Rotating shift workers with vitamin D deficiency have a higher risk of obstructive sleep apnea

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Research Article

Keywords: Obesity, Circadian Rhythm, Sleep apnea syndromes, Workers, Young adults

Posted Date: November 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-998748/v1>

Abstract

Objectives

The aim of the study is evaluate the association of obstructive sleep apnea syndrome (OSA) and vitamin D deficiency (VDD) in shift workers.

Methods

This cross-sectional study included rotating shift workers in an iron ore extraction company. Participants were classified as VDD when $25(\text{OH})\text{D} < 20 \text{ ng/mL}$ for a healthy population and $25(\text{OH})\text{D} < 30 \text{ ng/mL}$ for groups at risk for VDD. Risk of developing OSA classified by Berlin Questionnaire (BQ) and NoSAS score. Data were compared using chi-square analysis with Cramer's V as effect size, and Bonferroni correction. Multivariate logistic regression analysis was performed to investigate whether VDD was associated with OSA risk assessment.

Results

Among 1461 workers, mostly male (97.4%), younger, aged 30 to 39 years (53.9%), worked shifts for more than 5 years (75.8%). A prevalence of high risk of OSA by BQ was 15.9%, and 32.5% by NoSAS score. Besides, 28.9% had VDD. In multivariate analysis, controlled for confounding factors, workers with VDD had a 79% increased chance of OSA by BQ (OR: 1.79; CI95%: 1.27-2.51) and an 85% increased chance of OSA by NoSAS score (OR: 1.85; CI95% 1.35-2.53). After subgroup analyses, similar results were not observed in workers aged 20-29 years.

Conclusion

Rotating shift workers with vitamin D deficiency are more likely to have obstructive sleep apnea, assessed by Berlin questionnaire and NoSAS score.

Introduction

Obstructive sleep apnea (OSA) is the most common cause of sleepiness among individuals who consult their physician for sleep disorders [1]. In individuals with OSA, there is increased activation of the sympathetic nervous system, leading to daytime sleepiness, increased heart rate, arrhythmias, awakenings, and other clinical manifestations [2]. The prevalence of OSA ranges from 9 to 38% in the general population, and can be as high as 90% in some groups [3], can varies according to gender, age, and associated comorbidities [1].

Several studies have shown a strong association of vitamin D levels, with the exacerbated risk for OSA [4]. Vitamin D deficiency (VDD) is a global health problem, affecting more than one billion people worldwide [5]. Few studies address occupational aspects, such as working hours. Rotating shift workers are at high risk of VDD, perhaps with at least 80% of these workers having VDD [6]. Also, shift work is a predominant factor for changes in sleep architecture. Since, it can promote discontinuation of the worker's normal feeding and sleep times, inducing changes in circadian rhythm, and consequently hormonal imbalances and disruption of normal sleep architecture [7].

Despite the considerable prevalence of OSA in the general population, it is estimated that about 75 to 80% of this population remains undiagnosed [8]. Therefore, the use of indirect instruments such as Berlin Questionnaire (BQ) and the Neck, Obesity, Snoring, Age, Sex (NoSAS) score are very useful for assessing populations at risk for OSA [9,10]. Few studies evaluate these comorbidities in alternating shift workers, a young adult population with a high prevalence of OSA, higher than that estimated for the general population [11]. Therefore, this study aims to evaluate the association of OSA measured by BQ or NoSAS with vitamin D deficiency in alternating shift workers in two regions of Brazil.

Methodology

Design and Participants

A cross-sectional study carried out with a population of shift workers from an iron ore extraction company in two locations, in the Iron Quadrangle region, Minas Gerais, and the south of the state of Pará. In all three studies, the population of shift workers with the position of operators was invited to participate: a) The first was carried out in 2012, with 391 shifts workers from four mines in the Iron Quadrangle region; b) The second study was carried out in 2015 with 192 shifts workers from another mine in the Iron Quadrangle region; c) The third study was carried out in 2018 with 932 shift workers in the southern region of Pará[12]. Therefore, in total, 1461 shift workers were analyzed. This study followed reported guidelines dictated by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Participants of cross-sectional studies carried out in 2012 and 2015 had a rotating shift schedule (4x1) of the six hours of work, followed by 12 hours of rest. After finishing the weekly four-shift cycle, they receive one day off. Participants of the cross-sectional study carried out in 2018 had a rotating shift schedule of (5x2) eight hours of work, followed by 24 hours of rest. After finishing the weekly five-shift cycle, they receive two days off.

