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Serum vitamin D levels in relation to metabolic syndrome: A systematic review and dose–response meta-analysis of epidemiologic studies

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Summary

Several epidemiological studies examined the association of serum vitamin D with metabolic syndrome (MetS), but the findings were inconsistent. We conducted a systematic review and dose–response meta-analysis to quantify the association between blood vitamin D levels and MetS in adults. A systematic search up to December 2020 was conducted in MEDLINE (PubMed), ISI (Web of Science), Scopus, and Google Scholar databases for epidemiological studies that assessed the relation of serum 25-hydroxyvitamin D (as the exposure) and MetS (as the outcome) in adults. Eligible cross-sectional studies were restricted to those with representative populations. Finally, 43 studies were included in the analysis (38 cross-sectional, one nested case–control, and four cohorts studies). Combining 41 effect sizes from 38 cross-sectional studies included 298,187 general adult population revealed that the highest level of serum vitamin D, compared with the lowest level, was significantly related to a 43% decreased odds of MetS in developed countries (odds ratio [OR]: 0.57; 95% confidence interval [CI]: 0.49–0.65) and 40% in developing countries (OR: 0.60; 95% CI: 0.52–0.70). Linear dose–response analysis (including 222,175 healthy individuals and 39,308 MetS patients) revealed that each 25 nmol/L increase in serum vitamin D level was significantly associated with a 15% decreased odds of MetS (OR: 0.85; 95% CI: 0.80–0.91); however, we found no significant nonlinear association. Meta-analysis of five prospective studies with 11,019 participants revealed no significant relation (relative risk [RR]: 0.70; 95% CI: 0.37–1.32). This meta-analysis indicated an inverse association between serum vitamin D concentrations and risk of MetS in general adult populations in cross-sectional studies in a dose–response manner. However, no significant association was found in a small number of cohorts. More prospective studies are needed to confirm the causality of this relationship.

Abbreviations: AHA/NHLBI, American Heart Association/National Heart; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; BMI, body mass index; CI, 95% confidence interval; CLIA, chemiluminescent immunoassay; CVDs, cardiovascular disease; ECLI, electrochemiluminescence immunoassay; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; FBS, fasting blood sugar; GDM, gestational diabetes mellitus; GLUTs, glucose transporters; HDL, high-density lipoprotein; HR, hazard ratio; IA, immunoassay; IDF, International Diabetes Federation; KNHANES, Korea National Health and Nutrition Examination Survey; LPL, lipoprotein lipase; MetS, metabolic syndrome; NCDs, noncommunicable diseases; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; NHANES, National Health and Nutrition Examination Surveys; NOS, Newcastle–Ottawa Scale; OR, odds ratio; PBA, protein-binding assay; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RIA, radioimmunoassay; RR, relative risk; T2DM, type 2 diabetes mellitus; TG, triglyceride.

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KEYWORDS
meta-analysis, metabolic syndrome, serum vitamin D, systematic review, vitamin D deficiency

1 | INTRODUCTION

The metabolic syndrome (MetS) is a multiplex risk factor with metabolic origin.[1] This syndrome, a threatening condition characterized by the competence of different pathological and dysmetabolic processes including dyslipidemia, hypertension, abdominal obesity, and glycemic disorders, could lead to type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD).[2] The fundamental way to prevent and treat MetS is losing weight and having more physical activity. Among various definitions used for MetS, the one suggested by National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) is the easiest to apply epidemiologically and clinically, because of using straightforward criteria with easy measurements.[3]

Although different criteria are used for MetS definition and its prevalence varies in populations,[4] it is a highly common disorder with rising prevalence in most societies, due to the obesity epidemic.[5–7] Previous epidemiological studies have indicated strong associations between intrauterine nutrition, patterns of postnatal nutrition, and growth with MetS in adults.[8] Other investigations provided evidence supporting a profitable effect of traditional Mediterranean diet in preventing MetS.[9] Among micronutrients, vitamin D, known as the "sunshine vitamin," is a prohormone with various functions in the body.[10] Due to limited dietary sources and also the lack of fortified foods with vitamin D, its deficiency is very common among communities.[11] This deficiency involves in both musculoskeletal disorders and noncommunicable diseases (NCDs).[12]

Various epidemiological studies demonstrated inverse relations between serum vitamin D status and insulin resistance, T2DM, and MetS.[13,14] A previous meta-analysis showed an inverse linear relationship between 25-hydroxyvitamin D (25(OH)D) levels and the risk of MetS in 18 epidemiological studies (16 cross-sectional and two cohort studies) published before 2013. However, subgroup analysis by sex could not reveal a significant relation in women, due to small number of effect sizes ($n = 3$). In addition, not all included studies in the mentioned meta-analysis had random sampling method; therefore, the results were not generalizable to the whole adult population. After 2013, several other investigations have also assessed the relation of blood vitamin D status with risk of MetS; but the results were inconsistent.[15–20] For example, a large cross-sectional study in South Korea documented an inverse association between 25(OH)D concentration and odds of MetS in both men and women.[21] Similarly, inverse relations were seen in other population-based investigations conducted in Canada[22] and the Netherlands,[23] but not in Italy.[24] There was no comprehensive study to summarize the linkage between 25(OH)D and MetS especially in populations with representative samples of adults. So, we conducted a systematic review and meta-analysis to quantify the association between blood vitamin D levels and risk of MetS in adults. Dose–response analysis was also applied to examine the linear and nonlinear relation.

2 | METHODS AND MATHERIALS

2.1 | Search strategy

A systematic search of all published articles, up to December 2020, was conducted in the following electronic databases: MEDLINE (PubMed), ISI (Web of Science), Scopus, and Google Scholar. We also manually searched reference lists of all eligible articles and previous reviews on relevant topics for additional studies. There was not any limitation in time or language. The MeSH and non-MeSH terms were used as follows: ("Vitamin D" OR "vitamin d" OR "vitamin d2" OR "vitamin d3" OR "1-alpha hydroxyvitamin d3" OR "1-alpha-hydroxy-vitamin D3" OR "1-alpha hydroxycalciferol" OR "1-alpha-hydroxy-calciferol" OR "1,25 dihydroxyvitamin d3" OR "1,25-dihydroxy-vitamin D3" OR "1,25 dihydroxycholecalciferol" OR "25-hydroxycholecalciferol" OR "25 hydroxyvitamin d" OR "alfacalcidol" OR "calcitriol" OR "calcifediol" OR "calciferol" OR ergocalciferol OR cholecalciferol OR calciol OR hydroxycholecalciferol OR "hydroxyvitamin d" OR "Vitamin D Deficiency") and ("Metabolic Syndrome X" OR "metabolic syndrome"). We confirmed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. This study was also registered at Prospero (http://www.crd.york.ac.uk/Prospero; no. CRD 42020210263).

2.2 | Inclusion criteria

Studies were included in the meta-analysis if they fulfilled the following criteria: (1) they were population-based epidemiological studies (cohort, case–control, nested case–control, case–cohort, and cross-sectional studies); (2) they considered MetS as the outcome of interest and blood vitamin D measurements as the exposure; (3) they investigated adults aged 18 years old or older; and (4) they reported relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (95% CIs) for the outcome or adequate data to compute these values.

2.3 | Exclusion criteria

Studies were excluded from this meta-analysis if they (1) did not report RR, hazard ratio (HR), or ORs with 95% CIs or adequate data to compute these values; (2) considered MetS as the exposure and vitamin D levels as the outcome of interest; (3) were experimental

studies; (4) were primary literature, such as reviews, editorials, letters, and commentaries; and (5) were duplicated. In addition, publications with overlapped population were excluded from the analysis. There were six reports from Korea National Health and Nutrition Examination Survey (KNHANES 2010–2012),[25–30] four reports from KNHANES 2008–2010,[31–34] and two reports from KNHANES 2012–2013.[21,35] Moreover, six reports were from National Health and Nutrition Examination Surveys (NHANES 2001–2010)[36–41] and two other publications from NHANES 1988–1994.[42,43] Therefore, among the mentioned publications in each period of time, just the study with the highest sample size that reported RR or ORs with 95% CIs was included, such that KNHANES 2010–2012,[25] KNHANES 2008–2010,[31] KNHANES 2012–2013,[21] NHANES 2001–2006,[36] NHANES 2007–2010,[37] and NHANES 1988–1994[42] were included in the analysis. The total result of initial systematic search was 4045 studies. After excluding duplicated publications (n = 1115) and screening the title and abstract of remaining articles (n = 2933), the full text of 331 publications was assessed. The full text of unavailable articles was obtained through requesting the author; however, the full texts of some studies were not available, even through requesting the authors. Table S1 shows details of more relevant studies that were excluded in the first step of screening. Details of the 106 studies that passed the first step are presented in Table S2. In the second step, we restricted the included studies to those that reported adjusted RR, HR, or ORs with 95% CIs, without having overlapped population. In addition, in the case of cross-sectional studies, only those that used random sampling method and included representative populations were considered eligible for the analysis. Finally, 43 studies were eligible for the systematic review,[20–23,25,26,31,36,37,42,44–76] as shown in Figure 1. All processes were separately conducted by three investigators (FS, ZH, and FM) and were supervised by the principal researcher (PS).

2.4 | Data extraction

General characteristics (including first authors' last name, year of publication, study location, latitude, longitude, development status of countries, study design, unit of serum vitamin D, representativeness of the study population, recruitment source of population, sample size, sex, mean age, health status of participants, 25(OH)D levels, prevalence of MetS in vitamin D levels, ORs, RRs with 95% CIs for MetS, adjustments for confounders, definition of MetS, and method of vitamin D measurement) were extracted from the eligible studies. For dose–response analysis, we additionally gathered data of each vitamin D category, including number of MetS patients and total number of individual, as well as the mean or median of serum vitamin D levels. The ORs or RRs with 95% CIs for at least three categories of serum vitamin D levels were also needed for nonlinear dose–response analysis. Notably, the adjusted risk estimates that reflected the most comprehensive adjustments were extracted. Data extraction was independently conducted by three researchers (ZH, EM, and FS). Any discrepancies were resolved through the discussion.

