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Joint effects of OSA and self-reported sleepiness on incident CHD and stroke

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Abstract

Background—Although excessive daytime sleepiness (EDS) is a common symptom of obstructive sleep apnea (OSA), and both EDS and OSA have separately been associated with increased risk of cardiovascular disease (CVD), their joint association with CVD risk is unknown

Methods—Among 3,874 Sleep Heart Health Study (SHHS) participants without prevalent CVD, moderate to severe OSA was defined by an apnea hypopnea index (AHI) ≥ 15 on an in-home polysomnography. EDS was defined as an Epworth Sleepiness Scale score ≥ 11 . Incident CVD events included total CVD events (coronary heart disease (CHD) and stroke), as well as CHD and stroke separately. Cox proportional hazards models adjusted for age, sex, alcohol, smoking, and body mass index.

Results—Compared to those with AHI <15 , the hazard ratios (95% CI) for the association of moderate-severe OSA (AHI ≥ 15) were as follows: CVD 1.06 (0.85–1.33); CHD 1.08 (0.85–1.33); and stroke 1.18 (0.75–1.84). Weak associations between EDS and CVD risk = [1.22 (1.01–1.47)] and CHD risk [1.25 (1.02–1.53)] were present, however there were none for stroke risk [1.10 (0.75–1.63)]. When modeled jointly, both AHI ≥ 15 and EDS (compared with having AHI <15 and no EDS) was associated with HRs of 1.26 (0.91–1.73) for CVD, 1.24 (0.87–1.75) for CHD and 1.49 (0.78–2.86) for stroke. There were no statistically significant interactions between daytime sleepiness and OSA on the multiplicative or additive scales.

Conclusions—Having both EDS and moderate-severe OSA was not associated with an increased risk of CVD in the SHHS data.

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Background

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing characterized by the repetitive partial or total collapse of the upper airway during sleep. In severe cases, patients suffer from hypoxia, as well as arousal and sleep fragmentation, which may lead to motor vehicle accidents and lower quality of life.¹ OSA is highly prevalent among older adults; recent data from the Multi-Ethnic Study of Atherosclerosis suggests 15% of adults have severe OSA, defined as an apnea-hypopnea index (AHI) ≥ 30 events/hr.² Although excessive daytime sleepiness (EDS) is one of the most common symptoms of OSA,³ both the relationship between OSA and EDS, and the impact of presenting with both OSA and EDS (ie, symptomatic OSA), is only superficially understood. EDS increases in prevalence with greater AHI,⁴ but the majority of people who experience even severe OSA do not report EDS.⁵ EDS may be more common among individuals who attend sleep clinics to be screened for OSA, because sleepiness symptoms may prompt them to seek formal OSA evaluation.

Both OSA and EDS have been associated with adverse health outcomes. OSA has been adversely associated with cardiovascular risk factors and outcomes, including diabetes,⁶ hypertension,^{7,8} coronary heart disease,⁹ stroke,¹⁰ heart failure,⁹ atrial fibrillation,¹¹ and mortality,^{12,13} though results from many of these studies may have been influenced by measurement error and/or selection bias. Although less frequently studied, EDS has also been associated with increased incident cardiovascular morbidity and mortality.^{14,15} Few studies have explored the joint associations or interactions between OSA and EDS in relation to risk of cardiovascular disease (CVD). In prior longitudinal research, those with both snoring, a surrogate of OSA, and EDS had significantly elevated rates of incident CVD¹⁶ and mortality,¹⁷ compared to those who had neither. It is possible that symptomatic OSA may be a marker of more severe OSA or that the presence of symptoms may suggest greater susceptibility to both neurocognitive and cardiovascular sequelae of OSA. In either case, symptomatic OSA may therefore have greater CVD risk. However, it is presently unknown whether AHI and EDS are independent risk factors for CVD incidence and whether the impact of EDS on CVD risk is greater in the setting of OSA (ie, a synergistic interaction).

