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Daytime sleepiness and risk of coronary heart disease and stroke: results from the Nurses' Health Study II

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Abstract

Objective—The objective of this study was to determine whether daytime sleepiness is independently associated with coronary heart disease (CHD) and stroke or whether the positive association is explained by short sleep duration, disturbed sleep, and circadian disruption, conditions that are associated with cardiometabolic risk factors for vascular events.

Methods—Longitudinal analyses of data from the Nurses' Health Study II comprising 84,003 female registered nurses aged 37–54 at baseline were conducted in 2001 with follow-up until 2009. Multivariate Cox regression was used to explore the relationship between reported daytime sleepiness and the incidence of either CHD or stroke ($n = 500$ cases).

Results—Women who reported daytime sleepiness almost every day, compared with rarely/never, had an elevated adjusted risk of cardiovascular disease (CVD) (hazard ratio (HR) = 1.58, 95% confidence interval (CI) 1.15–2.17). Controlling for sleep variables (sleep duration, snoring, shift work, and sleep adequacy) or potential metabolic biological mediators of disrupted sleep

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2014.04.001>.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.sleep.2014.04.001>.

(diabetes, hypercholesterolemia, and hyper-tension) appreciably attenuated the relationship (HR = 1.17, 95% CI 0.84–1.65; and HR = 1.34, 95% CI 0.97–1.85, respectively). Controlling for both sleep variables and metabolic risk factors eliminated an independent association (HR = 1.09, 95% CI 0.77–1.53). A similar pattern was observed for CHD and stroke individually.

Conclusions—Daytime sleepiness was not an independent risk factor for CVD in this cohort of women, but rather, was associated with sleep characteristics and metabolic abnormalities that are risk factors for CVD.

Keywords

Sleep; Epidemiology; Coronary heart disease; Stroke; Metabolic syndrome; Daytime sleepiness

1. Introduction

Daytime sleepiness, defined as the inability to stay awake and alert during the major waking periods of the day, resulting in unintended lapses into drowsiness or sleep [1], has been estimated to affect about 20% of adults [2]. Excessive daytime sleepiness is a significant public health concern since it is associated with cognitive impairment, automobile accidents, injuries, medical errors, and lost productivity [3].

Multiple studies have also found daytime sleepiness to be associated with the incidence of stroke and coronary heart disease (CHD) (Table 1) [4–9]. Three primary explanations for this association have been proposed. First, daytime sleepiness could be symptomatic of insufficient sleep, disturbed sleep, and/or circadian disruption that in turn increase the risk of vascular events [4,5]. Second, daytime sleepiness could be due to an underlying medical illness that is a risk factor for cardiovascular disease (CVD) (including either stroke or CHD) [7,8]. Third, daytime sleepiness could be an independent risk factor for stroke and CHD [7].

Prior studies have had significant limitations in exploring an independent association between daytime sleepiness and CVD. If daytime sleepiness is an independent risk factor, then the association should remain significant after controlling for sleep and circadian disturbances and other risk factors for CVD. However, many previous studies did not have measures of important sleep characteristics including sleep duration [5–9], insomnia [4,9], or snoring [4] and no previous studies had measures for shift work. Further, most of the studies conceptualized the variables indicative of insufficient or disturbed sleep only as potential interaction variables whereby they explored whether the absence, presence, or degree of presence of these variables affected the strength of the association between daytime sleepiness and vascular events, rather than fully controlling for them [4–6,8,9]. Only one study of elderly subjects reported results that included snoring and insomnia in fully adjusted multivariate models [5]. Several studies failed to control for key cardiovascular risk factors: two of the studies did not control for depression [4,6] and two did not control for blood pressure, hypercholesterolemia, or diabetes [5,6]. Finally, whether there are sex differences in the relationship between sleep and CVD has not been fully explored. Three of the studies did not report results from stratified analyses by sex to

determine the unique association between daytime sleepiness and cardiovascular events in women [4,6,9].

