The Effect of Short Sleep Duration on Coronary Heart Disease Risk is Greatest Among Those with Sleep Disturbance: A Prospective Study from the Whitehall II Cohort

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Study Objectives: Short sleep duration is associated with increased CHD (coronary heart disease) mortality and morbidity, although some evidence suggests that sleep disturbance is just as important. We investigated whether a combination of short sleep duration and sleep disturbance is associated with a higher risk of CHD than their additive effects.

Setting: The Whitehall II study.

Patients or Participants: The Whitehall II study recruited 10,308 participants from 20 civil service departments in London, England. Participants were between the ages of 35 and 55 years at baseline (1985-1988) and were followed up for an average of 15 years.

Interventions: N/A.

Measurements: Sleep hours and sleep disturbance (from the General Heath Questionnaire-30) were obtained from the baseline survey. CHD events included fatal CHD deaths or incident nonfatal myocardial infarction or angina (ICD-9 codes 410-414 or ICD-10 I20-25).

Results: Short sleep duration and sleep disturbance were both associated with increased hazards for CHD in women as well as in men, although, after we adjusted for confounders, only those reporting sleep disturbance had a raised risk. There was some evidence for an interaction between sleep duration and sleep disturbance. Participants with short sleep duration and restless disturbed nights had the highest hazard ratios (HR) of CHD (relative risk:1.55, 95% confidence interval:1.33-1.81). Among participants who did not report any sleep disturbance, there was little evidence that short sleep hours increased CHD risk.

Conclusion: The effect of short sleep (≤ 6 hours) on increasing CHD risk is greatest among those who reported some sleep disturbance. However, among participants who did not report any sleep disturbance, there was little evidence that short sleep hours increased CHD risk.

Keywords: Short sleep, sleep disturbances, coronary heart disease, myocardial infarction, angina pectoris

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IT IS ESTIMATED THAT SLEEP PROBLEMS AFFECT APPROXIMATELY 20% OF THE ADULT POPULATION IN WESTERN COUNTRIES.[1,2] ALTHOUGH IT HAS BEEN shown that sleep problems lead to adverse physiologic changes in the short term,[3] the long-term consequences are less clear. In experimental and epidemiologic studies, both short and long sleep hours have been related to hypertension,[4] type-2 diabetes,[5] increased body mass index,[6] and alterations in blood lipids concentrations[7] and inflammatory markers[8]—all factors known to increase the risk of cardiovascular disease.[9]

The association between sleep duration and coronary heart disease (CHD) remains debatable.[10] In some studies, a positive, U-shaped association between short and long sleep duration and manifestation of CHD or CHD mortality has been shown.[11-15] In some studies, only short sleep duration[16,17] whereas, in others, only long sleep duration[18,19] were found to affect CHD. Furthermore, some studies report associations only among men,[13,19] whereas others, only among women.[11,12] It is possible that these contradictory results may have occurred because sleep duration is not a sufficient measure of the disturbances in the recovery and physiologic reinstitution of the body during sleep. Ekstedt et al.[20] reported an association between increased number of microarousals per hour in exhausted patients and an increase in blood lipids concentrations, cortisol levels, and blood pressure, although the total sleep time was not affected. Microarousals during sleep are associated with increased levels of lipid and cortisol and increased blood pressure.[21] Thus, one way of clarifying the debates on the sleep-CHD relationship may be to combine measures of short sleep and low sleep quality. A combination of sleep disturbance and short sleep duration together might be a much better measure of physiologic disturbances during sleep than is either one on its own. Such a combination may be a stronger predictor of CHD and cardiovascular mortality than are its components; however, this has not been previously studied. Complaints about disturbed sleep were linked to increased CHD risk in 1 study,[17] but they were not combined with sleep duration.

