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SCIENTIFIC INVESTIGATIONS

Sleep duration as an independent factor associated with vitamin D levels in the EPISONO cohort

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Study Objectives: Obstructive sleep apnea and short sleep duration have been separately associated with inadequate serum 25-hydroxyvitamin D [25(OH)D] levels. However, whether these 2 factors may concurrently influence 25(OH)D in the general population is unknown. We hypothesized that both obstructive sleep apnea and short sleep duration would be independently associated with lower concentrations of 25(OH)D in a sex-dependent manner.

Methods: In this cross-sectional study, 712 individuals, part of the prospective EPISONO cohort (Brazil), underwent polysomnography, answered sleep questionnaires, and had their blood collected for serum 25(OH)D quantification.

Results: Individuals with a sleep duration of < 6 hours had 2-fold increased odds of 25(OH)D < 20 ng/mL compared with those who reported 6 or more hours of sleep, even after adjusting for confounding factors. Subset sex analysis revealed that men with a sleep duration of < 6 hours had 4-fold increased odds of 25(OH)D < 20 ng/mL. In women, short sleep duration was not associated with lower 25(OH)D levels. The presence of obstructive sleep apnea (as classified according to the individual's apnea-hypopnea index) was not independently related to 25(OH)D concentrations in men or women. Sleep parameters, including sleep latency and sleep efficiency, had no association with 25(OH)D < 20 ng/mL.

Conclusions: Short sleep, but not apnea-hypopnea index, was an independent factor associated with low 25(OH)D serum levels in men, but not in women. Apnea-hypopnea index scores were not associated with 25(OH)D levels in either sex. These results raise the possibility of investigating sex-specific characteristics, such as gonadal hormone regulation, and re-evaluating obstructive events by classifying them in mild, moderate, and severe obstructive sleep apnea.

Keywords: sleep, sleep duration, obstructive sleep apnea, vitamin D, 25(OH)D serum levels.

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Evidence points to a separate effect of short sleep duration and obstructive sleep apnea on serum vitamin D levels. The concurrent impact of these 2 factors on systemic 25-hydroxyvitamin D has not been uncovered.

Study Impact: The results of this study suggest that short sleep duration has a significant association with lower 25-hydroxyvitamin D serum levels in men. Due to a significant effect of shorter sleep in males and a lack of significant effect of obstructive sleep apnea, it is proposed both that sex-specific characteristics should be evaluated and that classification of OSA in mild, moderate, and severe categories is conducted in future studies.

INTRODUCTION

Recently, a possible relationship between 25-hydroxyvitamin D [25(OH)D], the inactive form of vitamin D and the biological marker used to estimate vitamin D status,[1] and sleep has been cogitated.[2–5] Short sleep duration had been associated with lower serum 25(OH)D levels in studies of older adults[5] and Blacks.[6] It has been reported that patients with obstructive sleep apnea (OSA) have lower serum 25(OH)D concentrations compared to individuals without OSA,[7,8] while the disease severity has been inversely correlated with vitamin D levels.[5] Subjective sleep quality has also been shown to have a connection with vitamin D levels, with a weak correlation of 25(OH)D with self-reported napping having been found.[9] Moreover, in a double-blind clinical trial, vitamin D supplementation was associated with improvements in self-reported sleep quality.[10]

Studying the relationship linking vitamin D levels and sleep disorders is an important area of research, as low levels can have a variety of impacts on the health of individuals in addition to those caused by the sleep disorders themselves. Vitamin D deficiency has been suggested to have an association with hypertension, cardiomyopathy, coronary disease, and all-cause death, with supplementation improving survival rates of patients with a documented deficiency.[11] A number of original studies[12,13] and systematic reviews[14] have considered that the evolution of diabetes may be another condition influenced by low vitamin D levels. Similarly, a meta-analysis disclosed an association linking vitamin D deficiency and obesity, independent of age, the Human Development Index of the place where the studies were conducted, and their latitude (which affects the amount of sunlight exposure).[15]

When evaluating this complex network involving sleep, health, and vitamin D levels, a wide number of potentially

influential factors must be considered, including behavioral patterns, lifestyle characteristics, and life quality indicators. For example, substance consumption has been linked to 25(OH)D serum levels, with smoking being associated with lower levels,[16] although studies on the parallel between alcohol consumption and vitamin D levels have produced conflicting results, with 1 describing a deficiency of up to 40% compared to controls,[17] while another reported a positive correlation.[18] Psychiatric aspects, such as the presence of depression, may have a connection with vitamin D levels, with supplementation resulting in an improvement in the condition, as exposed in the study by Parker et al.[19] In addition to the aforementioned factors, social and lifestyle aspects must be considered with respect to their potential influence on vitamin D levels. Higher levels of education, being married, and having a healthy, more active lifestyle have been linked to higher 25(OH)D serum concentrations.[20,21] Finally, sex-specific differences are known to exist regarding sleep. It is widely known that OSA has a higher prevalence in male, overweight individuals[22] and increases the risk of cardiovascular outcomes.[23] Conversely, insomnia complaints tend to be more observed among the female population.[24] These sex-related disparities are also observed in respect of 25(OH)D levels, with evidence pointing that vitamin D deficiency is more common among women.[25,26]

Despite a broad body of evidence that links sleep to vitamin D levels, methodological limitations in previous studies have hampered data generalization. Most of these efforts were conducted in small samples and restricted groups in respect of age, sex, and body mass index (BMI). The present study is based on a carefully selected representative population sample from the city of São Paulo and investigated not only the potential reciprocal relationship between sleep and vitamin D, but considered social, psychiatric, and biological factors that may play a role in this pathway. We aimed to provide further evidence about the relationship that connects 25(OH)D levels and sleep quality, while considering the connections of these 2 factors with psychiatric, biological, and social traits.

