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REVIEW

Serum 25(OH)D levels and obstructive sleep apnea syndrome severity in patients without comorbidities: a systematic review and meta-analysis

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Abstract

Purpose The aim of the present systematic review was to corroborate existing evidence on how serum25(OH)D levels affect obstructive sleep apnea syndrome (OSAS) severity in the absence of comorbidities.

Methods From inception to May 2024, PubMed, Scopus, and Embase electronic databases were systematically screened to identify randomized controlled trials (RCTs), quasi-RCTs, prospective, and retrospective studies. A strict search protocol was applied following the application of PROSPERO, under the registration number CRD42023468744. The formulated question based on PICO process was: "how do serum25(OH)D levels affect the severity of OSAS or result in enhanced sleep function?". Collected results were finally reviewed for meta-analysis and quality assessment according to the ROBINS-I tool.

Results Data from 24 studies were pooled and divided into 15 case-control studies and 9 cross-sectional studies. All studies involved a total of 2640 OSAS subjects and 933 healthy subjects. All studies underwent qualitative analysis whereas only 20 were collected for meta-analysis. Mild OSAS showed 25(OH)D levels non-statistically significant ($P=0.12$) than the healthy patients whereas moderate OSAS ($P=0.004$) and severe OSAS ($P<0.001$) differed significantly from control groups. Meta-regression suggested that OSAS severity correlated inversely to the deficiency of 25(OH)D serum levels. Qualitative assessment and Egger's test revealed an elevated risk of bias but low presence of publication bias, respectively.

Conclusion Serum levels of 25(OH)D were observed to be inversely proportional to OSAS severity in patients without coexisting morbidities. 25(OH)D levels in mild OSAS patients were not significantly different from non-OSAS patients, suggesting vitamin supplementation to improve potential sleep disorders.

Keywords 25(OH)D · Meta-analysis · OSAS · Obstructive sleep apnea syndrome · Vitamin D

Introduction

Vitamins are organic compounds vital for sustaining life and ensuring optimal health. Unlike macronutrients such as carbohydrates, proteins, and fats, which the body requires in larger amounts, vitamins are needed in smaller quantities [1]. Despite that, the body cannot produce most vitamins in sufficient quantities, necessitating their intake through food or supplements. Deficiencies in these essential micronutrients can lead to a spectrum of health issues, underscoring their importance in maintaining overall physiological balance.

Vitamin D (Vit.D) represents a group of fat-soluble secosteroids normally provided as dietary supplements [2]. It is also endogenously produced as cholecalciferol (Vit.D_3)

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when ultraviolet-B rays from sunlight reach the skin and cause its synthesis from 7-dehydrocholesterol (7-DHC). Vit.D_3 is biologically inactive and requires two reactions to become active. The first takes place in the liver and transforms it to calcifediol (25(OH)D_3) or ercalcidiol (25(OH)D_2). The second reaction happens predominantly in the kidneys and forms calcitriol (1,25-$(OH)_2D_3$) or ercalcitriol (1,25-$(OH)_2D_2$), which are their respective physiologically active forms [3]. These forms mainly regulate calcium and phosphorus levels and promote bone resorption by causing osteoclast differentiation and by enhancing existing osteoclast activity [4]. They are both quantified together in blood as 25(OH)D.

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by repeated episodes of complete or partial obstruction of the upper airway during sleep. This obstruction leads to reduced airflow, causing apnea or hypopnea, which can result in disrupted sleep patterns [5]. Hypoxic stress, particularly intermittent hypoxia, plays a crucial role in the pathophysiology of OSAS. During apnea or hypopnea, patients experience repeated cycles of oxygen desaturation and subsequent reoxygenation, leading to oxidative stress and systemic inflammation. These fluctuations can contribute to vascular dysfunction, metabolic dysregulation, and increased inflammatory responses, which are related to the severity of OSAS.

There is evidence to suggest that there may be a relationship between OSAS and hormones, particularly hormones involved in regulating metabolism and stress response as vitamins [6]. The intersection of sleep medicine and vitamins may not seem obvious at first, but when delving deeper, potential correlations emerge that highlight the influence of vitamins on respiratory health; in fact, Vit.D may influence OSAS through several potential mechanisms. It plays a role in muscle function, potentially maintaining the strength of upper airway muscles and reducing airway collapse during sleep [7]. Additionally, its anti-inflammatory properties may alleviate inflammation in the upper airway, thus improving airway function [8]. Vit.D's modulation of the immune system could indirectly impact OSAS by reducing susceptibility to respiratory infections [9]. Neurologically, optimizing 25(OH)D levels may regulate pathways involved in sleep, potentially improving OSAS symptoms [10]. Also, effects on cardiovascular health and weight management may additionally mitigate OSAS risk factors such as obesity and cardiovascular diseases [11]. Moreover, most of them represent risk factors and comorbidities that might affect the vitamin's metabolism as well as their systemic quantities and availability.

Although obtaining vitamins naturally from a balanced diet is ideal, there are situations where supplementation may become necessary, especially if deficiencies are clinically detected such as those related to the grade of OSAS [12]. However, it's important to proceed with caution; over-supplementation can pose significant risks. By performing the present systematic review and meta-analysis regarding the serum levels of 25(OH)D in relation to the severity of OSAS and in absence of systemic comorbidities, researchers aim to consolidate existing knowledge, identify gaps in the current literature, and may provide evidence-based recommendations for both clinical practice and future investigations.

Materials and methods

Protocol and registration

This systematic review was conducted to comprehensively assess the current scientific literature regarding the correlation between the serum levels of 25(OH)D and sleep disorders and their severity. The protocol was prospectively registered with PROSPERO, under the registration number CRD42023468744, and reported in adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards of quality for reporting systematic reviews and meta-analyses [13].

Eligibility and inclusion criteria

The selection criteria were structured according to the PICO statement [14]: P (Population): Human populations affected by OSAS, classified depending on AHI (Apnea Hypopnea Index) by polysomnography, excluding any further systemic comorbidity associated with sleep disorders; I (Intervention): Quantification of serum 25(OH)D levels in any OSAS severity grade; C (Comparison): Subjects not affected by OSAS; O (Outcome): Serum 25(OH)D level changes in accordance with OSAS severity grade.

The formulated clinical question based on this PICO was: "Among subjects affected by OSAS, is the severity related to and dependent on the serum levels of 25(OH)D?"

Search strategy

The research was conducted by screening PubMed, Scopus, and Embase electronic databases from inception to May 2024. A combination of MeSH terms and free-text terms were employed: (*"vitamin D"* OR *"vitamin D supplementation"* OR *"calcidiol"* OR *"calcitriol"* OR *"cholecalciferol"* OR *"25-hydroxyvitamin D"* OR *"25(OH)D"*) AND (*"OSAS"* OR *"obstructive sleep apnea syndrome"* OR *"sleep disorder"*).

Two reviewers independently screened the titles, abstracts, and subsequently the full texts. The Inclusion

criteria during the study selection were the following ones: randomized controlled trials (RCTs), quasi-RCTs, observational studies, prospective and retrospective cohort studies; studies investigating the role or effect of 25(OH)D in relation to OSAS; articles published in English language with available full text or data.

Reports that did not satisfy the inclusion criteria, such as studies including risk factors and comorbidities except for overweight or obesity, were excluded during the screening process. Also, discrepancies during the study selection were reconciled through discussion and, if consensus was not reached, a third expert reviewer was consulted.

Data collection

Utilizing a predesigned data extraction form, the following details were documented into tables for the qualitative analysis: author(s) and publication year; country in which the study has been carried out; latitude of the center of study; study design; number of subjects who underwent the quantification of serum level of 25(OH)D, according to the severity of OSAS, and the number of subjects forming the control group; mean serum level of 25(OH)D and its standard deviation (SD) or median and confidence interval (95%CI) or range (Min-Max) for each severity group, as well as total means among subjects affected by any OSAS; BMI (Body Mass Index) and its standard deviation or equivalent median and range; laboratory method used for the quantification of 25(OH)D in blood; clinical method used for the quantification of OSAS severity; primary and secondary outcomes, including any measure of clinical relevance as well as the description of the study.

