Effects of Vitamin D Supplementation on General and Central Obesity: Results from 20 Randomized Controlled Trials Involving Apparently Healthy Populations

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Keywords

Vitamin D · Obesity · Body mass index · Waist circumference · Waist-to-hip ratio

Abstract

Background: The obesity pandemic has been paralleled by a high prevalence of vitamin D deficiency (VDD). There is growing epidemiological evidence linking low vitamin D status with obesity events. In addition, observational studies also show that obesity may increase the risk of VDD. However, there is insufficient knowledge to understand whether there is a causality between the two. Moreover, the impact of vitamin D supplementation on obesity indices has shown inconsistent outcomes. **Objective:** This meta-analysis aimed to assess whether vitamin D supplementation modified general and central obesity indices in apparently healthy populations. **Methods:** A systematic retrieval of relevant randomized controlled trials (RCTs) was undertaken using Pubmed, Embase, Web of Knowledge and Chinese National Knowledge Infrastructure databases. The pooled weighted mean difference (WMD) and 95% confidence intervals (CI) were used to assess the changes in body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and 25-hy-

droxyvitamin D (25[OH]D) from baseline. **Results:** Twenty RCTs involving 3,153 participants reporting either BMI, WC, WHR or 25(OH)D met the inclusion criteria. When compared with placebo, vitamin D supplementation had no significant decreases in BMI (WMD = -0.09 kg/m^2 , 95% CI -0.19 to 0.01 , $p = 0.08$), WC (WMD = -0.71 cm , 95% CI -1.58 to 0.16 , $p = 0.112$) or WHR (WMD = 0.00 , 95% CI -0.01 to 0.01 , $p = 0.749$). However, in the subgroups of females, Asia region studies and intervention duration ≥ 6 months, a beneficial and significant reduction in BMI and WC was noted (all $p < 0.026$). On the other hand, pooled results showed that there was a significant increase in serum 25(OH)D levels (WMD = 13.20 ng/mL , 95% CI 9.83 – 16.58 , $p < 0.001$) after vitamin D intervention. No publication bias was found in our study. **Conclusions:** Overall, supplementation with vitamin D produced no significant effect on the BMI, WC or WHR of healthy adults.

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Introduction

Obesity is defined as an abnormal or excessive accumulation of body fat resulting from an imbalance between energy intake and expenditure. The obesity epi-

demic affected an estimated 650 million adults and 124 million children in 2016 [1], and this condition increases the risk of chronic diseases like diabetes, cardiovascular diseases and cancer [2]. Currently, it is considered to be the fifth greatest risk factor for mortality [1]. A low serum vitamin D level is one of the metabolic disturbances associated with obesity [3]. The serum levels of 25-hydroxyvitamin D (25(OH)D) are commonly used as a biomarker for the long-term vitamin D nutritional status of an individual [4]. The Institute of Medicine defines vitamin D deficiency (VDD) as a medical outcome characterized by rickets and osteomalacia, with a serum 25(OH)D concentration <20 ng/mL (50 nmol/L) [5]. Currently, both obesity and VDD constitute worldwide epidemiological problems.

Obesity and VDD often coexist. Body mass index (BMI) and abdominal fat mass are known determinants of vitamin D status, and VDD is common in individuals with obesity [6]. Observational studies from a recent meta-analysis showed an inverse relationship between 25(OH)D levels and BMI both in diabetic and nondiabetic groups [7]. The first meta-analysis quantifying the association between obesity and VDD showed that the prevalence of VDD was 35% higher in the obesity group than in the control group [8]. However, it is still unclear whether VDD is a cause or an outcome of obesity. One proposed theory posits that vitamin D, being fat soluble, can be sequestered in cutaneous and visceral adiposity depots, resulting in low serum vitamin D levels in obese individuals [9]. An alternative theory proposes that volumetric dilution can explain most of the differences in serum 25(OH)D levels between obese and lean individuals [10]. Different mechanisms may explain why VDD is associated with a higher risk of adiposity. On the one hand, VDD increases parathyroid hormone levels and promotes a greater inflow of calcium (Ca) into adipocytes [11]. On the other hand, VDD might accelerate the differentiation of preadipocytes into adipocytes [12]. Both conditions could influence the obesity risk either directly (e.g., by increasing adipogenesis) or indirectly (by modulating inflammation, oxidative stress, metabolism and gene regulation) [13]. A study on diet-induced obesity in a mouse model showed that a high vitamin D and Ca intake can activate the Ca^{2+} -mediated apoptotic pathway in adipose tissue, which would alleviate obesity by reducing body fat [14]. In addition, the vitamin D receptor and the vitamin D-metabolizing enzymes which produce 25(OH)D and $1,25(\text{OH})_2\text{D}$ are expressed in human adipose tissue, strongly suggesting there is a complex relationship between vitamin D and obesity [13, 15].

