

Serum Vitamin D, Sleep Pattern and Cardiometabolic Diseases: Findings from the National Health and Nutrition Examination Survey

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Objective: Although poor sleep health and vitamin D deficiency may be associated with diabetes and hypertension, whether this association shows a trend depending on vitamin D concentration is unclear.

Subjects and Methods: We analyzed data from 10,742 participants (4997 men) from the 2007–2014 National Health and Nutrition Examination Survey. Abnormal sleep pattern (ie, short sleep duration, sleep complaint, and/or sleep disorder), lifestyle factors, serum vitamin D level, and the status of diabetes and hypertension were assessed. Logistic regression was performed to estimate the odds ratio (OR) and 95% confidence interval (CI).

Results: Serum vitamin D significantly interacted with short sleep duration and abnormal sleep pattern (both $p = 0.003$) on the association with diabetes in men. Short sleep duration (OR: 1.82, 95% CI = 1.29, 2.57) and abnormal sleep pattern (OR: 1.95, 95% CI = 1.38, 2.77) were associated with diabetes in men with serum vitamin D of >75 nmol/L. Serum vitamin D significantly interacted with sleep complaint on the association with hypertension in men and women (both $p < 0.05$). The magnitude of association between sleep complaint and hypertension in men was stronger when serum vitamin D level was <50 nmol/L (OR: 2.26, 95% CI = 1.57, 3.25) than when the level was >75 nmol/L (OR: 1.28, 95% CI = 0.90, 1.83). Similarly, the magnitude of association between sleep complaint and hypertension in women was stronger when serum vitamin D level was <50 nmol/L (OR: 2.09, 95% CI = 1.53, 2.86) than when the level was >75 nmol/L (OR: 1.64, 95% CI = 0.98, 2.72). No significant interactions were observed between serum vitamin D level and other sleep variables.

Conclusion: Abnormal sleep pattern is associated with a high risk of diabetes and hypertension. The relationship between sleep complaint and hypertension may be strong in people with vitamin D deficiency, and this observation should be verified by prospective studies.

Keywords: vitamin D, sleep, diabetes, hypertension, epidemiology

Introduction

Adequate sleep duration maintains body functions and improves cardiometabolic health, such as a low risk of diabetes and hypertension.^{1–3} Apart from sleep duration, how sleep complaints and sleep disorders associated with diabetes and hypertension have received increasing attention in recent years.^{1,4} A population survey in New Zealand suggests that people with self-reported sleep complaints (eg, difficulty in falling asleep, frequent nocturnal awakenings, and/or early

morning awakenings) had 92% and 58% increased chance of developing diabetes and hypertension, respectively.⁵ Another example is obstructive sleep apnea (OSA), a prevalent sleep disorder that may increase body weight via several pathways and by considerably elevating ghrelin levels, inducing leptin resistance, and decreasing melatonin level.⁶ Apart from its role in obesity etiology, OSA causes intermittent hypoxia, which can lead to increased insulin resistance, elevated sympathetic tone, and systemic inflammation, which are the precursors of an increased risk of diabetes and hypertension.^{7,8} These observations provide further intervention strategies for improving sleep and the effects of sleep improvement on cardiometabolic risks.

Preventing vitamin D deficiency is an approach for improving sleep. Vitamin D is responsible for multiple physiological functions, and its deficiency can lead to adverse health outcomes, such as diabetes and hypertension.^{9–11} Moreover, available evidence from clinical and preclinical studies has suggested the interaction between serum vitamin D and sleep health through several possible mechanisms.¹² First, vitamin D receptors are distributed in brain areas that are crucial to sleep regulation, including the hypothalamus and midbrain central gray.^{13,14} In addition, vitamin D regulates the conversion of tryptophan to serotonin, which is used in the production of melatonin, the hormone that controls circadian rhythms and sleep.^{12,15} In recent years, pooled analysis from multiple epidemiological studies has shown that people with serum vitamin D deficiency have a high risk of poor sleep quality, short sleep duration, and daytime sleepiness.¹⁶

Given the physiological relationship between vitamin D and sleep, the associations of sleep health, diabetes, and hypertension with serum vitamin D level should be explored. To provide epidemiological evidence to answer this research question, we analyzed data from the National Health and Nutrition Examination Survey (NHANES).