Risk of bias and assessment of study quality

Two researchers assessed the quality of the studies included in the present systematic review according to the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool, which evaluates the risk of bias in case-control and quasi-randomized studies across seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results [15]. Each domain was rated as having low, moderate, serious, or unclear risk of bias, and these ratings were used to determine an overall risk of bias and subsequent quality for each study.

Meta-analysis

Meta-analysis was performed using Review Manager software (RevMan, version 5.4; The Cochrane Collaboration, 2020) with an inverse variance method. The significance level was set at 0.05. Heterogeneity was assessed by I^2, distinguishing low (< 25%), moderate (25–50%), substantial (50–75%), and high (> 75%) heterogenicity. Since there was statistical heterogenicity between studies, the random-mixed effects method was used, even because more than five studies were included in the meta-analyses, also for subgroups. Mean differences (MDs) were calculated for all the comparisons since similar 25(OH)D quantification methods have been used. Therefore, forest plots were made comparing any OSAS group with control group and comparing single severity OSAS grade with control group, as well as among severity groups.

Finally, to deeper investigate heterogeneity across studies, subgroup analysis based on age, BMI, and latitude were also tested on "Any OSAS" groups. For these analyses those continuous variables were transformed to categorical ones; age was used to distinguish between adult (> 18 years) and pediatric (2–18 years) OSAS, BMI to compare normal weight (BMI < 24.9), overweight (25 < BMI < 29.9), and obesity (BMI≥30), and the latitude where the study was carried out was categorized as low-latitude (0–30 degrees), medium-latitude (30–60 degrees), and high-latitude (60–90 degrees).

Meta-regression

To explore the potential sources of heterogeneity among the included studies, meta-regression analyses were carried out. The dependent variable was the effect size (mean difference), and the independent variable was the severity of OSAS, categorized as mild, moderate, or severe. The severity was treated as a categorical variable and encoded numerically. Moreover, the covariates of patients' age, patients' BMI, and the latitude where each study was carried out were tested within "Any OSAS" groups with a regression model. Since a linear relationship between the 25(OH)D mean differences and the variables was expected, continuous covariates were also used and crossed with categorical ones. For OSAS severity regression, the method of moments regression was used to account for the varying precision of the effect size estimates, with weights equal to the inverse of the squared standard errors. For meta-regression performed on covariates the maximum likelihood estimation was used. The statistical significance threshold was set at 0.05.

Publication bias analysis

Finally, the presence of publication bias and heterogeneity among the included studies was assessed by visually inspecting a funnel plot, where the mean difference was plotted against the standard error. Symmetry of the funnel

plot was evaluated to detect potential biases, and asymmetry or the presence of outliers were further investigated using Egger's test for statistical significance.

Results

Data collection and descriptive analysis

The present systematic review investigates the role of serum 25(OH)D levels in relation to the severity of OSAS in patients without comorbidities. The first screening of electronic databases identified 891 studies; after the removal of duplicated and non-English written manuscripts, 747 studies were screened; the final selection returned 24 studies that were included for the qualitative analysis whereas only 20 studies were eligible for meta-analysis. PRISMA flow diagram (Fig. 1) reported the selection process and the causes of exclusion from the review.

Data from the selected studies were divided into 15 case-control studies [16–30] and 9 cross-sectional studies [31–39]. Seven studies were carried out in Turkey [16, 17, 19, 24, 34, 36, 39], 6 in Greece [23, 26–28, 30, 37], 5 in Italy [20, 21, 29, 32, 38], 2 in China [33, 35], 1 in India [25], 1 in USA [18], 1 in Ireland [31], and 1 in Tunisia [22]. Sixteen studies [16, 17, 19, 23–28, 30, 31, 33–37, 39] investigate OSAS among adult patients whereas 4 studies [18, 29, 32, 38] among pediatric patients. With the exception for 2 studies executed at low-latitude [25, 35], the remaining 18 were carried out into center at medium-latitude [16–19, 23–34, 36–39]. A total of 2986 participants were enrolled in the collected studies, divided into 2640 subjects affected by OSAS and 933 healthy subjects representing the control group. Table 1 showed the qualitative analysis of all the selected studies.

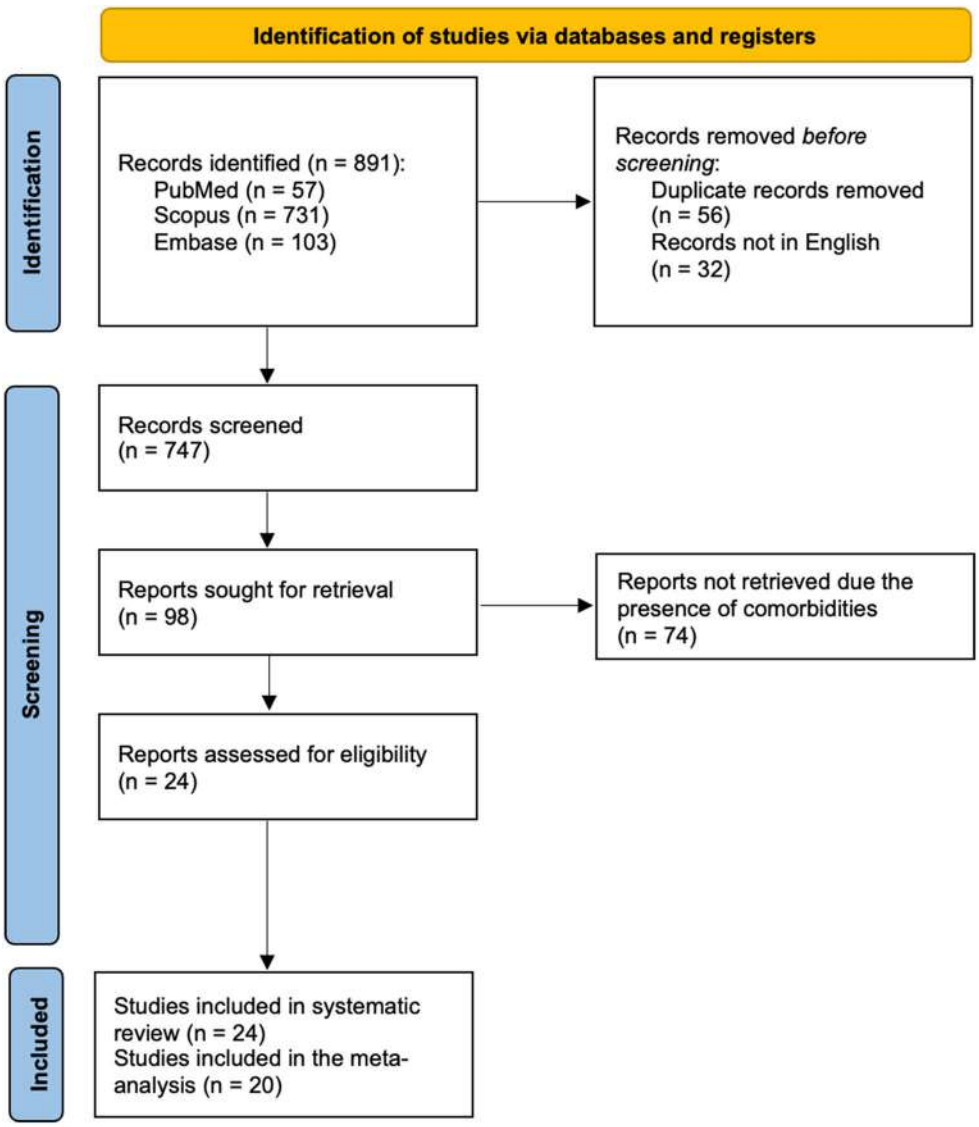

Fig. 1 PRISMA 2020 flow diagram of the selection process

Risk of bias and assessment of study quality

The risk of bias assessment, conducted using the ROBINS-I tool (Fig. 2), indicated that out of the total included studies, 5 studies were rated as having a low risk of bias [20, 22, 23, 33, 37], 8 studies were rated as having a moderate risk of bias [18, 26–28, 31, 32, 34, 36], and 11 studies were rated as having a serious risk of bias [16, 17, 19, 21, 24, 25, 29, 30, 35, 38, 39]. The domains most frequently associated with higher risk levels included bias due to confounding, highlighting the areas that warrant careful consideration in future research.