2.5 | Quality assessment of studies

Newcastle–Ottawa Scale (NOS)[77] was applied to assess the quality of each study, separately for cohort and cross-sectional studies. Based on NOS, a maximum of 10 scores was assigned for each cross-sectional research: 5 scores for individual selection (satisfaction of sample size, description of nonrespondents, representativeness of study population, and ascertainment of vitamin D status as the exposure), 2 scores for comparability (controlling for confounders including sun exposure or season of year, sex, and age), and 3 scores for outcomes (validated assessment of MetS as the outcome and doing appropriate statistical test for the analysis). Cross-sectional studies with quality scores of 9 or more were considered as "high quality," and the remaining were considered as "low quality." With regard to cohort studies, NOS assigned a maximum of 9 scores to each investigation: 4 scores for sample size selection (selection of the nonexposed cohort, representativeness of the exposed cohort and ascertainment of vitamin D status as the exposure, demonstration that MetS was not present at the start of the study), 2 scores for comparability (controlling for confounders including sun exposure or season of year, sex, and age), and 3 scores for assessment of outcomes (validated assessment of MetS as the outcome, adequacy of follow-up duration for MetS incidence, and enough follow-up in cohorts). Cohort studies with quality score of more than the median of 7 were considered as "high quality," and the remaining were considered as "low quality." Details of quality assessment of eligible studies are presented in Table S3.

2.6 | Statistical analysis

Log ORs or RRs and their standard errors were calculated through the use of reported OR/RR and 95% CI for the 25(OH)D–MetS relation. For those studies that reported OR/RR for the lowest versus the highest level of serum 25(OH)D, these values and their lower and upper limits were inverted to compute the OR/RR for the highest versus the lowest level. The overall effect size was calculated by using a random effects model, which incorporates between-study variability. Cochran's Q test and I^2 were used to examine between-study heterogeneity. In the case of significant between-study heterogeneity, subgroup analyses (based on study location, developmental status of countries, representativeness of the population, health status of participants, sex of subjects, quality of studies, adjustment for age and season, methods of vitamin D measurement, levels of vitamin D used for comparison, and criteria used for defining MetS) were conducted to find out the possible sources of heterogeneity. Meta-regression was also used to assess the effect of continuous variables (including latitude, longitude, age, and quality of studies) on overall estimate. Sensitivity analysis was performed to assess the extent to which inferences might depend on a particular study. Publication bias was also assessed through the visual inspection of Begg's funnel plots and statistical assessment of funnel plot asymmetry by Egger's test and Begg's test. A trim-and-fill method

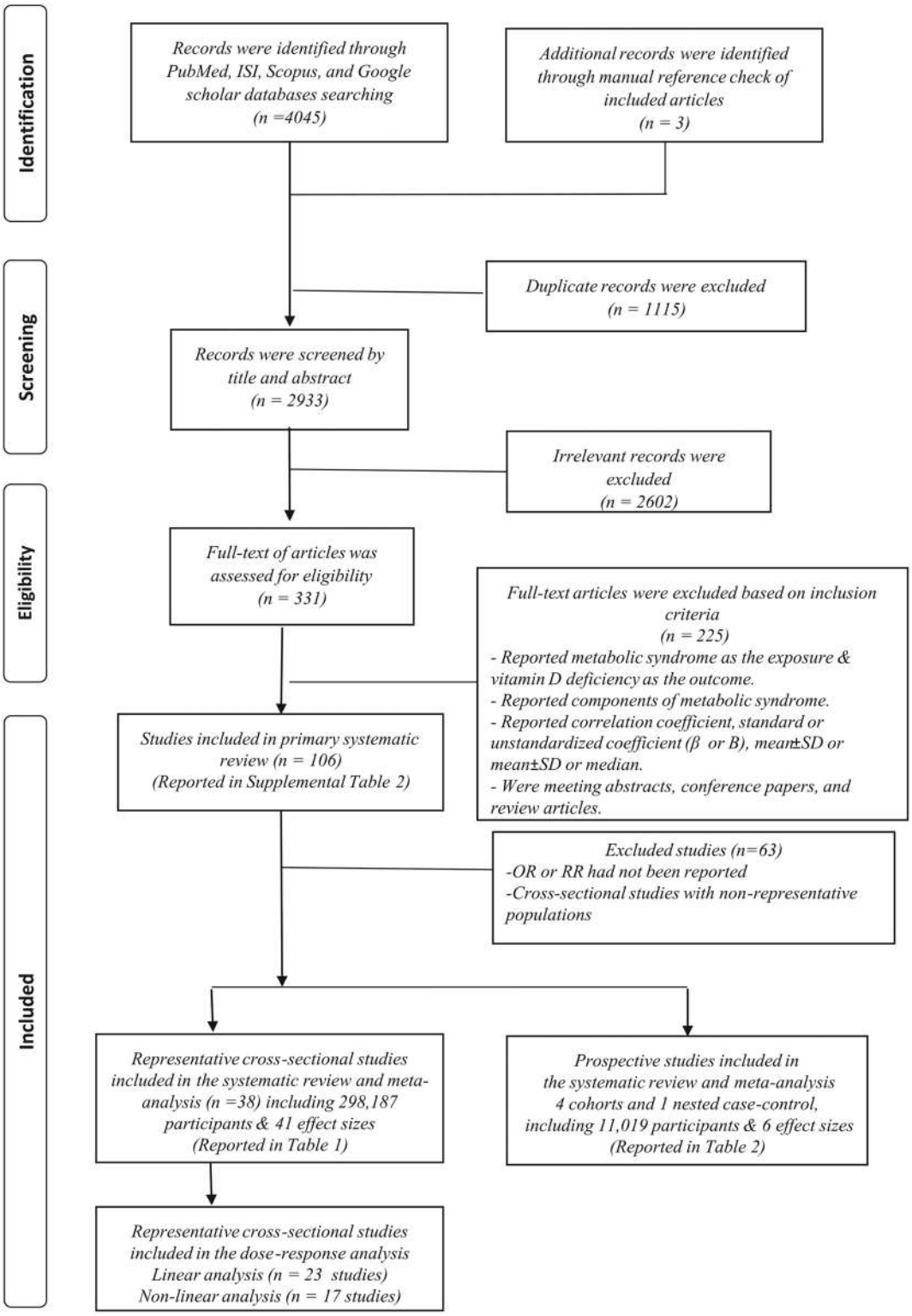

FIGURE 1 Flow diagram of search strategy and study selection

was used to detect the impact of missing investigations in the overall effect. For the dose–response analysis, according to described method by Greenland and Longnecker[78] and Orsini et al.,[79] we calculated study-specific slopes (linear trends) and 95% CIs for 25 nmol/L serum vitamin D by using natural logs of the ORs and their 95% CIs across categories of serum vitamin D. For nonlinear dose–response analysis, we required the following data for at least three categories of serum vitamin D levels: ORs/RRs and their 95% CIs, number of MetS patients, distribution of individuals, and median or mean level of serum vitamin D in each category. For studies that

TABLE 1 Main characteristics of representative cross-sectional studies included in the systematic review and meta-analysis of the association between serum vitamin D levels and metabolic syndrome

First author (year)/ref	Study design	Country/latitude °N	Sex	Age (years)	No. of participants	No MetS	25(OH)D levels, nmol/L
Chun (2020)/26	Cross-sectional (based on KNHANES V 2010–2012)	Korea	Women	46.13	8326		≥50 nmol/L
							<50
							≥50 nmol/L
							<50
Liu (2020)/48	Cross-sectional (based on CLHLS)	China	Both	85	2493		
					1029	484	<20 ng/ml
					890	373	20–30 ng/ml
					574	218	≥30 ng/ml
							10 ng/ml increase
Ganji (2020)/38	Cross-sectional (based on NHANES 2001–2006)	USA	Both	51	8241		
					1311	621	<30 nmol/L
					2570	1138	<30–50 nmol/L
					3068	1144	<50–75 nmol/L
					1292	323	≥75 nmol/L
Jeenduang (2020)/49	Cross-sectional	Thailand	Women	62.67 ± 9.76	340		
					146	60	≥30 ng/ml
					194	107	<30 ng/ml
Weldegiorgis (2020)/47	Cross-sectional	China	Men	>50/61.9 ± 5.76	1074		
					143		Q1: ≤12.08 ng/ml
					238		Q2: 12.08–16.65
					303		Q3: 16.66–22.90
					390		Q4: ≥22.91
			Women		1511		
					303		Q1: ≤8.60 ng/ml
					410		Q2: 8.61–12.34
					338		Q3: 12.35–16.91
					260		Q4: ≥16.92
Ganji (2020)/50	Cross-sectional (based on Qatar Bio bank database)	Qatar	Women	20–80/40.1 ± 12.7	700		
					196	51	Q1: <13.0 ng/ml

(Continues)

TABLE 1 (Continued)

First author (year)/ref	Study design	Country/latitude °N	Sex	Age (years)	No. of participants	No MetS	25(OH)D levels, nmol/L
					175	57	Q2: 13 ≤ 18
					162	52	Q3: 18 ≤ 25
					167	25	Q4: >25
Yeap (2020)/46	Cross-sectional (based on BHAS)	Australia	Men	58.1 ± 5.9	2207		
					104	36	<50 nmol/L
					1597	367	50–100
					507	58	>100
			Women	57.9 ± 5.7	2651		
					277	83	<50 nmol/L
					1929	399	50–100
					445	49	>100
Lee (2019)/53	Cross-sectional (baseline Korean Urban Rural Elderly cohort study)	Korea	Men	72.8 ± 4.6	987		
					245		Q1: 4.20–14.19 ng/ml
					245		Q2: 14.20–18.99
					249		Q3: 19.00–24.19
					248		Q4: 24.20–51.90
			Women	71.5 ± 4.6	1949		
					487		Q1: 4.10–11.19 ng/ml
					491		Q2: 11.20–15.59
					484		Q3: 15.60–21.59
					487		Q4: 21.60–54.90
Chen (2019)/54	Cross-sectional	Taiwan/25°N	Both	57.3 ± 11.9	1128		<20 ng/ml
							20–30
							>30
Mehri (2019)/52	Cross-sectional	Yazd, Iran	Women	40.77	450		≥30 ng/ml
							20–30
							<20
Mutt (2019)/51	Cross-sectional	Northern Finland/65°N	Both	69.0 ± 0.5	636		
					501	260	<75 nmoL/L

