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**A population-based Study of Short Sleep Duration and Hypertension:
the Strongest Association may be in Pre-Menopausal Women**

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ABSTRACT

Background: Recent evidence indicates that short sleep duration may be associated with an increased risk of hypertension with possibly stronger effects among women than men.

Objectives: To examine the cross-sectional gender-specific associations of sleep duration with hypertension in a large population-based sample from the Western New York Health Study (1996-2001).

Methods: Participants were 3,027 white men (43.5%) and women (56.5%) without prevalent cardiovascular disease (median age: 56 years). Hypertension was defined as blood pressure ≥ 140 or ≥ 90 mmHg or regular use of antihypertensive medications. Multivariable logistic regression analyses were performed to calculate odds ratios (OR) of hypertension comparing short (<6h) duration of daily sleep versus the midrange category (6-8h), while accounting for a number of potential confounders [i.e., age, marital status, annual household income, education, body mass index, waist circumference, physical activity, alcohol consumption, smoking habits, SF-36 mental and physical scores, and depressive symptoms).

Results: In multivariate analyses, short duration of sleep was associated with a significant increased risk of hypertension compared to sleeping 6-8h per day, only among women (OR=1.61 [1.08 to 2.41]). No significant associations were found among men (OR=0.88 [0.59 to 1.32]). In subgroup analyses by menopausal status, the effect was stronger among pre-menopausal women (OR=2.77 [1.23 to 6.25]) as compared to post-menopausal counterparts (OR=1.40 [0.88 to 2.23]).

Conclusion: Sleep deprivation, by increasing the risk of hypertension, may produce detrimental cardiovascular effects among women. The association is independent of socioeconomic status, traditional cardiovascular risk factors, and psychiatric co-morbidities, and is stronger among pre-menopausal women. However, prospective and laboratory evidence is necessary to support causality.

INTRODUCTION

Growing evidence indicates that sleep deprivation is associated with a number of health outcomes including hypertension (1-6). For example, in a prospective analysis of the first National Health and Nutrition Examination Survey (NHANES-I), short sleep duration (≤ 5 h per night) was associated with a 60% higher risk of incident hypertension in middle-aged US adults without apparent sleep disorders, during a mean follow-up of 8-10 years (7). In agreement with this, in a cross-sectional analysis from the Sleep Heart Health Study on a large sample of US adults there was a 66% higher prevalence of hypertension, among short sleepers (< 6 hours per night) (8). Finally, a recent analysis from the Whitehall II Study showed potential gender differences in the association of short sleep duration with the risk of hypertension, with stronger effects among women than men (9). These findings raise further concern that reduced durations of sleep might be associated with detrimental effects on cardiovascular outcomes among women, as supported by several independent studies (10-13).

While the relation of sleep-disordered breathing (SDB) with elevated blood pressure and risk of hypertension is well established even in terms of biological plausibility (14-18), the patho-physiological mechanisms underlying the association between sleep deprivation and hypertension are less clear, especially with regard to potential gender-specific effects.

In the present analysis we sought to examine the cross-sectional gender-specific associations of sleep duration with hypertension in a large population-based sample from the Western New York Health Study (1996-2001), with the inclusion of a number of potential confounding variables. Unlike previous studies, we performed subgroup analyses by menopausal status among women to provide further insights into potential mechanisms for the observed stronger effects of sleep deprivation on the risk of hypertension among women.

METHODS

Study population

Participants in this report were originally enrolled as healthy control participants in the Western New York Health Study (WNYHS), a series of case-control studies to examine the complex issue of alcohol drinking pattern and chronic disease risk, as described in detail elsewhere (24). The following eligibility criteria were used to identify potential controls: 1) residents of Erie and Niagara Counties; 2) age 35-79 years; 3) no cancer. Potential participants were identified through two sources: a) Department of Motor Vehicles of New York State for participants aged 35 to 64 years. This source was used because it is known that 95% of New York residents in this age group have a driver license; b) Health Care Financing Administration (HCFA) lists for participants aged 65 to 79 years. This source was used because it includes virtually all individuals in the age range of interest. Between 1996 and 2001, a total of 6,837 potential participants were identified, contacted and deemed eligible for the study. Of these, a total of 4,065 agreed to participate and were examined, for a participation rate of 59.5%. For the present analyses, participants from ethnic groups other than white were excluded ($n=381$), as well as those with missing sleep data ($n = 657$). The remaining 3,027 participants (56.5% women), aged 35-79 years (median: 56 years), were included in this study.