Examining the association of symptomatic OSA with CVD risk may help refine the OSA phenotype, and possibly result in stronger associations with risk of CVD events than when either OSA or EDS is evaluated alone. In the recent SAVE trial, which excluded OSA participants with EDS, there was no effect of CPAP therapy on cardiovascular event rates.¹⁸ It has been postulated the benefit of CPAP may be greater in symptomatic patients. An examination of the joint associations and interactions between AHI and EDS on CVD risk could shed light on these findings. Therefore, the objectives of this study were to determine the joint association of EDS and OSA with CVD incidence and to evaluate whether an interaction is present between these factors, using the community-based Sleep Heart Health Study (SHHS).

Methods

The SHHS is a longitudinal study designed to determine whether sleep disordered breathing is an independent risk factor for CVD.¹⁹ At its inception, it included participants from six different already existing cohort studies: the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study, the Strong Heart Study, the New York Hypertension Cohort, the Tucson Epidemiologic Study of Airways Obstructive Diseases, and the Health and Environment Study. Participants invited to take part in SHHS were at least 40 years of age, had no CPAP, oral device treatment, oxygen therapy, or tracheostomy. Young snorers were oversampled. A total of 6,441 participants were recruited for the baseline examination in 1995–1998.

De-identified data were obtained from the National Sleep Research Resource (www.sleepdata.org).²⁰ Review of the protocol by the University of Minnesota IRB determined the present analysis was exempt from human subject research requirements because it utilized de-identified.

Our analytic sample excluded all participants from the Strong Heart Study and the New York Hypertension Cohort due to data sharing and quality issues. Participants were also excluded if they were missing data on exposures ($n = 221$ for ESS, $n = 698$ for AHI) or follow-up time ($n = 17$), or reported CPAP use ($n = 7$). We also excluded participants with initially-prevalent myocardial infarction ($n = 284$), coronary revascularization ($n = 125$) or stroke ($n = 233$) as defined by the parent cohorts, as well as those missing data on myocardial infarction, coronary revascularization, stroke, and CVD death ($n = 578$). This left a final analytic sample of 3,874 participants.

Sleep variables

The Epworth Sleepiness Scale (ESS) was used to measure daytime sleepiness.²¹ This eight-item questionnaire asks about the likelihood of falling asleep on a scale from 0–3. These items are then summed, with scores ≥ 11 representing excessive daytime sleepiness.¹⁹ For analysis, ESS score was represented both dichotomously and continuously per one standard deviation.

In-home polysomnography was performed with the Compumedics P Series System (Abbotsford, Victoria, Australia). All sensors were placed and equipment calibrated during the home visit. Channels were recorded as follows: electroencephalogram, chin electromyogram, thoracic and abdominal displacement, airflow by thermal sensor, finger pulse oximeter, a single bipolar electrocardiogram, body position by an Hg gauge sensor, and ambient light level. Data were scored at a central reading center at Case Western Reserve University (Cleveland, OH). Apneas were defined as the absence or near absence of airflow ($<25\%$ of baseline) for at least ten seconds. Hypopneas were defined as below 70% of the baseline amplitude for at least ten seconds.¹⁹ Both apneas and hypopneas also required an associated 4% or higher oxyhemoglobin desaturation. AHI was calculated as the average number of apneas and hypopneas per hours of sleep and was modeled categorically (<15 vs ≥ 15 as well as <5 , $5-15$, $15-30$, ≥ 30) and continuously per one standard deviation.

Outcome ascertainment

All incident CVD events were defined as the first occurrence between baseline (the date of overnight polysomnography) and the end of follow-up, which ranged from 2008–2011 depending on the parent cohort. Event definitions were similar to those used in previous SHHS analyses.^{9,10} Within SHHS, event surveillance occurred according to individual cohort protocols, which included participant phone calls and mailings as well as surveillance of death certificates and hospital discharge records. Physicians classified events per cohort specific protocols.^{22–28}

For the present analysis, three separate CVD endpoints were considered. Incident coronary heart disease (CHD) was defined as first myocardial infarction (MI), coronary revascularization, or CHD death. MI occurrence was classified similarly across the cohorts, and was based on symptoms of cardiac pain, electrocardiograms suggesting ischemia, and/or elevated cardiac biomarker patterns.¹⁹ Incident stroke was defined as the first fatal or nonfatal ischemic stroke. Stroke classification used computed tomography and magnetic resonance images when available. Incident CVD included all CHD and stroke events as defined above.

