European Journal of Clinical Nutrition
https://doi.org/10.1038/s41430-018-0132-z

REVIEW ARTICLE

Vitamin D supplementation and body fat mass: a systematic review and meta-analysis

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Received: 14 July 2017 / Revised: 1 February 2018 / Accepted: 9 February 2018

Abstract

Studies have indicated that 25-hydroxyvitamin D (25(OH)D) level in obese is lower than normal weight subjects; however, results of studies that investigated relationship between 25(OH)D and fat mass are inconsistent. In addition, several randomized clinical trials (RCTs) have studied the influence of cholecalciferol supplement on percentage fat mass (PFM) but their results are conflicting. The objectives were to investigate the association between vitamin D3 and PFM pooling together observational studies and RCTs. PubMed/MEDLINE, Cochrane, and Scopus were comprehensively searched from inception to September 2016. The Fisher's Z (SE) of correlation coefficient and mean (SD) of changes in PFM from baseline were used to perform meta-analysis in observational studies and RCTs, respectively. To determine potential source of heterogeneity, subgroup and meta-regression analyses were conducted. Pooling correlation coefficients showed an inverse association between PFM (Fisher's Z: − 0.24, 95% CI: − 0.30 to −0 .18) and FM (Fisher's Z: − 0.32, 95% CI: − 0.43 to − 0.22) and 25(OH)D. Subgroup analysis revealed continent but not gender influence on the effect size. Meta-regression analysis indicated that age, latitude, and longitude are not sources of heterogeneity. Combining trials showed vitamin D3 supplementation had a mild but insignificant effect on PFM (− 0.31%, 95% CI: − 1.07 to 0.44). Subgroup analyses indicated that type of cholecalciferol and treatment regimens explain source of heterogeneity. Age, baseline body mass index, dose of cholecalciferol, length of study, female (%), and baseline 25(OH)D are not source of heterogeneity. In conclusion, our results state that 25(OH)D level is inversely correlated with PFM but cholecalciferol supplementation had no effect on PFM.

Introduction

Obesity is a major health problem that increased risk of chronic disease and mortality. Globally, in 1980 it was estimated that 921 million adults suffered from being overweight and obese, rising to 2.1 billion in 2013 (increased by 27.5% for adults) [1]. The prevalence of obesity was estimated to be 35% in US adults in 2011–2012 [2]. Observational studies have indicated that subjects with obesity have lower levels of 25-hydroxyvitamin D (25(OH)D) compared to subjects with normal weight [3–5]. Although several previous observational studies have stated an opposite correlation between 25(OH)D and fat mass (FM) [6–9], other studies have not found such an association [10–12].

The underlying mechanism of small amount of 25(OH)D level in obese individuals may be related to low dietary intake of vitamin D or little sun exposure due to low outdoor activity. In addition, accumulation of vitamin D in FM has been proposed as another potential mechanism [13]. It

Electronic supplementary material The online version of this article (https://doi.org/10.1038/s41430-018-0132-z) contains supplementary material, which is available to authorized users.

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Published online: 21 March 2018

has been suggested that adiposity is the most important reason of low 25(OH)D in subjects suffering from overweight and obesity [14]. However, results of an investigation have indicated that volume dilution may be responsible for low access of vitamin D in obese in compared with their non-obese counterparts [15].

Low serum 25(OH)D are related with parathroid hormone (PTH) elevation hormone and intracellular Ca^{2+} [16], both of which promote lipogenesis and suppress lipolysis, contributing to obesity [17]. Several randomized clinical trials (RCTs) have investigated the efficacy of vitamin D supplement on weight and body composition; however, their results are contrary [18–21]. Therefore, given the differing results between observational studies and RCTs, the aim of the present study was to conduct and aggregate data meta-analysis to investigate the correlation between cholecalciferol and FM or percentage FM (PFM). To the best of our knowledge, there is no study that evaluated the potential association between 25(OH)D and FM, and effect of vitamin D3 supplement on FM or PFM in framework of meta-analysis.

Materials and methods

The present systematic review and meta-analysis was performed based on the PRISMA guidelines [22].

Data source and search strategy

PubMed/MEDLINE, Cochrane, and Scopus databases were seek for English language RCTs that examined the effect of cholecalciferol on PFM and observational studies, which investigated correlation between 25(OH)D and PFM until September 2016, with no limitation for time of publication. The search terms included: "body weight", "overweight", "obesity", "body composition", body fat", "fat mass", "adipose tissue", "weight gain", "weight change", "adiposity", "cholecalciferol", "vitamin D_3 supplementation", "25 hydroxy-vitamin D," and "25(OH)D". The reference lists of published studies also were checked. All searched articles were downloaded into EndNote (version X7) to merge retrieved citations, remove duplicated, and simplify the review process.

Inclusion and exclusion pattern

Two independent reviewers (MG and SS-B) read all retrieved studies. To examine relationship between 25(OH)D and PFM, studies were included if they (a) had an observational design; (b) were conducted on individuals 15 years of age and greater; (c) measured serum 25(OH)D; and (d) reported correlation coefficients between 25(OH)D and PFM or FM. Animal studies, studies that did not report correlation coefficient between 25(OH)D and PFM or FM, and studies that reported regression coefficients were excluded. Exclusion criteria were as follows: if participants were children, adolescents aged < 15 years, pregnant and lactating women, or if participants suffered from renal disease, hypercalcemia, hyperthyroidism, or hyperparathyroidism.

To assess the effect of cholecalciferol on PFM, we included studies that (a) had a RCT design; (b) were conducted in individuals > 18 years of age; and (c) compared oral cholecalciferol supplementation vs. placebo. In addition, studies that applied cholecalciferol-fortified products as intervention vs. cholecalciferol-free-fortified products as placebo were included. We excluded animal and observational studies, trials that used other forms of vitamin D, studies that did not report PFM after the intervention, and studies that involved children, adolescents aged < 18 years, pregnant and lactating women, and subjects who suffered from renal disease, hypercalcemia, hyperthyroidism, or hyperparathyroidism. In addition, studies in which the dosing changed during follow-up were excluded. To keep away from overlapping, we included recent RCT or studies with larger participants.

