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Impact of weight loss and lifestyle intervention on vitamin D in men with obstructive sleep apnea: The INTERAPNEA trial

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ABSTRACT

Introduction: Vitamin D deficiency is commonly found among patients with obstructive sleep apnea (OSA). We aimed to determine the effect of an eight-week interdisciplinary weight loss and lifestyle intervention on circulating vitamin D levels in patients with moderate-to-severe OSA.
Methods: 89 men were assigned to a usual-care group (n = 49) or an 8-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (n = 40). Evaluations were conducted at baseline, intervention endpoint (i.e., 8 weeks), and 6 months post-intervention. Serum 25-hydroxyvitamin D (25(OH)D) was determined using a chemiluminescence immunoassay. Sleep (i.e., sleep efficiency, apnea-hypopnea index [AHI], and oxygen desaturation index) and body weight and composition (i.e., fat mass, and visceral adipose tissue) variables were also determined.
Results: Serum 25(OH)D concentrations showed an insufficient vitamin D status at baseline, which significantly increased (all $p \leq 0.034$) at intervention endpoint (19 %) and at 6 months after intervention (45 %) in the intervention group to the point of potentially resolving vitamin D deficiency. Higher serum 25(OH)D concentrations were related to increased sleep efficiency and reduced AHI, oxygen desaturation index, and body weight and composition variables (all $p < 0.001$) from baseline to 6 months and from 8 weeks to 6 months after intervention. These results were also noted from baseline to 8 weeks, except for body composition (all $p \leq 0.007$).
Conclusion: The intervention improved and potentially resolved vitamin D deficiency. Together with the improvement of adverse sleep patterns and body composition parameters, it may be considered as a promising approach in the treatment of OSA.
Clinical trial registration: (ClinicalTrials.gov NCT03851653).

1. Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by frequent episodes of upper airway collapse during sleep [1], affecting up to a billion of adults worldwide [2]. Numerous risk factors have been suggested for the current increase in OSA incidence, including older age, male gender, metabolic syndrome, cardiovascular disease (CVD), and obesity [3,4]. Indeed, obesity is the most important attributable cause of OSA, with 60 %–70 % of patients with moderate-to-severe OSA suffering from this pathological condition [5]. Thus, multi-component behavioral intervention programs focused on weight loss and lifestyle changes are potential strategies for the

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improvement of the prognosis and evolution of these patients [6,7].

Vitamin D has emerged as a feasible, novel, and useful parameter which could be strongly linked to OSA-related variables as it is involved in several neurochemical mechanisms which are related to sleep regulation including both the serotonergic and dopaminergic pathways [8]. Vitamin D presents receptors in the brain involved in the sleep-wake cycle, thus providing a mechanistic explanation for the contribution of vitamin D deficiency to sleep disorders [9]. Aerobic exercise is currently considered a catalyst of vitamin D since it helps to mobilize this hormone from adipose tissue [10]. In this line, reducing obesity through exercise without medication or medical surgery among patients with OSA may be an useful strategy to improve vitamin D levels and, therefore, their quality of life [11]. Moreover, other lifestyle habits may also affect vitamin D status (e.g., inadequate dietary habits [12], alcohol-induced liver damage [13], or the endocrine-disrupting role of tobacco smoke exposure) [14].

The Interdisciplinary Weight Loss and Lifestyle Intervention (INTERAPNEA) trial (i.e., nutritional behavior change, aerobic exercise, sleep hygiene, alcohol, and tobacco cessation) was aimed at improving OSA severity, body weight and composition, and cardiometabolic comorbidities in men with moderate-to-severe OSA and overweight/obesity [15]. As previously reported, this study demonstrated that an 8-week weight loss and lifestyle intervention resulted in clinically meaningful and sustainable improvements in the apnea-hypopnea index (AHI), body composition, and CVD risk [16]. Based on the above, it is reasonable that a potential improvement of vitamin D status over time may be linked to the above-referred clinical improvements. However, the nature of this association and its clinical implications remain unclear as it has not yet been clarified whether vitamin D deficiency is a cause or a consequence of OSA [17]. Given that the existing evidence regarding the relationship between OSA and vitamin D is mainly based on observational studies [18,19], there is a need of well-designed multi-component behavioral randomized controlled trials answering this research question [11]. The present secondary analyses from the INTERAPNEA trial were aimed at (I) determining the effect of an eight-week interdisciplinary weight loss and lifestyle intervention on circulating vitamin D levels, (II) exploring the relationship between changes in body composition and changes in vitamin D over time, and (III) evaluating the relationship between changes in vitamin D and changes in OSA-related outcomes as compared with usual-care (i.e., continuous positive airway pressure (CPAP)), in men with CPAP-treated moderate-to-severe OSA with overweight/obesity.

