequency of events characterized by nonapneic reduction in airflow may be independently associ-

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ated with prevalent cardiovascular disease even when such events are accompanied by less severe oxyhemoglobin desaturation.

METHODS

Study Sample

The specific aims and design of the Sleep Heart Health Study (SHHS) have been previously described (7). Briefly, the SHHS is a longitudinal cohort study of the cardiovascular consequences of SDB. Participants for the baseline cohort were recruited from ongoing epidemiologic studies of cardiovascular and respiratory disease. Participants from these "parent" studies were eligible if they were at least 40 years of age and were not being treated for SDB with positive-pressure therapy, oxygen, or tracheotomy. The SHHS cohort consists of 6,441 participants who completed the baseline examination, which included an overnight polysomnogram and several interview-administered questionnaires on sleep habits and medical history between November 1995 and January 1998. Informed consent was obtained from all participants, and the study protocol was approved by the institutional review board of each institution.

Polysomnography

Unattended, home polysomnography was conducted using a portable monitor (P-Series; Compumedics, Abbotsville, Australia). The following physiologic variables were recorded: EEG (montage: C_3/A_1 and C_4/A_2), right and left electrooculograms, a single bipolar electrocardiogram and a chin electromyogram, oxyhemoglobin saturation by pulse oximetry, chest and abdominal excursion by inductance plethysmography, airflow by an oronasal thermocouple, and body position by a mercury gauge. Recordings were stored in real time and sent to a central reading center for review and scoring. Details of polysomnographic equipment, hook-up procedures, failure rates, scoring, and quality assurance have been published (8). Apnea was identified if the airflow was absent or nearly absent for at least 10 seconds. Hypopnea was identified when there was at least a 30% reduction in airflow or thoracoabdominal movement below baseline values for at least 10 seconds. The apnea–hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of sleep. The apnea index and hypopnea index were defined as the number of apneas and hypopneas, respectively, per hour of sleep. Sensitivity analyses were also conducted using different thresholds of oxyhemoglobin desaturation ($\geq$4%, $\geq$3%, $\geq$2%, any desaturation) for apneas and hypopneas. Arousals were identified according to published criteria (9). Analyses examining the associations between the hypopnea index and cardiovascular disease were conducted with and without the inclusion of arousals in the definition of a hypopnea. Finally, an oxyhemoglobin desaturation index (ODI; events/h) was also constructed for varying thresholds (e.g., $\geq$2%, $\geq$3%, $\geq$4%) of drops in oxyhemoglobin saturation during sleep.

Ascertainment of Prevalent Cardiovascular Disease and Covariate Data

During the home visit, participants completed an interviewer-administered health questionnaire that included queries regarding physician-diagnosed angina, history of heart failure, a previous heart attack, or stroke, as well as a history of bypass surgery or coronary angioplasty. Participants were allowed to provide an "unsure" response for each question. Prevalent cardiovascular disease was defined if the participant had any of the aforementioned cardiovascular conditions or procedures. Cardiovascular disease was classified as missing in the presence of unsure responses to any of the previous questions. Self-reported information related to other relevant exposures such as smoking was obtained. Smoking status was categorized as current, former, or never. Other measurements during the home visit included body weight, neck circumference, and three successive measurements of systolic and diastolic blood pressure. Covariate data included demographic variables (e.g., race), anthropometric variables (e.g., waist), and plasma lipids (total cholesterol and high-density lipoprotein [HDL] cholesterol). Race was classified as white, African American, American Indian, Hispanic, or other.