Two patterns of obesity, general (peripheral) obesity and central (abdominal) obesity, are often involved in epidemiological anthropometry. The BMI is one of the most commonly used anthropometric indices to determine the presence of general obesity in clinical practice and in population surveys [16]. Most observational studies have confirmed that vitamin D status is inversely correlated with the BMI [7]. However, several randomized controlled trials (RCTs) and a recent meta-analysis on the effects of vitamin D supplementation on BMI did not seem to support this correlation [17–20]. On the other hand, several studies have suggested that central obesity is considered as a better predictor of several adverse health outcomes and mortality [21, 22]. Thus, more attention should be paid to the current prevalence of central obesity. Waist circumference (WC) and waist-to-hip ratio (WHR) are ideal indicators for evaluating central obesity [16]. A recent cross-sectional study of highly educated adults conducted by Mansouri et al. [23] demonstrated that serum 25(OH)D levels were negatively correlated with WC, and that participants with VDD had a 2.04-fold greater risk of central obesity than those with normal levels of 25(OH)D. Several RCTs have investigated the effects of vitamin D supplementation on WC and WHR [24–26]; however, the results are still under debate. Moreover, until now, we have not found any meta-analyses in the worldwide epidemiological literature investigating the quantitative association between vitamin D supplementation and central obesity indices.

Given this background, the aim of this study was to examine whether an improvement in vitamin D status correlated with reduced obesity indices in order to make informed decisions on the administration of vitamin D. Therefore, we conducted a meta-analysis of 20 RCTs involving apparently healthy populations who reportedly did not participate in any weight loss programs.

Methods

This systematic review with a meta-analysis was registered, and its protocol was published at the PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO/CRD42019130375). We conducted the study following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [27]. The complete PRISMA checklist is provided in online supplementary Material Table S1 (see www.karger.com/doi/10.1159/000507418 for all online suppl. material).

Data Sources and Literature Search Strategies

The searches were conducted by L.D. and Y.W. from January 1995 to December 2019 using Pubmed, Embase, Web of Knowl-

edge and Chinese National Knowledge Infrastructure databases with the following keywords or MeSH terms: “vitamin D,” “cholecalciferol,” “calcifediol,” “ergocalciferol,” “25(OH)D,” “1,25(OH)₂D,” “25-hydroxyvitamin D,” “1,25-dihydroxyvitamin D,” “vitamin D supplementation,” “body mass index,” “BMI,” “waist circumference,” “WC,” “waist to hip ratio,” “WHR,” “obesity,” “abdominal obesity,” “overweight” and “adiposity.” Further, the records were restricted to publications in English or Chinese and human studies. To complement the electronic search, we also perused studies included in relevant systematic reviews and reference lists of pertinent articles. Details on the literature search strategy are described in online supplementary Table S2.

Inclusion and Exclusion Criteria

Two authors (L.D. and Y.W.) independently reviewed the titles and abstracts to identify articles for potentially relevant sources. Full texts of them were requested to evaluate eligibility. Articles were included if they met the following criteria: (1) followed an RCT design; (2) investigated the association between vitamin D supplementation and effect of obesity indices; (3) included a general healthy population rather than specific disease patients; (4) separately reported changes in the BMI, WC or WHR in the intervention and control groups before and after the intervention. We excluded studies if: (1) data were not fully available after contacting the authors by e-mail; (2) they were meta-analyses or systematic reviews; (3) they were duplicate studies; (4) participants were children, pregnant women or subjects diagnosed with a chronic medical illness; (5) participants engaged in special occupations; (6) subjects participated in any kind of weight loss program, including bariatric surgery, weight-reducing drugs or exercise. Discrepancies between 2 authors were solved by discussion and after reaching a consensus with the third author (L.H.).