2. Materials & methods

2.1. Study design

The current study is a sub-study and secondary analysis of the INTERAPNEA trial. Detailed descriptions of the trial's rationale, design, and methodology have been previously published [6,15,16,20]. The INTERAPNEA trial was an investigator-initiated, parallel-group, open-label randomized clinical trial aimed at assessing the impact of an 8-week interdisciplinary weight loss and lifestyle intervention, combined with usual care (i.e., CPAP therapy), versus usual care alone, on the severity of OSA (measured by the AHI) and OSA-related comorbidities among adults diagnosed with moderate-to-severe OSA. Conducted between April 2019 and October 2020, this study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting randomized clinical trials. The authors affirm that all procedures involved in this research were in accordance with the ethical standards outlined by relevant national and institutional committees on human experimentation and complied with the principles set forth in the Helsinki Declaration of 1975, as revised in 2008. Approval for all human subject/patient-related procedures was obtained from the regulatory authorities and the Clinical Research Ethics Committees of the University of Granada (Granada, Spain), Virgen de las Nieves University Hospital (Granada, Spain), and Junta de Andalucía (Spain) (0770-N-19). Written informed consent was provided by all participants. This study was registered with the National Institutes of Health database (ClinicalTrials.gov NCT03851653).

2.2. Study participants

Potential participants were recruited from the sleep-disordered breathing unit of the collaborating hospital (Virgen de las Nieves University Hospital). Eligible participants were men aged 18–65 years with moderate-to-severe OSA (AHI $\geq$15 events/h of sleep) who were receiving CPAP therapy and had a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 25 or greater. The decision to exclusively include men was based on the higher incidence and prevalence of OSA in this population [21], established differences in OSA phenotypes between genders [22], and the efficacy of weight loss interventions among men compared to women [23,24]. Exclusion criteria comprised current participation in a weight loss program, presence of any psychological or psychiatric disorder, and concurrent primary sleep disorders not secondary to OSA. Potential participants underwent clinical and physical examinations after providing written informed consent to ensure their suitability for inclusion in the study. Eligibility criteria were established with careful consideration for the potential generalizability of results, hence no specific criteria pertaining to responsiveness, comorbidities, adherence rates, or use of nonhypnotic medications were set. Consequently, the study sample encompassed the heterogeneity observed among men with OSA. Further details regarding eligibility criteria and assessments for inclusion feasibility are available elsewhere [15].

For practical and feasibility reasons, the trial was divided into three consecutive sets, each accommodating a maximum of 30–35 participants (see Fig. S1). Initially, 156 men were screened for eligibility, resulting in the enrollment of 89 participants diagnosed with CPAP-treated moderate-to-severe OSA and overweight/obesity. These participants were randomly assigned to either the control group (49 participants) or the intervention group (40 participants) using a computer-generated simple (unrestricted) randomization process [25]. Due to the nature of the intervention, both participants and clinicians were aware of the clinical trial group assignments post-randomization. However, research personnel responsible for data collection and analysis remained blinded to group assignments during follow-up visits. Furthermore, rigorous standardization procedures were implemented for both data collection and intervention to ensure the internal and external validity of the clinical trial [26]. Loss to follow-up amounted to 14 participants from the control group (15.7 %), primarily attributed to the onset of the COVID-19 pandemic (10 participants). In total, 89 participants were included in the intention-to-treat analyses, while 75 were analyzed using the per-protocol approach (at the 8-week assessment intervention endpoint), adhering to pre-specified adherence criteria outlined in a previous publication [15].

2.3. Study intervention

The interdisciplinary weight loss and lifestyle intervention was meticulously designed following prior research [23] and established evidence-based clinical guidelines for managing obesity [27–29] and OSA [30–33]. Its practical applicability in clinical settings was carefully considered. Consequently, the intervention lasted eight weeks and consisted of five distinct components or modules: nutritional behavior modification, moderate aerobic exercise, smoking cessation, avoidance of alcohol intake, and sleep hygiene. Each module entailed weekly group sessions lasting 60–90 min, led and supervised by experts in respective fields (e.g., human nutrition and dietetics, sports sciences, psychology, and sleep medicine). Participants in the intervention group also continued to receive standard care with CPAP therapy. Compliance was considered an 80 % or greater attendance rate for intervention sessions.

A comprehensive description of the intervention, including evaluations of adherence and integrity, has been previously published [15]. Essentially, the intervention's cornerstone was the Transtheoretical Model of Health Behavior Change (TMHBC) [34], a widely recognized biopsychosocial framework integrating key strategies, processes, and principles of behavior change theories into a holistic approach to fostering sustainable health-related behaviors. Processes and strategies employed included consciousness-raising, self-reevaluation, stimulus control, goal-setting, self-monitoring, and self-efficacy enhancement. Conversely, participants randomized to the usual care group received general advice on weight loss and lifestyle modifications from a sleep disordered breathing specialist during a single 30-min session, in addition to standard care with CPAP therapy. A CPAP use for at least 4 h a day for 5 or more days per week reported by the participants was considered CPAP compliance. Following the completion of the trial, all participants were offered the opportunity to receive the intervention provided in the INTERAPNEA clinical trial.

2.4. Outcomes

Evaluations at baseline, the intervention endpoint (i.e., 8 weeks), and 6 months after intervention were conducted within a one to two-week timeframe including a fasting blood test and subsequent routinary blood parameters, a full-night ambulatory polysomnography, a set of questionnaires, and a full-body DXA scanner. Participants were instructed to abstain from CPAP usage for seven days preceding each assessment. Comprehensive details regarding the assessments and endpoints of the INTERAPNEA trial can be accessed in a previously published manuscript [15]. All adverse events, irrespective of severity or their association with the study intervention or participation, were meticulously documented during each assessment. Serious adverse events were identified following the guidelines endorsed by the International Conference on Harmonization of Good Clinical Practice.

