Accepted Manuscript

Serum 25-hydroxyvitamin D_3 levels and poor sleep quality in a Japanese population: the DOSANCO Health Study

Koshi Nakamura, Shu-Ping Hui, Shigekazu Ukawa, Emiko Okada, Takafumi Nakagawa, Hiroaki Okabe, Zhen Chen, Yusuke Miura, Hitoshi Chiba, Akiko Tamakoshi

PII: S1389-9457(18)30734-2

DOI: https://doi.org/10.1016/j.sleep.2019.01.046

Reference: SLEEP 4007

To appear in: *Sleep Medicine*

Received Date: 19 September 2018

Revised Date: 30 November 2018

Accepted Date: 8 January 2019

Please cite this article as: Nakamura K, Hui S-P, Ukawa S, Okada E, Nakagawa T, Okabe H, Chen Z, Miura Y, Chiba H, Tamakoshi A, Serum 25-hydroxyvitamin D_3 levels and poor sleep quality in a Japanese population: the DOSANCO Health Study, *Sleep Medicine*, https://doi.org/10.1016/j.sleep.2019.01.046.

Serum 25-hydroxyvitamin D_3 levels and poor sleep quality in a Japanese population: the DOSANCO Health Study

Koshi Nakamura[1], Shu-Ping Hui[2], Shigekazu Ukawa[1,3], Emiko Okada[1,4], Takafumi Nakagawa[5], Hiroaki Okabe[2], Zhen Chen[2], Yusuke Miura[6], Hitoshi Chiba[7], and Akiko Tamakoshi[1]

[1] Department of Public Health, Hokkaido University Faculty of Medicine, Sapporo, Japan
[2] Faculty of Health Sciences, Hokkaido University, Sapporo, Japan
[3] Research Unit of Advanced Interdisciplinary Care Science, Osaka City University Graduate School of Human Life Science, Osaka, Japan
[4] Department of Nutritional Epidemiology, National Institute of Health and Nutrition, Tokyo, Japan
[5] The Hokkaido Centre for Family Medicine, Sapporo, Japan
[6] Graduate School of Health Sciences, Hokkaido University, Sapporo, Japan
[7] Department of Nutrition, Sapporo University of Health Sciences, Sapporo, Japan

Running head: Vitamin D_3 and poor sleep quality

Type of Manuscript: Original research article
Word count in Abstract/Total: 245/3247
Number of References: 47
Number of Tables/Figures: 3/0

Corresponding author: Akiko Tamakoshi
Department of Public Health, Hokkaido University Faculty of Medicine
North 15, West 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan
Tel: +81-11-706-5068 Fax: +81-11-706-7805
E-mail: tamaa@med.hokudai.ac.jp

Abstract

Objective: The present cross-sectional study investigated the relationship between serum 25-hydroxyvitamin D_3 (25[OH]D_3) levels and the presence of poor sleep quality in a community-based Japanese adult population.

Methods: Poor sleep quality, defined as poor subjective sleep quality and/or use of sleep medications, was assessed using a self-administered questionnaire. The prevalence of poor sleep quality was compared among 512 Japanese participants aged 35 to 79 years, based on serum 25(OH)D_3 levels, which were determined using tandem mass spectrometry. A logistic regression model was used to calculate the odds ratios (ORs) for the presence of poor sleep quality in each group with the highest quartile of 25(OH)D_3 serving as the reference group.

Results: Poor sleep quality was reported by 33.2% of the total study population. The prevalence of poor sleep quality was crudely higher in the first quartile group (25[OH]D_3: 2.08–18.13 ng/mL) than in the second, third and fourth quartile groups (18.14–23.07 ng/mL, 23.08–28.32 ng/mL, and 28.33–78.83 ng/mL, respectively). The ORs for poor sleep quality were 1.86 (95% confidence interval, 1.08–3.20) for the first quartile group, 0.73 (0.41–1.29) for the second quartile group, and 0.73 (0.42–1.27) for the third quartile group after adjusting for age, sex, and sociodemographic, lifestyle, physical and environmental factors, while the ORs were 1.68 (0.96–2.95), 0.69 (0.39–1.24), and 0.65 (0.37–1.15) after further adjustment for overall health status and depression status.

Conclusions: The first quartile group of serum 25(OH)D_3 was associated with the presence of poor sleep quality.

Keywords: 25-hydroxyvitamin D_3; sleep quality; epidemiology; Japanese

1. Introduction

Sleep is an essential component of health and well-being. Complaints about sleep and associated difficulties are substantial issues in developed countries [1]. Among adults in the United States, based on the National Health Interview Survey in 2013–2015, 32.5% of males and 40.4% of females reported waking up without feeling well rested [2]. The National Health and Nutrition Survey in 2015 in Japan revealed that 19.3% and 21.6% of male and female adults, respectively, were unsatisfied with their sleep [3]. These issues concerning sleep not only increase the likelihood of poor quality of life but also can be a contributing root cause of various kinds of disorders and accidents [4-8].

