Sleep-disordered Breathing and Cardiovascular Disease
Cross-sectional Results of the Sleep Heart Health Study

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Disordered breathing during sleep is associated with acute, unfavorable effects on cardiovascular physiology, but few studies have examined its postulated association with cardiovascular disease (CVD). We examined the cross-sectional association between sleep-disordered breathing and self-reported CVD in 6,424 free-living individuals who underwent overnight, unattended polysomnography at home. Sleep-disordered breathing was quantified by the apnea–hypopnea index (AHI)—the average number of apneas and hypopneas per hour of sleep. Mild to moderate disordered breathing during sleep was highly prevalent in the sample (median AHI: 4.4; interquartile range: 1.3 to 11.0). A total of 1,023 participants (16%) reported at least one manifestation of CVD (myocardial infarction, angina, coronary revascularization procedure, heart failure, or stroke). The multivariable-adjusted relative odds (95% CI) of prevalent CVD for the second, third, and fourth quartiles of the AHI (versus the first) were 0.98 (0.77–1.24), 1.28 (1.02–1.61), and 1.42 (1.13–1.78), respectively. Sleep-disordered breathing was associated more strongly with self-reported heart failure and stroke than with self-reported coronary heart disease: the relative odds (95% CI) of heart failure, stroke, and coronary heart disease (upper versus lower AHI quartile) were 2.38 (1.22–4.62), 1.58 (1.02–2.46), and 1.27 (0.99–1.62), respectively. These findings are compatible with modest to moderate effects of sleep-disordered breathing on heterogeneous manifestations of CVD within a range of AHI values that are considered normal or only mildly elevated.

Sleep apnea and milder forms of sleep-disordered breathing are associated with acute and substantial cardiovascular stress. Respiratory events during sleep (apneas or hypopneas) often cause hypoxemia, sympathetic activation, acute pulmonary and systemic hypertension, and decreased stroke volume (1–4). Overnight electrocardiography in patients with sleep apnea sometimes detects signs of myocardial ischemia concurrent to respiratory events (5, 6), and anecdotal observations suggest that apneic episodes can trigger transient ischemic attacks (7). For reasons that are not fully understood, various manifestations of cardiovascular disease (CVD) show peak occurrence after awakening (8–10).

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Although the acute, unfavorable effects of sleep apnea on cardiovascular physiology have been well characterized, much less research has addressed questions of public health importance: is sleep-disordered breathing indeed a risk factor for symptomatic CVD and, if so, how strong is that effect? Previous studies of these questions were hospital based or relatively small (11–16), some lacked a control group (17, 18), and few have examined the association of sleep apnea with stroke (19, 20). Furthermore, little is known about the potential effect of mild to moderate sleep-disordered breathing, which is prevalent, often asymptomatic, and largely undiagnosed (21).

We report here cross-sectional associations between sleep-disordered breathing and CVD from the Sleep Heart Health Study, a multicenter cohort study of the cardiovascular consequences of sleep-disordered breathing.

METHODS

The complete design of the Sleep Heart Health Study is described elsewhere (22). In brief, between November 1995 and January 1998, a cohort of 6,424 individuals was assembled from more than 23,000 participants in several ongoing population-based studies of CVD in diverse United States populations. The lower age boundary of participants was 40 yr, but no upper boundary was dictated in the protocol. Only three exclusion criteria were mandated, all pertaining to conditions that posed technical difficulties for polysomnography: treatment of sleep apnea with continuous positive airway pressure or an oral device, oxygen treatment at home, and having a tracheostomy. Habitual snorers (subjects reporting snoring at least three nights per week) comprised 39% of the Sleep Heart Health Study cohort (versus 33% of the source population) due to self-selection and some intentional oversampling of habitual snorers from among the younger age group. Regardless of the mechanism, cohort enrichment with subjects who were more likely to have sleep-disordered breathing has served to increase the statistical power of the study.