Meta-analysis

First, the subjects included in the selected studies were divided according to the grade of OSAS severity based on the AHI: control (AHI < 5), mild OSAS (5 < AHI < 15), moderate OSAS (15 < AHI < 30), severe OSAS (AHI > 30). Furthermore, for each study and when not directly available, the weighted means and pooled standard deviations (SDs) of 25(OH)D levels and BMI were calculated to gather all the affected subjects into an "Any OSAS" group. Therefore, each group was tested and compared quantitatively considering the mean differences and applying a random-mixed effect model. From the qualitative dataset, 4 studies were removed from the meta-analysis calculation because their data reported interquartile o range values instead of standard deviations.

Subgroup analysis by OSAS severity

Intragroup and intergroup meta-analyses were performed (Fig. 3). The meta-analysis comparing the subgroup of Mild OSAS, composed by 302 affected and 347 healthy patients, presented low heterogenicity ($I^2 = 15\%$; $p = 0.31$) and no statistical significance between patients in terms of 25(OH)D serum levels (-1.13ng/mL; 95%CI [-2.56, 0.30]; $p = 0.12$). In contrast to this finding, moderate and severe OSAS showed opposing results. Moderate OSAS subgroup compared a total of 451 OSAS patients to 422 patients forming the control group; the difference of 25(OH)D levels was statistically significant (-3.36ng/mL; 95%CI [-5.63, -1.09]; $p = 0.004$) and with a substantial heterogenicity ($I^2 = 73\%$). Greater significant difference (-6.38ng/mL; 95%CI [-8.75, -4.02]; $p < 0.001$) and higher heterogenicity ($I^2 = 86\%$) were noted in the severe OSAS group, comparing a total of 955 affected with 484 control subjects.

Finally, the overall effect among the previously included studies presented high heterogenicity ($I^2 = 85\%$) and statistical significance (-4.08ng/mL; 95%CI [-5.65, -2.52]; $p < 0.001$); the heterogenicity among subgroups was also considerable ($I^2 = 86\%$) and the differences between them was reported to be statistically significant ($p = 0.0008$).

Also, a sensitivity analysis was performed within the subgroup to assess the robustness of the results including pediatric OSAS studies [20, 38], and no significant changes in the effect estimates or heterogeneity were observed, confirming the stability of the present findings.

Subgroup analysis by age

The pooled means and standard deviation were used to compare all the studies available for the meta-analysis; the overall effect previously reported (Fig. 4), in fact, did not test several studies since they did not present the OSAS classification based on severity. As a result, and to evaluate the influence of any variable among studies that may affect heterogeneity, the effect of "Any OSAS" group comprised 2159 subjects compared with 827 subjects in the control group was tests by stratifying data according to age. 1842 adult OSAS patients were compared to 317 pediatric OSAS patients.

For this subgroup comparison, a specification between adult and pediatric OSAS was made to evaluate if age can affect 25(OH)D levels. A dedicated forest plot (Fig. 4) indicated no significant differences ($p = 0.28$) in terms of 25(OH)D serum levels between adult and pediatric OSAS patients. Despite the difference in age and the high heterogeneity within subgroups, the overall effect showed very low heterogeneity among subgroups ($I^2 = 16\%$).

Subgroup analysis by BMI

BMI was also used to stratify the total sample (Fig. 5). The majority of studies were conducted on an obese OSAS population (1598 patients), followed by overweight (371 patients) and normal weight (190 patients) samples, indicating the BMI as a potential confounding factor. Whereas 25(OH)D levels changed significantly withing normal weight ($p = 0.002$) and obesity ($p < 0.001$) groups, not statistical significance was observed for overweight group ($p = 0.13$). Testing the subgroup differences showed no significant changes ($p = 0.30$) and very low heterogeneity ($I^2 = 16.6\%$) between subgroups based on weight.

Finally, studies were classified basing on the latitude of the centers where patients were enrolled (Fig. 6). Expect for 2 studies done on low-latitude (163 OSAS cases), the remaining 18 studies were conducted on medium-latitude (1996 OSAS cases). This characterization on latitude degrees confirmed high heterogeneity across subgroups ($I^2 = 75.9\%$), with difference of 25(OH)D levels between healthy and OSAS patients statistically significant ($p = 0.04$) among subgroups.

Table 1 Qualitative analysis of the selected and included studies

Author and year of publication	Country	Latitude (°)	Study design	Population	Mean age (SD) (yrs)	25(OH)D levels as mean and SD or median and IQR/ Min-Max (ng/mL)	BMI	25(OH)D quantification method	OSAS measurement	Primary and secondary outcomes
Bozkurt et al. 2012	Turkey	39	CCS	Any OSAS 143 *Mild OSAS 46* *Moderate OSAS 47* *Severe OSAS 50* Control 47	49.1 (10.4) * 47.8 (10.3) 49.8 (10.6) 49.7 (10.4) 42.8 (9.5)	17.4 (7.0) * 18.3 (6.5) 17.6 (7.4) 16.3 (7.0) 19.9 (7.8)	31.1 (4.6) * 29.0 (4.1) 30.8 (5.1) 33.4 (4.6) 29.2 (4.9)	Radioimmunoassay	PSG	Serum 25(OH)D lower among OSA compared with controls; decrement of 25OHD parallel to severity of OSAS
Mete et al. 2013	Turkey	39	CCS	Any OSAS 150 *Mild OSAS 50* *Moderate OSAS 50* *Severe OSAS 50* Control 32	47.2 (8.7) 46.6 (9.4) 47.6 (7.2) 47.4 (9.5) 46.9 (8.1)	17.9 (9.2) 20.6 (9.6) 18.4 (9.0) 14.7 (8.2) 19.2 (7.2)	32.9 (5.0) 32.2 (5.0) 32.8 (4.8) 33.7 (5.1) 32.0 (4.7)	Electrochemi-lumine-scence immunoassay	PSG	Severity of OSAS increased deficiency of 25(OH)D became more pronounced. None of patients with 25(OH)D deficiency was higher in OSAS group than controls
Kheirandish-Gozal et al. 2014	USA	41	CCS	Any OSAS 102 Control 74	6.5 (0.9) 7.1 (1.4)	83.4 (24.9) 94.8 (24.3)	0.16 (0.9) **** 0.22 (1.0)	ELISA assay	PSG	Children and children with OSA have lower 25(OH)D when compared to healthy controls even when adjusted for ethnicity If obesity and OSAS are both present, 25(OH)D levels further reduced
Erden et al. 2014	Turkey	36	CCS	Any OSAS 85 *Moderate OSAS 23* *Severe OSAS 62* Control 43	43.7 (9.7) * 24 (9) 51 (10) 45 (14)	23.1 (7.6) * 22.0 (7.2) 23.5 (7.7) 29.5 (9.1)	31.8 (5.5) * 29.4 (4.0) 32.7 (6.0) 27.8 (5.0)	Chemilu-minescence immunoassay	PSG	25(OH)D levels were lower and PTH levels were higher in OSAS patients than healthy controls and PTH and 25(OH)D levels were negatively correlated
Liguori et al. 2015	Italy	41	CCS	Severe OSAS 90 Control 32	61.1 (12.7) 59.1 (8.0)	19.3 (9.5) 32.8 (16.9)	31.9 (5.7) 30.9 (2.5)	Immunoassay	PSG	Significant improvement of 25(OH)D level in male OSAS responders. Short term CPAP treatment can promote recovery of 25(OH)D homeostasis
Kerley et al. 2016	Ireland	53	CSS	Any OSAS 75 *Mild OSAS 22* *Moderate OSAS 18* *Severe OSAS 35* Control 31	55.7 (17.5) * 54 (19) 57 (17) 55.5 (17) 53 (19)	15.1 (10.3) *, ** 16.0 (8.8) ** 14.4 (12.0) ** 14.8 (10.4) ** 24.0 (13.2) **	35.2 (7.8) * 31 (8) 33 (7) 39 (8) 32 (8)	Chemilu-minescence immunoassay	PSG	25(OH)D levels were highest in non-OSAS subjects and decreased with increasing OSAS severity. 25(OH)D is significantly and independently associated with AHI
Zicari et al. 2016	Italy	41	CSS	Any OSAS 22 Control 70	7.6 (3.1) 9.0 (3.9)	20.8 (7.6) 34.1 (11.1)	16.8 (4.0) 17.6 (4.8)	Chemilu-minescence immunoassay	PSG	25(OH)D levels were lower in primary snoring (PS) and OSAS patients when compared to healthy controls; the decrease in 25(OH)D is associated with an increase in the odds of having OSAS instead of PS
Liguori et al. 2017	Italy	41	CCS	Any OSAS 16 Control 10	50.7 (15.8) 54.1 (16.6)	18.4 (6.9) 17.0 (8.6)	26.3 (1.8) 31.0 (6.4)	Immunoassay	PSG	Significant improvement of 25(OH)D status after one year of useful CPAP therapy. Non-obese OSAS patients had significantly increased 25(OH)D serum levels after one year of CPAP treatment