Recently, interest in vitamin D as a possible substance implicated in sleep regulation has been increasing, because of the biological effects it experts on a wide variety of systems in the body [9,10]. However, the role of vitamin D in sleep regulation remains unclear. One possible mechanism by which effects may occur is via vitamin D receptors located in the brainstem [11]. Animal experiments have shown that vitamin D receptors in several areas of the brainstem regulate aspects of sleep, including the onset and maintenance of sleep, and coordination of the sleep-wake cycle [11]. Several cross-sectional epidemiological studies have reported that low serum vitamin D levels are associated with poor quality of sleep (or relevant problems) in general populations, although sleep parameters differed among studies [12-18]. Some clinical trials suggest that supplementation with vitamin D can improve sleep [19,20].

The majority of relevant epidemiological studies have measured serum total 25-hydroxyvitamin D (25[OH]D)—or the sum of 25-hydroxyvitamin D_2 and D_3 (25[OH]D_2 and 25[OH]D_3)—when assessing vitamin D in the body. However, evidence suggests the

importance of quantifying 25(OH)D_2 and 25(OH)D_3 separately when evaluating vitamin D status, although 25(OH)D_3 is the predominant form of vitamin D circulating in the blood [21,22]. Only 25(OH)D_3 is converted to 1α,25-dihydroxy vitamin D_3 in the kidneys and becomes the active form of vitamin D modulating our endocrine system [21]. The present study focused on the relationship between serum 25(OH)D_3 levels and the presence of poor sleep quality in a general population, using cross-sectional data collected from residents of a single community in Japan.

2. Methods

2.1.Study design and population

A cross-sectional study was conducted as part of the Dynamics of Lifestyle and Neighborhood Community on Health Study (DOSANCO Health Study), a community-based study conducted in the town of Suttu, Hokkaido, Japan, during 2015 [23]. Briefly, a total of 2100 participants (977 men and 1123 women) comprising 79.6% of all residents aged ≥three years (other than those living at nursing homes), completed a self-administered questionnaire; if participants were elementary school students or younger, the questionnaire was filled out by their parents. Blood samples were requested from 729 of the 2100 participants (aged 35–79 years); 545 participants (245 men and 300 women) complied and were screened for eligibility. A total of 33 participants were deemed ineligible for inclusion because of missing data related to vitamin D (n=0), sleep status (n = 9), or characteristics other than vitamin D and sleep status (n = 24). The remaining 512 individuals (226 men and 286 women) were considered eligible study participants and included in the subsequent analyses. The study protocol was approved by the Institutional Review Committee for Ethical Issues of the Faculty of Medicine

(15-002, 16-007) and the Faculty of Health Sciences (16-10), Hokkaido University. Written informed consent was obtained from all participants.

2.2.Data collection

Venous blood samples were collected by cubital venipuncture after an overnight fast. Serum was separated and centrifuged after blood coagulation. Serum samples were stored at −80°C until vitamin D was measured. Serum 25(OH)D_3 (ng/mL) measurements were performed at our laboratory for each study participant (Hokkaido University Faculty of Health Science) using tandem mass spectrometry (LC-MS/MS) [24].

Sleep status was assessed using a self-administered questionnaire which was extracted from the Pittsburgh Sleep Quality Index (PSQI) [25,26]. Subjective sleep quality was reported based on the responses to the following question: "*During the past month, how would you rate your sleep quality overall?*" Participants were required to select one of the four following responses that most closely represented their experience: "*very good*," "*fairly good*," "*fairly bad*," or "*very bad*." Poor subjective sleep quality was defined as "*fairly bad*" or "*very bad*" [27]. Because the parameter of sleep quality used in our study was the most influential component of the seven components making up the PSQI global score [28,29], it was considered useful for the assessment of overall sleep status without focusing on specific complaints or problems about sleep. Use of sleep medication was reported based on the responses to the following question: "*During the past month, how often have you taken medicine (prescribed or "over-the-counter") to help you sleep?*" Participants were required to select one of the four following responses that most closely represented their experience: "*not during the past month*," "*less than once a week*," "*once or twice a week*," or "*three or more times a week*." Use of sleep medication was defined as "*once or twice a week*," or "*three or*

more times a week" [27]. In this study, poor sleep quality was defined as poor subjective sleep quality and/or use of sleep medication.

Other data collected using the self-administered questionnaire included age, sex, marriage status, work status, exercise, smoking and alcohol drinking habits, overall health status, and depression status. Habitual exercise was classified as partaking in ≥10 minutes of physical exercise per day. Smoking habits were classified according to whether a participant had never smoked, was a former smoker, or was a current smoker. Habitual alcohol drinking was classified by whether a participant had never consumed an alcoholic drink, was a former drinker, or currently consumed an alcoholic drink on average <1 day per week, or was a current drinker consuming ≥1 day per week. Overall health status was reported based on the responses to the following question: "*How would you describe your physical condition?*" Participants were required to select one of the four following responses that most closely represented their experience: "*very well*," "*fairly well*," "*fairly poor*," or "*very poor*." Poor overall health was defined as "*fairly poor*" or "*very poor*." Depression status was assessed using the Patient Health Questionnaire-9 [30,31] in combination with a history of depression. Participants were asked to report the frequency with which they may have experienced any of the nine types of depressive episodes during the previous two weeks; response choices were "*not at all*," "*several days*," "*more than half the days*," and "*nearly every day*." Each episode was weighted equally on a 0−3 scale for frequency, and the scores for each episode were combined to yield a summary score ranging from 0−27 points, with higher scores representing a more depressed state. Being depressed was defined as ≥10 points overall [32] and/or having a history of depression. Body height and weight were measured, and body mass index was calculated as weight (kg)/height squared (m^2). Serum creatinine level was measured by the enzymatic method. Estimated glomerular filtration rate was calculated using the Chronic

Kidney Disease Epidemiology Collaboration equation [33], modified by the Japanese coefficient [34].