2.4.1. Vitamin D levels

Serum 25-hydroxyvitamin D (25(OH)D) concentrations (ng/mL) were assessed using a competitive chemiluminescence immunoassay employing paramagnetic particles via a Unicel DxI 800 immunoassay system (Beckman Coulter, Brea, CA, USA). A commercially available quality control (QC) material with average concentrations of 20 and 100 ng/mL was utilized. The QC material underwent duplicate testing twice daily over a span of five days, with a minimum interval of 2 h between analyses. The coefficient of variation (CV) % values for within-run, between-run, and total laboratory measurements were all under 5 %, 8 %, and 9 %, respectively, meeting the acceptable imprecision criteria of CV $\leq$ 10 %. According to the Endocrine Society, vitamin D deficiency was indicated by serum 25(OH)D levels below 20 ng/mL, levels of 20–30 ng/mL were considered insufficient, while normal levels were reserved for values above 30 ng/mL [35].

2.4.2. Sleep variables

Sleep outcomes were measured through a full-night in-laboratory polysomnography. The AHI quantifies the frequency of apnea and hypopnea events per hour of sleep. A range of 0–4 events indicates normal sleep (absence of obstructive sleep apnea), 5 to 14 events suggest mild OSA, 15 to 30 events indicate moderate OSA, and more than 30 events indicate severe OSA. A clinically significant change of at least 15 events can result in a two-level shift in OSA severity status (e.g., from severe to mild OSA), indicating a health benefit. Additionally, the AHI was determined through full-night, in-laboratory polysomnography. Other objective sleep metrics examined in this study included the oxygen desaturation index, which records the number of oxygen desaturation events of 3 % or more per hour of sleep, and sleep efficiency (%), calculated as the proportion of total sleep time to total time spent in bed.

2.4.3. Body weight and composition

Body weight and composition outcomes comprised measurements of body weight (kg), obtained using a calibrated scale and stadiometer (model 799, Electronic Column Scale, Hamburg, Germany); and fat mass (kg) and visceral adipose tissue (g), assessed via a full-body DXA scanner (Discovery Wi, Hologic, Inc., Bedford, MA, USA).

2.5. Statistical analysis

This study was ancillary to a parent study aimed at determining the effects of an interdisciplinary weight loss and lifestyle intervention on OSA severity, which was originally powered to detect changes in AHI. The primary analyses included linear mixed-effects models used to estimate intervention effects on the study outcomes with group, time of assessment, and their interaction terms as the main effect [36]. The restricted maximum-likelihood method and an unstructured covariance matrix were used in order to adjust for within-participant clustering resulting from the repeated-measures design. Missing data therefore were assumed to be missing-at-random; all values presented being model-based estimates. Nevertheless, a logistic model predicting attrition based on baseline values of set of participants, allocation group, OSA severity, age, and BMI was used in order to calculate attrition propensity. As expected, only set of participants significantly predicted attrition due to the occurrence of the COVID-19 pandemic at the trial endpoint (intervention endpoint assessment of the third set of participants). Thus, assumptions of missing data being missing-at-random were confirmed, which is also in agreement with recent recommendations for handling missing data in randomized trials affected by a pandemic [37]. An intention-to-treat approach (including all participants as originally allocated after randomization) was primarily used in all estimations and analyses. In addition, association of changes in vitamin D levels over time with changes in sleep and body weight and composition outcomes were examined by repeated measures correlation analysis (a statistical technique used to determine the within-individual association for paired measures assessed on two or more occasions for multiple individuals) [38]. The potential effects of changes in AHI on changes in vitamin D levels from baseline to 6 months after intervention with changes in body weight as a mediator variable were also tested; with unstandardized indirect effects being computed for each of 1000 bootstrapped samples, and 95 % confidence interval being computed by determining the indirect effects at the 2.5th and 97.5th percentiles. All analyses were performed using R version 4.0.3 (R Project for Statistical Computing).

3. Results

3.1. Study participants

Baseline characteristics of the study participants are summarized in Table S1. The two randomized groups were well balanced with respect to baseline characteristics and there were no differences in clinical measures at baseline values between the control and the intervention groups (all $p \geq 0.05$).

3.2. Changes in vitamin D levels and vitamin D status

Serum 25(OH)D concentrations increased from baseline to the intervention endpoint (19 %) and to 6 months after intervention (45 %) in the intervention group (all $p \leq 0.034$; Table 1 and Fig. 1A–B), whereas such effect was not observed in the control group (all $p \geq 0.583$; Table 1 and Fig. 1A–B). The intergroup analysis revealed augmented serum 25(OH)D concentrations at both intervention endpoint (22 %) and 6 months after intervention (38 %) in the intervention group compared to the control group (all p $\leq$ 0.015; Table 1). In this line, a sufficient vitamin D status was observed in only 1 out of 10 individuals in both groups, with 40–50 % presenting deficiency at baseline. However, 6 months after intervention, more than 50 % of individuals in the

Table 1
Vitamin D levels and vitamin D status over time.

