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CORRELATION OF SLEEP DEPRIVATION AND INSOMNIA WITH CORONARY HEART DISEASE IN WOMEN: A PROSPECTIVE STUDY AT TERTIARY CARE HOSPITAL FROM NORTH INDIA

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ABSTRACT

Long-term sleep deprivation and insomnia is common in today's society. Recent experiments have demonstrated that short-term sleep deprivation and insomnia in healthy subjects results in adverse physiologic changes including a decreased glucose tolerance, an increased blood pressure and coronary artery disease. Observational studies indicate that insomnia may increase the risk of developing and/or dying from cardiovascular diseases, especially coronary artery disease (CAD). Long-term sleep deprivation and insomnia is common in today's society. The objective of this study was to determine whether decreased sleep duration and insomnia (from self-reports) is associated with an increased risk of coronary events. We studied a cohort of 7150 Indian female health professionals (aged 45-65 years) without reported coronary heart disease (CHD) at baseline, who were enrolled in the Nurses' Health Study at UP University of Medical Sciences(UPUMS), India wef Apr 2008 to Ap 2017(09years) Subjects were mailed a questionnaire in 2008 asking about daily sleep duration. Subjects were followed up until Apr 2017 for occurrence of CHD-related events. We assessed the relationship between self-reported sleep duration and incident CHD. A total of 93 coronary events were documented (27 fatal and 66nonfatal) during the 09 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). Short self-reported sleep duration and insomnia are independently associated with a modestly increased risk of coronary events. Insomnia, which is categorized by insomnia early, insomnia late and insomnia middle, is highly prevalent in adults, especially in the population older than 65 years old The prevalence of sleep deprivation and insomnia symptoms are approximately 30% to 35% worldwide and the effects can be devastating for both patients and society Anecdotal evidence suggests that sleep deprivation and insomnia is related to a range of other disorders, such as anxiety disorders, alcohol abuse and major depression.

INTRODUCTION

Sleep deprivation and insomnia, which is categorized by insomnia early, insomnia late and insomnia middle, is highly prevalent in adults, especially in the population older than 65 years old.[1,2,3,4] The prevalence of insomnia symptoms is approximately 30% to 35% worldwide, and the effects can be devastating for both patients and society.[5,6,7,8] Anecdotal evidence suggests that insomnia is related to a range of other disorders, such as anxiety disorders, alcohol abuse, and major depression[9,10] Earlier evidence suggests an apparent association between insomnia symptoms and cardiovascular diseases under the prospective studies, researchers observed that insomnia increased the risk of adverse cardiovascular outcomes[11,12,13,14]; some researchers reported that insomnia increased the risk of myocardial infarction (MI) and heart failure[15,16,17] Some researchers reported that insomnia is significantly associated with the incidence of

hypertension[18,19,20] while others reported that insomnia moderately influenced the incidence of acute MI[21,22] Recently, a large-scale cohort study from Northern India, indicated that the number of insomnia symptoms was positively correlated with the overall risk of total cardiovascular diseases.[23,24] These results highlighted the importance of high-quality sleep for the prevention of cardiovascular diseases. However, the exact causality between sleep deprivation, insomnia and cardiovascular diseases remains unexplored.Although many epidemiological investigations show that multiple biomarkers are associated with complex diseases, the ability of traditional observational studies in determining whether these factors are causal is limited.

METHOD

Study population

The Nurses' Health Study cohort was established in 2008 when 121 70 females, married, registered nurses, aged 30 to 55 years and residing in north India, completed a mailed questionnaires 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 1990 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, 11 or more hours. Between 07Apr, 2008 and 07Apr 2017, the incidence rates of CHD-related events were assessed in the 71 61 women aged 40 to 65 years who answered these questions and were not diagnosed as having cardiovascular disease in 2017 .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 1990 questionnaire but before 07 Apr 2017. We requested permission to review medical records from women who reported having a nonfatal MI on a follow-up questionnaires. A nonfatal MI was confirmed if data in the record met the criteria of the World Health Organization[25] 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 estimated that follow-up for the deaths was more than 98% complete[26] 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 2 hour of the onset of symptoms). We included all confirmed and presumed fatal CHD cases plus those with sudden death in these analysis.

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. 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[27] 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, aspirin use, parental history of MI before the age of 60 years and a history of hypercholesterolemia. We also controlled for the duration of night shifts worked. This information was ascertained from the 1990 questionnaires 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, 1-3, 4-6, and ≥09 years). We did not control for a history of hypertension or diabetes mellitus in the primary analysis because decreased sleep duration may be associated with the development of hypertension or diabetes mellitus[28,29] Thus, the development of hypertension or diabetes mellitus may be an intermediate step in the causal pathway between decreased sleep duration and cardiovascular disease.

RESULT

The primary analysis was the ascertainment of incident CHD-related events during the 09-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. 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. 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, 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 sleepers. 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.

DISCUSSION

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.Our findings are consistent with and extend those of other investigators. Wingard and Berkman[4,14,29,32] 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 etal[2,22,32] 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.[28] 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 al 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 duration 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 al[6,16,26] 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 data[11,13,22,25] 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 predict a 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 relationship. Thus, the association of increased sleep duration and CHD remains unexplained 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 study[4,14,24] demonstrated little difference in the RRs of death in men and women from a decreased sleep time and another[23,27,31,32] 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 09-year study period. Nevertheless, questions about self-reported sleep duration have been investigated in other studies[29,30], 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 observational 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.

CONCLUSION

Long-term sleep deprivation is common in today's society. According to the 2001 National Sleep Foundation poll, approximately 31% of Indians 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. 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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