Statistical Analysis

Unadjusted differences in continuous and categorical predictor variables across cardiovascular disease status were assessed for significance using *t* tests or χ^2 tests, as appropriate. Of the 6,441 participants in the baseline SHHS cohort, 335 (5.2%) were classified as having "missing" cardiovascular disease status. Thus, the sample size for the current analysis consisted of 6,106 subjects. Participants with missing cardiovascular disease status were younger and included a higher proportion of African Americans than those with prevalent cardiovascular disease data (Table E1 of the online supplement). To assess the associations between prevalent cardiovascular disease and SDB using different definitions, logistic regression analysis was used. The independent variables included the AHI, the apnea index, the hypopnea index, and the ODI. Variables were categorized into four equal groups using quartiles for various oxyhemoglobin desaturation thresholds. In the development of the multivariable statistical models for prevalent cardiovascular disease, bivariate analyses were initially performed to determine the unadjusted relative odds ratios and the associated 95% confidence intervals for variables of interest comparing the second through fourth quartiles to the first quartile. Adjustments in these models included age, sex, race, body mass index, neck circumference, waist circumference, smoking status, total cholesterol, and HDL cholesterol. All statistical analyses were conducted using the SAS statistical software, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 6,106 SHHS participants with data on cardiovascular disease status, 16.8% (n = 1,025) reported prevalent cardiovascular disease. Table 1 shows the characteristics of the study cohort, including demographic and anthropometric variables by cardiovascular disease status. As expected, compared with participants without cardiovascular disease, those with cardiovascular disease were older and had a higher prevalence of other risk factors, including central obesity (i.e., larger waist and neck circumference), former or current tobacco use, prevalent hypertension, and lower HDL cholesterol levels. In addition, male sex and minority race were also associated with a higher prevalence of cardiovascular disease.

All bivariate and multivariable analyses were initially conducted with hypopneas or apneas using only the oxyhemoglobin desaturation criterion without an EEG arousal as part of the definition. At virtually every desaturation threshold by which hypopneas and apneas were defined, the unadjusted event frequency per hour of sleep was significantly higher in participants with cardiovascular disease (Table E2). To examine the degree of correlation between the apnea index and the hypopnea index, Pearson's correlation coefficients were computed (Table E3). As expected, regardless of the oxyhemoglobin desaturation threshold, the apnea index and the hypopnea index at varying oxyhemoglobin desaturation thresholds were modestly correlated (range of correlation coefficients, 0.15–0.40). These correlations indicate that, although apneas and hypopneas co-occur, there is moderate heterogeneity, which allows for an independent examination of the associations between the apnea index, the hypopnea index, and prevalent cardiovascular disease.

Multivariable logistic regression models were constructed for the apnea index and hypopnea index for each threshold of oxyhemoglobin desaturation (e.g., $\geq$4%, $\geq$3%, $\geq$2%) to determine their association with prevalent cardiovascular disease. In these multivariable models, the apnea index and the hypopnea index, each associated with a specific level of oxyhemoglobin desaturation, were included as an independent variable together with the following covariates: age, sex, race, body mass index, waist circumference, neck circumference, and other cardiovascular risk factors (i.e., smoking status, total cholesterol, and HDL cholesterol). Sensitivity analyses showed that inclusion of prevalent hypertension as a covariate in each of the multivariable models constructed had no material impact on the reported odds ratios and thus it was not included as a covariate. Using a 4% desaturation criterion, the adjusted odds ratios for prevalent

TABLE 1. CHARACTERISTICS OF THE STUDY SAMPLE BY CARDIOVASCULAR DISEASE STATUS

	% or Median (IQR*)		
Characteristic	CVD (*n = 1,025*)	No CVD (*n = 5,081*)	*P* Value
Sex, %			<0.0001
Men	58.4	44.7	
Women	41.6	55.3	
Race, %			<0.0001
White	74.6	78.6	
Native American	14.8	8.5	
African American	8.6	6.4	
Hispanic	1.6	4.9	
Other	0.4	1.6	
Smoking status, %			<0.0001
Never	36.9	47.6	
Former	52.7	41.0	
Current	10.4	11.4	
Hypertension, %	80.2	47.1	<0.0001
Age, yr	70.0 (62.0 – 76.0)	61.0 (54.0 – 70.0)	<0.0001
Body mass index, kg/m^2	28.0 (25.1 – 31.6)	27.7 (24.8 – 31.1)	0.14
Waist circumference, cm	99.7 (92.0 – 108.0)	97.0 (88.0 – 106.0)	<0.0001
Neck circumference, cm	39.0 (36.0 – 41.5)	37.5 (34.5 – 40.5)	<0.0001
Total cholesterol, mg/dl	201.0 (178.0 – 228.0)	204.0 (180.0 – 229.0)	<0.08
HDL cholesterol, mg/dl	43.0 (36.0 – 54.0)	48.0 (39.0 – 59.0)	<0.0001
Apnea–hypopnea index†, events/h	6.8 (2.5 – 14.7)	3.9 (1.2 – 10.3)	<0.0001
Apnea index†, events/h	0.7 (0.0 – 3.7)	0.3 (0.0 – 2.1)	<0.0001
Hypopnea index†, events/h	4.7 (1.9 – 9.8)	3.0 (0.9 – 7.3)	<0.0001