Second, the variable results that have been published concerning an association of CHD with sleep in men and in women may be due to the nature of the CHD measures used in various studies, especially in working younger populations. Although fatal CHD and myocardial infarction (MI) is a more common expression of CHD in men,[22] nonfatal angina pectoris is more common in women.[23] Thus, studies that only examine MI may be missing an important dimension of CHD among women. Analyses that include both MI and angina may be important in understanding if there is a sex difference in the effect of sleep on CHD.

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In a longitudinal epidemiologic study of healthy white-collar workers in London, we addressed the above debates by testing 2 hypotheses. (1) Sleep duration and sleep disturbances increase the risk of CHD independently of each other, among women and men. We combined fatal CHD, MI, and angina pectoris as an outcome measure. (2) Sleep hours and sleep problems interact so that the effect of sleep hours on CHD is greatest among those who report sleep disturbance.

METHODS

Study Sample and Design

The Whitehall II Cohort was recruited from 1985 to 1988 (phase 1) from 20 London-based civil service departments. Ten thousand, three hundred, eight participants aged 35 to 55 years were recruited at baseline: 3413 women and 6895 men. Follow-up screening examinations took place from 1991 to 1993 (phase 3), 1997 to 1999 (phase 5), and 2002 to 2004 (phase 7), whereas postal questionnaires were sent to participants in 1989 (phase 2), 1995 (phase 4), and 2001 (phase 6). In this study, exposure data from baseline (phase 1) were used, whereas CHD outcome data were measured until phase 7. More details on the study design are available elsewhere.[24]

Outcome

Incident CHD events included fatal CHD (ICD-codes 410-414 or ICD-10 I20-25) or incident nonfatal MI or angina (including angina from the Rose questionnaire[25] from phase 1 [1985-88] to phase 7 [2002-04]). Prevalent CHD cases at baseline were excluded from the analyses (n = 422). The average length of follow-up was 15 years, and the total follow-up time was 154,943 person years. For sensitivity analyses, only cases of MI and angina verified by clinical records were analyzed (i.e., eliminating participants with CHD diagnoses obtained from only questionnaire data, such as the Rose questionnaire).

Main Exposures

Main exposures were determined from baseline phase 1.

Sleep duration

Participants were asked "How many hours of sleep do you have on an average week night?" Response categories were 5 hours or less, 6 hours, 7 hours, 8 hours, and 9 hours or longer.

Sleep disturbance

The General Heath Questionnaire-30[26] includes 2 questions related to sleep: *Have you recently* "*lost much sleep over worry?*" and "*been having restless, disturbed nights*." Participants were asked to choose from *Not at all*, *No more than usual*, *Rather more than usual*, and *Much more than usual*. For the analyses, the last 2 categories were combined due to few participants in the last category (between 186 and 254 people, or approximately 2% of the sample).

Other covariates

Sociodemographic variables included age, sex, crude ethnic group (White/non-White), civil-service employment grade, car access, and housing tenure (owner occupier vs rented accommodation). Health behaviors measured consisted of smoking status (never/exsmokers vs current smokers), alcohol consumption (nondrinkers; drinkers within the recommended limits, 1-14 units for women or 1-21 units for men; unsafe drinkers, 14+ units for women/21+ units for men), self-reported frequency of vigorous and moderate activities (3+ times a week, at least once a week, at least once a month, never), and fruit or vegetable consumption (less than weekly, less than daily, and at least daily). Health-status factors considered were self-rated health status (5-point scale from *excellent* to *poor*), total cholesterol concentration (< 5, 5-6.5, 6.51-7.8, > 7.8 mg/dL), hypertension (blood pressure ≥ 130 mm Hg systolic, ≥ 85 mm Hg diastolic, or on antihypertensive medication), diabetes (self-reported), and body mass index (BMI; analyzed as a continuous measure and also dichotomized into *normal*: BMI < 25 kg/m^2 and *overweight* BMI > 25 kg/m^2).