The Nurses' Health Study II (NHS-II) provides a unique opportunity to explore the association between daytime sleepiness and CVD in women because it includes measures of daytime sleepiness, sleep parameters (sleep duration, snoring, sleep sufficiency, and shift work), as well as cardiovascular risk factors in a large and well-characterized sample of younger females followed longitudinally. We hypothesized that daytime sleepiness would be associated with increased risk of stroke and CHD, and we aimed to determine whether the association would be primarily explained by insufficient or disturbed sleep and by other risk factors for CVD.

2. Methods

2.1. Study population

The NHS-II cohort was established in 1989 and initially included 116,686 female registered nurses between the ages of 25 and 42 years who resided in 14 US states. Participants completed initial mailed questionnaires about their medical history and lifestyle and subsequently completed biennial questionnaires to update their lifestyle and health information. Daytime sleepiness was assessed in 2001 with the question: "On average, how often are your daily activities affected because you are sleepy during the day?" and the possible responses were: almost every day, 4–6 days/week, 1–3 days/week, rarely, and never. A total of 85,472 women answered the daytime sleepiness question in 2001. After excluding women who reported having a stroke or CHD before 2001, there were 84,003 women remaining in the study population. This study was approved by the Institutional Review Boards at Brigham and Women's Hospital and Columbia University/New York State Psychiatric Institute; women in this study provided implied consent by virtue of their voluntary return of mailed questionnaires and separate written consent for transfer of their medical records.

2.2. Ascertainment of stroke and CHD

The subjects were asked in each of the follow-up surveys whether they had physician-diagnosed stroke (cerebrovascular accident – CVA), transient ischemic attack (TIA), or CHD event since the previous survey. Nurses who reported one or more of these events were asked for permission to review their medical records. Fatal events were identified by next of kin, postal authorities, or the National Death Index. Medical records and death certificates were reviewed by physicians who had no knowledge of the subject's self-reported exposure status.

Strokes were confirmed using the National Survey of Stroke criteria [10], requiring neurological deficit of rapid or sudden onset lasting ≥ 24 h or until death, and we categorized types as ischemic (embolic or thrombotic), hemorrhagic (subarachnoid or intraparenchymal), or unknown. Cerebrovascular pathology due to infection, trauma, or malignancy and "silent" strokes discovered only by radiologic imaging were excluded. Strokes that required hospitalization and for which confirmatory information was obtained

from the participant but medical records were unavailable were designated as probable. We included both confirmed and probable strokes in this analysis. Of the 401 strokes reported between 2001 and 2009 (383 nonfatal and 18 fatal), 130 were confirmed by medical record review, eight by death certificate, and 107 by self-confirmation by the nurse, for a total of 245 confirmed cases. Of the 156 reported strokes that were not used as cases, 76 were rejected upon medical record review and 80 were rejected because the nurses who reported the strokes could not be reached again.

CHD was confirmed using the World Health Organization [11] criteria that require typical symptoms plus either diagnostic electrocardiographic findings or elevated cardiac enzyme levels. Potential fatal cases were identified if CHD was listed as the cause of death in autopsy reports, hospital records, or death certificates. Fatal CHD cases were then confirmed if there was a prior report of CHD and if there was no other more apparent or plausible cause of death. CHD was considered probable if study participants confirm diagnoses in telephone interviews or through mail but medical records were not obtained. We included both definite and probable nonfatal and fatal CHD cases in the current analysis. Of the 395 CHD cases reported between 2001 and 2009 (368 nonfatal and 27 fatal), 159 were confirmed by medical record review, 21 by death certificate, and 75 by self-confirmation by the nurse, for a total of 255 confirmed cases. Of the 140 reported strokes that were not used as cases, 55 were rejected upon medical record review and 85 were rejected because the nurses who reported the strokes could not be recontacted.

