HHS Public Access

Author manuscript

Am Heart J. Author manuscript; available in PMC 2021 August 31.

Published in final edited form as:

Am Heart J. 2020 May ; 223: 12–22. doi:10.1016/j.ahj.2020.02.006.

Mild Sleep Restriction Increases 24-Hour Ambulatory Blood Pressure in Pre-Menopausal Women With No Indication of Mediation by Psychological Effects

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Abstract

Studies assessing the impact of sleep restriction (SR) on blood pressure (BP) are limited by short study length, extreme SR (<4 h/night), and lack of attention to psychological distress as a possible mediator. A community-based cohort was assembled with 237 women (age 34.1±13.5y; BMI 25.4±5.4kg/m^2) and a randomized, crossover, intervention study was conducted in 41 women (24 completed: age 30.2±6.5y; BMI 24.3±2.8kg/m^2) to determine the causal effect of SR on BP. Sleep was maintained as usual (HS) or reduced by 1.5h/night (SR) for 6wk. In the cohort,

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Trial Registration: Clinicaltrials.gov #NCT02835261 https://clinicaltrials.gov/ct2/show/NCT02835261?recrs=a&cond=sleep&cntry=US&state=US%3ANY&city=New+York&age=1&rank=9

Conflict of Interest

None of the authors have any conflicts of interest to declare. All authors have made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of the data; drafted or revised the manuscript for important intellectual content; approved the final version and agree to be accountable for all aspects of the work reported herein. MPSO and BA had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

associations between sleep and psychosocial factors were evaluated using multivariable models adjusted for demographic and clinical confounders. In the intervention study, in-office BP was measured weekly; ambulatory BP was measured at endpoint. Psychological factors were assessed at baseline and endpoint. Mixed-model analyses with total sleep time (TST, main predictor), week and fraction of time spent in physical activity (covariates), and subject (random effect), were performed. Among the community cohort, higher perceived stress, stressful events and distress and lower resilience were associated with shorter sleep, worse sleep quality, and greater insomnia symptoms ($P<0.05$). In the intervention, systolic BP increased as TST decreased (TST x week interaction, [coefficient ± standard error] −0.0097±0.0046, P=0.036). Wake ambulatory diastolic (−0.059±0.022, P=0.021) and mean arterial pressure (−0.067±0.023, P=0.018) were higher after SR vs HS. Psychological distress variables were not affected by TST and did not mediate the effects of SR on BP. These results suggest that SR influences CVD risk in women via mechanisms independent of psychological stressors.

INTRODUCTION

Short sleep duration (SSD) is increasingly recognized as a risk factor for the development of cardiovascular disease (CVD). The American Heart Association has highlighted strong evidence from meta-analyses for associations between SSD and hypertension, stroke, coronary heart disease, and type 2 diabetes[1]. In particular, the relation between sleep duration and hypertension has been well-studied in epidemiological cohorts and it has been noted that SSD may be more strongly associated with hypertension in younger, versus older, individuals, ≥65 y of age, and women compared to men[2]. Women are especially susceptible to the effects of short sleep on CVD risk. Individuals reporting sleeping <6 h/night had increased risk of noncoronary plaque burden and this was mostly significant in women[3]. However, results from clinical intervention studies of sleep restriction (SR), where sleep duration is controlled, on blood pressure are conflicting. In one study of total sleep deprivation, systolic and diastolic blood pressure (SBP and DBP) were increased by 13 and 7 mmHg, respectively, after a single night without sleep compared to habitual sleep (HS)[4] but in another study of 6 nights of SR (4 h time in bed), blood pressure was not altered relative to an equivalent period of HS under otherwise identical conditions[5]. Although these studies were conducted under short-term, severe SR, Robertson et al. also found no difference in blood pressure in men randomized to a reduction in sleep of 1.5 h/night for 3 wk compared to those randomized to maintain their HS schedule[6]. No study to date has been done to assess the longer-term effects of inadequate sleep on ambulatory blood pressure and none have been performed in younger women.

In addition to sleep, psychological factors including perceived stress, life stressors and symptoms of distress (i.e., depression, anxiety) have also been proposed as contributors to allostatic burden leading to an increased risk of CVD. Exposure to psychological stressors has been associated with cardiovascular and cerebrovascular events in patients at high-risk of the disease but have also been discussed as underlying contributors to lifestyle behaviors that may elevate CVD risk (e.g. smoking, excessive drinking, sedentary behavior, poor diet quality, obesity)[7]. Interestingly, SSD and psychological stress often co-exist. Vgontzas et al. have reported that stress significantly predicted sleep duration in adult men and women[8]

and lack of sleep increased the risk for psychological stress in a large population of Korean adults[9]. The odds of being in the high-risk group for psychological stress was 1.5 in those reporting <6 h of sleep/night compared to those reporting 6-9 h/night. Sleep deprivation has also been shown to affect biomarkers of the stress system (e.g., heart rate variability, cortisol), which suggests that increased stress may help to explain the adverse effects of sleep restriction on BP[10,11]. In general, however, there has been a lack of attention to the bi-directionality of the relation between sleep duration and psychological stress and how their interaction could influence hypertension and CVD risk. Individual differences in reactivity to stressful events exist, and those who possess a phenotype that causes a large change in blood pressure due to exposure to psychological stressors are at increased risk for CVD death[12]. Inadequate sleep may be an underlying factor that increases psychological stress and distress resulting in a rise in blood pressure.