TABLE 1 (Continued)

First author (year)/ref	Study design	Country/latitude °N	Sex	Age (years)	No. of participants	No MetS	25(OH)D levels, nmol/L
					131	59	≥75
Chen (2019)/55	Cross-sectional (base on SPECT-China study 2014–2016)	East China	Both	54.9 ± 12.9	10,655	2722	Per 10 nmol/L increase in 25(OH)D
Mogili (2018)/57	Cross-sectional	Vellore, India	Women	20–40/26.50	256		≥30 ng/ml
							<30
Wang (2018)/56	Cross-sectional	Taiwan/22°50′	Both	76.0 ± 6.2	523		≥20 ng/ml
							<20
Zhang (2018)/39	Cross-sectional (based on NHANES 2007–2010)	USA	Both	≥20/46.8	4920		≥40 nmol/L
							<40
Sotunde (2017)/58	Cross-sectional (based on PURE-SA-NWP study)	South Africa	Women	≥43 59.6 ± 10.6	209	119	1 ng/ml increase in 25(OH)D
Raposo (2017)/59	Cross-sectional (based on PORMETS)	Portugal	Both	53	500	91	1 ng/ml
Akter (2017)/21	Cross-sectional	Japan	Both	43.81 ± 9.14	1790		
					730	96	<20 ng/ml
					921	109	<20–30
					139	14	≥30
						61	Q1: 7.9–17.8
						57	Q2: 17.9–21.1
						54	Q3: 21.2–25.0
						47	Q4: 25.1–38.7
Pannu (2017)/60	Cross-sectional (based on VHM May 2009 and April 2010)	Victoria, Australia	Both	49	3404		
					1109	252	10–44 nmol/L
					1162	237	45–65
					1133	120	65–204
Lally (2016)/62	Cross-sectional (based on NIHR)	England	Both	43.08 ± 10.1	324		16.5–51.7 ng/ml
							10.3–16.4
							7–10.2
							3.4–7
Chen (2016)/63	Cross-sectional	Taiwan	Both	56.4 ± 13.0	2113		

(Continues)

TABLE 1 (Continued)

First author (year)/ref	Study design	Country/latitude °N	Sex	Age (years)	No. of participants	No MetS	25(OH)D levels, nmol/L
					421	112	<20 ng/ml
					847	231	20–30 ng/ml
					847	214	>30 ng/ml
Sung (2016)/36	Cross-sectional (based on comprehensive health examination in the 2012–2013)	South Korea	Men	39.8 ± 8.1	98,412		
					24,650	14.5%	Q1: <12.9 ng/ml
					24,612	15.4%	Q2: 12.9–16.6
					24,578	15.7%	Q3: 16.7–21.4
					24,572	15.5%	Q4: ≥21.4
			Women	38.5 ± 8.7	82,506		
					20,691	5.8%	Q1: <9.7 ng/ml
					20,593	5.8%	Q2: 9.7–12.8
					20,604	5.4%	Q3: 12.8–17.2
					20,618	5.2%	Q4: ≥17.2
Pan (2016)/61	Cross-sectional	China/28°N	Both	65.81 ± 8.96	270		
					96	52.8%	T1: ≥25 ng/ml
					93	65.59%	T2: 19–25
					81	72.84%	T3: <19
Lerchbaum (2015)/67	Cross-sectional (based on SHIP-1)	Germany	Both		271		
			Men	55	1449	49.3%	8.66 ng/ml increase
			Women	54	1222	36.5%	9.53 ng/ml increase
Kim (2015)/27	Cross-sectional (based on fifth KNHANES (V-1) October to December 2010)	Korea	Both	≥50 years old	2624		
					656	45.7%	10.3–35.6 nmol/L
					654	44.3%	35.6–45.9
					657	38.2%	45.9–59.2
					657	37.3%	59.2–122.6
Lu (2015)/66	Cross-sectional (based on Cohort)	China/39.9°N	Both	60.17 ± 19.68	3265		
					305	30	<10 ng/ml
					1716	121	10–20
					883	25	20–30
					361	6	≥30
Bea (2015)/68	Cross-sectional	Arizona	Men	65.90 ± 8.70	1439	105	T1: <20 ng/ml

TABLE 1 (Continued)

First author (year)/ref	Study design	Country/latitude °N	Sex	Age (years)	No. of participants	No MetS	25(OH)D levels, nmol/L
					658	262	T2: 20–30
						205	T3: ≥30
			Women	65.39 ± 8		96	T1: <20 ng/ml
				.87		87	T2: 20–30
						34	T3: ≥30
Vitezova (2015)/64	Cross-sectional (based on Rotterdam Study)	The Netherlands	Both	72.3 ± 7.	3240		
				1	1833	766	<50 nmol/L
					874	286	50–75
					533	158	≥75
Dong (2014)/72	Cross-sectional	China	Both	59.47 ± 14.21	837		<13.5 nmol/L
							13.5–19.3
							>19.3
							10 nmol/L increase
Mitri (2014)/69	Cross-sectional (based on DPP study)	USA	Both	51 ± 10.8	2000		
					666	504	T1: 12.1 (9.7, 14.3)
					667	477	T2: 20.3 (18.3, 22.7)
					666	441	T3: 30.6 (27.5, 34.9)
Chung (2013)/32	Cross-sectional (based on KNHANES 2008–2010)	South Korea	Men	43.5 ± 0.3	7957		
					808	2.3%	≥30 ng/ml
					2854	8.4%	21–29
					4295	12.3%	<20
			Women	45.4 ± 0.3	10,348		
					524	0.9%	≥30 ng/ml
					2532	4%	21–29
					7292	9.2%	<20
Majumdar (2011)/75	Cross-sectional	India	Both	18–75	441		

(Continues)

TABLE 1 (Continued)

First author (year)/ref	Study design	Country/latitude °N	Sex	Age (years)	No. of participants	No MetS	25(OH)D levels, nmol/L
			Men	39.8 ± 13	237	31.8%	<28.2 nmol/L
				0		15.2%	28.2–38.0
						26.1%	38.1–47.0
						28.3%	47.1–57.8
						22.2%	>57.8
			Women	39.7 ± 12	204	28.9%	<25.2 nmol/L
				.7		34.2%	25.2–34.2
						38.5%	34.3–42.9
						26.3%	43.0–53.5
						38.5%	>53.5
Kim (2010)/76	Cross-sectional	Chungju, Korea	Both	65.8	1330		
						56.6%	10.0–29.7 nmol/L
						51.9%	30.0–39.2
						48.5%	39.4–49.4
						42.7%	49.7–61.2
						29.5%	61.4–116.8
Lu (2009)/77	Cross-sectional (based on NHAPC April to June 2005)	Beijing and Shanghai, China	Both	50–70/58	3262		
					652	335	≤28.7 nmol/L
					653	326	28.8–36.8
					652	279	36.9–45.5
					653	248	45.6–57.6
					652	193	≥57.7
Lee (2009)/78	Cross-sectional (based on EMAS)	Italy, Belgium, Poland, Sweden, UK, Spain, Hungary, Estonia	Men	40–79 60.0 ± 11.0	3069		
					617		<35.7 nmol/L
					620		35.7–49.4
					615		49.5–65.1
					610		65.2–85.9
					607		>85.9
Hypponen (2008)/79		UK	Both	44–46	6810		9–45 nmol/L

TABLE 1 (Continued)

First author (year)/ref	Study design	Country/latitude °N	Sex	Age (years)	No. of participants	No MetS	25(OH)D levels, nmol/L
	Cross-Sectional Study in the 1958 British Birth Cohort						46–67
							68–231
Reis (2007)/80	Cross-sectional (based on Rancho Bernardo study, 1997–1999)	USA	Both		1070		
			Men	74.5 ±	410		
				9.5		29.6%	<87.5 nmol/L
						26.7%	87.5–97.4
						22.7%	97.5–110.0
						21.4%	110.1–126.2
						21.8%	≥126.3
			Women	74.6	660	24.4%	<77.5 nmol/L
				±10.7		15.5%	77.5–92.4
						17.2%	92.5–103.7
						20.9%	103.8–119.9
						12.6%	≥120.0
Ford (2005)/44	Cross-sectional (based on NHANES III, 1988–1994)	USA	Both	≥20	8421		
						27.5%	≤48.4 nmol/L
						26.6%	48.5–63.4
						23.3%	63.5–78.1
						18.7%	78.2–96.3
						13.5%	≥96.4

Abbreviations: AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; ATP III, Adult Treatment Panel III; AusDiab, The Australian Diabetes, Obesity and Lifestyle Study; BHAS, Busselton Healthy Ageing Study; CCLS, Cooper Center Longitudinal Study; CLHLS, Chinese Longitudinal Healthy Longevity Survey; CLIA, chemiluminescence immunoassay; DPP, Diabetes Prevention Program; ECLIA, electrochemiluminescent immunoassay; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; EMAS, European Male Ageing Study; HPLC, high-performance liquid chromatography; IA, immunoassay; IDF, International Diabetes Federation; ILAS, I-Lan Longitudinal Aging Study; JIS, Joint Interim Statement; KNHANES, Korean National Health and Nutrition Examination Survey; LC-MS, liquid chromatography and mass spectrometry; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Surveys; NHAPC, Nutrition and Health of Aging Population in China; NIHR, National Institute for Health Research; NORNS, North Korea refugee health in South Korea; NR, not reported; PBA, protein-binding assay; PCOS, polycystic ovary syndrome; PORMETS, Portuguese Metabolic Syndrome; PROMISE, Prospective Metabolism and Islet Cell Evaluation; PURE-SA-NWP, Prospective Urban and Rural Epidemiology—South African North West Province; Ref, References; RIA, radioimmunoassay; SD, standard deviation; SHIP, Study of Health in Pomerania; TLGS, Tehran Lipid and Glucose Study; VHM, Victorian Health Monitor; WHI-CaD, Women's Health Initiative Calcium–Vitamin D.

