

REVIEW ARTICLE



Exploring the link between vitamin D deficiency and obstructive sleep apnea: A comprehensive review

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Summary

Despite the high prevalence and significant health burden of obstructive sleep apnea (OSA), its underlying pathophysiology remains incompletely understood. This comprehensive review explores the emerging connection between vitamin D deficiency and OSA, discusses potential mechanisms underlying this association, and explores the therapeutic implications of these findings. Recent research has consistently highlighted the high incidence of vitamin D deficiency among patients with OSA, which often occurs independently of geographical location. This suggests that factors beyond lack of sunlight exposure may be involved. This review also discusses how reduced vitamin D may be associated with more severe manifestations of OSA. In addition, it explores the potentiality of using vitamin D supplements as a therapeutic strategy for OSA, noting that some studies have found improvements in sleep quality and a reduction in OSA severity. Potential mechanisms are proposed, including the role of vitamin D deficiency in promoting inflammation, oxidative stress, hypoxia, impairing immune function, muscle function, and gene polymorphism of vitamin D receptors, all of which could contribute to the pathogenesis of obstructive sleep apnea. The paper underscores the need for future research to validate these observations, to determine optimal vitamin D supplementation dosage and duration, to explore potential side effects and risks, and to investigate potential interactions with other treatments.

KEYWORDS

mechanism, obstructive sleep apnea, supplementation, vitamin D deficiency

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a widespread sleep condition characterised by repeated instances of partial or total blockage of the

upper airway while sleeping, resulting in periodic low oxygen levels and disrupted sleep. This condition is linked to a variety of negative health effects, such as heart disease, metabolic disorders, and cognitive impairment (Diamond & Ismail, 2021; Giampá et al., 2023; Kerner & Roose, 2016). Despite the high prevalence and significant health burden of OSA, the underlying pathophysiology of this condition remains partially understood, and current treatment options are

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not universally effective or well tolerated (Bosi et al., 2018; Iannella et al., 2020). Therefore, there is a pressing need to identify novel risk factors and therapeutic targets for obstructive sleep apnea.

One potential factor that has garnered attention in recent years is vitamin D. This secosteroid hormone is primarily recognised for its contribution to the balance of calcium and phosphate in the body and the maintenance of bone health (Bhattarai et al., 2020; Sullivan et al., 2017). However, burgeoning evidence indicates that vitamin D might also influence other physiological processes pertinent to OSA, including inflammation, immune function, and muscle function (Du et al., 2018; Kerley et al., 2016). Furthermore, epidemiological research has consistently found a high incidence of vitamin D deficiency in individuals with obstructive sleep apnea, regardless of their geographical location or exposure to sunlight, suggesting a possible connection between vitamin D and obstructive sleep apnea (Chakhtoura et al., 2015). However, the nature of this link and its clinical implications remain unclear. Is low vitamin D level a cause or a consequence of obstructive sleep apnea? Could vitamin D deficiency contribute to the pathogenesis of obstructive sleep apnea, or is it merely a marker of disease severity? Could vitamin D supplementation serve as a novel therapeutic strategy for obstructive sleep apnea, and if so, what would be the optimal dose and duration of treatment? These are some of the questions that current research in this field is striving to answer.

This article aims to provide a summary of the present understanding of the connection between vitamin D and obstructive sleep apnea. We will review the epidemiological evidence linking vitamin D deficiency with obstructive sleep apnea, discuss potential mechanisms underlying this association, and explore the therapeutic implications of these findings. We will also highlight the constraints of the current studies and propose potential paths for upcoming research. Through this review, we hope to shed light on the possible involvement of vitamin D in the development and therapy of obstructive sleep apnea, and to encourage further research in this promising area.

2 | VITAMIN D AND OSA: AN EMERGING CONNECTION

2.1 | Vitamin D deficiency, presence and severity of obstructive sleep apnea

Numerous observational studies have reported a significantly higher prevalence of vitamin D insufficiency/deficiency in individuals diagnosed with obstructive sleep apnea, suggesting that it is not just because of inadequate exposure to sunlight, which is a main source of vitamin D (Chakhtoura et al., 2015). In research carried out by Kerley and colleagues, it was found that vitamin D levels were notably lower in patients suffering from severe obstructive sleep apnea compared with those with less severe forms of the condition (Kerley et al., 2016). In another research, 96 individuals with obstructive sleep apnea and 96 healthy participants were examined. The findings revealed a higher prevalence of vitamin D deficiency among the OSA group in comparison with the control group (Locci et al., 2023).