2.3. Covariates

Covariates in the analyses included: age (continuous); race (white, African American, Asian, or missing/other); Hispanic ethnicity (yes or no); caffeine intake (<150, 150–249, 250–349, 350–449, 450+ mg/day, or missing); menopausal status (premenopausal, postmenopausal, unsure, or missing); physical activity (<3, 3–8.9, 9–17.9, 18–26.9, 27–41.9, 42+ met-h/week, or missing); smoking status (never, past (>20, >10–20, >5–10, 5 years since quitting), current (1–14, 15–24, 25+ cigarettes per day), or missing); alcohol intake (none, <10, 10–19, 20–29, 30+ grams per day, or missing); Dietary Approaches to Stop Hypertension (DASH) diet score (quintiles or missing); aspirin use (nonuser, current user, or missing); acetaminophen use (nonuser, current user, or missing); nonsteroidal anti-inflammatory drug (NSAID) use (nonuser, current user, or missing); depressive symptoms (0–52, 53–75, 76–85, 86–100 Mental Health Index-5 score, or missing); body mass index (BMI kg/m²) (continuous); diabetes (yes or no); hyper-cholesterolemia (yes or no); hypertension (yes or no); sleep duration (5, 6, 7, 8, and 9 h, or missing); snoring (every night, most nights, a few nights per week, occasionally, almost never, or missing); lifetime rotating night-shift work (never, 1–11, 12–23, 24–59, 60–95, 96+ months, or missing); and sleep adequacy (yes, adequate sleep; no, due to work/family; no, due to medical problems; no, due to leisure/social activities; no, due to worrying or insomnia; no, missing reason, missing). Sleep duration, adequacy, snoring, and depression were assessed in 2001. Shift work, caffeine intake, menopausal status, smoking status, alcohol intake, aspirin use, acetaminophen use, other NSAID use, BMI, diabetes, hypercholesterolemia, and hypertension were assessed initially in 2001 and then updated with each biennial

questionnaire. DASH diet score was assessed and updated in 1999 and 2003. Physical activity was assessed initially in 2001 and then updated in 2005.

2.4. Statistical analyses

Chi-squared tests were used to explore differences between categorical covariates and Wald *F*-tests for differences between continuous covariates in bivariate analyses with daytime sleepiness. Cox proportional hazards models were used to calculate hazard ratios (HR) for stroke, CHD, or CVD (stroke or CHD) incidence. Women were censored upon first report of stroke or CHD, date of death, or end of the 8-year follow-up period on 1 June 2009. Caffeine use and physical activity were included in a separate Cox model to explore whether these variables could act as partial mediators of the relationship between daytime sleepiness and vascular events. Sleep duration, snoring, shift work, and sleep adequacy were also added to adjusted Cox models to explore whether their inclusion attenuated the HR for the relationship between daytime sleepiness and vascular events. BMI, diabetes, hypercholesterolemia, and hypertension were also added to adjusted Cox models to examine their effect on the relationship between daytime sleepiness and vascular events. The final multivariable model included all the covariates. We used the log likelihood ratio test to evaluate multiplicative interaction with analyses stratified by current shift work (yes/no), snoring regularly (every night, most nights, or a few nights per week/occasionally, or almost never), sleep adequacy (yes, adequate; no, due to medical problems, leisure or social activities, or worrying or insomnia), short sleep duration (<6 h/ >7 h), depression (Mental Health Index-5 score <53 /Mental Health Index-5 score ≥ 53), obesity (<30 / ≥ 30 kg/m²), diabetes (yes/no), hypercholesterolemia (yes/no), and hypertension (yes/no) to examine whether these variables acted as effect modifiers of the relationship between daytime sleepiness and vascular events. Tests for linear trend for daytime sleepiness were created by setting the participant's value to the median value within their category, and these were included ordinally in the regression models. All statistical analyses were conducted using the SAS statistical software version 9.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

The baseline characteristics for women in the NHS-II study population in 2001 according to their daytime sleepiness categories are shown in Table 2. At baseline, participants ranged in age from 37 to 54 years. Women with daytime sleepiness almost every day were more likely to have short sleep durations, long sleep durations, have trouble getting adequate sleep, snore, engage in shift work, and suffer from hypertension, diabetes, hypercholesterolemia, obesity, and depression.