The goal of the present randomized controlled SR intervention was to examine the impact of mild, long-term inadequate sleep, mimicking real-life conditions of short sleepers, on blood pressure and psychological outcomes in pre-menopausal women. We hypothesized that restricting sleep by 1.5 h/night for 6 wk would increase blood pressure and lead to adverse changes in psychological outcomes, and that psychological changes would be a mediator in the pathway from SR to elevated blood pressure. Given that the effects of diet on blood pressure can be achieved within 1 to 4 wk[13], a 6-wk intervention period was considered adequate to exert changes via sleep restriction. Women in this trial were also part of a larger, community-based sample of diverse women across the life span, the American Heart Association Go Red for Women Strategically Focused Research Network community-based study at Columbia University Irving Medical Center (CUIMC), in which we further examined the relation between sleep and psychological factors.

METHODS

Women, age 20-79 years, were enrolled in the community-based study, an ongoing prospective cohort study established as part of the American Heart Association Go Red for Women Strategically Focused Research Network at CUIMC. Women were family members or friends of patients at New York-Presbyterian Hospital or nearby hospitals, living in the neighboring communities, and/or respondents to flyers or online recruitment postings. Bilingual staff members recruited both English- and Spanish-speaking women. The protocol was approved by the CUIMC Institutional Review Board and all women provided informed consent prior to enrolling in the study.

Women enrolled in the randomized, crossover, controlled trial at CUIMC were pre-menopausal women referred from the community-based cohort described above and also separately recruited from the surrounding community. Women from the community-based cohort were provided information about the clinical trial and contacted by the study coordinator if they expressed interest. For the clinical trial, all women were required to have a body mass index (BMI) between 25 and 29.9 kg/m^2 or 20-24.9 kg/m^2 if they had a first-degree family member with obesity, type 2 diabetes, CVD, or other risk factor for CVD. We chose this BMI range to include women who were at risk of CVD while minimizing the likelihood of current chronic disorders. Women were carefully screened for

sleep disorders or depression using standardized questionnaires (low-risk of sleep apnea on the Berlin Sleep Apnea Questionnaire[14]; Pittsburgh Sleep Quality Index ≤5[15], Epworth Sleepiness Scale <12[16], no sleep disorders[17] or significant delayed or advanced sleep phase[18], Beck Depression Inventory II score <13[19]). In addition, all women were required to undergo a 2-wk screening period with actigraphy (GT3X+, Actigraph Corp, Pensacola, FL) to verify adequate sleep duration. To be eligible, women had to sleep, on average, at least 7 h/night with 10/14 nights with sleep duration ≥7 h. The protocol was approved by CUIMC Institutional Review Board and all women provided informed consent prior to their enrollment in the study. This project is registered on clinicaltrials.gov (NCT02835261).

Upon successful screening into the study, women were randomized to either SR or HS for 6 wk. The alternate sleep duration phase was performed after a 6-wk washout period. Target bedtimes and wake times during HS corresponded to average bed and wake times during the screening period. For SR, the goal was to achieve a 1.5 h reduction in total sleep time by delaying bedtimes. Sleep was monitored using wrist actigraphy (Actigraph GT3X+), enhanced by daily sleep diaries, throughout each 6-wk period and verified weekly; adjustments were made to ensure adherence sleep duration targets.

Anthropometric and blood pressure measurements were taken weekly. Blood pressure was measured twice, on the left arm, after a 5-min resting period, in a seated position with legs uncrossed using an automated blood pressure monitor (OnTrak, Spacelabs Healthcare, Snoqualmie, WA). The two measures were averaged for data analyses. In addition, in the last week of each study phase, women were fitted with an ambulatory blood pressure monitor (model 90227, Spacelabs Healthcare) for 24 h. Only endpoint assessments were performed to reduce participant burden. The monitor was set to record every 30 min throughout the day and night. Erroneous or missed readings were repeated after a 2-min interval. Wake and sleep periods were defined based on each participant's bedtime and wake time in each study phase. A successful wake blood pressure report was defined as having at least 10 successful readings during wake and 5 during night[20]. Some women (n=7) performed this test outside of the intervention period for SR and those data were not included in the analyses.

Psychological Measures

Psychological measures for both studies were secondary outcomes, which were added after the onset of each study. Participants in the community-based cohort completed a brief battery of 5 questionnaires assessing levels of perceived stress, stressful events, depressive symptoms, and psychological resilience. The Perceived Stress Scale (PSS-4) consists of 4 items assessing the degree to which situations in one's life are appraised as stressful during the previous month[21]. The Global Perceived Stress Scale assesses chronic stress experienced throughout the previous year[22]. A 4-item subset of the 8-item original measure (GPSS-4) was used to assess chronic stress related to work, relationships, caregiving and meeting basic needs. The Life Events Checklist (LEC) addresses 8 stressful events that participants may have experienced after turning age 18 (e.g. divorce, victim of violence or abuse, major financial crisis)[23,24]. The two-item Patient Health Questionnaire (PHQ-2) is a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) and has been used to determine depression levels in the past two weeks[25]. The 6-item Brief

Resilience Scale (BRS) assesses one's ability to rebound from difficult situations using a 5-point scale[26].