METHODS

Population sample

This study is a cross-sectional evaluation of data of 712 individuals who participated in the follow-up study of the São Paulo Epidemiological Sleep Study (EPIS ONO) cohort between July 2015 and April 2016. This assessment was performed after an 8-year interval following the baseline EPISONO study of 2007. The EPISONO cohort is an initiative to assess the self-reported and objective sleep quality of a large-scale, representative sample of the city of São Paulo, the largest urban center in the Southern Hemisphere and 1 of the most populous cities of the world. In addition to evaluating sleep, general health parameters and socioeconomic characteristics of the studied samples were collected, allowing the creation of a large database. The full methodology regarding the initial recruitment of the EPISONO cohort was previously described by Santos-Silva and colleagues.[27]

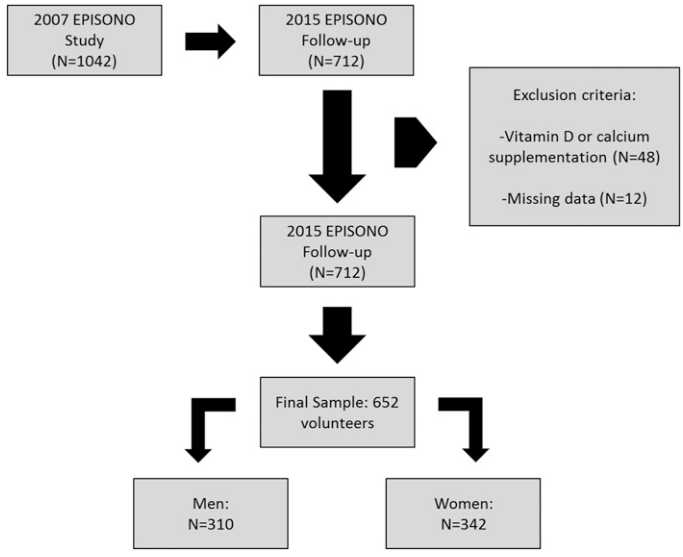
Design of the EPISONO cohort

In 2007, a 3-stage clustering technique was used to select a representative sample of the city of São Paulo. The survey managed to recruit 1,042 participants, who were invited to attend the Sleep Institute, a sleep research center in São Paulo to complete a series of questionnaires assessing self-reported sleep quality, the presence of different health conditions, lifestyle characteristics, and socioeconomic profile. Following application of the questionnaires, a polysomnographic exam was performed. In 2015, volunteers from the 2007 study were contacted by phone and invited to participate in the follow-up study, which aimed to evaluate the progression of sleep complaints in the 8-year interval, as well as the development of comorbidities. As in 2007, the participants completed a set of questionnaires assessing self-reported sleep, general health, and socioeconomic parameters before undergoing polysomnography (PSG).

The study protocol was approved by the Ethics Committee of the Universidade Federal de Sao Paulo (#2014/610514), and all the participants signed a consent form authorizing the use of their data for research analysis.

From the total of 712 people who agreed to participate in the 2015 follow-up study, 60 were excluded due to vitamin D or calcium supplementation (n = 48) or missing data (n = 12), resulting in a total of 652 individuals (342 women; mean age 49.5 ± 13.1 years) eligible for the statistical analysis. Considering the extended period of data collection, seasonality (a binary categorical variable with winter as the reference) was always considered as a covariate in this study. **Figure 1** depicts the flowchart of volunteer selection across the EPISONO cohort regarding this study.

Figure 1—Flowchart highlighting the volunteer selection for the present analysis.



The sample comprised the participants of the 2015 EPISONO follow-up study, which was a prospective assessment of the sample of the previous 2007 EPISONO study.

25(OH)D measurements

Blood samples were collected on the morning after the PSG following 10–12 hours of fasting. The samples were centrifuged to separate the blood fractions for metabolic marker assays. A colorimetric assay was used to measure the concentrations of calcium, glucose (enzymatic assay) and creatinine (Jaffé assay – Advia 1650/2400/Siemens Healthcare Diagnostics Inc.). Chemiluminescence assays were used to assess 25(OH)D concentrations (ARCHITECT 25-OH Vitamin D, Abbott Laboratories, Wiesbaden, Germany). Serum levels of 25(OH)D ≥ 20 ng/mL [approximately 25(OH)D ≥ 50 nmol/L] were used as a reference cutoff for adequate values, according to Institute of Medicine guidelines.[1] Intra-assay and interassay variation coefficients of serum 25(OH)D were 3% and 3.8%, respectively, according to the manufacturer.