[a]1, Age; 2, Education level; 3, Household income; 4, Marital status; 5, Residential region; 6, Subjective stress level; 7, Dietary supplement consumption; 8, Smoking status; 9, Alcohol consumption status; 10, Exercise; 11, Sex; 12, Race; 13, Physically active; 14, Body mass index (BMI); 15, Ethnicity; 16, Poverty income ratio; 17, Vitamin D supplementation; 18, Multivitamin supplementation; 19, Fish oil intake; 20, Use of sunscreen; 21, Religion; 22, Exam season; 23, Total serum cholesterol; 24, Low-density lipoprotein cholesterol (LDL); 25, Creatinine; 26, Menopause; 27, Years after menopause; 28, Season of blood sampling; 29, Parathyroid hormone (PTH); 30, Estradiol (E2); 31, Exercise region; 32, Season; 33, NAFLD status; 34, Energy intake; 35, Husband's education; 36, Number of delivery; 37, Wealth score; 38,

(Continues)

TABLE 1 (Continued)

First author (year)/ref	Study design	Country/latitude ° N	Sex	Age (years)	No. of participants	No MetS	25(OH)D levels, nmol/L

Menstruation; 39, OCP use; 40- Lifestyle change; 41, Serum calcium; 42, Omega-3 supplementation; 43, Family history of CVD and diabetes; 44, Urban or rural residence; 45, Living and literacy statuses; 46, Occupation; 47, Nutrition status; 48, Cognitive function; 49, 25(OH)D concentration; 50, Log (osteocalcin); 51, Log (HOMA-IR); 52, hs-CRP; 53, Dietary habit scores; 54, Calcium intake; 55, Hypertension; 56, Diabetes mellitus; 57, Hyperlipidemia; 58, Menopausal status; 59, Reproductive factors; 60- Sleeping pattern; 61, Consumption of fruits, vegetables, dairy, red meat, and whole grains; 62, Family history of DM, heart attack, angina, or cardiometabolic diseases; 63, Health insurance status; 64, Rheumatoid arthritis; 65, Depression; 66, Asthma; 67, Osteoporosis; 68, Postpartum breastfeeding; 69, Last childbearing age; 70, Sleep duration; 71, Sugar consumption; 72, Estimated glomerular filtration rate (eGFR); 73, Total and trunk body fat dual-energy X-ray absorptiometry (DXA); 74, Survey cycle; 75, Lipid and antihyperglycemic medications; 76, Obesity; 77, Carbohydrates, sodium, protein, vitamin C, and fat intake; 78, Metabolic profile; 79, SLE-related variables (age at diagnosis, disease duration, SLEDAI, SDI, CRP, ESR, C3, C4, history of lupus nephritis, glucocorticoid use, current HCQ use, current immunosuppressant use, photoprotection, and vitamin D supplementation); 80, Leisure-time physical activity; 81, Night or rotating shift work; 82, Logarithmic; 83, Country of birth; 84, Body weight; 85, Dietary fiber, Mg, and retinol; 86, Fiber intake; 87, Center; 88, Calcium supplement; 89, Insulin; 90, HOMA-IR; 91, Total cholesterol (TC); 92, High-density lipoprotein cholesterol (HDLC); 93, Fasting blood sugar (FBS); 94, Systolic blood pressure (SBP); 95, Diastolic blood pressure (DBP); 96, Sun exposure; 97, Waist circumference; 98, Triglyceride; 99, Fasting plasma glucose (FPG); 100, Length of residence in South Korea; 101, Waist–hip ratio (WHR); 102, C-reactive protein (CRP); 103, Month of blood sampling; 104, Diet quality score; 105, Year of blood draw; 106, Baseline cardiometabolic diseases; 107, Various confounding factors; 108, Serum phosphorus; 109, Vitamin D intake; 110, Phosphorus intake; 111, Diary intake; 112, Dialysis duration; 113, Albumin; 114, Hemoglobin; 115, Total K_t/V urea; 116, Residual renal function (RRF); 117, Doses of oral vitamin analogs; 118, Use of hormone therapy (HT); 119, Baseline supplement use and change in supplement use; 120, Baseline physical activity and change in physical activity; 121, Ultraviolet radiation index; 122, Blood pressure; 123, Hemoglobin A1c; 124, Ferritin; 125, White blood cell (WBC); 126, Day of blood sampling; 127, HOMA2-IR; 128, Serum cotinine; 129, Healthy Eating Index scores; 130, Case–control status; 131, Visit date; 132, Self-reported CHD and stroke; 133, Interleukin 6 (IL-6); 134, PTH in 25(OH)D analysis and 25(OH)D in PTH analysis; 135, urinary albumin-to-creatinine ratio; 136, Insulin resistance; 137, IGF-I; 138, Hour of measurement.

reported the serum 25(OH)D levels as ranges, midpoint of each category was estimated through the calculating average of the lower and upper bounds. In the case of the open-ended highest category, the length of interval was assumed to be the same as the adjacent interval. In the case of the open-ended lowest category, the lower boundary was considered 0. We applied restricted cubic splines (three knots at fixed percentiles of 10%, 50%, and 90% of the distribution) to assess potential nonlinear dose–response relation between serum vitamin D levels and risk of MetS. Stata Version 14.0 (StataCorp, College Station, TX, USA) was used for statistical analyses. All tests including Cochran's *Q* test were defined significant if they had *P*-values < 0.05.

3 | RESULTS

3.1 | Study characteristics

The characteristics of 43 included studies in the systematic review are presented in Tables 1 and 2. These researches have totally investigated 309,206 participants and were published between 2005 and 2020.[20–23,25,26,31,36,37,42,44–76] Most of these reports had cross-sectional design (n = 38) (including 298,187 individuals), except four cohort studies[22,66,67,70] and one nested case–control[69] with a total of 11,019 participants. Because all included cross-sectional studies used random sampling method, their samples were representative of whole population. Among eligible studies, seven investigations were conducted in China,[45,46,53,59,62,68,73] six in Korea,[21,25,26,31,51,72] five in the United States,[36,37,42,65,76] three in Australia[44,58,70] and Taiwan,[52,54,61] two in Canada,[22,66] England,[60,75] India,[55,71] Iran,[50,69] and Spain,[67,74] and others were performed in Arizona,[64] Finland,[49] Germany,[63] Japan,[20] Portugal,[57] the Netherlands,[23] Qatar,[48] South Africa,[56] and Thailand.[47] Twenty-three of them were reported from Asian countries, and other reports were from non-Asian regions. Twenty-nine investigations were conducted in developed countries, and 14 others were from developing countries. Serum vitamin D status was assessed through the use of different methods, including chemiluminescent immunoassay (CLIA) (n = 13), radioimmunoassay (RIA) (n = 11), electrochemiluminescence immunoassay (ECLIA) (n = 5), enzyme-linked immunosorbent assay (ELISA) (n = 4), immunoassay (IA) (n = 3), enzyme immunoassay (EIA) (n = 3), protein-binding assay (PBA) (n = 1), and chromatography (n = 2); one of the researches did not report the applied method for vitamin D assessment. Different criteria were also applied to define MetS, including the ones proposed by NCEP-ATP III (n = 22), Joint Interim Statement (JIS) (n = 14), International Diabetes Federation (IDF) (n = 6), and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) (n = 1). Only nine studies have conducted stratified analysis by gender for the relation of serum vitamin D and MetS, 27 other publications were considered both genders together in the analysis, and in the remaining studies, just women (n = 6) or men (n = 1) were investigated. The effects of confounders including age and season were, respectively, controlled in 36 and 15 reports. Based on NOS, most cross-sectional (27 of 38)

TABLE 1 (Continued)

First author (year)/ref	OR/RR (95% CI)	Method (exposure)	Definition. Mets	Adjustments[a]	Participants/representative of general population	Quality score
Chun (2020)/26	1.00 (Ref) 1.267 (0.889, 1.805) 1.00 (Ref) 1.263 (1.059 , 1.507)	RIA	NCEP-ATP III	1–10	Premenopausal Postmenopausal/yes	9
Liu (2020)/48	1.00 (Ref) 0.70 (0.52, 0.92) 0.63 (0.45, 0.88) 0.79 (0.69, 0.90)	ELISA	Modified ATP III (2009)	1, 2, 4, 8, 9, 11–14	Elderly Chinese individuals/yes	9
Ganji (2020)/38	2.98 (2.14, 4.16) 2.84 (2.22, 3.64) 1.78 (1.38, 2.31) 1.00 (Ref)	RIA	NCEP-ATP III	1, 7, 12–16	US adults/yes	7
Jeenduang (2020)/49	1.00 (Ref) 1.847 (1.124, 3.035)	ECLIA	NCEP-ATP III	1, 2, 8, 9, 13, 14, 17–20	Thai postmenopausal women/yes	9
Weldegiorgis (2020)/47	1.00 (Ref) 0.93 (0.54–1.59) 0.89 (0.50–1.56) 0.48 (0.28–0.84) 1.00 (Ref) 1.04 (0.66–1.63) 0.71 (0.43–1.16) 0.58 (0.34–0.99)	ECLIA	JIS (2009)	1, 8, 9, 13, 23–25	Middle-aged and elderly Chinese/yes	9
Ganji (2020)/50		NR	IDF	1–3, 26	Women/yes	9