2.3.Statistical analysis

Initially, we compared the prevalence of poor sleep quality in the study participants grouped according to quartiles of serum 25(OH)D_3. Although vitamin D deficiency is commonly defined as a total serum 25(OH)D concentration of <20 ng/mL [35], the clinical threshold of serum 25(OH)D_3 has not been established. Therefore, we primarily used quartiles to categorize serum 25(OH)D_3 levels. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated for the presence of poor sleep quality using a logistic regression model for each study group categorized by quartile of serum 25(OH)D_3. The group with the highest quartile of serum 25(OH)D_3 was the reference group. The model incorporated the following covariates as potential confounding factors: age (years, as a continuous variable), sex (male or female), marriage status (yes or no), work status (yes or no), exercise habits (yes or no), smoking habits (current, former, or never smoker, using two dummy variables with never smoker as the reference), alcohol drinking habits (≥1 day per week, <1 day per week, former drinker, or never drinker, using three dummy variables with never drinker as the reference), body mass index (kg/m^2, as a continuous variable), estimated glomerular filtration rate (ml/min/1.73m^2, as a continuous variable), and months of vitamin D measurement (August–September or October–November). Vitamin D is associated with various diseases [10], some of which can disrupt sleep. Because we assumed that such diseases would be potential mediators for the association between vitamin D and poor sleep quality, the logistic regression model further incorporated the following covariates as potential mediators: overall health status (poor or well), and depression status (yes or no).

Also, we examined the association of serum 25(OH)D_3 levels with poor subjective sleep quality and the use of sleep medication separately.

Next, we compared the prevalence of poor sleep quality in the study participants grouped by reference to the common clinical threshold used for total serum 25(OH)D (serum 25(OH)D_3 concentration <20 ng/mL and ≥20 ng/mL). Similar analyses were repeated after stratifying the study population by the absence or presence of poor overall health and/or depression, to evaluate whether the association between serum 25(OH)D_3 levels and poor sleep quality was independent of poor overall health and depression. The significance of the interaction between serum 25(OH)D_3 levels and the status of these health problems was assessed using an interaction term for the categorical variables in the multivariate-adjusted model.

Analyses were performed using Stata 15 (StataCorp LP, College Station, TX, USA). All probability values were two-tailed, and the significance level was set at $p < 0.05$.

3. Results

3.1.Characteristics of the study population

The mean age ± standard deviation of the 512 study participants was 58.5 ± 12.3 years. The median and interquartile range of serum 25(OH)D_3 concentration was 23.08 (18.14–28.33) ng/mL for the overall population. Participants classified as having poor sleep quality accounted for 33.2% of the study population. Age, sex, smoking, and alcohol drinking habits, estimated glomerular filtration rate, and months of vitamin D measurement were significantly different among groups of participants categorized by serum 25(OH)D_3 ranges according to

quartile concentrations (Table 1). Poor overall health and depression tended to be higher in the first serum 25(OH)D_3 quartile group than in most of the other groups.

(Insert Table 1)

3.2.Serum 25(OH)D_3 and poor sleep quality

Among the four study groups, the prevalence of poor sleep quality was highest in the first quartile group (serum 25[OH]D_3: 2.08–18.13 ng/mL) (Table 2). The first quartile group, but not the second or third quartile groups, had a significantly higher likelihood of poor sleep quality, compared with the fourth quartile reference group after adjusting for major potentially confounding factors (multivariate-adjusted OR [model 2] 1.86 [95% CI, 1.08–3.20]). The likelihood of poor sleep quality in the first quartile group was attenuated and no longer significant after further adjustment for overall health status and depression status (multivariate-adjusted OR [model 3] 1.68 [95% CI, 0.96–2.95]). When examining the association of serum 25(OH)D_3 levels with poor subjective sleep quality and use of medication separately, a similar pattern was observed for both individual sleep problems.

(Insert Table 2)

Results using the clinical threshold of 20 ng/mL showed that the serum 25(OH)D_3 <20 ng/mL group had a significantly higher likelihood of poor sleep quality compared with the serum 25(OH)D_3 ≥20 ng/mL group, after adjusting for major potentially confounding factors (multivariate-adjusted OR [model 2] 1.83 [95% CI, 1.22–2.73]) (Table 3). The likelihood of poor sleep quality in the serum 25(OH)D_3 <20 ng/mL group was attenuated but remained

significant after further adjustment for overall health status and depression status (multivariate-adjusted OR [model 3] 1.75 [95% CI, 1.15–2.66]).

