Sleep Health 1 (2015) 50–54

Contents lists available at ScienceDirect

Sleep Health

Journal of the National Sleep Foundation

journal homepage: http://www.elsevier.com/locate/sleh

Sleep maintenance difficulties in insomnia are associated with increased incidence of hypertension

Philip Cheng, PhD, Vivek Pillai, PhD, Heather Mengel, Thomas Roth, PhD, Christopher L. Drake, PhD *

Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI

ARTICLE INFO

Article history:
Received 2 November 2014
Received in revised form 18 November 2014
Accepted 21 November 2014

ABSTRACT

Study objectives: We examined the relative contributions of sleep onset and sleep maintenance difficulties in insomnia as predictors of incidence and development of hypertension.
Design: This study is cross-sectional and longitudinal.
Participants: There were 967 adults with *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*–based current insomnia.
Measurements and results: At baseline, participants were divided into 2 groups based on current diagnosis of hypertension. Prevalence of hypertension in this sample was 34.7%, which is higher than the prevalence in the general population previously documented at approximately 28%. Participants completed a follow-up assessment 1 year later that revealed a 5.4% incidence of hypertension. Analyses revealed that increases in sleep maintenance difficulties, not sleep initiation difficulties, between baseline and follow-up significantly predicted increased risk for incidence of hypertension. Analyses at baseline also revealed that sleep maintenance rather than sleep initiation difficulties marginally predicted increased severity of hypertension. Results suggest that risk for hypertension may be conferred through disruptions to blood pressure with nightly repeated or prolonged awakenings.
Conclusions: This study provides novel information regarding the risk of hypertension in insomnia via sleep maintenance difficulties. Findings from this study provide preliminary evidence for examining nighttime fluctuations of blood pressure and concomitant physiological changes (ie, catecholamines, heart rate, and sympathetic activation) due to wake during sleep as a mechanism for subsequent hypertension.

Introduction

Insomnia is a commonly occurring sleep disorder that is characterized by chronic difficulties in initiating or maintaining sleep, resulting in impairments to daytime functioning. Such impairments include increased rates of absenteeism, decreased productivity, diminished quality of life, and impaired cognitive and emotional functioning.[1] However, insomnia also confers additional health risks beyond its acute consequences. Most notably, individuals with insomnia are at higher risk for developing medical morbidities,[2] especially cardiovascular illnesses such as hypertension.[3-5] Because of the high prevalence and mortality rates associated with cardiovascular illnesses, research has increasingly focused on insomnia as a risk factor for hypertension and similar comorbidities.

Research examining insomnia as a risk factor for hypertension has produced mixed results. Notably, although many studies find that insomnia predicts increased incidence of hypertension,[4] some do not [6-8] One potential explanation may be the fact that the underlying mechanism of risk between insomnia and hypertension remains poorly understood, and studies may therefore find varying results based on differing variables used. Vgontzas et al[9] have argued that risk for hypertension may be conferred through decreased sleep duration, as well as in conjunction with insomnia, with an adjusted odds ratio estimated at 5.12, which is significantly higher than that for insomnia alone (range estimated between 1.05 and 2.24).[4] However, reduced sleep duration in insomnia may arise from difficulties falling asleep and/or difficulties maintaining sleep, and it is still unclear how risk may differ based on this distinction. There is evidence that specific patterns of sleep difficulties predict risk for hypertension. For example, one prospective study using a large sample of Japanese male workers found that both difficulty initiating and maintaining sleep independently predicted development of hypertension.[10] Another recent meta-analysis of prospective studies found that difficulties maintaining sleep and early morning awakening predicted incidence of hypertension, but no significant effect was detected for difficulty falling asleep.[4] However, these studies did not directly compare distinct patterns of sleep difficulties, thereby precluding discernment of their relative contribution in predicting hypertension.

