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Etiology and Pathophysiology

Obesity and vitamin D deficiency: a systematic review and meta-analysis

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Summary

Over the past decade, there have been an increasing number of studies on the association between vitamin D deficiency and anthropometric state. However, we did not identify any meta-analyses of the relationship between obesity and vitamin D deficiency in different age groups. Thus, we evaluated the association between obesity and vitamin D deficiency. We searched for observational studies published up to April 2014 in PubMed/Medline, Web of Science and Scopus databases. We performed a meta-analysis in accordance with the random-effects model to obtain the summary measurement (prevalence ratio, PR). Among the 29,882 articles identified, 23 met the inclusion criteria. The prevalence of vitamin D deficiency was 35% higher in obese subjects compared to the eutrophic group (PR: 1.35; 95% CI: 1.21–1.50) and 24% higher than in the overweight group (PR: 1.24; 95% CI: 1.14–1.34). These results indicate that the prevalence of vitamin D deficiency was more elevated in obese subjects. The vitamin D deficiency was associated with obesity irrespective of age, latitude, cut-offs to define vitamin D deficiency and the Human Development Index of the study location.

Keywords: 25-hydroxy vitamin D, meta-analysis, obesity, vitamin D deficiency.

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Introduction

Obesity is defined as an excess amount of body fat and constitutes a worldwide epidemiological problem (1). Currently, it is the fifth greatest risk factor for mortality (1) and it is also associated with vitamin D deficiency (2). There has been an increase in the number of studies on the association between vitamin D insufficiency and anthropometric state over the past decade, and obesity and vitamin D deficiency have both been recognized as major public health issues worldwide (2–4). Observational studies have identified that obesity is associated with vitamin D deficiency (2–4), although there is no consistent evidence for the causal relationship between these events (5).

Vitamin D is essential for the development and maintenance of bone tissue, as well as for normal homeostasis of calcium and phosphorus (6,7). Moreover, it is related to differentiation, cell proliferation and hormone secretion. An estimated 80–90% of vitamin D from the human body originates from skin synthesis, with sunlight activation, while the rest is supplied through supplements or food (8). Vitamin D status is measured by means of the plasma levels of 25-hydroxyvitamin D [25(OH)D] (2). The Institute of Medicine proposed that serum 25(OH)D concentrations below 50 nmol L^{-1} or 20 ng mL^{-1} should be considered to represent the deficiency of this nutrient (9).

Vitamin D deficiency has been reported in all phases of life throughout the world (10,11), which makes this issue an important health concern. This deficiency underpins the aetiology of several chronic endocrine and metabolic disorders (2). In this regard, meta-analysis of data has shown that sufficient vitamin D concentrations among adults were associated with reduction of the risk of occurrence of cardiovascular diseases, diabetes and metabolic syndrome (12).

In the epidemiological literature on anthropometric profiles and vitamin D concentrations, we identified a meta-analysis study that investigated the correlation between serum concentrations of 25(OH)D and body mass index (BMI) among adults living in developed and developing countries. This showed a weak correlation between BMI and vitamin D concentrations (13). This was one of the first studies to quantify and evaluate the association between different categories of BMI and vitamin D deficiency. On the other hand, we did not identify any meta-analyses in the worldwide epidemiological literature about the association between obesity and vitamin D deficiency in different populations and age groups. Thus, it is pertinent to aggregate evidence and systematize information on the relationship between vitamin D deficiency and obesity, aiming to provide information to support the planning of future studies and public policies for prevention of this deficiency in different populations. Therefore, the aim of the present study was to evaluate the association between obesity and vitamin D deficiency in different age groups.

Methodology

Identification and selection of articles

We conducted a systematic review with meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) norms (14), on studies that evaluated the association between 25(OH)D concentrations and obesity. To do so, an online search was performed in PubMed/Medline, Web of Science and Scopus for articles published between 30 December 1995 and April 2014. The search terms were 'vitamin D', 'cholecalciferol' and 'ergocalciferol', combined with 'obesity', 'body mass index' and 'weight'. Additionally, we evaluated the references of the articles and reviews on vitamin D so as to identify studies that were not indexed in the databases, but would be pertinent for inclusion in this review.