Definition of abbreviations: CVD = cardiovascular disease; HDL = high-density lipoprotein; IQR = interquartile range.
* IQR = 25th–75th percentile.
† Apneas and hypopneas based on a 4% oxyhemoglobin desaturation criterion.

cardiovascular disease for quartile of the hypopnea index were as follows: 1.00 (quartile I: <1.01 events /h), 1.10 (quartile II: 1.01–3.20 events/h), 1.33 (quartile III: 3.21–7.69 events/h), and 1.41 (quartile IV: >7.69 events/h). Figure 1 shows that, for oxyhemoglobin desaturation thresholds of 4, 3, and 2%, the hypopnea index was independently associated with prevalent cardiovascular disease. In contrast, regardless of the oxyhemoglobin desaturation threshold, the apnea index was not associated with prevalent cardiovascular disease (Figure E1). Because the quartile cut points for the hypopnea index based on different

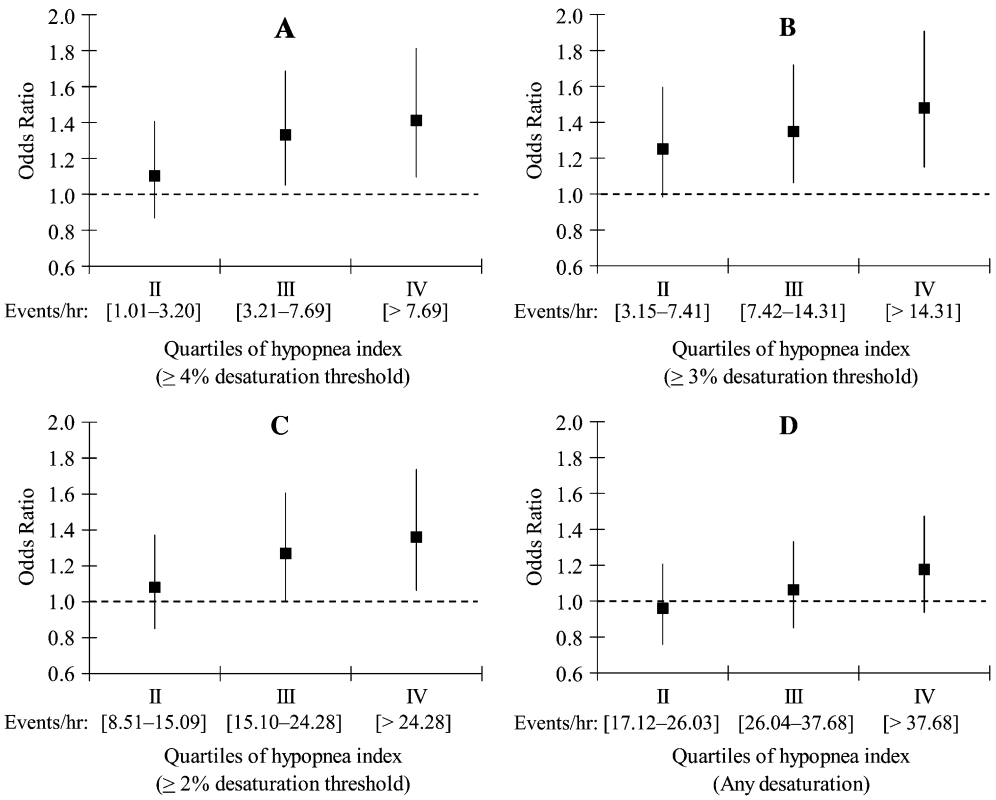

Figure 1. Adjusted odds ratios for prevalent cardiovascular disease derived from multivariable logistic regression models for the hypopnea index at different oxyhemoglobin desaturation thresholds (*A*: ⩾4%, *B*: ⩾3%, *C*: ⩾2%, *D*: any desaturation). Covariates include age, sex, race, body mass index, waist circumference, neck circumferences, total cholesterol, high-density lipoprotein cholesterol, smoking status, and the apnea index at the same threshold as the hypopnea index. Cut points for the first quartile were as follows: (*A*) <1.01 events/hour; (*B*) <3.15 events/hour; (*C*) <8.51 events/hour; and (*D*) <17.12 events/hour.

desaturation thresholds are dissimilar, the odds ratios for prevalent cardiovascular disease cannot be compared across the different multivariable models shown in Figure 1.