* Corresponding author at: Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI 48202. Tel.: +1 313 916 4455.
E-mail address: cdrake1@hfhs.org (C.L. Drake).

http://dx.doi.org/10.1016/j.sleh.2014.11.004
2352-7218/

Such discernment is important because it may increase specificity and effectiveness of clinical interventions.

Among different endophenotypes of insomnia, the biological processes specific to sleep maintenance difficulties may be of particular relevance to hypertension. Although blood pressure decreases with sleep onset,[11,12] nighttime awakenings result in surges in the sympathetic nervous system. These surges trigger the release of catecholamines such as norepinephrine, which is associated with rises in blood pressure. Disruptions to blood pressure with nightly repeated or prolonged awakenings may increase risk for hypertension. To further explore this hypothesis, this study examined the relative contributions of sleep onset vs maintenance difficulties in insomnia as predictors of prevalence and incidence of hypertension. This was a prospective study of a large sample of individuals with insomnia that measured incidence of hypertension across 2 years. Two sets of analyses were used to examine risk of hypertension in insomnia. The first used a cross-sectional design in comparing sleep onset and maintenance difficulties between those with and without hypertension at baseline. We hypothesized that prevalence of hypertension will be higher compared with that of the general population and that individuals with increased sleep maintenance difficulties will have additionally increased risk for hypertension. The second set of analyses used a longitudinal design in examining incident hypertension at follow-up. If risk for hypertension is indeed augmented by sleep maintenance difficulties, exacerbation of sleep maintenance difficulties from baseline would increase risk for hypertension at follow-up.

Methods

Participants

Participants in this study were recruited as part of the Evolution of Pathways to Insomnia Cohort study, which was a longitudinal investigation examining insomnia in a large sample of adults living in southeastern Michigan (specific information regarding the larger investigation is detailed elsewhere).[13] Prospective participants were derived from a major health maintenance organization database, where a randomly selected sample of individuals (n = 36,002) were recruited by mail. Twenty-one percent (n = 7608) of these individuals responded by completing a Web-based survey that assessed eligibility for this study. Approximately 34% of these individuals (n = 2590) reported current/lifetime insomnia and were invited for study participation. Of all eligible individuals, 54% (n = 1388) elected to enroll and completed baseline questionnaires. See Table 1 for demographic and descriptive information for study participants and the Figure for the breakdown of sample by time points.

Procedure and measures

All study protocols were approved by the Henry Ford Hospital Institutional Review Board.

Insomnia

Diagnosis of insomnia was established based on *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition* criteria, using the following questions: "Have you experienced difficulty falling asleep?," and "Have you experienced difficulty staying asleep?," Participants met *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition* diagnostic criteria if 1 or more of the above symptoms were reported for at least 3 nights a week for a duration of 3 months or longer. In addition, insomnia criteria included daytime consequences or distress from sleep difficulties as determined by a response of 2 ("somewhat") or higher on a 5-point Likert scale to the question: "To what extent do you consider your sleep problems to interfere with your daily functioning?" Responses ranged from "0" ("not at all") to "4" ("very much").

Table 1
Demographic and descriptive information for study participants.

	No HTN (n = 631)	HTN (n = 336)	*P*
Sex	452 ♀	216 ♀	<.05
Age	43.1 (12.7)	53.3 (8.9)	<.001
Race:			<.001
White	68.3%	59.2%	
African American	22.8%	39.0%	
Other	8.9%	2.0%	
High risk for OSA (%)	41.2%	61.0%	<.001
Use of antihypertensive medication	–	88.4%	–
Days of impairment due to physical/mental health difficulties in the last year	4.7%	13.8%	<.01
SOL (min)	69.8 (65.5)	73.9 (77.3)	NS
No. of night awakenings	4.7 (8.0)	5.4 (9.0)	NS
WASO (min)	95.5 (100.8)	111.7 (108.5)	<.05
Average sleep duration (min)	336.3 (78.1)	324.2 (83.0)	<.05
Sleep quality	1.84 (.5)	1.79 (.6)	<.05
Chronicity of insomnia (mo)	66.6 (83.2)	86.9 (104.5)	<.01

Abbreviations: *NS*, not significant; HTN, hypertension.

