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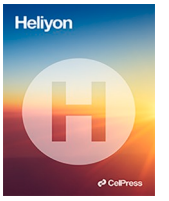

Effects of vitamin D supplementation on cardiometabolic parameters among patients with metabolic syndrome: A systematic review and GRADE evidence synthesis of randomized controlled trials

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ABSTRACT

Various pathophysiologic mechanisms were proposed to underlie the effect of vitamin D on MetS components. In this systematic review, we reviewed randomized control clinical trials to verify whether vitamin D supplementation (VDS) at different doses is effective concomitantly in controlling high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), fasting glucose level, blood pressure, and central obesity in adults diagnosed with MetS. The following scientific databases were searched from 1998 until April 2023: EMBASE, MEDLINE (PubMed), Web of Science, Latin American and Caribbean Health Sciences Literature (Lilacs), the Cochrane Central Register of Controlled Trials, clinicaltrial.gov, and Google Scholar. No language restrictions were applied. Seven studies were included, and they showed a high level of heterogeneity. All studies reported a significant increase in serum 25(OH)D levels in the intervention groups. Of these, only two noted a significant decrease in triglyceride (TG) level and waist circumference. However, the certainty levels of the evidence rating were very low and low for triglyceride (TG) level and waist circumference, respectively, and moderate for fasting glucose level, blood pressure, and HDL-c. In conclusion, despite these benefits, considering the low certainty, the evidence does not support that VDS decreases triglyceride (TG) level and waist circumference in adults with MetS.

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1. Introduction

Metabolic syndrome (MetS) is characterized by the simultaneous presence of cardiovascular disease risks and type 2 diabetes mellitus. Insulin resistance is one of the disorders included in this syndrome's etiopathology [1]. A reduced level of 25-hydroxyvitamin D [25(OH)D] is known to be a predictor of MetS [2]. Low concentrations of plasma vitamin D have been reported in individuals diagnosed with alterations in components that define MetS, such as central obesity (waist circumference [WC]), hypertension, hyperglycemia, elevated serum triglycerides (TG) and cholesterol levels, and reduced high-density lipoproteins (HDL-c) levels [3,4].

These extraskeletal actions of vitamin D could be explained by the presence of vitamin D receptors in the cells of different human tissues (kidney, pancreas, prostate, or immune system) and by vitamin D production depending on where it is expressed in each tissue [4].

A meta-analysis of epidemiologic studies revealed that serum vitamin D level was inversely associated with the risk of abdominal obesity in adults [5]. In addition, vitamin D deficiency has a negative impact on the levels of cholesterol, TG, HDL-c and low-density (LDL-c) lipoproteins. The 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D3] can impact the serum lipid by lipogenesis and assist enzyme lipoprotein lipase activity in adipocytes, resulting in reduced TG levels [6].

In vivo [7] and in vitro [8] studies have proposed potential roles of vitamin D in glucose metabolism. The most plausible explanation is that vitamin D assists insulin secretion via vitamin D receptors on pancreatic β cells, modulating immune responses and lowering systematic inflammation, and reducing peripheral insulin resistance through vitamin D receptors in the muscles and liver [9,10].

Vitamin D has been shown to have antihypertensive properties because VDR can reduce expression of the angiotensinogen gene (AGT) and the aldosterone synthase gene (CYP11B2) [11]. However, the amount of 25(OH)D provided by diet or sun exposure does not seem sufficient for individuals with MetS, mainly since metabolic disorders interfere with vitamin D activation pathways [4]. Furthermore, there is an inverse relationship between vitamin D status and other chronic diseases, such as type 2 diabetes, insulin resistance, and obesity [12–17].

As expected, most discrepancies found among the studies can be attributed to differences in doses, types of vitamin D supplements, and duration of the interventions. Furthermore, the intervention periods in these studies varied from 2 to 12 months, and these studies were conducted in different geographic regions [18–27,].

This review differs from the previously published ones [28,29], as it was developed using a protocol that addresses the results of randomized clinical trials (RCTs) that simultaneously evaluated the effects of vitamin D supplementation (VDS) on the five components of MetS, including only individuals with a confirmed diagnosis. A recently published systematic review with meta-analysis developed with RCTs [28] explored only two components of MetS, HDL-c and TG, and reported that VDS did not affect these components [28]. Another systematic review without a meta-analysis encompassed observational and interventional studies. However, limitations included a lack of a confirmed MetS diagnosis and baseline measurements of vitamin D. The narrative synthesis stated that VDS positively affected blood pressure, abdominal obesity, and glucose metabolism [29]. Both systematic reviews reported high heterogeneity of the studies and discrepancies in effect measures [28,29]. Furthermore, AlAnouti et al., 2020 [28] analyzed two components of MetS and assessed the evidence's certainty using GRADE, an important tool recommended by the Cochrane Handbook. Meanwhile, we have analyzed RCTs assessing all MetS components using the same tool. Other systematic reviews conducted by Hajhashemy et al., 2021 [5] and Theik et al., 2021 [29] did not use the GRADE tool.

