

A Prospective Study of Sleep Duration and Coronary Heart Disease in Women

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Background: Long-term sleep deprivation is common in today's society. Recent experiments have demonstrated that short-term sleep deprivation in healthy subjects results in adverse physiologic changes, including a decreased glucose tolerance and an increased blood pressure. However, the long-term health consequences of long-term sleep deprivation are unclear. The objective of this study was to determine whether decreased sleep duration (from self-reports) is associated with an increased risk of coronary events.

Methods: We studied a cohort of 71 617 US female health professionals (aged 45-65 years), without reported coronary heart disease (CHD) at baseline, who were enrolled in the Nurses' Health Study. Subjects were mailed a questionnaire in 1986 asking about daily sleep duration. Subjects were followed up until June 30, 1996, for the occurrence of CHD-related events. We assessed the relationship between self-reported sleep duration and incident CHD.

Results: A total of 934 coronary events were docu-

mented (271 fatal and 663 nonfatal) during the 10 years of follow up. Age-adjusted relative risks (95% confidence intervals) of CHD (with 8 hours of daily sleep being considered the reference group) for individuals reporting 5 or fewer, 6, and 7 hours of sleep were 1.82 (1.34-2.41), 1.30 (1.08-1.57), and 1.06 (0.89-1.26), respectively. The relative risk (95% confidence interval) for 9 or more hours of sleep was 1.57 (1.18-2.11). After adjusting for various potential confounders, including snoring, body mass index, and smoking, the relative risks of CHD (95% confidence intervals) for individuals reporting 5 or fewer, 6, and 7 hours of sleep were 1.45 (1.10-1.92), 1.18 (0.98-1.42), and 1.09 (0.91-1.30), respectively. The relative risk (95% confidence interval) for 9 or more hours of sleep was 1.38 (1.03-1.86).

Conclusion: Short and long self-reported sleep durations are independently associated with a modestly increased risk of coronary events.

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ACCORDING TO a recent National Sleep Foundation poll,¹ many Americans have long-term sleep deprivation. Only about one third of the population (37%) obtain 8 hours of sleep per night, and 31% report 6 or fewer hours of sleep each night. The long-range adverse health consequences of long-term sleep restriction are unclear. Most previous studies²⁻⁴ that have attempted to address this question lacked adequate power to assess clinical end points or were unable to control for potential confounders. However, short-term sleep restriction causes adverse physiologic effects. Short-term partial sleep deprivation (ie, 4 hours per night for 6 nights) imposed on a group of healthy subjects increased cortisol levels, decreased glucose tolerance, and increased sympathetic nervous system activity.⁵ In another study,⁶

partial sleep deprivation for one night (3.6 hours of sleep) in healthy subjects increased blood pressure and sympathetic activity compared with a night of normal sleep duration. Therefore, we hypothesized that sustained partial sleep deprivation could lead to adverse cardiovascular consequences. To test this possibility, we investigated the association between reported sleep duration and the incidence of major coronary heart disease (CHD)-related events during 10 years of follow-up among women enrolled in the Nurses' Health Study.

METHODS

STUDY POPULATION

The Nurses' Health Study cohort was established in 1976 when 121 700 female, married, registered nurses, aged 30 to 55 years and re-

siding in 11 large US states, completed a mailed questionnaire about their medical history and lifestyle. Follow-up questionnaires have been sent every 2 years to update information on potential risk factors and to identify newly diagnosed cases of coronary and other diseases. On the 1986 questionnaire, subjects were requested to provide the following information: "Indicate total hours of actual sleep in a 24-hour period." Subjects were asked to choose one of the following options: 5 or fewer, 6, 7, 8, 9, 10, or 11 or more hours. Between July 1, 1986, and June 30, 1996, the incidence rates of CHD-related events were assessed in the 71 617 women aged 40 to 65 years who answered these questions and were not diagnosed as having cardiovascular disease or cancer in 1986 (the baseline year for these analyses).