The articles identified in the databases were selected independently by two reviewers using forms containing the eligibility criteria for the articles. At the end of the review, articles for which there were divergences of opinion were selected according to a consensus reached between the reviewers. In the absence of a consensus, a third reviewer evaluated whether the study in question was eligible.

The included articles had an observational design, included 25(OH)D serum assays, analysed the association between vitamin D status and obesity, and identified the prevalence of hypovitaminosis D. Articles that involved individuals who had undergone bariatric surgery, those that were literature reviews, communications or editorials, and those with methodological weakness, such as inference data for the population from a non-representative sample, and studies that evaluated the relationship between vitamin D deficiency and nutritional status, but did not explain in the methodology the parameters used to evaluate these events were excluded.

The eligible articles were read in full, and information about the study's year of publication and design and the variables investigated was recorded using a form designed for gathering this information. The information obtained from the selected studies comprised eutrophic, overweight and moderate obese individuals. Thus, information about underweight and morbid obese individuals was excluded.

The serum level of 25(OH)D was used as an indicator for vitamin D status because this metabolite reflects the supply of vitamin D metabolites both in the diet and through skin synthesis. Moreover, hydroxylation of 25(OH)D to 1.25(OH)2D3 (active vitamin D) occurs in several tissues: the half-life of 25-OH-D is 2–3 weeks while the half-life of 1.25(OH)2D3 is approximately 6 h (15).

Statistical analysis

We gathered data on the prevalence of vitamin D deficiency in groups of obese, overweight and eutrophic individuals. These data were later used to calculate the summary measurements of the study and the confidence intervals (CIs).

The prevalence ratio (PR) was used as the summary measurement for the meta-analysis and the results were presented as forest plots. The PR and its respective CI (95% CI) were obtained through a fixed or random-effects model, depending on the heterogeneity among the studies (16). Heterogeneity and inconsistency of the measurements were identified through Cochran's Q statistical test. If heterogeneity was confirmed, then the random-effects model was applied with inverse variance and weighting according to the results of the individual studies (17). The inconsistency test ($I^2 > 50\%$) was used as an indicator for moderate heterogeneity. The publication bias was assessed through a funnel plot and Egger's regression model (17).

To compare the association between obesity and vitamin D deficiency, subgroup analysis was performed according to age (1 – children and adolescents; 2 – adults and the elderly). For the subgroup analysis, the cut-offs used for vitamin D deficiency in the studies were 1 – ≤ 25 nmol L^{-1}, ≤ 35 nmol L^{-1}; 3 – ≤ 50 nmol L^{-1}.

The heterogeneity of the meta-analysis was investigated by means of a meta-regression, testing the following as potential confounding variables: latitude, Human Development Index (HDI) of the country in which the study was carried out, sample size and cut-offs to define vitamin D deficiency. Furthermore, the influence of age group in the overall PR was evaluated using the meta-regression.

In all analyses, P values less than 0.05 were considered statistically significant. The statistical analysis was carried

out using the Stata 12 software (Stata Corp, College Station, TX, USA) and, to obtain the PR, the metan command was used.

Results

Characteristics of the eligible studies

Our search strategy identified 29,882 articles in the selected databases. After analysing the title, we excluded 29,348 articles and, after analysing the abstract, a further 480. After making this selection, we thus analysed the complete text of 84 studies, of which 23 met the inclusion criteria and were included in the review (Fig. 1) (18–40). The reasons for exclusion were as follows: absence of categorization of the anthropometric state through BMI (18), methodological weakness (14), non-use of cut-off points for the serum concentration of vitamin D (8), unreported prevalence of vitamin D deficiency (18) and non-observational study design (3).

The main characteristics of the studies included in this review are presented in Table 1. Most articles (76.16%) were published between 2010 and 2013. Assays of 25(OH)D used a number of different techniques while the anthropometric status was evaluated in most studies through the BMI.