(Continues)

TABLE 1 (Continued)

First author (year)/ref	OR/RR (95% CI)	Method (exposure)	Definition. Mets	Adjustments[a]	Participants/representative of general population	Quality score
	1.92 (1.06, 3.49) 1.76 (0.99, 3.11) 1.79 (1.02, 3.14) 1.00 (Ref)					
Yeap (2020)/46		IA	IDF	-	Adults/yes	8
	4.10 (2.52, 6.68) 2.31 (1.72, 3.11) 1.00 (Ref) 3.46 (2.34, 5.12) 2.11 (1.54, 2.89) 1.00 (Ref)					
Lee (2019)/53		CLIA	NCEP-ATP III	1, 8, 9, 29, 31, 32	Elderly people/yes	10
	2.25 (1.48–3.43) 1.83 (1.22–2.74) 1.51 (1.02–2.24) 1.00 (Ref) 1.65 (1.27–2.16) 1.44 (1.12–1.87) 1.43 (1.11–1.85) 1.00 (Ref)					
Chen (2019)/54	1.77 (1.145, 2.736) 1.673 (1.220, 2.295) 1.00 (Ref)	RIA	NCEP-ATP III	1, 11, 14, 33	Adults/yes	9
Mehri (2019)/52	1.00 (Ref) 0.98 (0.49, 1.94) 1.23 (0.46, 3.32)	ELISA	NCEP-ATP III	1, 2, 4, 13, 17, 18,34–40, 42, 43, 88	Female teachers residing in Yazd city/yes	7
Mutt (2019)/51		EIA	IDF	11, 17, 28	Older subjects/yes	9
	1.65 (1.08–2.53) 1.00 (Ref)					

TABLE 1 (Continued)

First author (year)/ref	OR/RR (95% CI)	Method (exposure)	Definition. Mets	Adjustments[a]	Participants/representative of general population	Quality score
Chen (2019)/55	0.921 (0.888, 0.954)	CLIA	NCEP-ATP III	1, 3, 8, 11, 44	Adults/yes	9
Mogili (2018)/57	1.00 (Ref) 1.41 (0.54, 3.69)	CLIA	AHA/NHLBI	-	Infertile women with polycystic ovarian syndrome/yes	7
Wang (2018)/56	0.98 (0.96–0.99) 1.00 (Ref)	RIA	NCEP-ATP III	1, 8, 9, 11, 13, 14, 45–52	Elderly people/yes	8
Zhang (2018)/39	1.00 (Ref) 1.13 (0.75, 1.7)	Chromatography	NCEP-ATP III	1–4, 12–14, 34, 62–71	Adults/yes	8
Sotunde (2017)/58	1.04 (0.99, 1.10)	ECLIA	JIS (2009)	1, 8, 13, 32, 72	Urban black women/yes	9
Raposo (2017)/59	0.967 (0.930–1.007)	CLIA	JIS (2009)	1, 11, 14	Adults/yes	9
Akter (2017)/21	 1.00 (Ref) 0.79 (0.55–1.15) 0.52 (0.25–1.04) 1.00 (Ref) 0.89 (0.55–1.43) 0.75 (0.46–1.22) 0.61 (0.36–1.01)	PBA	JIS (2009)	1, 8, 9, 11, 13, 14, 54, 80–82	Japanese working/yes	9
Pannu (2017)/60	 1.00 (Ref) 0·77 (0·58, 1·04) 0·35 (0·26, 0·48)	CLIA	JIS (2009)	1–3, 8, 9, 11, 13, 32, 34, 54, 83–86	Nondiabetic adults aged 18–75 years/yes	10
Lally (2016)/62	1.00 (Ref) 2.93 (1.46, 5.89) 3.62 (1.8,7.28) 2.48 (1.22, 5.3)	CLIA	IDF	-	Individuals with established psychotic disorders/yes	6
Chen (2016)/63	 1.423 (1.029, 1.967) 1.247 (0.971, 1.600) 1.00 (Ref)	RIA	NCEP- ATP III	-	Adults/yes	8
Sung (2016)/36		IA	JIS (2009)	1, 2, 8, 9, 13, 32, 74, 87	Adults/yes	10

(Continues)

TABLE 1 (Continued)

First author (year)/ref	OR/RR (95% CI)	Method (exposure)	Definition. Mets	Adjustments[a]	Participants/representative of general population	Quality score
	1.00 (Ref) 0.99 (0.94–1.04) 0.92 (0.87–0.97) 0.81 (0.76–0.86) 1.00 (Ref) 0.97 (0.87–1.08) 0.84 (0.76–0.94) 0.65 (0.58–0.73)					
Pan (2016)/61	1.00 (Ref) 1.43 (0.74, 2.77) 1.85 (0.88,3.91)	CLIA	JIS (2009)	1, 5, 11, 14, 52, 88–90	Middle-aged and elderly patients with type 2 diabetes mellitus/yes	8
Lerchbaum (2015)/67	0.67 (0.57, 0.78) 0.74 (0.62, 0.89)	IA (automated analyzer)	JIS (2009)	1, 8, 13, 14, 58, 72, 103	Participants of SHIP study/yes	10
Kim (2015)/27	1.00 (Ref) 0.90 (0.70–1.15) 0.76 (0.59–0.97) 0.76 (0.59–0.98)	RIA	JIS (2009)	1–3, 5, 8, 9, 11, 13, 14	Middle-aged and older Korean adults/yes	9
Lu (2015)/66	3.137 (1.17, 8.42) 2.317 (0.946, 5.67) 1.178 (0.452, 3.07) 1.00 (Ref)	ECLIA	IDF	1, 11, 14, 24, 92, 94, 95, 98, 99	Adults/yes	9
Bea (2015)/68	1.00 (Ref) 0.70 (0.49–1.00) 0.45 (0.31–0.65) 1.00 (Ref) 0.70 (0.46–1.06)	RIA	ATP-III	1, 11, 12, 15, 88, 101	Colorectal neoplasia patients after adenomas removing/yes	8

TABLE 1 (Continued)

First author (year)/ref	OR/RR (95% CI)	Method (exposure)	Definition. Mets	Adjustments[a]	Participants/representative of general population	Quality score
	0.55 (0.33–0.93)					
Vitezova (2015)/64		CLIA	JIS (2009)	1–3, 8, 11, 13, 28, 62, 104–106	Middle-aged and elderly adults/yes	10
	1.00 (Ref)					
	0.70 (0.58–0.84)					
	0.61 (0.49, 0.77)					
Dong (2014)/72	1.00 (Ref)	ELISA	NCEP-ATP III	1, 11, 14, 41, 102, 108, 112–116	Peritoneal dialysis patients/yes	9
	0.65 (0.35, 1.23)					
	0.66 (0.34, 1.29)					
	0.78 (0.56, 1.07)			1, 11, 41, 102, 108, 112–117		
Mitri (2014)/69		LC-MS	NCEP-ATP III	1, 5, 8, 9, 11–14, 34, 102, 103, 121	Adults at high risk for the disease/yes	10
	1.00 (Ref)					
	0.81 (0.71, 0.93)					
	0.62 (0.45, 0.84)					
Chung (2013)/32		RIA	NCEP-ATP III	1, 8–10, 14, 46, 89, 90–95, 97, 98, 123–125	Adults/yes	9
	1.00 (Ref)					
	1.16 (0.83–1.56)					
	1.45 (1.05–2.02)					
	1.00 (Ref)					
	1.32 (0.44–1.31)					
	1.60 (1.21–2.11)					
Majumdar (2011)/75		EIA	Modified NCEP-ATP III	1, 8, 14	Adult/yes	7
	1.00 (Ref)					
	0.30 (0.10–0.90)					
	0.80 (0.03–2.00)					
	0.90 (0.30–2.30)					
	0.60 (0.20–1.70)					
	1.00 (Ref)					
	1.1 (0.4–3.4)					
	1.1 (0.4–3.4)					
	1.5 (0.5–4.9)					
	1.2 (0.4–3.6)					
Kim (2010)/76		CLIA		1, 8–11, 14, 28, 29, 34, 41, 54, 77, 90	Middle-aged Korean subjects/yes	9

(Continues)

TABLE 1 (Continued)

First author (year)/ref	OR/RR (95% CI)	Method (exposure)	Definition. Mets	Adjustments[a]	Participants/representative of general population	Quality score
	1.00 (Ref) 0.72 (0.47–1.09) 0.72 (0.46–1.12) 0.55 (0.35–0.89) 0.34 (0.21–0.58)		Modified NCEP-ATP III			
Lu (2009)/77	1.52 (1.17–1.98) 1.71 (1.32–2.21) 1.33 (1.03–1.71) 1.28 (1.00–1.64) 1.00 (Ref)	RIA	Modified NCEP-ATP III	1, 2, 5, 8, 9, 11, 13, 43, 102, 131–133	Middle-aged and elderly Chinese individuals/yes	10
Lee (2009)/78	1.00 (Ref) 0.94 (0.62–1.43) 0.78 (0.56–1.08) 0.61 (0.36–1.04) 0.60 (0.47–0.78)	RIA	NCEP-ATP III	1, 5, 8, 9, 13, 29, 32, 134	Middle-aged and older European men/yes	9
Hypponen (2008)/79	1.00 (Ref) 0.58 (0.48–0.72) 0.33 (0.26–0.42)	ELISA	NCEP-ATP III	11, 49, 103, 137	People births in England, Scotland, and Wales during 1 week in March 1958/yes	9
Reis (2007)/80	1.00 (Ref) 0.83 (0.39–1.73) 0.68 (0.32–1.43) 0.65 (0.32–1.34) 0.57 (0.26–1.25) 1.00 (Ref) 0.96 (0.48–1.90) 0.96 (0.51–1.79) 1.33 (0.69–2.57) 0.88 (0.43–1.80)	CLIA	NCEP-ATP III	1, 9, 10, 22, 118	Older adults/yes	10