Sleep onset and maintenance difficulties were quantified via questions that probed for average minutes to sleep onset and duration of wake after sleep onset (WASO) during the last month. Prior research has demonstrated high correlations between results attained from retrospective sleep questionnaires and sleep diaries,[14] suggesting accuracy in the use of retrospective sleep questions. Previous research using large samples of adults has also indicated that measurement of sleep-related impairments has higher sensitivity and specificity to quantitative thresholds.[15,16] The reported sleep variables were subsequently categorized based on quantitative measures of sleep difficulties to maximize sensitivity and specificity in detecting sleep-related impairment to blood pressure. Specifically, individuals who reported sleep onset latencies (SOLs) of longer than 30 minutes

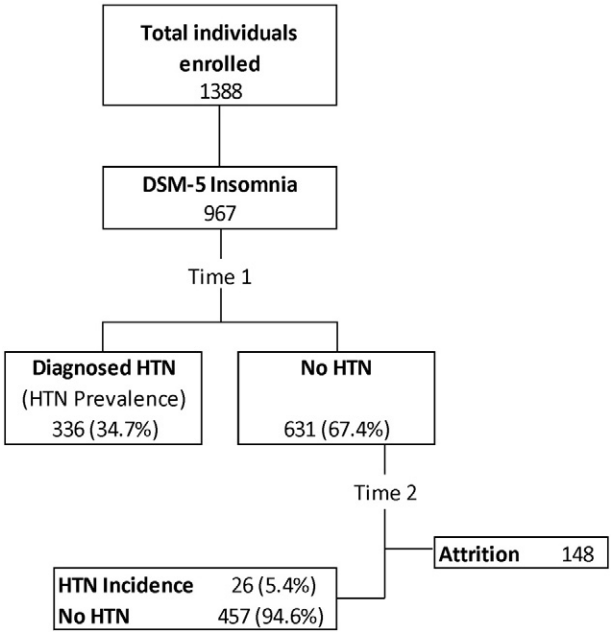

Figure. Breakdown of sample by time point. *HTN*, hypertension.

were categorized as having increased sleep onset difficulties. Sleep maintenance difficulties were also similarly quantified using WASO. Individuals who reported a WASO of longer than 30 minutes were categorized as having increased sleep maintenance difficulties.

Hypertension

Hypertension was measured by self-report of "high blood pressure/hypertension" via questionnaire. Previous research comparing self-report hypertension to medical diagnosis of hypertension has demonstrated good specificity and agreement, indicating validity in the use of questionnaire data in measuring a diagnosis of hypertension.[17] Severity of hypertension was determined based on chronicity of hypertension and number of oral medications used to manage hypertension. Individuals who reported having hypertension for 10 or more years and reported taking 2 or more medications at time 1 (T1) were categorized as having more severe hypertension.

Risk for obstructive sleep apnea and other covariates

Participants also completed the Berlin Apnea Questionnaire (BAQ) as an assessment of risk for obstructive sleep apnea (OSA) (16). The BAQ identifies individuals at risk for OSA based on 3 categories of symptoms: snoring; daytime sleepiness and fatigue; and obesity as indexed by a body mass index and hypertension. For the purposes of this study, hypertension was removed from the third category. In a validation study, the BAQ achieved high sensitivity in correctly identifying polysomnography-diagnosed OSA patients with an apnea-hypopnea Index greater than 5.[18]

Other covariates included age, sex, race, sleep duration, chronicity of insomnia, and general health. These were determined based on previous research indicating that individuals who are older, male, and of African American descent are at higher risk for hypertension.[19] Sleep duration and chronicity of insomnia were included based on previous research indicating increased risk for hypertension.[9,20,21] Finally, general health was included to account for other physical and mental health difficulties that may contribute to risk for hypertension. This was indexed by days of functional impairment in the last year due to physical or mental health difficulties.