Statistical Analysis

Cox regression models of incident CHD were used to estimate the HR (and 95% confidence intervals [CI]) associated with the main exposures (the sleep variables). Initially, the analyses were stratified by sex (hypothesis 1) and BMI (normal vs overweight). Stratification by BMI was used to investigate the potential confounding effect of sleep apnea. If apnea is a confounder, we would expect little effect of the sleep variables on CHD among the normal-weight participants because the prevalence of sleep apnea in this group is extremely low.

We first analyzed the bivariate associations of the sleep variables on CHD independently of each other, stratified by sex. If there was no evidence of effect modification by sex, we then pooled the data together. In the multivariate-analyses models, we first analyzed the unadjusted effects of the sleep variables on CHD (Model 1); separate models for each of the sleep variables were estimated. We then adjusted for potential confounding factors (Model 2), which included age, sex, ethnicity, socioeconomic position, and the other 2 sleep variables, and then for potential mediating variables (Model 3), which included biologic and behavior risk factors that could lie on the causal pathway from sleep to CHD.

We analyzed 2-way interaction effects for the main exposures in the multivariate analyses. In particular, we looked at whether sleep hours and sleep problems interact. Due to small numbers, we regrouped the sleep variables into binary groups (up to 6 hours of sleep vs 6 hours or more, and the presence or absence of reported sleep problems). Multiplicative and additive evidence for statistical interaction were examined. The relative excess risk due to interaction (RERI) was calculated,[27] which is the increase in hazard due to both exposures (short sleep and sleep problems) minus the sum of the increased risks due to 1 factor alone.

RESULTS

Table 1 shows the distribution of the main variables in the analysis by sleep duration. Shorter sleep duration is associated with higher CHD risk and risk factors, greater sleep disturbances, older age, and greater BMI and is more common among women.

Table 2 shows the association among sleep hours, sleep disturbances, and CHD, stratified by sex. Among men and women, sleeping 5 hours or less, compared with 7 hours of sleep, was as-

sociated with an increased HR of CHD events. Sleeping 8 hours or more was not associated with an increased HR (we could not analyze data from those who slept 9 hours or more separately because there were too few CHD cases in this group). Sleep disturbance in terms of losing sleep over worry and having restless or disturbed nights was also associated with increased HR of CHD. There was little evidence for any sex difference in the effects of these sleep variables on CHD, so data from men and women were combined for the multivariate analyses in Table 3.

We also stratified the analyses by BMI category (normal vs overweight—analyses not shown). There was little evidence that the sleep variables differed by BMI category; the effect of short sleep duration and sleep disturbance on CHD HR was similar in both groups. Hence, the data were pooled for the multivariate analyses in Table 3.

Table 3 shows the multivariate analyses of the effect of the sleep variables on CHD among both men and women combined. Short sleep (< 5 and between 5 and 6 hours) was associated with higher HR of CHD, compared with those sleeping 7 hours. Those who "lost sleep over worry" and "had restless disturbed nights" had increased HR compared with those who did not report any sleep problems. After adjustment for potential confounders (age, sex, ethnicity, socioeconomic position, and all if the sleep variables), there was an increased hazard for those reporting less than 5 hours of sleep, but this was not statistically significant. Only the reporting of restless disturbed nights was significantly associated with an increased hazard. Adding potential mediators such as biologic and behavior CHD risk factors reduced the effect of short sleep, and having restless disturbed nights remained significantly associated with CHD.

There was some evidence of an interaction effect between short sleep hours and sleep disturbance (Table 4). Short sleep alone was not associated with any increased risk of CHD if the participant did not report any problems with restless disturbed nights. However, those who reported sleeping less than 6 hours and reported restless disturbed sleep had an increased hazard (HR = 1.6, 95% CI = 1.3-1.8) compared with those who reported sleeping longer and better. Although there was weak evidence for multiplicative interaction (P = 0.12), there was some evidence of additive interaction. The RERI was greater than 0, implying an increased risk due to an additive interaction between short sleep and restless disturbed nights. After adjusting for confounders (age, sex, ethnicity and socioeconomic position), the RERI was borderline significant.