(Insert Table 3)

After stratifying the study population by the absence or presence of poor overall health and/or depression, a similar pattern was observed for both subpopulations. In the subpopulation without both poor overall health and depression (n = 368), the multivariate-adjusted OR for poor sleep quality in the serum $25(OH)D_3$ <20 ng/mL group was 1.62 (95% CI, 0.97–2.69) relative to the serum $25(OH)D_3$ ≥20 ng/mL group. In the subpopulation with poor overall health and/or depression (n = 144), the corresponding OR in the serum $25(OH)D_3$ <20 ng/mL group was 1.83 (95% CI, 0.82–4.07). There was no significant interaction between serum $25(OH)D_3$ levels and the status of these health problems for poor sleep quality (p = 0.42 for the interaction).

4. Discussion

Study participants with the lowest serum $25(OH)D_3$ concentrations, 2.08–18.13 ng/mL in the first quartile group, showed a significantly higher likelihood for the presence of poor sleep quality compared with those having higher serum $25(OH)D_3$ levels in the second-to-fourth quartile groups after adjustment for major potential confounding factors, such as age, sex, and sociodemographic, lifestyle, physical and environmental factors. However, the likelihood of poor sleep quality was attenuated in the first serum $25(OH)D_3$ quartile group after further adjusting for the potential mediators, overall health status and depression status.

To our knowledge, this is the first evidence reported on the relationship between serum 25(OH)D_3 and sleep problems in a general population. The biological effects of vitamin D occur only as a consequence of the metabolite of 25(OH)D_3 (i.e., 1α,25-dihydroxy vitamin D_3) binding to vitamin D receptors [21]. A recent study reported that serum 25(OH)D_2 was detected in 16.4% of patients at one hospital in China using a low detection limit of 2.5 ng/mL [22]. Of the patients with detectable 25(OH)D_2 in serum, the proportion of 25(OH)D_2 contributing to overall 25(OH)D ranged from 1.3% to 100%, and an inverse correlation between 25(OH)D_2 and 25(OH)D_3 [22] was observed. Therefore, it was valuable to measure serum 25(OH)D_3, rather than total 25(OH)D when investigating the biological effects of vitamin D on human health. Also, the serum concentrations of 25(OH)D_3 in our study were measured using tandem LC-MS/MS which is considered a standard methodology [21,22,24].

Several relevant studies have measured total serum 25(OH)D levels in conjunction with assessments of the overall quality of sleep based on a questionnaire the same as or closely resembling the questionnaire used in this study. Ataie-Jafari et al. [12] reported poor sleep quality resulting in difficulties with daily activities among approximately 1000 school students in Iran after adjustment for major potentially confounding factors; the ORs (95% CIs) according to serum 25(OH)D levels of <10 ng/mL and 10–30 ng/mL were 1.472 (1.004–2.157) and 1.348 (0.917–1.982), respectively, compared with serum 25(OH)D >30 ng/mL. Jung et al. [13] reported that, among approximately 1500 fixed day workers in Korea, sleep quality assessed by the same questionnaire used in our study was worse when serum 25(OH)D was <10 ng/mL compared with when serum 25(OH)D was ≥10 ng/mL. For poor sleep quality, defined as a PSQI global score of ≥6 points, the OR was 1.36 (1.01–1.82) when serum 25(OH)D was <10 ng/mL compared with ≥10 ng/mL after adjustment for major potentially confounding factors [13]. The results of our study were roughly in accordance

with the results of these previous studies. In our study, the presence of poor sleep quality appeared to increase when serum 25(OH)D_3 was 2.08–18.13 ng/mL.

Because of the possible links between vitamin D deficiency and many diseases [10], low levels of vitamin D may result in insufficient sleep via the development of diseases that present with symptoms leading to sleep disturbance. Obstructive sleep apnoea syndrome, characterized by recurrent episodes of upper airway occlusion leading to recurrent arterial hypoxemia and sleep fragmentation/daytime sleepiness, is associated with low levels of vitamin D [36]. Restless legs syndrome, a chronic neurological movement disorder characterized by the urge to constantly move the affected body part to stop an uncomfortable sensation, is also associated with low levels of vitamin D [37]. An association between vitamin D deficiency and depression has also been reported [38]. Many conditions that present with uncomfortable symptoms, such as pain, itching, nasal discharge, and cough can also disrupt sleep. Because of a lack of data on such conditions (except for depression), we could not identify those that were more prevalent with lower levels of vitamin D. Also, it was unclear what diseases were associated with poor sleep quality in relation to low levels of vitamin D. We allowed for overall health status and depression status to evaluate the dependent and independent effect of vitamin D deficiency and health problems on sleep. Despite the higher prevalence of poor overall health and depression in participants with lower serum 25(OH)D_3 levels, low levels of serum 25(OH)D_3 were likely to be associated with poor sleep quality independent of these health problems. Because we did not allow for specific sleep-related diseases linked to vitamin D deficiency, there may have been a residual effect of potential mediators on the association of interest. Additional studies are required to clarify the effect of these potential mediators.

Taken together, our results and those of other relevant studies suggest that a strategy for the prevention or improvement of poor sleep quality is needed. Several lifestyle and environmental factors may determine vitamin D status in humans. For example, not smoking or consuming alcohol and having adequate exposure to sunlight, particularly during outdoor activities in the summer season, can help the synthesis of vitamin D in the body. Consuming foods such as fatty fish and egg yolks as well as vitamin D supplements [39-42] may also help. Lifestyle and environmental factors can contribute to improvements in poor sleep quality by increasing vitamin D levels in the body. In fact, consumption of a large amount of fish has been directly related to good quality and long duration of sleep [43,44].