Study selection

All retrieved articles were evaluated based on titles and abstracts by two reviewers (MG and SS-B) independently. A screen form according to the study design, population, exposure, and outcome were designed and articles that did not meet the inclusion pattern were excluded. Then articles were evaluated for eligibility based on full text by the same reviewers. If there was a disagreement, it was resolved by consensus.

Extraction of datum and assessment of quality

Data were extracted from RCTs included sample size of each group, age, gender, year of publication, dose of cholecalciferol, type of supplementation, duration of intervention, mean (SD) of 25(OH)D of both groups at baseline and at the end of the study, and mean (SD) of PFM of both groups at baseline and at the end of the study. Sample size, age, gender, race, location, publication date, mean and SD of PFM or FM and 25(OH)D, and correlation coefficient between 25(OH)D and PFM or FM were extracted from observational studies.

Jadad score and Newcastle–Ottawa Scale (NOS) were used to assess quality of RCTs and cross-sectional studies, respectively [23, 24].

Table 1 Characteristics of included observational studies

Author, year	Location	Latitude and longitude	Population study	Sample size	Age (year)	PFM or FM	25OHD (ng/mL)	*r*- and *p*- value
Arunabh et al. [9]	New York, USA	40.70 N, 73.79 W	Healthy women	410	20–80	36.2%	22	− 0.13, 0.01
Gomez et al. [48]	L'Hospitalet de Llobregat, Spain	41.38 N, 2.11 E	Adults	253	15–71	NP	NP	− 0.28, NP
Rahman et al. [7]	Kuala Lumpur	3.13 N, 101.68 E	Postmenopausal women	274	50–65	38%	22	− 0.24, < 0.001
Bolland et al. [31]	Auckland, New Zealand	36.84 S, 174.74 E	Healthy Men	378	> 40	37%	22	− 0.23, < 0.001
Bolland et al. [46]	Auckland, New Zealand	36.84 S, 174.74 E	Postmenopausal women	116	46–89	27 kg	21.6	− 0.16, NP
Vilarrasa et al. [43]	L'Hospitalet de Llobregat, Spain	41.38 N, 2.11 E	Women	121	NP	40%	17	− 0.53, < 0.001
McKinney et al. [38]	Galveston, USA	29.30 N, 94.79 W	Women	800	16–33	36.1%	21	− 0.28, < 0.001
Kremer et al. [49]	Quebec, Canada	46.81 N, 71.20 W	Women	90	16–22	37%	30	− 0.32, 0.002
Moschonis et al. [50]	Athens, Greece	37.96 N, 23.71 E	Postmenopausal women	112	55–65	43.4%	26.5	− 0.25, 0.02
Frost et al. [47]	Odense, Denmark	55.40 N, 10.40 E	Adults men	783	20–29	NP	26	− 0.18, < 0.01
Vilarrasa et al. [6]	L'Hospitalet de Llobregat, Spain	41.38 N, 2.11 E	Healthy adults	305	15–70	33%	20	− 0.18, NP
Boot et al. [32]	Rotterdam, Netherlands	51.91 N, 4.47 E	Healthy adults	464	18–31	28%	33	− 0.12, NP
Caron-Jobin et al. [55]	Quebec, Canada	46.81 N, 71.20 W	Women	42	37.6–54	27 kg	22	− 0.41, < 0.01
Palacios et al. [39]	San Juan, Puerto Rico	18.46 N, 66.10 W	Overweight and obese	98	40–65	31%	30.7	− 0.24, 0.02
Nimitphong et al. [53]	Bangkok, Thailand	13.75 N, 100.50 E	Healthy adults	1900	25–54	25%	24	− 0.04, 0.02
Agbaht et al. [30]	Balikesir, Turkey	39.55 N, 27.73 E	Obese	548	35–51	NP	NP	− 0.28, < 0.001
Bhatt et al. [10]	New Delhi, India	28.61 N, 77.20 E	Adults	137	18–60	36%	18.9	0.01, 0.83
Forney et al. [11]	Louisiana, USA	30.98 N, 91.96 W	Healthy adults	39	20–38	24%	35	0.24, 0.10
Hao et al. [34]	Shanghai, China	31.23 N, 121.47 E	Adult men	567	50.7–61	22%	16	− 0.16, < 0.001
Kozakowski et al. [8]	Warsaw, Poland	52.23 N, 21.01 E	Obese PCOS women	26	19–49	46%	14	− 0.95, < 0.001
Sadiya et al. [51]	Ajman, UEA	25.40 N, 55.51 E	Obese type 2 diabetic	309	30–60	43%	13.5	− 0.16, 0.01
Dasarathy et al. [56]	Cleveland, USA	41.49 N, 81.69 W	NAFLD adults	148	37–63	36 kg	21.2	− 0.27, < 0.05
Fitzgerald et al. [33]	Minnesota, USA	46.27 N, 94.68 W	Athletes	53	18–23	12%	36	− 0.50, 0.001
Heller et al. [35]	Wyoming, USA	43.00 N, 107.50 W	Athletes	42	18–22	22%	40	− 0.45, < 0.05
Shantavasikul et al. [40]	Bangkok, Thailand	13.75 N, 100.50 E	Obese	163	15–70	43%	23	− 0.23, 0.003
Stokic et al. [41]	Novi Sad, Serbia	45.26 N, 19.26 E	Adults	86	27–50	32%	14	− 0.64, < 0.001
Tosunbayraktar et al. [52]	Ankara, Turkey	39.93 N, 32.85 E	Adults	90	18–63	23.8%	21.6	− 0.41, < 0.001
Kerley et al. [36]	Dublin, Irland	53.34 N, 6.26 W	OSPS patients	106	34–72	37%	17.4	− 0.22, 0.04
Kim and Kim [37]	Korea	35.90 N, 127.76 E	Adults	4771	≥ 19	29.4%	17.8	− 0.09, < 0.001
ter Horst et al. [42]	Amsterdam, Netherlands	52.37 N, 4.89 E	Obese women	37	> 18	53.5%	17.8	− 0.46, < 0.01
Zhang et al. [45]	Jinan, China	36.65 N, 117.12 E	Adults	1865	20–82	31.7%	16.1	− 0.07, 0.01
Abdelkarem et al. [29]	Sakaka, Saudi Arabia	29.87 N, 40.10 E	Adults	147	18–25	37.7%	44.4	− 0.38, 0.001
Zhang et al. [45]	Tianjin, China	39.08 N, 117.20 E	Adults	1105	20–70	30.8%	36.4	− 0.16, NP
Obispo Entrenas et al. [54]	Malaga, Spain	36.72 N, 4.42 W	Obese	56	33–53	63%	14.5	− 0.50, 0.009
George et al. [57]	Johannesburg, South Africa	26.19 S, 28.03 E	Adults	714	18–65	23 kg	21.3	− 0.09, NP