Therefore, this systematic review aimed to confirm whether VDS at different doses effectively controls dyslipidemia, fasting glucose level, blood pressure, HDL-c level, and central obesity in adults diagnosed with MetS. The results were expected to guide clinical decision-making for treating vitamin D deficiency in this population.

2. Materials and methods

2.1. Protocol and registration

This systematic review was carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [30] (Table S1) and synthesis without meta-analysis (SWiM) guidelines [31]. The protocol was recorded in the International prospective register of systematic reviews (PROSPERO) database (CRD42019123212) and was previously published (DOI: 10.1186/s13643-020-01433-3) [32].

2.2. Eligibility criteria

The eligibility criteria based on PICOS (population, intervention, comparison, outcome, and type of study) were selected as follows: Population (P) individuals aged >18 years and diagnosed with MetS by The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [33] and International Diabetes Federation (IDF) criteria [34]; Intervention (I) RCTs conducted with oral VDS in the form of vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol) consumed daily, weekly, or monthly; Comparison (C) placebo; Outcome (O), electing lipid profile (TG and HDL-c) as the primary outcome. The secondary outcomes were fasting glucose level, blood pressure, and WC. RCTs were the type of study (S) chosen. The following RCTs were excluded: RCTs with vitamin D combined with other vitamin and chemical element supplements, RCTs with VDS in fortified foods (as the amount of vitamin cannot be defined accurately), and studies using active VDS [1,25$(OH)_2$D3].

2.3. Search strategy

A search was conducted using a combination of free text and medical subject heading search terms, text words, and keywords based on each database characteristic, with a focus on synonyms of VDS. The primary search strategy included the following terms: (metabolic syndrome) AND (vitamin D supplementation OR vitamin D3 (cholecalciferol) supplementation OR vitamin D2 (ergocalciferol) supplementation) AND (Clinical Trials OR Randomized Clinical Trials) (Table S2).

The following databases were searched between 1998 (the first definition of MetS issued by the World Health Organization) [35] and April 2023: EMBASE, MEDLINE (PubMed), Web of Science Core Collection (Clarivate Analytics), Latin American and Caribbean Health Sciences Literature (Lilacs), the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Google Scholar. Bibliographies of included RCTs and relevant reviews were hand-searched for eligible studies. No language restrictions were applied.

2.4. Selection of studies

This systematic review was conducted using Rayyan QCRI software [36]. Two researchers (SLSA and ATOC) independently screened all abstracts identified from the literature research. Disagreements were resolved by a third reviewer (KCMSE). Data, such as first authors' last names, year of publication, place of the study (country), study design, primary objective, population, sample size, follow-up period, inclusion/exclusion criteria, type of vitamin D supplement, type of control used, and primary results, were carefully extracted from all eligible reports using Cochrane form [37].

2.5. Data synthesis and analyses

The results of eligible studies in the systematic review were described according to a narrative SWiM [31], including the type of intervention (dose, duration, and frequency), characteristics of the target population, and outcome type. Owing to the variety of interventions and heterogeneity in studies, combining all included studies in a meta-analysis was not statistically appropriate.