Sleep duration

Sleep duration in the past week was ascertained with the Seven-Day Physical Activity Recall questionnaire (25) by the question “On the average, how many hours did you sleep each night during the last five weekday nights (Sunday-Thursday)?”. Response categories were collapsed in three main groups: short sleep duration (< 6 hours), normal sleep duration (6-8 hours), and long sleep duration (> 8 hours). This classification is consistent with those employed in the

majority of previous studies on the health effects of habitual sleep duration (1-12).

Covariates

The following correlates were examined: marital status, education, annual household income (SES), body mass index (BMI) and waist circumference, smoking and drinking habits, physical activity, SF-36 physical and mental health scores, and depressive symptoms.

Marital status was categorized as married/unmarried. As a proxy measure of current or recent socioeconomic status, annual household income was used and divided in three categories in order of decreasing income: >\$70,000, \$30,000-70,000, <\$30,000. Several anthropometric measures were made, including height, weight, and waist circumference. Body mass index (BMI) was calculated as weight in kilograms (kg)/height in meters (m²). Smoking status was divided in two categories: current smoker/non-current smoker. Current alcohol consumption was recorded in the previous 30 days. Current physical activity in the past week was ascertained with the Seven-Day Physical Activity Recall questionnaire used in the Stanford Five-City Project (25). General health status was assessed using the physical and mental health component summaries of the Short Form-36 (SF-36) health survey questionnaire (26). These summary measures are standardized as *t*-scores and have higher reliability than the individual scales. The presence of depressive symptoms was assessed by using the Center for Epidemiologic Studies Depression Scale (CES-D) (27); participants were divided in two groups based on the cut point for major depressive symptoms (score ≥ 22). Diabetes was defined either as fasting glucose ≥ 126 mg/dl (≥ 7.0 mmol/L) or use of antidiabetic medications

Hypertension

Blood pressure was measured three times in the sitting position using a standard mercury sphygmomanometer by trained and certified technicians. The onset of the first phase (systolic) and fifth phase (diastolic) Korotkoff sounds were recorded. The mean of the second and third measures were used in the analyses. Hypertension was defined as blood pressure $\geq 140/90$ mmHg or regular use of antihypertensive medications.

Ethical approval

Ethical approval was obtained from the University at Buffalo Institutional Review Board.

Statistical analysis

For continuous and categorical variables, respectively, Kruskal Wallis and χ^2 tests were used to determine the statistical significance of any difference in the distribution of baseline variables at phase 5 across categories of sleep duration. The statistical significance of the interaction between each baseline characteristic and sleep duration, adjusted for other important baseline variables, was tested in multivariate logistic regression models that included this interaction and the corresponding main effect terms. The interaction between sleep duration and gender was significant ($p < 0.05$), therefore all analyses were stratified by gender. No significant interactions were found between sleep duration and age or other relevant covariates. Univariate and multivariate regression analyses were conducted to test the association between categories of sleep duration and prevalent hypertension. Covariates included: baseline age, employment, alcohol consumption, smoking, physical activity, BMI, CVD drugs (other than antihypertensive medications), the SF-36 mental and physical health component scores, depression, and use of hypnotics. In these analyses, 7h of sleep was selected as the reference category. All techniques were implemented using STATA 9.0.

RESULTS

Descriptives

Characteristics for both male (Table 1a) and female (Table 1b) participants at phase 5 (baseline) are reported by categories of sleep duration. Among men, participants sleeping 9h or more were, on average, older than other participants; in addition, they were less likely to be physically active, and more likely to be under medication for CVD drugs. On the other hand,

male participants sleeping 5h or less had a lower employment status, had higher mean levels of BMI and waist circumference, were more likely to be depressed and under medication for hypnotics, and reported lower scores for mental and physical health than other participants. No significant differences in drinking and smoking habits were reported across categories of sleep duration. For blood pressures, no consistent pattern of association was noted; however, the mean levels of systolic blood pressure (and pulse pressure) as well as the prevalence of hypertension were significantly higher among participants sleeping 8h than in other participants.

Among women, participants at the two extreme categories of sleep duration (ie, 5h or less and 9h or more) were characterized, in general, by a poorer health status and lifestyle profile. In particular, they had a lower employment status, were less likely to be physically active, more likely to be under medication for CVD drugs or hypnotics, more likely to be depressed, and reported lower scores for mental and physical health than other categories. No significant differences in drinking and smoking habits were reported across categories of sleep duration. For blood pressures, there was a consistent pattern of association among female participants sleeping 5h or less, who reported higher mean levels of systolic blood pressure (and pulse pressure) as well as a significantly higher prevalence of hypertension than other participants (in both treated and untreated individuals).