Table 1 (continued)

Author and year of publication	Country	Latitude (°)	Study design	Population	Mean age (SD) (yrs)	25(OH)D levels as mean and SD or median and IQR/ Min-Max (ng/mL)	BMI	25(OH)D quantification method	OSAS measurement	Primary and secondary outcomes
Toujani et al. 2017	Tunisia	36	CCS	Severe OSAS 92 Control 30	52.3 (12.7) 45.7 (14.7)	7.9 (2.9) 16.8 (3.1)	36.2 (6) 32 (4.2)	Enzyme-linked immunosorbent assay	PSG	Patients with severe OSAS suffered lower 25(OH)D and higher serum IL-17 than controls. Serum IL-17 was negatively correlated with 25(OH)D levels in severe OSAS
Archontogeorgis et al. 2018	Greece	40	CCS	Any OSAS 139 Control 30	53.9 (12.8) 44.9 (12.8)	17.8 (7.8) 23.9 (12.4)	35.9 (12.8) 29.9 (6.8)	Radioimmunoassay	PSG	Serum 25(OH)D level lower in OSAS than non-OSAS. 25(OH)D level negatively correlated with sleep stage transitions, AHI, oxygen desaturation index, percentage of time with oxyhemoglobin saturation, and positively correlated with average oxyhemoglobin saturation, forced expiratory volume, and oxygen partial pressure. 25(OH)D level lower in OSAS and correlated with indices of OSAS severity
Qiao et al. 2018	China	37	CSS	Any OSAS 87 *Mild/moderate OSAS 32* *Severe 55* Control 32	49.5 (9.2) * 51.8 (8.1) 48.2 (9.9) 50.1 (7.3)	13.3 (6.5) * 17.6 (5.9) 10.8 (6.8) 27.2 (7.6)	31.7 (2.3) * 30.1 (1.4) 32.7 (2.7) 32.1 (2.2)	Electrochemiluminescence immunoassay	PSG	No significant difference of BMD in subjects among the obesity, mild-to-moderate OSAS, and severe OSAS groups. The correlation analysis suggested no relationship between BMD and AHI or between BMD and SaO2 min
Pazarli et al. 2019	Turkey	40	CCS	Any OSAS 68 *Mild OSAS 28* *Moderate OSAS 13* *Severe OSAS 27* Control 21	48.9 (12.2) * 46.5 (11.8) 51.0 (13.8) 50.4 (11.9) 42.1 (1.8)	- 17.1 (11.2–25.7) *** 17.2 (10.9–30.9) *** 13.1 (10.1–24.4) *** 19.9 (12.4–33.8) ***	- 29.5 (26.4–31.9) *** 28.3 (26.6–32.8) *** 28.9 (25.8–32.3) *** 27.3 (26.1–30.7) ***	Chemiluminescence immunoassay	PSG	No significant difference in bone mineral density (BMD) and 25(OH)D level in OSAS severity categories. No relationship between OSAS and BMD values
Yassa et al. 2019	Turkey	41	CSS	Any OSAS 90 *Mild OSAS 30* *Moderate OSAS 30* *Severe OSAS 30* Control 31	34.8 (7.2) 38.9 (6.8) 39.0 (8.1) 38.5 (8.29 34.8 (7.2)	19.0 (5.9) 18.1 (8.0) 19.7 (9.6) 18.6 (9.1) 18.8 (8.8)	27.3 (2.1) * 26.9 (2.0) 27.1 (2.5) 27.9 (1.9) 26.8 (2.3)	Chemiluminescence immunoassay	PSG	No significant difference in the distribution of 25(OH)D levels between patients and control groups and also within OSAS subgroups. Serum levels of 25(OH)D do not alter the severity of OSAS

Table 1 (continued)

Author and year of publication	Country	Latitude (°)	Study design	Population	Mean age (SD) (yrs)	25(OH)D levels as mean and SD or median and IQR/ Min-Max (ng/mL)	BMI	25(OH)D quantification method	OSAS measurement	Primary and secondary outcomes
Fan et al. 2019	China	23	CSS	Any OSAS 104 *Mild OSAS 18* *Moderate OSAS 29* *Severe OSAS 46* Control 8	46.2 (10.8) * 47.8 (13.2) 49.0 (12.7) 43.8 (8.6) 40.6 (11.1)	18.9 (4.9) * 20.4 (5.6) 19.5 (5.5) 17.9 (4.3) 20.0 (4.5)	28.0 (4.2) * 26.1 (2.8) 27.6 (4.7) 29.1 (4.4) 25.1 (1.7)	Electrochemiluminescence immunoassay	PSG	Negative correlation between 25(OH)D and AHI. 25(OH)D insufficiency was independently associated with insulin resistance (IR) in OSAS patients. PTH was negatively correlated to 25(OH)D. Severe OSAS may have lower 25(OH)D level associated with increased risk of IR
Kirac et al. 2019	Turkey	41	CSS	Any OSAS 50 Control 50	48.8 (11.0) 45.9 (8.5)	11.6 (3.7) 21.8 (7.2)	27.4 (2.5) 21.9 (1.9)	NA	PSG	VDR and VDBP mutations highly related with OSAS
Bouloukaki et al. 2021	Greece	35	CSS	Any OSAS 617 *Mild OSAS 94* *Moderate OSAS 150* *Severe OSAS 373* Control 68	55.5 (13.8) * 45 (13) 56 (14) 58 (14) 41 (18)	23.1 (10.3) * 25.0 (11.1) 26.1 (11.9) 21.4 (9.5) 26.1 (9.9)	33.4 (6.3) * 29 (5) 32 (5) 35 (7) 27 (7)	Radioimmunoassay	PSG	Large proportion of patients referred for OSAS evaluation had 25(OH)D deficiency and independently associated with severity of OSAS
Sadaf et al. 2021	India	27	CCS	Any OSAS 59 *Mild OSAS 15* *Moderate OSAS 17* *Severe OSAS 27* Control 34	48.0 (8.4) NA NA NA 46.3 (7.3)	21.0 (7.3) 24.1 (6.3) 20.1 (7.5) 19.9 (7.4) 24.5 (7.0)	33.7 (5.1) - - - 29.7 (4.9)	Chemiluminescence immunoassay	PSG	Decrease in mean BMD with increasing OSAS severity. Statistically negative correlation between AHI and BMD. Mean 25(OH)D in case group significantly lower than control. Negative correlation between AHI and serum 25(OH)D levels
Siachpazidou et al. 2021	Greece	39	CCS	Any OSAS 30 Mild OSAS 1 Moderate OSAS 11 Severe OSAS 18 Control 30	56.1 (8.1) - - - 50.3 (13.8)	23.5 (10.9) - - - 23.2 (7.5)	33.9 (6.3) - - - 28.4 (4.2)	Chemiluminescence immunoassay	PSG	No difference in 25(OH)D levels between OSAS patients and controls. OSAS cases with good CPAP adherence showed significantly higher 25(OH)D levels after 1 year compared with those not adequately using CPAP
Kotsiou et al. 2022	Greece	39	CCS	Any OSAS 15 *Mild OSAS 1* *Moderate OSAS 4* *Severe OSAS 10* Control 15	57.2 (8.2) NA NA NA 55.5 (13.7)	24.9 (10.2) NA NA NA 21.9 (5.8)	40.8 (2.7) - - - 38.7 (4.7)	Chemiluminescence immunoassay	PSG	IL-6 levels were significantly elevated in OSAS group compared to control. IL-6 levels were positively correlated with OSAS severity and nocturnal hypoxemia as well as with BMI
Archontogeorgis et al. 2022	Greece	40	CCS	Any OSAS 30 Control 30	56 (52.8–65) *** 56 (48.8–64.3) ***	18.6 (13.2–25.2) *** 21.6 (17.8–33.6) ***	36.9 (34.5–41.6) *** 33.6 (29.9–40.2) ***	Radioimmunoassay	PSG	25(OH)D levels strongly correlated with AHI. 25(OH)D levels were decreased in patients with overlap syndrome compared to both OSAS patients and non-apnoeic controls