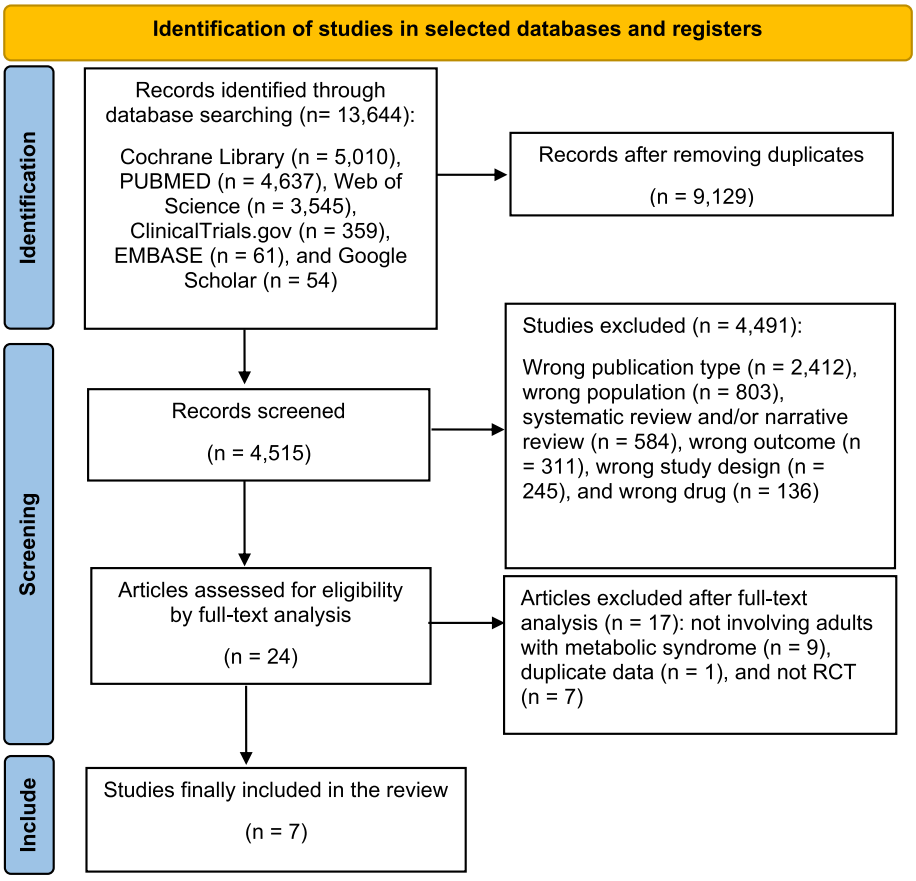

Fig. 1. PRISMA flow diagram of the study selection process.

Table 1
Characteristics of included studies.

First Author, Year	Geographic Setting, Data Collection, Time Period	Study Design	Study Population	Diagnostic of MetS criteria	Intervention	Dose, Frequency, Duration	Daily Vitamin D Dose	Control Group	Co-intervention	Compliance	Drop-out
Farag et al., 2019	Halabja (Kurdistan Region of Iraq)/March to May 2016	Parallel randomized placebo-controlled trial	I1: n = 24 I2: n = 21 C: n = 25 Ethnicity: NR Mean age (SD): I1: 41(5.94) y I2: 40(5.89) y C: 43(5.62) y %Female: I1: 66.7 % I2: 66.7 % C: 48.0 %	IDF	I1. Vitamin D without PA I2. Vitamin D + PA	I1: 2000 IU/d 12 w I2: 2000 IU/d 12 w + 30 min of endurance PA, d	2000 IU	Placebo without endurance PA	None	NR	I1: 20 % I2: 30 % C: 16 %
Salekzamani et al., 2016	Tabriz, Iran. from October 2014 to June 2015	Randomized Placebo-controlled, double-blind, parallel trial	I: 35 C: 36 Mean age (SD): 40(5.04) y	IDF	I: vitamin D	I: 50,000 UI for 16 w	50,000 UI	Placebo	None	–	I: 13 % C: 10 %
Yin et al., 2016	Jinan, North China/ November 2011 to February 2012	Randomized Placebo-controlled intervention trial	I: n = 61; C: n = 62 with vitamin D deficiency (25(OH)D <50 nmol/L) Ethnicity: Northern Chinese Mean age (SD): 50(8.72) y %Male (total): 54.0 % (data per group: NR)	Updated NCEP-ATP III for Asian Americans	Vitamin D3	700 IU/d 1 y	700 IU	Placebo	600 mg elemental Calcium (Calcium citrate), daily	95 % in both groups	I: 3.2 % C: 1.6 %
Wongwiwatthananukit et al., 2013	Bangkok, Thailand/ January to September 2011	Prospective randomized, double-blind, double-dummy, Parallel trial	I1: n = 28; I2: n = 28; C: n = 28 Ethnicity: NR Mean age (SD): I1: 62(10.63) y;	NCEP-ATP III	I1: vitamin D2 I2: vitamin D2 + Placebo	I1: 40,000 IU/w, 8 w I2: 20,000 IU/w, 8 w + 1 placebo	I1: 5714 IU I2: 2857 IU	Placebo	None	100 % in the 3 groups	I1: 6.7 % I2: 6.7 % C: 6.7 %

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Table 1 (*continued*)

First Author, Year	Geographic Setting, Data Collection, Time Period	Study Design	Study Population	Diagnostic of MetS criteria	Intervention	Dose, Frequency, Duration	Daily Vitamin D Dose	Control Group	Co-intervention	Compliance	Drop-out
			I2: 64(13.25) y C: 65(11.31) y %Male: I1: 53.3 %; I2: 50.0 %; C: 50.0 %			capsule/w, 8 w					
Makariou et al., 2017	Greece/March to September 2012	Pilot study Prospective, randomized, open-label, blinded end-point trial	I: n = 25; C: n = 25 Ethnicity: NR Mean age (SD): I: 52(9.00) y C: 51(12.00) y %Male: I: 60.0 %; C: 44.0 %	NCEP-ATP III	Vitamin D3 + dietary intervention according to the NCEP-ATP III guidelines	2000 IU/d 12 w	2000 IU	Dietary intervention according to NCEP-ATP III guidelines	None	The compliance with dietary instructions and medications was assessed during follow-up visits and tablet counts, at week 12.	0 %
Makariou et al., 2019	Greece/March to September 2012	Prospective, randomized, open-label, blinded end-point trial	I: n = 25; C: n = 25 Ethnicity: NR Mean age (SD): I: 53(7.00) y; C: 52(15.00) y %Males: I: 60.0 %; C: 40.0 %	NCEP-ATP III	Vitamin D3 + dietary intervention according to NCEP-ATP III guidelines	2000 IU/d 12 w	2000 IU	Dietary intervention according to NCEP-ATP III guidelines	None	I: 100 %; Poor compliance with dietary instructions C: Poor compliance with dietary instructions	0 %
Mahmood et al., 2017	Bengaluru, India/August 2012 to January 2013	Double-blind Randomized controlled trial	I: n = 49 C: n = 49 Ethnicity: NR Mean age (SD) I: 48(8.97) y C: 47(8.51) y %Males of group: NR	IDF	Powdered form of oral vitamin D3	60,000 IU/w for 8 w followed by monthly for 4 months	First: 8571 IU/d second: 2000 IU/d	Placebo	None	NR	I: 16 % C: 14 %