Covariates

Demographic data, including information on age, sex, race/ethnicity, and education, were self-reported. Weight and height were measured at the baseline SHHS visit using a standardized protocol. Body mass index (BMI) was calculated in kg/m². Smoking status was categorized as current, former, or never smoker. Habitual alcohol intake was measured in drinks per week in the parent cohorts.

Analysis

Descriptive statistics were calculated by AHI at baseline. Person-time was calculated from the baseline examination until an event, loss to follow-up, death, or the end of the follow-up period for each cohort. The proportional hazards assumption was checked using interactions with time and tests of correlations of the residuals, and no meaningful violations were found. Cox proportional hazards models were used to model hazards of incident CVD as a function of AHI categories and EDS. The main associations of daytime sleepiness and sleep apnea categories, separately, on CVD, CHD, and stroke are presented, as well as the joint associations. We then evaluated independence of the associations in the main models by controlling jointly for AHI categories and EDS. The presence of an interaction was assessed on both the additive scale using the relative excessive risk due to interaction (RERI) and on the multiplicative scale using cross-product terms and presented in accordance with published recommendations.²⁹ To further demonstrate the joint associations, we presented hazard ratios (HRs) with confidence intervals (CIs) and p-values for each stratum of daytime sleepiness and AHI with one reference category, as well as the association of AHI with the outcomes within strata of daytime sleepiness and the association of daytime sleepiness on the outcomes within strata of OSA. For the joint models, categorization of the exposures was as follows: AHI <15 & ESS < 11, AHI 15 & ESS < 11, AHI < 15 & ESS ≥ 11, and AHI ≥ 15 & ESS ≥ 11 (symptomatic OSA). Effect modification by sex and age was also examined, and stratified results were reported in supplemental material.

In a sensitivity analysis, we examined the joint association of OSA and fatigue, as assessed by the vitality subscale of the SF-36, on incident CVD. Results from this analysis are also presented in the supplemental material.

Potential confounders including age, race, sex, education, alcohol, smoking status, and BMI were included as covariates in multivariable models. Diabetes, dyslipidemia, and hypertension are likely to lie on the causal pathway between sleep disorders and CVD and were thus not included in the models. SAS version 9.4 (SAS Institute, Cary, NC) was used to analyze the data.

Results

The mean age at baseline was 63.0 (SD=4.3) years and 55.4% of the sample was female. The prevalence of moderate to severe OSA was 19.0% and the prevalence of EDS was 23.4%. AHI and ESS were somewhat correlated: among those with AHI < 5, mean ESS score was 7.2, while mean ESS score for those with AHI ≥ 15 was 8.4. Among those with no EDS, mean AHI was 8.6 events/hour, while mean AHI was 11.6 events/hour among those with EDS. A description of sociodemographic and behavioral characteristics by AHI category can be found in Table 1.

Over a median of 10.4 years of follow-up, we identified 653 incident cases of CVD, 538 incident cases of CHD, and 165 incident cases of stroke. The crude incidence rate per 1000 person-years was 16.5 (95% CI: 15.3–17.8) for CVD, 13.4 (12.3–14.6) for CHD and 3.9 (3.4–4.6) for stroke.

Tables 2 & 3 shows adjusted HRs and 95% CIs of the association between AHI and EDS respectively with incident CVD, CHD and stroke. After adjustment for demographics and compared to AHI <15, the HRs (95% CIs) for AHI ≥ 15 and risks of CVD, CHD, and stroke were 1.06 (0.88–1.27), 1.05 (0.86–1.29) and 1.06 (0.73–1.54), respectively. Secondary analyses using four categories of AHI (<5, 5–<15, 15–<30, ≥ 30) (Supplemental Table 1) demonstrate that those with AHI 5–<15 had a slightly higher risk of CHD and CVD compared to those with AHI <5. For EDS, there were modest associations with incident CVD (HR: 1.17 (0.97–1.40)) and CHD (HR: 1.19 (0.98–1.45)) but not stroke (HR: 1.05 (0.72–1.52)). Results for both exposures were similar after adjustment for alcohol, smoking, and BMI.