The present study had several limitations. First, our study was a cross-sectional design and lacked a prospective aspect in relation to serum 25(OH)D_3 insufficiency and the development of poor sleep quality, here characterized by poor subjective sleep quality and/or use of sleep medication. Second, our results were derived from residents in one northern rural community of Japan. Caution should be exercised when generalizing our results. Based on lifestyle and environmental factors in this community, lower levels of vitamin D were found in our study population compared to residents in other areas of Japan [42,45-47]. However, the lower vitamin D levels observed in this study population facilitated our investigation into the effects of a vitamin D deficiency on sleep. Third, because we only collected data on serum 25(OH)D_3 levels at a single time point, we, therefore, could not consider annualized serum 25(OH)D_3 levels. Also, we only measured 25(OH)D_3, not total 25(OH)D, and therefore could not compare the two markers. Furthermore, sleep status was assessed using two simple questions at a single time point. Fourth, we did not collect data on medications the might lead to sleep disturbances. Finally, analyses stratified by sex were complicated by the insufficient number

of males and females; it was necessary to combine males and females to achieve valid comparisons in this study.

5. Conclusions

Serum 25(OH)D_3 levels of 2.08–18.13 ng/mL were associated with poor sleep quality in a general Japanese population, at least partially via other health problems. For individuals experiencing poor sleep quality, it may be necessary to incorporate lifestyle modification and alter environmental factors known to be associated with suboptimal concentrations of vitamin D to improve poor sleep quality.

Acknowledgments

We express special gratitude to all participants, Suttu town municipal government officers, Suttu town clinic staff members, and other people who were involved in the DOSANCO Health Study.

Funding

This study was supported by grants from Integration Research for Agriculture and Interdisciplinary Fields (14538261), and from the Japan Society for the Promotion of Science, KAKENHI (26670322 and 16K16272)

Conflict of Interest

None declared.

References

1. Skaer TL, Sclar DA. Economic implications of sleep disorders. Pharmacoeconomics. 2010;28:1015–23.
2. Galinsky AM, Ward BW, Joestl SS, Dahlhamer JM. Sleep duration, sleep quality, and sexual orientation: findings from the 2013-2015 National Health Interview Survey. Sleep Health. 2018;4:56–62.
3. Ministry of Health, Labour and Welfare, Japan. The National Health and Nutrition survey in 2015, Japan. Available at: https://www.mhlw.go.jp/file/04-Houdouhappyou-10904750-Kenkoukyoku-Gantaisakukenkouzoushinka/kekkagaiyou.pdf (Accessed on 1 Augst 2018) [In Japanese].
4. Zeitlhofer J, Schmeiser-Rieder A, Tribl G, Rosenberger A, Bolitschek J, Kapfhammer G, Saletu B, Katschnig H, Holzinger B, Popovic R, Kunze M. Sleep and quality of life in the Austrian population. Acta Neurol Scand. 2000;102:249–57.
5. Lou P, Zhang P, Zhang L, Chen P, Chang G, Zhang N, Li T, Qiao C. Effects of sleep duration and sleep quality on prevalence of type 2 diabetes mellitus: A 5-year follow-up study in China. Diabetes Res Clin Pract. 2015;109:178–84.
6. Hoevenaar-Blom MP, Spijkerman AM, Kromhout D, van den Berg JF, Verschuren WM. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study. Sleep. 2011;34:1487–92.
7. Uehli K, Miedinger D, Bingisser R, Dürr S, Holsboer-Trachsler E, Maier S, Mehta AJ, Müller R, Schindler C, Zogg S, Künzli N, Leuppi JD. Sleep quality and the risk of work injury: a Swiss case-control study. J Sleep Res. 2014;23:545–53.
8. Takada S, Yamamoto Y, Shimizu S, Kimachi M, Ikenoue T, Fukuma S, Onishi Y, Takegami M, Yamazaki S, Ono R, Sekiguchi M, Otani K, Kikuchi SI, Konno SI, Fukuhara

S. Association between subjective sleep quality and future risk of falls in older people: results from LOHAS. J Gerontol A Biol Sci Med Sci. 2018;73:1205–11.

9. Lips P, van Schoor NM. The effect of vitamin D on bone and osteoporosis. Best Pract Res Clin Endocrinol Metab. 2011;25:585–91.

10. Wimalawansa SJ. Non-musculoskeletal benefits of vitamin D. J Steroid Biochem Mol Biol. 2018;175:60–81.

11. Gominak SC, Stumpf WE. The world epidemic of sleep disorders is linked to vitamin D deficiency. Med Hypotheses. 2012;79:132–5.

12.Ataie-Jafari A, Qorbani M, Heshmat R, Ardalan G, Motlagh ME, Asayesh H, Arzaghi SM, Tajadini MH, Nejatinamini S, Poursafa P, Kelishadi R. The association of vitamin D deficiency with psychiatric distress and violence behaviors in Iranian adolescents: the CASPIAN-III study. J Diabetes Metab Disord. 2015;14:62.