I: Intervention group; **C**: Control group; **Y:** Years; **W:** Week; **D:** daily; **NR**: Not Reported; **SD**: Standard Deviation; **25(OH)D**: 25-Hydroxyvitamin D; **NCEP-ATP**: National Cholesterol Education Program Adult Treatment Panel III; **IDF**: International Diabetes Federation; **NHLBI**: National Heart, Lung, and Blood Institute; **AHA**: American Heart Association; **PA**: Physical Activity; **IU**: International Unit.

Table 2
Main findings of included studies.

First Author, year	Assessment of vitamin D level	Baseline 25 (OH)D level (nmol/L)	Endline 25(OH) D level (nmol/L)[1]	Baseline MetS components[2] mean (SD)	Endline MetS components[2] mean (SD)	Main findings
Farag et al., 2019	25(OH)D: immunoassay	Mean (SD) I1: 26.70 (6.98) I2: 25.95 (7.98) C: 30.20 (9.73)	Mean (SD) I1: 57.90 (12.23) I2: 72.38 (13.72) C: 31.44 (9.98)	TC I1: 173.5 (60.8) I2: 194.7 (32.2) C: 185.9 (39) HDL-C I1: 34.9 (17.3) I2: 40.9 (14.4) C: 30.04 (8.5) LDL-C I1: 120.7 (64.4) I2: 149.6 (35.8) C: 150.4 (39.8) TG I1: 229.3 (113.8) I2: 184.5 (98.5) C: 174.4 (43)	TC I1: 160.5 (33.4) I2: 181.7 (31.3) C: 196.8 (39.4) HDL-C I1: 33.7 (10.6) I2: 39 (10) C: 31.8 (7) LDL-C I1: 107 (36.6) I2: 138.3 (31.4) C: 158.8 (39) TG I1: 233.8 (97) I2: 178.1 (80.8) C: 158.6 (35.4)	Daily supplementation with vitamin D (2000 IU) for 12 weeks, along with moderate-endurance physical activity, significantly increased vitamin D concentration and induced a reduction in TC and LDL-C, but not improve components of diagnosis of MetS.
Salekzamani et al., 2016	25(OH)D: chemiluminescent immunoassay	Mean (SD) I: 16.45 (15.50) C: 23.47 (21.34)	Mean (SD) I:78.38 (21.71) C: 21.46 (17.74)	TG I: 269 (97) C: 185 (61) HDL I: 45 (8.08) C: 45 (10.08) FBG I: 93 (15) C: 95 (12) SBP I: 133 (14) C: 130 (10) DBP I: 85 (10) C: 83 (8.0) WC I: 106.7 (11.8) C: 105 (9.7)	TG I: 242 (82) C: 196 (72) HDL I: 47 (6.63) C: 47 (8.24) FBG I: 96 (12) C: 95 (12) SBP I: 125 (13) C: 127(12) DBP I: 82 (11) C: 81 (9.0) WC I: 105.7 (11.8) C: 105 (9.1)	The sample size might not have enough power to detect the effectiveness of vitamin D supplementation.
Yin et al., 2016	25(OH)D: double antibody radioimmunoassay	Mean (SD) I: 36.44 (5.44) C: 35.44 (6.36)	Mean (SD) I: 82.61 (10.90) C: 36.44 (6.98)	TG I:295.82 (60.23) C: 280.77 (35.43) HDL I: 41.38 (3.09) C: 38.28 (2.71) FBG I: 106.49 (4.86) C: 103.60 (5.41) SBP I: 142 (4.86) C: 139 (5.52) DBP I: 90.1 (3.86) C: 88.9 (4.64) WC I: 95.2 (3.27) C: 93.3 (3.84)	TG I: 250.65 (36.31) C: 255.08 (19.49) HDL I: 42.15 (2.71) C: 40.22 (2.32) FBG I: 100.54 (4.14) C: 99.27 (4.32) SBP I: 138 (4.07) C: 136 (3.77) DBP I: 88.1 (2.82) C: 87.8 (3.64) WC I: 93.5 (3.04) C: 92.6 (3.89)	Correction of hypovitaminosis D did not improve metabolic disorders
Wongwiwatthananukit et al., 2013	25(OH)D: chemiluminescent immunoassay	Mean (SD) I1: 35.66 (8.36) I2: 37.63 (7.88) C: 40.43 (7.46)	Mean (SD) I1: 75.95 (17.39) I2: 66.89 (15.89) C: 47.39 (16.74)	TG I1: 139.32 (61.26) I2: 132.29	TG I1: 144.82 (64.07) I2: 137.79	Vitamin D2 supplementation was able to increase serum 25(OH)D concentration