Figure 1 shows the crude incidence rates for incident CVD by EDS and OSA status jointly. Although those with AHI ≥ 15 had much higher incidence rates than those with AHI < 15, those with EDS had only slightly higher CVD incidence rates across AHI categories. This is consistent with Table 2 Model 3, where the hazard ratio for OSA was altered little by adjustment for daytime sleepiness.

Table 4 and Supplemental Tables 2–3 show in more detail adjusted hazard ratios and 95% confidence intervals for the joint associations of OSA and EDS with CVD, CHD, and stroke. Compared to those without EDS and OSA, those with symptomatic OSA (AHI ≥ 15 & ESS ≥ 11) had a slightly higher risk of incident CVD (HR: 1.26 (0.91–1.73)), CHD (HR: 1.24 (0.87–1.75)), and stroke (HR: 1.49 (0.78–2.86)) that did not reach statistical significance. On

both the additive and multiplicative scales, there were no statistically significant interactions between OSA and EDS for any outcomes.

The joint associations of AHI and EDS with CVD was also examined by age (<70 vs ≥70 to be consistent with previous SHHS studies⁹) and sex. While there was no association between symptomatic OSA and incident CVD for those under age 70 (HR: 0.94 (0.58–1.54)), those 70 and older with symptomatic OSA had a higher risk of incident CVD compared to those without EDS and OSA (HR: 1.71 (1.12–2.60)) (Supplemental Tables 4 & 5). The joint associations did not differ in men versus women (data not shown).

The joint associations of OSA and fatigue with CVD can be found in Supplemental Table 6. Results were similar to when EDS was used.

Discussion

This prospective community-based cohort, presents some of the first recorded data on the association of symptomatic OSA with risk of incident CVD. In a multiplicative proportional hazards model, EDS added little beyond OSA as a risk factor for CVD, likewise there was no statistically significant interaction between EDS and OSA with any of the CVD outcomes. The lack of interaction is not entirely surprising, since our sample size was not big enough to rule out a small independent or synergistic association and the magnitude of the ‘main effect’ associations were modest for both OSA and EDS. These findings suggest that symptomless OSA is associated with CVD risk similar to that observed for symptomatic CVD, and as such symptomless OSA should not be ignored in clinical settings.

As previously mentioned, there were small associations that did not reach statistical significance between symptomatic OSA and incident CVD, CHD, and stroke but no statistically significant interaction on either the multiplicative or additive scale. Previous research evaluating the interrelationship between symptomatic OSA and CVD events used snoring as a surrogate for OSA and did not examine statistical interaction or independence.^{16,17} In one study of older adults, those reporting both snoring and EDS were significantly more likely to develop an incident CVD event over ten years of follow-up compared to those reporting no snoring or sleepiness, while there was no association when either snoring or sleepiness occurred in isolation.¹⁶ Another study of middle-aged men found a nearly two-fold HR of overall mortality for the combination of snoring and EDS (versus having neither), but a smaller non-significant association with CVD mortality over ten years of follow-up (HR=1.2).¹⁷ Both joint associations were associated with a nearly three-fold higher risk of overall and CVD-specific mortality for those under the age of sixty, but were null among those over age sixty. In contrast, our study found that the magnitude of the joint association was much higher for adults seventy and over, while there was no association for those under seventy.

Counter to our expectations, there was no strong or statistically significant association between OSA (as defined by AHI ≥15) and incident CVD. In underpowered supplementary analyses with additional AHI categories, there was a statistically significant association only for mild OSA. It is possible that more serious OSA was treated after baseline, since

treatment later during the follow-up period was not captured in the dataset. Treatment may have lowered CVD risk among those with higher AHI while those with lower AHI remained untreated. It is also possible that only severe OSA (AHI ≥ 30) is associated with elevated CVD risk, but that our analyses were underpowered since only 6.6% of the study population had severe OSA. In meta-analyses, OSA has been associated with greater risk of incident CVD,^{30,31} with associations stronger and more consistent for stroke than CHD. However, many of these studies contain threats to validity, including non-objective measurement of OSA, clinic-based samples, and short follow-up. Few community-based studies have examined polysomnography-measured OSA in association with incident CHD and stroke.^{9,10,32} Published SHHS data reported adverse associations between OSA and CHD only among men with AHI ≥ 30 , but there was no association among women or men with mild or moderate OSA. For stroke, OSA was associated with a two to three-fold higher risk in men but not women in SHHS. We were able to recreate these results in sensitivity analyses which however lacked power due to the smaller size of our publicly available dataset. In the younger Wisconsin Sleep Cohort consisting of both men and women, severe OSA was associated with nearly 2.5 times greater risk of incident CHD,³² suggesting that the association may be stronger and more consistent among middle-aged adults.