ASCERTAINMENT OF END POINTS

The primary end point for this study was incident CHD-related events (defined as a nonfatal myocardial infarction [MI] or fatal CHD) that occurred after the return of the 1986 questionnaire but before June 1, 1996. We requested permission to review medical records from women who reported having a nonfatal MI on a follow-up questionnaire. Study physicians (J.E.M. and others) with no knowledge of the self-reported risk factor status reviewed the records. A nonfatal MI was confirmed if data in the record met the criteria of the World Health Organization⁷ of symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzyme levels. Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable (17%). We included all confirmed and probable cases in these analyses.

Deaths were reported by next of kin and the postal system or ascertained through the National Death Index. We estimate that follow-up for the deaths was more than 98% complete.⁸ A fatal MI was confirmed by hospital records or autopsy or if CHD was listed as the cause of death on the death certificate and evidence of previous CHD was available. We designated as presumed fatal CHD cases in which CHD was the underlying cause on the death certificate but no records were available. These cases constituted about 14.7% of fatal CHD cases. We also included sudden deaths (defined as death within 1 hour of the onset of symptoms). We included all confirmed and presumed fatal CHD cases plus those with sudden death in these analyses.

STATISTICAL ANALYSES

The person-time for each exposure category (sleep duration of ≤ 5 , 6, 7, 8, or ≥ 9 hours per night) was accumulated. Incidence rates were calculated by dividing the number of events by person-time of follow-up in each category. Because of small numbers of subjects, we chose to combine the subjects from the 9, 10, and 11 or more hours of sleep groups into one group. In our analysis, each participant contributed person-years to the analysis until an event occurred (either a fatal or a nonfatal MI). Once an event occurred, the participant was removed from the analysis and no longer contributed any further person-years. The relative risk (RR) was computed as the rate in a specific category of exposure divided by that in the reference category (sleep duration of 8 hours per night), with adjustment for age. We chose a reference category of 8 hours per night for 2 reasons. First, 8 hours is conventionally considered to be the appropriate duration of sleep. Second, this category was associated with the lowest rate of CHD in our cohort. In multivariate analyses using pooled logistic regression,⁹ we simultaneously included age (5-year interval), smoking status (never,

past, and current smoking of 1-14, 15-24, and ≥ 25 cigarettes per day), body mass index (in quintiles), alcohol consumption (0, 1-4, 5-14, and ≥ 15 g/d), physical activity (weekly energy expenditure in metabolic equivalent hours), menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement), depressed mood from 1992 (depression was defined as a 36-Item Short-Form Health Survey mental health index of ≤ 52), aspirin use (3 categories), parental history of MI before the age of 60 years, and a history of hypercholesterolemia. To control for snoring, we used information from a question contained in the 1986 survey: "Do you snore?" Subjects were asked to check 1 of 3 responses: never, occasionally, or regularly. In our analysis, we used these 3 categories to control for frequency of snoring. We also controlled for the duration of night shifts worked. This information was ascertained from the 1988 questionnaire in which subjects were asked how many years of rotating shifts they performed. Subjects were then divided into 4 groups depending on the duration of night shift working (0, 1-5, 6-14, and ≥ 15 years). We did not control for a history of hypertension or diabetes mellitus in the primary analyses because decreased sleep duration may be associated with the development of hypertension or diabetes mellitus.^{5,6} Thus, the development of hypertension or diabetes mellitus may be an intermediate step in the causal pathway between decreased sleep duration and cardiovascular disease. In secondary analyses, we adjusted for both of these variables.

RESULTS

The primary analysis was the ascertainment of incident CHD-related events during the 10-year study period. During this period, we documented 934 incident cases of CHD (271 fatal and 663 nonfatal).

At baseline, 5% of the women reported sleeping 5 or fewer hours a day, 26% slept 6 hours a day, 41% slept 7 hours a day, 24% slept 8 hours a day, and 5% slept 9 hours or more a day (percentages do not total 100 because of rounding). Baseline characteristics of the women in the various sleep duration categories are shown in **Table 1**. Increased and decreased sleep durations were associated with an increased prevalence of diabetes mellitus, hypertension, and hypercholesterolemia. Women in these sleep categories also tended to be heavier. Regular snoring was slightly more common in those who slept for a longer duration. Nurses who slept less tended to report more shift working. The amount of weekly exercise did not differ substantially among the groups.