NP, no report; OSPS, obstructive sleep apnea syndrome; PCOS, poly cystic ovary syndrome; PFM, percent fat mass; r, correlation coefficient

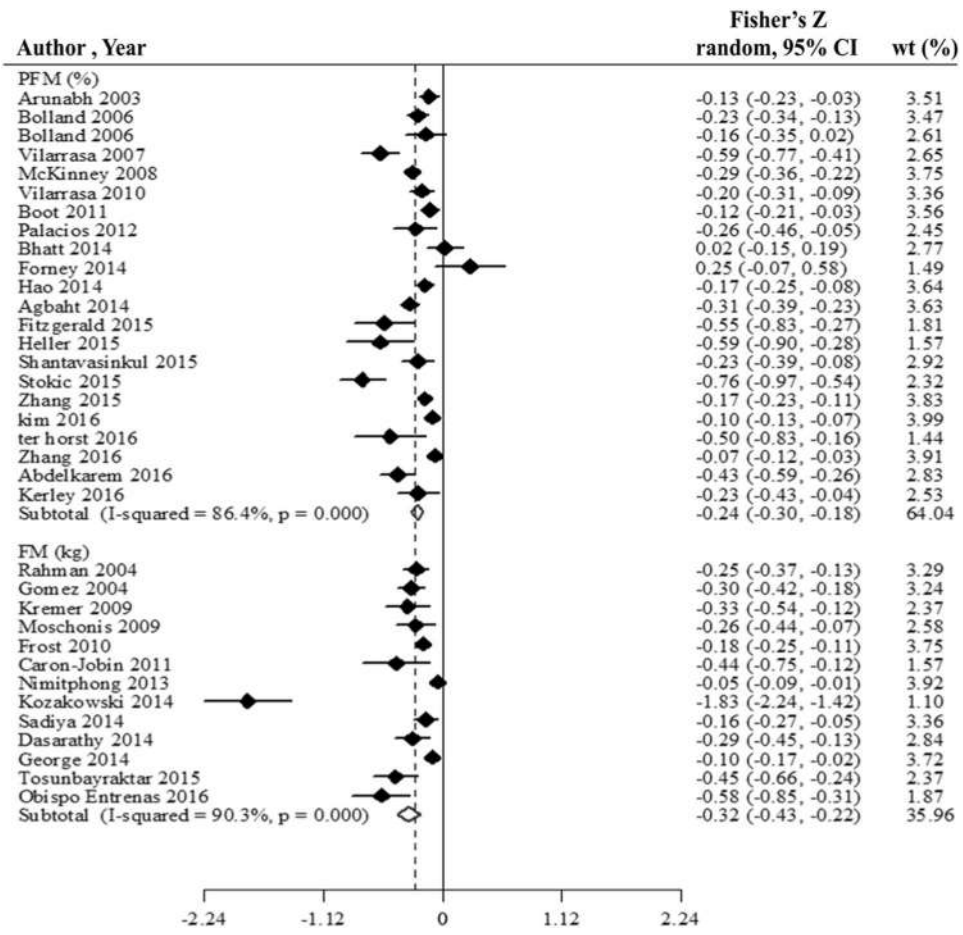

Fig. 1 Forest plot of studies that assessed association between 25 (OH)D and PFM and FM

Statistical analysis

Stata software (version 12) was applied to perform all statistical analyses. The mean and SD of changes in PFM from baseline was used to conduct meta-analysis in RCTs. To assess correlation between 25(OH)D and PFM or FM, Fisher's Z and its SE using correlation coefficients and sample size were used. A fixed-effect model was used to calculate pooled weighted mean differences by the user written "metan" command [25]. If the heterogeneity existed, random-effects model (DerSimonian–Laird) was run. Cochrane's Q-test and I-squared (I^2) was used to determine heterogeneity among included studies [26]. To evaluate the predefined sources of heterogeneity, subgroup analysis and meta-regression analysis were conducted using a fixed-effect model with the user written "metan" command ("by option") and metareg command, respectively, in Stata software (version 12) [25]. We considered gender (female %), age, baseline body mass index (BMI), dose of cholecalciferol, duration of study, type of cholecalciferol (supplementation or fortified products), treatment regiments (daily or intermittent types), and baseline 25(OH)D as predefined source of heterogeneity for RCTs ($n = 10$). For observational studies ($n = 35$), gender, age, latitude, longitude, and continent were considered as a predefined sources of heterogeneity. Nonlinear dose–response association was assessed using fractional polynomial model [27]. Season also is a source of heterogeneity, but there was no data on season of data collection; hence, it was ignored in the analyses. Sensitivity analysis was conducted by elimination one study at a time [28] with the user written "metaninf" command. The funnel plot with the user written "metabias" command was used to assess publication bias. $P < 0.05$ was considered as a significant level.