Results from the meta-analysis

The results from the meta-analysis can be seen in Figs 2 and 3. In Fig. 2, twenty-one studies were grouped comparing the risk of deficiency among obese vs. eutrophic individuals (1,18–20,22–33,35–40). Independent of the age group, obese individuals presented a 35% greater prevalence of vitamin D deficiency if compared to eutrophic individuals (PR: 1.35; 95% CI: 1.21–1.50). In the subgroup analysis of eight studies (20,23,25,29,30,35,38,39), illustrated in Fig. 2, up to 37% of obese children and adolescents were vitamin D deficient (PR: 1.37; 95% CI: 1.20–1.56), while in obese adults and elderly individuals this prevalence was 33% (PR: 1.33; 95% CI: 1.15–1.54) (18,19,22,24,26–28,31–33,36,37,40). The result from the inconsistency test showed that there was high heterogeneity among the studies analysed (87.3%; $P = 0.00$). Thus, the random-effects model was used to calculate the summary measurement. No publication bias was identified according to the funnel plot (Fig. 2) and Egger's test ($P = 0.30$).

In the second analysis involving 19 studies (18–24,26,28–31,33,34,36–40) in which obese individuals were compared with overweight individuals, being overweight reduced the association between obesity and vitamin D deficiency (PR: 1.21; 95% CI: 1.14–1.29) (Fig. 3). This reduction in the overall summary measurement was

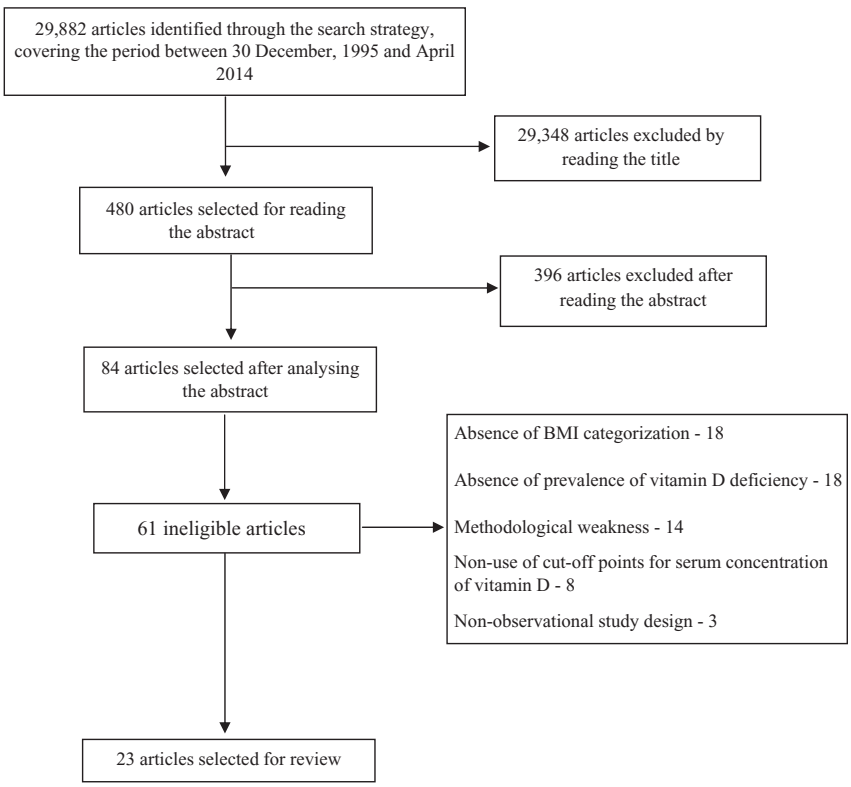
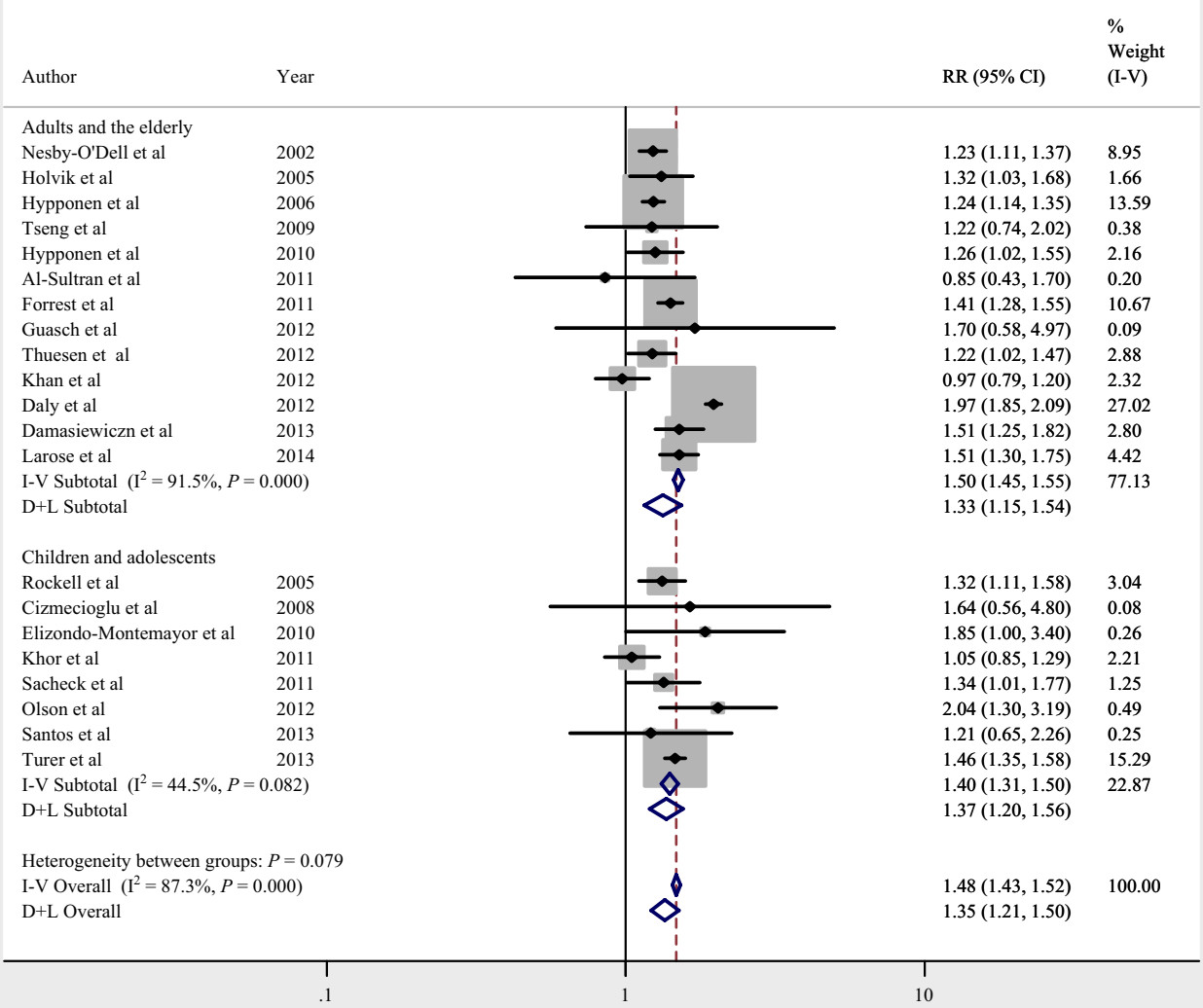