Polysomnography

Participants underwent a single night, unattended polysomnography at home, using a portable monitor (Compumedics P Series System; Abbotsford, Victoria, Australia). The following channels were recorded: electroencephalogram (C3/A1, C4/A2), electrooculogram (bilateral), electrocardiogram, chin electromyogram, oxyhemoglobin saturation (finger pulse oximetry), chest and abdominal excursion (inductance plethysmography), airflow (oronasal thermocouple), body position, and ambient light. The sleep studies from each field center were shipped to a central reading center where they were reviewed and scored. Technical details of the hook-up procedure, failure rates, scoring of the studies, quality assurance, and quality control are described elsewhere (23, 24).

A respiratory event (an apnea or a hypopnea) was defined as a decrease in airflow or chest wall movement to an amplitude that was smaller than approximately 25% (an apnea) or 70% (a hypopnea) of the baseline amplitude. A qualifying event should have lasted at least

10 s and should have been associated with oxyhemoglobin desaturation of 4% or greater as compared with the baseline. Central apneas were scored if airflow (detected by the thermocouple) was absent, or nearly absent, for 10 s or more, and there was no evidence of effort from both the abdominal and thoracic channels. Microarousals were identified according to the recommendations of the American Sleep Disorders Association (25).

We examined the association of CVD with three variables of interest: the average number of respiratory events per hour of sleep (apnea–hypopnea index, AHI), percent of sleep time with oxyhemoglobin saturation below 90% (hypoxemia index), and the average number of microarousals per hour of sleep (arousal index). The intraclass correlation coefficients for interscorer reliability, determined early in the study, were 0.99 and 0.54 for the AHI and arousal index, respectively (26). A central apnea index was computed by dividing the number of central apneas by the total sleep time. To keep criteria similar to those used for the AHI, only events that were associated with a 4% or more desaturation were included in the index.

Interviews and Other Measurements

During the home visit, a study technician interviewed the participant according to a standardized questionnaire, collecting information on medical history and health-related characteristics. The interviewer asked if a doctor had ever told the participant that she or he had angina, heart attack, heart failure, or stroke and if the participant ever underwent coronary bypass surgery or coronary angioplasty. An "unsure" response was allowed for each data item. We defined prevalent CVD as a positive response to one or more of the aforementioned conditions or procedures. Prevalent coronary heart disease was similarly defined, excluding the questions about heart failure (which sometimes has a noncoronary etiology) and stroke. Those who responded "No" to all of the questions were considered CVD free. The remainder (i.e., a combination of "No" and "Unsure" responses to all of the items) were classified as unknown disease status and were considered missing in these analyses.

Another part of the interview evaluated smoking status (current, former, or never smoking). Current smokers were asked to estimate the number of cigarettes they smoked per day. The interviewer also recorded medications, both prescribed and nonprescribed, and users of antihypertension medications were subsequently identified (27).

Body weight was measured by a portable scale, and three successive measurements of systolic and diastolic blood pressure were taken. The average of the second and third blood pressure values was used in this analysis. Detailed protocols for these measurements are described in a manual of operation (23).

Parent Study Data

The parent studies of the cohort provided data on numerous covariates: demographic variables (e.g., race), anthropometric variables (e.g., height), plasma lipids (e.g., total cholesterol and high-density lipoprotein [HDL] cholesterol), and history of several diseases as reported by the participant (e.g., diabetes and hypertension). These variables were measured prior to the sleep study, within a time interval that did not exceed 5 yr. Race was classified as white, black, American Indian/Alaskan, or "other" (mostly Hispanic origin). Body mass index was calculated as weight (kg), measured on the night of the sleep study, divided by the square of height (m^2), obtained from the parent study database.

Analysis

The primary sample for this analysis included 6,424 participants. Of these, 335 were excluded because of missing data on CVD status, leaving 6,089 observations for univariate analyses. Because of missing data for some of the covariates, the sample size for multivariable models was further reduced, up to a minimum of 5,250 observations. The primary covariate with missing data was HDL cholesterol (n missing = 478).