Results

Meta-analysis for correlation coefficients

The flow chart of included studies is presented in Supplementary Figure 1. The initial search from PubMed ($n = 1441$) and Scopus ($n = 2340$) provided 3781 articles; after exclusion of duplicates ($n = 720$), a total of 2724 studies were retrieved for title and abstract assessment. A total of 2457 articles were removed based on inclusion criteria; 267

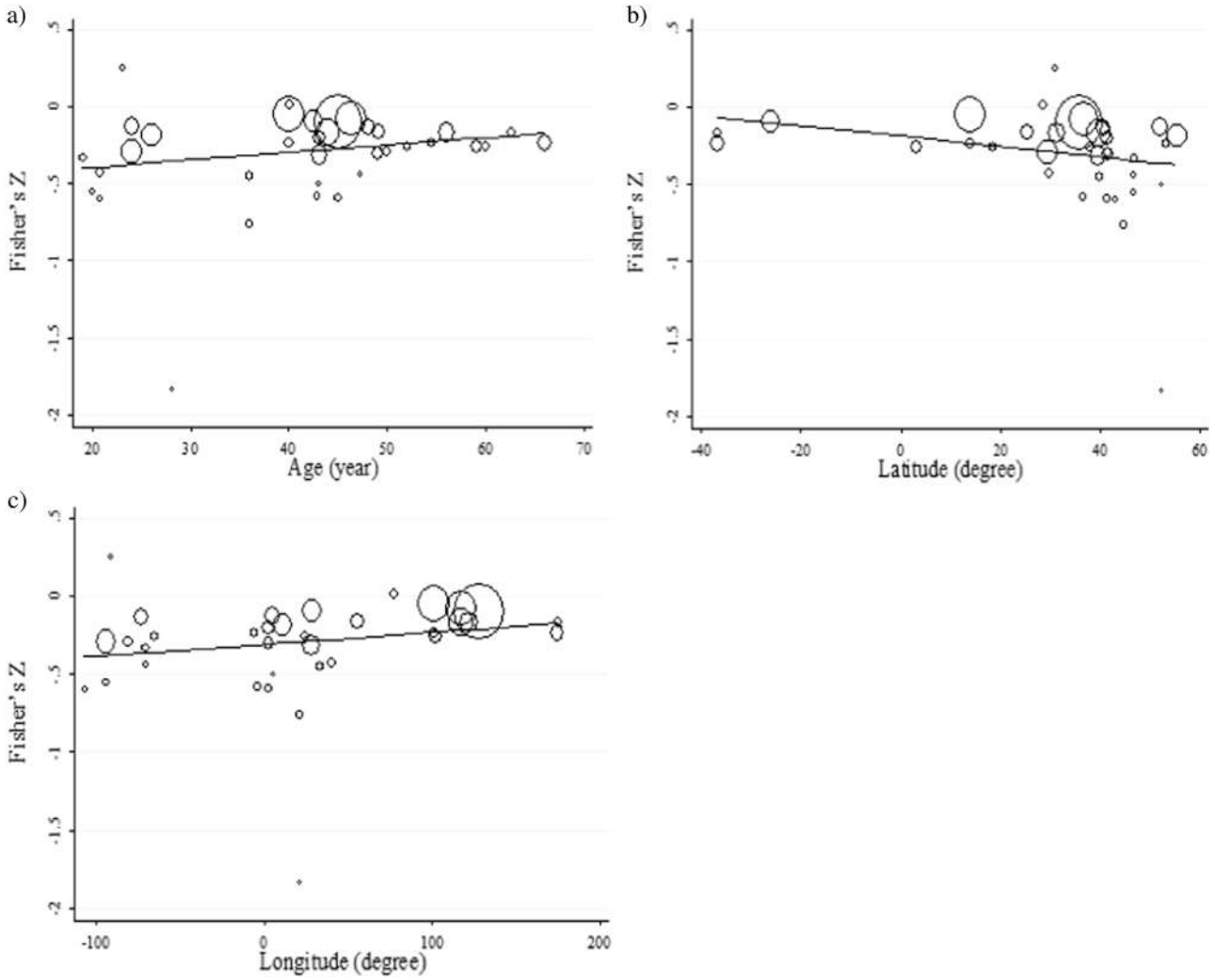

Fig. 2 Meta-regression analysis of correlation coefficient between 25(OH)D and PFM or FM by **a** baseline age, **b** latitude, and **c** longitude. Size of the circles corresponds to the weight of each study

were retrieved for full-text screening. After full-text evaluation, 232 were excluded and finally 35 articles (including 17,245 persons) met the inclusion criteria were included.

Table 1 is showing general traits of the included studies. Mean age was 41.2 ± 13.0 years. Mean PFM was 35.1 ± 1.0% and 25(OH)D level was 22.9 ± 7.1 ng/mL. Twenty-two of studies [6, 9–11, 29–46] reported correlation coefficients between PFM and 25(OH)D; the rest [7, 8, 47–57] reported correlation coefficients between FM and 25(OH)D.

The forest plots of correlation between 25(OH)D, and PFM and FM are presented in Fig. 1. There was a significant reverse relationship between 25(OH)D and PFM (Fisher's Z: − 0.24, 95% confidence interval (CI): − 0.30 to − 0.18, $P < 0.001$) and 25(OH)D and FM (Fisher's Z: − 0.32, 95% CI: − 0.43 to − 0.22, $P < 0.001$). Sensitivity analysis has revealed that significant association between PFM and 25(OH)D are affected by Kim et al. [37] study; however, after exclusion of this study the pooled effect size of relation between 25(OH)D and PFM remained unchanged. Results of sensitivity analysis have indicated that no study has significant impact on the pooled effect size of correlation between 25(OH)D and FM.

Subgroup analyses based on gender and continent was conducted to assess these factors as potential sources of heterogeneity (Supplementary Table 1). Subgroup analysis revealed that gender did not contribute to the effect size. However, they indicated that continent is source of heterogeneity [in America (Fisher's Z: − 0.28, 95% CI: − 0.38 to − 0.17), in Europe (Fisher's Z: − 0.44, 95% CI: − 0.59 to − 0.29), in Asia (Fisher's Z: − 0.19, 95% CI: − 0.26 to − 0.12), Oceania (Fisher's Z: − 0.21, 95% CI: − 0.30 to − 0.12), and Africa (Fisher's Z: − 0.09, 95% CI: − 0.16 to − 0.02)].