Furthermore, among the group with OSA, individuals with severe conditions exhibited lower vitamin D levels than those with less severe manifestations of the disease. These results align with other research conducted across diverse populations (Albayrak et al., 2022; De Luca et al., 2023). In a study analysing 90 patients with overlap syndrome (OVS), the coexistence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea, Archontogeorgis et al. found that serum vitamin D levels were decreased in patients with OSA and OVS. Compared with the control group, moreover, the OVS patients were associated with the lowest levels of vitamin D (Archontogeorgis et al., 2022). Additionally, Li et al. conducted a meta-analysis which revealed that patients with obstructive sleep apnea may exhibit a reduced level of serum vitamin D. Furthermore, the serum vitamin D levels in patients with moderate to severe OSA were found to be significantly lower than those observed in the control group (Li et al., 2020).

Beyond the established correlation between vitamin D deficiency and obstructive sleep apnea, it is imperative to consider the impact of gender, ethnicity, and comorbidities on this relationship. Gender differences in the prevalence and severity of obstructive sleep apnea are well documented, with men typically exhibiting a higher predisposition to obstructive sleep apnea, potentially influencing their vitamin D status. Hormonal variations, differences in fat distribution, and upper airway anatomy are among the factors contributing to these gender-specific disparities (Fietze et al., 2019; Kim & Taranto-Montemurro, 2019). Ethnicity also plays a significant role, as varying levels of melanin in the skin can affect vitamin D synthesis, with individuals having darker skin tones being more susceptible to vitamin D deficiency. This factor, combined with genetic and lifestyle variations, contributes to the differing prevalence rates of obstructive sleep apnea across ethnic groups (Patiño et al., 2021; Wimms et al., 2016). Furthermore, comorbid conditions commonly associated with obstructive sleep apnea, such as obesity, diabetes, and cardiovascular diseases, can further complicate the interplay between vitamin D levels and obstructive sleep apnea. For instance, obesity, a major risk factor for OSA, is often linked with lower vitamin D levels due to the sequestration of vitamin D in adipose tissues (Hein et al., 2017). Similarly, the presence of diabetes and cardiovascular diseases in patients with obstructive sleep apnea can influence their vitamin D status, thereby potentially exacerbating the severity of sleep apnea (Basoglu et al., 2015; Bouloukaki et al., 2019). These findings underscore the necessity for a multifactorial approach in understanding and managing obstructive sleep apnea, considering the intricate interactions between vitamin D levels, OSA, and these additional influencing factors. Table 1 highlights the most relevant studies that link the relationship between vitamin D, and the presence and severity of obstructive sleep apnea.

2.2 | Vitamin D deficiency as a cause or consequence of OSA

Despite ongoing clinical research efforts to investigate the relationship between vitamin D and sleep, there is a paucity of published literature on direct investigations of the impact of vitamin D metabolism

TABLE 1 Relevant studies linking the relationship between vitamin D, presence and severity of obstructive sleep apnea.

Study	Design	Samples, <i>n</i>	Conclusions
Chakhtoura et al., 2015	One case report and review	1 case	OSA contributes to bone loss through mechanisms that overlap with obesity, including hypogonadism, altered adrenergic tone, inflammation, oxidative stress, vitamin D deficiency, and diabetes mellitus
Kerley et al., 2016	Cross-sectional study	106 participants	Vitamin D deficiency or insufficiency is highly prevalent in individuals with OSA. Additionally, significant and independent inverse relationships have been observed between vitamin D levels and OSA
Locci et al., 2023	Case-control study	96 OSA patients and 96 healthy controls	Severe cases of OSA have lower vitamin D levels
Albayrak et al., 2022	Cross-sectional study	137 participants	1,25(OH) ₂ -vitamin D ₃ levels were significantly lower in all disease (OSA with/or without psoriasis) groups compared with the control group
De Luca et al., 2023	Case-control study	66 OSA cases and 64 controls	Statistically significant differences were observed between the AOSA group and the control group with respect to plasma concentrations of vitamin D
Archontogeorgis et al., 2022	Cross-sectional study	90 participants	The levels of serum vitamin D levels decreased among OSA and overlap syndrome (OVS), the coexistence of chronic obstructive pulmonary disease and OSA patients, compared with control group, moreover, OVS patients were associated with the lowest levels of vitamin D
Li et al., 2020	Meta-analysis	NA	OSA patients could have a low serum vitamin D level
Fietze et al., 2019	Cross-sectional study	1208 participants	The occurrence of obstructive sleep apnea tends to rise as individuals age, regardless of gender, although women may experience it later in life compared with men
Kim & Taranto-Montemurro, 2019	Editorial	NA	OSA severity is higher in men than women with similar BMI, but this difference decreases with age
Wimms et al., 2016	Review	NA	OSA is less common in women, but its consequences are equally severe or worse when the severity levels match those in men
Patiño et al., 2021	Cross-sectional study	709 participants	Men had greater severity in most of the parameters measured by polysomnography
Hein et al., 2017	Cross-sectional study	1311 participants	The risk factors for moderate to severe OSA in insomnia sufferers include being male, snoring, having metabolic syndrome, and obesity
Bouloukaki et al., 2019	Cross-sectional study	6716 participants	Female gender was associated with less typical OSA symptoms
Basoglu et al., 2015	Cross-sectional study	1104 participants	Female gender, obesity, and sleepiness were related with prevalence of gastroesophageal reflux disease in OSA patients