To examine associations between sleep-disordered breathing and prevalent CVD, we created four equal size groups (quartiles) for each index of sleep-disordered breathing using its percentile distribution in the sample. The unconditional confounding structure of the data set was examined by displaying proportions (categorical covariates) or mean values (continuous covariates) for each quartile. Because of space constraints, we show these data only for quartiles of the AHI—the main index of interest.

The lower quartile (< 25th percentile) of the index distribution served as a reference category for the computation of the effect size. Associations were quantified by computing relative prevalence odds: the odds of prevalent CVD for a given category divided by the odds of prevalent CVD for the reference category.

To determine the confounding effect of individual covariates, we entered each covariate individually into a logistic regression model that included three indicator variables for the quartiles of each index of sleep-disordered breathing. Next, we forced into the models the following covariates (presumed causes, or surrogates of causes, of CVD): age (continuous), race (three indicator variables), sex, smoking status (two indicator variables for three categories), number of cigarettes currently smoked per day (continuous), self-reported diabetes, self-reported hypertension, use of antihypertension medications, systolic blood pressure (continuous), body mass index (continuous), total cholesterol (continuous), and HDL cholesterol (continuous). We refer to this model as the "full model." To test the robustness of the results against another method of covariate selection, we used a forward selection procedure to identify a parsimonious model of the covariates, into which we subsequently forced each sleep variable. That forward selection procedure eliminated body mass index, number of cigarettes currently smoked per day, self-reported hypertension, and systolic blood pressure from the pool of candidate covariates but retained "use of antihypertension medications." Because of some concern that adjustment for a hypertension indicator is "overadjustment" (i.e., adjustment for a variable on a causal pathway), we excluded "use of antihypertension medications" from the final set of covariates. We refer to the latter set as the "parsimonious model." Throughout, we show adjusted effect estimates for the sleep variables from both models: full and parsimonious. These models were also fit to three subcategories of CVD: prevalent coronary heart disease, prevalent heart failure, and prevalent stroke.

We used three approaches to examine the dose–response relation between sleep-disordered breathing and CVD. First, we carried out statistical tests for linear trends by modeling a four-level ordinal variable that took the value of the natural logarithm of the within quartile median, and computing a p value for the coefficient of that variable. Second, we divided the upper quartile into subcategories to examine potential heterogeneity of effects at the right tail of the distribution. Finally, we fit restricted cubic spline regression models (28) to the AHI data with knots placed at AHI values of 0.2 (5th percentile), 1.3 (25th percentile), 4.4 (50th percentile), 11.0 (75th percentile), and 33.7 (95th percentile).

RESULTS

A total of 1,023 participants reported one or more manifestation of CVD (16% of the cohort). Of these, 426 were women and 597 were men, 838 were coronary heart disease cases, 232 were stroke cases, and 123 were cases of heart failure, with 148 participants reporting more than one manifestation of CVD. Prevalent coronary heart disease included 244 cases of myocardial infarction, 207 cases of both myocardial infarction and angina, 289 cases of angina but no myocardial infarction, and 98 cases of revascularization procedures alone.

The median value of the AHI in the sample was 4.4 and the interquartile range (25th percentile to 75th percentile) was 1.3 to 11.0. The median of the hypoxemia index was 0.26% of total sleep time and the 75th percentile was 2.2% of total sleep time. The 25th, 50th, and 75th percentiles of the arousal index were 11.6, 16.6, and 23.6, respectively. All three distributions were skewed to the right.

Of the three sleep variables, two were strongly correlated in the data set: the AHI and the hypoxemia index ($r_{spearman}$ = 0.73). By contrast, the correlation of the arousal index with either the AHI or the hypoxemia index was much weaker ($r_{spearman}$ = 0.36 and 0.24, respectively).