Data Extraction

Data on the studies’ characteristics and related information were collected in Excel format using a premade checklist by one reviewer (L.D.), and then double-checked by another author (Y.W.). The following information was extracted: (1) information of study (surname of the first author, year of publication, region of study, sample size of each group, intervention type and amount, duration of intervention and intervention combined with calcium or not); (2) characteristics of participants (age, gender, 25[OH]D levels at baseline and health status of participants); (3) changes in the BMI, WC, WHR or 25(OH)D in the intervention and control groups before and after the intervention. Attempts were made to contact the corresponding or first author for unavailable information.

Risk for Bias Assessment

Two authors (L.D. and Y.W.) independently assessed the quality of all included studies by following the Cochrane Collaboration’s tool [28] (online suppl. Table S3). Seven aspects (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias) were estimated. Summary assessments for studies were assigned as “high,” “low” or “unclear” according to the risk bias in each important outcome. Disagreements were solved through group discussion.

Data Synthesis and Statistical Analysis

The weighted mean difference (WMD) and 95% confidence interval (CI) were used to assess the combined changes in BMI,

WC, WHR and 25(OH)D from baseline to follow-up between the randomly assigned intervention and placebo groups. If the SE was reported for the variation in the mean, we calculated the corresponding standard deviation (SD) by multiplying by $\sqrt{n}$. If the mean and SD for changes in BMI, WC, WHR and 25(OH)D before and after intervention were not reported, we calculated them based on the following formula, described in the *Cochrane Handbook for Systematic Reviews of Interventions* [28]:

$$\text{Mean}_{\text{change}} = \text{Mean}_{\text{final}} - \text{Mean}_{\text{baseline}}$$

$$\text{SD}_{\text{change}} = \sqrt{\text{SD}_{\text{baseline}}^2 + \text{SD}_{\text{final}}^2 - (2 \times \text{Corr} \times \text{SD}_{\text{baseline}} \times \text{SD}_{\text{final}})}$$

The correlation coefficient (Corr) was estimated based on calculations of other parameters which provided complete data for $\text{SD}_{\text{baseline}}$, SD_{final} , $\text{SD}_{\text{change}}$ in both the intervention and placebo groups.

Statistical heterogeneity between different studies was measured using χ^2 -based Q and I^2 statistics. Depending on the heterogeneity, either a fixed-effect model or a random-effect model was adopted (if the heterogeneity I^2 was above 50%, the random-effect model was used; otherwise, the fixed-effect model was applied). Separate meta-analyses were carried out for different subgroups including gender, region, duration of intervention, dose of intervention, vitamin D status at baseline (VDD or not), baseline BMI (≥ 30 or not), risk of bias (high, low or unclear) and whether it was combined with Ca administration (yes or no).

Sensitivity analyses were performed to assess the robustness of the summary estimates by omitting 1 study at a time and repeating the meta-analysis with the rest. Publication bias was assessed through visual inspection of Begg’s funnel plots and by Egger’s linear regression tests. If some publication bias was detected, the trim-and-fill method was used to adjust the meta-analysis results by adding data from potential missing studies [29]. p values < 0.05 were considered statistically significant. Analyses were performed using the Stata 12.0 statistical software package.

Results

Study Selection and Characteristics

Of the 1,412 studies identified, 20 studies were selected for the present meta-analysis. They included 24 intervention groups with 3,153 participants ($n = 1,768$ in the intervention group and $n = 1,385$ in the placebo group). Of these, 20 articles investigated vitamin D supplementation and BMI changes [17–19, 24–26, 30–43], 12 articles studied vitamin D supplementation and WC changes [17, 18, 24–26, 32, 36, 37, 40–43], 6 articles investigated vitamin D supplementation and WHR changes [19, 24–26, 31, 42], and 7 articles studied vitamin D supplementation and serum 25(OH)D changes [19, 24, 30–32, 36, 37] (Table 1). A list of the excluded articles and the reasons for exclusion is shown in the flow chart (Fig. 1).

All participants were considered healthy, except for the fact that part of them suffered from simple obesity.