Table 1—Distribution of key variables in the analyses by sleep duration

	Sleep duration, h				P	
Variable[a,b]	≤ 5	6	7	8+	Value	No.
Age, y[a]	46.2	44.9	44.2	44.0	< 0.001	10,264
BMI, kg/m^2[a]	25.4	25.0	24.4	24.5	< 0.001	10,251
Total cholesterol, mmol/L[a]	6.04	5.98	5.94	5.95	0.22	10,221
Incident CHD[b]						
All	18.0	14.7	12.4	12.3	< 0.001	9841
Validated	10.4	7.9	7.4	7.6	0.14	10,155
More than usual "Lost Sleep over Worry"[b]	31.1	17.5	12.5	10.6	< 0.001	10,234
More than usual "Restless Disturbed Nights"[b]	38.7	26.6	18.8	16.4	< 0.001	10,232
Women[b]	44.5	32.6	30.7	38.1	< 0.001	10,264
Non-White ethnicity[b]	16.3	10.9	9.0	15.2	< 0.001	10,264
Current smokers[b]	23.3	20.4	17.4	16.5	< 0.001	10,256
Hypertensive[b]	13.1	8.7	7.2	8.1	< 0.001	10,256
Diabetes[b]	1.9	0.8	0.9	0.9	0.15	10,191
Poor self-rated health[b]	12.0	5.3	4.2	5.3	< 0.001	10,230
Heavy drinkers[b]	16.7	16.4	16.0	13.3	< 0.05	10,173
No vigorous exercise[b]	66.4	59.3	54.3	59.8	< 0.001	9925
No moderate exercise[b]	27.1	16.5	13.8	17.2	< 0.001	10,037
< Recommended daily fresh fruit & vegetable intake[b]	45.2	43.1	31.3	40.2	0.08	10,235

Data are presented as mean[a] or percentage[b]. BMI refers to body mass index; CHD, coronary heart disease.

Table 2—Association between sleep duration and sleep disturbance with CHD: stratified by sex

	Men			Women			P Value for interaction of sex
Usual sleep duration, h	Persons at risk, no.	CHD, no.	Unadjusted[a]	Persons at risk, no.	CHD, no.	Unadjusted[a]	
≤ 5	254	47	1.66 (1.23, 2.25)	202	35	1.39 (0.97, 1.98)	0.47
6	1836	261	1.21 (1.03, 1.41)	868	137	1.21 (0.97, 1.50)	0.97
7	3459	417	1.00	1522	201	1.00	
≥ 8	1052	132	1.06 (0.87, 1.28)	648	77	0.91 (0.70, 1.18)	0.38
Lost sleep over worry							
Not at all	2809	324	1.00	1163	146	1.00	
No more than usual	2954	394	1.17 (1.01, 1.36)	1519	211	1.11 (0.90, 1.37)	0.95
More than usual	855	141	1.48 (1.22, 1.80)	552	93	1.36 (1.05, 1.76)	0.92
Restless, disturbed nights							
Not at all	2326	246	1.00	1024	124	1.00	
No more than usual	3000	388	1.24 (1.05, 1.45)	1404	196	1.19 (0.95, 1.49)	0.96
More than usual	1291	225	1.69 (1.41, 2.03)	805	130	1.33 (1.04, 1.70)	0.79

[a]Data are presented as relative risk (95% confidence interval). CHD refers to coronary heart disease.

Sensitivity analyses were carried out using a stricter definition of CHD—only including cases of MI and angina when they were verified by clinical records (i.e., eliminating participants with CHD diagnoses obtained from only questionnaire data). The overall pattern remained very similar, and all of the associations reported in Tables 1 to 3 remained statistically significant. Furthermore, there was stronger evidence for both multiplicative and additive interaction effects between short sleep and sleep problems (Table 4).