	Control (n = 49)			Intervention (n = 40)			
	Mean (95 % CI)		Change from baseline, mean (95 % CI)	Mean (95 % CI)	Change from baseline, mean (95 % CI)		Difference between groups, mean (95 % CI)[a]
25(OH)D (ng/mL)							
At baseline	20.9 (18.8–23.1)		–	21.2 (18.8–23.5)	–		–
At 8 weeks	20.7 (18.4–23.0)		−0.3 (−3.2 to 2.7)	25.3 (23.0–27.6)	4.1 (1.2–7.1)[b]		4.4 (0.9–7.8)[c]
At 6 months	22.3 (19.8–24.9)		1.4 (−1.9 to 4.6)	30.6 (28.3–33.0)	9.5 (6.4–12.6)[d]		8.1 (4.4–11.8)[d]
Vitamin D status (%)	**Deficiency**	**Insufficiency**	**Sufficiency**	**Deficiency**	**Insufficiency**	**Sufficiency**	
At baseline	50.0	42.1	7.9	41.2	47.0	11.8	–
At 8 weeks	40.6	53.1	6.3	13.5	62.2	24.3	–
At 6 months	40.7	48.1	11.1	6.3	40.6	53.1	–

Abbreviations: CI, confidence interval. 25(OH)D, 25-hydroxyvitamin D.
a Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.
[b] $p < 0.05$ from the time × study group interactions.
[c] $p < 0.01$ from the time × study group interactions.
[c] $p < 0.001$ from the time × study group interactions.
Data of vitamin D status are presented as percentages (%). According to the Endocrine Society, vitamin D deficiency was indicated by serum 25(OH)D levels below 20 ng/mL, levels of 20–30 ng/mL were considered insufficient, while normal levels were reserved for values above 30 ng/mL (36).

intervention group reached sufficient vitamin D status, with only 6.3 % showing deficiency, whereas no changes were observed in the control group over time. Additional information regarding changes from intervention endpoint to 6 months after intervention is shown in Table S2. The intervention group not only maintained the improvements achieved, but also continued improving serum 25(OH)D concentrations over time ($p < 0.001$; Table S2).

3.3. Association of changes in vitamin D levels over time with changes in OSA and body weight and composition outcomes

Changes in serum 25(OH)D concentrations from baseline to 6 months and from 8 weeks to 6 months after intervention were significantly associated with changes in OSA, body weight and composition outcomes. Higher serum 25(OH)D concentrations were related with increased sleep efficiency and reduced AHI, oxygen desaturation index, body weight, fat mass, and visceral adipose tissue (all $p < 0.001$; Table 2 and Fig. 2A–F). The previous mentioned results persisted when evaluating changes in serum 25(OH)D concentrations from baseline to 8 weeks in the case of sleep variables and body weight (all $p \leq 0.007$; Table 2 and Fig. 2A–D).

3.4. Mediating effects of changes in body weight on the effects of changes in OSA severity on vitamin D levels

Changes in body weight completely mediated the effects of changes in OSA severity (as measured by AHI) on vitamin D levels. Thus, changes in serum 25(OH)D concentrations were explained by changes in AHI from baseline to 6 months after intervention via changes in body weight. As Fig. 3 illustrates, the regression coefficient between changes in AHI and changes in vitamin D levels, and the regression coefficient between changes in body weight and vitamin D levels, were both significant (all $p < 0.05$). We tested the significance of the indirect effect using bootstrapping procedures. Unstandardized indirect effects were computed for each of 1000 bootstrapped samples, and the 95 % confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. The bootstrapped unstandardized indirect effect was −0.09, and the 95 % confidence interval ranged from −0.20 to −0.01. Thus, the indirect effect was statistically significant ($p = 0.038$).

4. Discussion

The present investigation demonstrates the efficacy of an eight-week interdisciplinary weight loss and lifestyle intervention in improving vitamin D levels among men with overweight/obesity and CPAP-treated moderate-to-severe OSA, these effects being especially remarkable at 6 months after the intervention. Indeed, vitamin D deficiency was resolved in more than one third of individuals, with more than 50 % of them presenting sufficient vitamin D status at this point. In addition, changes in serum 25(OH)D concentrations were significantly associated with improvements in sleep patterns, body weight, and body composition variables over time. Considering the potential mechanisms by which the intervention had these beneficial effects, according to our results, changes in OSA severity (measured by AHI) resulted in changes in vitamin D levels through changes in body weight. Consequently, our intervention presents compelling and pioneering evidence regarding the impact of this multifaceted approach on vitamin D status in individuals suffering of OSA, thus providing a promising alternative for further exploration in clinical practice and research in these patients.