Table 1. Characteristics of included RCT studies

Author, year	Study region	Sample size, <i>n</i>	Vitamin D dose, IU/day	Study duration, months	Report measures of obesity/25(OH)D				Total bias ^a
					BMI	WC	WHR	25(OH)D	
Major [43], 2007	Canada	63	200	3.75	√	√			Low
Pittas [30], 2007	USA	222	700	36	√			√	Unclear
Nagpal [24], 2008	India	71	8,571	1.5	√	√	√	√	High
Sneve [31], 2008	Norway	292	2,857	12	√		√	√	Low
Sneve [31], 2008	Norway	302	5,714	12	√		√	√	Low
Zittermann [32], 2009	Germany	165	3,332	12	√	√		√	Low
Zhou [33], 2010	USA	542	1,100	48	√				Low
Kjærgaard [34], 2011	Norway	230	5,714	6	√				High
Zhu [35], 2012	Georgia	37	2,000	4	√				Low
Salehpour [36], 2012	Iran	77	1,000	3	√	√		√	Low
Rosenblum [37], 2012	USA	71	100	4	√	√		√	Low
Rosenblum [37], 2012	USA	83	100	4	√	√		√	Low
Forsythe [38], 2012	Ireland	118	600	5.5	√				High
Forsythe [38], 2012	Ireland	109	600	5.5	√				High
Wood [39], 2012	UK	204	400	12	√				Low
Wood [39], 2012	UK	203	1,000	12	√				Low
Wamberg [40], 2013	Denmark	52	7,000	6.5	√	√			High
Zhu [41], 2013	China	43	125	3	√	√			High
Mitchell [42], 2015	USA	90	5,714	3	√		√		Low
Sun [18], 2016	Japan	95	420	12	√	√			Low
Tepper [17], 2016	Israel	130	1,666	12	√	√			Unclear
Mousa [19], 2017	Australia	54	4,000	4	√		√	√	Low
Khosravi [25], 2018	Iran	53	7,142	1.5	√	√	√		Unclear
Al-Bayyari [26], 2018	Jordan	98	7,142	2	√	√	√		Low

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; *n*, number of participants in each study; 25(OH)D, 25-hydroxyvitamin D. ^a Risk for bias assessed by following the Cochrane Collaboration's tool.

The majority of studies were conducted with female or mixed (male/female) participants; only 2 studies included male subjects only [17, 24] (Table 2). The daily doses of vitamin D supplementation varied from 100 to 8,571 IU/day. The duration of supplementation ranged from 1.5 to 36 months (Table 1). Assessments of bias risk for included trials are shown in online supplementary Table S3. All studies had low risk of bias for incomplete outcome data and selective reporting. There was insufficient information about random sequence generation in 4 studies [24, 25, 38, 43] and high risk of bias in one study [34]. Three studies had high risk of bias for blinding of participants and personnel and outcome assessment [34, 38, 41]. In 2

studies, risk of allocation concealment was unclear [41], and one was high [34].

Meta-Analysis of General Obesity

A forest plot showing the effects of vitamin D supplementation on the BMI changes was constructed, including data from 20 RCTs. Overall, no effect of vitamin D supplementation on BMI change was found (pooled WMD -0.09 kg/m²; 95% CI -0.19 to 0.01 ; $p = 0.08$; $I^2 = 63.1\%$, $p_{\text{heterogeneity}} < 0.001$; Fig. 2). Considering this borderline significance and the moderate heterogeneity, subgroup meta-analysis was conducted to investigate interactions based on the characteristics of the participants

Fig. 1. Flow chart showing the article selection process.

Fig. 2. Forest plot of the effects of vitamin D supplementation on BMI [17–19, 24–26, 30–43].