Data collect

In all studies, data collection was performed face-to-face by teams trained to administer the questionnaires, measure anthropometric data, and collect biological samples.

The social, demographic, and economic variables evaluated were: sex, age, self-reported skin color, scholarly, and shift working time. Age was categorized as 20-29 years, 30-39 years, 40-49 years, 50-59 years, and 60 years or more; the self-declared skin color was categorized as not white (black, brown-skinned yellow or indigenous) and white; scholarly was categorized into up to 1st degree complete, 2nd degree complete, technician, graduated and postgraduate; shift working time in less five and greater than five years.

The clinical evaluation was carried out employing a questionnaire about pre-existing diseases, use of medication, smoking, alcohol consumption, physical activity; and measuring blood pressure. Smoking was classified as non-smokers, those who had never smoked or had quit smoking more than six months ago, and smokers, those who currently smoke or had quit smoking less than six months ago. Alcohol consumption was assessed using the Alcohol Use Disorders Identification Test (AUDIT) [13]. For analysis purposes, participants with no risk and low risk were grouped into the same category. The instrument used to assess the level of physical activity was the International Physical Activity Questionnaire (IPAQ) version 8 - long form. The workers were classified as low physical activity < 600 measure total energy (MET) - min/week [14].

The pre-existing diseases evaluated were: cardiovascular diseases, respiratory diseases, and chronic kidney disease. Blood pressure was measured in triplicate with a digital semi-automatic device. The measurement protocol followed the recommendations of the Brazilian Society of Cardiology and was classified as hypertension values of systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg [15].

Biochemical data

The evaluation of the biochemical profile was performed by analysis of the lipid profile, vitamin D, and glycemia. In the first two studies (2012 and 2015), blood samples were collected after a 10-hour fast and in 2018 it was collected without a previous fast.

Total cholesterol (TC), high-density lipoprotein-cholesterol (HDL), and triglycerides (TG), which were determined by the enzymatic-colorimetric method. Low-density lipoprotein-cholesterol (LDL) was calculated using Friedewald's Equation (1972). The TC was classified as normal < 190 mg/dL, HDL > 40 mg/dL, LDL < 130 mg/dL, and TG < 150 mg/dL with fasting and < 175 mg/dL without fasting [16]. Dyslipidemia classified when at least one of the parameters was altered, or use of lipid-lowering drugs. Blood glucose was determined by fasting plasma glucose (FPG) in first two studies, and glycated hemoglobin (HbA1c) in third study. Was classified as normoglycemia (FPG < 100 mg/dL or HbA1c < 5.7%) and hyperglycemia (FPG ≥ 100 mg/dL or HbA1c $\geq 5.7\%$) [17]. Vitamin D was determined by the chemiluminescence method and classified as deficiency 25(OH)D ≤ 20 ng/mL to a healthy population and 25(OH)D ≤ 30 ng/mL for groups at risk for VDD (body mass index ≥ 30 kg/m², age ≥ 60 years, and presence of chronic kidney diseases) [18]. The seasonality of blood sample collection was classified as

either autumn (March 20 to June 20), winter (June 21 to September 23), spring (September 21 to December 20), or summer (December 21 to March 19).

Anthropometric data

The assessment of body fat was performed by body mass index (BMI), waist circumference (WC), and neck circumference (NC). Height was measured using a stadiometer with a scale in centimeters and an accuracy of one millimeter. Weight was measured on a portable body composition monitor. BMI was calculated and classified according to the World Health Organization (WHO) as eutrophic (BMI 18.5-24.9 kg/m²), overweight (BMI 25.0-29.9 kg/m²) and obesity (BMI $\geq$ 30.0 kg/m²) [19]. WC was measured, in triplicate, with a simple and inelastic measuring tape at the midpoint between the iliac crest and the last costal arch, and classified as central obesity values $\geq$ 102 cm in men and $\geq$ 88 cm in women [20]. NC was measured at the level of the cartilage, just above the laryngeal prominence, and classified as increased values $\geq$ 40 cm [9].

NoSAS score

The NoSAS score was calculated according to Marti Soler et al. (2016): NC $\geq$ 40 cm, 4 points; BMI 25–29 kg/m² and BMI $\geq$ 30 kg/m², 3 and 5 points, respectively; the presence of snoring, 2 points; age $\geq$ 55 years, 4 points; and male sex, 2 points. Workers were considered to be at high risk for OSA when the NoSAS score was $\geq$ 8 points (0–17 points) [9].