Vitamin D deficiency has emerged as a major public health concern worldwide in all age groups, even in countries with sun exposure all year round [39]. Specifically, among Spanish population, vitamin D sufficiency is very uncommon, highlighting the need of programs aimed at enhancing vitamin D status [40]. Circulating 25(OH)D levels are robustly associated with different genetic and environmental (e.g., sunlight exposure, dietary intake, and body composition) factors [41]. In this line, hypovitaminosis D is recognized to be associated with overweight and obesity, a condition that may imply higher requirements of vitamin D [42]. In our study, around 90 % of participants presented low vitamin D status at baseline, over half of them being deficiency. The intervention had a great impact on serum 25(OH)D concentrations, with increments of 19 % at the intervention endpoint, and reducing the prevalence of deficiency to 6.3 % of participants after 6 months post-intervention (increments of 45 %). Interdisciplinary weight-loss and lifestyle interventions conducted among populations with obesity have previously demonstrated an elevation in serum 25(OH)D concentrations, this implying that the bioavailability of vitamin D is an outcome rather than a predisposing factor to obesity [43]. Within the framework of a one-year interdisciplinary weight loss and lifestyle intervention, children with obesity manifested an increase in vitamin D levels from 11 ng/mL to 16 ng/mL, with deficiency persisting following

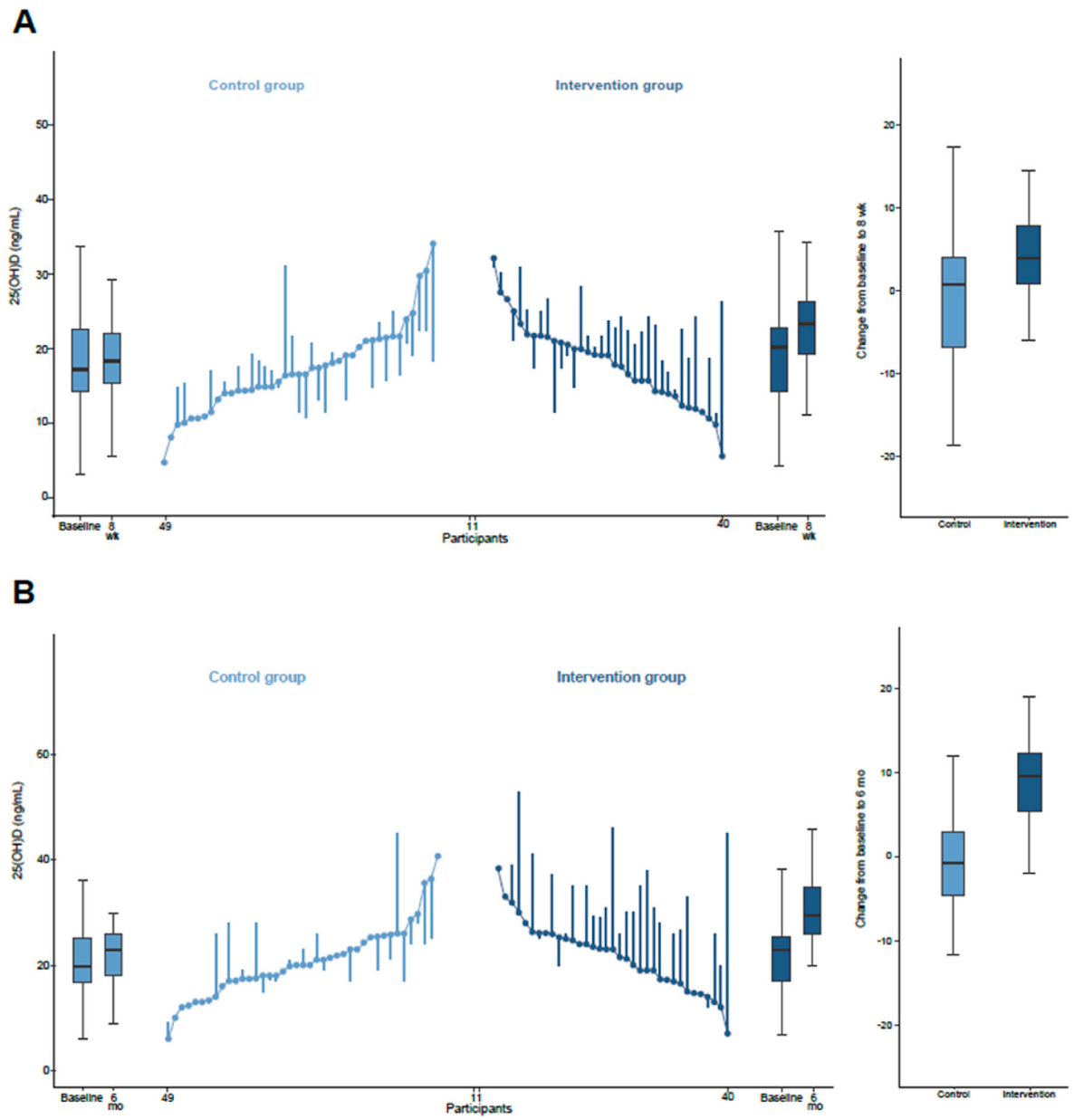

Fig. 1. Vitamin D levels over time. The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their baseline value to their 8-week value (A) or 6-month value (B). Ascending lines indicate an improvement in the outcome. Baseline values are placed in ascending order for the control group and descending order for the intervention group. 25(OH)D, 25-hydroxyvitamin D.

the intervention [44]. Furthermore, middle-aged individuals who had either overweight or obesity and participated in a one-year interdisciplinary weight loss and lifestyle intervention experienced an enhancement in their vitamin D status from 25 ng/mL to 28 ng/mL [45] and from 19 ng/mL to 23 ng/mL [46], respectively, both showing an insufficient vitamin D status after the intervention. Nevertheless, notwithstanding the previous reported post-intervention rise in vitamin D levels, none of the participants of these studies attained a state of sufficiency in vitamin D. Thus, the present results show the potential of our intervention, which may be a promising strategy to enhance vitamin D status and reach vitamin D sufficiency, concretely in men with moderate-to-severe OSA and overweight/obesity.