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Table 2 (*continued*)

First Author, year	Assessment of vitamin D level	Baseline 25 (OH)D level (nmol/L)	Endline 25(OH) D level (nmol/L)[1]	Baseline MetS components[2] mean (SD)	Endline MetS components[2] mean (SD)	Main findings
				(62.36) C: 129.46 (59.75) HDL I1: 53.18 (12.46) I2: 52.36 (11.86) C: 53.43 (12.73) FPG I1: 122.89 (53.28) I2: 112.39 (32.47) C: 113.89 (26.74) SBP I1: 134.32 (17.03) I2: 135.71 (14.79) C: 136.46 (14.99) DBP I1: 76.57 (12.62) I2: 78.54 (11.47) C: 80.25 (23.18) WC I1: 94.11 (8.73) I2: 94.39 (8.09) C: 90.00 (7.86)	(53.48) C: 135.75 (71.40) HDL I1: 52.54 (13.49) I2: 50.96 (12.21) C: 53.46 (11.75) FPG I1: 126.89 (48.21) I2: 113.07 (22.53) C: 116.14 (28.29) SBP (not measured) DBP (not measured) WC (not measured)	significantly. However, HOMA-IR was not significantly different among groups.
Makariou et al., 2017	25(OH)D: enzyme immunoassay	Median (min–max) I: 39.93 (7.48–87.36) C: 24.96 (9.98–117.84)	Median (min–max) I: 76.37 (20.96–167.23) C: 32.44 (8.73–92.35)	TG median (min–max) I: 150 (56–336) C: 146 (84–339) HDL I: 48 (10) C: 50 (9) FBG I: 103 (15) C: 97 (11) SBP I: 134 (14) C: 132 (12) DBP I: 85 (6) C: 85 (9) WC I: 107 (13) C: 111 (10)	TG median (min–max) I: 136 (46–261) C: 131 (73–307) HDL I: 49 (9) C: 49 (10) FBG I: 102 (23) C: 96 (14) SBP I: 129 (13) C: 130 (16) DBP I: 83 (6) C: 82 (10) WC I: 106 (13) C: 107 (9)	Vitamin D supplementation (2000 IU/day) did not affect various CVD risk factors in the participants with MetS
Makariou et al., 2019	25(OH)D: enzyme immunoassay	Median (95 % CI) I: 40.18 (25.70–61.90) C: 24.71 (13.72–39.18)	Median (95 % CI) I: 76.37 (64.14–103.58) C: 32.94 (19.96–58.65)	WC I: 107.7 (12) C: 110 (9)	WC I: 106.3 (13,8) C: 107.6 (9.6)	Compared with dietary intervention alone, vitamin D supplementation (2000 IU/day for 3 months) plus dietary intervention had no effect on oxidative stress markers (ox-LDL, PON-1 activities, and urine 8-isoprostane

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Table 2 (*continued*)

First Author, year	Assessment of vitamin D level	Baseline 25 (OH)D level (nmol/L)	Endline 25(OH) D level (nmol/L)[1]	Baseline MetS components[2] mean (SD)	Endline MetS components[2] mean (SD)	Main findings
						level) in participants with MetS.
Mahmood et al., 2018	Standard techniques in an accredited laboratory at St Johns National Academy of Medical Sciences, Bengaluru, India	Mean (SD) I: 38.4 (22.5) C: 33.2 (19.7)	Mean (SD) I: 65.1 (29.5) C: 33.2 (17.8)	SBP I: 134 (14.9) C: 128 (11.4) DBP I: 88.1 (9.17) C: 84.8 (6.73) WC I: 95.9 (6.66) C: 96.0 (8.07) FBS I: 103 (15.9) C: 103 (24.8)	SBP I: 131 (14.6) C: 130 (12.2) DBP I: 85.9 (8.35) C: 84.7 (8.27) WC I: 94.6 (7.47) C: 95.5 (8.02) FBS I: 103 (20.7) C: 103 (20.7)	Vitamin D supplementation over 6 months did not show any significant effect on fasting glucose insulin or insulin resistance indices. However, a significant decrease in BMI and WC was noted.

I: Intervention group; **C**: Control group; **TG**: Triglycerides; **HDL-c**: High-density lipoprotein cholesterol; **TC**: total cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **FBG**: Fasting Blood Glucose; **WC**: Waist Circumference; **SBP**: Systolic Blood Pressure; **DBP**: Diastolic Blood Pressure; **HOMA-IR:** Homeostasis model assessment of insulin resistance; **CVD:** cardiovascular disease; **BMI:** body mass index[1] 25(OH)D level (nmol/L) = ng/mL; *2.496 = nmol/L.
[2] HDL-C, TG, FBG (mg/dL); SBP, DBP (mmHg); WC (cm).