Results of meta-regression analysis indicated that age ($\beta = 0.004$, $P = 0.21$), latitude ($\beta = -0.003$, $P = 0.10$), and longitude ($\beta = 0.0007$, $P = 0.22$) did not explain the effect size (Fig. 2).

Table 2 Characteristics of included RCTs

Author [ref.]	Location	Population study	Subjects (*n*) In/Pl	Age (years) In/Pl	BMI (kg/m^2) In/Pl	Vitamin D3 dose (IU/d)	Duration of study	Outcomes	Diff. in baseline 25OHD between groups
Seneve et al. [20]	Norway	Overweight and obese subjects	116/112	46/49	35/35.1	5714	12 mo	In: wt: 0.1 kg, BMI: 0.0 kg/m^2, WHR: – 0.01, PFM: – 0.3% ; Pl: wt: 0.5 kg, BMI: 0.2 kg/m^2, WHR: – 0.01, PFM: – 0.5%	0.5 ng/mL
Seneve et al. [20]	Norway	Overweight and obese subjects	106/112	48/49	34.4/35.1	2857	12 mo	In: wt: 0.3 kg, BMI: 0.1 kg/m^2, WHR: – 0.01, PFM: – 0.4%; Pl: wt: 0.5 kg, BMI: 0.2 kg/m^2, WHR: – 0.01, PFM: – 0.5%	0.9 ng/mL
Zittermann et al. [60]	Germany	Overweight and obese subjects	82/83	47/49	33.7/33	3332	12 mo	In: wt: – 5.7 kg, BMI: – 2.0 kg/m^2, WC: – 6.5 cm, FM: – 4.1 kg ; Pl: wt: – 6.4 kg, BMI: – 2.2 kg/m^2, WC: – 7.5 cm, FM: – 4.9 kg	0.09 ng/mL
Nikooyeh et al. [19]	Iran	Type 2 diabetic patients	30/30	51/51	29.2/29.9	1000	3 mo	In: wt: – 2.9 kg, BMI: – 0.9 kg/m^2, WC: – 3.6 cm, PFM: 0.8%, WHR: – 0.03 ; Pl: wt: – 0.1 kg, BMI: 0.1 kg/m^2, WC: – 0.9 cm, PFM: 1.2%, WHR: – 0.1	1.1 ng/mL
Shab-Bidar et al. [21]	Iran	Type 2 diabetic patients	50/50	53/52	28.6/30	1000	3 mo	In: wt: – 0.6 kg, BMI: – 0.2 kg/m^2, WC: – 0.7 cm, PFM: – 1.5%; Pl: wt: 0.7 kg, BMI: 0.2 kg/m^2, WC: 0.8 cm, PFM: 0.8%	0.2 ng/mL
Salehpour et al. [59]	Iran	Overweight and obese subjects	39/38	38/37	30.1/29.5	1000	3 mo	In: wt: – 0.3 kg, BMI: – 0.1 kg/m^2, WC: – 0.3 cm, FM: – 2.7 kg, FFM: 1.8 kg ; Pl: wt: – 0.1 kg, BMI: – 0.04 kg/m^2, WC: 0.4 cm, FM: – 0.4 kg, FFM: 0.4 kg	4.0 ng/mL
Wamberg et al. [63]	Denmark	Overweight and obese subjects	22/21	40/41	36.1/35	7000	6 mo	In: wt: 0.0 kg, BMI: 0.1 kg/m^2, FM: 1.6 kg, FFM: – 0.4 kg; Pl: wt: 0.0 kg, BMI: – 0.2 kg/m^2, FM: 0.3 kg, FFM: 0.4 kg	0.4 ng/mL
Ghavamzadeh et al. [58]	Iran	Type 2 diabetic patients	26/25	52/49	28.9/27.9	400	3.5 mo	In: wt: 0.5 kg, BMI: 0.3 kg/m^2, WC: 3.9 cm, PFM: 0.4%, FFM: – 0.2 kg, TBW: 0.0 kg; Pl: wt: 0.5 kg, BMI: 0.2 kg/m^2, WC: 0.8 cm, FM: 0.7%, FFM: – 0.2 kg, TBW: – 0.7 kg	0.3 ng/mL
Cangussu et al. [62]	Brazil	Postmenopausal women	70/70	59/59	29.2/29.9	1000	9 mo	In: BMI: 0.4 kg/m^2, WC: 1.1 cm, PFM: 0.0%, FFM: 0.5 kg; Pl: BMI: 0.3 kg/m^2, WC: 0.6 cm, FM: – 0.1%, FFM: – 0.6 kg	1.9 ng/mL
Mason et al. [3]	USA	Postmenopausal women	90/91	60/59	32.3/32.5	2000	12 mo	In: wt: – 7.1 kg, BMI: – 2.8 kg/m^2, PFM: – 4.1%, FFM: – 0.8 kg ;Pl: wt: – 7.4 kg, BMI: – 2.8 kg/m^2, FM: – 3.5%, FFM: – 1.1 kg	0.0 ng/mL

Table 2 (continued)

Author [ref.]	Location	Population study	Subjects (*n*) In/Pl	Age (years) In/ Pl	BMI (kg/ m^2) In/Pl	Vitamin D3 dose (IU/d)	Duration of study	Outcomes	Diff. in baseline 25OHD between groups
Sadiya et al. [61]	UAE	Obese type 2 diabetic patients	45/42	49/48	38/37.6	6000	3 mo	In: wt: − 0.5 kg, BMI: − 0.2 kg/m^2, WC: 0.0 cm, PFM: − 0.5%, FFM: 0.1 kg, TBW: − 0.2 kg; Pl: wt: 0.8 kg, BMI: 0.2 kg/m^2, WC: 1.0 cm, FM: − 1.3%, FFM: 0.5 kg, TBW: − 0.4 kg	0.8 ng/mL

Ca, calcium; FFM, fat-free mass; FM, fat mass; In, intervention; PFM, percent fat mass; Pl, placebo; TWB, total body water; VD3, vitamin D3; WC, waist circumference; WHR, waist to hip ratio; wt, weight

Funnel plots of PFM are shown in Supplementary Figure 2a. The Egger's symmetry test indicated a significant small study effects among studies ($P < 0.001$).