Table 1 (continued)

Author and year of publication	Country	Latitude (°)	Study design	Population	Mean age (SD) (yrs)	25(OH)D levels as mean and SD or median and IQR/ Min-Max (ng/mL)	BMI	25(OH)D quantification method	OSAS measurement	Primary and secondary outcomes
Locci et al. 2023	Italy	40	CSS	Any OSAS 127 *Mild OSAS 27* *Moderate OSAS 55* *Severe OSAS 45* Control 96	5 (2–14) *** NA NA NA 6 (4–8) ***	22.4 (7.7) 23.3 (7.5) 23.0 (8.3) 20.9 (7.5) 25.5 (8.7)	15.4 (14.4–17.4) *** - - - 15.5 (14.3–16.8) ***	Chemiluminescence immunoassay	PSG	Serum 25(OH)D levels were significantly lower in OSAS patients, particularly severe OSAS compared to age matched healthy controls. No significant difference in BMI in OSAS patients and controls
Akyıldız et al. 2023	Turkey	39	CSS	Any OSAS 239 *Mild OSAS 33* *Moderate OSAS 62* *Severe OSAS 144* Control 23	52 (18–80) *** NA NA NA 40.5 (18–61) ***	13.3 (4.2–53.7) *** 17.2 (4.2–37) *** 13.2 (4.2–34) *** 13.2 (4.2–53.7) *** 16.6 (4.2–36.9) ***	31.6 (18.8-68-7) *** - - - 29.8 (18.9–35.7) ***	NA	PSG	OSAS has a significant association with 25(oh)D serum levels. A negative correlation between increased BMI and 25(OH)D also exists
Anatolou et al. 2023	Greece	40	CCS	Any OSAS 144 Control 32	53.2 (12.4) 47.6 (14.3)	19.0 (12.0–27.0) *** 27.0 (16.5–32) ***	35.4 (6.9) 30.3 (6.4)	Radioimmunoassay	PSG	LRP2 CC and CUBN GG genotypes were associated with significantly lower 25(OH)D concentration in patients with OSAS compared to healthy controls. Differences in 25(OH)D levels between patients and controls are noticed within distinct LRP2 and CUBN genotypes
De Luca et al. 2023	Italy	40	CCS	Any OSAS 66 Control 64	6.7 (2.2) 6.9 (2.4)	17.0 (6.3) 22.0 (9.4)	17 (4.6) 17.5 (3.4)	Chemiluminescence immunoassay	PSG	Patients with adenotonsillar hypertrophy had 25(OH)D levels statistically significantly lower than control group

NA, not available; PSG, polysomnography; *, data calculated as pooled mean and combined standard deviation; **, transformed from nmol/L to ng/mL, considering the Eq. 1 ng/ml = 0.400641 nmol/l; ***, data expressed as median and range; ****, data expressed as BMI z-scor

Fig. 2 Graphical representation of ROBINS-I tool applied to all the studies included in the systematic review. Studies were classified as low, moderate, severe, and unclear risk of bias

Meta-regression

The meta-regression analysis revealed that the severity of OSAS significantly and inversely influenced the mean differences of 25(OH)D. It was demonstrated that as the severity of OSAS increased the mean difference decreased significantly ($p = 0.008$). The model accounted for approximately 34.8% of the variability in the effect sizes (R-squared = 0.348). This finding suggests that studies involving more severe cases of OSAS tended to report larger negative mean differences, indicating a greater impact of OSAS severity on the measured outcomes.

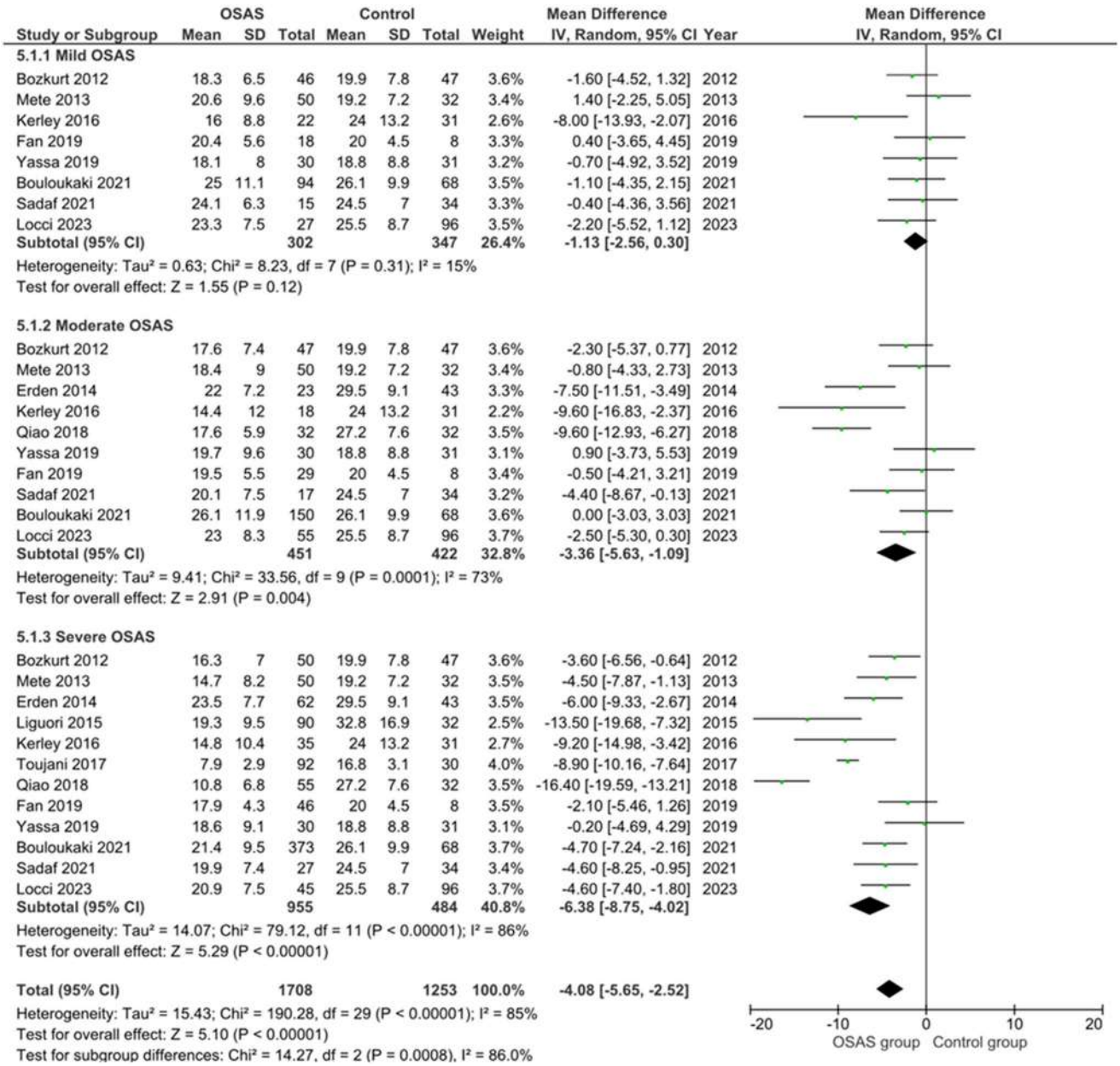

Fig. 3 Forest plot showing meta-analysis results with OSAS severity subgroups comparison and the overall effect estimate

Meta-regression performed between 25(OH)D levels and age, BMI, and latitude covariates did not show any correlation. One study was excluded from the meta-regression based on BMI since it reported BMI z-score [18]. Age (R-squared = 0.02; $p = 0.841$), BMI (R-squared = 0.08; $p = 0.662$), and latitude (R-squared = 0.04; $p = 0.692$) were tested as continuous and categorical covariates simultaneously but, despite that, no significant results were observed.