Table 3 shows the relationship between daytime sleepiness at baseline and subsequent CVD, stroke, and CHD incidence. Participants who reported daytime sleepiness almost every day had significantly increased age-adjusted hazard ratios of CVD (HR = 2.22, 95% CI 1.64–3.00), stroke (HR = 1.77, 95% CI 1.12–2.81), and CHD (HR = 2.71, 95% CI 1.81–4.05) compared with participants who reported rarely or never having daytime sleepiness. The inclusion of standard cardiovascular covariates (base adjusted model) (Model 2) attenuated the associations. The only slight attenuation in the associations with the inclusion of caffeine

use and physical activity in Model 3 is inconsistent with these variables acting as partial mediators. Further controlling for sleep characteristics, including sleep duration, snoring, shift work, and sleep adequacy, eliminated an independent association with daytime sleepiness (Model 3). The addition of potential metabolic biological mediators for the effect of poor sleep, including BMI, diabetes, hypercholesterolemia, and hypertension, to the base adjusted model (Model 4) also appreciably attenuated the hazards. After inclusion of both the sleep and metabolic variables (Model 5), there was no independent association between daytime sleepiness and cardiovascular outcomes (HR = 1.09, 95% CI 0.77–1.53 for CVD; HR = 0.97, 95% CI 0.58–1.62 for stroke; HR = 1.17, 95% CI 0.73–1.85 for CHD). Tests for trend were significant for Models 1, 2, and 4 for CVD and CHD and for Model 1 for stroke. The results and overall conclusions were not appreciably different when the highest category of daytime sleepiness included both daytime sleepiness almost every day and 4–6 days per week.

We did not find evidence of significant effect modification of the relationship between daytime sleepiness and CVD, stroke, or CHD by shift work, snoring, sleep adequacy, short sleep duration, depression, obesity, diabetes, hypercholesterolemia, or hypertension. To examine whether daytime sleepiness could act as a mediator in the relationship between the sleep variables and vascular events, we conducted analyses whereby the daytime sleepiness variable was entered into the multivariate model after the sleep variables. We found no appreciable attenuation in the hazard ratios for the sleep variables after the inclusion of daytime sleepiness in the multivariate models (see Supplementary Table). The results are therefore not consistent with daytime sleepiness acting as a mediator in the relationship between the sleep variables and vascular events.

4. Discussion

We observed associations between daytime sleepiness and the incidence of CVD, stroke, and CHD, but the associations were not independent of sleep characteristics and cardiometabolic risk factors. Our results expand upon previous findings on the relationship between daytime sleepiness and cardiovascular events by controlling simultaneously for multiple sleep characteristics and cardiovascular risk factors. Only one previous study reported results after controlling for snoring, insomnia, and prevalent CVD [5]. The authors of that study concluded that daytime sleepiness was independently associated with a 58% increased risk of vascular events, but the study was unable to control for sleep duration, shift work, diabetes, hypertension, or hypercholesterolemia. In our study, controlling for these additional factors eliminated an independent association between daytime sleepiness and cardiovascular events in middle-aged women. By contrast, our findings appear to support a model whereby short sleep duration, disturbed sleep, and circadian disruption may concurrently contribute toward daytime sleepiness, metabolic abnormalities, and CVD. A pictorial representation of this model is shown in Fig. 1. Although for heuristic purposes we picture all of the associations in the figure as unidirectional, it is possible that bidirectional relationships also exist between variables. For instance, daytime sleepiness could also impact sleep duration and sleep adequacy.