In main effect analyses, we also found EDS to be associated with slightly greater risk of incident CVD and CHD but not stroke. Several community-based cohorts, which utilized a variety of different measures of daytime sleepiness, have found EDS to be associated with significantly greater risk of CVD events, including CHD and stroke.^{14,33–35} In this study, the prevalence of EDS was 23.4%; other community-based studies using the ESS found a EDS prevalence that ranged from 10.8 to 25.7%.^{36–40}

An important limitation of this analysis is that the Sleep Heart Health Study participants had a relatively low prevalence of symptomatic OSA (five% of sample). This limited precision and thus statistical power to detect as statistically significant the weak effect sizes observed. Given the small magnitude of our findings, strong associations are unlikely even if we had the power to detect statistical significance. Moreover, the low prevalence of OSA in this sample made it necessary to categorize OSA using the combination of moderate and severe OSA (AHI ≥ 15), therefore we are unable to provide information about the joint association of severe OSA (AHI ≥ 30) and EDS with risk CVD. Although, we did provide information about the main effect of severe OSA in a supplemental table. Another limitation is the use of only one night of polysomnography, so the obtained data may not be indicative of habitual sleep patterns due to the “first-night effect”, where sleep architecture and efficiency are altered as a result of measurement.⁴¹ Additionally, those with OSA may have obtained treatment, and if protective, it could have depressed the magnitude of the associations, although data from other cohorts suggests this is small percentage of the sample.³² Despite these weaknesses, the study also has several strengths, which include OSA assessed via polysomnography, a longitudinal design, and physician review and classification of CVD events.

In summary, OSA is a common condition associated with moderately greater risk of CVD events and risk factors in many observational studies, while experimental studies in both human and animal models suggest a pathophysiological role.³⁰ Although Symptoms of EDS

can prompt patients to go to the doctor for diagnosis, the majority of those with OSA do not have EDS.⁵ Because EDS is easy to assess and represents habitual sleepiness, it could be useful as a clinical screening tool for identifying OSA. This would be especially important if a strong interaction between EDS and OSA were found for risk of developing CVD, as it could suggest that it may be useful to add EDS to OSA screening with an aim to reduce CVD events. However, in the present study there was no statistically significant interaction between EDS and OSA on CVD risk and the joint associations suggested that collecting information on daytime sleepiness adds little beyond OSA in relation to incidence of CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Balachandran JS, Patel SR. In the clinic. Obstructive sleep apnea. Ann Intern Med. 2014; 161(9):ITC1–15. quiz ITC16.
2. Chen X, Wang R, Zee P, et al. Racial/Ethnic Differences in Sleep Disturbances: The Multi-Ethnic Study of Atherosclerosis (MESA). Sleep. 2015; 38(6):877–888. [PubMed: 25409106]
3. Baldwin CM, Griffith KA, Nieto FJ, O'Connor GT, Walsleben JA, Redline S. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. Sleep. 2001; 24(1):96–105. [PubMed: 11204058]
4. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. Chest. 1993; 103(1):30–36. [PubMed: 8417909]
5. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002; 165(9):1217–1239. [PubMed: 11991871]
6. Wang X, Bi Y, Zhang Q, Pan F. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Respirology. 2013; 18(1):140–146. [PubMed: 22988888]
7. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA. 2012; 307(20):2161–2168. [PubMed: 22618923]
8. Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation. 2003; 107(1):68–73. [PubMed: 12515745]
9. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010; 122(4):352–360. [PubMed: 20625114]
10. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med. 2010; 182(2):269–277. [PubMed: 20339144]
11. Lin GM, Colangelo LA, Lloyd-Jones DM, et al. Association of Sleep Apnea and Snoring With Incident Atrial Fibrillation in the Multi-Ethnic Study of Atherosclerosis. American journal of epidemiology. 2015; 182(1):49–57. [PubMed: 25977516]
12. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep. 2008; 31(8):1071–1078. [PubMed: 18714778]

13. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep*. 2008; 31(8): 1079–1085. [PubMed: 18714779]
14. Newman AB, Spiekerman CF, Enright P, et al. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The Cardiovascular Health Study Research Group. *Journal of the American Geriatrics Society*. 2000; 48(2):115–123. [PubMed: 10682939]
15. Jaussent I, Empana JP, Ancelin ML, et al. Insomnia, daytime sleepiness and cardio-cerebrovascular diseases in the elderly: a 6-year prospective study. *PloS one*. 2013; 8(2):e56048. [PubMed: 23457496]
16. Endeshaw Y, Rice TB, Schwartz AV, et al. Snoring, daytime sleepiness, and incident cardiovascular disease in the health, aging, and body composition study. *Sleep*. 2013; 36(11):1737–1745. [PubMed: 24179308]
17. Lindberg E, Janson C, Svardsudd K, Gislason T, Hetta J, Boman G. Increased mortality among sleepy snorers: a prospective population based study. *Thorax*. 1998; 53(8):631–637. [PubMed: 9828847]
18. McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med*. 2016; 375(10):919–931. [PubMed: 27571048]
19. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep*. 1997; 20(12):1077–1085. [PubMed: 9493915]
20. Dean DA 2nd, Goldberger AL, Mueller R, et al. Scaling Up Scientific Discovery in Sleep Medicine: The National Sleep Research Resource. *Sleep*. 2016; 39(5):1151–1164. [PubMed: 27070134]
21. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991; 14(6):540–545. [PubMed: 1798888]
22. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *American journal of epidemiology*. 1989; 129(4):687–702. [PubMed: 2646917]
23. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke*. 2009; 40(4):1032–1037. [PubMed: 19211484]
24. Zhang Y, Galloway JM, Welty TK, et al. Incidence and risk factors for stroke in American Indians: the Strong Heart Study. *Circulation*. 2008; 118(15):1577–1584. [PubMed: 18809797]
25. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*. 1999; 30(4):736–743. [PubMed: 10187871]
26. El-Saed A, Kuller LH, Newman AB, et al. Factors associated with geographic variations in stroke incidence among older populations in four US communities. *Stroke*. 2006; 37(8):1980–1985. [PubMed: 16794204]
27. Howard BV, Lee ET, Cowan LD, et al. Rising tide of cardiovascular disease in American Indians. The Strong Heart Study. *Circulation*. 1999; 99(18):2389–2395. [PubMed: 10318659]
28. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Ann Epidemiol*. 1995; 5(4):278–285. [PubMed: 8520709]
29. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol*. 2012; 41(2):514–520. [PubMed: 22253321]
30. Dong JY, Zhang YH, Qin LQ. Obstructive sleep apnea and cardiovascular risk: meta-analysis of prospective cohort studies. *Atherosclerosis*. 2013; 229(2):489–495. [PubMed: 23684511]
31. Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circulation. Cardiovascular quality and outcomes*. 2012; 5(5):720–728. [PubMed: 22828826]
32. Hla KM, Young T, Hagen EW, et al. Coronary heart disease incidence in sleep disordered breathing: the Wisconsin Sleep Cohort Study. *Sleep*. 2015; 38(5):677–684. [PubMed: 25515104]
33. Elwood P, Hack M, Pickering J, Hughes J, Gallacher J. Sleep disturbance, stroke, and heart disease events: evidence from the Caerphilly cohort. *J Epidemiol Community Health*. 2006; 60(1):69–73. [PubMed: 16361457]