Publication bias analysis

Examination of the funnel plot for publication bias (Fig. 7) revealed general symmetry, but with several studies falling outside the 95%CI, indicating potential publication bias or heterogeneity. This visual inspection was further supported by Egger's test, which yielded a 1-tailed p-value of 0.126, suggesting the absence of potential publication bias in the present meta-analysis.

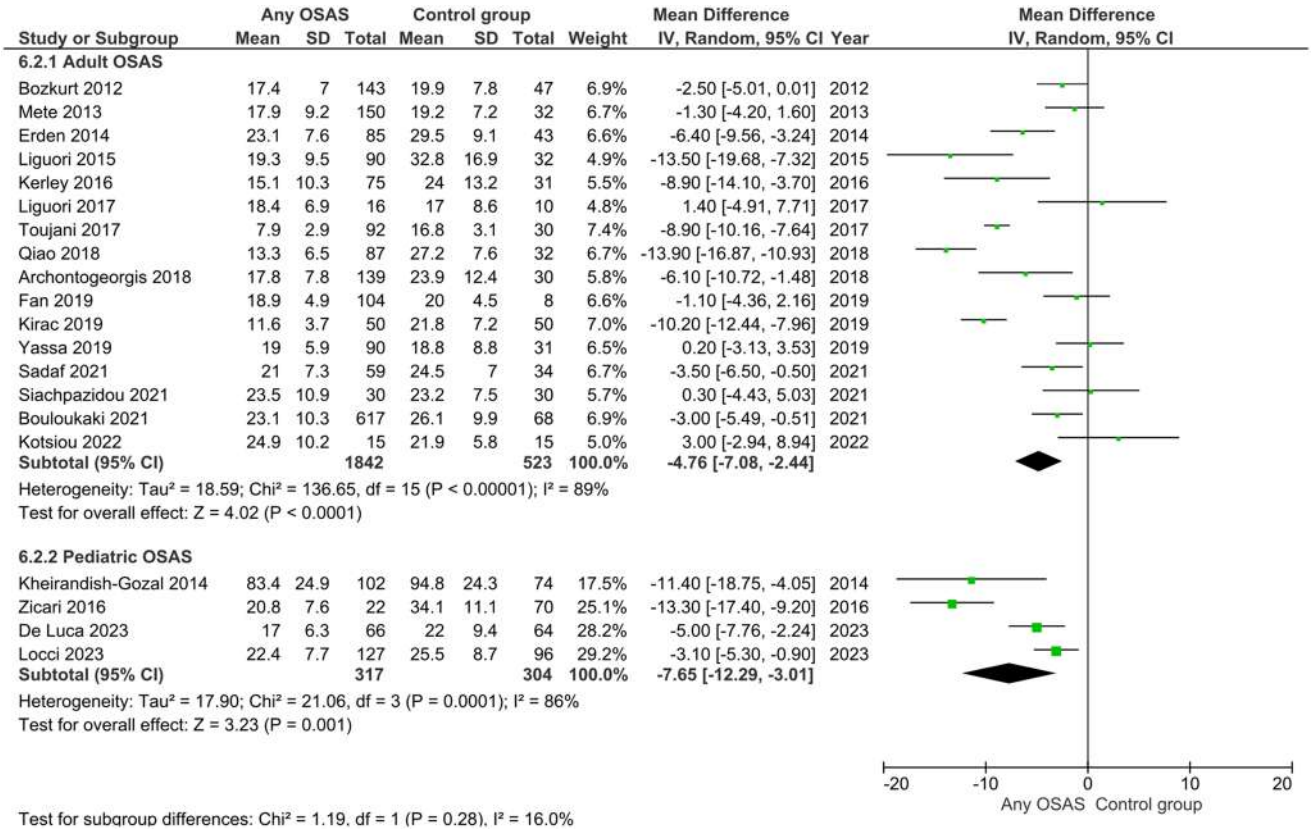

Fig. 4 Forest plot showing meta-analysis results with any OSAS group analysis divided into adult and pediatric OSAS, and the effect estimate for subgroups differences

Discussion

The impact of 25(OH)D serum levels on OSAS patients remains partially unclear, to date. This systematic review assessed the current evidence on how 25(OH)D serum levels affect OSAS severity or vice versa. Our review focuses on patients without comorbidities to isolate the effect of Vit.D on OSAS severity. By analyzing the existing literature, this review aims to shed light on the potential benefits of vitamin supplementation in improving treatment efficacy for sleep disorders.

Beyond its role in bone health, Vit.D, has emerged as a factor influencing sleep patterns. Low 25(OH)D levels are linked to shorter sleep duration, while adequate levels are deemed essential for maintaining sleep quality and reducing nocturnal awakenings [40]. The precise mechanisms connecting Vit.D to sleep regulation involve its receptors in brainstem areas controlling sleep, affecting the sleep-wake cycle. This connection extends to neurocognition through various mechanisms, including neuroprotection, oxidative stress modulation, calcium homeostasis, and inflammation suppression. In the context of OSAS, Vit.D inhibits inflammatory cytokines and promotes anti-inflammatory responses [8]. Furthermore, the presence of 25(OH)D in muscles regulates cell proliferation, differentiation, and muscle fiber contraction. Its deficiency may contribute to abnormal muscle function, potentially playing a role in sleep apnea [41]. Reduced sleep quality can lead to daytime sleepiness, obesity, and diminished outdoor activities, causing insufficient 25(OH)D synthesis and subsequent deficiency. Consequently, its supplementation might be recommended not only for bone health but also for immune support and improved sleep quality in OSAS patients [42].

Prior to the analysis of previous studies, it may be useful to revise all the meta-analyses performed regarding the topic. In 2017, Neighbors et al. published the first meta-analysis including 13 studies stratified by OSAS severity [43]. The difference between the control group and OSAS patients (4.69ng/mL) was similar to the one found in the present review (5.21ng/mL), as well as the subdivisions for mild, moderate, and severe OSAS groups. The findings of their study support the inverse relationship between 25(OH)D serum levels and OSAS severity, but it was not clear if its deficiency was a risk factor for OSAS or vice versa. Li et al. in 2020 published an updated meta-analysis [44]. Twenty-eight studies were included in the statistics; by transforming our means into a standardized mean difference (0.69ng/mL), a slight difference between OSAS and non-OSAS