Subjects and Methods

Study Design

In the present study, we used data from the 2007–2014 NHANES (N = 37,520), which is a survey conducted by the Center for Disease Control and Prevention and designed for the evaluation of the health status of adults in the United States. Written informed consent was obtained from each participant. We excluded participants with incomplete exposure (sleep duration, sleep problems,

and sleep disorder; N = 12,399), without serum vitamin D data (N = 2314), and with missing covariate data (N = 9475). To reduce the influence of pre-existing medical condition on sleep, we further excluded participants diagnosed with congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack or stroke, and/or cancer as reported by the participants (N = 2590).^{17,18}

Exposure and Outcome Assessment

The exposure variables were sleep duration, sleep problems, and sleep disorder.¹⁹ The questions on sleep were administered using a computer-assisted personal interviewing system as part of the household interview of the survey participants. The questions on sleep habits included those selected from the instruments of the Sleep Heart Health Study¹⁹ and have demonstrated validity and internal consistency in white and black adults.²⁰ The participants reported their usual sleep duration at night. Short sleep was defined as <7 hours according to the recommendation of the National Sleep Foundation for adults.²¹ Participants with sleep complaints were self-reported in the sleep questionnaire via the question “Have you ever told a doctor or other health professional that you have trouble sleeping?” Diagnosed sleep disorders were self-reported in the sleep questionnaire via the question “Have you ever been told by a doctor or other health care professional that you have a sleep disorder?” We then created a composite variable “abnormal sleep pattern,” which is defined by any occurrence of short sleep, sleep complaint, or sleep disorder.

The outcomes were participant-reported status of diabetes or hypertension. In accordance with the classification standard of the American Diabetes Association,²² diabetes was defined as fasting blood glucose ≥ 126 mg/dL, hemoglobin A1C $\geq 6.5\%$, doctor-informed diagnosis (“have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?”), and/or the self-reported use of antidiabetic drugs. In accordance with the guidelines of the American Heart Association,²³ hypertension was defined as systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg, doctor-informed diagnosis (“have you ever been told by a doctor or health professional that you have hypertension, also called high blood pressure?”), and/or the self-reported use of anti-hypertensive drugs.

Vitamin D Assessment

Total serum vitamin D (25-hydroxyvitamin D) was measured using ultra-high-performance liquid

chromatography–tandem mass spectrometry. The analytes were chromatographically separated generally on a pentafluorophenyl (PFP) column (Thermo Scientific Hypersil GOLD PFP 2.1 mm × 100 mm, 1.9 μm particle size column or Phenomenex Kinetex PFP 2.1 mm × 100 mm, 1.7 μm). A detailed methodology was described elsewhere (<https://wwwn.cdc.gov/nchs/nhanes/vitaminD/analyticalnote.aspx>). To classify participants with vitamin D deficiency, we used the cutoff values proposed by the US National Academy of Medicine (50 nmol/L) and US Endocrine Society (75 nmol/L).²⁴

Covariates for Analysis

The covariates included age, sex, race/ethnicity (dichotomized into non-Hispanic white versus others), education level (dichotomized into college graduate or above versus others), marital status (married versus others), the use of at least 100 cigarettes in lifetime (yes versus no), time spent on physical activity in hours per week (continuous), family poverty income ratio (continuous), systolic blood pressure (average values of four measurements), dietary energy in kcal and total vitamin D intake in mcg (both assessed by 2-day food records), and the time period for data collection (November 1 through April 30 or May 1 through October 31). Waist circumference in cm was measured at the high point of the iliac crest at minimal respiration and was treated as a continuous variable in the analysis.²⁵