Table 1 shows the distribution of covariates and prevalent

TABLE 1

UNIVARIATE RELATION OF THE APNEA–HYPOPNEA INDEX (AHI) TO VARIOUS CHARACTERISTICS AND PREVALENT CARDIOVASCULAR DISEASE

	AHI Quartile			
Variable (*mean or %*)	I	II	III	IV
Quartile range	0–1.3	1.4–4.4	4.5–11.0	> 11.0
Age, yr (mean)	61	63	65	66
Race, % white	78	79	78	77
Sex, % female	70	57	49	35
Body mass index, kg/m^2 (mean)	25.9	27.7	29.3	30.9
Smoking status, % never smoked	49	48	44	43
Total cholesterol, mg/dl (mean)	203	208	207	205
HDL cholesterol, mg/dl (mean)	54	50	48	46
Diabetes, %	6	9	11	15
Self-reported hypertension, %	30	35	42	46
Systolic blood pressure, mm Hg (mean)	126	130	132	133
Use of antihypertension medications, % using	32	36	43	50
Prevalent cardiovascular disease, n (%)	163 (11)	205 (14)	303 (20)	352 (23)
Prevalent coronary heart disease, n (%)	134 (9)	166 (11)	248 (16)	290 (19)
Prevalent heart failure, n (%)	13 (0.9)	22 (1.5)	38 (2.5)	50 (3.3)
Prevalent stroke, n (%)	35 (2.3)	47 (3.1)	70 (4.6)	80 (5.3)

Definition of abbreviation: HDL = high-density lipoprotein.

CVD across the AHI quartiles. As expected, the proportion of women declined from quartile I to IV, whereas mean body mass index increased. The concentration of HDL cholesterol was inversely related to the AHI, in part because of the known relation between HDL cholesterol and sex. Self-reported diabetes, self-reported hypertension, other indicators of hypertension, and self-reported CVD (total, coronary heart disease, heart failure, and stroke) were all positively associated with the AHI. The associations of age, race, and smoking status with the AHI were weak to moderate.

Univariate associations of the AHI and the hypoxemia index with prevalent CVD are shown in Table 2 along with estimates from selected single covariate-adjusted models. Prevalent CVD was fairly strongly associated with the AHI and its correlate, "percent of sleep time in hypoxemia," and adjustment for any single covariate only moderately attenuated these associations. Age appeared to be the strongest individual confounder. Prevalent CVD was weakly associated, at best, with the arousal index, and this relation was attenuated further or nullified by adding almost any single covariate to the model (data not shown).

TABLE 2

RELATIVE ODDS OF PREVALENT CARDIOVASCULAR DISEASE ACCORDING TO QUARTILE OF SLEEP-DISORDERED BREATHING VARIABLES, ADJUSTED FOR SINGLE COVARIATES

	Quartile			
	I	II	III	IV
Apnea–hypopnea index				
Univariate	1.0	1.30	2.03	2.50
Age adjusted	—	1.11	1.61	1.96
Sex adjusted	—	1.23	1.87	2.18
BMI adjusted	—	1.34	2.12	2.66
Hypertension adjusted	—	1.25	1.89	2.26
HDL adjusted	—	1.23	1.83	2.16
Percent of sleep time O_2 < 90%				
Univariate	1.0	1.17	1.67	2.16
Age adjusted	—	1.01	1.34	1.64
Sex adjusted	—	1.13	1.53	1.94
BMI adjusted	—	1.19	1.71	2.25
Hypertension adjusted	—	1.12	1.55	1.92
HDL adjusted	—	1.14	1.54	1.96

Definition of abbreviations: BMI = body mass index; HDL = high-density lipoprotein.