2.6. Assessment of risk of bias and certainty of the evidence

Two authors (SLSA and ATOC) independently assessed the risk of bias using Cochrane Risk of Bias 2.0 (RoB) tool for RCTs [38]. Disagreements were solved through consensus with the third reviewer (LFCP). The following five criteria were examined, and the risk was assessed as low, high, or unclear: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [38].

The certainty of the evidence for TG, HDL-c, and fasting glucose levels; blood pressure; and WC was assessed independently by three review authors (SLSA, LFCP, and RNC) using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines [39]. The differences in judgments were resolved through consensus.

3. Results

3.1. Selection of studies

A total of 13,644 articles were identified through the search strategy, of which 9129 duplicates were removed. Hence, the titles and abstracts of 4515 articles were analyzed, resulting in 484 articles; 24 studies were found to be eligible, and after full reading, 7 RCTs were finally included in the systematic review (Fig. 1).

None of the articles yielded data that could be combined in a meta-analysis because of different measures of effects applied and the high level of heterogeneity between them with regard to MetS components. Three studies reported the difference from baseline using standard deviation and 95 % confidence intervals [20,26,40], while two reported the same data using only standard deviation [22,41]. One study reported the percentage difference and standard deviation [24]. Finally, one study showed only the mean difference but no standard deviation [23].

3.2. Characteristics of RCTs

The characteristics of the included studies are presented in Table 1. Two of the studies were conducted in Greece [23,40], and the other studies were conducted in Iran [20], Iraq [41], China [22], Thailand [26], and India [23]. The sample sizes ranged from 50 to 120 participants aged 40–65 years, diagnosed with MetS using the NCEP-ATP III [22,24,26,40] or IDF criteria [20,23,41]. The follow-up period varied from 2 [26] to 12 months [22]. The average daily dose of VDS ranged from 700IU [22] to 8,571IU [23] per day.

Among the seven studies included, three used only vitamin D3 [20,22,23], and two used vitamin D3 and diet [24,40]. One study used vitamin D but did not specify the chemical form of the supplement. In addition, it also included a physical activity intervention [41]. Only Wongwiwatthananukit et al. (2013) performed supplementation with vitamin D2. The mean daily dose of VDS ranged from 700 IU [22] to 8571 IU per day [23], and three studies used 2000 IU per day [24,40,41]. Five had an RCT placebo-controlled design [20,22,23,26,41]. The comparator group of two other RCTs [24,40] had an additional dietary intervention according to the NCEP-ATP III (2001) guidelines. One study included a co-intervention of calcium supplementation [22]. All studies, with different supplementation protocols, reported a significant increase in serum vitamin D in the intervention groups [20,22–24,26,40,41] (Table 2).

3.3. Effect of vitamin D supplementation on lipid profile

The effects of VDS on lipid profile were assessed in five studies. Only Salekzamani et al. (2016) observed a significant decrease in TG levels ($p = 0.01$) after VDS. This responsive protocol for TG offered a daily dose of 7142 IU/d for 4 months. Other studies did not show a significant improvement in the lipid profile of individuals with MetS [22,24,26,41] (Table 2). In the RCT performed by Farag et al. (2019), the group supplemented with vitamin D plus 30 min/d of physical activity had higher serum levels of HDL-c than the VDS alone and placebo groups ($p = 0.029$). Furthermore, the placebo group had lower serum levels of TG than the vitamin D plus 30 min/d of physical activity and vitamin D alone groups ($p = 0.003$).

3.4. Effect of vitamin D supplementation on WC

Five studies assessed the effect of VDS on WC. However, only Mahmood et al. (2017) observed a decrease in WC ($p = 0.001$) in the vitamin-treated individuals who received a dose of vitamin D (8571 IU/d) for 6 months. The other four studies did not report a significant effect on WC [20,22,24,40] (Table 2).

3.5. Effect of vitamin D supplementation on fasting blood glucose

The effect of VDS on fasting blood glucose (FBG) levels was assessed in five studies, but none reported a significant effect of VDS [20,22–24,26] (Table 2).

3.6. Effect of vitamin D supplementation on blood pressure

Four studies assessed the effect of VDS on blood pressure, but no study reported significant improvement in the blood pressure of the participants with MetS after VDS [20,22–24] (Table 2).

3.7. Assessment of the risk of bias

Among the included studies, three had a low RoB score [20,23,26], and three were classified as having some concerns [22,24,40] because of domain deviations from the intended intervention, and one had a high RoB, mainly in the measurement of the outcome domain [41] (Fig. 2).