Berlin questionnaire

The BQ was used in the adapted and validated Portuguese version [10]. The BQ has three categories: snoring (category 1), excessive daytime sleepiness (category 2), and comorbidities (category 3). Workers were considered to be at high risk for OSA when two of the three categories in the BQ were positive[10].

Statistical analysis

Statistical analyses were performed using Stata (version 15.0), with a significance level of 5%. The data were compared using the chi-square analyses with Bonferroni correction. For Chi-squared analyses, Cramer's V was used as an effect size, with 0.10, 0.30, and 0.50 as the thresholds for small, medium, and large effect sizes, respectively.

A binary logistic regression analysis was performed to investigate whether VDD was associated with OSA risk assessment by BQ and NoSAS score. Independent variables that had an association at a p-value of 0.2 were used in multivariate logistic regression with a stepwise backward elimination. Collinearity among the covariates was evaluated. Hosmer-Lemeshow test and Akaike Information Criterion (AIC) was used to assess the goodness-of-fit of the models.

Sampling power (a posteriori) was performed on proportion and sample size data of similar studies using the G*Power program (version 3.1.9.2). The analysis was performed with an alpha level of 0.05 (using a

two-tailed test), with an estimated power of 0.98.

Ethical issues

This study was conducted following the guidelines by the Declaration of Helsinki, and all procedures involving human participants were approved by the Research Ethics Committee of the Federal University of Ouro Preto (2012: CAAE: 0018.0.238.00-11; 2015 CAAE: 39682014.7.0000.5150; 2018: CAAE: 93760618.5.0000.5150). Written informed consent was obtained from all participants.

Results

The study included 1461 rotating shift workers from two different mining regions in Brazil, and 28.9% had VDD. Most workers were male (97.4%), and age 30 to 39 years (53.9%), with a minimum of 20 and maximum of 65 years, 73.4% self-reported as non-white, had up to 2nd degree complete (70.7%), and worked shifts for more than 5 years (75.8%). Regarding anthropometric, clinical, and behavioral variables, most workers had high WC and NC (62.5% and 61.7%, respectively), 77.8% had dyslipidemia, almost half had a low level of physical activity (48.9%), and 61.9% consumed alcohol (Table 1).

The shift workers evaluated had 15.9% high risk of OSA assessed by the BQ, and 32.5% high risk of OSA assessed by NoSAS score. Both were higher in individuals with VDD ($p < 0.001$) (Table 1).

Table 1: Characteristics of rotating shift workers, total and by vitamin D deficiency.					
Vitamin D					
Characteristics	Total (n=1461)	Normal 71.1% (n=1039)	Deficient 28.9% (n=422)	<i>p</i>	<i>V</i>
Sex					
Female	38 (2.6)	30 (2.9)	8 (1.9)	0.280	0.028
Male	1423 (97.4)	1009 (97.1)	414 (98.1)		
Age, years					
20 – 29	228 (15.6)	173 (16.6)	55 (13.0)	0.004	0.086
30 – 39	788 (53.9)	575 (55.3)	213 (50.5)		
≥ 40	445 (30.5)	291 (28.0)	154 (36.5)		
Skin color					
White	392 (26.6)	291 (27,9)	101 (26.3)	0.093	0.044
Not white	1069 (73.4)	748 (72.1)	321 (76.4)		
Scholarly					
1st degree complete	56 (3.8)	34 (3.3)	22 (5.2)	0.007	0.091
2nd degree complete	1033 (70.7)	729 (70.2)	304 (72.0)		
Technician	337 (23.1)	257 (27.7)	80 (19.0)		
Graduated	35 (2.4)	19 (1.8)	16 (3.8)		
Shift work, years					
< 5	354 (24.2)	268 (25.8)	86 (20.5)	0.029	0.057
≥ 5	1107 (75.8)	711 (74.2)	336 (79.5)		
Anthropometric data					
High WC	912 (62.5)	556 (53.6)	356 (84.4)	< 0.001	0.288
High NC	902 (61.7)	742 (71.4)	160 (37.9)	< 0.001	0.313
Chronic diseases					
Hyperglycemia	460 (31.7)	290 (28.1)	170 (40.6)	< 0.001	0.121
Dyslipidemia	1137 (77.8)	768 (73.9)	369 (87.4)	< 0.001	0.147
Hypertension	526 (36.0)	328 (31.6)	198 (46.9)	< 0.001	0.145