Two potential causal pathways by which daytime sleepiness could conceivably affect risk of vascular events include changes in caffeine consumption and physical activity. Individuals who are sleepy during the day may increase their consumption of caffeine and engage in less physical activity, which in turn could increase risk of CVD. However, our results are not consistent with caffeine use and physical activity acting as mediating variables in the relationship between daytime sleepiness and vascular events. This finding is likely due to the potentially bidirectional relationships between these variables. Daytime sleepiness could increase caffeine consumption or caffeine consumption could disrupt sleep and lead to daytime sleepiness [12]. Physical activity could improve sleep quality and decrease daytime sleepiness, yet daytime sleepiness could result in less energy to engage in regular physical activity [13].

The most common causes of daytime sleepiness are getting too little sleep, having irregular sleep schedules, and suffering from undiagnosed or untreated sleep disorders [14], all of which result in a chronic sleep debt and a cumulative increase in homeostatic sleep drive. We found strong associations between daytime sleepiness and sleep duration, snoring, shift work, and sleep adequacy. Previous studies have shown sleep duration [15,16], snoring [17], and shift work [18,19] to be independent risk factors for CVD. When we controlled for variables indicative of inadequate or disrupted sleep in multivariate models, the association between daytime sleepiness and CVD was appreciably attenuated. Daytime sleepiness therefore appears to largely be a manifestation of inadequate and poor quality sleep, which are each associated with cardiovascular events. Daytime sleepiness could also be symptomatic of depression. Fatigue, loss of energy, insomnia, and hypersomnia are cardinal symptoms of depression. Depression has been shown to increase the risk of heart disease [20] and mortality [21]. Patel et al. found depression to attenuate the relationship between long sleep duration and mortality, consistent with depression acting as a significant confounder or causal intermediate in the relationship between long sleep duration and mortality [22]. Consistent with this, we found that participants with either depressive symptoms or long sleep durations were significantly more likely to report experiencing daytime sleepiness almost every day and controlling for these variables attenuated the relationship between daytime sleepiness and CVD.

Sleep parameters that can cause daytime sleepiness have also been linked to components of the metabolic syndrome. Experimental sleep restriction has been shown to increase appetite [23], compromise insulin sensitivity [24], raise blood pressure [25], and increase total and low-density lipoprotein (LDL) cholesterol levels [26]. Short sleep duration [27], snoring [28], and shift work [29] have also been found to increase the risk of the metabolic syndrome. The inflammatory process associated with the metabolic syndrome can also cause daytime sleepiness. Proinflammatory cytokines have been shown to play key roles in both the pathogenesis and pathophysiology of metabolic disorders such as obesity and diabetes [30]. Proinflammatory cytokines contribute toward sleepiness and fatigue, and these effects are presumed to be adaptations that evolved to promote rest and recovery from illness [31]. The association between daytime sleepiness and CVD in our analyses was appreciably attenuated after controlling for BMI, diabetes, hypertension, and hypercholesterolemia. Our results suggest that in middle-aged women, daytime sleepiness is an epiphenomenon of the relationships between short/disrupted sleep, cardiometabolic abnormalities, and the risk of

cardiovascular events. However, since daytime sleepiness is a noticeable symptom, its presence may indicate increased cardiovascular risk due to these underlying conditions.

Our findings must be considered in light of the limitations of this study. First, we were not able to control for the presence of sleep apnea which has been shown to increase the risk of cardiovascular events [32], but we were able to control for snoring and body weight, both of which are closely related to sleep-disordered breathing. Second, our study included only one question to assess daytime sleepiness and we did not have repeated measures of daytime sleepiness over the follow-up period. We do not know how representative the baseline measure was of the study population's daytime sleepiness over the 8 years of follow-up. Given that some studies have shown poor correlation of sleepiness assessed with different measurement tools and poor agreement between subjective and objective measures of sleepiness [33], the use of a single question to measure daytime sleepiness could have led to measurement error that could have tempered a potential association. However, single-item measures of sleepiness have also been shown to serve as effective screening tools [34,35]. Third, we had limited power to observe significant associations due to low case counts, particularly for stroke, which had only 18 cases for women who reported experiencing daytime sleepiness almost every day. Importantly, our study also has several unique strengths including assessment of sleepiness and other sleep characteristics, detailed assessment of other cardiovascular risk factors, and careful prospective follow-up for cardiovascular events in a large cohort of women.