34. Blachier M, Dauvilliers Y, Jaussent I, et al. Excessive daytime sleepiness and vascular events: the Three City Study. *Ann Neurol*. 2012; 71(5):661–667. [PubMed: 22271307]
35. Boden-Albala B, Roberts ET, Bazil C, et al. Daytime sleepiness and risk of stroke and vascular disease: findings from the Northern Manhattan Study (NOMAS). *Circulation. Cardiovascular quality and outcomes*. 2012; 5(4):500–507. [PubMed: 22787063]
36. Buysse DJ, Hall ML, Strollo PJ, et al. Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/polysomnographic measures in a community sample. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2008; 4(6):563–571. [PubMed: 19110886]
37. Pallesen S, Nordhus IH, Omvik S, Sivertsen B, Tell GS, Bjorvatn B. Prevalence and risk factors of subjective sleepiness in the general adult population. *Sleep*. 2007; 30(5):619–624. [PubMed: 17552377]
38. Beaudreau SA, Spira AP, Stewart A, et al. Validation of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in older black and white women. *Sleep Med*. 2012; 13(1):36–42. [PubMed: 22033120]
39. Gjevre JA, Pahwa P, Karunanayake C, et al. Excessive daytime sleepiness among rural residents in Saskatchewan. *Can Respir J*. 2014; 21(4):227–233. [PubMed: 24791255]
40. Blackwell T, Yaffe K, Laffan A, et al. Associations of objectively and subjectively measured sleep quality with subsequent cognitive decline in older community-dwelling men: the MrOS sleep study. *Sleep*. 2014; 37(4):655–663. [PubMed: 24899757]
41. Toussaint M, Luthringer R, Schaltenbrand N, et al. First-night effect in normal subjects and psychiatric inpatients. *Sleep*. 1995; 18(6):463–469. [PubMed: 7481418]

Highlights

Approximately five% of the sample had symptomatic obstructive sleep apnea

There was no interaction between daytime sleepiness and sleep apnea with cardiovascular disease

Those with symptomatic OSA were not at higher risk for incident cardiovascular disease

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Figure 1. Crude incidence rates per 1000 person-years for cardiovascular disease by daytime sleepiness and AHI status

Abbreviations: AHI – apnea-hypopnea index, ESS – Epworth Sleepiness Scale

Table 1

Participant characteristics by Apnea-Hypopnea Index (AHI) category: The Sleep Heart Health Study

N total	AHI <5 1975	AHI 5 & < 15 1162	AHI 15 737
Demographics			
Age, mean years $\pm$ SD	61.0 $\pm$ 10.8	64.4 $\pm$ 10.7	66.1 $\pm$ 10.0
% Female, n (%)	1314 (66.5)	560 (48.2)	272 (36.9)
Race, n (%) [*]			
White	1693 (50.5)	1008 (30.0)	654 (19.5)
Black	131 (51.6)	70 (27.6)	53 (20.9)
Other	151 (57.0)	84 (31.7)	30 (11.3)
Ethnicity, n (%) [*]			
Hispanic/Latino	114 (56.4)	62 (30.7)	26 (12.9)
Not Hispanic/Latino	1861 (50.7)	1100 (30.0)	711 (19.4)
Education, n (%) [*]			
Less than high school	114 (39.2)	110 (37.8)	67 (23.0)
High School	963 (50.0)	589 (30.6)	376 (19.5)
College	608 (53.5)	314 (27.6)	214 (18.8)
Post-college	70 (43.2)	59 (36.4)	33 (20.4)
Behavioral Characteristics			
Daytime Sleepiness, n (%)	402 (20.4)	288 (24.8)	216 (29.3)
Smoking status, n (%) [*]			
Current Smoker	239 (63.2)	87 (23.0)	52 (13.8)
Former Smoker	761 (46.1)	549 (33.2)	342 (20.7)
Never Smoker	969 (52.9)	523 (28.6)	339 (18.5)
Body mass index, mean $\pm$ SD	27.0 $\pm$ 4.4	29.0 $\pm$ 4.9	30.7 $\pm$ 5.6
Alcohol use, drinks per day	2.3 $\pm$ 4.7	2.9 $\pm$ 5.9	3.1 $\pm$ 7.4

^{*} Row percentages

Table 2

Adjusted hazard ratios (95% confidence interval) of Apnea-Hypopnea Index with risk of incident cardiovascular disease: The Sleep Heart Health Study