Table 2. Characteristics of participants

Author, year	Participant characteristics	Vitamin D intervention			Placebo		
		age, years	gender/ <i>n</i>	baseline 25(OH)D level, ng/mL ^a	age, years	gender/ <i>n</i>	baseline 25(OH)D level, ng/mL ^a
Major [43], 2007	Healthy, overweight or obese women	43.6±5	F/30	–	41.6±6.1	F/33	–
Pittas [30], 2007	Nondiabetic adults	70.6±4.2	B/108	32.61±15.4	71.7±4.2	B/104	28.29±11.66
Nagpal [24], 2008	Apparently healthy men	42.4±6.6	M/30	14.62±5.83	45.0±9.2	36/0	12.02±5
Sneve [31], 2008	Healthy, overweight and obese subjects	47.6±11.9	B/143	20.59±7.37	48.9±11	B/149	21.31±6.17
Sneve [31], 2008		46.4±11.3	B/153	21.83±6.69			
Zittermann [32], 2009	Healthy overweight subjects	47.4±10.3	B/82	12.02±7.0	48.8±10.1	B/83	12.14±8.0
Zhou [33], 2010	Postmenopausal women in good health	66.5±7.5	F/336	29.29±7.53	65.2±6.5	B/206	27.92±10.23
Kjærgaard [34], 2011	Adults with low levels of serum 25(OH)D	53.4±10.3	B/120	18.99±6.33	53.3±10.1	B/110	19.11±6.21
Zhu [35], 2012	Apparently healthy adults	31.1±10	B/19	14.18±4.53	31.9±10.3	B/18	16.31±6.29
Salehpour [36], 2012	Healthy overweight and obese women	38±7	F/39	14.74±12.02	37±8	F/38	18.79±12.82
Rosenblum [37], 2012	Overweight and obese adults	40±14	B/33	26±10	39±14	B/38	27±13
Rosenblum [37], 2012		39±13	B/42	31±12	43±11	B/41	33±11
Forsythe [38], 2012	Healthy young adults	28±5.6	B/56	30.4 (22.3–35.9)	29±5	B/62	26.5 (22.6–38.6)
Forsythe [38], 2012	Healthy older adults	71±5.3	B/51	22.0 (15.4–27.9)	68±6.2	B/58	23.2 (16.1–31.5)
Wood [39], 2012	Healthy postmenopausal women	63.5±1.9	F/102	13.12±5.1	63.9±2.3	F/102	14.5±6.85
Wood [39], 2012		64.1±2.3	F/101	13.0±4.66			
Wamberg [40], 2013	Healthy obese adults	39.5±8	B/26	34.5±10.8	41.2±6.8	F/26	13.62±3.61
Zhu [41], 2013	Generally healthy adults	20.1±11.1	B/22	–	20.3±0.8	B/21	–
Mitchell [42], 2015	Healthy adults with low vitamin D	28±7	B/40	18±7	29±9	B/50	–
Sun [18], 2016	Healthy adults	27–57	B/48	13.14±1.12	29–58	B/47	12.82±1.12
Tepper [17], 2016	Healthy men	–	M/78	15.3±3.46	–	M/52	15.41±3.49
Mousa [19], 2017	Healthy but overweight or obese	30.5±6	B/28	12.58±5.05	29.5±7	B/26	13.7±4.0
Khosravi [25], 2018	Overweight and obese women	29.1±9.6	F/26	–	26.9±9.1	F/27	–
Al-Bayyari [26], 2018	Women who were not diagnosed with any chronic disease	23.8±4.4	F/50	8.38±1.2	23.3±5.2	F/48	8.63±4.64

F, female; M, male; B, both female and male; *n*, number of females, males or both; –, not reported. ^aIn order to facilitate calculation and reduce heterogeneity, 25(OH)D units were unified, 25(OH)D in ng/mL could be converted to nmol/L by multiplying by 2.5.

and intervention. These results suggested that variables including gender, region where the study was conducted, intervention duration, baseline BMI and risk of bias could be the potential source of the heterogeneity. Notable findings from the subgroup analysis included beneficial effects of supplementing vitamin D on the BMI decline when participants were female, when the study was conducted in Asia, and when the intervention duration was ≥ 6 months ($p < 0.026$; Table 3).

Meta-Analysis of Central Obesity

A forest plot showing the effects of vitamin D supplementation on the WC changes was constructed, including data from 11 RCTs. There was no statistically significant difference between the intervention and placebo

groups for WC changes (pooled WMD -0.71 cm; 95% CI -1.58 to 0.16 ; $p = 0.112$; $I^2 = 68.0\%$, $p_{\text{heterogeneity}} < 0.001$; Fig. 3a). Subgroup analysis demonstrated that heterogeneity decreased in the following subgroups: male, European region, BMI ≥ 30 at baseline, non-VDD at baseline, duration of intervention ≥ 6 months, and bias at high risk (Table 3). Similarly, notable findings from the subgroup analysis included beneficial effects of vitamin D supplementation on the WC reduction when participants were female, when the study was conducted in Asia, and when the duration of the intervention was ≥ 6 months ($p < 0.003$; Table 3). When compared with the placebo group, however, the pooled meta-analysis and subgroup analysis all indicated that there was no effect of vitamin D supplementation on WHR changes (pooled WMD 0.00 ; 95% CI