TABLE 1 (Continued)

First author (year)/ref	OR/RR (95% CI)	Method (exposure)	Definition. Mets	Adjustments[a]	Participants/representative of general population	Quality score
Ford (2005)/44		RIA	NCEP-ATP III	1, 2, 7–9, 11–13, 15, 22, 61, 91, 102, 128	Adult/yes	10
	1.00 (Ref)					
	0.82 (0.60–1.10)					
	0.75 (0.55–1.02)					
	0.60 (0.44–0.83)					
	0.46 (0.32–0.67)					

Abbreviations: AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; ATP III, Adult Treatment Panel III; AusDiab, The Australian Diabetes, Obesity and Lifestyle Study; BHAS, Busselton Healthy Ageing Study; CCLS, Cooper Center Longitudinal Study; CLHLS, Chinese Longitudinal Healthy Longevity Survey; CLIA, chemiluminescence immunoassay; DPP, Diabetes Prevention Program; ECLIA, electrochemiluminescent immunoassay; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; EMAS, European Male Ageing Study; HPLC, high-performance liquid chromatography; IA, immunoassay; IDF, International Diabetes Federation; ILAS, I-Lan Longitudinal Aging Study; JIS, Joint Interim Statement; KNHANES, Korean National Health and Nutrition Examination Survey; LC-MS, liquid chromatography and mass spectrometry; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Surveys; NHAPC, Nutrition and Health of Aging Population in China; NIHR, National Institute for Health Research; NORNS, North Korea refugee health in South Korea; NR, not reported; PBA, protein-binding assay; PCOS, polycystic ovary syndrome; PORMETS, Portuguese Metabolic Syndrome; PROMISE, Prospective Metabolism and Islet Cell Evaluation; PURE-SA-NWP, Prospective Urban and Rural Epidemiology—South African North West Province; Ref, References; RIA, radioimmunoassay; SD, standard deviation; SHIP, Study of Health in Pomerania; TLGS, Tehran Lipid and Glucose Study; VHM, Victorian Health Monitor; WHI-CaD, Women's Health Initiative Calcium–Vitamin D.

[a]1, Age; 2, Education level; 3, Household income; 4, Marital status; 5, Residential region; 6, Subjective stress level; 7, Dietary supplement consumption; 8, Smoking status; 9, Alcohol consumption status; 10, Exercise; 11, Sex; 12, Race; 13, Physically active; 14, Body mass index (BMI); 15, Ethnicity; 16, Poverty income ratio; 17, Vitamin D supplementation; 18, Multivitamin supplementation; 19, Fish oil intake; 20, Use of sunscreen; 21, Religion; 22, Exam season; 23, Total serum cholesterol; 24, Low-density lipoprotein cholesterol (LDL); 25, Creatinine; 26, Menopause; 27, Years after menopause; 28, Season of blood sampling; 29, Parathyroid hormone (PTH); 30, Estradiol (E2); 31, Exercise region; 32, Season; 33, NAFLD status; 34, Energy intake; 35, Husband's education; 36, Number of delivery; 37, Wealth score; 38, Menstruation; 39, OCP use; 40- Lifestyle change; 41, Serum calcium; 42, Omega-3 supplementation; 43, Family history of CVD and diabetes; 44, Urban or rural residence; 45, Living and literacy statuses; 46, Occupation; 47, Nutrition status; 48, Cognitive function; 49, 25(OH)D concentration; 50, Log (osteocalcin); 51, Log (HOMA-IR); 52, hs-CRP; 53, Dietary habit scores; 54, Calcium intake; 55, Hypertension; 56, Diabetes mellitus; 57, Hyperlipidemia; 58, Menopausal status; 59, Reproductive factors; 60- Sleeping pattern; 61, Consumption of fruits, vegetables, dairy, red meat, and whole grains; 62, Family history of DM, heart attack, angina, or cardiometabolic diseases; 63, Health insurance status; 64, Rheumatoid arthritis; 65, Depression; 66, Asthma; 67, Osteoporosis; 68, Postpartum breastfeeding; 69, Last childbearing age; 70, Sleep duration; 71, Sugar consumption; 72, Estimated glomerular filtration rate (eGFR); 73, Total and trunk body fat dual-energy X-ray absorptiometry (DXA); 74, Survey cycle; 75, Lipid and antihyperglycemic medications; 76, Obesity; 77, Carbohydrates, sodium, protein, vitamin C, and fat intake; 78, Metabolic profile; 79, SLE-related variables (age at diagnosis, disease duration, SLEDAI, SDI, CRP, ESR, C3, C4, history of lupus nephritis, glucocorticoid use, current HCQ use, current immunosuppressant use, photoprotection, and vitamin D supplementation); 80, Leisure-time physical activity; 81, Night or rotating shift work; 82, Logarithmic; 83, Country of birth; 84, Body weight; 85, Dietary fiber, Mg, and retinol; 86, Fiber intake; 87, Center; 88, Calcium supplement; 89, Insulin; 90, HOMA-IR; 91, Total cholesterol (TC); 92, High-density lipoprotein cholesterol (HDLC); 93, Fasting blood sugar (FBS); 94, Systolic blood pressure (SBP); 95, Diastolic blood pressure (DBP); 96, Sun exposure; 97, Waist circumference; 98, Triglyceride; 99, Fasting plasma glucose (FPG); 100, Length of residence in South Korea; 101, Waist–hip ratio (WHR); 102, C-reactive protein (CRP); 103, Month of blood sampling; 104, Diet quality score; 105, Year of blood draw; 106, Baseline cardiometabolic diseases; 107, Various confounding factors; 108, Serum phosphorus; 109, Vitamin D intake; 110, Phosphorus intake; 111, Diary intake; 112, Dialysis duration; 113, Albumin; 114, Hemoglobin; 115, Total K_t/V urea; 116, Residual renal function (RRF); 117, Doses of oral vitamin analogs; 118, Use of hormone therapy (HT); 119, Baseline supplement use and change in supplement use; 120, Baseline physical activity and change in physical activity; 121, Ultraviolet radiation index; 122, Blood pressure; 123, Hemoglobin A1c; 124, Ferritin; 125, White blood cell (WBC); 126, Day of blood sampling; 127, HOMA2-IR; 128, Serum cotinine; 129, Healthy Eating Index scores; 130, Case–control status; 131, Visit date; 132, Self-reported CHD and stroke; 133, Interleukin 6 (IL-6); 134, PTH in 25(OH)D analysis and 25(OH)D in PTH analysis; 135, urinary albumin-to-creatinine ratio; 136, Insulin resistance; 137, IGF-I; 138, Hour of measurement.

TABLE 2 Main characteristics of prospective studies examined the association between serum vitamin D levels and metabolic syndrome

First author (year)/ref	Study design/study name	Follow-up (years)/study duration	Country/latitude °N	Sex	Age (years)	No. of participants	No MetS
Pham (2015)/65	Cohort/Preventive Health Program	NR/2007–2014	Canada	Both	52 ± 15	5510	1393
Kayaniyil (2014)/70	Cohort/PROMIS	3 years/2004–2006	Toronto London Ontario Canada	Both	49.18 ± 9.30	301	
Gonzalez-Molero (2014)/71	Cohort/Pizarra study	NR/baseline: 1996–1998 Follow-up: 2002–2004 Follow-up: 2005–2007	Spain	Both	46.28 ± 13.76	1226	
Amirbaigloo (2013)/73	Nested case–control/(based on TLGS)	6.8 years/Phase 1: 1999–2001 Phase 2: 2005–2008	Iran	Both	≥20	648	
				Men		166	87
						124	60
						35	16
				Women		217	105
						27	14
						74	39
Gagnon (2012)/74	Cohort/AusDiab	5 years/baseline: 1999–2000 Follow-up: 2004–2005	Australia	Both	≥25	3334	
						811	108
						829	134
						828	98
						843	103
						853	85

Abbreviations: AusDiab, The Australian Diabetes, Obesity and Lifestyle Study; CLIA, chemiluminescence immunoassay; ECLIA, electrochemiluminescent immunoassay; EIA, enzyme immunoassay; IDF, International Diabetes Federation; JIS, Joint Interim Statement; NR, not reported; PROMISE, Prospective Metabolism and Islet Cell Evaluation; TLGS, Tehran Lipid and Glucose Study.

[a]1, Age; 2, Education level; 3, Residential region; 4, Smoking status; 5, Alcohol consumption status; 6, Sex; 7, Physically active; 8, Body mass index (BMI); 9, Ethnicity; 10, Season; 11, Family history of DM, heart attack, angina, or cardiometabolic diseases; 12, Estimated glomerular filtration rate (eGFR); 13, Logarithmic; 14, HOMA-IR; 15, Waist circumference; 16, Triglyceride; 17, Fasting plasma glucose (FPG); 18, Baseline supplement use and change in supplement use; 19, Baseline physical activity and change in physical activity; 20, Blood pressure; 21, HOMA2-IR.