Meta-analysis in RCTs

The flow chart of studies is displayed in Supplementary Figure 3. Using search terms 1724 published studies (983 from Pub Med, 92 from Cochrane, and 649 from Scopus) were screened. We excluded duplicate articles ($n = 302$) and the remaining studies were evaluated based on title and abstract assessment. Of those, 1329 were excluded and 93 articles were evaluated based on full text. Finally, we removed 83 studies according to the inclusion and exclusion pattern; 10 studies [3, 19–21, 58–63] with 11 arms (study by Sneve et al. [20] had two arms), including 1350 persons, were included in the meta-analysis.

General traits of the included studies are presented in Table 2. Mean PFM was 40.6 ± 4.5% and 41.3 ± 4.3% in intervention and placebo groups, respectively. Mean 25(OH)D concentration was 16.0 ± 4.5 ng/mL in intervention and 16.2 ± 4.4 ng/mL in placebo group. Eight [3, 20, 58–63] studies used cholecalciferol as an oral supplementation and two of those [19, 21] used it as a cholecalciferol-fortified product. Dosages of cholecalciferol varied between 400 and 7000 IU/d. Mean duration of studies were 7.2 ± 4.4 months (range 3–12 months). All of the included studies had high quality based on the Jadad score (> 3) and reported randomization, blindness, and withdrawal *******(Supplementary Table 2).

Forest plot for the effects of cholecalciferol on PFM is shown in Fig. 3. Cholecalciferol supplementation slightly reduced PFM (− 0.31%, 95% CI: − 1.07 to 0.44) but it was not significant. The heterogeneity of studies was 90.0% ($P < 0.001$). Sensitivity analysis indicated that no study significantly affected the pooled effect size. In order to examine effect of cholecalciferol supplement alone on PFM, two studies [3, 60] that applied vitamin D3 supplement plus weight loss program were excluded and then meta-analysis conducted again. Our findings revealed that cholecalciferol supplementation had no influence on PFM (− 0.40%, 95% CI: − 1.34 to 0.54). Dose–response analysis indicated that there is a nonlinear association between vitamin D3 supplement and PFM (P-nonlinearity = 0.01). The mean changes of PFM from baseline decreased by − 2.0% with increasing intake of vitamin D3 supplement up to 2000 IU/d. No beneficial effect was observed with increasing dose upper this value (Fig. 4).

We conducted subgroup analysis to investigate the sources of heterogeneity (Supplementary Table 1). Results of subgroup analysis indicated that treatment regimens and type of cholecalciferol explain source of heterogeneity.

Meta-regression analysis showed age ($\beta = -0.07$, $P = 0.47$), baseline BMI ($\beta = 0.14$, $P = 0.51$), dose of cholecalciferol ($\beta = 0.0003$, $P = 0.31$), duration of the

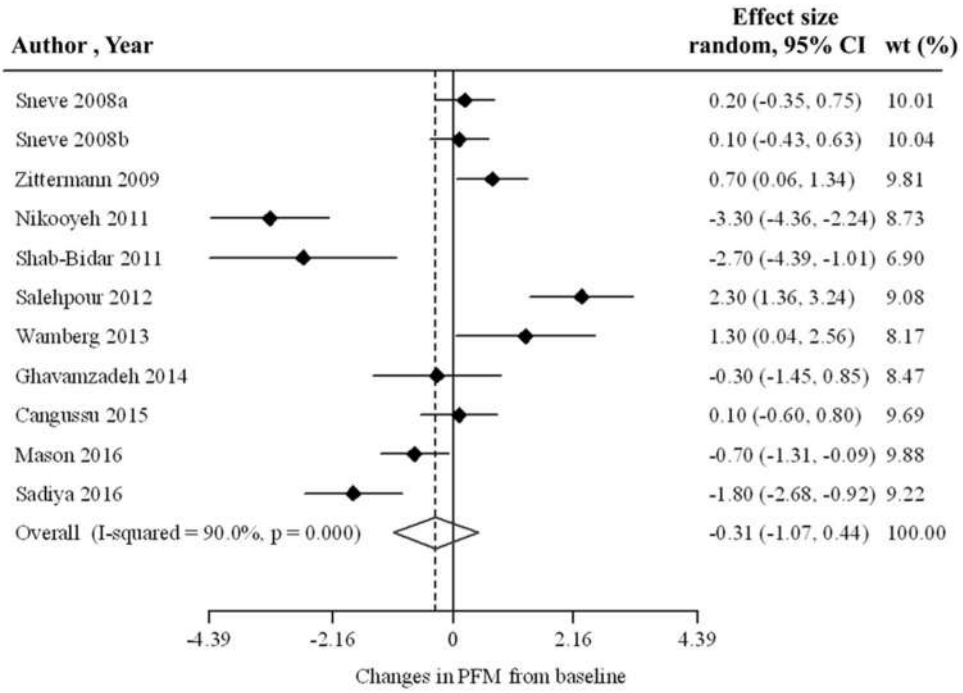

Fig. 3 Forest plot of studies that assessed effect of cholecalciferol on PFM

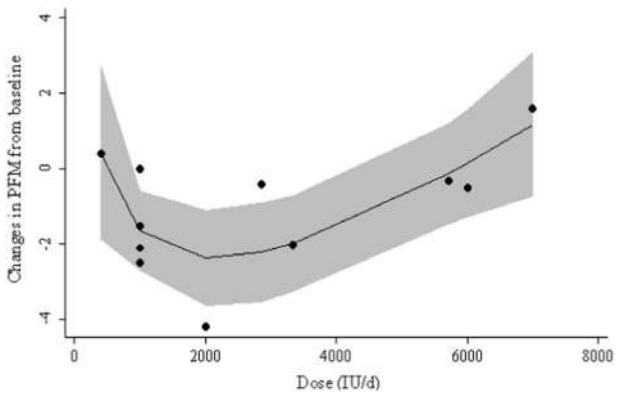

Fig. 4 Dose–response relations between vitamin D3 supplement (IU/d) and mean changes in PFM from baseline

intervention ($\beta = -0.06$, $P = 0.70$), baseline 25(OH)D ($\beta = -0.13$, $P = 0.39$), and female (%) ($\beta = -0.03$, $P = 0.43$) are not source of heterogeneity (Fig. 5). We also conduct a meta-regression with all these potential source of heterogeneity that presented in supplementary Table 3. Funnel plots of PFM is presented in Supplementary Figure 2b. There was no publication bias among included studies on PFM (Egger's regression symmetry test = 0.56).