Statistical Analysis

Continuous data were reported as means and standard deviations, and categorical data were presented as frequencies with percentages. Demographic characteristics by serum vitamin D status (>75, 50–74.9, and <50 nmol/L) were compared using one-way ANOVA and chi-square tests, respectively. To examine the association between sleep indicators and the likelihood of cardiometabolic diseases (diabetes and hypertension), we built logistic regression models for each disease and reported the odds ratios (ORs) and 95% confidence intervals (CIs). To prevent collinearity, we placed sleep variables into separate regression models. The results of regression analysis were stratified by sex (men, women) and the levels of serum vitamin D (>75, 50–74.9, and <50 nmol/L). Potential interactions between sleep and serum vitamin D were determined by placing cross-product terms (the product between sleep indicators and level of serum vitamin D) into the regression models. All analyses were conducted

using SPSS 23.0 (SPSS Inc., Chicago, IL, USA) with complex sampling for the prevention of sampling bias, unequal probability of selection, and oversampling. Statistical significance level was set at 0.05.

Results

A total of 10,742 participants (4997 men) in NHANES with complete data were included for analysis. Table 1 compares the characteristics of the participants by their serum vitamin D status. In general, significant differences were found across multiple variables. For example, people who had low serum vitamin D levels had short sleep durations and high waist circumferences. The exceptions were the insignificant difference in the rate of sleep disorder, rate of diabetes, level of systolic blood pressure, and dietary energy.

Table 2 demonstrates the association between sleep and cardiometabolic diseases as stratified by sex and serum vitamin D. Serum vitamin D significantly interacted with short sleep duration and abnormal sleep pattern with the association of diabetes in men. Short sleep duration was associated with diabetes (OR: 1.82, 95% CI = 1.29, 2.57) in men with serum vitamin D level of >75 nmol/L. Abnormal sleep pattern was associated with diabetes (OR: 1.95, 95% CI = 1.38, 2.77) in men with serum vitamin D level of >75 nmol/L. Serum vitamin D did not interact with sleep complaint and sleep disorder to influence the relationship with diabetes. Sleep complaint was associated with diabetes regardless of sex and serum vitamin D level, except in men (OR: 1.02, 95% CI = 0.72, 1.44) and women (OR: 1.32, 95% CI = 0.98, 1.77) with serum vitamin D level of <50 nmol/L. The presence of a sleep disorder was associated with diabetes in men with a serum vitamin D level of 50–74.9 nmol/L (OR: 1.88, 95% CI = 1.26, 2.81).

Moreover, serum vitamin D significantly interacted with sleep complaint on the association with hypertension in men ($p = 0.044$) and women ($p = 0.039$). The magnitude of the association between sleep complaint and hypertension in men was stronger when serum vitamin D level was <50 nmol/L (OR: 2.26, 95% CI = 1.57, 3.25) than when the level was >75 nmol/L (OR: 1.28, 95% CI = 0.90, 1.83). Similarly, the magnitude of the association between sleep complaint and hypertension in women was stronger when serum vitamin D level was <50 nmol/L (OR: 2.09, 95% CI = 1.53, 2.86) than when the level was >75 nmol/L (OR: 1.64, 95% CI = 0.98, 2.72). Serum vitamin D did not interact with sleep duration, sleep disorder, and abnormal

Table 1 Characteristics of Included Participants Stratified by Levels of Serum Vitamin D