Sociodemographic and clinical assessment

Sociodemographic parameters

Sex, self-reported ethnicity, smoking status (current, former, or never), current alcohol use (yes/no), and work pattern (day workers, night workers, shift workers and inactive) were assessed by questionnaires.

Anthropometric and clinical parameters

Participants were asked about their use of medications and their medical history of hypertension, diabetes, renal disease, hyperthyroidism, and depression. Trained professionals evaluated body weight, height, and systolic/diastolic blood pressure. BMI was obtained from the ratio between the body weight and the square of height. Hypertension was considered to be present in the case of 1) self-report of a medical diagnosis of the disease, 2) systolic blood pressure/diastolic blood pressure ≥ 140/90 mm Hg, or 3) self-report of antihypertensive medication use. Blood pressure was measured 3 times at 5-minute intervals using a calibrated digital electronic pressure transducer approved by the Brazilian Society of Cardiology (Geratherm Desktop 995, Geratherm, Germany). Measurements were taken on the morning after the PSG exam with the participant seated after resting for at least 10 minutes. The averages of the second and third systolic blood pressure and diastolic blood pressure measurements from the left arm were used for the analysis, according to international recommendations.[28] Presence of diabetes was considered in the case of 1) self-report of medical diagnosis of the disease, 2) fasting blood glucose ≥ 126 mg/dL[29] (American Diabetes Association, 2013), or 3) self-report of use of insulin or antiglycemic medication. Renal function was evaluated by the estimated glomerular filtration rate. The estimated glomerular filtration rate was calculated by means of the Modification of Diet in Renal Disease Study equation, which allows the estimation of glomerular filtration rate in microliters per minute per 1.73 meters squared from serum creatinine, age, sex, and ethnicity.[30] A glomerular filtration rate < 60 mL/min/1.73 m^2 was considered to indicate renal disease. Depression symptoms were assessed by the Beck Depression Inventory.[31] This questionnaire consists of 21 categories assessing emotional condition in the previous week. The higher the score, the greater the depression symptoms of the individuals.

Sleep assessment

For a complete evaluation of the sleep quality and detection of potential sleep disorders, both self-reported and objective data were considered during the analysis; the variables included in the questionnaire and polysomnographic assessments are described below.

PSG parameters

All participants underwent full-night PSG at the Sleep Institute, Sao Paulo, Brazil, and were assessed by a polysomnographic technologist using a digital system (EMBLA N7000, Embla Systems Inc., Broomfield, CO). The exam was scheduled according to the participant's availability, trying to respect their habitual sleep schedules. The physiological variables evaluated during PSG were electroencephalogram (6 channels: F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), electrooculogram (2 channels: EOG-Left-M2, EOG-Right-M1), surface electromyogram (4 channels: submentonian region, masseter region, temporal and anterior tibialis muscle), electrocardiogram (1 channel: modified D2 derivation), air flow (2 channels: thermocouple and nasal pressure), respiratory effort (2 channels: thorax and abdomen) by inductance plethysmography belts, snoring and body position (1 channel each) by EMBLA sensors, and percutaneous oxygen saturation by EMBLA oximeter. The exam was performed according to the recommended criteria of the American Academy of Sleep Medicine for the scoring of sleep stages and sleep-related respiratory events and arousals.[32] Variables that were considered during data analysis were total sleep time; sleep efficiency; N1, N2, and N3 (slow wave) sleep time; rapid eye movement sleep time; rapid eye movement sleep onset latency; arousal index; number of awakenings; percutaneous oxygen saturation; and number of desaturations (which were the basis for calculation of the apnea-hypopnea index [AHI] for each volunteer).

Sleep questionnaires

The UNIFESP Sleep Questionnaire was used to assess sleep habits,[33] in which we asked 4 questions to estimate the weighted average of sleep duration: (1) What time do you usually go to bed during the week? (2) What time do you usually wake up during the week? (3) What time do you usually go to bed at the weekend? and (4) What time do you usually wake up during the weekend? We used the participants' responses regarding both weekday (Monday–Friday, 5 days) and weekend (Saturday and Sunday, 2 days) sleep schedules. Weekdays and weekends were weighted (5/7 and 2/7) to yield self-reported habitual sleep duration. Henceforth, "sleep duration" refers to the weighted average of these 4 questions for each participant and may be further distinguished as either "short" or "long sleep duration", with a cutoff value of 6 hours of sleep duration being used in the study to define short or long sleepers. The cutoff value was chosen based on previous large-scale studies that chose this threshold value and/or detected significant deficits related to it.[34,35]