Discussion

A total of 35 observational and 10 intervention studies were included in the analyses. According to our findings, a significant inverse association between PFM or FM and 25(OH)D exist. After subgroup analysis based on type of reported FM, the opposite correlation between PFM and FM and 25(OH)D remained unchanged. Age, latitude and longitude had no effect on the pooled effect size of association between PFM or FM and 25(OH)D level. The pooled result of the direct pair wise meta-analysis on RCTs showed that vitamin D3 interventions did no significantly alter PFM from baseline.

In recent years, the extra-skeletal effects of vitamin D have been widely studied. A growing body of epidemiological evidence has emerged concerning the role of vitamin D in obesity, including observational studies that demonstrated the association between vitamin D intake and body composition. In the present studies, we found a significant inverse relationship, suggesting that a low 25(OH)D level is associated with a larger FM. Previous published reviews [64, 65] also systematically have reported this correlation and their findings are in accord with our results. It has been stated that FM is the major reservoir of vitamin D that sequestrated vitamin D resulting in low availability of vitamin D for metabolic function among obese in compared with their non-obese counterparts [66]. However, Drincic et al. [15] using a hyperbolic model of 25(OH)D showed that volume dilution of vitamin D may describe low 25(OH)D level in obese subjects. They revealed that accumulation of vitamin D in obese is similar to normal weight subjects, but due to large body size and fat tissue in obese the most of oral and synthesized vitamin D enters FM and decrease available vitamin D to convert 25(OH)D. In contrary FM

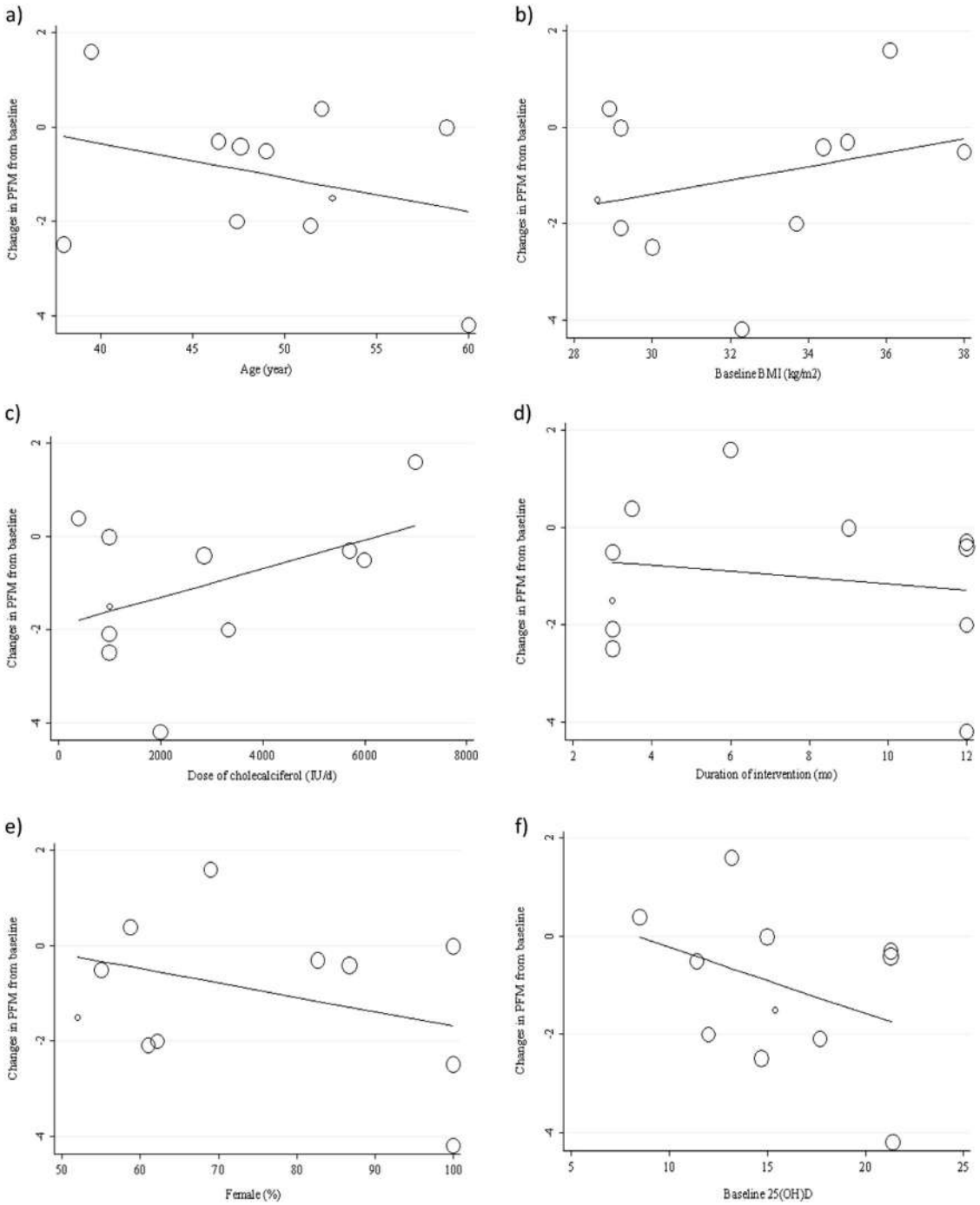

Fig. 5 Meta-regression analysis of changes in PFM from baseline by **a** baseline age, **b** BMI, **c** dose of cholecalciferol, **d** duration of intervention, **e** female (%), and **f** baseline 25(OH)D. Size of the circles corresponds to the weight of each study