The results from this study support the hypothesis that the association between daytime sleepiness and cardiovascular events is primarily explained by inadequate/disrupted sleep and diseases associated with the metabolic syndrome that are established risk factors for CVD. The presence of daytime sleepiness in patients may therefore cue clinicians to assess for sleep disorders that often go undiagnosed and untreated. Treatment of sleep problems might help lower the risk of diseases associated with the metabolic syndrome and for cardiovascular events [36,37]. Adequate uninterrupted sleep may also help individuals follow other healthy lifestyle practices, such as allowing sufficient energy to engage in regular physical activity and controlling appetite to follow dietary regimens. Getting sufficient quality sleep on a regular basis may represent a lifestyle practice that contributes to the prevention of CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

A pictorial representation of a model whereby short sleep duration, disturbed sleep, and circadian disruption may concurrently contribute toward daytime sleepiness, metabolic abnormalities, and CVD.

Table 1

Summary of prospective epidemiologic studies that examined the association between daytime sleepiness and incident cardiovascular disease.

Source	Sample	Covariates in multivariate analyses	Results
Blachier et al. [8]	7007 French women and men 65 years	Age, sex, study center, smoking, living alone, BMI, fasting glycemia, hypercholesterolemia, hypertension, depression, mini-mental state examination score, and instrumental activities of daily living disability	Frequently excessively sleepy during the day associated with incident CHD and stroke HR= 1.73 (95% CI: 1.15—2.60)
Boden- Albala et al. [9]	2088 US women and men 40 years	Age, sex, race, education, waist circumference, alcohol use, smoking, physical activity, fasting glucose, systolic BP, diastolic BP, ratio of total cholesterol to HDL, peripheral vascular disease, coronary artery disease, depression, and medication usage	Severe dozing as measured by modified Epworth Sleepiness Scale associated with vascular death and incident stroke and myocardial infarction HR = 2.48 (95% CI: 1.57—3.91)
Elwood et al. [6]	1986 UK men aged 55—69	Age, social class, smoking, alcohol consumption, BMI, and neck circumference	Daytime sleepiness as measured by responses to the Wisconsin sleep questionnaire associated with ischemic heart disease OR = 1.41 (95% CI: 1.04—1.92)
Empana et al. [7]	9294 French women and men 65 years	Age, sex, study center, prior CVD, BMI, alcohol, smoking, diabetes, MMSE, systolic BP, Total and HDL cholesterol, medications, and depression	Daytime sleepiness associated with CVD mortality HR= 1.46 (95% CI: 1.02—2.09)
Newman et al. [5]	5888 US women and men 65 years	Age, sex, race, marital status, smoking, alcohol, cohort membership, obesity, arthritis, prevalent CVD, depression, disability in daily living, snoring, and insomnia	Daytime sleepiness associated with CVD mortality and CVD incident morbidity in women HR = 1.58 (95% CI: 1.21—2.06) and in men HR= 1.28 (95% CI: 0.98—1.68)
Qureshi et al. [4]	7844 US women and men 32 years	Age, sex, race, education, smoking, systolic BP, cholesterol, diabetes, and BMI	Daytime somnolence associated with incident stroke RR = 1.4 (95% CI: 1.1—1.8) and incident CHD RR = 1.2 (95% CI: 1.0—1.5)

Table 2

Baseline characteristics by baseline daytime sleepiness category among 84,003 women in the Nurses' Health Study II.