Figure 1 Flow chart for article selection.

Table 1 Characteristics of selected studies investigating the association between obesity and vitamin D deficiency

First author	Year	Country	Design	Age range, mean (DP)	*N*	Obese (%)	Method used for assessing serum 25(OH)D level	Vitamin D deficiency (nmol L^{-1})
Nesby-O'Dell *et al.* (18)	2002	USA	Cohort	15–49	2,835	718 (25.32)	RIA	37.5
Holvik *et al.* (19)	2005	Norway	Cross-sectional	31–60	1,000	157 (15.7)	RIA	25
Rockell *et al.* (20)	2005	New Zealand	Cross-sectional	1,585	1,585	288 (18.17)	RIA	37.5
Bischof *et al.* (21)	2006	Austria	Cross-sectional	48.2 (16)	483	286 (59.21)	RIA	22
Hypponen *et al.* (22)	2006	England	Cohort	45	7,198	1,214 (16.87)	Enzyme immunoassay	50
Çizmecioglu *et al.* (23)	2008	Turkey	Cross-sectional	11–19	301	102 (33.8)	Immundiagnostic	50
Tseng *et al.* (24)	2009	USA	Cross-sectional	49.6 (8.4)	194	50 (25.77)	CLIA	37.5
Elizondo-Montemayor *et al.* (25)	2010	Mexico	Cross-sectional	6–12	198	99 (50.00)	Competitive immunoluminometric direct assay	50
Hyppönen *et al.* (26)	2010	England	Cohort	45	6,538	1,440 (22.00)	ELISA	25
Al-Sultran *et al.* (27)	2011	Saudi Arabia	Case–control	18–25	160	76 (47.50)	HPLC	37.5
Forrest *et al.* (28)	2011	USA	Cross-sectional	20–80	4,495	1,563 (34.77)	RIA	50
Khor *et al.* (29)	2011	Malaysia	Cross-sectional	7–12	402	66 (16.42)	Diaspora Liaison	37.5
Sacheck *et al.* (30)	2011	USA	Cross-sectional	11.7 (1.5)	263	65 (24.11)	RIA	50
Daly *et al.* (31)	2012	Australia	Cross-sectional	48 (15.7)	12,188	2,456 (20.15)	CLIA	50
Guasch *et al.* (32)	2012	Spain	Cohort	46.85	316	90 (28.48)	Electrochemiluminescence immunoassay	25
Khan *et al.* (33)	2012	Pakistan	Cross-sectional	32.68 (8.3)	275	132 (48.00)	Electrochemiluminescence immunoassay	50
Minambres *et al.* (34)	2012	Spain	Cross-sectional	42 (11)	343	151 (44.02)	RIA	50
Olson *et al.* (35)	2012	USA	Cross-sectional	11.7 (2.6)	498	411 (82.53)	Chemiluminescent immunoassay	50
Thuesen *et al.* (36)	2012	Denmark	Cross-sectional	18–65	5,447	913 (16.76)	HPLC	25
Damasiewicz *et al.* (37)	2013	Australia	Cohort	50.6 (12.3)	5,738	1,188 (20.70)	CLIA	37.5
Santos *et al.* (38)	2013	Brazil	Cross-sectional	13.17 (1.7)	198	18 (9.09)	RIA	54
Turer *et al.* (39)	2013	USA	Cross-sectional	6–18	12,292	1,897 (15.43)	RIA	50
Larose *et al.* (40)	2014	Norway	Cross-sectional	19–55	2,498	300 (12.01)	CLIA	50

CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; RIA, radioimunoensaio; SD, standard deviation.