Abbreviation: BMI, body mass index; NA, not applicable; OSA, obstructive sleep apnea.

on the initiation and progression of obstructive sleep apnea. By analysing 90 patients with posttraumatic brain injury chronic fatigue (pTBI-CF), Schnieders et al. found vitamin D deficiency was one of the most important factors associated with pTBI-CF. Appropriate treatment of this disorder may help to reduce fatigue in these patients (Schnieders et al., 2012). A previous systematic review and meta-analysis has demonstrated that inadequate levels of vitamin D, particularly those below 50 nmol/L, are linked to a heightened risk of sleep disorders (Gao et al., 2018). These disorders can manifest as poor sleep quality, shorter sleep duration, and excessive daytime sleepiness, all of which may contribute to the deterioration of OSA

symptoms. Liguori and colleagues discovered that serum vitamin D levels increased after 1 year of continuous positive airway pressure (CPAP) treatment. More importantly, patients with obstructive sleep apnea who received effective CPAP treatment for 1 year exhibited significantly higher serum vitamin D levels, as well as a more frequent transition from insufficient to sufficient levels of vitamin D compared with patients with obstructive sleep apnea who did not comply with adequate CPAP treatment. This effect was more pronounced in obese patients (Liguori et al., 2017). In another study comprising 30 patients, no significant changes were observed in vitamin D levels over the course of 3 and 12 months of CPAP therapy. After 1 year, patients

who adhered to CPAP therapy exhibited a significantly lesser reduction in vitamin D levels compared with those who did not adhere (21.18 ± 9.3 vs. 12.13 ± 3.8 ng/mL, $p = 0.022$). Table 2 presents the most relevant studies focussing on whether vitamin D deficiency is a cause or consequence of obstructive sleep apnea.

2.3 | Vitamin D supplementation for OSA

Only two studies have been conducted to explore the effect of vitamin D supplementation on the post-intervention OSA severity. One study led by Feride and his team found that vitamin D supplementation may have a positive effect on the prognosis of mild obstructive sleep apnea (Ayyıldız et al., 2021). The patients in the study showed a

significant decrease in the number of obstructive apneas, apneas, and hypopneas, apnea index, hypopnea index, and apnea-hypopnea index after vitamin D supplementation. Another pilot, double-blind, randomised, placebo-controlled trial found a significant increase in vitamin D levels and a decrease in both low-density lipoprotein and lipoprotein-associated phospholipase A2 in the group that received daily supplementation of 4000 IU vitamin D3 compared with the placebo group. Additionally, trends were noted towards decreased fasting glucose and increased high-density lipoprotein in the treatment group compared with the placebo group, despite the lack of assessment of post-intervention OSA severity (Kerley et al., 2017).

Vitamin D is generally considered safe, but excessive intake can lead to hypercalcaemia, a condition characterised by abnormally high levels of calcium in the blood that can cause kidney stones

TABLE 2 The relevant studies linking the relationship between vitamin D, risk of obstructive sleep apnea (OSA), and vitamin D supplementation for OSA.