Statistical analyses

Three analyses using a binary logistic regression model were used to test sleep onset difficulties and sleep maintenance difficulties as predictors for incidence of hypertension. All analyses were adjusted for age, sex, race, general health, risk for OSA, average sleep duration, and chronicity of insomnia as covariates. Risk for OSA was determined by the BAQ, which has high sensitivity to PSG-diagnosed OSA.[22]

The first logistic regression tested both sleep onset difficulties and sleep maintenance difficulties at T1 as correlates of current diagnosis of hypertension. The second logistic regression tested sleep onset and maintenance difficulties as correlates of severity of hypertension, which was codified based on chronicity and number of oral medications used. The third logistic regression tested sleep onset and maintenance difficulties in predicting incident hypertension at time 2 (T2).

Results

Descriptive: incidence of hypertension and insomnia

At T1, results revealed that 34.8% (n = 336) reported a preexisting diagnosis of hypertension, compared with the prevalence rate of approximately 28% in the general population.[23] At follow-up 1 year later (T2), an additional 5.4% (n = 26) of individuals reported a new diagnosis of hypertension. Demographics of each group are reported in Table 1. Preliminary analyses comparing sleep variables between those with and without hypertension revealed that individuals with preexisting hypertension reported significantly longer WASO, shorter sleep duration, and longer history of insomnia (see Table 1). No significant group differences were detected for SOL or number of awakenings.

Table 2
Multivariable-adjusted odds ratio (95% CI) of hypertension prevalence, severity, and incidence.

Independent variables	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)	Model 3[c] OR (95% CI)
WASO >30 min at T1	1.13 (.78-1.60)	1.75* (1.00-3.10)	–
SOL >30 min at T1	1.23 (.88-1.70)	0.83 (.51-1.34)	–
WASO increased >30 min at T2	–	–	4.10*** (1.71-9.82)
SOL increased >30 min at T2	–	–	.45 (.09-2.19)

Abbreviation: *OR*, odds ratio.
All models include age, sex, race, risk for OSA, general health, sleep duration, and chronicity of insomnia as covariates.
[a] Outcome variable = prevalence of hypertension at T1.
[b] Outcome variable = severity of hypertension at T1.
[c] Outcome variable = incident hypertension at T2.
* $P \leq .05$.
*** $P \leq .001$.

Correlates with hypertension at T1

Results from the first logistic regression revealed that neither sleep maintenance nor sleep onset reports were significantly correlated with a preexisting diagnosis of hypertension at T1 after adjusting for age, sex, race, risk for apnea, general health, sleep duration, and chronicity of insomnia (see Table 2A). The second logistic regression was completed to assess for SOL and WASO as correlates of hypertension severity. Of the total sample, 102 individuals were categorized as higher in severity. Results revealed that WASO more than 30 minutes significantly conferred increased risk for more severe hypertension (see Table 2B).

Prediction of incident hypertension at T2

Of 631 people with insomnia but no hypertension at T1, 76.5% (n = 483) completed follow-up assessment 1 year later. This sample was used in the third logistic regression, which tested exacerbation of sleep onset difficulties and sleep maintenance difficulties as predictors of incident hypertension at T2. Results indicated that individuals with insomnia who experienced exacerbated WASO (>30 minutes increase) from T1-T2 experienced increased risk for developing hypertension (see Table 2C). Exacerbation of insomnia via increases in SOL of more than 30 minutes did not contribute significantly to risk of incident hypertension.

Discussion

This study aimed to examine the relative contribution of sleep initiation and sleep maintenance difficulties as risk factors for hypertension in a prospective sample of individuals with insomnia. To the best of our knowledge, this is the first study to prospectively compare quantitative measures of sleep onset vs sleep maintenance difficulties as risk factors for hypertension in insomnia.