Statistical analysis

All analyses were performed using the statistical software SPSS 23.0 (IBM, Armonk, NY). To make comparisons between

categorical variables such as sex and ethnicity, chi-square tests were performed. The adjusted residual was used as a parameter for measuring statistical differences in these cases. Generalized Linear Models were conducted to assess the effect of independent variables on binary dependent variables, through the execution of binary logistic regression models. When considering inadequate 25(OH)D serum levels [25(OH)D < 20 ng/mL] as the primary outcome, the following independent variables were tested: sleep duration, AHI, sex, age, seasonality, glomerular filtration index, hypertension, diabetes, BMI, ethnicity, smoking, alcohol intake, work pattern, serum calcium levels, and Beck Depression Inventory score. The level of significance was set at $P < .05$. Initially, each of these independent variables was tested individually as a predictor of 25(OH)D < 20 ng/mL. After this initial assessment, only variables that were significant were added to a single multivariate model. This decision was necessary to avoid possible false-positive results, and to assure a statistically significant model. It should be noted that a group of variables was included as covariates to control for possible confounding factors, which could interfere in the relationship of vitamin D serum levels with the aforementioned independent variables. The covariates used for this study were chosen based on the biological plausibility and the previously cited evidence of their influence on both sleep parameters and vitamin D. The covariates used in this model were age, sex, seasonality, diabetes, BMI, hypertension, glomerular filtration rate, ethnicity, smoking, alcohol intake, work pattern, calcium serum, and Beck Depression Inventory score. As only 1 participant was categorized as having hyperparathyroidism, this variable was not included in the model.

Reporting of the study conforms to the STROBE statement conforms to the STROBE statement and the broader EQUATOR guidelines.[36]

RESULTS

Sociodemographic and clinical parameters are presented in **Table 1**. Overall sample mean serum 25(OH)D concentration was 21.84 ng/mL. Average levels for males were 22.92 ng/mL and 20.85 ng/mL for females. Significant associations were observed between 25(OH)D < 20 ng/mL and sleep duration < 6 hours ($\chi^2 = 4.08$, degrees of freedom [df] = 1, $P = .04$, adjusted ratio [AR] = 2.0), winter seasonality ($\chi^2 = 4.66$, df = 1, $P = .03$, AR = 2.2), diabetes ($\chi^2 = 7.81$, df = 1, $P < .01$, AR = 2.8), African-Brazilian individuals ($\chi^2 = 7.86$, df = 3, $P = .04$, AR = 2.1), and daytime workers ($\chi^2 = 8.39$, df = 3, $P = .03$, AR = 2.7). Sleep parameters, such as sleep latency, sleep efficiency, arousal index, percutaneous oxygen saturation, and desaturations did not have any significant association with 25(OH)D < 20 ng/mL (data not shown).

Multiple logistic binary regression models were performed to determine independent associated factors of 25(OH)D < 20 ng/mL serum levels in the whole sample (Model 1) (**Table 2**). Short sleep duration (odds ratio [OR] = 2.06, 95% confidence interval [CI] 1.04–4.09, $P = .03$), African-Brazilian ethnicity (OR = 1.80, 95% CI 1.14–2.84, $P = .01$), nonwinter seasonality (OR = 0.68, 95% CI 0.49–0.95, $P = .02$), having diabetes (OR = 1.81, 95% CI 1.15–2.85, $P = .01$), work pattern (shift work) (OR = 0.61, 95% CI 0.40–0.94, $P = .02$), work pattern (inactive) (OR = 0.51, 95% CI 0.32– 0.80, $P < .01$), and serum calcium levels ($\beta = -.41$, $P = .02$) were determined as independent factors. AHI, age, sex, BMI, and depressive symptoms did not show any significant association with 25(OH)D < 20 ng/mL.

To further investigate the possible influence of sex, 2 multiple logistic binary regression models were performed separately. **Table 2** (Model 2) exhibits the results for the men (n = 310), with short sleep duration (OR = 4.10, 95% CI 1.37–12.23, $P = .01$) and work pattern (inactive) (OR = 0.33, 95% CI 0.13–0.80, $P = .01$) remaining as independent factors of 25(OH)D < 20 ng/mL. **Table 2** (Model 3) presents the data for the women (n = 342) participants, with ethnicity (African-Brazilian) (OR = 3.45, 95% CI 1.81–6.60, $P < .01$), diabetes (yes) (OR = 2.30, 95% CI 1.18-–4.46, $P = .01$), work pattern (inactive) (OR = 0.53, 95% CI 0.29–0.95, $P = .03$), work pattern (shift work) (OR = 0.50, 95% CI 0.25–0.98, $P = .04$), and serum levels of calcium ($\beta = -0.58$, $P = .02$) remaining significantly associated with 25(OH)D levels, but short sleep duration no longer was.

Table 3 addresses the models that included objectively measured sleep duration together with self-reported sleep duration (Model 4) or that replaced self-reported sleep duration altogether (Model 5). There were no changes in significance for any of the factors and covariates included in the model and no significant effect was found for objectively measured sleep duration in either model.

To expand the understanding of the link between the factors of our model and fluctuations in vitamin D levels, a sensitivity analysis was performed by changing the cutoff value for 25(OH)D serum levels to 30 ng/mL. Similarly, to evaluate alternative definitions of short sleep duration, another analysis, changing the cutoff value for short sleep duration definition to 7 hours, was added. All the additional analyses are included in the supplemental material, where they are appropriately addressed and discussed. While the model using the 30 ng/mL threshold led to changes in statistical significance of the covariates and factors, no significant changes were noted for models using a different threshold for short sleep duration, including social jetlag or objectively measured total sleep time.