Table 3. Subgroup analysis of vitamin D supplementation on BMI and WC

Subgroup	BMI			WC, cm		
	studies	participants	WMD (95% CI)	<i>p</i> value	<i>I</i> ² , %	
Total	20	3,153	-0.09 (-0.19 to 0.01)	0.080	63.1	12
Gender						1,091
Female	6	1,138	-0.30 (-0.56 to -0.04)	0.026	79.1	4
Male	2	201	-0.06 (-0.27 to 0.16)	0.603	0.0	2
Mixed	12	1,814	-0.00 (-0.11 to 0.11)	0.960	38.7	6
Region						599
America	5	1,071	0.02 (-0.16 to 0.21)	0.808	45.7	3
Europe	6	1,424	0.04 (-0.05 to 0.13)	0.411	0.0	2
Asia	8	658	-0.33 (-0.57 to -0.08)	0.009	79.2	7
Duration of intervention, months						567
≥6	9	2,186	-0.09 (-0.14 to -0.04)	<0.001	0.0	4
<6	11	967	-0.17 (-0.38 to 0.04)	0.112	77.1	8
Dose of intervention, IU/day						442
>2,000	9	1,258	-0.14 (-0.41 to 0.12)	0.281	76.8	6
≤2,000	11	1,895	-0.06 (-0.15 to 0.04)	0.242	45.8	6
VDD at baseline						562
Yes	13	1,352	-0.16 (-0.34 to 0.02)	0.085	73.3	10
No	7	1,801	-0.03 (-0.13 to 0.07)	0.569	31.7	2
Obesity (BMI ≥30) at baseline						995
Yes	7	1,010	-0.05 (-0.21 to 0.11)	0.507	0.0	5
No	13	2,143	-0.11 (-0.23 to 0.01)	0.077	76.2	7
Combined with Ca						580
Yes	7	1,559	-0.04 (-0.17 to 0.09)	0.580	29.8	4
No	13	1,594	-0.14 (-0.29 to 0.01)	0.069	71.9	8
Risk of bias						350
High	5	765	0.04 (-0.05 to 0.14)	0.372	0.0	3
Low	12	2,142	-0.09 (-0.21 to 0.04)	0.191	60.2	6
Unclear	3	246	-0.34 (-0.79 to 0.12)	0.145	68.8	3
						276

The *p* value is for the WMD. BMI, body mass index; WC, waist circumference; WMD, weighted mean difference; CI, confidence interval; VDD, vitamin D deficiency (defined by serum 25(OH)D <20 ng/mL); Ca, calcium.

Fig. 3. Forest plots of the effects of vitamin D supplementation on WC [17, 18, 24–26, 32, 36, 37, 40–43] (**a**) and WHR [19, 24–26, 31, 42] (**b**).

-0.01 to 0.01; $p = 0.749$; Fig. 3b; online suppl. Table S4). In addition, no heterogeneity was detected ($I^2 = 41.1\%$; $p_{\text{heterogeneity}} = 0.131$; Fig. 3b).

Meta-Analysis of Serum 25(OH)D

A forest plot showing the effects of vitamin D supplementation on serum 25(OH)D changes was constructed, including data from 7 RCTs. Following vitamin D supplementation, there was a significant beneficial effect on serum 25(OH)D levels (pooled WMD 13.20 ng/mL; 95% CI 9.83–16.58; $p < 0.001$; $I^2 = 75.7\%$, $p_{\text{heterogeneity}} < 0.001$; Fig. 4). Subgroup analysis demonstrated that heterogeneity decreased in the subgroups of studies conducted in European and Asian regions, and those with BMI <30 at baseline (Table 4).

Sensitivity and Publication Bias Analyses

Sensitivity analysis utilizing the leave-one-out method did not show any major change on primary outcomes, an indication of the good stability of the results. Neither Begg's test nor Egger's test showed significant publication bias with respect to the effects of vitamin D supplementation on BMI ($t = -0.19$, $p = 0.852$), WHR ($t = -0.60$, $p = 0.582$) and 25(OH)D ($t = -1.29$, $p = 0.245$; online suppl. Table S5 and Fig. S1). Considering the borderline significance for the publication bias in WC ($t = 2.20$, $p = 0.050$), the trim-and-fill method was applied to adjust the results. However, this methodology indicated that after 2-step iterations, the number of missing studies was 0. No alterations were found in the adjusted WMD and 95% CI (-0.71 cm, [-1.58 to 0.17]). Therefore, the outcome was stable in terms of WC.