AHI category N	Normal/Mild (AHI <15) 3137	Moderate/Severe (AHI ≥ 15) 737	Continuous per 1 SD
CVD			
N event	490	163	
Model 1	Ref.	1.06 (0.88, 1.27)	1.06 (0.98, 1.14)
Model 2	Ref.	0.98 (0.81, 1.20)	1.01 (0.94, 1.10)
Model 3	Ref.	0.98 (0.80, 1.19)	1.01 (0.93, 1.10)
CHD			
N event	402	136	
Model 1	Ref.	1.05 (0.86, 1.29)	1.06 (0.98, 1.15)
Model 2	Ref.	0.99 (0.80, 1.23)	1.02 (0.93, 1.11)
Model 3	Ref.	0.98 (0.79, 1.22)	1.01 (0.93, 1.11)
Stroke			
N event	126	39	
Model 1	Ref.	1.06 (0.73, 1.54)	0.99 (0.85, 1.16)
Model 2	Ref.	1.00 (0.68, 1.49)	0.98 (0.82, 1.16)
Model 3	Ref.	1.00 (0.67, 1.49)	0.97 (0.82, 1.16)

*
p < 0.05

Model 1 adjusted for age, race, sex, ethnicity, and education.

Model 2 added alcohol, smoking status, pack-years, and BMI

Model 3 added daytime sleepiness

Abbreviations: OSA – obstructive sleep apnea, AHI – apnea-hypopnea index, SD – standard deviation, CVD – cardiovascular disease, CHD – coronary heart disease

Table 3

Adjusted hazard ratios (95% confidence interval) of daytime sleepiness with risk of incident cardiovascular disease: The Sleep Heart Health Study

N	ESS < 11 2,968	ESS 11 906	ESS per 1 SD
CVD			
N events	484	169	
Model 1	Ref.	1.17 (0.97, 1.40)	1.05 (0.97, 1.13)
Model 2	Ref.	1.22* (1.01, 1.47)	1.06 (0.98, 1.15)
Model 3	Ref.	1.22* (1.01, 1.47)	1.06 (0.97, 1.15)
CHD			
N events	392	146	
Model 1	Ref.	1.19 (0.98, 1.45)	1.06 (0.97, 1.16)
Model 2	Ref.	1.25* (1.02, 1.53)	1.07 (0.98, 1.17)
Model 3	Ref.	1.25* (1.02, 1.53)	1.07 (0.98, 1.17)
Stroke			
N events	129	36	
Model 1	Ref.	1.05 (0.72, 1.52)	1.02 (0.87, 1.19)
Model 2	Ref.	1.10 (0.75, 1.63)	1.03 (0.87, 1.22)
Model 3	Ref.	1.07 (0.98, 1.17)	1.03 (0.88, 1.22)

*
p < 0.05

Model 1 adjusted for age, race, sex, ethnicity, and education.

Model 2 added alcohol, smoking status, pack-years, and BMI

Model 3 added OSA

Joint association of excessive daytime sleepiness and Apnea-Hypopnea Index with risk of incident cardiovascular disease: The Sleep Heart Health Study

Table 4

	AHI <15		AHI 15		HR (95% CI); <i>P</i> for AHI 15 vs AHI <15 within ESS strata
	N with/without outcome	HR (95% CI); <i>P</i>	N with/without outcome	HR (95% CI); <i>P</i>	
ESS <11	370/2077	<i>Referent</i>	114/407	0.95 (0.75–1.20); <i>p</i> = 0.66	0.95 (0.75–1.20); <i>p</i> = 0.66
ESS 11	120/570	1.19 (0.96–1.49); <i>p</i> = 0.12	49/167	1.26 (0.91–1.73); <i>p</i> = 0.16	1.09 (0.76–1.57); <i>p</i> = 0.65
HR (95% CI); <i>P</i> for ESS 11 vs ESS <11 within AHI strata		1.19 (0.96–1.49); <i>p</i> = 0.12		1.32 (0.92–1.90); <i>p</i> = 0.14	

Measure of interaction on additive scale (95% CI); *P* *RERI* = 0.11 (−0.37, 0.58); *p* = 0.66

Measure of interaction on multiplicative scale (95% CI); *p* = 0.63

Hazard ratio is adjusted for age, sex, race, ethnicity, education, alcohol, smoking status, pack-years, and BMI

Abbreviations: ESS – Epworth Sleepiness Scale, AHI – apnea-hypopnea index, HR – hazard ratios, CI – confidence intervals