Results from this study suggested that risk for hypertension may either be specific to, or augmented by, sleep maintenance reports via prolonged wakefulness during the night. This finding adds specificity to previous studies suggesting that risk for hypertension in insomnia may interact with reduced sleep duration.[9] After adjusting

for sleep duration, increased WASO in insomnia predicted incidence of hypertension with an odds ratio estimated at 4.10, whereas no significant effect was detected with increased SOL insomnia. Together, this suggests that the distinction of sleep onset difficulties vs sleep maintenance difficulties is additionally relevant, with the latter adding to the risk for developing hypertension in insomnia. However, given the wide confidence interval (CI), the estimated odds ratio should be interpreted with caution. Future studies with larger sample sizes may also be able to include additional covariates such as specific health-related behaviors (e.g., alcohol/substance use, amount of physical activity, and other anthropometric measures).

The distinction of specific profiles of sleep difficulties in risk for hypertension is important because there are potential clinical benefits, especially if risk for hypertension and other morbidities differs by endophenotypes of insomnia. If risk for hypertension is conferred through specific endophenotypes of insomnia, this may allow for increased precision in identifying individuals at higher risk for medical morbidities and may also enhance the precision of targets for intervention to reduce such risks. For example, adjunctive interventions to specifically increase sleep continuity may be provided for hypertensive individuals with increased WASO.

One possible explanation for increased hypertension risk specific to sleep maintenance difficulties may be related to the biological mechanisms involved. Sleep maintenance difficulties may result in more fluctuations in blood pressure with wakefulness throughout the night. Contrasted with the sustained dip in blood pressure with undisturbed sleep, these fluctuations may lead to alterations to the functioning of the sympathetic nervous system. In fact, extensive fluctuations in blood pressure have been implicated as a mechanism of risk for hypertension in OSA, where apneic events trigger repeated bursts of sympathetic nervous system activity that lead to spikes in blood pressure.[24] Furthermore, a recent study using an animal model of sleep fragmentation demonstrated that chronic exposure to fragmented sleep resulted in vascular dysfunction, including increased blood pressure.[25] Although this indicates a biological mechanism by which WASO may increase risk for hypertension, it also points to the importance of controlling for sleep apnea and other sleep disorders as potential confounding variables. As such, risk for sleep apnea was accounted for in this study using the BAQ, which assesses risk based on significant predictors such as snoring, witnessed apneas, and body mass index. The BAQ has previously been shown to have high sensitivity in identifying those with PSG-diagnosed sleep apnea.[18] Furthermore, previous studies that excluded for OSA based on polysomnography[9] have demonstrated that the relationship between insomnia and hypertension persists even in the absence of sleep apnea. Results revealed that increases in WASO remained a significant predictor of incident hypertension after controlling for risk of sleep apnea. However, future research should include objective measures of sleep, sleep apnea, blood pressure, and catecholamines throughout the night to further clarify the mechanisms of incident hypertension in insomnia.

The relationship between sleep maintenance difficulties and hypertension was also supported by the association of more severe hypertension with increased WASO. This result appears consistent with the theory that increased nighttime awakenings and consequential disruptions to blood pressure may increase risk for hypertension. Although there is some evidence that certain antihypertensive medications may disturb sleep,[26] the effects may only be specific medications.[27] Moreover, prior epidemiologic research has concluded that use of antihypertensive medications is an unlikely confounding variable in the relationship between sleep and hypertension.[28] Finally, most individuals with hypertension in this sample reported use of medication, further suggesting that the relationship detected between sleep and hypertension severity is not likely confounded by medication use.

Although results showed increased prevalence of hypertension in individuals with insomnia (34.8%) compared with the prevalence rate in the general population (~28%; 17), neither sleep maintenance nor sleep onset difficulties significantly correlated with hypertension at T1 after controlling for covariates. This may be a limitation based on the cross-sectional nature of the first analysis, where we were unable to determine the temporal relationship between insomnia and hypertension. Our results also showed a 1-year 5.4% incidence of hypertension in insomnia. Assuming a linear incidence rate, a crude comparison with 4-year incidence of hypertension in normotensive individuals from the Framingham Study[29] indicates a somewhat higher incidence of hypertension in insomnia (4-year incidence estimated at 21.5 per 100 cases) compared with that of normotensive individuals in the general population, estimated at 17.6 per 100 cases (95% CI, 15.2-20.3).