	>75 nmol/L (N=3227)	50–74.9 nmol/L (N=4082)	<50 nmol/L (N=3433)	
	Mean (SD)/Number (%) ^a			p-values
Age	51.9±16.6	47.1±15.9	44.0±15.6	<0.001
% sleep duration <7 hours	1105 (34.2%)	1550 (38.0%)	1540 (44.9%)	<0.001
% have sleep complaint	922 (28.6%)	970 (23.8%)	758 (22.1%)	<0.001
% have sleep disorder	265 (8.2%)	328 (8.0%)	271 (7.9%)	0.89
% have abnormal sleep pattern	1629 (50.5%)	2056 (50.4%)	1858 (54.1%)	0.002
% as men	1321 (40.9%)	2068 (50.7%)	1608 (46.8%)	<0.001
% as Non-Hispanic White	2139 (66.3%)	1902 (46.6%)	749 (21.8%)	<0.001
% that smoked at least 100 cigarettes in life	1381 (42.8%)	1728 (42.3%)	1347 (39.2%)	0.005
% as college graduate of above	1047 (32.4%)	1127 (27.6%)	737 (21.5%)	<0.001
% married	1916 (59.4%)	2321 (56.9%)	1555 (45.3%)	<0.001
Poverty to income ratio	3.0±1.7	2.6±1.5	2.4±1.6	<0.001
Average systolic blood pressure (mmHg)	122.2±17.7	121.9±16.8	122.7±17.5	0.15
Waist circumference (cm)	96.4±15.2	99.3±15.6	101.4±17.7	<0.001
Physical activities in hours per week	4.2±6.6	3.9±6.5	3.6±6.9	0.002
% with diabetes at baseline	408 (12.6%)	525 (12.9%)	442 (12.9%)	0.95
% with hypertension at baseline	1303 (40.4%)	1380 (33.8%)	1159 (33.8%)	<0.001
Dietary energy (kcal)	2068.9±857.2	2102.8±893.1	2072.8±921.4	0.19
Vitamin D intake from diet and supplements (mcg)	22.2±53.5	8.7±10.6	4.8±6.9	<0.001
Time period for data collection				<0.001
November 1 through April 30	1162 (36.0%)	1817 (44.5%)	2064 (60.1%)	
May 1 through October 31	2065 (64.0%)	2265 (55.5%)	1369 (39.9%)	

Note: ^aSubgroup differences were tested by one-way ANOVA for continuous variables and by chi-square for categorical variables.

sleep pattern to influence the relationship with hypertension. Short sleep duration was associated with hypertension in men with serum vitamin D level of <50 nmol/L (OR: 1.37, 95% CI = 1.04, 1.80) and women with serum vitamin D level ranging from 50 nmol/L to 74.9 nmol/L (OR: 1.37, 95% CI = 1.06, 1.78). Sleep disorder remained significantly associated with the chance of hypertension in women with serum vitamin D levels of 50–74.9 nmol/L (OR: 2.46, 95% CI = 1.53, 2.86) and <50 nmol/L (OR: 1.64, 95% CI = 1.00, 2.68). Abnormal sleep pattern was associated with hypertension in men with serum vitamin D levels of <50 nmol/L (OR: 1.62, 95% CI = 1.23, 2.13) and women with serum vitamin D levels of 50–74.9 nmol/L (OR: 1.59, 95% CI = 1.23, 2.05) and <50 nmol/L (OR: 1.38, 95% CI = 1.05, 1.80).

Discussion

In the present study, short sleep duration and the presence of sleep complaint, sleeping disorder, and/or abnormal sleep pattern were associated with a high chance of diabetes and hypertension. Serum vitamin D and sleep complaint had

significant interactions to influence the likelihood of hypertension. Furthermore, the magnitude of the association between sleep complaint and hypertension appeared to be stronger in participants with the lowest level of serum vitamin D levels than in the participants with the highest levels. Although the present study did not provide prospective evidence because of the cross-sectional design, this observation may provide a hypothesis that is worth verifying in future prospective studies.