Table 3—Multivariate analyses between sleep duration and sleep disturbance with CHD mortality, myocardial infarction, and angina: data from men and women combined

Usual sleep duration, h	Persons at risk, no.	Incident CHD, no.	Unadjusted[a]	Adjusted for confounders[a,b]	Adjusted for confounders & mediators[a-c]
≤ 5	411	69	1.55 (1.23, 1.96)	1.20 (0.95, 1.52)	1.05 (0.92, 1.20)
6	2475	370	1.20 (1.06, 1.36)	1.10 (0.97, 1.25)	0.98 (0.83, 1.16)
7	4584	579	1.00	1.00	1.00
≥ 8	1528	187	1.01 (0.86, 1.18)	1.02 (0.87, 1.19)	0.99 (0.77, 1.27)
Lost sleep over worry					
Not at all	3633	434	1.00	1.00	1.00
No more than usual	4080	554	1.15 (1.02, 1.30)	1.02 (0.88, 1.17)	0.97 (0.84, 1.13)
More than usual	1285	217	1.44 (1.23, 1.69)	1.04 (0.84, 1.29)	1.02 (0.82, 1.28)
Restless, disturbed nights					
Not at all	3063	340	1.00	1.00	1.00
No more than usual	4019	538	1.21 (1.06, 1.38)	1.17 (1.01, 1.37)	1.15 (0.98, 1.35)
More than usual	1916	327	1.55 (1.34, 1.79)	1.49 (1.22, 1.82)	1.36 (1.10, 1.68)

[a]Data are presented as relative risk (95% confidence interval); [b]Confounders include all of the sleep variables, age, sex, ethnicity, employment grade, car access, and housing tenure; [c]Mediators include self-rated health status, total cholesterol concentration, hypertension, body mass index, diabetes, smoking, alcohol consumption, vigorous and moderate exercise, and fruit and vegetable consumption. CHD refers to coronary heart disease.

Table 4—Interaction effects between short sleep and having restless/disturbed nights on the hazard of CHD

Exposure	Unadjusted	Adjusted for confounders[a]	Adjusted for confounders & mediators[a,b]	No.
> 6 h sleep and no sleep problems	1.00	1.00	1.00	2335
< 6 h sleep only	1.04 (0.82, 1.31)	1.01 (0.80, 1.28)	0.98 (0.77, 1.25)	794
Restless/disturbed nights only	1.21 (1.05, 1.40)	1.23 (1.07, 1.43)	1.17 (1.01, 1.35)	3893
< 6 h sleep & disturbed nights	1.55 (1.33, 1.81)	1.45 (1.24, 1.70)	1.28 (1.08, 1.51)	2122
Interaction between short sleep hours and sleep problems using ALL CHD events				
P value for multiplicative interaction	0.12	0.24	0.46	9144
RERI	0.30 (0.01, 0.59)	0.21 (-0.08, 0.49)	0.12 (-0.16, 0.40)	9144
Interaction between short sleep hours and sleep problems using verified CHD events				
P value for multiplicative interaction	0.02	0.03	0.10	9429
RERI	0.46 (0.14, 0.77)	0.37 (0.06, 0.68)	0.26 (-0.04, 0.57)	9429

Data are presented as relative risk (95% confidence interval).
[a]Confounders include all of the sleep variables, age, sex, ethnicity, employment grade, car access, and housing tenure; [b]Mediators include self-rated health status, total cholesterol concentration, hypertension, body mass index, diabetes, smoking, alcohol consumption, vigorous and moderate exercise, and fruit and vegetable consumption. CHD refers to coronary heart disease; RERI, relative excess risk due to interaction.

DISCUSSION

The present study has found evidence from a longitudinal, large-cohort study that short sleep duration and sleep disturbance increase the risk of CHD independently of each other, among women and men. However, after adjusting for confounders, only participants with restless disturbed sleep had higher HR of CHD. The present study also found some evidence that sleep hours and sleep disturbances interact, so that the effect of short sleep hours on CHD is greatest among those with restless or disturbed nights. Among participants who did not report any sleep disturbance, there was little evidence that short sleep hours increased CHD risk.