Women in the clinical trial completed the Brief Resilience Scale, the Patient Health Questionnaire 2, and the 10-item Perceived Stress Scale[27] at baseline (n=22 for SR and 22 for HS) and endpoint (n=23 for HS and 24 for SR) of each study phase. They also completed the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) subscale, which uses seven items to assess levels of anxiety symptoms[28].

Statistical Analyses

For the community-based cohort data, psychological variables were used as continuous variables; sleep variables were dichotomized as follows: sleep duration (<7 vs ≥7 h/night)[29], sleep quality (Pittsburgh Sleep Quality Index Score >5 vs ≤5)[15], insomnia symptoms (Insomnia Severity Index score ≥8 vs <8)[30], obstructive sleep apnea (Berlin Questionnaire score "high risk" vs "low risk")[14], and presence of snoring (yes vs no). Multivariable logistic regression models were used to evaluate associations between psychological and sleep variables; age, race/ethnicity, menopausal status, marital status, health insurance, BMI, and history of chronic illness were used as covariates in the model. Data were analyzed using R and SAS version 9.4.

Sleep during each intervention period was characterized using actigraphy data informed from nightly sleep diaries. Total sleep duration was the total amount of time that women spent asleep at night. Sleep onset latency (SOL) is the time taken to fall asleep (difference between time in bed from sleep diary data and actigraphy-assessed sleep [10 min of continuous detected sleep]). Wake after sleep onset (WASO) is the total amount of time, detected by actigraphy, that the participant is awake after the first 10-min period of continuous sleep. Sleep efficiency is the percent of time in bed that is spent sleeping.

Data from the clinical trial were analyzed using linear mixed-model analysis, with sleep (HS vs. SR) as the main predictor, and separately with total sleep time (TST) as the main predictor. Separate analyses were also done with and without adjusting for fraction of time spent in physical activity (activity counts divided by actigraph wear time) as a covariate. Subject was used as a random effect. Blood pressure and psychological variables were treated as continuous outcomes. Phase and week (for in-office BP measurements) were used as covariates. In each case, an initial analysis was performed to detect phase effect, carryover (phase x sleep), and any interaction of sleep x week, whenever data were recorded for multiple weeks. Other than sleep, week, and their interaction, terms that were not significant were removed from the final models. Baseline blood pressure values for phase 1 for one participant were considered outliers (>30% lower than values at week 1 and at baseline of phase 2) and were excluded from the analyses. For both SBP and DBP, partial-eta-squared for sleep (HS vs SR) was 0.02. Additionally, between-group Cohen's d for 24-hour SBP and DBP were 0.260 and 0.269 respectively. One woman had 5 successful ABPM readings during the waking period. Removing her from our analyses did not change our interpretation and her data were kept in the analyses reported herein. Data reported in the text are from TST predictor analyses adjusted for physical activity. Data for psychological variables were not adjusted for physical activity because we could not include both week and physical

activity in the models. Data in tables and figures are unadjusted raw means±SD by phase (HS vs SR). Results of all analyses are presented in Supplemental Table 1.

Mediation analysis was performed with Baron and Kenny's method[31] as well as with other methods. Each blood pressure and psychological outcome pair for which each measure was separately significantly affected by sleep, was considered for potential mediation of the effect of sleep on blood pressure by the psychological outcome. All analyses were done as linear mixed-effect models with subject as a random effect, and fraction of time in physical activity as a covariate. If any other independent variables (such as phase and carryover effects, interactions with covariates) were kept in the analyses reported above, they were also kept as independent variables for the mediation analyses.

In addition to Baron and Kenny's method for mediation analyses, we have performed a variety of other methods to investigate mediation: Sobel Test, Path Analysis/Structural Equation and Bootstrapping using R. However, none of the psychological factors had a significant mediation effect between sleep and any of the BP measures (Supplemental table 2). Data reported below are from the Baron and Kenny method, as well as direct and indirect effects, proportion of effects mediated, goodness-of-fit chi-square, and p-value from path analysis.

We investigated the missingness pattern of the data, separately for each analysis, and concluded that most data are missing completely at random (MCAR). (That is, the missingness is not associated with any data related to the study.) For MCAR, the observed data are not biased due to missing values, and consequently, we have performed complete case analysis. That is, we have excluded the missing part for each analysis. Data were considered significant at a P-level <0.05 and are reported as raw means±SD. All analyses were done using R version 3.6.0, with packages Ime4, ImerTest, nlme, Pwr, sem and multilevel.

RESULTS

Study Participants

Our community-based cohort (n=237) was diverse, with ~70% of the participants identified as a racial and/or ethnic minority, and the mean age was 34.1±13.5 y (Table 1). A total of 33 pre-menopausal women were enrolled in the clinical trial and 24 completed both phases (Table 2). These women were part of the community-based cohort. Of the 9 women who failed to complete both phases of the study, 6 were excluded by the investigators for failing to adhere to the sleep schedule (SR, n=3; HS, n=3), starting shift work (exclusionary criterion for the study, n=1), becoming a caregiver (n=1) and vaso-vagal response lasting <2 s during a baseline procedure (n=1).