The association between sleep and diabetes in this study was consistent with previous literature.^{1,26} Insufficient sleep, poor sleep, or sleep disorder may upregulate ghrelin (the hormone that promotes appetite), reduce energy expenditure, and increase the time for eating.^{27,28} These factors may induce weight gain and impaired glucose metabolism, leading to an increased risk of diabetes. Moreover, the significant association between sleep complaint and hypertension was consistent with the findings from a recent meta-analysis on the relationship between subjective sleep quality and hypertension.²⁹ Subjective sleep quality was mainly assessed using the Pittsburgh sleep quality index,

Table 2 Sex and Serum Vitamin D-Stratified Associations Between Sleep, Diabetes and Hypertension

	Levels of Serum Vitamin D			p-value for Interaction
	>75 nmol/L	50–74.9 nmol/L	<50 nmol/L	
	OR (95% CI) ^a			
Men, diabetes				
Sleep duration <7 hours [#]	1.82 (1.29, 2.57) **	0.98 (0.76, 1.28)	0.88 (0.66, 1.18)	0.003**
Sleep complaint [#]	1.54 (1.07, 2.23)*	1.43 (1.05, 1.95)*	1.02 (0.72, 1.44)	0.282
Sleep disorder [#]	1.36 (0.81, 2.27)	1.88 (1.26, 2.81) **	0.84 (0.52, 1.35)	0.553
Abnormal sleep pattern [#]	1.95 (1.38, 2.77) ***	1.11 (0.85, 1.43)	0.87 (0.65, 1.16)	0.003**
Women, diabetes				
Sleep duration <7 hours [#]	0.95 (0.70, 1.29)	1.17 (0.88, 1.55)	1.21 (0.92, 1.58)	0.516
Sleep complaint [#]	1.52 (1.13, 2.05) **	1.54 (1.15, 2.07) **	1.32 (0.98, 1.77)	0.845
Sleep disorder [#]	1.54 (0.99, 2.41)	1.01 (0.63, 1.60)	1.31 (0.82, 2.07)	0.483
Abnormal sleep pattern [#]	1.26 (0.94, 1.69)	1.23 (0.93, 1.62)	1.29 (0.98, 1.70)	0.728
Men, hypertension				
Sleep duration <7 hours [#]	1.24 (0.92, 1.68)	0.99 (0.78, 1.25)	1.37 (1.04, 1.80)*	0.282
Sleep complaint [#]	1.28 (0.90, 1.83)	1.75 (1.30, 2.34) ***	2.26 (1.57, 3.25) ***	0.044*
Sleep disorder [#]	1.04 (0.61, 1.78)	1.67 (1.08, 2.56)*	1.78 (1.05, 3.02)*	0.190
Abnormal sleep pattern [#]	1.30 (0.97, 1.75)	1.17 (0.93, 1.47)	1.62 (1.23, 2.13) **	0.350
Women, hypertension				
Sleep duration <7 hours [#]	1.08 (0.81, 1.43)	1.37 (1.06, 1.78)*	1.14 (0.87, 1.49)	0.522
Sleep complaint [#]	1.37 (1.04, 1.80)*	1.66 (1.26, 2.20) ***	2.09 (1.53, 2.86) ***	0.039*
Sleep disorder [#]	1.64 (0.98, 2.72)	2.46 (1.52, 3.97) ***	1.64 (1.00, 2.68)*	0.328
Abnormal sleep pattern [#]	1.10 (0.84, 1.43)	1.59 (1.23, 2.05) ***	1.38 (1.05, 1.80) **	0.375

Notes: ^aMultivariate logistic regression was performed to examine the association between sleep variables, diabetes and hypertension. Adjusted variables: Age, ethnicity, smoking habit, education level, marital status, poverty to income ratio, systolic blood pressure, waist circumference, physical activity, dietary energy, vitamin D intake, time period for data collection. *p<0.05, **p<0.01, ***p<0.001 [#]Reference category: sleep duration <7 hours, no trouble in sleeping and/or no sleep disorder.