As shown in Table 3, multivariable adjustment resulted in substantial attenuation of the association between the AHI and prevalent CVD. Nonetheless, the adjusted relative odds still show departure from the null hypothesis (and sometimes "significant" departure), as well as a modest and significant linear component to the trend across quartiles I through IV. We found no evidence, however, for significant incremental risk at the right tail of the distribution (data not shown). The association of the hypoxemia index with prevalent CVD was qualitatively similar to that of the AHI but somewhat weaker. By contrast, the estimates for the arousal index did not show any clear dose–response pattern. There was considerable consistency of the results from full and parsimonious models although the confidence intervals were usually narrower in the latter models.

Table 4 shows the association of the AHI with self-reported coronary heart disease, heart failure, and stroke. The associations of the AHI with heart failure and stroke appeared stronger than with coronary heart disease, but the effect estimates for the former associations were less precise due to the smaller number of cases. Division of the upper AHI quartile at its median (AHI = 19) did not reveal further incremental risk of either coronary heart disease or heart failure at the tail of the distribution, but possibly modest incremental risk of stroke (adjusted relative odds of 1.80 for AHI > 19). These associations remained essentially unchanged after excluding 533 participants with a central apnea index ⩾ 1 (data not shown).

The shape of the dose–response curve is further elucidated in Figures 1A–1D, using restricted cubic spline regression models and adjusting for the full set of covariates. The *y*-axis in each graph is a measure of disease risk (quantified as the log of the prevalence odds), with larger values (smaller absolute values) indicating greater risk. The results from categorical analysis are largely supported by these graphs. In particular, the prevalence odds of each disease entity appear to increase within the range of mild to moderate sleep-disordered breathing (AHI < 10) and to plateau thereafter except, perhaps, in the case of stroke and total CVD. It should be recalled, however, that inference on the dose–response pattern at the right tail (for example, AHI > 20) is based on limited amount of data.

To investigate how much of the AHI effect can be attributed to

TABLE 3

ADJUSTED* RELATIVE ODDS (95% CONFIDENCE INTERVAL) OF PREVALENT CARDIOVASCULAR DISEASE ACCORDING TO QUARTILE OF SLEEP-DISORDERED BREATHING VARIABLES

	Quartile				
	I	II	III	IV	p Value†
Apnea–hypopnea index					
Full model	1.0	0.99 (0.77–1.28)	1.24 (0.97–1.59)	1.30 (1.01–1.67)	0.01
Parsimonious model	1.0	0.98 (0.77–1.24)	1.28 (1.02–1.61)	1.42 (1.13–1.78)	0.0003
Percent of sleep time $O_2 < 90\%$					
Full model	1.0	0.91 (0.71–1.17)	1.05 (0.82–1.34)	1.21 (0.95–1.55)	0.05
Parsimonious model	1.0	0.90 (0.71–1.13)	1.10 (0.88–1.38)	1.25 (1.00–1.55)	0.007
Arousal index					
Full model	1.0	0.81 (0.64–1.03)	0.88 (0.70–1.11)	0.90 (0.72–1.11)	0.51
Parsimonious model	1.0	0.80 (0.64–1.00)	0.82 (0.66–1.02)	0.91 (0.74–1.12)	0.45

* The full model included the following covariates: age, race, sex, smoking status, number of cigarettes smoked per day (for current smokers), self-reported diabetes, self-reported hypertension, use of antihypertension medications, systolic blood pressure, body mass index, total cholesterol, and high-density lipoprotein cholesterol. The parsimonious model excluded from this list five variables: number of cigarettes smoked per day, self-reported hypertension, systolic blood pressure, use of antihypertensive medications, and body mass index.
† For a linear trend across quartiles I through IV, *see* METHODS.

hypoxemic stress, we included both variables in several multivariable models, comparing the AHI coefficients in models with and without "percent of sleep time in hypoxemia." The hypoxemia index explained 10 to 40% of the AHI effect (data not shown).