	Daytime sleepiness				P-value
	Rarely/never	1–3 Days per week	4–6 Days per week	Almost every day	
N(%)	55,142 (65.6)	18,582 (22.1)	5715 (6.8)	4564 (5.4)	
Covariates	Mean				
Age	46.9	46.3	46.2	46.8	<0.0001
	N (%)				
<i>Sleep duration in hours</i>					
5 h	2437 (4.4)	1266 (6.8)	478 (8.4)	762 (16.7)	<0.0001
6h	11,687 (21.2)	5289 (28.5)	1776 (31.1)	1361 (29.8)	
7h	24,119 (43.7)	7690 (41.4)	2188 (38.3)	1221 (26.8)	
8h	14,310 (26.0)	3415 (18.4)	889 (15.6)	667 (14.6)	
9h	2589 (4.7)	922 (5.0)	384 (6.7)	553 (12.1)	
<i>Sleep adequacy</i>					
No – Cannot sleep	5456 (9.9)	3573 (19.3)	1300 (22.9)	1198 (26.4)	<0.0001
No – Other reasons	14,722 (26.8)	9539 (51.6)	3153 (55.7)	2673 (59.0)	
Yes - Adequate	34,693 (63.2)	5377 (29.1)	1213 (21.4)	668 (14.7)	
Snore regularly	2994 (5.4)	1455 (7.8)	600 (10.5)	835 (18.3)	<0.0001
Current shift worker	10,859 (19.7)	4568 (24.6)	1531 (26.8)	1210(26.5)	<0.0001
<i>Race</i>					
Caucasian	51,130 (92.7)	17,284 (93.0)	5383 (94.2)	4201 (92.1)	<0.0001
African American	766 (1.4)	242 (1.3)	71 (1.2)	89 (2.0)	
Other	3246 (5.9)	1056 (5.7)	261 (4.6)	274 (6.0)	
Hispanic ethnicity	758 (1.4)	266 (1.4)	79 (1.4)	57 (1.3)	0.8136
Hypertension	9088 (16.5)	3504 (18.9)	1240 (21.7)	1200 (26.3)	<0.0001
Diabetes	1323 (2.4)	572 (3.1)	239 (4.2)	276 (6.1)	<0.0001
Hypercholesterolemia	16,099 (29.2)	6179 (33.3)	2089 (36.6)	1926 (42.2)	<0.0001
Body mass index 30	6820 (12.4)	2625 (14.1)	934 (16.3)	780 (17.1)	<0.0001
Postmenopausal	13,276 (24.1)	4088 (22.0)	1338 (23.4)	1236 (27.1)	<0.0001
Total activity <9 METS per week	20,887 (37.9)	8167 (44.0)	2807 (49.1)	2543 (55.7)	<0.0001
Current smoker	4352 (7.9)	1704 (9.2)	589 (10.3)	532 (11.7)	<0.0001
Caffeine 245Mgperday	21,927 (39.8)	7228 (38.9)	2269 (39.7)	1766 (38.7)	<0.0001
Alcohol >28 grams per day	1494 (2.7)	386 (2.1)	132 (2.3)	97 (2.1)	<0.0001
DASH score in bottom quintile	8,632 (15.7)	2,923 (15.7)	916 (16.0)	913 (20.0)	<0.0001
Current aspirin	49,042 (88.9)	16,366 (88.1)	4965 (86.9)	3899 (85.4)	<0.0001
Current acetaminophen	44,527 (80.8)	13,706 (73.8)	4277 (74.8)	3152 (69.1)	<0.0001
Current NSAID	20,149 (36.5)	8239 (44.3)	2324 (40.7)	1992 (43.7)	<0.0001
Depressive symptoms	3457 (6.3)	2804 (15.1)	1099 (19.2)	1470 (32.2)	<0.0001

Table 3

Multivariate analyses using Cox proportional hazards models exploring the relationship between daytime sleepiness, incident stroke, incident coronary heart disease, and incident cardiovascular disease (either stroke or coronary heart disease) (Hazard ratios, 95% Confidence intervals).