Current evidence has directed attention towards the plausible rationale concerning diminished levels of vitamin D in individuals afflicted by overweight or obesity, attributing this phenomenon to the deposition of vitamin D within adipose tissue owing to its lipophilic properties [47], together with volumetric dilution, limited sunlight exposure, and diminished vitamin D synthesis in the skin and liver [48]. These pathogenic mechanisms could partially explain the inverse relationships observed between higher serum 25(OH)D concentrations and body weight, fat mass, or visceral adipose tissue in our study. In contrast, diminished vitamin D levels may be involved in the differentiation and growth of adipose tissue, thereby contributing to obesity either through the regulation of gene expression or via modulation of parathyroid hormone, calcium, and leptin [49]. Recent animal studies have demonstrated that vitamin D decreases fat mass by the induction of Ca^{2+}-mediated apoptosis in mature adipocytes, thus improving other biomarkers related to adiposity [50]. Conversely, it should be noted that OSA has been associated with increased risk of cardiovascular disturbances or diabetes (independently of obesity), which may be caused by

Table 2
Repeated measures correlation analyses examining association of changes in vitamin D levels over time with changes in sleep and body weight and composition outcomes.

Outcomes	25(OH)D levels		
	r	95 % CI	P value
Changes from baseline to 8 weeks			
Apnea-hypopnea index, events/hr	−0.53	−0.73 to −0.24	<0.001
Oxygen desaturation index ≥3 %, events/hr	−0.45	−0.68 to −0.14	0.007
Sleep efficiency, %	0.46	0.15 to 0.69	0.005
Body weight, kg	−0.48	−0.70 to −0.17	0.003
Fat mass, kg	−0.32	−0.59 to 0.02	0.064
Visceral adipose tissue, g	−0.26	−0.54 to 0.08	0.136
Changes from baseline to 6 months after intervention			
Apnea-hypopnea index, events/hr	−0.65	−0.82 to −0.38	<0.001
Oxygen desaturation index ≥3 %, events/hr	−0.62	−0.80 to −0.34	<0.001
Sleep efficiency, %	0.63	0.36 to 0.81	<0.001
Body weight, kg	−0.65	−0.82 to −0.38	<0.001
Fat mass, kg	−0.67	−0.83 to −0.41	<0.001
Visceral adipose tissue, g	−0.74	−0.87 to −0.52	<0.001
Changes from 8 weeks to 6 months after intervention			
Apnea-hypopnea index, events/hr	−0.52	−0.68 to −0.32	<0.001
Oxygen desaturation index ≥3 %, events/hr	−0.53	−0.69 to −0.34	<0.001
Sleep efficiency, %	0.53	0.33 to 0.68	<0.001
Body weight, kg	−0.48	−0.64 to −0.27	<0.001
Fat mass, kg	−0.51	−0.67 to −0.30	<0.001
Visceral adipose tissue, g	−0.50	−0.66 to −0.29	<0.001

Abbreviations: CI, confidence interval. 25(OH)D, 25-hydroxyvitamin D.

an exacerbated adipose tissue dysfunction given the increased tissue hypoxia [51]. Therefore, it is plausible that feedback mechanisms, presently undisclosed, may exist between the status of vitamin D and adipose tissue in a bidirectional manner and could be influenced by the presence of OSA.

In this regard, another beneficial and important aspect of this intervention was the improvement of sleep related variables [16]. Specifically, higher serum 25(OH)D concentrations were related with increased sleep efficiency and reduced AHI and oxygen desaturation index over time. These results concur with previous studies, where vitamin D levels were inversely associated to OSA severity [52], and the risk of new-onset OSA in more than 400,000 participants with overweight/obesity [18]. Therefore, vitamin D has been proposed as a potential modifiable factor for primary and secondary prevention or comprehensive management of OSA [18,52]. However, our results showed that changes in AHI from baseline to 6 months after intervention leaded to changes in serum 25(OH)D concentrations via changes in body weight. In this regard, OSA has been previously described as a significant independent risk factor of sarcopenic obesity, which may induce vitamin D deficiency [53]. Moreover, CPAP treatment has been suggested as a feasible strategy to improve vitamin D status in men with severe OSA, which concurs with our results [54].

Although vitamin D deficiency is supposed to be involved in managing sleep disturbances, the complex relationships between vitamin D and OSA are not completely understood yet [52]. As OSA and vitamin D deficiency seem to have almost similar pathogenesis and share common risk factors (e.g., obesity or increasing age) [55], the association between them, either directly or indirectly, has been frequently discussed in the literature. In this regard, the reported results are contradictory and the possible bidirectional link between both entities remaining unclear at present [19], since different factors could be modulating this association: I) the presence of OSA may condition lifestyle, causing a reduction in outdoor activities and the lack of sun exposure [56], II) hypoxia is related to vitamin D deficiency via hypoxia-inducible factor 1-α (HIF1-α) [57], and III) vitamin D deficiency may produce non-inflammatory myopathy of upper airway muscle and reduced pharyngeal patency which may worsen OSA [58,59]. Further investigation is therefore warranted to fully understand the complex possible bidirectional relationship between vitamin D and OSA.