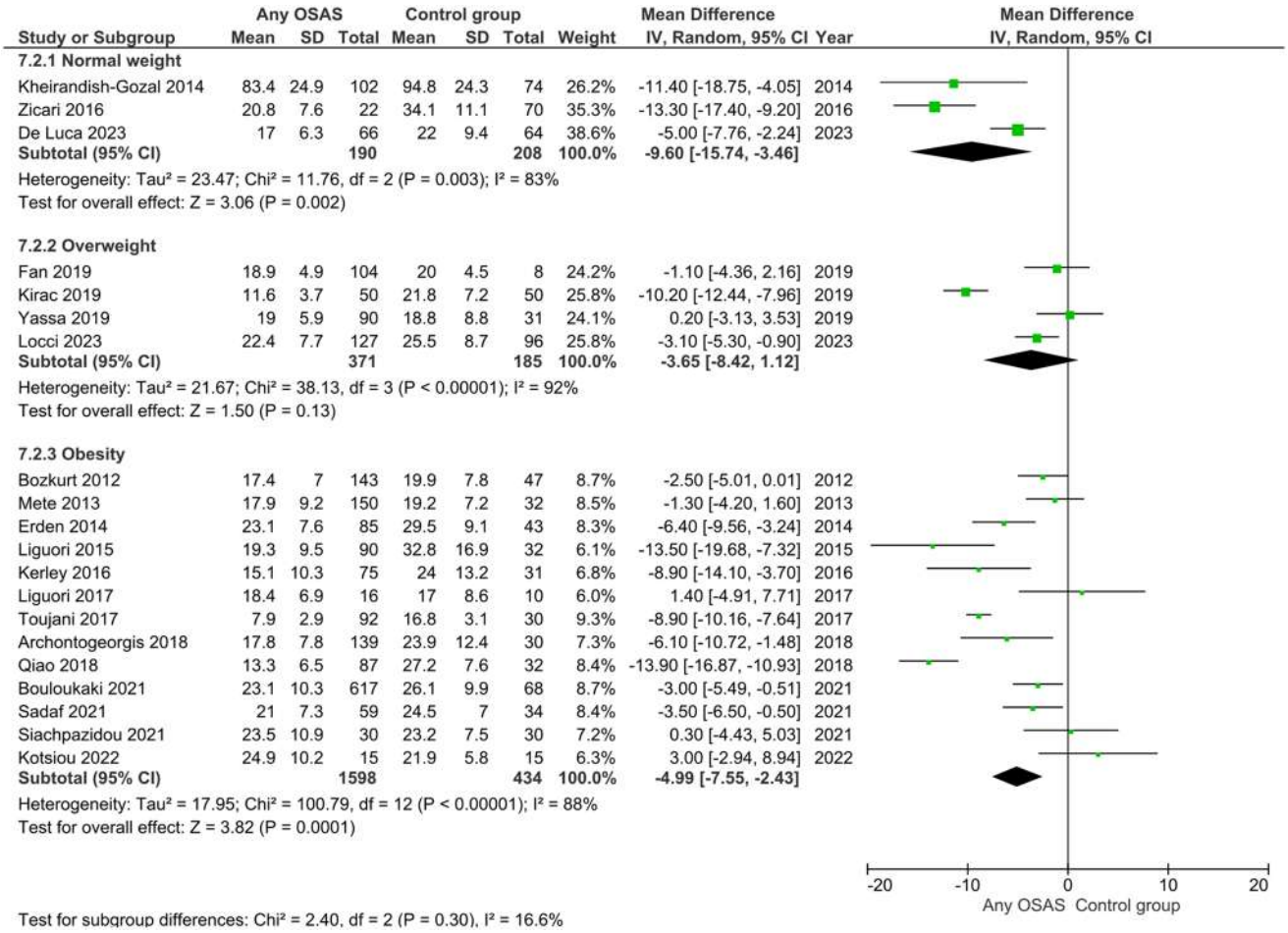

Fig. 5 Forest plot showing meta-analysis results with any OSAS group analysis divided into normal weight, overweight, and obesity group based on BMI, and the effect estimate for subgroups differences

patients was found with that meta-analysis (0.84ng/mL). Similar results were reported in the subdivision into severity groups. The greater number of studies included was due to the inclusion of studies that analyzed OSAS in patients with comorbidity, even though the same inverse correlation between OSAS severity and 25(OH)D serum levels was confirmed. Recently in 2023, Loh et al. reported the results of a new meta-analysis that included 18 studies [45]. Their pooled mean was 0.74ng/mL, which is similar to the results of other studies and our own, despite including a smaller number of studies. The main difference between previous meta-analyses and the present one lies in the selection criteria, which generated a substantial amount of data from patients whose comorbidity could have presented a potential bias.

Comparison with previous research

Despite these numerous investigations, as well as meta-analysis, the relationship between low 25(OH)D levels as a risk factor for OSAS or vice versa remains unclear. This question remains unanswered even as studies from Bozkurt et al. [16], Mete et al. [17], Toujani et al. [22], Kerley et al. [31], Sadaf et al. [25], and Bouloukaki et al. [37] demonstrated a significant inverse relationship between 25(OH)D levels and AHI. In contrast, Salepci et al. [46] and Kotsiou et al. [26] failed to identify a clear trend based on OSAS severity.

Kerley et al. noted that serum 25(OH)D levels were highest in non-OSAS patients and decreased progressively with increasing OSAS severity [31]. Li et al. similarly found with increasing OSAS severity, serum 25(OH)D levels decreased [44]; this was particularly pronounced in patients of Chinese ethnicity, in which greater disease severity was seen, potentially due to genetic polymorphisms in vitaminic receptors and metabolic genes. These genetic polymorphisms were described by Kirac et al. [36], where they found that VDR and VDBP mutations were highly linked to OSAS. Therefore, more cofounding factors may exist, including genetic ones, making any correlation extremely complex.

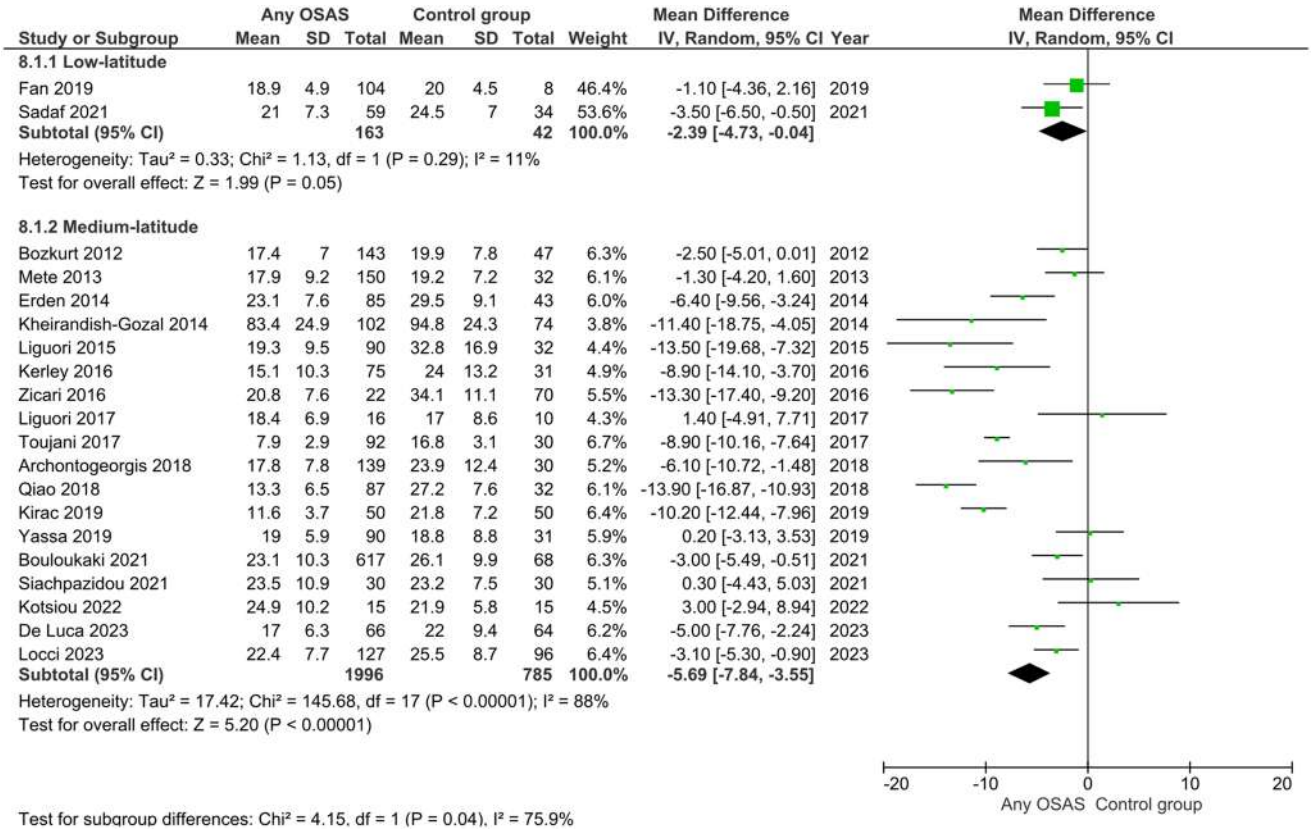

Fig. 6 Forest plot showing meta-analysis results with any OSAS group analysis divided into low, medium, and high latitude, and the effect estimate for subgroups differences