Given that the association between cardiovascular disease and the hypopnea index defined using a given threshold of oxyhemoglobin desaturation (e.g., ⩾2%, ⩾3%, ⩾4%) could be influenced by more severe oxyhemoglobin desaturations, further analyses were undertaken to determine whether hypopneas with oxyhemoglobin desaturations within a specific range (0–2%, 2–3%, 3–4%) were associated with cardiovascular disease after accounting for hypopneas with oxyhemoglobin desaturation above the cut point (e.g., >2%, >3%, >4%). Hierarchical models were constructed with a stepwise addition of covariates as before. Table 2 shows that the frequency of hypopneas associated with a 4.0–4.9% oxyhemoglobin desaturation was associated with prevalent cardiovascular disease after adjusting for the frequency of hypopneas with oxyhemoglobin desaturations above 5%. However, no significant associations were noted between prevalent cardiovascular disease and hypopnea-related oxyhemoglobin desaturations of less than 4%. Analyses were also conducted by including arousals as part of the hypopnea definition. The odds ratios relating prevalent cardiovascular disease to the quartiles of the hypopnea index on the basis of presence of oxyhemoglobin desaturation at various thresholds or occurrence of an arousal were either materially unchanged or lower in magnitude compared with those in Figure 1 (Figure E2). Thus, inclusion of an arousal in defining hypopneas did not improve the association between the hypopnea index and prevalent cardiovascular disease.

Additional analyses were also undertaken to characterize the association between prevalent cardiovascular disease and the ODI using different desaturation thresholds. The ODI is a frequency of desaturation events per hour of sleep that is determined independent of changes in airflow. Tables 3 and 4 show the adjusted odds ratio for cardiovascular disease for quartiles of ODI based on desaturations at or above a specific threshold (Table 3) and within specific range of oxyhemoglobin desaturation after adjusting for events with desaturation that exceeded the range (Table 4). These analyses revealed that the frequency of

TABLE 2. ADJUSTED ODDS RATIOS (95% CONFIDENCE INTERVALS) FOR PREVALENT CARDIOVASCULAR DISEASE AS A FUNCTION OF THE HYPOPNEA INDEX BASED ON OXYHEMOGLOBIN DESATURATION (ΔSa_{O_2}) WITHIN SPECIFIC RANGES

Hypopnea index quartile (*events/h*)	Model 1*	Model 2†	Model 3‡
ΔSa_{O_2} range: 4.0–4.9%			
⩽0.60	1.00	1.00	1.00
0.61–1.69	1.64 (1.33–2.04)	1.36 (1.08–1.72)	1.34 (1.05–1.70)
1.70–3.46	1.93 (1.56–2.39)	1.41 (1.11–1.77)	1.32 (1.04–1.68)
>3.46	2.25 (1.78–2.84)	1.49 (1.15–1.92)	1.38 (1.05–1.79)
ΔSa_{O_2} range: 3.0–3.9%			
⩽1.88	1.00	1.00	1.00
1.89–3.76	1.52 (1.23–1.89)	1.15 (0.92–1.45)	1.15 (0.91–1.47)
3.77–6.32	1.87 (1.51–2.31)	1.32 (1.05–1.66)	1.28 (1.01–1.63)
>6.32	1.84 (1.46–2.32)	1.20 (0.93–1.55)	1.13 (0.87–1.47)
ΔSa_{O_2} range: 2.0–2.9%			
⩽4.19	1.00	1.00	1.00
4.20–6.64	1.14 (0.93–1.40)	0.97 (0.78–1.20)	0.97 (0.77–1.22)
6.65–10.06	1.20 (0.98–1.47)	1.00 (0.80–1.24)	0.98 (0.78–1.23)
>10.06	1.37 (1.12–1.69)	1.03 (0.82–1.28)	0.99 (0.78–1.25)
ΔSa_{O_2} range: 0.0–1.9%			
⩽5.22	1.00	1.00	1.00
5.23–8.84	0.87 (0.71–1.05)	0.90 (0.73–1.11)	0.88 (0.71–1.09)
8.85–14.33	0.88 (0.73–1.07)	0.83 (0.67–1.02)	0.85 (0.68–1.05)
>14.33	0.95 (0.79–1.15)	0.92 (0.75–1.13)	0.91 (0.73–1.13)

Each set of odds ratios represents a distinct multivariable logistic regression model.

* Model 1 includes the following covariates: apnea index and hypopnea index based on oxyhemoglobin desaturation above the threshold being examined.