Study	Design	Samples, n	Conclusions
Vitamin D deficiency as a cause or consequence of OSA			
Schnieders et al., 2012	Cross-sectional study	90 participants	Vitamin D deficiency was one of the most important factors associated with posttraumatic brain injury chronic fatigue
Gao et al., 2018	Systematic review and meta-analysis	NA	Vitamin D deficiency is associated with a higher risk of sleep disorders
Liguori et al., 2017	Case-control study	39 OSA cases and 10 controls	Long-term continuous positive airway pressure treatment is a viable therapeutic option for correcting both sleep apnea and vitamin D deficiency in middle-aged males with OSA
Vitamin D supplementation for OSA			
Ayyıldız et al., 2021	Prospective study	19 male participants	Vitamin D supplementation may have a positive effect on the disease prognosis of mild OSAS
Kerley et al., 2016	Pilot, double-blind, randomised, placebo-controlled trial	19 participants	Vitamin D3 supplementation increased vitamin D levels and decreased metabolic markers compared with placebo
Chiodini & Bolland, 2018	Review	NA	Vitamin D is important for preventing and treating osteoporosis. However, calcium supplements can have gastrointestinal side effects and increase the risk of kidney stones
de Oliveira et al., 2017	Review	NA	Supplementing vitamin D along with good sleep hygiene may have a therapeutic role in treating sleep disorders and preventing chronic pain conditions
Laird et al., 2010	Review	NA	The role of vitamin D in preventing fractures may be via its mediating effects on muscle function and inflammation
Shuler et al., 2012	Review	NA	Having adequate levels of the storage form of vitamin D in the bloodstream may impact the prevention and recovery of musculoskeletal injuries
Pfeifer et al., 2002	Review	NA	Taking 800 IU of cholecalciferol and elemental calcium can reduce the risk of hip and non-vertebral fractures. It is recommended for those with deficiencies in calcium and vitamin D
Kottler, 2013	Comment	NA	Personalised treatment is crucial, considering factors such as OSA severity, vitamin D status, and response to continuous positive airway pressure therapy
Pérez-López, 2007	Review	NA	Incorporating vitamin D supplementation into clinical practice requires assessing cost-effectiveness, patient compliance, and the need for continuous monitoring to prevent potential adverse effects

Abbreviation: NA, not applicable.

(Chiodini & Bolland, 2018). Moreover, it is also important to consider the potential interactions between vitamin D supplementation and other treatments for obstructive sleep apnea. For instance, vitamin D supplementation may potentially enhance the efficacy of CPAP therapy, the mainstay treatment for OSA. Conversely, vitamin D supplementation may interfere with the effects of certain medications used in the treatment of obstructive sleep apnea (de Oliveira et al., 2017).

The emerging evidence of the role of vitamin D in obstructive sleep apnea offers a new therapeutic possibility, but its clinical application requires careful consideration of various factors. Studies suggest potential benefits of vitamin D in the management of obstructive sleep apnea, but understanding the underlying mechanisms, such as its impact on muscle strength and inflammation, is crucial for identifying suitable patients (Laird et al., 2010; Shuler et al., 2012). Optimal dosing is another critical aspect, with the need to balance efficacy against risks such as hypercalcaemia, especially in vulnerable populations (Pfeifer et al., 2002). Personalised treatment approaches are essential, considering factors such as OSA severity, baseline vitamin D status, and response to standard treatments such as CPAP therapy (Kottler, 2013). The interaction of vitamin D supplementation with other treatments for obstructive sleep apnea, including potential enhancements to CPAP efficacy or interactions with medications such as modafinil, needs further exploration (Liguori et al., 2017). Finally, implementing vitamin D supplementation in clinical practice involves evaluating cost-effectiveness, patient adherence, and the necessity for ongoing monitoring to mitigate potential side effects (Pérez-López, 2007). This comprehensive approach ensures that vitamin D supplementation, while promising, is applied in a manner that maximises patient benefit and minimises risk. Data linking the relationship between vitamin D supplementation and obstructive sleep apnea are summarised in Table 2.

3 | POTENTIAL MECHANISMS

The mechanisms underlying the relationship between vitamin D and obstructive sleep apnea are not fully understood. However, several theories have been suggested, which include the involvement of

vitamin D in inflammation, hypoxia, immune response, muscle functionality, and vitamin D receptors gene polymorphism (Figure 1).

3.1 | Inflammation and oxidative stress

One theory suggests that a lack of vitamin D may aid in the onset of obstructive sleep apnea by encouraging inflammation and oxidative stress, both of which are acknowledged as pivotal in the emergence and advancement of obstructive sleep apnea (Adam-Bonci et al., 2021; Jamilian et al., 2019). Vitamin D is known to possess anti-inflammatory characteristics, and a deficiency in it has been linked to heightened levels of inflammatory indicators. In the context of obstructive sleep apnea, the intermittent hypoxia and sleep fragmentation can lead to systemic inflammation and oxidative stress, which can cause damage to the upper airway structures and contribute to the pathogenesis of the disease (Meliante et al., 2023; Polasky et al., 2021). Therefore, it is plausible that vitamin D deficiency may exacerbate this inflammatory process, thereby contributing to the severity of obstructive sleep apnea.