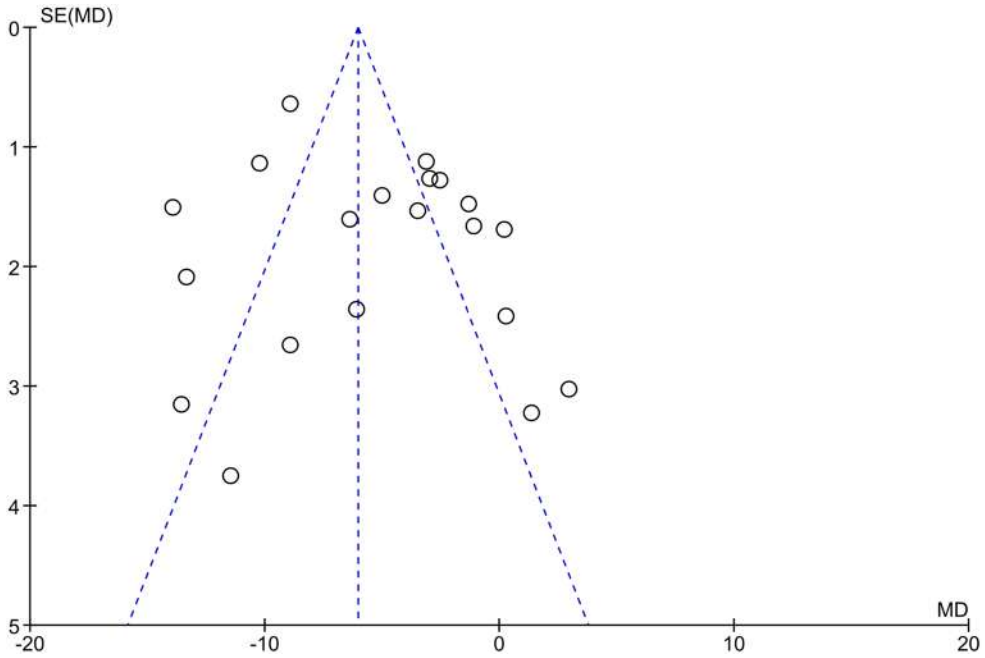

Fig. 7 Funnel plot assessing publication bias in the present meta-analysis

Biological plausability

Several studies have reported on the link between systemic inflammation, low serum 25(OH)D and OSAS. Kheirandish-Gozal et al. found that serum 25(OH)D levels were strongly associated with measures of insulin resistance and hsCRP [18]. Also, both OSAS and obesity were correlated to a further reduction of 25(OH)D levels, which was also highlighted by Qiao et al. [33]; since our study focuses on patients without systemic comorbidities, these confounding factors were controlled. In relation to this, Kotsiou et al. found that IL-6 levels were positively correlated with OSAS severity and nocturnal hypoxemia as well as BMI [26]. This is because intermittent hypoxia, which is common in OSAS patients, may induce the polarization of macrophages, adipose tissue inflammation and the production of adipocyte derived mediators such as IL-6.

Intermittent hypoxia is a hallmark of OSAS and is associated with a cascade of physiological and pathological changes that exacerbate the severity of the syndrome. As the matter of fact, it disrupts normal homeostasis, promoting systemic inflammation through the activation of inflammatory cytokines, such as IL-6, and increasing the levels of reactive oxygen species. Moreover, recurrent oxygen desaturation and subsequent reoxygenation generate oxidative stress, leading to endothelial dysfunction and altered immune responses [47]. The oxygen desaturation index (ODI) is a critical marker for assessing hypoxic stress, and future studies should consider correlating ODI with systemic biomarkers, including 25(OH)D levels, to better understand the relationship between hypoxia and OSAS severity [48].

A previous study by Fan et al. concluded that systemic inflammation might be the cause of OSAS severity and insulin resistance or diabetes mellitus [35]. In a recently published article in 2024 by Archontogeorgis et al. [49], the authors found that low 25(OH)D levels may lead to excessive daytime sleepiness through the upregulation of inflammatory cytokines, suggesting a potential connection between inflammation, 25(OH)D levels and OSAS severity. Similarly to our own study, a recent review by Schiza et al. 2024 described that although current literature supports a connection between OSAS severity, insufficient 25(OH)D levels and sleep quality [40]; it is likely that multiple mechanisms are involved and so it is important to further investigate confounding factors. The aforementioned study agrees that the majority of studies in the literature demonstrate a decrease in Vit.D levels with worsening OSAS.

Potential for therapeutic interventions

Some authors such as Liguori et al. have demonstrated significant improvements in Vit.D status and OSAS symptoms following long-term continuous positive airway pressure (CPAP) therapy in male patients [21]. This suggests that vitaminic supplementation, possibly in conjunction with CPAP, could be a viable strategy for managing OSAS particularly in male patients. This difference was also already observed by Liguori et al. [20], Siachpazidou et al. [30], and previously reviewed by Loh et al. [45], who noted that CPAP therapy was associated with a recovery of Vit.D homeostasis. This phenomenon is particularly interesting as it suggests two possibilities: OSAS severity might affect the endogenous metabolism of Vit.D, or lower serum levels of 25(OH)D might exacerbate the severity of sleep disorders.

Cui et al. demonstrated significant improvements in behavior, learning and hyperactivity among children with OSAS through appropriate Vit.D supplementation [50]. Their findings indicated a neuroprotective and improvement role on neurons damaged by hypoxia. Most recently, a review by Yao et al. suggested a more comprehensive approach of Vit.D supplementation alongside other lifestyle changes such as weight loss to manage the disease [6].

Effect of covariates on OSAS

To investigate the high heterogenicity among studies, especially in moderate and severe OSAS, subgroup analyses and meta-regressions were done.

As previously reported in the result section, a meta-regression revealed that the severity of OSAS significantly and inversely influenced the mean differences of 25(OH)D. Furthermore, this inverse relationship suggest the presence of cofounding factors that should be investigated.

Stratification of OSAS studies according to age did not show statistically significant differences between adult and pediatric patients in term of Vit.D levels; heterogeneity reduced to very low but without statistical significance, indicating that overall heterogeneity cannot be explained by age only. Despite that, the result cannot be generalizable since very few studies analyzed Vit.D serum levels in pediatric OSAS. Moreover, meta-regression crossing the mean differences in 25(OH)D levels and patients' age revealed no significant correlation between these variables, supporting that heterogenicity could depend on other factors than age. Not only, sensitivity analysis on OSAS score comparison did not show changes in heterogenicity supporting the idea that co-factors such as BMI and latitude can increase variability between studies. Also, age was reported to be not correlated to OSAS severity by a previous study even it tested different age's group in adult OSAS only [45].

Stratification based on BMI score, similarly to age covariate, revealed non-significant differences between subgroups, with the greater discrepancy between healthy and OSAS patients for normal weight group whereas no

significative differences were noted for overweight subgroup. Heterogeneity among subgroups reduced to very low but the absence of statistical significance could not explain how BMI may affect the overall heterogeneity, as well as it occurred with age and confirmed by meta-regression. The present findings were in accordance with the meta-regression by Loh et al. and Li et al., supporting the idea of that BMI does not contribute as factor in explaining OSAS score [44, 45]. Neighbors et al. supported BMI as cofounder but only observing that 25(OH)D serum level decreased from normal to overweighted and obese patients [43]. It was clear that BMI increase while OSAS severity increases as well, but this relation is not valid at all underlying the necessity of further studies that might help in isolate BMI-related factors.

Finally, latitude was not useful in clarify heterogenicity among studies despite subgroup comparison was statistically significant. Latitude data can resume aspects related to the ethnicity of the sample, as well as all the environmental factors and cultural habits. Similarly to previous meta-analyses and also proved by non-statistically significant results by meta-regression, latitude was not considered as cofounding fact explaining 25(OH)D deficiency [43, 44].

Limitations

Our study had several limitations which must be acknowledged; many of the included articles were cross-sectional studies which makes it difficult to determine cause and effect. Moreover, variations in study designs, populations and 25(OH)D measurement methods introduce heterogeneity that could affect the robustness of our conclusions. For example, some studies did not find statistically significant differences in 25(OH)D levels between OSAS patients and controls, emphasizing the need for more uniform research methodologies, particularly in patients without comorbidities.

Moreover, excluding all cofounding factors such as BMI resulted in poor scientific evidence; while most of cofactors were isolated, heterogenicity across study was not sufficiently explained by the analyzed covariates.

Conclusions

The present systematic review and meta-analysis highlight a significant association between lower 25(OH)D serum levels and increased severity of OSAS in patients without systemic or genetic comorbidities. These findings have important implications for both clinical practice and future research, suggesting a potential role for Vit.D group in the management of OSAS. The observed statistically significant inverse relationship between serum levels of 25(OH)D and the severity of OSAS raises intriguing possibilities for therapeutic intervention. Covariates such as age, BMI, and latitude was excluded to be significantly related to OSAS. However, the complexity of their interaction necessitates further research to develop targeted interventions and doses; investigating the impact of confounding factors such as lifestyle and systemic comorbidities will also be crucial in understanding this relationship.

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Data availability All data supporting the findings of this study are available within the paper.

Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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