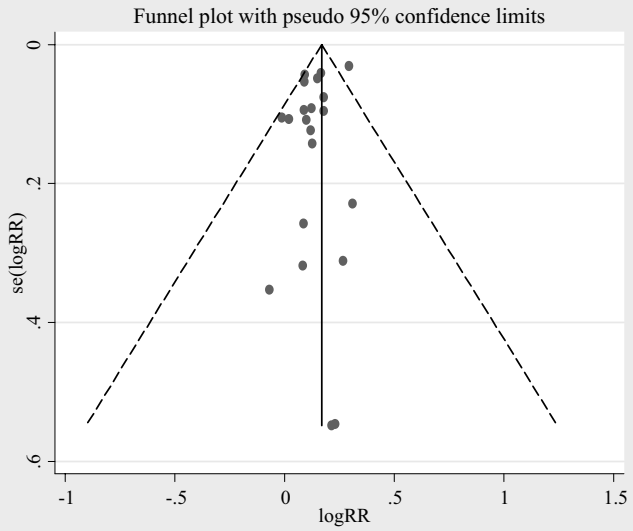
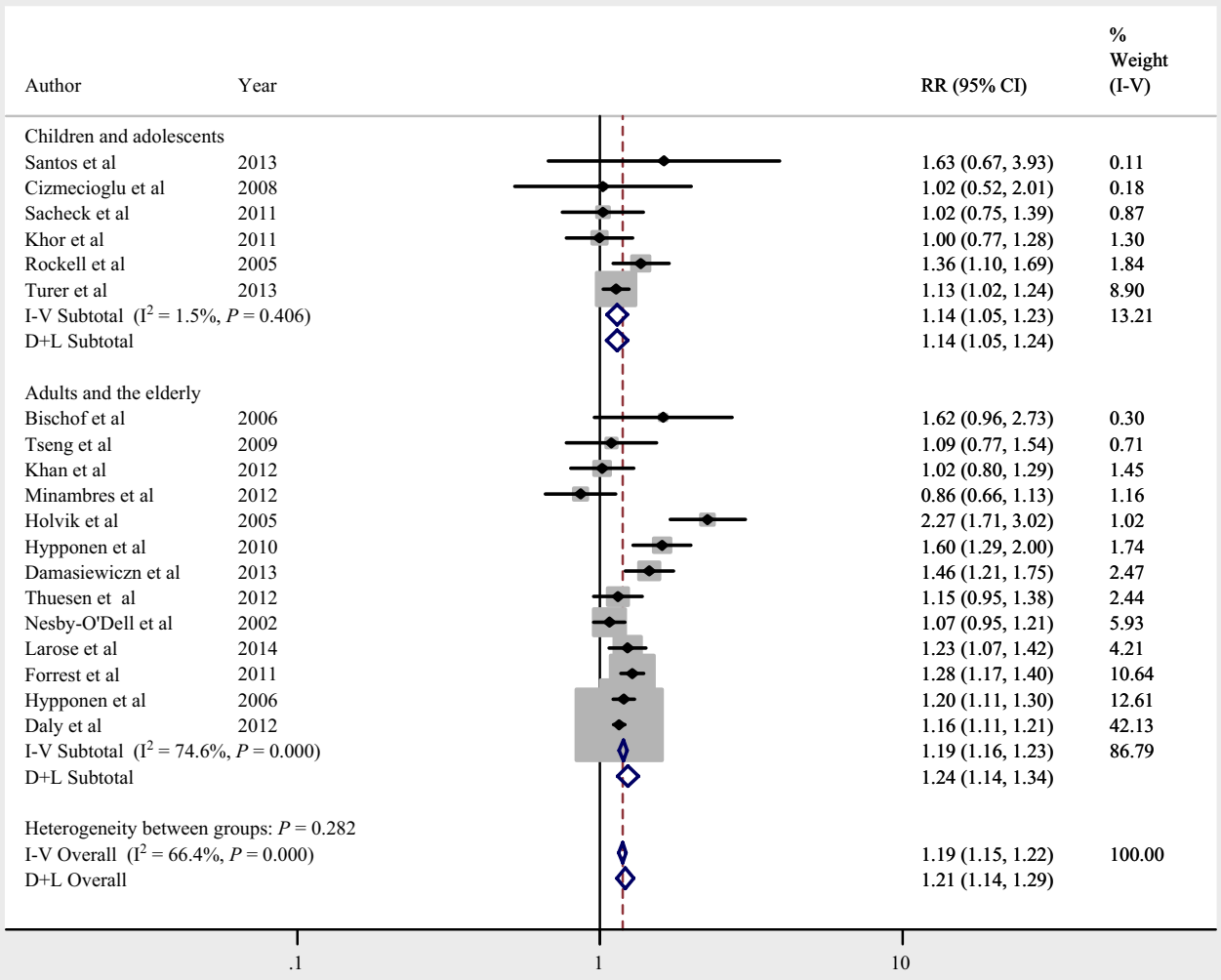


Figure 2 Prevalence ratio and funnel plot of the association between vitamin D deficiency in obese individuals and eutrophic individuals.



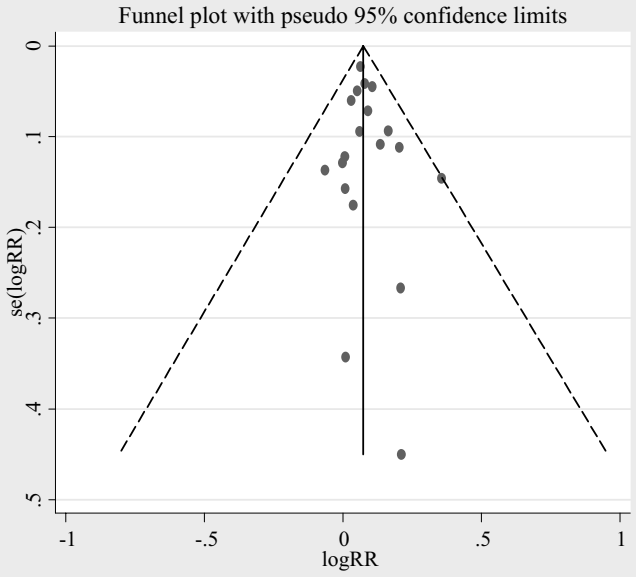


Figure 3 Prevalence ratio of the association between vitamin D deficiency in obese and overweight individuals.