Although this study possesses strength in the prospective nature of the assessment, one limitation was the smaller sample of individuals with insomnia who developed hypertension at T2. This may be related to the sample, which included predominantly individuals with long-term insomnia (mean of 5 years), many of whom reported a preexisting diagnosis of hypertension at T1. With a sample of individuals who report long-term insomnia, it is possible that the effect of the findings was minimized by the presence of particular individuals possessing protective factors that reduce their risk for hypertension despite having long-term insomnia. To address this, future research may follow up individuals at risk for insomnia and document the incidence of hypertension and insomnia prospectively. This approach would also enable more sensitive measurements of both hypertension (via measurements of blood pressure) and insomnia (via sleep diary and/or actigraphy).

Despite the lack of objective measurements of blood pressure in this study, previous research has established good specificity and agreement between self-report and medical diagnosis of hypertension.[17] Other research has also found that discrepancies between self-report and medical diagnosis of hypertension are disproportionately higher for false-negatives than false-positives,[30] suggesting that the prevalence and incidence statistics found in this study may be an underestimate. Although insomnia in this study was also determined based on self-report data without corroboration from sleep diary or actigraphy data, this is not unlike standard procedure in clinical practice (ie, use of patient reports of insomnia symptoms during an intake interview for a clinical diagnosis). Furthermore, previous research has also established reliability and validity between use of retrospective sleep questionnaires and sleep diary.[14]

Conclusion

In summary, this study provides novel information regarding the risk of hypertension in insomnia. Specifically, results suggest that individuals with insomnia who also report greater WASO durations are at higher risk for developing hypertension, after adjusting for age, sex, race, risk for OSA, general health, sleep duration, and chronicity of insomnia. Findings from this study provide preliminary evidence for examining nighttime fluctuations of blood pressure and concomitant physiological changes (ie, catecholamines, heart rate, and sympathetic activation) due to wake during sleep as a mechanism for subsequent hypertension.

Disclosure statement:

This study was supported by an National Institute of Mental Health grant (R01 MH082785) and an investigator-initiated research award from Merck & Co, both to Dr Christopher L. Drake. Dr Roth has served as consultant for Abbott, Accadia, AstraZenca, Aventis, AVER,

Bayer, BMS, Cypress, Ferrer, Glaxo Smith Kline, Impax, Intec, Jazz, Johnson and Johnson, Merck, Neurocrine, Novartis, Proctor and Gamble, Pfizer, Purdue, Shire, Somaxon, and Transcept; has received research support from Cephalon, Merck, and Transcept; and has served on speakers bureau for Purdue. Dr Drake has served as consultant for Teva; has received research support from Merck and Teva; and has served on speakers bureau for Jazz, Purdue, and Teva. Dr Cheng indicated no financial conflicts of interest.