DISCUSSION

Analysis of cross-sectional data from the Sleep Heart Health Study cohort showed that before adjustment, the AHI and its correlate, "percent of sleep time in hypoxemia," were fairly strongly associated with prevalent CVD with relative odds of 2.1 to 2.5 for the upper quartile of their distributions. Multivariable adjustment explained much, but not all, of the univariate associations. Sleep fragmentation per se, at least as measured by the arousal index, was not associated with CVD in these data. Our main results were consistent in two analytical models: a model with extensive covariate adjustment (and possibly overadjustment) and a parsimonious model, which excluded intermediaries on postulated causal pathways, such as hypertension and blood pressure. Much of the confounding in the data set appeared to have resulted from the joint distributions of covariates in the AHI quartiles rather than from the confounding effect of any single covariate.

The adjusted relative odds from multivariable models are compatible with modest to moderate effects of sleep-disordered breathing on CVD manifestations within a range of the AHI that is typically considered "normal" or only mildly elevated (1–10 respiratory events per hour of sleep). AHI values of this magnitude are not uncommon in the general population but, for most individuals, remain unrecognized (21). If the observed associations are indeed causal, a modestly elevated risk coupled with a high prevalence of mild sleep-disordered breathing might have considerable public health implications.

Somewhat surprising was the plateauing of the effect size at moderately elevated AHI values except, perhaps, in the case of prevalent stroke (Figure 1). This finding could indicate that the effect of sleep-disordered breathing on CVD risk is fully realized at some level. Alternatively, failure to show escalating risk may be related to inherent limitations of commonly used polysomnographic variables, to uncertainty about whether the AHI captures the relevant pathogenetic factor, and to relative imprecision of the estimates at the right tail of the AHI distribution.

Although much work has focused on sleep-disordered breathing and hypertension (29–32), relatively few studies have examined the relation between polysomnographic indices of the disorder and symptomatic CVD. The prevalence of sleep apnea is reportedly high among patients with coronary disease (11, 12, 17, 18) and several case–control studies found

TABLE 4

ADJUSTED* RELATIVE ODDS (95% CONFIDENCE INTERVAL) OF PREVALENT CORONARY HEART DISEASE, HEART FAILURE, OR STROKE, ACCORDING TO QUARTILE OF THE APNEA–HYPOPNEA INDEX

	Quartile				
	I	II	III	IV	p Value†
Coronary heart disease					
Full model	1.0	1.01 (0.77–1.32)	1.20 (0.92–1.57)	1.22 (0.93–1.59)	0.08
Parsimonious model	1.0	0.92 (0.71–1.20)	1.20 (0.93–1.54)	1.27 (0.99–1.62)	0.004
Heart failure					
Full model	1.0	1.19 (0.56–2.53)	1.96 (0.99–3.90)	2.20 (1.11–4.37)	0.008
Parsimonious model	1.0	1.13 (0.54–2.39)	1.95 (0.99–3.83)	2.38 (1.22–4.62)	0.002
Stroke					
Full model	1.0	1.24 (0.76–2.01)	1.38 (0.86–2.83)	1.55 (0.96–2.50)	0.06
Parsimonious model	1.0	1.15 (0.72–1.83)	1.42 (0.91–2.21)	1.58 (1.02–2.46)	0.03

* The full model included the following covariates: age, race, sex, smoking status, number of cigarettes smoked per day (for current smokers), self-reported diabetes, self-reported hypertension, use of antihypertension medications, systolic blood pressure, body mass index, total cholesterol, and high-density lipoprotein cholesterol. The parsimonious model excluded from this list five variables: number of cigarettes smoked per day, self-reported hypertension, systolic blood pressure, use of antihypertensive medications, and body mass index.
† For a linear trend across quartiles I through IV, *see* METHODS.