After adjustment for age, sleep duration was associated with a significantly increased risk of incident CHD (**Table 2**). For short sleepers (ie, those who slept ≤ 5 hours per night), the RRs of CHD were 1.82 for all CHD, 1.67 for fatal CHD, and 1.89 for nonfatal MI. For long sleepers (ie, those who slept ≥ 9 hours per night), the RRs were 1.57 for all CHD, 1.71 for fatal CHD, and 1.50 for nonfatal MI.

After adjusting for smoking status, body mass index, and other covariates (Table 1), the positive associations for CHD were attenuated but remained statistically significant. Without adjustment for diabetes mellitus or hypertension, multivariate RRs were 1.45 for short-duration sleepers and 1.38 for 9-hour or longer sleep-

Table 1. Baseline Characteristics and Risk Factors for Cardiovascular Disease According to Self-reported Sleep Duration in 1986*

Characteristic	Sleep Duration, h/d				
	≤5	6	7	8	≥9
Age, mean, y	52.9	52.3	51.9	52.4	52.7
BMI, mean	25.4	25.1	24.5	24.6	25.0
Alcohol consumption, g/d	4.9	5.7	6.2	6.7	7.9
Physical activity, mean, METs/wk	14.2	14.2	14.5	14.0	12.1
Fat intake (% of energy), mean					
Saturated	11.8	11.8	11.7	11.7	11.7
Polyunsaturated	5.9	6.1	6.2	6.2	6.1
Trans-fatty acids	1.6	1.7	1.7	1.7	1.7
Dietary cholesterol, mean, mg/1000 kcal	155	152	150	150	150
Mental health component score from the SF-36, mean†	73	76	77	77	76
History of diabetes	5	3	3	4	4
History of hypercholesterolemia	14	11	11	12	12
History of hypertension	29	25	22	24	27
Current smoking	23	23	21	20	22
Parental history of MI before the age of 60 y	16	15	14	14	14
Regular snoring	10	10	8	10	12
Night shift work >5 y‡	28	20	15	14	16
Supplement use					
Multivitamin	41	42	43	42	43
Vitamin E	17	17	16	15	14
Aspirin use (≥15 d/mo)‡	17	16	14	15	16
Postmenopausal hormone use	16	21	23	22	22

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); MET, metabolic equivalent; MI, myocardial infarction; SF-36, 36-Item Short-Form Health Survey.

*Data are given as percentage of women unless otherwise indicated.

†Reported in 1992.

‡Reported in 1988.

ers. After additional adjustment for a history of hypertension or diabetes mellitus, multivariate RRs of CHD were slightly less, but still significant. This suggests that long and short sleep durations are independent risk factors for CHD.

COMMENT

In this prospective study of women, we observed a modest, but significant, positive association between reported sleep duration and incidence of CHD. Short and long sleep durations were associated with an increased risk of incident CHD. After controlling for smoking status, body mass index, and other relevant covariates, the RRs were attenuated, reflecting the confounding effects of these variables. However, a significant positive association between sleep duration and CHD persisted.

PREVIOUS STUDIES

Our findings are consistent with and extend those of other investigators. Wingard and Berkman⁴ studied 2491 women and 2222 men aged between 30 and 69 years. They found that women who reported not sleeping 7 to 8 hours per night had an increased 9-year mortality rate compared with subjects who reported 7 to 8 hours of sleep (RR, 1.6). However, the study was not powered adequately to demonstrate if decreased sleep duration alone was a significant independent risk factor

for cardiovascular-related mortality. Similarly, Kripke et al² studied the mortality rate of a large cohort of American Cancer Society volunteers who had completed a survey that contained a question about sleep duration. Although they were not able to control for various relevant confounders, they demonstrated that a reported sleep duration of fewer than 4 hours per night was associated with an increased 6-year all-cause mortality rate in men and women. Interestingly, in that study, the effects of sleep duration were more prominent in men than in women. In women, the RR of deaths from CHD was slightly less than in our study. That is, in those with no history of diabetes mellitus or hypertension, the RR was 1.1 for those sleeping fewer than 4 hours per night and 1.04 for those sleeping 4 to 5 hours per night. The discrepancy between our study and that of Kripke et al may have been partially related to their use of death certificates to assess cause of mortality. Relying on death certificates for this purpose potentially results in nonrandom misclassification of death.¹⁰