Table 2 displays the odds ratios (OR) and 95% confidence intervals (CI) of prevalent hypertension across categories of sleep duration at phase 5, using 7h of sleep as the reference category. Among men, no consistent pattern of association was noted. Among women, in fully adjusted analyses short duration of sleep (≤ 5 h per night) was associated with a significant higher risk of hypertension compared to the group sleeping 7h (OR 2.01; 95% CI 1.13 to 3.58), independent of several potential confounders, with a significant inverse linear trend across decreasing hours of sleep ($p=0.003$).

Other analyses

We also carried out linear regression analyses to test the association between sleep duration and blood pressures (systolic, diastolic, and pulse pressures) at phase 5 (cross-sectional analyses), as well as the association between sleep duration at phase 5 and changes in blood pressures between the two phases (prospective analyses), among participants not taking antihypertensive medications. In cross sectional analyses, there were consistent, significant inverse associations ($p < 0.05$) between duration of sleep and either systolic blood pressure ($\beta = -1.24$ mmHg per h sleep; 95% CIs, -2.23 to -0.24) or pulse pressure ($\beta = -0.91$ mmHg per h sleep; -1.63 to -0.20), only among women, in fully adjusted models. In prospective analyses, no significant associations were found for any of the blood pressure measures among either male or female participants (data not shown).

DISCUSSION

Findings from the Whitehall II cohort showed gender-specific associations between sleep duration and hypertension. Specifically, short duration of sleep was associated with higher risks of prevalent and incident hypertension only among women. We could not detect consistent associations among men or for long duration of sleep. For the latter finding, it should be noted, however, that there were very few individuals (~1.3% of the overall sample) in our study who reported sleeping 9h or more per night thus yielding a limited statistical power to examine the association between sleep duration and hypertension in this subgroup. Furthermore, our findings point to the importance of a comprehensive scrutiny of potential confounders and mediators when examining the associations between durations of sleep and health outcomes. In fact, the observed associations among women were attenuated after accounting for a number of cardiovascular risk factors, measures of general health, and psychiatric co-morbidities.

A substantial amount of evidence exists about the link between sleep-disordered

breathing (SDB) and hypertension (1-5). The epidemiological data has been corroborated by findings of mechanistic studies emphasising the critical role of sympathetic overactivity in the aetiology of SDB-related hypertension (24-25), although other mechanisms are likely to be involved (19). More recently, sleep deprivation has been indicated as a risk factor for several chronic health outcomes in individuals without overt sleep disorders (6-12). However, we are aware of only two population-based studies so far, both coming from the US, that have attempted to examine the association between self-reported durations of sleep and risk of hypertension (13-14). Specifically, in a longitudinal analysis of the NHANES-I (n=4,810), short sleep duration (≤ 5 h per night) was associated with a 60% higher risk of incident hypertension, in fully adjusted models, among middle-aged (32-59 years) American adults without apparent sleep disorders (13). No association was found in individuals 60 years of age or older. However, in this study the diagnosis of incident hypertension was based on self-report with a potential of misclassification (under-diagnosis), as suggested by a lower cumulative incidence ($647/4,810 = \sim 13.5\%$) as compared to that observed in our study ($740/3,691 = 20.0\%$), despite comparable age-ranges between the two studies and a longer follow-up period in the NHANES-I (8-10 years vs. 5 years, respectively). In addition, no gender-specific analyses were included in the NHANES-I. Moreover, in a cross-sectional analysis of the large sample of the Sleep Heart Health Study ($\sim 6,000$ US adults) a significant higher prevalence of hypertension was reported among either short (< 6 h per night) or long sleepers (≥ 9 h per night) as compared to the median duration of sleep of 7 to less than 8h per night (14). However, the association was stronger among short sleepers than in long sleepers (ie, 66% vs. 30% higher risk of hypertension, respectively). While this study accounted for a number of potential covariates including psychiatric and cardiovascular co-morbidities, the cross-sectional design does not allow to exclude the possibility of residual confounding by unknown variables as well as to exclude the potential of reverse causality. In addition, the Sleep Heart Health Study sample was, on average, older than both NHANES-I and Whitehall II, thus with a higher

likelihood of geriatric co-morbidities potentially affecting sleep patterns (26).

Strengths

Unlike these earlier investigations, our study examined both cross-sectional and prospective gender-specific associations between sleep duration and hypertension with the inclusion of a number of potential confounding variables. Our findings suggest a potential role of sleep deprivation in the aetiology of hypertension and other adverse health outcomes.