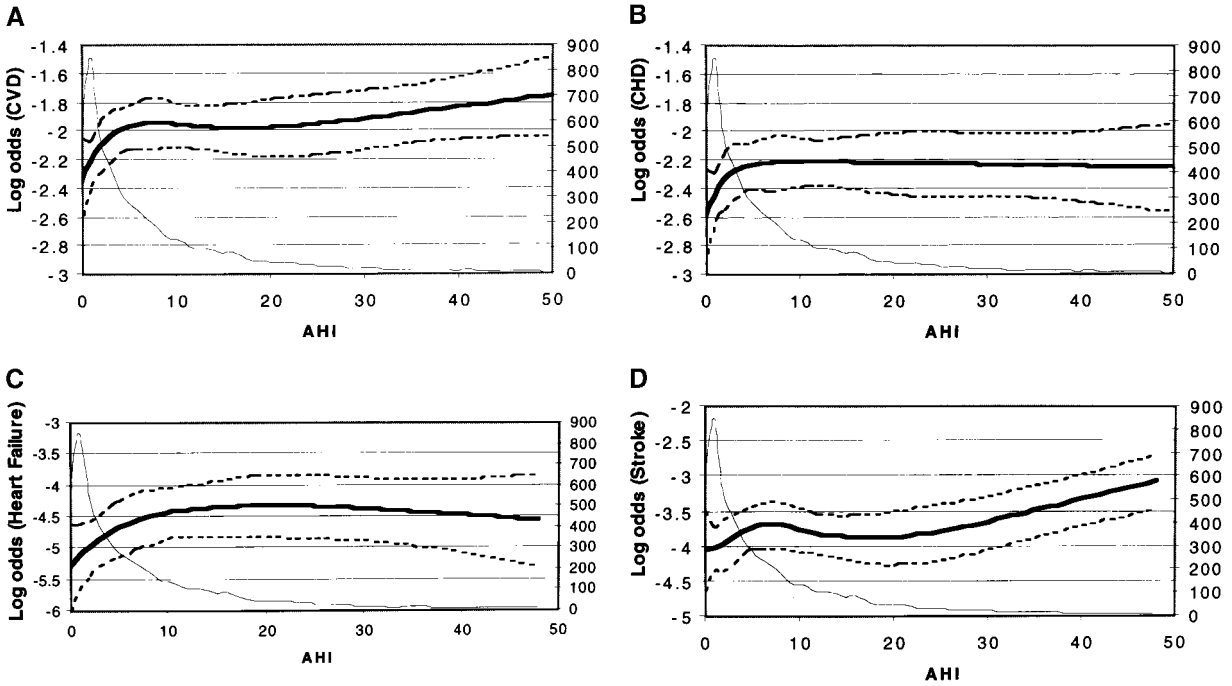

Figure 1. Restricted cubic spline regression of the log odds of cardiovascular disease (CVD) (*A*), coronary heart disease (CHD) (*B*), heart failure (*C*), and stroke (*D*) on the apnea–hypopnea index (AHI). Knots were placed at AHI values of 0.2 (5th percentile), 1.3 (25th percentile), 4.4 (50th percentile), 11.0 (75th percentile), and 33.7 (95th percentile) except in the case of heart failure where the middle knot was omitted due to the small number of cases. *Solid thick line* indicates the predicted log odds (a measure of risk); *dashed lines* are the 95% confidence intervals; and *solid thin line* indicates the number of participants at various AHI values (frequency distribution; right *y*-axis).

positive cross-sectional associations between sleep apnea and various manifestations of coronary heart disease (13–16). A strong association was reported in one study of myocardial infarction patients (13), with adjusted relative odds of 23.3 for the upper quartile of the apnea index (> 5.3) versus the lowest quartile (< 0.4). Another group reported an adjusted relative odds of coronary artery disease of 4.1 for women with AHI values of five or greater (15). The literature on polysomnographic indices of sleep-disordered breathing and stroke is sparse. Nonetheless, obstructive sleep apnea appeared to be highly prevalent among patients with stroke or transient ischemic attacks (19, 33), and one case–control study (20) reported a positive association between hemispheric stroke and the AHI (measured after the stroke). To our knowledge, no study has investigated prospectively the relation between polysomnographic indices of sleep-disordered breathing and incident CVD.