Fig. 4. Forest plots of the effects of vitamin D supplementation on serum 25(OH)D [19, 24, 30–32, 36, 37].

Table 4. Subgroup analysis of vitamin D supplementation on 25(OH)D (ng/mL)

Subgroup	Studies	Participants	WMD (95% CI)	<i>p</i> value	<i>I</i> ² , %
Total	7	1,188	13.20 (9.83–16.58)	<0.001	75.7
Gender					
Female	1	77	13.46 (9.02–17.90)	<0.001	0.0
Male	1	71	13.82 (9.89–17.75)	<0.001	0.0
Mixed	5	1,040	12.93 (8.40–17.46)	<0.001	89.5
Location					
America	2	376	6.91 (0.42–13.40)	0.037	80.9
Europe	2	610	16.12 (14.95–17.29)	<0.001	0.0
Asia	2	148	13.66 (10.72–16.60)	<0.001	0.0
Australia	1	54	22.08 (18.16–26.00)	<0.001	0.0
Duration of intervention, months					
≥6	3	832	15.07 (12.24–17.89)	<0.001	60.9
<6	4	356	11.60 (4.97–18.23)	0.001	90.1
Dose of intervention, IU/day					
>2,000	4	736	17.20 (14.08–20.32)	<0.001	70.5
≤2,000	3	452	8.69 (3.71–13.65)	0.001	77.7
VDD at baseline					
Yes	4	367	16.73 (12.40–21.05)	<0.001	73.7
No	3	821	9.49 (3.61–15.36)	0.002	91.4
Obesity (BMI ≥30) at baseline					
Yes	5	1,003	13.12 (8.38–17.86)	0.476	88.8
No	2	185	12.88 (10.37–15.38)	0.110	0.0
Combined with Ca					
Yes	3	821	9.49 (3.61–15.36)	0.002	91.4
No	4	367	16.73 (12.40–21.05)	<0.001	73.7
Risk of bias					
High	1	222	12.23 (8.98–15.48)	<0.001	0.0
Low	6	966	13.12 (8.38–17.86)	<0.001	88.8

The *p* value is for the WMD. WMD, weighted mean difference; CI, confidence interval; VDD, vitamin D deficiency (defined by serum 25[OH]D <20 ng/mL); Ca, calcium.

Discussion

There is great interest in investigating possible preventive effects of vitamin D beyond its traditional role in maintaining skeletal health. The possible role of vitamin D in the pathogenesis of obesity is an important topic for public health and for issuing clinical guidelines. However, based on the literature published to date in apparently healthy populations, our pooled results indicate nonperceptible effects of vitamin D supplementation in terms of reducing the BMI, WC and WHR.

These 3 obese indices (BMI, WC and WHR) are readily available, noninvasive and inexpensive, which can frequently be applied in epidemiological surveys and clinical practice. The most widely used anthropometric index, the BMI, reflects both fat and muscle mass, but it does not accurately represent the distribution of body fat, especially abdominal fat [44]. Therefore, several studies suggested that the additional measurement of WC and WHR is better than the BMI alone to identify individuals with obesity, distinguishing the types of obesity and examining the prevalence of various types of obesity [16, 45]. To our knowledge, this is the first meta-analysis for the effects of vitamin D supplementation on general and central obesity indices in apparently healthy populations. Statistically, a potential reduction in BMI following vitamin D supplementation ($p = 0.08$) was noted as the sample size expands. However, such a small point estimate and narrow CI (-0.09 , 95% CI -0.19 to 0.01), these puny effects would not be expected to have a clinical benefit. These results were consistent with previous studies that showed no significant effect on BMI change by use of vitamin D supplementation [46, 47]. The WC measures adipose tissue accumulation around the organs of the abdominal cavity. Abdominal fat is a good storage site for vitamin D, inhibiting its release into the blood and reducing its bioavailability, which is the main explanation offered for VDD in individuals with obesity [9]. Nevertheless, in the present meta-analysis of 11 RCTs for WC and 6 RCTs for WHR, vitamin D treatment did not decrease the WC and WHR, with the WMD and 95% CI (-0.71 cm [-1.58 to 0.16], $p = 0.112$; and 0 [-0.01 to 0.01], $p = 0.749$, respectively). Although no obvious benefits of vitamin D supplementation were seen based on these 3 obesity indices, we found notable improvements in serum 25(OH)D levels after vitamin D supplementation, with a WMD of 13.20 ng/mL and 95% CI of 9.83 – 16.58 ($p < 0.001$). In agreement with our results, previous meta-analysis also showed a significant effect of vitamin D supplementation on serum 25(OH)D concentrations [48].