† Model 2 was adjusted for all covariates in model 1 plus age, sex, race, body mass index, neck circumference, and waist circumference.

‡ Model 3 was adjusted for all covariates in model 2 plus other cardiovascular risk factors (total cholesterol, high-density lipoprotein cholesterol, and smoking).

TABLE 3. ADJUSTED ODDS RATIOS FOR PREVALENT CARDIOVASCULAR DISEASE FOR THE OXYHEMOGLOBIN DESATURATION INDEX AT VARIOUS OXYHEMOGLOBIN DESATURATION (ΔSa_{O_2}) THRESHOLDS

ODI Quartile (*events/h*)	Model 1*	Model 2†	Model 3‡
ΔSa_{O_2} threshold: ⩾4.0%			
⩽1.70	1.00	1.00	1.00
1.71–4.13	1.41 (1.14–1.74)	1.20 (0.96–1.51)	1.17 (0.92–1.49)
4.14–9.38	1.84 (1.50–2.26)	1.35 (1.08–1.69)	1.31 (1.03–1.65)
>9.38	2.33 (1.91–2.85)	1.56 (1.24–1.95)	1.52 (1.20–1.92)
ΔSa_{O_2} threshold: ⩾3.0%			
⩽4.49	1.00	1.00	1.00
4.49–8.99	1.51 (1.22–1.86)	1.30 (1.03–1.63)	1.27 (1.00–1.60)
9.00–16.92	1.75 (1.42–2.15)	1.25 (1.00–1.57)	1.19 (0.94–1.51)
>16.92	2.27 (1.86–2.78)	1.54 (1.23–1.94)	1.52 (1.20–1.92)
ΔSa_{O_2} threshold: ⩾2.0%			
⩽19.83	1.00	1.00	1.00
19.84–29.46	1.37 (1.11–1.67)	1.13 (0.91–1.41)	1.13 (0.90–1.42)
29.46–41.24	1.57 (1.29–1.92)	1.16 (0.93–1.44)	1.16 (0.92–1.46)
>41.24	1.76 (1.45–2.15)	1.32 (1.06–1.65)	1.30 (1.03–1.64)

Definition of abbreviation: ODI = oxyhemoglobin desaturation index.

Each set of odds ratios represents a distinct multivariable logistic regression model.

* Model 1 was unadjusted.

† Model 2 was adjusted for age, sex, race, body mass index, neck circumference, and waist circumference.

‡ Model 3 was adjusted for all covariates in model 2 and other cardiovascular disease risk factors (total cholesterol, high-density lipoprotein cholesterol, and smoking).

TABLE 4. ADJUSTED ODDS RATIOS FOR PREVALENT CARDIOVASCULAR DISEASE FOR OXYHEMOGLOBIN DESATURATION INDEX FOR VARIOUS OXYHEMOGLOBIN DESATURATION (ΔSa_{O_2}) WITHIN SPECIFIC CUT POINTS

ODI Quartile (*events/h*)	Model 1*	Model 2†	Model 3‡
ΔSa_{O_2} range: 4.0–4.9%			
⩽0.94	1.00	1.00	1.00
0.95–2.08	1.40 (1.13–1.74)	1.17 (0.93–1.47)	1.18 (0.93–1.51)
2.09–4.01	1.93 (1.57–2.38)	1.41 (1.12–1.77)	1.38 (1.09–1.75)
>4.01	2.07 (1.66–2.58)	1.39 (1.09–1.77)	1.34 (1.04–1.73)
ΔSa_{O_2} range: 3.0–3.9%			
⩽2.47	1.00	1.00	1.00
2.48–4.29	1.44 (1.17–1.76)	1.19 (0.95–1.48)	1.16 (0.92–1.45)
4.30–7.00	1.44 (1.17–1.76)	1.08 (0.86–1.35)	1.02 (0.81–1.28)
>7.00	1.51 (1.22–1.87)	1.14 (0.91–1.44)	1.09 (0.86–1.38)
ΔSa_{O_2} range: 2.0–2.9%			
⩽12.93	1.00	1.00	1.00
12.94–18.05	1.08 (0.89–1.30)	0.99 (0.81–1.21)	0.98 (0.80–1.22)
18.06–23.94	1.00 (0.82–1.21)	0.95 (0.78–1.17)	0.95 (0.77–1.18)
>23.94	0.91 (0.75–1.11)	0.93 (0.76–1.15)	0.92 (0.74–1.14)

Definition of abbreviation: ODI = oxyhemoglobin desaturation index.