13. Jung YS, Chae CH, Kim YO, Son JS, Kim CW, Park HO, Lee JH, Shin YH, Kwak HS. The relationship between serum vitamin D levels and sleep quality in fixed day indoor field workers in the electronics manufacturing industry in Korea. Ann Occup Environ Med. 2017;29:25.

14. Beydoun MA, Gamaldo AA, Canas JA, Beydoun HA, Shah MT, McNeely JM, Zonderman AB. Serum nutritional biomarkers and their associations with sleep among US adults in recent national surveys. PLoS One. 2014;9:e103490.

15. Kim JH, Chang JH, Kim DY, Kang JW. Association between self-reported sleep duration and serum vitamin D level in elderly Korean adults. J Am Geriatr Soc. 2014;62:2327–32.

16. Bertisch SM, Sillau S, de Boer IH, Szklo M, Redline S. 25-Hydroxyvitamin D concentration and sleep duration and continuity: Multi-Ethnic Study of Atherosclerosis. Sleep. 2015;38:1305–11.

17. Massa J, Stone KL, Wei EK, Harrison SL, Barrett-Connor E, Lane NE, Paudel M, Redline S, Ancoli-Israel S, Orwoll E, Schernhammer E. Vitamin D and actigraphic sleep outcomes in older community-dwelling men: the MrOS sleep study. Sleep. 2015;38:251–7.

18. Piovezan RD, Hirotsu C, Feres MC, Cintra FD, Andersen ML, Tufik S, Poyares D. Obstructive sleep apnea and objective short sleep duration are independently associated with the risk of serum vitamin D deficiency. PLoS One. 2017;12:e0180901.

19. Rorie A, Goldner WS, Lyden E, Poole JA. Beneficial role for supplemental vitamin D_3 treatment in chronic urticaria: a randomized study. Ann Allergy Asthma Immunol. 2014;112:376–82.

20. Ghaderi A, Banafshe HR, Motmaen M, Rasouli-Azad M, Bahmani F, Asemi Z. Clinical trial of the effects of vitamin D supplementation on psychological symptoms and metabolic profiles in maintenance methadone treatment patients. Prog Neuropsychopharmacol Biol Psychiatry. 2017;79:84–9.

21. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr. 2008;88:491S–9S.

22. Yu S, Zhang R, Zhou W, Cheng X, Cheng Q, Xia L, Xie S, Yin Y, Sun D, Su W, Qiu L. Is it necessary for all samples to quantify $25OHD_2$ and $25OHD_3$ using LC-MS/MS in clinical practice? Clin Chem Lab Med. 2018;56:273–7.

23.Nakamura A, Miyoshi H, Ukawa S, Nakamura K, Nakagawa T, Terauchi Y, Tamakoshi A, Atsumi T. Serum adiponectin and insulin secretion: A direct or inverse association? J Diabetes Investig. 2018;9:1106–9.

24. Okabe H, Shimizu C, Yamamoto M, Kikuchi R, Minami A, Chen YF, Imai H, Mizuta M, Chen Z, Chiba H, Hui SP. Determination of serum 25-hydroxyvitamin D_3 by LC/MS/MS and its monthly variation in Sapporo indoor workers. Anal Sci. 2018;34:1043–7.

25. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ.The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193–213.

26. Doi Y, Minowa M, Uchiyama M, Okawa M. Development of the Japanese version of the Pittsburgh Sleep Quality Index. Jpn J Psychiatry Treat. 1998;13:755–63 [In Japanese].

27. Nakashima M, Morikawa Y, Sakurai M, Nakamura K, Miura K, Ishizaki M, Kido T, Naruse Y, Suwazono Y, Nakagawa H. Association between long working hours and sleep problems in white-collar workers. J Sleep Res. 2011;20:110–6.

28. Bush AL, Armento ME, Weiss BJ, Rhoades HM, Novy DM, Wilson NL, Kunik ME, Stanley MA. The Pittsburgh Sleep Quality Index in older primary care patients with generalized anxiety disorder: psychometrics and outcomes following cognitive behavioral therapy. Psychiatry Res. 2012;199:24–30.

29. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res. 1998;45:5–13.

30. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999;282:1737–44.

31. Muramatsu K, Miyaoka H, Kamijima K, Muramatsu Y, Yoshida M, Otsubo T, Gejyo F. The patient health questionnaire, Japanese version: validity according to the mini-international neuropsychiatric interview-plus. Psychol Rep. 2007;101:952–60.

32. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–13.

33. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease

Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604−12 (Errata: Ann Intern Med. 2011;155:408).

34. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis. 2010;56:32−8.
35. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–81.
36. Archontogeorgis K, Nena E, Papanas N, Steiropoulos P. The role of vitamin D in obstructive sleep apnoea syndrome. Breathe (Sheff). 2018;14:206−15.
37. Wali S, Alsafadi S, Abaalkhail B, Ramadan I, Abulhamail B, Kousa M, Alshamrani R, Faruqui H, Faruqui A, Alama M, Hamed M. The association between vitamin D level and restless legs syndrome: a population-based case-control study. J Clin Sleep Med. 2018;14:557−64.
38. Berridge MJ. Vitamin D and Depression: Cellular and Regulatory Mechanisms. Pharmacol Rev. 2017;69:80−92.
39. Cutillas-Marco E, Fuertes-Prosper A, Grant WB, Morales-Suárez-Varela M. Vitamin D deficiency in South Europe: effect of smoking and aging. Photodermatol Photoimmunol Photomed. 2012;28:159–61.
40. Naude CE, Carey PD, Laubscher R, Fein G, Senekal M. Vitamin D and calcium status in South African adolescents with alcohol use disorders. Nutrients. 2012;4:1076-1094.
41. Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and skin physiology: a D-lightful story. J Bone Miner Res. 2007;22: V28–33.
42. Nakamura K, Nashimoto M, Hori Y, Yamamoto M. Serum 25-hydroxyvitamin D concentrations and related dietary factors in peri- and postmenopausal Japanese women. Am J Clin Nutr. 2000;71:1161–5.

43. Del Brutto OH, Mera RM, Ha JE, Gillman J, Zambrano M, Castillo PR. Dietary fish intake and sleep quality: a population-based study. Sleep Med. 2016;17:126–8.

44. Komada Y, Narisawa H, Ueda F, Saito H, Sakaguchi H, Mitarai M, Suzuki R, Tamura N, Inoue S, Inoue Y. Relationship between self-reported dietary nutrient intake and self-reported sleep duration among Japanese adults. Nutrients. 2017;9: E134.

45. Nakamura K, Tsugawa N, Saito T, Ishikawa M, Tsuchiya Y, Hyodo K, Maruyama K, Oshiki R, Kobayashi R, Nashimoto M, Yoshihara A, Ozaki R, Okano T, Yamamoto M. Vitamin D status, bone mass, and bone metabolism in home-dwelling postmenopausal Japanese women: Yokogoshi Study. Bone. 2008;42:271–7.

46. Tanaka S, Kuroda T, Yamazaki Y, Shiraki Y, Yoshimura N, Shiraki M. Serum 25-hydroxyvitamin D below 25 ng/mL is a risk factor for long bone fracture comparable to bone mineral density in Japanese postmenopausal women. J Bone Miner Metab. 2014;32:514–23.

47. Tamaki J, Iki M, Sato Y, Kajita E, Nishino H, Akiba T, Matsumoto T, Kagamimori S; JPOS Study Group. Total 25-hydroxyvitamin D levels predict fracture risk: results from the 15-year follow-up of the Japanese Population-based Osteoporosis (JPOS) Cohort Study. Osteoporos Int. 2017;28:1903–13.

Table 1. Characteristics of study participants from Suttu town, Hokkaido, Japan.

	Overall	Serum 25-hydroxyvitamin D_3 (ng/mL)				p-value for
	(N = 512)	1st quartile group ≤18.13 (2.08–18.13) (n = 128)	2nd quartile group 18.14–23.07 (n = 128)	3rd quartile group 23.08–28.32 (n = 129)	4th quartile group ≥28.33 (28.33–78.83) (n = 127)	difference
Age (yr)	58.5 ± 12.3	55.7 ± 12.0	56.3 ± 13.0	59.9 ± 11.6	61.9 ± 11.6	<0.001
Women (%)	55.9% (286)	63.3% (81)	60.9% (78)	53.5% (69)	45.7% (58)	0.02
Married (%)	70.5% (361)	67.2% (86)	73.4% (94)	69.0% (89)	72.4% (92)	0.66
Working (%)	68.0% (348)	71.9% (92)	71.9% (92)	66.7% (86)	61.4% (78)	0.22
Regular exercise (%)	42.2% (216)	34.4% (44)	43.8% (56)	45.0% (58)	45.7% (58)	0.22
Smoking habits (%)						0.02
Never smoker	46.3% (237)	51.6% (66)	54.7% (70)	43.4% (56)	35.4% (45)	
Former smoker	32.0% (164)	25.8% (33)	25.0% (32)	34.9% (45)	42.5% (54)	
Current smoker	21.7% (111)	22.7% (29)	20.3% (26)	21.7% (28)	22.1% (28)	
Alcohol drinking habits (%)						0.03
No drinking	32.8% (168)	39.1% (50)	29.7% (38)	31.8% (41)	30.7% (39)	
Former drinker	10.4% (53)	11.7% (15)	10.2% (13)	9.3% (12)	10.2% (13)	
<1 day per week	19.9% (102)	25.8% (33)	22.7% (29)	18.6% (24)	12.6% (16)	
≥1 day per week	36.9% (189)	23.4% (30)	37.5% (48)	40.3% (52)	46.5% (59)	
Body mass index (kg/m^2)	23.9 ± 3.8	24.1 ± 4.0	23.9 ± 3.5	23.9 ± 3.8	23.6 ± 3.8	0.70
Estimated glomerular filtration rate ($ml/min/1.73m^2$)	80.8 ± 11.5	82.7 ± 10.3	82.1 ± 11.3	80.5 ± 11.4	77.8 ± 12.3	0.003
Months of vitamin D measurement (%)						<0.001
August–September	34.0% (174)	28.1% (36)	24.2% (31)	30.2% (39)	53.5% (68)	

October–November	66.0% (338)	71.9% (92)	75.8% (97)	69.8% (90)	46.5% (59)	
Poor overall health (%)	20.7% (106)	24.2% (31)	16.4% (21)	25.6% (33)	16.5% (21)	0.13
Depressed (%)	13.7% (70)	18.0% (23)	12.5% (16)	12.4% (16)	11.8% (15)	0.44

Data are the means ± standard deviations, or the % (number) of participants in that category.