DISCUSSION

In this cross-sectional study, individuals with a sleep duration of < 6 hours had 2-fold increased odds for 25(OH)D <20 ng/mL independently of age, sex, seasonality, diabetes, BMI, ethnicity, calcium, and depression symptoms. In the analysis stratified by sex, these odds were 2 times greater in men, but not significant in women. Unexpectedly, we observed that AHI was not associated with having 25(OH)D < 20 ng/mL. Moreover, 42.17% of the sample presented low levels of 25(OH)D.

The connection between sleep and vitamin D levels

In the US Centers for Disease Control 2005–2006 National Health and Nutrition Examination Survey (NHANES),[37] vitamin D was a predictive factor of self-reported sleep duration and was associated with longer sleep latency.[37] In studies using actigraphy, lower vitamin D values had an association with short

Table 1—Frequencies and unadjusted mean ± SE of sociodemographic and clinical parameters in the EPISONO follow up cohort according to the groups with 25(OH)D ≥ 20 ng/mL (n = 377) and 25(OH)D < 20 ng/mL (n = 275).

Sociodemographic and Clinical Parameters	Vitamin D Serum Concentration		*P*
	25(OH)D ≥ 20 ng/mL	25(OH)D < 20 ng/mL	
Age (years) [n]	49.2 ± 13.6 [377]	49.9 ± 12.5 [275]	.51
Sex, % [n]			
Female	28.5 [186]	23.9 [156]	.06
Male	29.3 [191]	18.3 [119]	
Race and ethnicity, % [n]			
Caucasian	32.7 [213]*	19.5 [127]*	.04
African-Brazilian	8.3 [54]*	8.7 [57]*	
Multiracial	13.3 [87]	11.0 [72]	
Other	3.5 [23]	2.9 [19]	
Seasonality, % [n]			
Winter	23.5 [153]*	20.7 [135]*	.03
Non-Winter	34.4 [224]*	21.5 [140]*	
Work pattern, % [n]			
Inactive	15.6 [102]	9.0 [59]	.03
Night workers	1.2 [8]	1.2 [8]	
Day workers	27.3 [178]*	24.4 [159]*	
Shift workers	13.7 [89]	7.5 [49]	
BMI, % [n]			
≤24.9 kg/m^2	17.9 [117]	10.7 [70]	.19
25.0–29.9 kg/m^2	22.1 [144]	16.1 [105]	
≥30.0 kg/m^2	17.8 [116]	15.3 [100]	
Diabetes, % [n]			
Yes	8.0 [52]*	9.4 [61]*	< .01
Hypertension, % [n]			
Yes	22.1 [144]	17.0 [111]	.57
Smoking, % [n]			
Ex-smoker	17.5 [114]	13.8 [90]	.26
Current smoker	10.3 [67]	9.0 [59]	
eGFR, % [n]			
≤60 mL/min/1.73 m^2	1.8 [12]	1.2 [8]	.84
>60 mL/min/1.73 m^2	56.0 [365]	41.0 [267]	
Alcohol intake, % [n]			
Yes	29.0 [189]	19.0 [124]	.20
Calcium (ng/mL) [n]	9.3 ± 0.4 [377]	9.2 ± 0.4 [275]	.01
BDI score [n]	9.7 ± 8.8 [377]	10.4 ± 9.5 [275]	.33
AHI [n]	17.4 ± 19.5 [377]	17.5 ± 17.7 [275]	.99
Sleep duration			
<6 hours	2.5 [16]*	3.4 [22]*	.04
≥6 hours	55.4 [361]*	38.8 [253]*	

AHI = apnea-hypopnea index, BDI = Beck Depression Inventory, BMI = body mass index, eGFR = estimated glomerular filtration rate, 25(OH)D, 25-hydroxyvitamin D, * = *P* < .05.

total sleep time in a sample of male older adults[5] and in a multiethnic cohort.[6] In a recent study, vitamin D supplementation decreased sleep latency and increased sleep duration, according to the results of the Pittsburg Sleep Quality Index questionnaire, in middle-aged individuals.[10] In a recent meta-analysis,[38] vitamin D deficiency was associated with higher risk of sleep disorders.[38] Those with vitamin D deficiency had a significantly increased risk of sleep disorders, poor sleep quality, short sleep duration,

Table 2—Multiple logistic binary regression model of 25(OH)D serum levels in the sample of the EPISONO follow-up cohort study.