Each set of odds ratios represents a distinct multivariable logistic regression model.

* Model 1 includes the following covariates: ODI based on desaturations above the threshold being examined.

† Model 2 was adjusted for all covariates in model 1 plus age, sex, race, body mass index, neck circumference, and waist circumference.

‡ Model 3 was adjusted for all covariates in model 2 plus other cardiovascular disease risk factors (total cholesterol, high-density lipoprotein cholesterol, and smoking).

oxyhemoglobin desaturation in the 4.0–4.9% range is associated with prevalent cardiovascular disease even after adjusting for desaturations higher than 5%. However, the associations between prevalent cardiovascular disease and the ODI based on desaturation of less than 4% were not statistically significant.

DISCUSSION

The current investigation presents several unique findings. First, SDB in a community sample of middle-aged and older adults is characterized more by the occurrence of hypopneas than apneas. Second, independent of apnea index, the hypopnea index was associated with self-reported prevalent cardiovascular disease. Third, while keeping a fixed threshold of airflow reduction and regardless of an arousal criterion, the current study identified a clinically relevant hypopnea definition that best correlated with prevalent cardiovascular disease after accounting for several confounding covariates. Specifically, the frequency of hypopneas defined by a threshold of oxyhemoglobin desaturation of at least 4% was associated with cardiovascular disease. The strength or precision of association was not improved by reducing the desaturation threshold criterion to less than 4% or by including arousals in the definition. Similarly, examination of the ODI, which does not include the degree of airflow reduction, showed that desaturations based on a threshold of 4% or more were also associated with cardiovascular disease. Including less severe desaturation events showed no improvement in the association with cardiovascular disease compared with the 4% threshold.

Over the last decade, substantial evidence has accumulated linking SDB to excess morbidity and mortality. The risk of many clinical sequelae attributed to SDB appears to increase as the AHI increases. By including both apneas and hypopneas in this disease-defining metric, an implicit assumption is that these events are alike in their impact on clinical outcomes. Although this assumption may in fact be correct, there is a relative paucity of supporting evidence. Moreover, there are no empirical data indicating whether certain criteria for defining hypopneas are better associated with adverse SDB-related outcomes than others. A major challenge in defining the health-related implications of hypopneas is the inconsistency in defining these events. Differences in the amount of airflow reduction, degree of oxyhemoglobin desaturation, and the inclusion of arousal can lead to significant variability in hypopnea detection across different laboratories. Compounding this variability are the differences in the methods used to detect breathing abnormalities during sleep (e.g., thermistor vs. nasal pressure transducer). Thus, an outcome-based hypopnea definition is lacking and consensus recommendations are commonly used in research and clinical practice. For example, in a 2001 consensus report (10) by a task force of the American Academy of Sleep Medicine (AASM), it was recommended that a hypopnea be defined as an abnormal respiratory event characterized by a 30% or more reduction in airflow that is associated with an oxyhemoglobin desaturation of at least 4%. A 2005 update of those recommendations incorporated alternate criteria that included a discernible reduction in airflow associated with an oxyhemoglobin desaturation of at least 3% or an arousal from sleep (11). Most recently, the AASM published a comprehensive manual for scoring sleep and associated events in which both of the aforementioned definitions were also permitted (6). By allowing alternate criteria, there is an embedded recognition that the current level of evidence is insufficient for defining event criteria that are associated with adverse health outcomes. The work presented herein attempts to fill some of these gaps by carefully considering different thresholds of oxyhemoglobin desaturation and by including and excluding arousal from the definition of a hypopnea. Overall, our results suggest that hypopneas associated with an oxyhemoglobin desaturation of at least 4% are correlated with cardiovascular disease, whereas those associated with lesser degrees of hypoxemia or arousals show no association. Whether similar findings also emerge for other SDB-related outcomes, such as daytime sleepiness, neurocognitive dysfunction, and altered glucose homeostasis, remains to be determined.