3.2 | Hypoxia

The link between vitamin D deficiency and obstructive sleep apnea has been suggested to involve hypoxia through the mediation of hypoxia-inducible factor 1- α (HIF1- α) (Siachpazidou et al., 2021). HIF1- α is a key regulator of oxygen metabolism homeostasis, and its expression has been shown to increase in obstructive sleep apnea. Studies have demonstrated that vitamin D3 supplementation can reduce the protein expression, transcriptional activity, and target genes of HIF1- α in various human cancer cells, thus affirming the relationship between vitamin D deficiency and hypoxia (Ben-Shoshan et al., 2007). Clinical investigations have further supported this association by demonstrating that patients with obstructive sleep apnea who received adequate treatment with CPAP therapy exhibited an improvement in vitamin D levels as well as a reduction in hypoxia (Liguori et al., 2017; Theorell-Haglöw et al., 2018).

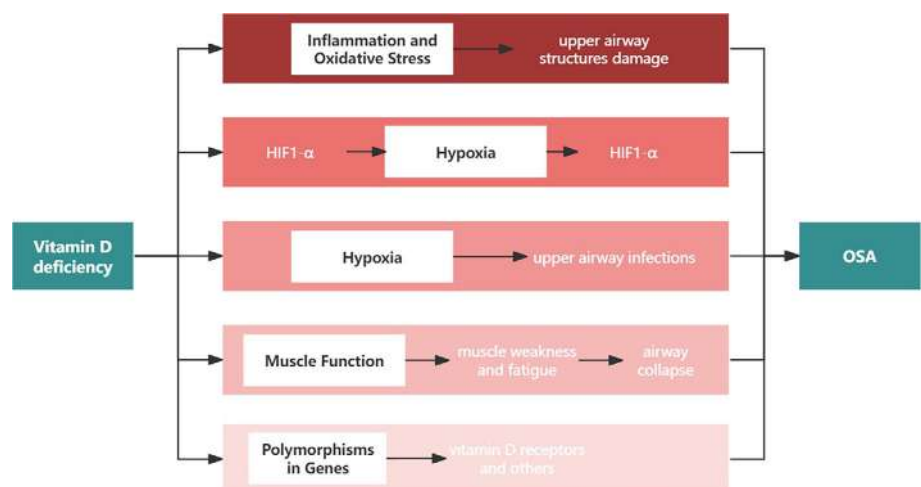


FIGURE 1 The mechanisms underlying the relationship between vitamin D deficiency and obstructive sleep apnea (OSA)

3.3 | Immune function

Vitamin D is also known to play a crucial role in immune function. It modulates both the innate and adaptive immune responses, and a lack of it has been linked to a heightened vulnerability to infections (Bikle, 2011; Wintergerst et al., 2007). In the context of obstructive sleep apnea, recurrent upper airway infections can lead to inflammation and swelling of the upper airway tissues, which can contribute to the development and progression of the disease (Bayazian et al., 2018; Tan et al., 2020). Therefore, vitamin D deficiency, by impairing immune function, may increase the susceptibility to upper airway infections and thereby contribute to the pathogenesis of obstructive sleep apnea.

3.4 | Muscle function

Another hypothesis proposes that a deficiency in vitamin D may play a part in the muscle dysfunction seen in patients with obstructive sleep apnea. Vitamin D is recognised for its significant role in muscle functionality, and a lack of it has been linked to muscle weakness and fatigue (Russo et al., 2022). In the context of obstructive sleep apnea, dysfunction of the upper airway muscles can lead to collapse of the airway during sleep, which is a key feature of the disease (Stål & Johansson, 2012). Therefore, vitamin D deficiency, by impairing muscle function, may contribute to the pathogenesis of obstructive sleep apnea.

3.5 | Polymorphisms in genes

Vitamin D receptors (VDRs) are crucial in mediating the effects of vitamin D, including its role in sleep regulation. The VDR gene, which encodes the vitamin D receptor, exhibits polymorphisms such as the VDR FokI variant. Studies have shown a higher prevalence of the VDR FokI CC genotype in patients with obstructive sleep apnea, correlating with reduced vitamin D levels (Abbas et al., 2019; Bhatt & Guleria, 2021). This polymorphism not only influences susceptibility to obstructive sleep apnea but also appears to affect the severity of OSA symptoms, particularly daytime somnolence (Bhatt & Guleria, 2021).