Sleep Duration

Per protocol, women in the clinical trial had excellent adherence to the sleep duration requirements in both HS and SR (Figure 1). Average sleep duration, measured with actigraphy, over each 6-wk phase was 7.58±0.53 h/night during HS and 6.17±0.52 h/night during SR (P< 0.0001). SOL was shorter during SR relative to HS (SOL: 4.21±4.12

vs 6.15±5.18 min, *P*=0.016) but there was no difference in WASO or sleep efficiency between phases (WASO: SR: 32.0±18.1 vs HS: 41.7±20.5 min; *P*=0.17; sleep efficiency: SR: 91.3±3.8% vs HS: 90.6±4.0%, *P*=0.90).

Blood Pressure

Blood pressure data from the community-based cohort have been reported previously[32]. Briefly, higher sleep apnea risk score, assessed by the Berlin questionnaire, was associated with higher DBP after adjustment for confounders (β=2.31, *P*=0.01).

In the clinical trial, there was a significant sleep x week interaction on SBP (*P*=0.036), showing an increase over time with SR relative to HS. There was a trend for sleep x week interaction on weekly measures of DBP (*P*=0.11). (Figure 2, Table 3).

Twenty-four-hour ambulatory DBP (*P*=0.024) was higher after 6 wk of SR compared to HS (Figure 2). This was due entirely to higher wake values during SR relative to HS (DBP and mean arterial pressure *P*=0.021 and 0.018, respectively; SBP *P*=0.421). No statistically significant difference was observed between SR and HS for sleeping SBP, DBP, and mean arterial pressure. Similarly, SBP and DBP dipping were not significantly different between SR and HS.

Psychological Outcomes in the Community-Based Cohort

The univariate and multivariate associations between psychological outcomes and sleep measures in the community-based cohort are presented in Supplemental Table 3 and in Table 4, **respectively**. Higher perceived stress (PSS-4) was significantly associated with sleeping <7h/night (OR, 1.21; 95% CI, 1.09-1.34), insomnia score ≥8 (OR, 1.26; 95% CI, 1.13-1.39), and poor sleep quality (PSQI >5) (OR, 1.16; 95% CI, 1.05-1.28), and high-risk for OSA (OR 1.18; 95% CI, 1.04-1.34). Higher chronic stress (GPSS-4) was significantly associated with sleeping <7 h/night (OR, 1.26; 95% CI, 1.11-1.44), insomnia severity index ≥8 (OR, 1.27; 95% CI, 1.12-1.44), and poor sleep quality (OR 1.17; 95% CI, 1.04-1.33). Higher depressive symptoms (PHQ-2) were significantly associated with sleeping <7 h/night (OR, 1.46; 95% CI, 1.14-1.86) and insomnia severity score ≥8 (OR, 1.31; 95% CI, 1.05-1.64). Lower psychological resilience (BRS) was associated with insomnia score ≥8, as well as poor sleep quality (OR, 0.90; 95% CI, 0.85-0.96 and OR, 0.94; 95% CI, 0.89-0.99, respectively). A greater number of stressful life events (LEC) was significantly associated with sleeping <7 h/night (OR, 1.37; 95% CI, 1.11-1.70), insomnia severity index score ≥8 (OR, 1.38; 95% CI, 1.12-1.70), poor sleep quality (OR 1.43; 95% CI, 1.16-1.77), and high risk for sleep apnea (OR 1.35; 95% CI, 1.05-1.74).

Psychological Outcomes in the Clinical Trial

There was no sleep x week interaction or main effect of TST on any of the psychological outcomes (Table 3).

Because there was a sleep x week interaction (P=0.017) on perceived stress (PSS-10) when data were analyzed using HS vs SR, we performed mediation analyses to examine whether perceived stress was a mediator in the sleep-BP outcomes. This was not significant.

DISCUSSION

This study provides, for the first time, solid evidence related to the causality of the short sleep-high blood pressure association. Indeed, this is the longest SR intervention conducted to date and our study shows that sustained, long-term SSD, similar to the sleep duration of ~38% of American adults age 25-44 y[33], leads to increased office-based measurements of SBP as well as wake ambulatory DBP and mean arterial pressure. The greater ambulatory blood pressure observed a result of SR is similar to the impact of an 8-wk, 5% weight gain in normal weight, young adults[34]. The differences in wake ambulatory blood pressure between SR and HS are on par with results of other lifestyle interventions, such as the Dietary Approaches to Stop Hypertension with[35] or without exercise[36], for blood pressure management.

Increases of approximately 3.5 mmHg in 24-h SBP and DBP and closer to 4 mmHg in 24-h mean arterial pressure as a result of 6 wk of mild SR, leading to total sleep times of ~6 h/night, have meaningful health implications from a population perspective. Indeed, several studies have found that a 10-mmHg increase in SBP in midlife is linearly associated with increased risk of CVD[37,38] and dementia[39]. In participants <50 y of age, a one SD increase in 24-h ambulatory DBP (~8.2 mmHg) was associated with hazard ratios for total mortality, cardiovascular mortality, and all cardiovascular events of 2.05, 4.07, and 1.74, respectively[40]. A 1 mmHg/y increase in brachial pulse pressure and yearly increase in mean arterial pressure have been associated with 61% and 68%, respectively, increased risk of mortality over 5.8 y of follow-up[41].