reduction rising 25(OH)D level via releasing vitamin D into circulation. Results of this study indicated that after adjustment for body size, there was no significant differences between 25(OH)D level in obese and non-obese subjects and body weight is the best prognosticator of 25 (OH)D level afterwards FM. Pannu et al. [66], in a systematic review, have indicated weight loss and subsequently FM loss causes a mild elevation of 25(OH)D level (each 10% reduction in PFM increased 25(OH)D by 4.2 ng/mL). This study was in agreement of volumetric dilution of vitamin D hypothesis; however, they did not reject sequestration of vitamin D and suggested that small elevation in 25(OH)D after weight reduction may be related to vitamin D conversion into ineffective compounds. In

another systematic review, also, Mallard et al. [67] reported that weight reduction slightly increase 25(OH)D level by 1.5 ng/mL. They suggested that release of vitamin D from fat and fat-free mass after weight loss is responsible for 25 (OH)D rising.

Our findings of sub-group analysis showed that sex was not a source of heterogeneity; however, heterogeneity between studies defined by continent where study was conducted was a source of heterogeneity.

The results of a systematic review by Renzaho et al. [68] on the relation between 25(OH)D and adiposity were conflicting and the opposite association was only significant in females. This study proposed that ethnicity, gender, and age might have a role in mediating the relationship between 25 (OH)D level. However, they did not conduct any quantitative analysis on their data due to high heterogeneity. Moreover, a meta-analysis by Saneei et al. [69] on the association of 25(OH)D and BMI showed a statistical significant correlation between vitamin D status and BMI in adults. It is noteworthy that they used BMI as index of obesity. Vimaleswaran et al. [70] in another meta-analysis on 21 prospective studies demonstrated that each 1 kg/m^2 increase in BMI lowering 25(OH)D level by 1.15%. This phenomenon had more powerful association in North America (− 1.58%) and women (− 1.43%) compared with Europe (− 0.91%) and men (− 0.75%), respectively. Drincic et al. [15] have indicated that BMI is not a good predictor of 25(OH)D level compared with body weight and both of weight and FM. In addition, a numerous studies have stated that the relation between BMI and mortality is U-shaped [71], because the differential health consequences of fat and fat-free mass can be masked by the use of BMI [72].

Accumulated evidence have reported inverse association between serum 25(OH)D and FM, in which obese women have lower serum vitamin D than non-obese women [73, 74]. The possible explanation for these findings is that women generally have a higher percentage of body fat than men [75].

Differences in the relationship of adiposity with vitamin D partly may be explained by differences in race [76, 77]. It has been observed in adolescents and women evaluated in the cohort of National Health and Examination Nutrition Survey III (1988–94) cohort [78]. Apart from racial differences, the extent of vitamin D sequestration in adipose tissue due to the confounding effects of racial differences in skin color may be related to the abovementioned relationship. Inverse relationship between FM and serum vitamin D varied by race and was stronger in whites compared with blacks [79].

The inverse associations of low vitamin D status with a larger FM as well as a greater risk of weight gain over time has also been reported [64]. A causal relationship from human studies is still inconclusive, as we do not know whether vitamin D deficiency is a result of obesity or the etiology is related to vitamin D status [80]. Most of the included observational studies have confirmed an inverse association between vitamin D with either total body fat or regional one. The mechanism behind this association is unclear. A few studies suggest that higher PTH levels may be involved in the regulation of body weight or adipose tissue [47, 81]. Moreover, it is possible that overweight or obese persons have limited mobility, are less likely to have outdoors physical activity, and have low exposure to sunshine [82]. The other possibility is that excess body fat results in increased sequestration of vitamin D and its lower level [83]. If vitamin D has a causal impact, then changes in body weight may be related to changes in vitamin D status.

To explore the causality of the association between vitamin D status and body weight or FM, intervention studies are necessary to assess whether vitamin D supplementation leads to changes in body weight and FM. The effects of vitamin D3 supplementation on body fatness were assessed either directly or indirectly in 10 included studies. Some of them found no significant effect of vitamin D intervention on changes of body FM [3, 20, 58, 61, 62], whereas others have shown significant reductions in PFM [19, 21, 59, 60]. Our results was in accord with Pathak et al. [84] meta-analysis observed that vitamin D supplementation without weight loss program had no effect on FM (− 0.01 kg, 95% CI: − 0.34 to 0.31).

A long-term RCT study has recommended that higher serum vitamin D (30.2 vs. 14.5 ng/mL) at 6 months was associated with greater weight loss at 2 years (− 5.3 vs. − 3.3 kg) [85]. Moreover, women with greater fat loss, over 2 weeks, had higher vitamin D levels at baseline [86]. In contrast, Forouhi et al. [87] did not show any relationship between vitamin D status and waist circumference in a cohort study, over a 4.5- or 10-year period. Overall, based on evidence an inverse association exists between vitamin D and obesity; however, RCTs do not come up with conclusions for causality.

The major explanation for this finding may be related to the type of vehicle used in these studies, which were dairy products. Dairy sources of calcium in combination with other bioactive compounds in dairy products such as angiotensin-converting enzyme inhibitory activity, which regulate adipocyte lipogenesis [88], were shown to exert significantly anti-obesity effects possibly.

The present study had several limitations. The number of included RCTs was low to show the potential effect of vitamin D on body fatness. Most existing data comes from secondary data, which may contribute to systemic differences in trials results. Moreover, we have no access to complete data of all related published papers. We included studies in which cholecalciferol was administered;

therefore, the effect of other vitamin D analogues might be different. Further clinical trial on different forms and doses of vitamin D are needed for more comprehensive and precise conclusion.

In conclusion, correlation analysis showed serum vitamin D is inversely associated with body FM, the meta-analysis of RCTs has not support the hypothesis that vitamin D supplementation augments body-fat loss.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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