Predictors of 25(OH)D < 20 ng/mL	Model 1 (n = 652)		Model 2 (Men = 310)		Model 3 (Women = 342)	
	OR [95% CI]	*P*	OR [95% CI]	*P*	OR [95% CI]	*P*
Age	0.009^{β}	.24	0.001^{β}	0.91	0.01^{β}	.23
Sex						
Female	1.31 [0.91–1.89]	.13	–	–	–	–
Male	Reference		–	–	–	–
Race and ethnicity						
Other	1.44 [0.73–2.85]	.29	1.26 [0.49–3.24]	0.61	1.70 [0.59–4.86]	.31
African-European	1.44 [0.96–2.14]	.07	1.32 [0.73–2.40]	0.35	1.51 [0.86–2.64]	.14
Multiracial	1.80 [1.14–2.84]	.01	0.97 [0.48–1.96]	0.93	3.45 [1.81–6.60]	< .01
Caucasian	Reference		Reference		Reference	
Seasonality						
Non-Winter	0.68 [0.49–0.95]	.02	0.62 [0.38–1.02]	0.06	0.77 [0.48–1.22]	.27
Winter	Reference		Reference		Reference	
BMI						
≥30.0 kg/m^2	1.30 [0.84–2.03]	.23	1.09 [0.55–2.15]	0.78	1.27 [0.67–2.40]	.45
25.0–29.9 kg/m^2	1.18 [0.78–1.79]	.41	0.88 [0.48–1.59]	0.67	1.40 [0.76–2.59]	.27
≤24.9 kg/m^2	Reference		Reference		Reference	
Diabetes						
Yes	1.81 [1.15–2.85]	.01	1.78 [0.88–3.59]	0.10	2.30 [1.18–4.46]	.01
No	Reference		Reference		Reference	
Work pattern						
Inactive	0.51 [0.32–0.80]	< .01	0.33 [0.13–0.80]	0.01	0.53 [0.29–0.95]	.03
Shift work	0.61 [0.40–0.94]	.02	0.75 [0.42–1.32]	0.32	0.50 [0.25–0.98]	.04
Night shift	1.23 [0.43–3.51]	.69	2.22 [0.53–9.29]	0.27	0.67 [0.13–3.34]	.62
Day shift	Reference		Reference		Reference	
Calcium serum	$-.41^{\beta}$	.02	-0.33^{β}	0.24	-0.58^{β}	.02
BDI score	0.001^{β}	.90	-0.02^{β}	0.21	0.01^{β}	.17
AHI	-0.003^{β}	.54	-0.004^{β}	0.53	0.004^{β}	.68
Sleep duration						
<6 hours	2.06 [1.04–4.09]	.03	4.10 [1.37–12.23]	0.01	1.16 [0.44–3.04]	.75
≥6 hours	Reference		Reference		Reference	

AHI = apnea-hypopnea index, BDI = Beck Depression Inventory, BMI = body mass index, CI = confidence interval, OR = odds ratio, 25(OH)D, 25-hydroxyvitamin D, β = beta coefficient, used solely for continuous variables in this table.

and sleepiness. In this analysis, studies using both self-reported and objective methods were included.[38] Our findings were partially in agreement with these reports, suggesting that short sleep duration may predict inadequate levels of vitamin D, although it must be acknowledged that our study concerned mainly self-reported sleep evaluation.

It must be noted that the nature of the link uniting sleep duration and vitamin D deficiency and its consequences are not unanimous. A systematic review and meta-analysis showed that a higher risk for osteoporosis was directly associated with long sleep duration (> 8 h), although this study was focused in a sex-specific sample.[39] As osteoporosis is frequently encompassed by vitamin D deficiency, the role of length of sleep duration in bone metabolism mediated by 25(OH)D warrants further investigation, as it still presents many unanswered questions. Another possibility could be the bimodal effect of both short and long sleepers. As mentioned before, long sleep duration may be related to osteoporosis, which is a consequence of vitamin D deficiency.[39] This is a possible explanation given the fact that studies have found that both short and long sleepers have a higher risk of morbidity and mortality.[40–42]

The effects of age and sex

Regarding age, no association with values for 25(OH)D < 20 ng/mL was seen in this study, possibly due to the individuals in our sample being mostly middle-aged adults. Usually, a higher risk of presenting lower concentrations of 25(OH)D is found in older individuals.

Table 3—Binary logistic models of sufficient or deficient 25(OH)D considering objective and/or self-reported sleep time in the EPISONO follow-up cohort study.