The lack of effect of SR on blood pressure dipping was unexpected. Cross-sectional studies have linked poor sleep quality to reduced blood pressure dipping in adults[42–44] and prior research has shown that repeated exposures to acute SSD of 4 h bedtimes/night for 3 nights followed by one night of 8 h bedtimes, repeated over 4 cycles, significantly attenuated blood pressure dipping in young, healthy men and women[45]. It is possible that mild reductions in sleep are not sufficient to induce changes in blood pressure dipping in young females. To our knowledge, no other intervention study has been done to assess the impact of SR on 24-h ambulatory blood pressure in adults. However, it is worth noting that non-dipping has not been related to cardiac structure abnormalities whereas wake and sleep SBP and DBP have [20]. Therefore, our findings related to wake SBP and DBP are relevant for CVD risk.

Our cohort study also showed that worse scores on measures of psychological functioning were associated with poor sleep. These findings are consistent with previous studies linking psychological stress with inadequate sleep[46–48]. Resilience, a positive psychosocial factor which reflects the ability to bounce back from stress, was related to sleep quality and insomnia symptoms in our study. Resilience has previously been shown to buffer the negative impact of perceived stress on sleep disturbances[49]. The relation between sleep and resilience may also be bi-directional, as some studies suggest longer and more restorative sleep may boost levels of resilience[50].

Given the association between sleep duration and psychological functioning, the causality of this relation has been understudied. Our clinical trial shows that reduced TST, in young

healthy women, does not influence psychological stress and distress. However, assignment of SR, vs HS, was associated with greater stress and lower resilience, consistent with observational findings in our community-based study. Those markers of psychological functioning were not mediators in the SR-blood pressure pathway. The lack of a mediation effect may be due to the fact that participants were restricted on the total amount of sleep but did not have impairments in sleep quality as shown by optimal sleep efficiency and lack of negative effects on SOL and WASO. The body may be unable to maintain normal hypothalamic-pituitary-adrenal functioning in an acute psychological stress situation after a period of poor sleep *quality*; however, it may be able to retain its capacity to function during extended times of sleep deprivation[51]. Therefore, the biological mechanism of stress reactivity dysfunction after SR leading to increased blood pressure would not be applicable here and we propose that inadequate sleep duration can increase CVD risk via two separate pathways, one implicating increases in blood pressure and another implicating increases in psychological stress. Our separate analyses showing that objective TST does not influence psychological stress but assignment to the SR phase does, support this notion. The absence of a mediation effect could also be explained by a potential lack of association between self-reported and objective measures of stress. Because we did not assess biomarkers of stress system activation in this study, we cannot test these possible explanations for our findings.

Our clinical trial has a few limitations. First, all women were young and healthy. However, despite youth and general good health, we were able to exert increases in blood pressure from a 1.5 h reduction in sleep maintained for 6 wk. Second, participants were required to maintain this degree of SR daily for 6 wk. In free-living situations, sleeping in on weekends is available and may somewhat compensate for inadequate weekday SSD. However, population studies fail to report this behavior. In a large Swedish cohort of over 38,000 adults, approximately 56.5% remained in the same sleep category on weekdays and weekends; only 3.8% of short sleepers (≤5 h/night) reported medium (7 h) or long (≥9 h) sleep on weekends, a proportion slightly lower than that of weekday short sleepers who maintained short sleep on weekends (4.2%)[52]. Similarly, data from NHANES 2003-2006 showed that sleep in women from our age group was relatively stable across days of the week, with a difference between shortest and longest objectively-measured sleep duration of 32-47 min[53]. However, repetitive SR to 4 h sleep/night for 3 nights, followed by catch-up sleep of 8 h/night for one night, over 4 cycles, blunts blood pressure dipping relative to constant adequate sleep[45]. Other metabolic risk factors have not been shown to improve following weekend recovery sleep in participants subjected to short term severe SR[54]. Together, data do not suggest that catch-up sleep is an effective strategy to compensate for short-term pronounced inadequate sleep. Third, our participants were forced to restrict their sleep, which may not be truly representative of individuals who voluntarily curtail their sleep. Nonetheless, the end result remains the same: SSD of ~6 h/night maintained for 6 wk has detrimental blood pressure effects. Finally, our study used actigraphy to track nightly sleep duration rather than polysomnography. Polysomnography would have provided additional information on the influence of alterations of various sleep stages on our outcomes. However, repeated polysomnography assessments increase burden on participants. The community study results are limited by the subjectivity of self-reported

measures and the prohibition of any inference regarding cause and effect. However, our clinical trial, which informs causality, indicates that SSD induces some degree of psychological distress. In addition, for both studies, psychological measures were added after the study onset. This likely has little impact since some data were missing in only 2 women in the clinical intervention.