Our findings are of public health and clinical relevance highlighting the potential of weight loss lifestyle interventions as a non-pharmacological treatment strategy for OSA management [16]. Importantly, the observed synergy between improved vitamin D levels and sleep and body composition metrics may amplify the therapeutic effects on OSA severity, serving as an adjunctive therapy and offering a comprehensive approach that addresses both symptoms and the underlying risk factors for OSA management [52]. Of note, the sustainability of these improvements six months post-intervention highlights the importance of adopting long-term lifestyle and behavioral modifications rather than relying solely on short-term pharmacological, medical or surgical interventions [60]. Clinicians should consider integrating interdisciplinary care models including INTERAPNEA components together with vitamin D optimization as part of routine management for OSA patients, ultimately enhancing their quality of life and reducing long-term healthcare costs [15].

A notable strength of this study lies in the pioneering evidence concerning the beneficial impact of a weight loss and lifestyle regimen on vitamin D levels within the context of OSA. Given the structured nature of the intervention and the resultant outcomes, this investigation serves as a compelling rationale for the effective formulation and execution of a novel interdisciplinary approach to weight loss and lifestyle modification, one that holds promise for seamless integration into real-world clinical settings. Additionally, the utilization of full-night in-laboratory polysomnography at key study intervals (baseline, intervention endpoint, and 6 months post-intervention) stands as a noteworthy strength, affording a comprehensive and gold-standard assessment of sleep patterns and OSA severity. The study is also subject to certain limitations. A primary constraint is the exclusive enrollment of men with moderate-to-severe OSA and overweight/obesity, thereby restricting the applicability of our findings solely to this demographic subgroup and hindering the generalizability of results to women and to individuals without obesity and/or with mild OSA. Moreover, factors that could potentially affect sun exposure, such as daily activities and occupation, as well as the presence of depression or anxiety and the use of medication, which may influence vitamin D levels, were not considered. Lastly, the sample composition comprising solely Spanish individuals further confines the scope of our results to this specific ethnic cohort. As a result, the generalization of our findings is constrained to this specific demographic. Thus, future accurately designed studies, incorporating diverse participant populations, longer follow-up durations, and comprehensive assessment protocols, are imperative to further elucidate the efficacy and broader applicability of interdisciplinary interventions in managing OSA-related complications.

5. Conclusion

This study provides evidence indicating that an eight-week interdisciplinary weight loss and lifestyle intervention is effective at improving, and even potentially resolving, vitamin D deficiency at 6-months after intervention in men with moderate-to-severe OSA and overweight/obesity. Considering the widespread prevalence of vitamin