Behavioral variables						
^a Low physical activity	715 (48.9)	501 (48.2)	214 (50.7)	0.388	0.022	
Smoking	226 (15.5)	154 (14.8)	72 (17.1)	0.283	0.028	
^b Alcohol consumption	150 (10.3)	101 (9.7)	49 (11.6)	0.281	0.028	
Seasonality						
Winter	536 (36.7)	371 (35.7)	165 (39.1)	< 0.001	0.166	
Spring	579 (39.6)	382 (36.8)	197 (46.7)			
Autumn	156 (10.7)	142 (13.7)	14 (3.3)			
Summer	190 (13.0)	144 (13.9)	46 (10.9)			
Mining regions						
Minas Gerais	529 (36.2)	347 (33.4)	182 (43.1)	< 0.001	0.091	
Pará	932 (63.8)	692 (66.6)	240 (56.9)			
OSA risk assessment						
Berlin questionnaire	232 (15.9)	107 (10.3)	125 (29.6)	< 0.001	0.239	
NoSAS score	475 (32.5)	224 (21.6)	251 (59.5)	< 0.001	0.367	
OSA: obstructive sleep apnea; <i>p</i> : p-value of Pearson's chi-square test; V: value of Cramer's V test; WC: Waist circumference; NC: Neck circumference.						
^a Low physical activity (< 600 measure energy total - min/week); ^b AUDIT medium- and high-risk alcohol consumption.						

Individuals with VDD demonstrated higher positive scores for BQ categories 1 and 2 ($p < 0.001$). Category 2 had the lowest percentage of positive scores (5.2%). For the NoSAS score, workers with VDD had high positive criteria for overweight, obesity, high NC, and the presence of snoring ($p < 0.01$) (Table 2).

In multivariate analysis, controlled for confounding factors, workers with VDD had 79% increased chance of high risk for OSA from BQ (OR: 1.79; CI95%: 1.27-2.51) and 85% increased chance of high risk for OSA

Table 2: Berlin Questionnaire values (workers positive in each category) and NoSAS score criterion (workers positive in each criterion) of rotating shift workers according to vitamin D.						
Vitamin D						
	Total (n=1461)	Normal (n=1039)	Deficient (n= 422)	OR (95% CI)	<i>p</i>	<i>V</i>
Categories of BQ, n (%)						
Category 1, positive	348 (23.8)	207 (19.9)	141 (33.4)	2.02 (1.56-2.59)	< 0.001	0.143
Category 2, positive	76 (5.2)	49 (4.7)	27 (6.4)	1.38 (0.85-2.24)	0.189	0.034
Category 3, positive	677 (46.3)	639 (35.5)	308 (73.0)	4.90 (3.82-6.29)	< 0.001	0.341
NoSAS criterion, n (%)						
Overweight	743 (50.9)	596 (57.4)	147 (34.8)	1.85 (1.30-2.63)	< 0.001	0.204
Obesity	307 (21.0)	80 (7.7)	227 (53.8)	13.95 (10.36-18.79)	< 0.001	0.512
High NC	431 (29.5)	212 (20.4)	219 (51.9)	1.43 (1.34-1.52)	< 0.001	0.313
Snoring	633 (43.3)	415 (39.9)	218 (51.7)	1.26 (1.13-1.42)	< 0.001	0.107
Age > 55 years	20 (1.4)	15 (1.4)	5 (1.2)	0.95 (0.73-1.22)	0.700	0.010
Sex, men	1423 (97.4)	1009 (97.1)	414 (98.1)	1.24 (0.83-1.83)	0.280	0.028
<p>BQ: Berlin questionnaire; NC: Neck circumference; OR: Odds ratio; CI: Confidence interval; <i>p</i>: p-value of Pearson's chi-square test; <i>V</i>: value of Cramer's V test.</p> <p>Category 1 of BQ includes five questions on snoring, category 2 three questions on daytime somnolence and sleepiness when driving, and category 3 one question on the history of hypertension and obesity.</p> <p>Overweight: BMI 25.0-29.9 kg/m²; Obesity: BMI ≥ 30.0 kg/m²; Snoring: Self-report of presence of snoring during sleep</p>						

from NoSAS score (OR: 1.85; CI95% 1.35-2.53) (Table 3).