Predictors of 25(OH)D < 20 ng/mL	Self-Reported and Objective Sleep Time: Model 4		Objective Sleep Time: Model 5		Final Model (n = 652)	
					OR [95% CI]	*P*
Age	0.006$^{\beta}$	0.40	0.006	0.39	0.009$^{\beta}$	.24
Sex						
Female	1.33 [0.92–1.92]	0.13	1.33 [0.92–1.91]	0.13	1.31 [0.91–1.89]	.13
Male	Reference		Reference		Reference	
Race and ethnicity						
Other	1.45 [0.73–2.87]	0.28	1.41 [0.72.279]	0.32	1.44 [0.73–2.85]	.29
Multiracial	1.44 [0.97–2.15]	0.07	1.46 [0.98–2.17]	0.06	1.44 [0.96–2.14]	.07
African-Brazilian	1.82 [1.15–2.86]	0.01	1.85 [1.18–2.90]	0.01	1.80 [1.14–2.84]	.01
Caucasian	Reference		Reference		Reference	
Seasonality						
Non-Winter	0.68 [0.49–0.95]	0.02	0.69 [0.50–0.96]	0.03	0.68 [0.49–0.95]	.02
Winter	Reference		Reference		Reference	
BMI						
≥30.0 kg/m^2	1.31 [0.84–2.05]	0.23	1.30 [0.84–2.02]	0.25	1.30 [0.84–2.03]	.23
25.0–29.9 kg/m^2	1.20 [0.79–1.81]	0.39	1.17 [0.78–1.77]	0.45	1.18 [0.78–1.79]	.41
≤24.9 kg/m^2	Reference		Reference		Reference	
Diabetes						
Yes	1.83 [1.16–2.89]	0.01	1.83 [1.16–2.87]	0.01	1.81 [1.15–2.85]	.01
No	Reference		Reference		Reference	
Work pattern						
Inactive	0.50 [0.32–0.79]	<0.01	0.51 [0.33–0.81]	<0.01	0.51 [0.32–0.80]	< .01
Shift work	0.62 [0.41–0.95]	0.03	0.63 [0.41–0.96]	0.03	0.61 [0.40–0.94]	.02
Night shift	1.18 [0.41–3.36]	0.76	1.15 [0.40–3.27]	0.80	1.23 [0.43–3.51]	.69
Day shift	Reference		Reference		Reference	
Calcium serum	−0.42	0.03	−0.42	0.03	−0.41$^{\beta}$	.02
BDI score	0.001	0.90	0.001	0.91	0.001$^{\beta}$	.90
AHI	−0.003	0.48	−0.003	0.49	−0.003$^{\beta}$	.54
TST (min)	−0.001	0.28	−0.001	0.35		
Sleep duration						
<6 hours	2.12 [1.07–4.22]	0.03			2.06 [1.04–4.09]	.03
≥6 hours	Reference				Reference	

AHI = apnea-hypopnea index, BDI = Beck Depression Inventory, BMI = body mass index, CI = confidence interval, OR = odds ratio, TST = total sleep time, 25(OH)D, 25-hydroxyvitamin D, β = beta coefficient, used solely for continuous variables in this table.

Some studies have reported contrasts in sleep duration according to sex and whether sleep was measured using self-reported or objective measures. In an older adult community, women had shorter sleep duration and worse sleep quality only when considering self-reported measures, whereas objective measures were correlated to less total sleep and more fragmented sleep in men.[43] Women are usually described as presenting more sleep complaints than men.[44,45] Thus, sex-specific sleep perception, as well as the differences in objective vs self-reported sleep measures could explain, at least in part, the present data.

It is important to consider the association between menopausal status and sleep. There is strong evidence that postmenopausal sleep quality is worse than premenopausal sleep quality.[46] As the population evaluated in this study had an average age of 49.3 years, it must be considered that menopause could be in some way modulating the sleep alterations in this population.

Another aspect that surfaced in sex comparisons is the type of work pattern. While inactivity in regard to employment seems to exert a contributing effect to reduced serum 25(OH)D levels in both sexes, shift work was an independent factor only among women. Parallels in the literature are scarce concerning shift work and vitamin D in female workers. Lehnert et al[47] detected slightly lower levels of 25(OH)D in shift-working female health care workers, but not enough to achieve statistically significant differences. In another

study, rotating shift workers had constantly lower year-round 25(OH)D levels compared to daytime workers, but no distinction regarding sex was made in the results.[48] Further research in respect of shift work and vitamin D levels in female workers is necessary to detect whether a sex-dependent influence of work patterns exist. A significant portion of studies concerning shift work and 25(OH)D levels are focused on male populations.[49,50] To the best of our knowledge, this study is the first to perform a comparison between all 3 factors of sex, work patterns, and 25(OH)D and, furthermore, to detect an effect of shift work in women, but not in men.

In our cohort, shorter sleep was associated with lower 25(OH)D in men. Lower levels of testosterone might have a connection with reduced vitamin D levels,[51] and shorter sleep may be associated with significant decreases in testosterone levels in men.[52] These results reinforce the existence of a potential network connecting sleep, endocrine regulation, and vitamin D levels. No effects of vitamin D supplementation on testosterone levels have currently been reported[53] and further studies exploring a possible link connecting vitamin D and gonadal hormone regulation are required. Our findings did not cover the evaluation of gonadal hormone levels and their link with vitamin D, but nonetheless our sex-specific results highlight the future necessity of performing this assessment.

The role of OSA and of serum calcium levels

While most initiatives did not uncover significant differences in 25(OH)D levels in OSA groups compared to non-OSA individuals,[4,54] a recent study revealed that both short sleep duration and OSA were independent factors associated with 25(OH)D < 30 ng/mL in an adult population.[55] Some methodological distinctions to our study must be considered, such as a different form of recruitment, an older sample, and a cutoff for 25(OH)D of 30 ng/mL. In some studies, continuous positive airway pressure increased 25(OH)D values, promoting changes on serum 25(OH)D levels from < 20 ng/mL to > 20 ng/mL in patients with obesity and OSA[56] and on bone turnover serum markers,[57] suggesting OSA could influence serum 25(OH)D levels as well as other biomarkers involved in bone metabolism. However, the samples included in the studies[56,57] comprised patients with obesity, while the present study used a general population sample. Reclassifying volunteers according to OSA severity instead of AHI values could potentially change the observed results for this factor. Using OSA severity as a criterion for analysis would potentially eliminate subtleties that are inherent to using AHI as a numerical variable but allow identifying differences between mild, moderate, and severe OSA cases in regard to 25(OH)D levels.