Despite those limitations, our study has notable strengths. First, our clinical trial is the longest study to date to induce SR to provide a realistic representation of habitual short sleepers. Prior studies have been short-term, acute SR studies that necessitated in-patient settings and reduced the generalizability of the results to a free-living population. As such, this provides the best available evidence of a causal influence of mild, sustained inadequate sleep duration on CVD risk with objective measures of sleep duration over the entire duration of each intervention phase. Our participants were highly compliant with the sleep protocols for both HS and SR and our retention rate was outstanding. The use of ambulatory blood pressure monitoring is also superior to office measurements in predicting long-term CVD outcomes[55]. Our study is further strengthened by information from a community-based study of >230 women from diverse backgrounds which corroborate our findings. In addition, this is the only study, to our knowledge, that explores psychological factors as potential mediators of the SSD-blood pressure relation.

Finally, our study, representing the longest SR study to date, and inducing sleep durations representative of the general adult short sleeper, shows for the first time that SSD causes increases in blood pressure that are relevant for cardiovascular health. In normotensive populations, persistent reductions in average blood pressure similar to the differences observed between HS and SR herein, could avoid large numbers of premature deaths and strokes[56]. This knowledge, and information from this study, justify public health campaigns to promote adequate sleep in short sleepers and funding research to test the cardiovascular health effects of sleep extension in short sleepers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank all of the women who have participated in this research as well as the graduate students who have contributed to its implementation.

Sources of Funding

Funding was provided by the American Heart Association Go Red for Women Strategically Focused Research Network 16SFRN27950012 (PI: St-Onge), 16SFRN28060011 (PI: Aggarwal), and 16SFRN28850003 (PI: Spruill). The clinical trial was also supported in part by an NIH Clinical and Translational Science Award (CTSA) through its Center for Advancing Translational Sciences, grant UL1TR001873.

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Novelty and Significance

What Is New?

This is the longest intervention study to date to test the impact of short sleep duration on blood pressure in healthy young women. Results from our randomized, controlled crossover study show that reducing sleep by 1.5 h/night for 6 wk leads to higher ambulatory blood pressure and is associated with no adverse changes in psychological functioning.

What Is Relevant?

A mild sleep reduction, equivalent to the sleep duration of habitual short sleepers, sustained over time, leads to similar increase in blood pressure as a 5% weight gain. Elevated blood pressure as a result of sustained short sleep duration can increase cardiovascular disease risk independently of stress and anxiety.

Summary:

Sustained mild sleep restriction, in healthy young pre-menopausal women, increases waking blood pressure. Our results contribute further evidence that insufficient sleep is a causal factor in the development of elevated blood pressure.