	Incident cases <i>n</i>	Model 1	Model 2	Model 3 (Base Model)	Model 4	Model 5	Model 6
<i>Cardiovascular disease (Either stroke or coronary heart disease)</i>							
Daytime sleepiness							
Rarely/never	281	1.00	1.00	1.00	1.00	1.00	1.00
1–3 Days per week	120	1.32 (1.06–1.63)	1.19 (0.95–1.48)	1.17 (0.94–1.47)	1.06 (0.84–1.33)	1.12 (0.90–1.40)	1.04 (0.82–1.30)
4–6 Days per week	49	1.86 (1.37–2.52)	1.54 (1.13–2.10)	1.51 (1.11–2.07)	1.26 (0.91–1.74)	1.33 (0.97–1.82)	1.17 (0.84–1.61)
Almost every day	50	2.22 (1.64–3.00)	1.62 (1.18–2.22)	1.58 (1.15–2.17)	1.17 (0.84–1.65)	1.34 (0.97–1.85)	1.09 (0.77–1.53)
<i>P</i> -value, test for trend		<i>P</i> < 0.0001	<i>P</i> < 0.0002	<i>P</i> = 0.0005	<i>P</i> = 0.1706	<i>P</i> = 0.0226	<i>P</i> = 0.4309
<i>Stroke</i>							
Daytime sleepiness							
Rarely/never	145	1.00	1.00	1.00	1.00	1.00	1.00
1–3 Days per week	57	1.22 (0.89–1.65)	1.09 (0.79–1.49)	1.09 (0.80–1.50)	0.98 (0.71–1.36)	1.05 (0.76–1.44)	0.96 (0.69–1.33)
4–6 Days per week	22	1.58 (1.01–2.48)	1.33 (0.84–2.11)	1.34 (0.84–2.12)	1.13 (0.70–1.82)	1.20 (0.75–1.90)	1.05 (0.65–1.70)
Almost every day	21	1.77 (1.12–2.81)	1.33 (0.83–2.15)	1.33 (0.82–2.14)	1.03 (0.62–1.70)	1.17 (0.72–1.90)	0.97 (0.58–1.62)
<i>P</i> -value, test for trend		<i>P</i> = 0.0025	<i>P</i> = 0.1237	<i>P</i> = 0.1279	<i>P</i> = 0.7568	<i>P</i> = 0.3812	<i>P</i> = 0.9941
<i>Coronary heart disease</i>							
Daytime sleepiness							
Rarely/never	136	1.00	1.00	1.00	1.00	1.00	1.00
1–3 Days per week	63	1.43 (1.06–1.93)	1.30 (0.95–1.78)	1.27 (0.93–1.74)	1.15 (0.83–1.59)	1.22 (0.89–1.66)	1.12 (0.81–1.55)
4–6 Days per week	27	2.16 (1.43–3.26)	1.77 (1.15–2.71)	1.70 (1.11–2.60)	1.38 (0.89–2.16)	1.47 (0.96–2.26)	1.27 (0.81–1.98)
Almost every day	29	2.71 (1.81–4.05)	1.92 (1.25–2.93)	1.84 (1.20–2.81)	1.31 (0.83–2.07)	1.50 (0.97–2.31)	1.17 (0.73–1.85)
<i>P</i> -value, test for trend		<i>P</i> < 0.0001	<i>P</i> < 0.0003	<i>P</i> = 0.0008	<i>P</i> = 0.1275	<i>P</i> = 0.0225	<i>P</i> = 0.3410

Model 1 – Adjusted for age.

Model 2 – Adjusted for age, race, Hispanic ethnicity, menopause, smoking, alcohol intake, dash diet total score, aspirin user, acetaminophen user, NSAID user, and depressive symptoms.

Model 3 – Adjusted for variables in Model 2 plus caffeine intake and physical activity.

Model 4 – Adjusted for variables in Model 3 plus sleep duration, snoring, shift work, and sleep adequacy.

Model 5 – Adjusted for variables in Model 3 plus BMI, diabetes, hypercholesterolemia, and hypertension.

Model 6 – Adjusted for variables in Model 3 plus sleep duration, snoring, shift work, sleep adequacy, BMI, diabetes, hypercholesterolemia, and hypertension.