While serum calcium had statistically significant differences, they were not clinically relevant. It is possible that the minimal differences among the groups were only statistically significant due to a type I error.

Confronting objective and self-reported sleep assessment

In an attempt to understand the interplay of objective and self-reported sleep duration, 2 additional models were added, 1 based on total sleep time as defined by the polysomnographic exams and 1 that included both objective and self-reported data. Significance-wise, both were similar to the final model in **Table 2** (Model 1, with inclusion of both sexes). Possibly, homoscedasticity and multicollinearity interfered with statistical inference when both parameters were included in the model, a risk that was assumed when this approach was designed. A second explanation would be that, for an adequate mapping of the role of objectively measured total sleep time on vitamin D concentrations, an alternative model that included other objective sleep variables should be considered, something that would require a revision of the factors and covariates included in this model. As a final possibility, PSG, while an objective evaluation method and the gold standard for sleep parameters, might not have reflected the usual sleep duration of the participants due to the environmental novelty the exam represents for the volunteers; the objective sleep duration might exhibit deviations from the natural sleep pattern, due to a different sleep ambient, first night effect, and others. Considering this, a mean value of self-reported sleep duration during the week might be a more accurate estimate of participants' sleep duration to use in the comparison with 25(OH)D serum levels.

A previous large-scale epidemiological study[58] did not find a significant correlation between objective total sleep duration (including both day and nighttime sleep duration) and vitamin D levels, or with self-reported sleep parameters. At the same time, objectively measured night sleep time (and midsleep time) had a significant correlation with serum vitamin D concentrations. This study provides a reasonable comparison to our data, due to its focus, but the distinct approaches to the connection of sleep and vitamin D and the approach to objectively evaluating sleep (actigraphy) need to be considered.[58]

Psychiatric disorders (eg, depression) may affect sleep perception and contribute for the observed difference between objective and self-reported parameters. Self-perceived sleep quality is usually worse among individuals with mood disorders.[59,60] Nonetheless, it would be necessary to consider that sleep, depression, and vitamin D levels compose a complex network in which other undisclosed factors may participate, as no significant associations between depressive symptoms alone and 25(OH)D levels was detected either.

Prevalence of vitamin D deficiency

The present sample demonstrated a high prevalence of 25(OH)D < 20 ng/mL, in line with global data on vitamin D deficiency. Some studies met an overall prevalence of approximately 30% (cut point < 20 ng/mL)[61] and national rates varying from < 5% to > 70%,[62] evidencing a high variability. In comparison to reports from countries in a similar latitude of the Sao Paulo state (ie, Australia and South Africa), our sample might have a similar prevalence of vitamin D deficiency. A study on a nationally representative sample of adults (age ≥ 25 years) in Australia had a prevalence of 25(OH)D < 50 nmol/L of 20%,[63] while a similar study encountered a rate of 31% of < 50 nmol/L 25(OH)D.[64] A recent meta-analysis of African studies stated that in South Africa, prevalence of low (< 50 nmol/L) serum vitamin D in adults' ranges between 4.13% and 62%, while the largest study declared that 35% of its sample had 25(OH)D deficiency.[65] In this

sense, it may be reasonable to hypothesize that the high prevalence of low 25(OH)D found in our study is part of a global trend.[62]

Limitations and perspectives

The limitations of this study include the following. 1) The cross-sectional study design did not allow a temporal effect acting over vitamin D levels and sleep duration to be inferred. 2) Due to the epidemiological design of the study, it was not possible to perform a night of adaptation for the PSG, which may have affected some sleep parameters.[66] 3) The self-report of sleep duration could be biased, possibly being underestimated or overestimated depending on the participant. 4) While the use of AHI as a continuous variable is useful to precisely identify the impact of increases in this scale values in relation to 25(OH)D levels, categorization of volunteers according to their AHI levels (mild, moderate, or severe OSA cases) would be necessary to assess clinical applicability and could show the effect of OSA severity. 5) In the models produced in this study, physical activity was not included. Nevertheless, evidence points to a significant role of physical activity in vitamin D levels regulation, indicating this factor must be considered in the future. 6) Data assessing sunlight exposure would be of utmost importance in future analyses and could change perspective regarding other factors and covariates in our models. Self-reported sleep duration, however, still yielded important results in this study and can be considered a reliable tool to investigate presence of sleep complaints in an epidemiological approach, uncovering the perception of sleep-related problems by the general population.

In conclusion, short sleep duration is an independent predictor of low 25(OH)D levels in men, and it is clear that further experimental and prospective studies are required to establish the possible causal relationship between vitamin D and sleep duration, as well as to try to understand the mechanisms involved.

ABBREVIATIONS

AHI, apnea-hypopnea index
AR, adjusted ratio
BMI, body mass index
CI, confidence interval
df, degrees of freedom
OR, odds ratio
OSA, obstructive sleep apnea
PSG, polysomnography
25(OH)D, 25-hydroxyvitamin D

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