The implications for using outcome-based thresholds for hypopnea definition in SDB are numerous. Although it is appealing to believe that using less stringent thresholds for SDB may benefit the individual patient, there are reasons to believe that this may not be the case. First, the evidence supporting the use of less stringent criteria for SDB events is lacking. Such evidence should be based on rigorous analyses that test hypotheses on whether a threshold in oxyhemoglobin desaturation or the inclusion of arousals for defining hypopneas is associated with a clinical outcome in cross-sectional and longitudinal studies. A simple comparison of the AHI based on a 3% versus a 4% oxyhemoglobin desaturation threshold as a predictor of a clinical outcome is insufficient. Rather, analyses that examine a specific level of oxyhemoglobin desaturation for a hypopnea need to take into account events with oxyhemoglobin desaturation that are above the threshold. Moreover, because endpoints may vary with the type and severity of SDB events, the clinical value for different event definitions has to be individually determined. Second, lowering the criteria for detecting hypopneas will undoubtedly increase the number of patients who are diagnosed with SDB and started on treatment. Although serious side effects of positive-pressure therapy are rare, the benefits of treatment may be small, particularly for those patients who received a diagnosis on less stringent criteria. Third, given the large reservoir of undiagnosed disease, priority should be initially placed on identifying and treating those patients who meet the most stringent and uncontroversial definition of SDB. Finally, lowering disease-defining thresholds without supporting evidence will raise the prevalence of disease and impose additional burden on already limited public heath resources. The foregoing considerations argue that adopting a particular set of criteria will require a concerted effort to define the clinical sequelae associated with varying definitions of SDB.

There are several important limitations in this study that merit discussion. The first limitation is that causal inferences are not possible given the cross-sectional nature of our analysis. Thus, although including arousals in the hypopnea definition did not augment the association with cardiovascular disease, sleep fragmentation cannot be excluded as a putative factor linking SDB to cardiovascular outcomes. The lack of an association with hypopnea-related arousals may merely reflect the poor reliability of scoring EEG arousals (12). Similarly, hypoxemia cannot be implicated as a causal factor because reverse causality (i.e., cardiovascular disease causing SDB) is also certainly possible. The second limitation is that assessments of breathing abnormalities during sleep were based on inductive plethysmography and an oronasal thermistor. A comprehensive survey of validity and reliability of scoring respiratory events concluded that the thermistor, as used in the SHHS, is far inferior in detecting hypopneas when compared with a nasal pressure device (13). However, the underdetection of hypopneas is likely to be similar in those with and without cardiovascular disease and thus any bias in the measures of association is probably small. The use of a thermistor to assess airflow also limited our ability to examine whether different levels of airflow reduction would be associated with prevalent cardiovascular disease. The third limitation comes from our use of self-reports to assess prevalent cardiovascular disease. Previous work from one of the SHHS parent cohorts has shown that proportions of confirmed self-reported myocardial

infarction is 75.5 and 60.6% in men and women, respectively (14). For a diagnosis of heart failure, these estimates were 73.3 and 76.6%, respectively, confirming an underreporting of cardiovascular conditions. Nonetheless, in all probability, the degree of underreporting is likely to be unrelated to the abnormalities on the polysomnogram and thus would not lead to biased estimates of association. Finally, it is also important to recognize that the SHHS cohort is not representative of a population-based cohort. The older age of the sample, the recruitment of subjects from other epidemiologic cohorts with oversampling on snoring subjects, and the relatively low burden of SDB limit the generalizability of the reported results. These limitations notwithstanding, the current study also has several strengths. These include the use of full-montage polysomnography to characterize SDB with varying event definitions in a large community cohort. Furthermore, adjustments for cardiovascular risk factors and other demographic factors allowed for an unconfounded examination of how different hypopnea definitions correlate with prevalent cardiovascular disease. Finally, inclusion of hypopneas associated with severe oxyhemoglobin desaturation in multivariable models for a specific oxyhemoglobin desaturation threshold is also a major strength. Such adjustments are necessary to ensure that the measures of association derived for a specific threshold in oxyhemoglobin desaturation are not biased by events that are associated with severe degrees of oxyhemoglobin desaturation.

In summary, the results of this cross-sectional analysis of the SHHS data show that hypopneas with a 4% reduction in oxyhemoglobin saturation are associated with cardiovascular disease, even after accounting for events with greater degrees of desaturation. In contrast, there was no association between the frequency of hypopneas with less than 4% desaturation and cardiovascular disease. Additional research is needed to compare different event definitions in their association with other SDB-related consequences in cross-sectional and longitudinal analyses. Without such evidence, expanding event definitions will certainly increase the number of patients with mild disease, but at the expense of identifying and adequately treating those that are severely affected but remain undiagnosed.

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