TABLE 2 (Continued)

First author (year)/ref	25(OH)D levels, nmol/L	OR/RR (95% CI)	Method (exposure)	Definition. Mets	Adjustments[a]	Participants/representative of general population	Quality score
Pham (2015)/65	<50	1.00 (Ref)	CLIA	JIS (2009)	1, 4–7, 10	Adults/no	8
	50–<75	0.78 (0.60–1.01)					
	<75–100	0.49 (0.37–0.64)					
	<100–125	0.37 (0.27–0.52)					
	≥125	0.24 (0.16–0.34)					
Kayaniyil (2014)/70	Per SD increase in 25(OH)D	0.63 (0.44, 0.90)	CLIA	JIS (2009)	1, 6, 9, 10, 14, 18, 19	Nondiabetic individuals with preexisting MetS risk factors/no	6
Gonzalez-Molero (2014)/71	≥20 ng/ml	1.00 (Ref)	ECLIA	IDF	1, 6	Participants of cohort study in Spain/yes	8
	< 20 ng/ml	0.99 (0.57, 1.7)					
Amirbaigloo (2013)/73			EIA	JIS (2009)	4, 8, 13, 15–17, 20	Adult (≥20 years old)/yes	7
	<20 ng/ml	0.62 (0.23–1.64)					
	20–20.99	0.53 (0.20–1.42)					
	>30	1.00 (Ref)					
	<20	0.87 (0.42–1.81)					
	20–20.99	0.88 (0.28–2.72)					
	>30	1.00 (Ref)					
Gagnon (2012)/74			CLIA	JIS (2009)	1–4, 6, 7, 9–12, 21	Adult/yes	8
	<18 ng/ml	1.15 (0.80–1.67)					
	18–23	1.47 (1.04–2.09)					
	24–27	1.10 (0.77–1.57)					
	28–33	1.13 (0.79–1.61)					
	34–93	1.00 (Ref)					

Abbreviations: AusDiab, The Australian Diabetes, Obesity and Lifestyle Study; CLIA, chemiluminescence immunoassay; ECLIA, electrochemiluminescent immunoassay; EIA, enzyme immunoassay; IDF, International Diabetes Federation; JIS, Joint Interim Statement; NR, not reported; PROMISE, Prospective Metabolism and Islet Cell Evaluation; TLGS, Tehran Lipid and Glucose Study.

[a]1, Age; 2, Education level; 3, Residential region; 4, Smoking status; 5, Alcohol consumption status; 6, Sex; 7, Physically active; 8, Body mass index (BMI); 9, Ethnicity; 10, Season; 11, Family history of DM, heart attack, angina, or cardiometabolic diseases; 12, Estimated glomerular filtration rate (eGFR); 13, Logarithmic; 14, HOMA-IR; 15, Waist circumference; 16, Triglyceride; 17, Fasting plasma glucose (FPG); 18, Baseline supplement use and change in supplement use; 19, Baseline physical activity and change in physical activity; 20, Blood pressure; 21, HOMA2-IR.

and cohort studies (three of five) were categorized as high-quality studies.

3.2 | Findings from meta-analysis of highest versus lowest serum vitamin D levels and MetS in cross-sectional studies with representative populations

Combining 41 effect sizes extracted from 38 studies, which included 298,187 individuals, revealed that the highest level of serum vitamin D, compared with the lowest level, was significantly related to 43% decreased risk of MetS (OR: 0.57; 95% CI: 0.51–0.65) (Figure 2); however, between-study heterogeneity was high (I^2 = 91.9%, P < 0.001). To explain the source of heterogeneity, subgroup analysis was conducted based on development status of countries. Highest versus lowest blood vitamin D level was significantly associated with lower odds of MetS by 43% in developed countries (OR: 0.57; 95% CI: 0.49–0.65) and 40% in developing countries (OR: 0.60; 95% CI: 0.52–0.70) (Figure 2) ($P_{\text{heterogeneity between subgroups}}$ < 0.001). Although heterogeneity was completely removed in developing countries (I^2 = 0.0%, P = 0.951), it was still significant in developed countries (I^2 = 94.1%, P < 0.001). So, subgroup analysis was conducted based on several other confounders (including adjustment for age and season, study location, methods of MetS and serum vitamin D assessment, categories of serum vitamin D used for comparison, health status of subjects, and quality of studies), and the results are presented in Table 3. In almost all subgroups, higher serum vitamin D value was protectively associated with lower odds of MetS, although

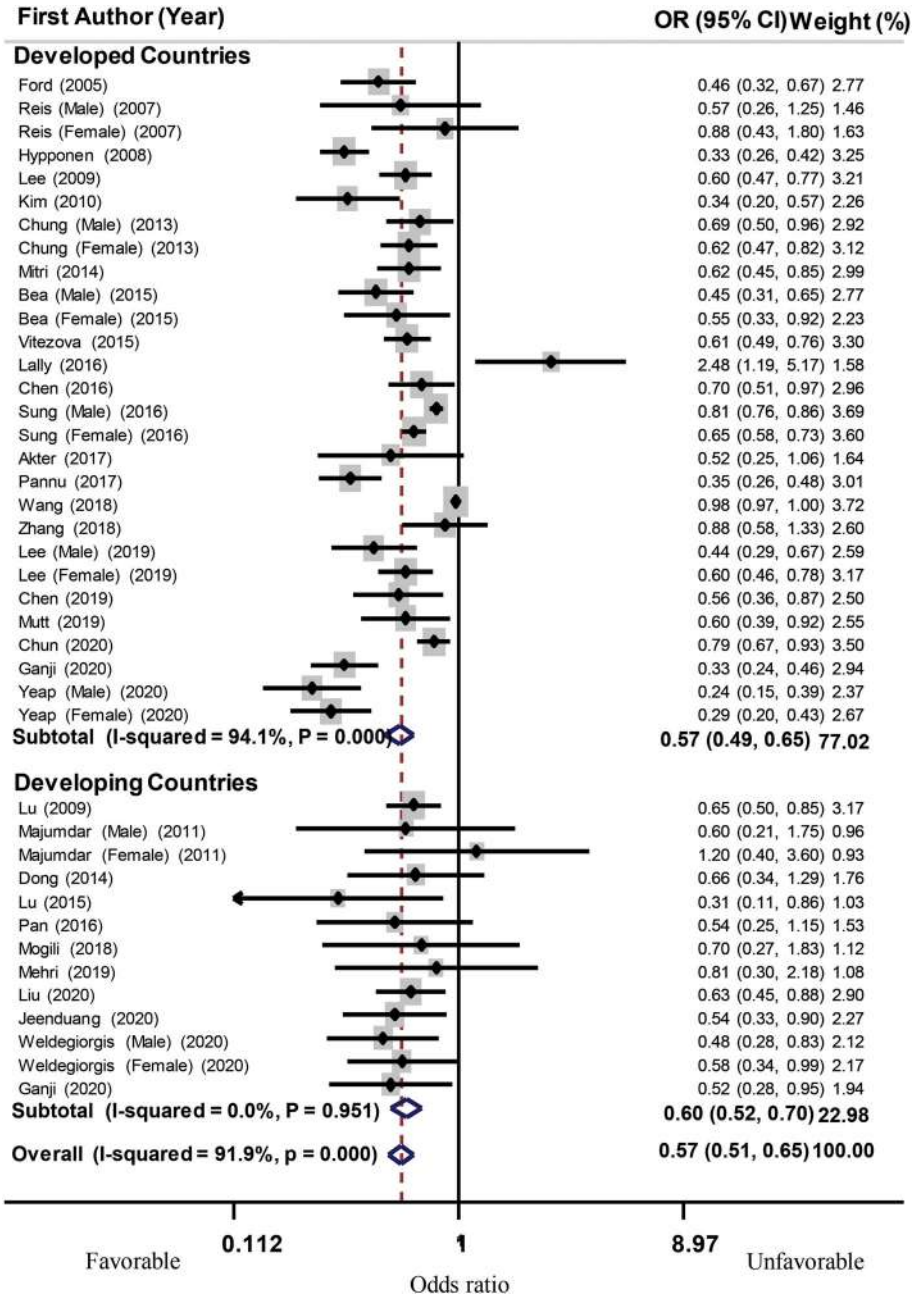

FIGURE 2 Forest plots of the association of the highest versus the lowest level of serum vitamin D and metabolic syndrome in cross-sectional studies with representative adult populations, stratified by developmental status of countries

TABLE 3 Results of subgroup analyses of serum vitamin D levels in relation to metabolic syndrome in cross-sectional studies with representative adult populations

	No. of effect sizes	OR (95% CI)	*P* within[a]	I^2 (%)	*P* between[b]
Overall	41	0.57 (0.51, 0.65)	<0.001	91.9	
Gender					<0.001
Male	9	0.53 (0.40, 0.69)	<0.001	83.2	
Female	13	0.61 (0.52, 0.71)	0.011	53.7	
Both	19	0.57 (0.45, 0.73)	<0.001	93.2	
Adjustment for season					<0.001
Yes	14	0.54 (0.45, 0.64)	<0.001	87.4	
No	27	0.60 (0.50, 0.71)	<0.001	88	
Adjustment for age					<0.001
Yes	34	0.59 (0.52, 0.67)	<0.001	90.3	
No	7	0.52 (0.33, 0.83)	<0.001	87.5	
Health status of participants					<0.001
Healthy	32	0.57 (0.50, 0.65)	<0.001	92.5	
Unhealthy	9	0.61 (0.45, 0.81)	0.001	70.7	
Asian vs. non-Asian countries					<0.001
Asian	25	0.64 (0.57, 0.72)	<0.001	87.6	
Non-Asian	16	0.51 (0.41, 0.62)	<0.001	79.9	
Developed vs. developing countries					<0.001
Developed	28	0.57 (0.49, 0.65)	<0.001	94.1	
Developing	13	0.60 (0.52, 0.70)	0.951	0.0	
Quality score[c]					<0.001
Low quality (scores < median of 9)	14	0.61 (0.43, 0.86)	<0.001	91.2	
High quality (scores ≥ median of 9)	27	0.57 (0.51, 0.64)	<0.001	77.4	
Methods of vitamin D measurement					<0.001
CLIA and ECLIA	14	0.55 (0.45, 0.68)	0.001	61.2	
RIA	12	0.60 (0.49, 0.75)	<0.001	91.8	
Other assay	12	0.53 (0.41, 0.67)	<0.001	89.1	
Chromatography	2	0.72 (0.51, 1.01)	0.186	42.8	
NR	1	0.52 (0.28, 0.95)	0.0	0.0	
Methods of metabolic syndrome definition					<0.001
NCEP-ATP	26	0.59 (0.50, 0.71)	<0.001	90.9	
JIS	8	0.58 (0.47, 0.71)	<0.001	83.9	
IDF	6	0.50 (0.27, 0.90)	<0.001	85.5	
AHA/NHLBI	1	0.70 (0.27, 1.83)	0.0	0.0	
Vitamin D categories					<0.001
Q_5 vs. Q_1	8	0.57 (0.47, 0.69)	0.217	26.5	
Q_4 vs. Q_1	9	0.60 (0.48, 0.75)	<0.001	86.7	
T_3 vs. T_1	7	0.46 (0.36, 0.58)	0.024	58.7	
Sufficiency vs. deficiency	17	0.60 (0.49, 0.73)	<0.001	88.7	

Abbreviations: AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; AHA/NHLBI, American Heart Association/National Heart; CLIA, chemiluminescent immunoassay; EIA, enzyme immunoassay; ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; IA, immunoassay; IDF, International Diabetes Federation; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; PBA, protein-binding assay; RIA, radioimmunoassay.