References

1. Roth T, Roehrs T. Insomnia: epidemiology, characteristics, and consequences. *Clin Cornerstone* 2003;5(3):5–15.
2. Taylor DJ, Mallory LJ, Lichstein KL, Durrence H, Riedel BW, Bush AJ, et al. Comorbidity of chronic insomnia with medical problems. *Sleep* 2007;30(2):213–8.
3. Li M, Zhang X-W, Hou W-S, Tang Z-Y. Insomnia and risk of cardiovascular disease: a meta-analysis of cohort studies. *Int J Cardiol* 2014;176(3):1044–7.
4. Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertens Res* 2013;36(11):985–95.
5. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur J Prev Cardiol* 2014;21(1):57–64.
6. Phillips B, Mannino DM. Do insomnia complaints cause hypertension or cardiovascular disease? *J Clin Sleep Med* 2007;3(5):489–94.
7. Vozoris NT. The relationship between insomnia symptoms and hypertension using United States population-level data. *J Hypertens* 2013;31(4):663–71.
8. Vozoris NT. Insomnia symptom frequency and hypertension risk: a population-based study. *J Clin Psychiatry* 2014;75(6):616–23.
9. Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep* 2009;32(4):491–7.
10. Suka M, Yoshida K, Sugimori H. Persistent insomnia is a predictor of hypertension in Japanese male workers. *J Occup Health* 2003;45(6):344–50.
11. Bristow JD, Honour AJ, Pickering TG, Sleight P. Cardiovascular and respiratory changes during sleep in normal and hypertensive subjects. *Cardiovasc Res* 1969;3:476–85.
12. Pickering TG. The clinical significance of diurnal blood pressure variations. Dippers and nondippers. *Circulation* 1990;81(2):700–2.
13. Pillai V, Roth T, Mullins HM, Drake CL. Moderators and mediators of the relationship between stress and insomnia: stressor chronicity, cognitive intrusion, and coping. *Sleep* 2014;37(7):1199–208.
14. Libman E, Fichten CS, Bailes S, Amsel R. Sleep questionnaire versus sleep diary: which measure is better? *Int J Rehabil Health* 2000;5(3):205–9.
15. Drake CL, Vargas I, Roth T, Friedman NP. Quantitative measures of nocturnal insomnia symptoms predict greater deficits across multiple daytime impairment domains. *Behav Sleep Med* 2015;13(1):73–87.
16. Lichstein KL, Durrence HH, Taylor DJ, Bush AJ, Riedel BW. Quantitative criteria for insomnia. *Behav Res Ther* 2003;41(4):427–45.
17. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004;57(10):1096–103.
18. Sharma SK, Vasudev C, Sinha S, Banga A, Pandey RM, Hande KK. Validation of the modified Berlin questionnaire to identify patients at risk for the obstructive sleep apnoea syndrome. *Indian J Med Res* 2006;124(3):281–90.
19. Ford ES, Cooper RS. Risk factors for hypertension in a national cohort study. *Hypertension* 1991;18(5):598–606.
20. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, et al. Short sleep duration as a risk factor for hypertension analyses of the first national health and nutrition examination survey. *Hypertension* 2006;47(5):833–9.
21. Vgontzas AN, Liao D, Bixler EO. Insomnia and hypertension. *Sleep* 2009;32(12):1547.
22. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;131(7):485–91.
23. Saydah S, Bullard KM, Cheng Y, Ali MK, Gregg EW, Geiss L, et al. Trends in cardiovascular disease risk factors by obesity level in adults in the United States, NHANES 1999-2010. *Obesity* 2014;22(8):1888–95.
24. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA* 2000;283(14):1829–36.
25. Carreras A, Zhang SX, Peris E, Qiao Z, Gileles-Hillel A, Li RC, et al. Chronic sleep fragmentation induces endothelial dysfunction and structural vascular changes in mice. *Sleep* 2014;37(11):1817–24.
26. Dahlöf C, Dimenäs E. Side effects of beta-blocker treatments as related to the central nervous system. *Am J Med Sci* 1990;299(4):236–44.
27. Yilmaz MB, Erdem A, Yalta K, Turgut OO, Yilmaz A, Tandogan I. Impact of beta-blockers on sleep in patients with mild hypertension: a randomized trial between nebivolol and metoprolol. *Adv Ther* 2008;25(9):871–83.
28. Gottlieb DJ, Redline S, Nieto FJ, Baldwin CM, Newman AB, Resnick HE, et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep* 2006;29(8):1009–14.
29. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. *Lancet* 2001;358(9294):1682–6.
30. Goldman N, Lin I-F, Weinstein M, Lin Y-H. Evaluating the quality of self-reports of hypertension and diabetes. *J Clin Epidemiol* 2003;56(2):148–54.