The finding that inadequate or disturbed sleep increases CHD risk has been previously shown.[11-18] However, these results were not consistent among men and women and also differed by CHD measure. In the present study, we combined CHD outcomes more typical for men (MI, CHD-related mortality), as well as for women (angina pectoris). Previous analyses finding sex-specific effects of sleep on CHD may not have been reliable due to small numbers of CHD (MI) cases among women.[16,17] The combination of CHD outcomes appears to eliminate the sex differences in the association between sleep duration and disturbance and CHD risk.

The increase in CHD risk associated with short sleep duration and sleep disturbance was similar in the bivariate analyses. However, after controlling for a number of CHD risk factors, only disturbed sleep remained a predictor of incident CHD. This is a novel finding. Thus, the present study extends previous findings from the same population on increased CHD risk due to short sleep duration[14] and sleep disturbance.[28]

The second finding in our study is the suggestion that the interaction of short sleep and sleep disturbances results in even better CHD-risk prediction than do these indexes studied separately. This finding suggests that disturbances of the physiologic processes during sleep, rather than sleep duration itself, might be crucial for increasing CHD disease risk. Disturbances in the restoration of energy resources and repair and regeneration of tissue, as well as conservation of energy and rest

in some bodily systems,[29,30] is probably not related to only the short sleep duration. For some people, short sleep duration may be adequate enough for such restorative physiologic processes. On the other hand, complaints about sleep problems are quite widespread and often poorly related to the more objective polysomnographic measurements of sleep.[31] Thus, the combination of information about sleep duration and sleep difficulties may be a better indicator of physiologic disturbances while people are asleep.

We can only speculate about the mechanisms between chronically disturbed and shortened sleep and the increased risk for CHD in this study, since we have no direct measures of sympathetic activity or immune function measured at baseline in the study. Disturbed sleep may contribute to the increased risk by an inability of the organism to diminish sympathetic stimulation of the cardiovascular system at night and, thus, prevent rest and restoration.[32] It may also act through disturbances of the immune function and promote inflammation in the cardiovascular vessels.[33] Disturbed sleep may also increase cholesterol concentrations, blood pressure, and blood glucose concentrations,[34] all of which are risk factors for CHD.

This study has several important limitations. One is the self-reported nature of the data measuring sleep hours and sleep disturbances. However, it is not feasible to obtain more detailed and objective measures of sleep, such as sleep diaries, actigraphs, and polysomnography, from large populations. Small-scale investigations have shown high correlations between subjective estimates of sleep duration and diary, actigraph, or polysomnography data.[35,36] There is also a tendency in the general population to report more subjective sleep problems than are measured objectively.[30]

We used different measures of self-reported sleep disturbance and each showed similar associations with CHD. Another serious limitation is the absence of information about the presence of sleep apnea among our participants. However, the estimation of the frequency of clinically verified sleep apnea in the general population is about 0.5% to 1.5%,[37] whereas, in our study, the prevalence of disturbed sleep (more than usual) ranged from 14% to 21%. Second, since the prevalence of sleep apnea in people with a BMI less than 25 kg/m^2 is rare, we repeated our analyses separately in the 2 BMI groups (BMI under and over 25 kg/m^2) and found no differences in the risk estimation. We also included BMI as a covariate in our analysis. Finally, patients with sleep apnea often complain about tiredness rather than short sleep or sleep difficulties,[38] so there may not be a strong correlation between sleep apnea and the sleep-disturbance questions used in this study.

Although the rates of CHD in working populations has declined considerably in Western countries, this progress may be hampered by an increasing trend to shorten sleep hours and increased complaints about disturbed sleep.[1] The sources of both these sleep disturbances may be due to extensive work and active leisure time,[39] as well as an inability to unwind before going to sleep[40] due to excessive stress. The effect of short sleep hours ($\leq$ 6 h) on increasing the risk of CHD is greatest among those with restless or disturbed nights. Sleep disturbance may be a more important predictor of CHD risk than is short sleep duration.

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DISCLOSURE STATEMENT

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