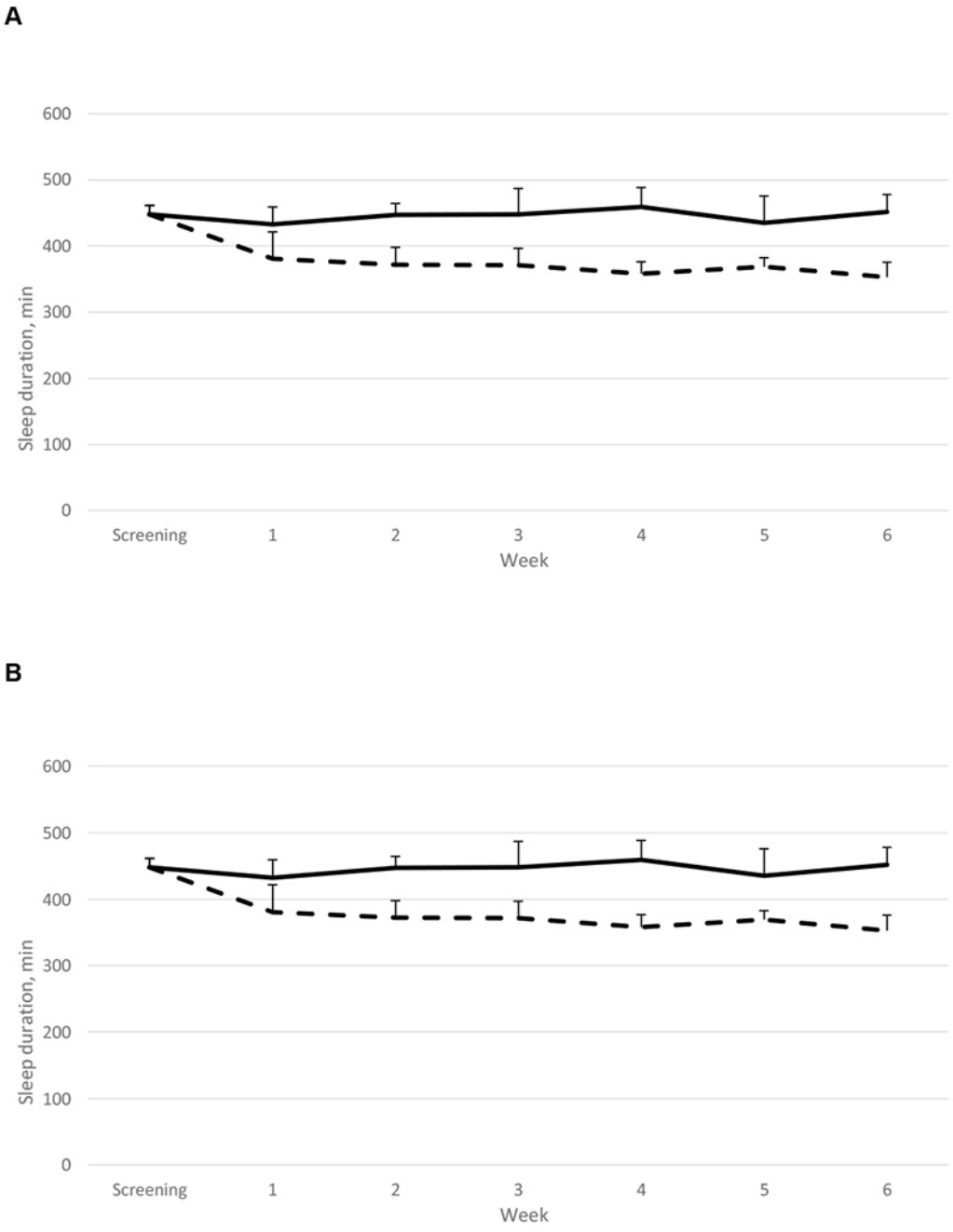

Figure 1.

Weekly sleep duration measured by actigraphy during the 6-wk intervention periods (HS, solid line, and SR, hatched line). Panel A represents data from all women who completed the clinical trial (n=24); panel B represents data from women who have provided ambulatory blood pressure measurements (n=17). Week 0 sleep duration represents average sleep duration during the screening period. Data are weekly averages and SD.

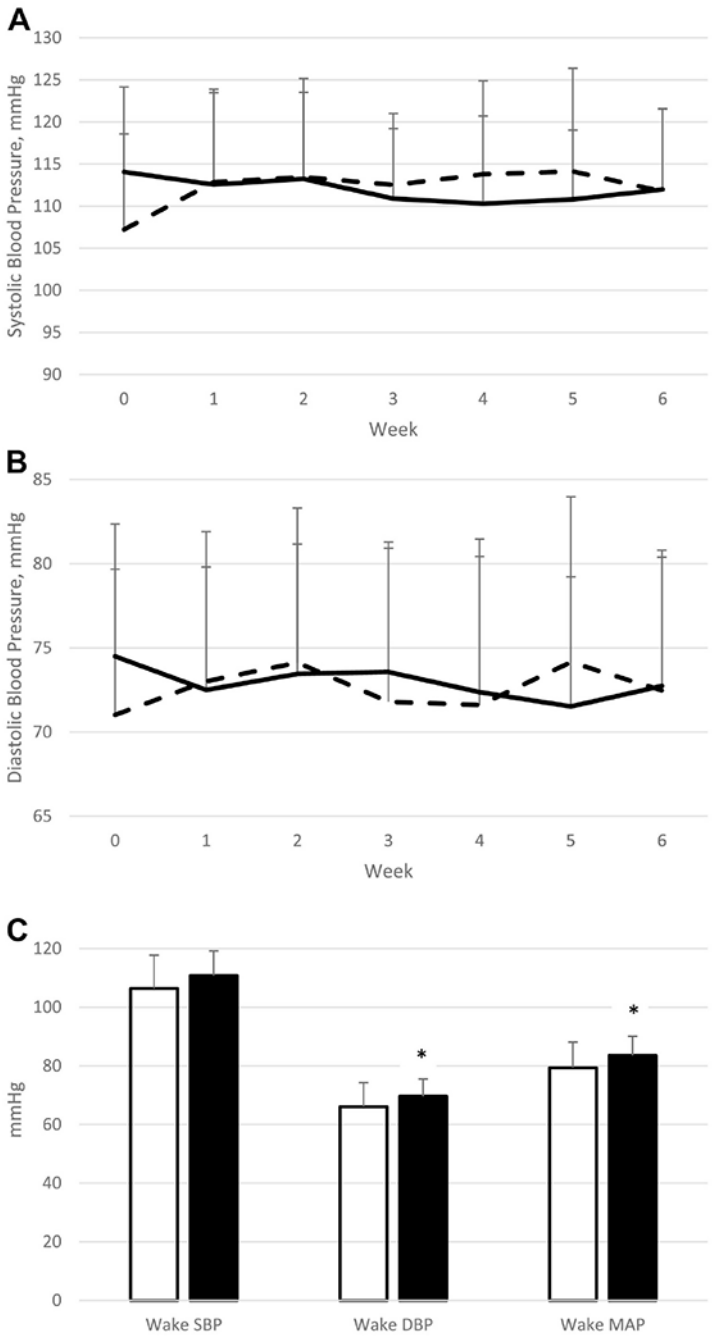

Figure 2.

Weekly SBP (panel A) and DBP (panel B) during the 6-wk intervention periods (HS, solid line, and SR, hatched line). Data are unadjusted raw means±SD; n=24. There is a significant sleep x week interaction on SBP (P=0.0048) and trend for main effect of sleep (P=0.061). Twenty-four-hour wake SBP, DBP, and mean arterial pressure after 6 wk of HS (white bars) and SR (black bars) is shown in panel C. Data are unadjusted raw means±SD; n=17 for HS and 14 for SR. * Significantly higher than HS, P<0.05.