First, the observation that reduced duration of sleep may be associated with a higher risk of hypertension only among women is a novel finding. Indeed, while previous investigations have emphasized the potential impact of both short and long durations of sleep on chronic disease risk among women (6-9), the mechanisms underlying the gender-specific association between sleep deprivation and hypertension, observed in our study, are unknown. Given the mean age of our female participants falling around the menopausal period (~ 55 years), we can speculate that the periods marking shifts in the reproductive stages, such as menopause, are particularly vulnerable times for women, because they are associated with major hormonal turmoil and psychosocial stresses that may in turn lead to adverse health outcomes (27). For example, in our sample of female participants, the prevalence of depression cases was higher among women reporting short duration of sleep (≤ 5 h per night) than in other subgroups. In addition, as shown in our descriptive analyses, the distribution of correlates of short sleep duration that have the potential to affect hypertension risk was different between genders and may have partially contributed to the observed associations. Finally, we cannot rule out the possibility of differential self-reporting of sleep habits between men and women, as suggested in a previous analysis from the Sleep Heart Health Study examining the relationship of gender to subjective measures of sleepiness (28).

Second, while findings from cross-sectional analyses consistently showed a strong, significant association between short sleep duration and risk of hypertension among women, in

prospective analyses the risk estimates were attenuated after accounting for cardiovascular risk factors, measures of general health, and psychiatric co-morbidities. Thus, these findings emphasize the importance of a comprehensive examination of correlates that are likely to confound or may be on the causal pathway between sleep deprivation and adverse health outcomes. Nevertheless, recent prospective analyses from the MONICA Augsburg survey indicate a modest but significant association between short sleep duration and incident myocardial infarction in middle-aged women, but not men, from the general population (29).

Third, our descriptive analyses clearly demonstrate that both short and long duration of sleep may indeed identify population subgroups with a distinct cluster of socio-demographic characteristics, lifestyle behaviours, and disease conditions, that is likely to be affected by the cultural setting in which the research is being conducted (30-33). In this regard, the study of health consequences related to curtailments of sleep seems to be epidemiologically relevant in the general population, given the downward trends in the average duration of sleep and the increasingly higher prevalence of “short sleepers” in many Western countries (34-35). Conversely, it may be difficult for epidemiological studies to examine the health consequences of long durations of sleep in middle-aged, healthy populations, considering the relatively low prevalence of “long sleepers” in the absence of overt psychiatric co-morbidities (36).

Limitations

There are limitations in this study. First, the population under investigation is an occupational cohort of white-collar workers and limited to whites, which may reduce the generalizability of our findings to other populations. However, this would not affect the internal validity of our results with respect to the prospective analyses. Second, information about sleep duration was self-reported by the participants. Nevertheless, self-report assessments of sleep have been shown to be valid measures compared to quantitative sleep assessments with actigraphy (37-38). Moreover, because the outcome was also assessed prospectively, any misclassification of

sleep duration would be non-differential with respect to incident hypertension, thus resulting in underestimation of the true effects. A further limitation of this study is the relatively short time of follow-up (5 years), which may have precluded us from detecting larger and significant effects of sleep deprivation on subsequent hypertension incidence. The strengths of this study include the simultaneous inclusion of a number of covariates known to be related to both sleep patterns and hypertension. A further strength is that the diagnosis of incident hypertension was also based on directly measured blood pressures at both examinations, thus minimizing the potential of misclassification that occurs when using self report alone.

Conclusions

In summary, findings from the Whitehall II cohort suggest gender-specific associations between sleep duration and hypertension risk. Specifically, cross-sectional analyses showed a significant, consistent association between short sleep duration (≤ 5 h per night) and risk of hypertension only among women, which was attenuated in prospective analyses after multivariate adjustment.

Perspectives

Sustained sleep curtailment, ensuing excessive daytime sleepiness and the higher cardiovascular risk are causes for concern. Emerging evidence also suggests a potential role for sleep deprivation as predictor or risk factor for conditions like obesity, diabetes and metabolic syndrome not only in adults (39) but also in children (40). Further prospective studies with improved assessment of long-term exposure (repeated self-reported sleep duration or repeated actigraphy), and better control for confounders are needed before causality can be determined.

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Competing interests

F.P.C. holds the Cephalon Chair, an endowed post at Warwick Medical School, the result of a donation from the company. The appointment to the Chair was made entirely independently of the company and the postholder is free to devise his own programme of research. Cephalon do not have any stake in IP associated with the postholder and the Chair has complete academic independence from the company.