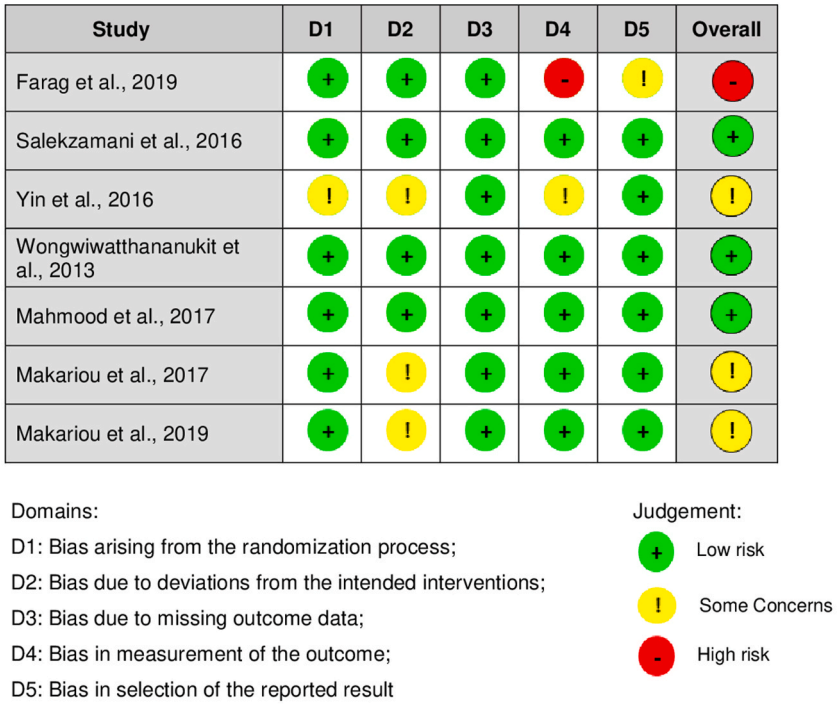

Fig. 2. Results of the risk of bias assessment using Cochrane Risk of Bias 2.0 tool (Sterne et al., 2019).

3.8. Certainty of the evidence

The certainty of the evidence for primary outcomes provided very low evidence to decrease TG (mg/dL) and increase HDL-c (mg/dL) after VDS. Regarding secondary outcomes, we observed low certainty of evidence to decrease WC (cm) and a moderate degree for decreased FBG level (mg/dL) and improved blood pressure (mmHg) (Table 3).

4. Discussion

To the best of our knowledge, this is the first review to assess RCTs on the effect of vitamin D supplementation on the set of five MetS components in adults. Among the seven RCTs included in this review, only two reported a significant decrease in TG (7142 IU/d at 4 months) [22] and WC (8571 IU/d at 6 months) [23] but showed very low and low certainty of the evidence, respectively.

The RCTs included in this review examined different doses, frequencies, and durations of VDS. Nevertheless, the performance of studies with different protocols and the lack of therapeutic goals to achieve serum 25(OH)D level was associated with better non-musculoskeletal health outcomes. This is compatible with the recommended guidelines for vitamin D intake, i.e., from 400 to 1000 IU/d, according to age group and sex [42].

The positive impact of VDS on the lipid profile can be clarified because vitamin D causes the deactivation of lipogenic genes, as the sterol regulatory element binding transcription factor (SREBP) gene controls lipid synthesis [43]. Experimental studies [44,45] have reported that $1,25(OH)_2D3$ inhibits adipocyte differentiation resulting in decreased TG levels, new fatty acid synthesis, and increased fatty acid β-oxidation. In addition, vitamin D plays a role in mitigating arterial stiffness, reducing activity of the renin-angiotensin-aldosterone system and inflammatory cytokines, and increases activity of lipoprotein lipase enzyme [4].

Mahmood et al. (2017) reported a significant decrease in WC in adults who received VDS. There is an inverse relationship between serum vitamin D and adipose tissue, as measured by BMI, WC, and lipid profile. This association is mainly due to the chemical characteristic of vitamin D as a fat-soluble agent. Thus, individuals with these altered parameters are at a high risk of inadequate vitamin D status; therefore, VDS should be prioritized in this patient population [46].

Dibaba (2019) performed a systematic review and meta-analysis by aggregating adults with overweight and obese status (without

Table 3
Certainty of evidence for outcomes according to Grading of Recommendations, Assessment, Development, and Evaluations.

Certainty assessment							N° of patients		Certainty
Outcomes	N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Vitamin D supplementation	Placebo	
Decrease TG (mg/dL) follow-up: range 8 weeks to 1 year	5	Randomized trials	Serious[a]	Serious[b]	Not serious	Serious[c]	194	176	⨁◯◯◯ Very low
Increase HDL-c (mg/dL) follow-up: range 8 weeks to 1 year	5	Randomized trials	Serious[a]	Serious[b]	Not serious	Serious[c]	194	176	⨁◯◯◯ Very low
Decrease FBG (mg/dL) follow-up: range 8 weeks to 1 year	5	Randomized trials	Not serious	Serious[b]	Not serious	Not serious	198	200	⨁⨁⨁◯ Moderate
Decrease WC (cm) follow-up: range 12 weeks to 1 year	5	Randomized trials	Not serious	Serious[b]	Serious[d]	Not serious	195	197	⨁⨁◯◯ Low
Improve SBP (mmHg) follow-up: range 12 weeks to 1 year	4	Randomized trials	Not serious	Serious[b]	Not serious	Not serious	170	172	⨁⨁⨁◯ Moderate
Improve DBP (mmHg) follow-up: range 12 weeks to 1 year	4	Randomized trials	Not serious	Serious[b]	Not serious	Not serious	170	172	⨁⨁⨁◯ Moderate

TG: Triglycerides; **HDL-c**: HDL cholesterol; **FBG**: Fasting Blood Glucose; **WC**: Waist Circumference; **SBP**: Systolic Blood Pressure; **DBP**: Diastolic Blood Pressure.