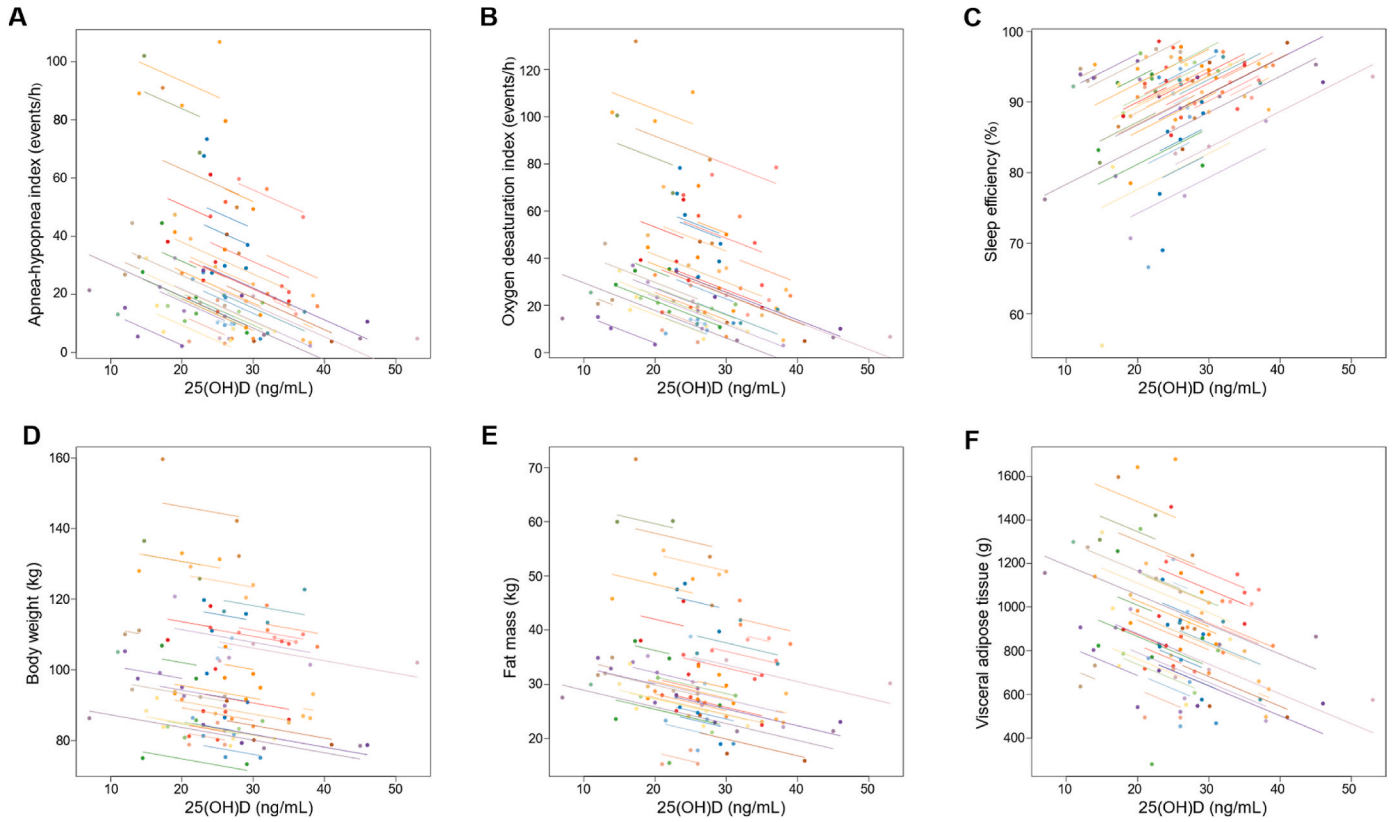

Fig. 2. Association of changes in 25(OH)D levels over time with changes in sleep and body weight and composition outcomes. Each dot represents one of three separate observations (baseline, 8 weeks, and 6 months after intervention) of 25(OH)D levels and sleep and body weight and composition outcomes for a participant. Observations from the same participant are given the same color, with corresponding lines to show the repeated measures correlation fit for each participant. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

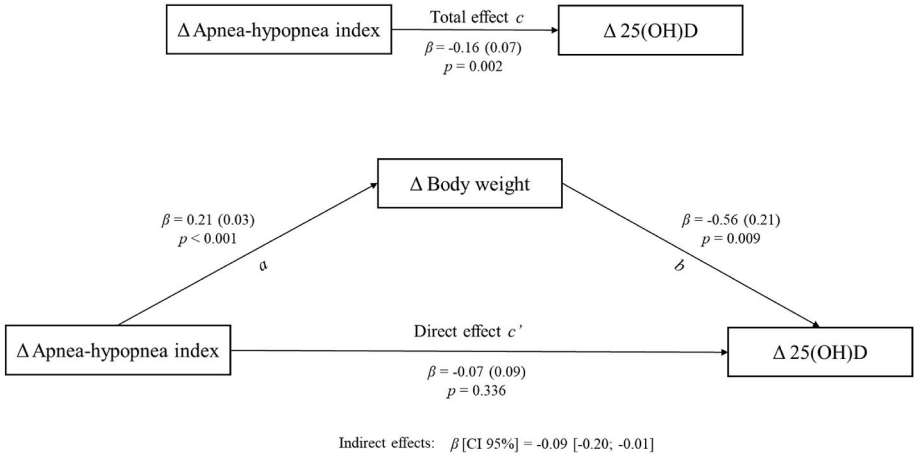

Fig. 3. Mediation model of the effects of changes on apnea-hypopnea index on changes on 25(OH)D levels with changes on body weight as a mediator variable. Paths a, b, c, and c' are presented as unstandardized coefficients (standard error). [Lower-limit CI; upper-limit CI], lower and upper levels for 95 % bias-corrected CIs of the indirect effects based on 1000 bootstraps. CI, confidence interval. 25(OH)D, 25-hydroxyvitamin D.

D deficiency and its relationship with adverse sleep patterns and body composition parameters, this intervention may be considered as a holistic approach to address the multifaceted challenges caused by sleep disorders and the substantial impact of vitamin D on human health and well-being. Healthcare professionals should thus contemplate this approach in the treatment of these patients.

CRediT authorship contribution statement

Héctor Vázquez-Lorente: Writing – original draft, Visualization, Software, Formal analysis, Conceptualization. **Lourdes Herrera-Quintana:** Writing – original draft, Visualization, Software, Formal analysis, Conceptualization. **Jonatan R. Ruiz:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Francisco J. Amaro-Gahete:** Writing – review &

editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Almudena Carneiro-Barrera:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Data availability statement

This data has not been previously presented anywhere and will be shared upon reasonable request to the corresponding authors. Héctor Vázquez-Lorente & Almudena Carneiro-Barrera (email: hectorvazquez@ugr.es; acarneiro@uloyola.es).

Patient consent statement

All participants gave their oral and written informed consent to be included before their enrollment, including consent regarding publishing their data.

Ethics approval statement

Approval for all human subject/patient-related procedures was obtained from the regulatory authorities and the Clinical Research Ethics Committees of the University of Granada (Granada, Spain), Virgen de las Nieves University Hospital (Granada, Spain), and Junta de Andalucía (Spain) (0770-N-19) in accordance with the last revised ethical guidelines of the Declaration of Helsinki.

Clinical trial registration

This study was registered with the National Institutes of Health database (ClinicalTrials.gov NCT03851653).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used no tool or service.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2025.01.011.

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