One-way analysis of variance or Chi-square test was used to compare each characteristic in each serum 25-hydroxyvitamin D_3 quartile.

Table 2. The odds ratio for poor sleep quality in participants grouped by serum 25-hydroxyvitamin D_3 quartiles.

	Serum 25-hydroxyvitamin D_3 (ng/mL)			
	1st quartile group ≤18.13 (2.08–18.13) (n = 128)	2nd quartile group 18.14–23.07 (n = 128)	3rd quartile group 23.08–28.32 (n = 129)	4th quartile group ≥28.33 (28.33–78.83) (n = 127)
Poor sleep quality				
Cases, n	61	34	34	41
Prevalence (%)	47.7	26.6	26.4	32.3
Age and sex-adjusted OR (95% CI), model 1	1.88 (1.11–3.17)	0.75 (0.43–1.30)	0.75 (0.43–1.28)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 2	1.86 (1.08–3.20)	0.73 (0.41–1.29)	0.73 (0.42–1.27)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 3	1.68 (0.96–2.95)	0.69 (0.39–1.24)	0.65 (0.37–1.15)	1.00 (Reference)
Poor subjective sleep quality				
Cases, n	50	30	31	32
Prevalence (%)	39.1	23.4	24.0	25.2
Age and sex-adjusted OR (95% CI), model 1	1.77 (1.02–3.06)	0.85 (0.47–1.52)	0.92 (0.52–1.62)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 2	1.72 (0.97–3.03)	0.83 (0.45–1.51)	0.89 (0.50–1.60)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 3	1.52 (0.84–2.76)	0.78 (0.42–1.46)	0.77 (0.42–1.42)	1.00 (Reference)
Use of sleep medication				
Cases, n	26	8	11	16
Prevalence (%)	20.3	6.3	8.5	12.6
Age and sex-adjusted OR (95% CI), model 1	2.03 (0.99–4.15)	0.50 (0.20–1.24)	0.65 (0.29–1.48)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 2	1.83 (0.87–3.88)	0.47 (0.18–1.21)	0.63 (0.27–1.46)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 3	1.58 (0.73–3.45)	0.43 (0.16–1.12)	0.57 (0.24–1.35)	1.00 (Reference)

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

Poor sleep quality was defined as poor subjective sleep quality and/or use of sleep medication.

Three different logistic regression models were used to calculate OR (95% CI) with the 4th quartile group serving as the reference group: model 1 was adjusted for age and sex. Model 2 was adjusted for the same covariates used in model 1 in addition to marriage status, work status, exercise habits, smoking habits, alcohol drinking habits, body mass index, estimated glomerular filtration rate, and months of vitamin D measurement. Model 3 was adjusted for the same covariates used in model 2 in addition to overall health status and depression status.

Table 3. The odds ratio for poor sleep quality in participants grouped by the threshold of 20 ng/mL for serum 25-hydroxyvitamin D_3.

	Serum 25-hydroxyvitamin D_3 (ng/mL)	
	<20 (2.08–19.99) (n = 165)	≥20 (20.00–78.83) (n = 347)
Poor sleep quality		
Cases, n	70	100
Prevalence (%)	42.4	28.8
Age and sex-adjusted OR (95% CI), model 1	1.82 (1.22–2.69)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 2	1.83 (1.22–2.73)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 3	1.75 (1.15–2.66)	1.00 (Reference)
Poor subjective sleep quality		
Cases, n	58	85
Prevalence (%)	35.2	24.5
Age and sex-adjusted OR (95% CI), model 1	1.59 (1.05–2.39)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 2	1.58 (1.04–2.40)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 3	1.49 (0.96–2.32)	1.00 (Reference)
Use of sleep medication		
Cases, n	29	32
Prevalence (%)	17.6	9.2
Age and sex-adjusted OR (95% CI), model 1	2.45 (1.39–4.30)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 2	2.35 (1.31–4.20)	1.00 (Reference)
Multivariate-adjusted OR (95% CI), model 3	2.18 (1.19–3.99)	1.00 (Reference)

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

Poor sleep quality was defined as poor subjective sleep quality and/or use of sleep medication.

Three different logistic regression models were used to calculate OR (95% CI) with the 4th quartile group serving as the reference group: Model 1 was adjusted for age and sex. Model 2 was adjusted for the same covariates used in model 1 in addition to marriage status, work status, exercise habits, smoking habits, alcohol drinking habits, body mass index, estimated glomerular filtration rate, and months of vitamin D measurement. Model 3 was adjusted for the same covariates used in model 2 in addition to overall health status and depression status.

Highlights

This study provides evidence for a relationship between serum 25-hydroxyvitamin D_3 (25[OH]D3) levels and poor sleep quality in a general population.

The prevalence of poor sleep quality was highest in the first quartile group of 25(OH)D_3 levels (2.08–18.13 ng/mL).

The likelihood of poor sleep quality in the first serum 25(OH)D_3 quartile group was smaller following consideration of overall health status and depression status.