[a] Among the five studies, two had a low risk of bias, two were had some concerns of risk of bias, and one had a high risk of bias.

[b] The five studies with differences in intervention protocol of vitamin D.

[c] One study had a high risk of bias, arising from domain measurement of the outcome.

[d] One study evaluated oxidative stress components as the primary outcomes and not the metabolic syndrome components.

MetS) in 41 RCTs, with a mean dose of 2795 IU (range, 20–8570 IU; meantime, 6.9 months) [47]. The benefits of supplementation included a reduction in total cholesterol, low-density lipoprotein cholesterol (LDL-c), and TG levels. Similarly, Salekzamani et al. (2016) found a significant decrease in TG level (269–242 mg/dL) after 4 months ($p < 0.001$) of VDS. In one meta-analysis, no effect of VDS on lipid profile was observed in adults with MetS [28].

Among the studies included in this systematic review, only Wongwiwatthananukit et al. (2013) used vitamin D2 (ergocalciferol) in the supplementation protocol. The other studies used vitamin D3 (cholecalciferol) [22,24,41]. None of the studies reported vitamin D toxicity, and both chemical forms of vitamin D were effective in optimizing 25(OH)D status, an aspect previously reported in a systematic review and meta-analysis [48]. In this sense, the type of VDS (cholecalciferol or ergocalciferol) is not a variable that limits the effectiveness of VDS on MetS components. Therefore, both types of vitamin D (ergocalciferol and cholecalciferol) in the RCTs included in this review effectively changed the 25(OH)D status of individuals with MetS.

The paradox of the relationship between vitamin D and MetS is that cross-sectional studies show an inverse association between hypovitaminosis D and the presence of MetS [12–14]. However, it is still unclear whether the alterations in MetS components favor vitamin D inadequacy or if hypovitaminosis D is the risk factor for the alterations in MetS components. In addition, while the correction of hypovitaminosis D was observed in some RCTs, improvements in the components of MetS [49] have not been consistently demonstrated.

Interestingly, the authors proposed that the interventions with vitamin D should ensure that the level of 25(OH)D is between 100 and 150 nmol/L [46] to protect from cardiovascular risks related to MetS components, which was not found in this review [50]. The discrepancy between the RCT supplementation protocols included in this systematic review reinforces the limitations for establishing evidence on the dose-response obtained with VDS in the MetS components and clinical recommendations [20,22–24,26,40,41].

Our study had some limitations. First, a small number of RCTs addressed the effects VDS on all components of MetS simultaneously. Second, the protocols were not aligned on the VDS, causing high heterogeneity as various regimens, doses, and duration, reasons why limited comparisons between studies and the aggregation of results in a meta-analysis. Such factors also difficulted the generalization of the results. Third, all RCTs included in our review reported the baseline vitamin D status of individuals with inadequate vitamin D status in both the intervention and control groups, but some studies [20,23,24] did not mention whether there was a difference in baseline vitamin D status between the groups. Fourth, most studies originated from Eastern countries; thus, extrapolating these results to Western populations is questionable. Finally, many of the RCTs suffer from significant sources of bias, and the certainty of the evidence on the outcomes showing significant improvement with VDS was low. Another important aspect is that vitamin D status can be influenced by different factors, such as genetic factors/polymorphisms, seasons, and geographic location. Unfortunately, these variables were not explored in the clinical trials included in this review [51–53].

5. Conclusions

There were significant improvements in only two components, TG level and WC, in adults who received VDS. However, the low certainty of evidence does not support that VDS improves these MetS components. The balance between VDS benefits observed in only two of the five components of MetS, RoB assessed, and certainty of evidence rating suggested caution in adopting this intervention in patients with MetS.

Therefore, there is an extreme need for well-designed RCTs investigating the effectiveness of VDS in adults with MetS, simultaneously exploring all components and different phenotypes.

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Availability of data

Data generated and utilized for analyses of results presented in this manuscript are available from the corresponding author on reasonable requests.

CRediT authorship contribution statement

Séphora Aquino: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Aline Cunha:** Writing – review & editing, Investigation. **Josivan Gomes Lima:** Writing – review & editing, Validation, Methodology. **Karine Sena-Evangelista:** Writing – review & editing, Validation, Methodology, Data curation. **Anronio Gouveia Oliveira:** Writing – review & editing, Methodology, Formal analysis. **Ricardo Ney Cobucci:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Lucia FC Pedrosa:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20845.

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