Beyond VDR polymorphisms, other genetic variations in the vitamin D metabolic pathway have been implicated in obstructive sleep apnea. For instance, polymorphisms in genes encoding enzymes critical for vitamin D metabolism, such as CYP2R1 and CYP27B1, have been studied. CYP2R1 is responsible for converting vitamin D to its active form, and variations in this gene may affect vitamin D availability and function. Similarly, CYP27B1, which also plays a role in vitamin D activation, has been linked to OSA severity. These genetic variations can modulate the effectiveness of vitamin D in the body and potentially influence the pathophysiology of obstructive sleep apnea (Hussein et al., 2012; Leung et al., 2015).

Furthermore, research has suggested that interactions between these polymorphisms and environmental factors, such as dietary

vitamin D intake and sunlight exposure, could further influence OSA risk and severity. This highlights the complex interplay between genetics, environmental factors, and vitamin D in the context of obstructive sleep apnea (Jennings et al., 2005).

While these hypotheses offer credible explanations for the observed correlation between vitamin D and obstructive sleep apnea, it is crucial to acknowledge that they are primarily grounded in observational data. Further research, particularly mechanistic and interventional studies, is required to validate these hypotheses and to thoroughly understand the processes that underpin the relationship between vitamin D and obstructive sleep apnea.

4 | ARTIFICIAL INTELLIGENCE (AI) AND MACHINE LEARNING (ML) IN OSA RESEARCH

Considering the complexities and multifaceted nature of obstructive sleep apnea, the application of AI and ML methodologies presents a promising frontier for advancing our understanding and management of this condition. Artificial intelligence and machine learning techniques, with their robust data processing capabilities, can be instrumental in analysing large datasets to uncover patterns and correlations that may not be immediately apparent through traditional analytical methods. For instance, Tsuiki et al. demonstrated the use of a deep convolutional neural network for image-based detection of patients with severe OSA, highlighting the potential of AI in identifying individuals with obstructive sleep apnea with high accuracy (Tsuiki et al., 2021). This is particularly relevant in the context of vitamin D deficiency and obstructive sleep apnea, where AI can aid in dissecting the intricate interplay between genetic, environmental, and physiological factors. Furthermore, AI-driven predictive models could be developed to identify individuals at higher risk of obstructive sleep apnea or to predict responses to vitamin D supplementation, thereby enabling more personalised and effective treatment strategies. Aiyer et al. reviewed the application of ML as a screening tool for the diagnosis of obstructive sleep apnea, emphasising the potential of these technologies in simplifying the diagnostic process and improving accuracy (Aiyer et al., 2022). The integration of AI and ML in OSA research could also streamline the diagnostic process, enhance the accuracy of sleep apnea detection, and optimise treatment modalities. However, the implementation of these advanced technologies necessitates careful consideration of data privacy, ethical standards, and the need for interdisciplinary collaboration to ensure the development of reliable and clinically relevant AI tools in the field of sleep medicine.

5 | CONCLUSION

Emerging evidence suggests a potential link between vitamin D deficiency and the severity of obstructive sleep apnea. This relationship has implications for the understanding of the pathogenesis of obstructive sleep apnea and the development of potential therapeutic strategies. Further research is required to thoroughly understand the

mechanisms underlying this relationship and to explore the potential therapeutic role of vitamin D in obstructive sleep apnea. Given the widespread occurrence of vitamin D deficiency among OSA patients, regular checks for vitamin D levels could prove advantageous for this group. Furthermore, considering the possible involvement of vitamin D in the development of obstructive sleep apnea, supplementing vitamin D could be a hopeful treatment approach for these patients. Finally, it is important to note that while vitamin D deficiency might contribute to the development of obstructive sleep apnea, it is likely to be just one piece of the puzzle. Obstructive sleep apnea is a complex disease with multiple contributing factors, including obesity, age, and lifestyle factors. Therefore, a comprehensive approach to the management of OSA, including lifestyle modifications, weight loss, and potentially vitamin D supplementation, is likely to be the most effective strategy.

AUTHOR CONTRIBUTIONS

Nan Yao: Writing – Original draft preparation; **Chenyuan Ma:** Validation; **Ruixue Dou:** Visualization; **Chao Shen:** Investigation; **Ye Yuan:** Resources; **Wei Li:** Investigation; **Jun Qu:** Conceptualization, Supervision.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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