Besides, we also evaluated the association of VDD with risk for OSA stratified by age groups. Workers

Table 3: Odds ratio (95% confidence interval) of risk assessment of obstructive sleep apnea by vitamin D deficiency in rotating shift workers.		
Berlin questionnaire		
OR (95% CI)	<i>p</i>	AIC
3.88 (2.90–5.19)	< 0.001	1626.739
1.79 (1.27-2.51)	0.001	1426.172
OR: Odds ratio; CI: Confidence interval		
Model crude: Prevalence of obstructive sleep apnea vs vitamin D		
Model adjusted: Model crude addition of seasonality, skin color, geographic location, waist circumference, hyperglycemia, dyslipidemia, and hypertension		

aged 20-29 years had no association of VDD with a high risk for OSA for BQ or NoSAS. In workers with 30-39, those with VDD had an 83% and 87% increased chance of high risk for OSA on BQ and NoSAS, respectively. In workers 40 and older, those with VDD had a 107% and 148% increased chance of high risk for OSA, on BQ and NoSAS, respectively (Table 4).

Table 4: Odds ratio (95% confidence interval) for adjusted multivariate analysis of risk assessment of obstructive sleep apnea associated with vitamin D deficiency, stratified by age in rotating shift workers.				
	Berlin questionnaire			NoSAS score
n (%)	OR (95% CI)	<i>p</i>	AIC	OR (95% CI)
228 (15.6)	1.27 (0.43-3.68)	0.660	204.552	0.99 (0.40-2.47)
788 (53.9)	1.83 (1.12-2.96)	0.015	763.858	1.87 (1.18-2.96)
445 (30.5)	2.07 (1.20-3.56)	0.009	472.941	2.48 (1.48-4.17)
OSA: Obstructive Sleep apnea; OR: Odds ratio; CI: Confidence interval				
Multivariate analysis included seasonality, skin color, geographic location, waist circumference, hyperglycemia, dyslipidemia, and hypertension				

Discussion

This is the first study of male rotating shift workers in an iron ore extraction company- to examine the association of VDD and the risk of OSA. We found that workers with VDD were more likely to have a high risk of OSA by BQ and NoSAS scores.

We found that 28.9% of the workers evaluated had VDD, and was more prevalent in workers older than 40 years, with longer working time in rotating shifts, high WC and NC, with chronic diseases, and in workers at high risk for OSA. The prevalence of VDD found was similar to the Brazilian population (33%) [21] and lower than found by Sowah et al. (2017), in which up to 80% of rotating shift workers have VDD. Previous studies have suggested that a higher prevalence of VDD is due to lack of sunlight exposure in shift workers [6]. The lower prevalence of VDD in our study may be partially explained due to the workday, where the work schedule provides day shift periods (e.g., 7 am to 1 pm and 1 am to 7 am), or time off, which may increase their sun exposure at these times.

Besides, we found that 15.9% and 32.5% of workers were classified as high risk for OSA by BQ and NoSAS, respectively. And it was almost twice as high in workers with VDD, with 29.6% and 59.5% at high risk for OSA by BQ and NoSAS. Almost eight in ten individuals do not receive a diagnosis of OSA [8], because the gold standard (polysomnography) is inaccessible. Thus, alternative, more accessible and simplified instruments, have been used in the screening of OSA [22,23] and may be useful for assessing determinants, in populations at high risk for OSA, such as rotating shift workers [24].

The prevalence of high risk for OSA ranges from 9% to 38% in the general population, depending on gender and age [3]. A population-based cohort from Switzerland, HypnoLaus, with 2121 participants, found an estimated prevalence of 25.0% and 43.0% of OSA for BQ and NoSAS, respectively [9]. Furthermore, in a population-based cohort conducted in Brazil, EPISONO, with 1042 individuals, the estimated prevalence of OSA using BQ was 30.0% and NoSAS was 35.0% [9]. In both studies, the prevalence measured by the BQ was at least two times higher than that found in our study. This difference may be related to the age of the participants, in which 43% of the subjects assessed were 60 years or older, different from our study which was with young adults. And also with the fact that the BQ may not be the most appropriate instrument for this population, since in category 2 questions are asked about excessive sleepiness when driving vehicles. Only 5.2% of workers were scored positively in this category, a value 78.9% lower than that found by Tan et al. (2017) in a study of the general population [25]. Demonstrating a possible high rate of BQ underreporting for our study sample, where the majority of shift workers, were heavy machine operators (e.g., off-road trucks capable of hauling 25-400 tons of mining material), and may have underreported this information due to their occupational role [24].