Table 1.

Characteristics of Participants in the Community-based Cohort (n=237)

Characteristic	n	%	Mean	SD
Age, y			34.1	13.5
Race/ethnicity				
White	122	51		
Minority race	115	49		
Hispanic	73	31		
Minority race and/or Hispanic ethnicity	163	69		
Education less than college	52	22		
Single/Widowed/Divorced/Separated	176	74		
Postmenopausal	55	23		
No health insurance	70	30		
History of chronic illness	62	26		
Body Mass Index, kg/m^2			25.1	5.4
Sleep Habits				
Pittsburgh Sleep Quality Index score(range=0-21)			5.4	3.5
Poor Pittsburgh Sleep Quality Index score (>5)	85	36		
Snore (Yes)	68	29		
Insomnia Severity Index Score (range=0-28)			6.9	5.8
Some/Moderate/Severe Insomnia (Insomnia Severity Index Score ≥8)	88	37		
Obstructive sleep apnea score (Berlin Questionnaire, range=0-3)			0.7	0.8
High-risk obstructive sleep apnea (Berlin Questionnaire ≥2)	37	16		
Sleep Duration (hours/night)			6.79	1.18
Short sleep duration (<7 hours/night)	99	42		
Psychological Factors				
Perceived Stress Scale-4			5.14	2.96
Global Perceived Stress Scale-4			3.84	2.37
Patient Health Questionnaire-2			0.86	1.24
Brief Resilience Scale			15.73	4.67
Life Events Checklist			1.77	1.57

Table 2.

Screening characteristics of women enrolled in the clinical trial

Characteristic	All enrolled (n=33)	Completers (n=24)	Completers ABPM (n=17)
Age, y	30.1±7.3	30.2±6.5	30.7±7.4
Race, Black/White/Asian/Other	9/176/6/1	5/13/5/1	3/10/3/1
Ethnicity, Hispanic/Non-Hispanic	4/29	3/21	3/21
Body mass index, kg/m^2	24.4±2.4	24.3±2.8	24.7±2.9
Total sleep time, h	7.6±0.6	7.7±0.5	7.6±0.9
Sleep onset latency, min	4.5±3.0	4.7±3.2	5.7±5.0
Wake after sleep onset, min	44.1±15.2	41.6±15.1	34.9±21.5
Sleep efficiency, %	90.7±2.7	91.2±2.6	91.3±4.5
Bedtime, h:min	23:05±3:20	23:39±1:20	23:55±1:15
Wake time, h:min	07:58±0:48	07:54±0:52	07:28±1:19

Data are means±SD.

Table 3.

Clinic blood pressure and psychological outcomes at baseline and endpoint of each intervention phase during the clinical trial

Sleep	Week	SBP*	DBP	BRS	HADS	PHQ-2	PSS-10
Habitual sleep	Baseline	114.1±10.1	74.5±7.9	24.0±4.2	12.6±6.2	0.14±0.47	12.5±6.1
	Endpoint	112.0±9.6	72.7±7.6	24.4±3.5	12.6±6.1	0.39±0.72	11.4±6.5
Sleep restriction	Baseline	107.2±11.3	71.0±8.7	24.1±3.7	12.3±6.2	0.55±0.91	12.9±5.6
	Endpoint	111.7±9.8	72.5±8.3	23.2±4.9	12.8±5.2	0.57±1.12	14.8±7.2

Data are means ± SD, n=24 for SBP and DBP data; sample sizes for psychological variables: n=22 for baseline (both sleep conditions); n=23 (habitual sleep) and 24 (sleep restriction) for endpoint.

*Significant sleep x week interaction, $P<0.05$ (TST adjusted for physical activity).

Table 4.

Multivariate Associations between Psychological Factors and Sleep in the Community-based Cohort (n=237)

Sleep measures	Comparisons	PSS-4		GPSS-4		PHQ-2		BRS		LEC	
		OR	*P*-value	OR	*P*-value	OR	*P*-value	OR	*P*-value	OR	*P*-value
Sleep Duration	<7 vs ≥7 h/night	1.21	<0.001*	1.26	<0.001*	1.46	0.003*	0.97	0.250	1.37	0.004*
Insomnia	≥8 vs <8	1.26	<0.001*	1.27	<0.001*	1.31	0.017*	0.90	0.001*	1.38	0.002*
Pittsburgh Sleep Quality Index	>5 vs ≤5	1.16	0.004*	1.17	0.010*	1.22	0.084	0.94	0.048*	1.43	0.001*
Obstructive Sleep Apnea	High-risk vs low-risk	1.18	0.011*	1.34	0.097	1.08	0.597	0.98	0.523	1.35	0.020*
Snore	Yes vs no	1.03	0.538	1.07	0.291	1.07	0.599	1.03	0.423	1.14	0.208

Abbreviations: BRS, Brief Resilience Scale; LEC, Life Events Checklist; GPSS-4, global perceived stress scale; PHQ-2, patient health questionnaire; PSS-4, perceived stress scale.

Models were adjusted for age, race/ethnicity, menopausal status, marital status, health insurance, BMI, and history of chronic illness

*$P<0.05$