Numerous mechanisms might link the broad spectrum of sleep-disordered breathing to clinical CVD, the most plausible of which is an adverse effect on blood pressure (29–32). However, several other mechanisms can be hypothesized: obstructive sleep apnea has been associated with daytime sympathetic hyperactivity (34–37), which might increase the risk of thrombotic events through platelet activation, and might also contribute to chronic hypertension. Sleep-disordered breathing might promote atherogenesis through recurrent exposure to hypoxemia, a putative atherogenic factor (38), or might act as an acute risk factor, causing vulnerable plaques to rupture (39). Obstructive sleep apnea can cause pulmonary hypertension, thereby contributing to right ventricular failure, and might also aggravate left ventricular failure (40). Excess risk of stroke in sleep apnea patients might be related not only to the associated hypertension but also to changes in cerebral blood flow (41). It should also be noted that left ventricular hypertrophy, a known predictor of cardiovascular events, is more common in patients with obstructive sleep apnea even in the absence of hypertension (42).

Cross-sectional associations might reflect reverse causal pathways whereby sleep-disordered breathing has been the consequence, rather than the cause, of one or more CVD entities. In particular, both stroke and heart failure are assumed to be causes of central sleep apnea (43, 44). This competing explanation, however, did not appear to hold in our data. Central apneas accounted for a small proportion of respiratory events in the Sleep Heart Health Study cohort and the associations between the AHI and stroke or between the AHI and heart failure were not attenuated at all after excluding 533 participants with a central apnea index $\geqslant 1$. It should be noted, however, that it is uncertain whether typical montages allow for accurate identification of central respiratory events. At any rate, the direction of the arrow of causation (which might be pointing in opposite directions in different individuals) can be determined only by analysis of incident CVD in the cohort in the coming years and repeated polysomnography after the occurrence of incident events.

The AHI definition in these analyses was fairly conservative, requiring that changes in breathing amplitude be coupled with desaturation of 4%. This definition was chosen because of its high interscorer and intrascorer reliability and its comparability to definitions that were used in other studies (21). Although varying criteria for respiratory events yield highly correlated AHI scales, the magnitude of the index does vary substantially across various AHI definitions (45). Therefore, one should be careful when extrapolating cutoff-dependent findings from this study to other settings.

Several other methodological issues should be borne in mind while interpreting our results. First, if sleep-disordered breathing is not only a cause of CVD but also adversely affects

survival once CVD has developed, the relative prevalence odds typically underestimate the causal parameter of interest (i.e., the relative incidence odds) due to prevalence–incidence (survival) bias (46). Competing risks, such as the overall mortality risk of sleep apnea patients (47, 48), are expected to have a similar attenuating effect, and both sources of potential bias could also have obscured an escalating risk at the right tail of the AHI distribution. Second, whereas future analyses of incident CVD in the cohort will be based on validated events, the present work is probably affected by some inaccuracy of self-reported CVD status at baseline. Third, our ability to reliably identify arousals varied across sleep studies, accounting, in part, for moderate reliability of the arousal index, which, in turn, undermines the usefulness of a single night measurement of this variable. Future analyses will consider whether different sets of sleep-disordered breathing variables better predict CVD in smaller subsets of the sample. Finally, despite our attempts to adjust for confounders, it is possible that residual confounding by one or more of the modeled covariates, or by an unknown variable, accounts for the remaining association after multivariable adjustment.

In summary, cross-sectional associations from the baseline examination of the Sleep Heart Health Study cohort are compatible with modest to moderate effects of sleep-disordered breathing on various manifestations of CVD within a range of AHI values that is considered normal or only mildly elevated. These results, if replicated in prospective, cohort data, should be of public health importance, especially in light of unfavorable secular trends in obesity, a major determinant of sleep-disordered breathing.

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APPENDIX

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