OSA is a multifactorial chronic disease, with risk factors well described in the literature, such as gender, age, obesity, alcohol, and tobacco consumption [3]. However, some recent studies have shown that vitamin D deficiency may be an important risk factor [26]. In our study, we observed that after adjustment for confounding variables, workers with vitamin D deficiency were 79% more likely to have a high risk for OSA by QB and 85% more likely to have a high risk for OSA by NoSAS score. Similar results were found by others studies, in which patients with OSA, the higher the apnea-hypopnea index (AHI), the lower were the 25(OH)D levels [26]. However, caution is needed in interpreting the data, as there is an inverse association between vitamin D metabolites and excess body fat [5]. Goswami et al. (2016) discuss that the association between serum 25(OH)D (vitamin D) levels < 20 ng/mL and OSA may be explained by some confounding factors, mainly BMI and neck circumference [27]. In this regard, it is important to

mention that in our study there was an association of VDD with section 1 (witnessed snoring and apnea), in which workers with VDD were 102% more likely to have scored positively in this category, which corroborates with some studies that evaluated the association of VDD with OSA by objective measures such as polysomnography [28]. Furthermore, when assessing NoSAS scores, we observed that workers with VDD were 26% more likely to self-report the presence of snoring during sleep, one of the most frequently seen clinical signs in OSA [22].

In addition to obesity, another extremely relevant risk factor for the occurrence of OSA is aging. Piovezan et al. (2017) verifying the association of vitamin D levels and apnea, found that individuals with 25(OH)D levels < 30ng/mL had a higher percentage of OSA than individuals with 25(OH)D > 30ng/mL, only in participants over 50 years old [28]. In this study, demonstrated the association between vitamin D and OSA starts earlier (age $\geq$ 30 years) in shift workers. Also, in concordance with previous studies, with increasing age the greater the chances of OSA. Shift workers are at higher risk of developing OSA because of the work schedule, which appears to contribute to the increased risk in younger adults. The hypotheses of this association are vitamin D deficiency can increase the risk of developing obstructive sleep apnea through the promotion of adenotonsillar hypertrophy, airway muscle myopathy, and/or chronic rhinitis [29]. In addition to OSA, aging also affects endogenous vitamin D synthesis. There is a decrease in concentrations of the precursor (7-dehydrocholesterol) of vitamin D in the skin with aging, decreasing its production from the sun's rays [30].

Therefore, after adjusting for confounding variables, we concluded that workers with vitamin D deficiency are more likely to be at high risk for OSA, as measured by QB or NoSAS. We agree that the gold standard method for diagnosing OSA is polysomnography, however, it is an expensive test that requires qualified professionals and structure to be conducted. Thus, subjective analysis, through questionnaires or indicators, can provide very useful data for a better understanding of the presence of sleep apnea risk and its determinants. Furthermore, very little is explored in the literature about OSA in rotating shift workers, and also its relationship with deficient vitamin D levels. This is a population at risk for several comorbidities [12] and we encourage that similar studies be conducted with this population.

Conclusion

Rotating shift workers have a high risk for obstructive sleep apnea, and workers with vitamin D deficiency have higher chances of apnea, even after adjustment for confounding factors. After subgroup analyses, the association of VDD and OSA was maintained for only workers aged 30 years and older. The impact of these comorbidities reinforces the need for prevention, early identification, and intervention on the potential health harms of these workers. And we hope that more research will be conducted using direct methods, such as polysomnography examination to assess sleep in populations prone to OSA, as a way to promote healthy habits and prevent accidents.

Declarations

Not applicable

Funding

This study was supported by the Conselho Brasileiro de Desenvolvimento Científico e Tecnológico (CNPq, Distrito Federal, Brazil) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brazil (CAPES)- finance code 001 for PhD student scholarship.

Conflicts of interest/Competing interests

This was not an industry-supported study. The authors have indicated no financial conflicts of interest. There is no off-label or investigational use in this study.

Availability of data and material

'Not applicable'

Code availability

'Not applicable'

Authors' contributions

All authors made substantial contributions to the conception and design of the work, analysis, and interpretation of data. Drafted the work and revised it critically for important intellectual content. All authors approved the version to be published.

Ethics approval

All procedures involving human subjects were approved by the Research Ethics Committee of the Federal University of Ouro Preto (2012: CAAE: 0018.0.238.00-11; 2015 CAAE: 39682014.7.0000.5150; 2018: CAAE: 93760618.5.0000.5150).

Consent to participate

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and written informed consent was obtained from all subjects.

Consent for publication

Informed consent was obtained from all individual participants included in the study

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