BIOLOGICAL MECHANISMS

The association between decreased sleep duration and CHD may be mediated through several potential mechanisms, including sympathetic overactivity, increases in blood pressure, or decreased glucose tolerance. Spiegel et al⁵ restricted sleep in 11 healthy young men to 4 hours per night for 6 nights and then allowed them to have a sleep recovery period of 6 nights. Despite the short du-

Table 2. The RRs of CHD According to Self-reported Sleep Duration at Baseline

Variable	Sleep Duration, h/d				
	≤5	6	7	8*	≥9
Total CHD†					
No. of cases	67	267	348	193	59
Person-years of follow-up	30 115	175 629	288 731	162 662	31 015
Age-adjusted RR‡	1.82 (1.34-2.41)	1.30 (1.08-1.57)	1.06 (0.89-1.26)	1	1.57 (1.18-2.11)
Multivariate model RR‡§					
Not adjusted for diabetes mellitus or hypertension	1.45 (1.10-1.92)	1.18 (0.98-1.42)	1.09 (0.91-1.30)	1	1.38 (1.03-1.86)
Adjusted for diabetes mellitus and hypertension	1.39 (1.05-1.84)	1.18 (0.98-1.43)	1.10 (0.92-1.31)	1	1.37 (1.02-1.85)
Nonfatal MI					
Age-adjusted RR‡	1.89 (1.35-2.66)	1.43 (1.15-1.79)	1.19 (0.97-1.48)	1	1.50 (1.04-2.17)
Multivariate model RR‡§					
Not adjusted for diabetes mellitus or hypertension	1.58 (1.12-2.22)	1.31 (1.04-1.64)	1.21 (0.98-1.50)	1	1.34 (0.93-1.93)
Adjusted for diabetes mellitus and hypertension	1.52 (1.08-2.14)	1.32 (1.05-1.65)	1.23 (0.99-1.52)	1	1.35 (0.93-1.95)
Fatal CHD					
Age-adjusted RR‡	1.67 (1.02-2.74)	1.05 (0.75-1.46)	0.80 (0.58-1.09)	1	1.71 (1.05-2.77)
Multivariate model RR‡§					
Not adjusted for diabetes mellitus or hypertension	1.20 (0.73-1.97)	0.92 (0.66-1.29)	0.84 (0.61-1.16)	1	1.45 (0.89-2.35)
Adjusted for diabetes mellitus and hypertension	1.12 (0.68-1.84)	0.91 (0.65-1.28)	0.83 (0.60-1.14)	1	1.45 (0.89-2.36)

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; RR, relative risk.

*Reference.

†Includes nonfatal MIs and fatal CHD-related events.

‡Data in parentheses are 95% confidence intervals.

§Adjusted for shift work (from 1988), hypercholesterolemia, body mass index, smoking, snoring, exercise level, alcohol consumption, depression (from 1992), aspirin use (from 1988), postmenopausal hormone use, and family history of MI.

ration of partial sleep deprivation, the subjects in that study demonstrated impaired glucose tolerance, higher evening cortisol levels, and increased sympathetic nervous system activity (assessed with heart rate variability) during sleep deprivation when compared with their recovery period. Similarly, Tochibuko et al⁶ measured blood pressure during the day using a portable biomedical recorder in 18 men after a night of normal sleep (mean, 8 hours) vs a night of insufficient sleep (mean, 3.6 hours). A significant increase in blood pressure was found during waking hours in the sleep-deprived group. Hence, there are short-term experimental data that suggest mechanisms by which long-term sleep deprivation may lead to adverse cardiovascular events.