16% in comparison with the summary measurement presented in Fig. 2. Based on the subgroup analysis of 13 studies (18,19,21,22,24,26,28,31,33,34,36,37,40), the prevalence of vitamin D deficiency in obese adults and elderly individuals was 24% (PR: 1.24; 95% CI: 1.14–1.34), while in obese children and adolescents it was 14% (PR: 1.14; 95% CI: 1.05–1.24) (20,23,29,30,38,39). The studies analysed presented moderate heterogeneity ($I^2 = 66.4\%$; $P = 0.000$), and no publication bias was observed according to the funnel plot and Egger's test ($P = 0.32$).

The PR comparison between obese and eutrophic individuals varied with the different cut-offs used for Vitamin D in the studies. In six studies using the cut-off ≤37.5 nmol L^{-1}, the PR was 1.25 (95% CI: 1.12–1.40); in the three articles that adopted the cut-off ≤25 nmol L^{-1}, this association measure was very similar (PR: 1.26; 95% CI: 1.11–1.42), but when more cut-offs used in studies were ≤50 nmol L^{-1}, the PR identified was 1.44 (95% CI: 1.24–1.68). When comparing the PR of obese and overweight individuals, according to the different cut-offs for vitamin D deficiency, there was a PR of 1.19 (95% CI: 1.02–1.3) for five studies using the cut-off ≤37.5 nmol L^{-1}, a PR of 1.59 (95% CI: 1.09–2.31) for the cut-off ≤25 nmol L^{-1}, and a PR of 1.17 (95% CI: 1.13–1.21) for the cut-off ≤50 nmol L^{-1} (data not shown in graphs).

Meta-regression results

Three meta-regressions were carried out to investigate the heterogeneities identified in the meta-analyses on the association between obesity and vitamin D. In the first meta-regression, which was performed comparing the group of obese individuals with the eutrophic individuals, the HDI ($P = 0.13$), sample size ($P = 0.09$), cut-offs to define vitamin D deficiency ($P = 0.54$) and latitude ($P = 0.18$) of the cities where the studies were carried out did not contribute significantly towards the size of the summary measurement of the meta-analysis. Similarly in the second meta-regression, neither HDI ($P = 0.67$), sample size ($P = 0.57$), cut-offs to define vitamin D deficiency ($P = 0.16$) nor latitude ($P = 0.54$) explained the heterogeneity of the meta-analysis regarding obesity vs. overweight.

In the third meta-regression, age groups were shown not to influence the association between vitamin D deficiency in obese vs. eutrophic individuals ($P = 0.89$) or between obese and overweight individuals ($P = 0.45$). These results indicate that the overall effect is similar for both groups, suggesting that there is no interaction of age in the association evaluated.

Discussion

The results from the present meta-analysis indicate that obesity was associated with vitamin D deficiency regardless of the age group. The World Health Organization has projected that there will be approximately 2.3 billion overweight adults worldwide and that obesity will affect among more than 700 million in 2015 (41). Taking into account the association between vitamin D deficiency and obesity, these two morbid events may constitute important current health issues during this period.

The results from the meta-analysis indicate that overweight and obese individuals in different age groups have a similar chance of presenting with vitamin D deficiency. Thus, the age does not seem to contribute significantly on this association.

Recently, the effects of low levels of vitamin D on imprinting during childhood and adolescence and subsequent occurrence of bone diseases such as osteoporosis and osteoarthritis during later stages of life have been investigated, along with the growing risk of development of metabolic syndrome and cardiovascular, respiratory and psychological disorders (42,43). On the other hand, among adults, vitamin D deficiency predisposes the individual to increased risk of chronic diseases such as hypertension, diabetes, cardiovascular diseases, different types of cancer and excess weight (2,12,44,45).