The overall results may be explained by several reasons. First, clinical trials that assess the effects of vitamin

D on obesity vary with different study designs. Therefore, the published studies are distinguished by methodologies, including participant characteristics, intervention times, intervention doses, as well as vitamin D formulations, making it difficult to pool the results. It is also a potential reason for the high heterogeneity of the present meta-analysis. Second, the utilization of vitamin D undergoes a series of physiological and biochemical processes, making it difficult to evaluate the ultimate bioavailability of participants [49]. Third, BMI, WC and WHR are all indirect indicators of obesity, making it hard to quantify amounts of fat accurately, and thus the direct effect of vitamin D supplementation on adipose tissue is hard to describe. Finally, 25(OH)D is an intermediate product of vitamin D metabolism which reflects circulating vitamin D levels in blood over a period of time. Production of $1,25(\text{OH})_2\text{D}_3$, an active form of vitamin D, depends on the enzyme 1α -hydroxylase, which catalyzes the synthesis of $1,25(\text{OH})_2\text{D}_3$ from 25(OH)D [15]. Following vitamin D supplementation, the likelihood that 25(OH)D will be used as a substrate in the catalytic reaction is reduced, so the levels of 25(OH)D in circulating blood will increase. This may be a reasonable explanation for the elevated serum 25(OH)D levels.

In any meta-analysis, the heterogeneous nature of the pooled results presents a challenge for the interpretation of any quantitative outcomes [47]. Subgroup analysis, a common method of exploring sources of heterogeneity, was performed in this study. Interestingly, when conducting a subgroup analysis in BMI and WC, beneficial and more significant effects were found in the subgroup of females, Asia region studies, and duration of intervention ≥ 6 months (all $p < 0.026$). Reasonable explanations for the increased effect of vitamin D treatment in special groups may be the fact that obesity prevalence among women and Asians is higher than that in men and other areas [50, 51]. In particular, Asians are more likely to have central fat deposition despite having a lower BMI [52, 53]. Therefore, those participants have a more sensitive response to vitamin D supplementation and more easily display the beneficial effects. In addition, vitamin D must be administered for a certain period of time before changes in the BMI and WC become evident [54].

Some limitations of this analysis deserve consideration, including the inability to completely collect all related published papers. Moreover, the sample size of most included RCTs was low. Additionally, the effects of seasonality, vitamin D formulations and sun exposure were not evaluated. However, there are 2 important advantages that differentiate it from previous studies. All partici-

pants were reported to be in good health (except for the simple obesity), therefore the results can be generalized to the general population. In addition, none of the subjects participated in any type of weight loss program (including exercise, weight loss medications or weight loss surgery). This maximizes the observed separate effect of vitamin D supplementation on obesity indicators.

Conclusion

In summary, this study is the first meta-analysis quantifying the effects of vitamin D supplementation on general and central obesity indices. Despite increased serum 25(OH)D levels, the obesity indices (BMI, WC and WHR) did not improve significantly. Therefore, the management and clinical application of vitamin D should be made with caution. However, it does not rule out that it may have potential clinical implication along with other weight loss programs.

Acknowledgments

We thank all the investigators in this study.

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Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding supports this work.

Author Contributions

Y.W. and L.H. contributed to the study conception and design. L.D. and Y.W. contributed to the acquisition of data, the development of the protocol and the drafting of the manuscript. L.D. and Y.Z. contributed to the analysis and interpretation of the quantitative data. L.D. and Q.L. contributed to the critical revising of the final draft. L.D. and L.W. contributed to the analysis and interpretation of the descriptive data and the revision of the final draft. All authors approved the final version.

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