In contrast, we have no reason to suspect that increased sleep duration would cause CHD and were somewhat surprised by the observation. In searching for possible explanations for this association, only 2 basic concepts emerged. First, some confounder could lead to CHD and an increased need for sleep. An example might be obstructive sleep apnea. There are data¹¹⁻¹³ to show that sleep apnea is associated with adverse cardiovascular outcomes and that it is known to fragment sleep, potentially increasing the need for sleep. However, to our knowledge, no evidence shows that patients with sleep apnea sleep longer than subjects without sleep apnea. Thus, this explanation for our findings seems unlikely. Second, reverse causality may be a possible explanation. That is, increased sleep duration may be an early symptom of cardiac disease and may predate an official diagnosis of CHD. Third, increased sleep itself could lead to cardiovascular disease. Although this concept is consistent with the results of this study, we know of no plausible explanation for such a cause-and-effect relation-

ship. Thus, the association of increased sleep duration and CHD remains unexplained.

STRENGTHS AND LIMITATIONS

Strengths of the present study include the large sample size and the high rate of follow-up. Also, CHD was assessed prospectively, eliminating possible bias due to retrospective recall that may be present in case-control and cross-sectional analyses.

We also acknowledge that there are several limitations in the present study. First, all subjects were women. It is possible that men differ from women in effects of sleep duration on incident CHD. However, a prior epidemiologic study⁴ demonstrated little difference in the RRs of death in men and women from a decreased sleep time, and another² showed that the adverse risk in women may actually be lower than in men. Second, information about sleep duration and other potential risk factors was self-reported by female nurses. The reliability of self-reported sleep duration was not validated and its stability over time is not known. Indeed, given the age range of the participants of the study, changes in lifestyle and sleep pattern in some subjects likely occurred during the 10-year study period. Nevertheless, questions about self-reported sleep duration have been investigated in other studies,^{14,15} and have been demonstrated to be valid measures when compared with quantitative sleep assessments with actigraphy. Despite this, some misclassification of the sleep duration variable seems likely. However, because outcomes were assessed prospectively, any misclassification of sleep duration would be nondifferential for CHD. Therefore, this would tend to underestimate, rather than overestimate, the effects of sleep duration. Third, our study was observa-

tional in design and, thus, we cannot conclude definitively that decreased sleep duration caused CHD. We cannot rule out the presence of unknown confounders that were not accounted for in the final analysis. Because of the substantial change in the RRs by adding known confounders, it is possible that some residual confounding remains. However, it is doubtful that this residual unexplained confounding would completely eliminate the effect seen. Finally, the cause of restricted sleep was not ascertained in our study. Subjects may have had a decreased sleep duration from insomnia (an inability to fall or stay asleep), work or family responsibilities, or staying up late to watch television. It is possible that the cause of sleep restriction may differentially affect the risk of CHD. However, this cannot be determined from our study.

CLINICAL SIGNIFICANCE

Long-term sleep deprivation is common in today's society. According to the 2001 National Sleep Foundation poll,¹ approximately 31% of Americans sleep 6 or fewer hours per day. The cause of this is multifactorial. About 45% of adults report that they sleep less to get more work done, 43% stay up watching television or using the Internet, and 22% report having difficulty falling asleep.¹⁶ Our study suggests that curtailing sleep may have adverse cardiovascular consequences. Indeed, sleeping 5 or fewer hours per night was associated with a 39% increase in risk of CHD, and 6 hours per night with an increase of 18%, compared with sleeping 8 hours per night. Given these results and those of the short-term experimental studies cited previously, adequate daily sleep should not be considered a luxury, but an important component of a healthy lifestyle.

In conclusion, our data suggest that a short self-reported sleep duration is associated with an increased risk of CHD. This association persists even after adjustment for age, smoking status, obesity, hypertension, diabetes mellitus, and other cardiovascular risk factors. Although cause and effect cannot be proved definitively in this observational study, our results suggest that insufficient duration of sleep may increase CHD risk. Further studies are needed to elucidate better the biological mechanism underlying this association, and to determine whether the cause of the sleep deprivation (insomnia vs lifestyle choices) affects its cardiovascular consequences. Finally, the explanation for the increased CHD in patients sleeping 9 hours or longer is unclear and must

await data defining why these individuals slept as much as they did. Such information might lead to a logical explanation for the observed increase in CHD.

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