Abbreviations: CI, confidence interval; OR, odds ratio.

a validated tool for evaluating the several important aspects of sleep, including sleep duration, sleep problems, and sleep medications.³⁰ People with poor sleep quality have a 48% increased probability of having hypertension.²⁹ A meta-analysis of prospective cohorts showed that vitamin D deficiency is associated with a 24% increased risk of developing hypertension.⁹

Although our findings suggested that the association between sleep complaint and hypertension may show a trend depending on vitamin D concentration, the mechanism behind this relationship warrants further investigation. First, deficient serum vitamin D may be related to the level of blood pressure through the renin–angiotensin system (RAS) and endothelial vasodilator dysfunction.^{31,32} Animal experiments indicate that vitamin D deficiency can activate the RAS system, thereby causing hypertension, left ventricular hypertrophy, and atherosclerosis.^{33,34}

Moreover, a pooled analysis of case–control studies showed that OSA, a type of sleep disorder, is associated with the high levels of the biomarkers of RAS system activities (eg aldosterone), especially in patients with hypertension.³⁵ A clinical experiment showed that RAS activity as reflected by aldosterone fluctuates with circadian rhythm.³⁶ These findings imply that poor sleep health may cause hypertension by stimulating RAS. Further studies are needed to explore the common pathways (eg, RAS system) and associated biomarkers for vitamin D and sleep health to exert their physiological effects.

For research on serum vitamin D, sleep, and cardiometabolic health, another unanswered question is whether vitamin D from diet or supplements associates with better cardiometabolic outcomes by improving sleep health. A meta-analysis of randomized controlled trials suggested that vitamin D supplementation for more than 3 months

has a modest but significant reduction in systolic blood pressure.³⁷ Another randomized controlled trial showed that 50,000 IU vitamin D supplementation significantly improves sleep quality, reduces sleep latency, and increases the sleep duration of people with sleep disorders after 8 weeks. Patients in the trial showed significant improvements in serum vitamin D level (25.00 ng/mL before the intervention to 37.69 ng/mL after intervention).³⁸ However, the authors did not examine how vitamin D supplementation may influence cardiometabolic risks. In addition, the efficacy of intervention may vary among geographical regions and with baseline serum vitamin D level. A subgroup analysis of another meta-analysis found a significant decrease in peripheral systolic blood pressure and diastolic blood pressure in patients with vitamin D deficiency, studies performed in Asia, trials lasted for at least 8 weeks, and studies that administered >5000 IU vitamin D to each patient daily.³⁹ In summary, vitamin D supplements have preferable changes when administered at high dosages and for long intervention periods to people with vitamin D deficiency.

The current study has several limitations that should be noted for cautious interpretation. First, the current study is cross-sectional in nature. Therefore, bias due to reverse causation may exist. For example, participants with the lowest serum vitamin D levels had the lowest prevalence of hypertension. Possibly, participants with chronic diseases were more aware of their lifestyle and therefore had a lower percentage of vitamin D deficiency than those without. Despite the limitation from reverse causation, the association between sleep and cardiometabolic disease and the health benefit of vitamin D agreed with the physiological mechanisms. Further prospective studies should simultaneously consider the effect of vitamin D and sleep health to establish a temporal relationship. Second, exposure and outcomes were self-reported and may thus have introduced misclassification bias. Future studies can improve the validity by using objective measurements (eg, polysomnography or actigraphy for sleep measurement) and medical records to verify disease outcomes. Third, not every participant had available vitamin D data, and thus the representativeness of the study population may have been affected. Fourth, personal sun exposure, a main predictor of serum vitamin D level, was not determined in this study. We took the seasonality effect of sun exposure on serum vitamin D into account by adjusting the time period for data collection.

Conclusions

In the participants of NHANES, abnormal sleep pattern is associated with a high risk for diabetes and hypertension. Although the relationship between sleep complaint and hypertension may be stronger in people with vitamin D deficiency, this observation should be verified by prospective cohorts. Further studies are needed to explore the common pathways and associated biomarkers for vitamin D and sleep health to exert their physiological effects.

Data Sharing Statement

The data access from the NHANES is freely available.

Ethics and Consent Statement

The study was conducted following the Declaration of Helsinki. Ethical approval was obtained from National Center for Health Statistics Ethics Review Board (Protocol #98-12, #2005-06, #2011-17). Informed written consent was obtained from all subjects enrolled in the study.

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Disclosure

The authors report no conflicts of interest in this work.

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