The variables that could be associated with the prevalence of vitamin D deficiency, such as latitude, HDI, sample size and cut-offs to define vitamin D deficiency, did not influence the meta-analysis summary measurement in the present study, although moderate heterogeneity was identified in most of the analyses, thus indicating variation among the results from the studies analysed. For this reason, the random-effects model was used to calculate the summary measurements of this study.

A recent meta-analysis study on the relationship between vitamin D concentrations and BMI also did not record any significant contribution from latitude or from the development situation of the country in which the study was performed, to the magnitude of the summary measurement of the meta-analysis (13). Thus, the association relationship between vitamin D deficiency and obesity can occur independently from latitude, age and the conditions of human development (HDI).

Furthermore, it was observed that the different cut-offs to define vitamin D deficiency used in the studies included in this meta-analysis did not influence the overall PR between the subgroups and also did not affect the heterogeneity of the results.

Different theories can be proposed to explain the relationship between obesity and vitamin D deficiency. First, because of issues of low social acceptance, it is suggested that obese individuals reduce their exposure to sunlight, perform fewer outdoor activities and/or use clothes that cover more of the body, which limits exposure to the sun and, consequently, cutaneous vitamin D synthesis. However, in a study based on the Framingham cohort,

which evaluated the association between obesity and vitamin D, it was reported that after adjustments for practising outdoor physical activities, this theory was insufficient to explain the relationship between obesity and vitamin D deficiency (45). Thus, different levels of sun exposure seem to be an unlikely explanation for the relationship between vitamin D deficiency and adiposity.

Alternatively, it has been suggested that excess body fat retains the vitamin D metabolites and that the cholecalciferol produced through the skin or acquired through the diet is partially sequestered by the body fat before being transported to the liver for the first hydroxylation (4). Moreover, the significant level of the vitamin D activation enzyme 1-α-hydroxylase in the adipose cells of obese individuals would explain the greater local use of 25(OH)D. According to this hypothesis, variations in serum 25(OH)D and vitamin D reserves can be directly related to the amount of subcutaneous body fat (45). Wortsman *et al*. (4) reported that after exposure to sunlight, the increase in the serum concentration of 25 vitamin D was 53% lower among obese individuals than among eutrophic volunteers, independent of the amount of cutaneous precursor of vitamin D that was present.

On the other hand, some experimental data have suggested that vitamin D deficiency can favour greater adiposity by promoting increased parathyroid hormone levels and greater inflow of calcium into adipocytes, thereby increasing lipogenesis (46). Accumulated evidence suggests that 1.25(OH)D inhibits adipogenesis through actions modulated by vitamin D-dependent receptors (47). Thus, depletion of vitamin D can lead to excessive differentiation of pre-adipocytes to adipocytes.

The results of this current study emphasize the prevalence of vitamin D deficiency in obese and overweight individuals. However, the impact of several confounding factors, such as diet intake, physical activity, educational level, season of the year and presence of secondary hyperparathyroidism, should be recognized as these were not included in this meta-analysis due to methodological divergences in the studies analysed and the absence of this information. In addition, most of the studies included in the present meta-analysis had cross-sectional designs, which makes it more difficult to examine the relationship of causality between obesity and vitamin D deficiency. Despite these limitations, the results from this study are consistent, especially given the absence of publication bias, according to Egger's test and the funnel plot, and considering the results of the meta-regression for the major confounders of the association studied.

In conclusion, the results of this first meta-analysis quantifying the association between different levels of BMI and vitamin D deficiency revealed a positive association between BMI and vitamin D deficiency. Future prospective studies are necessary to evaluate the potential causal relationship between serum concentrations of vitamin D and obesity. In addition, these data suggest the necessity to monitor serum vitamin D levels among obese individuals. Research is needed to identify standardized cut-off points for 25(OH)D because of the differing climatic and dietary characteristics of each country. Moreover, we recommend that awareness of the relationship between obesity and vitamin D levels should lead to changes in clinical approaches used by healthcare professionals such as nutritionists and doctors.

Conflict of interest statement

No conflict of interest was declared.

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