[a]*P* for heterogeneity within subgroup.

[b]*P* for heterogeneity between subgroups.

[c]Quality scores were according to Newcastle–Ottawa Scale.

heterogeneity was not completely removed in some of these subgroups. Meta-regression was also conducted and showed that latitude (β = −0.0034, P = 0.589, $I^2_{residual}$ = 82.56%), longitude (β = −0.0014, P = 0.323, $I^2_{residual}$ = 91.13%), mean age of participants (β = −0.0023, P = 0.646, $I^2_{residual}$ = 87.63%), and quality score of studies (β = −0.0381, P = 0.553, $I^2_{residual}$ = 88.03%) did not significantly contribute to the pooled OR and 95% CI. A slight asymmetry was seen in funnel plot, and findings from the Begg's test (P < 0.001) and Egger's test (P < 0.001) rejected the null hypothesis about publication bias (Figure S1). When trim and fill was applied filling added no study to the funnel plot, indicating a low degree of asymmetry and no change in the overall effect.

3.3 | Findings from dose–response meta-analysis of serum vitamin D levels and MetS in cross-sectional studies with representative populations

Linear dose–response analysis of 23 studies (including 222,175 healthy individuals and 39,308 MetS patients)[20,21,23,26,31,36,42,44,46–49,53,56–58,61–63,71–73,76] revealed that each 25 nmol/L increase in serum vitamin D levels was significantly associated with a 15% decreased odds of MetS (OR: 0.85; 95% CI: 0.80–0.91) (Figure 3). Nonlinear dose–response was also conducted on 17 studies[20,21,23,26,31,36,42,44,46,48,58,61,62,71–73,76] (including 211,746 healthy subjects and 34,730 MetS patients). Although a steeper

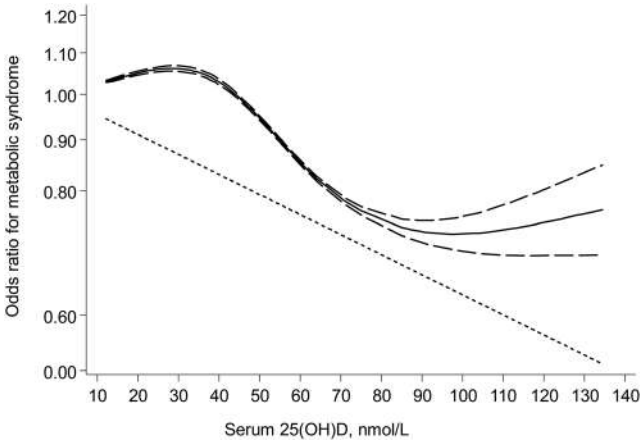

FIGURE 4 Nonlinear dose–response association between serum vitamin D levels and metabolic syndrome in cross-sectional studies with representative adult populations. - - -, linear model; ____, spline model

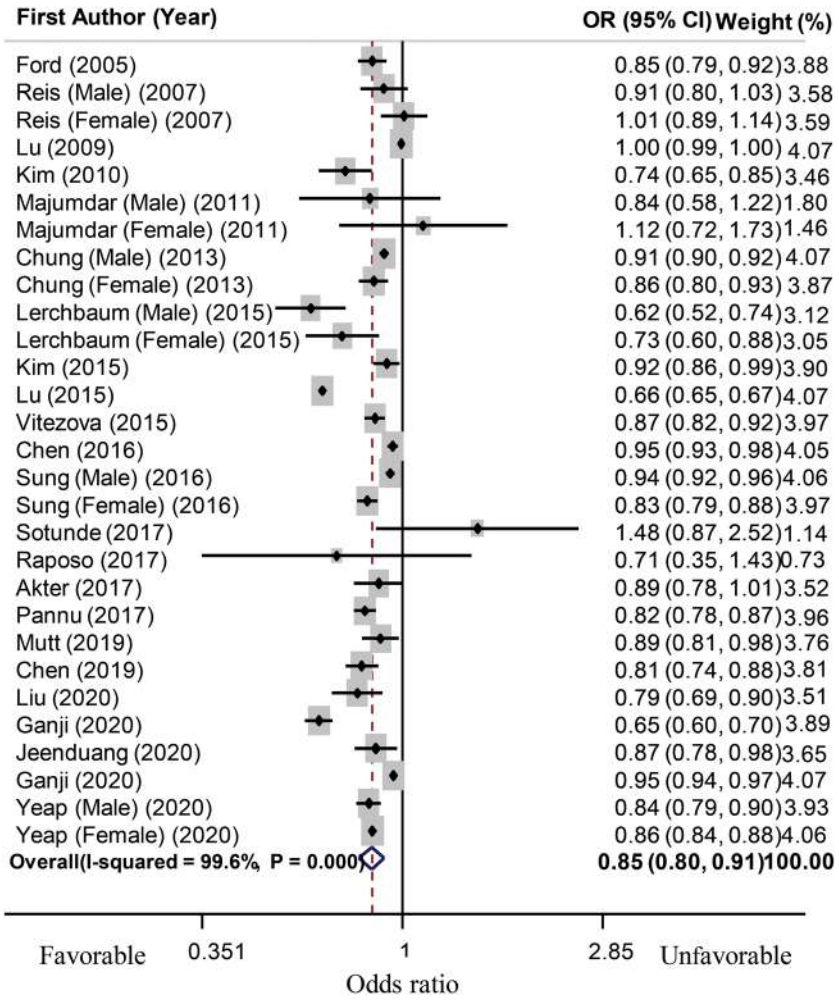

FIGURE 3 Forest plots of linear dose–response meta-analysis of the association between each 25 nmol/L increment in serum 25(OH)D levels and metabolic syndrome in cross-sectional studies with representative adult populations

reduction in odds of MetS was seen when serum vitamin D levels increased from 30 to 75 nmol/L, no significant nonlinear association between serum vitamin D levels and MetS was found ($P_{nonlinearity}$ = 0.87) (Figure 4).

3.4 | Findings from meta-analysis of highest versus lowest serum vitamin D levels and MetS in prospective studies

Five publications including four cohorts and one nested case–control study, which investigated 11,019 participants, were included in this analysis. Meta-analysis of prospective studies revealed no significant relation between 25(OH)D concentrations and MetS (RR: 0.70; 95% CI: 0.37–1.32) (Figure 5). Between-study heterogeneity was high (I^2 = 86.9%, P < 0.001). Stratified analysis by representativeness of populations was conducted (Figure 5). Heterogeneity was completely removed in either representative (I^2 = 0.0%, P = 0.66) or non-representative (I^2 = 0.0%, P = 0.36) studies. Highest versus lowest serum 25(OH)D was related to a 74% decreased risk of MetS in studies with nonrepresentative populations (RR: 0.26; 95% CI: 0.18–0.36); but no significant relation was found among representative populations (RR: 0.99; 95% CI: 0.75–1.30). Although a slight visual asymmetry was observed in funnel plot, findings from the Begg's test (P = 0.57) and Egger's test (P = 0.42) did not reject the null hypothesis about publication bias (Figure S2).

4 | DISCUSSION

This meta-analysis illustrated that the highest level of blood vitamin D in comparison with the lowest level was significantly linked to lower odds of MetS in cross-sectional studies on adult population. This inverse significant relation between blood vitamin D concentration and MetS was also revealed in almost all subgroups. In addition, based on dose–response analysis, each 25 nmol/L (or 10 ng/ml) increment in 25(OH)D was associated with 15% decreased chance of MetS. However, a small number of cohort studies did not confirm a significant linkage.

MetS is a combination of abdominal obesity, abnormal glycemic, and lipid profiles with blood pressure abnormality.[80] Previous studies indicated that people with MetS have higher risk of cardiovascular morbidity and mortality,[81] nonalcoholic fatty liver, steatohepatitis,[82] progression of diabetic nephropathy,[83] stroke,[84] Alzheimer,[85] and cancers.[86] We illustrated that subjects with lower circulating 25(OH)D levels have higher risk of MetS; so, this point could be clinically recommended to persons to keep their serum vitamin D levels in normal ranges in a hope to decrease the risk of MetS.

The relationship between circulating 25(OH)D levels and NCDs and mortality was investigated in several previous meta-analyses. Similar to our study, Ju et al.[87] conducted a meta-analysis on 16 cross-sectional and two cohort studies published until 2013 and found a linear inverse association between 25(OH)D levels and MetS; however, considering the low number of effect sizes in this meta-analysis (n = 3), they could not find a significant relation in women. Furthermore, representativeness of study samples has not been considered in the mentioned meta-analysis; so, the results could not be generalizable to whole adult population. The current meta-analysis with sufficient number of effect sizes included a large population of adults and documented significant associations in both men and women. Also, our findings could be generalized to adult populations, because we included only studies that used random sampling method to select their community. In line with our findings, other meta-analyses of epidemiologic studies indicated inverse relations between serum vitamin

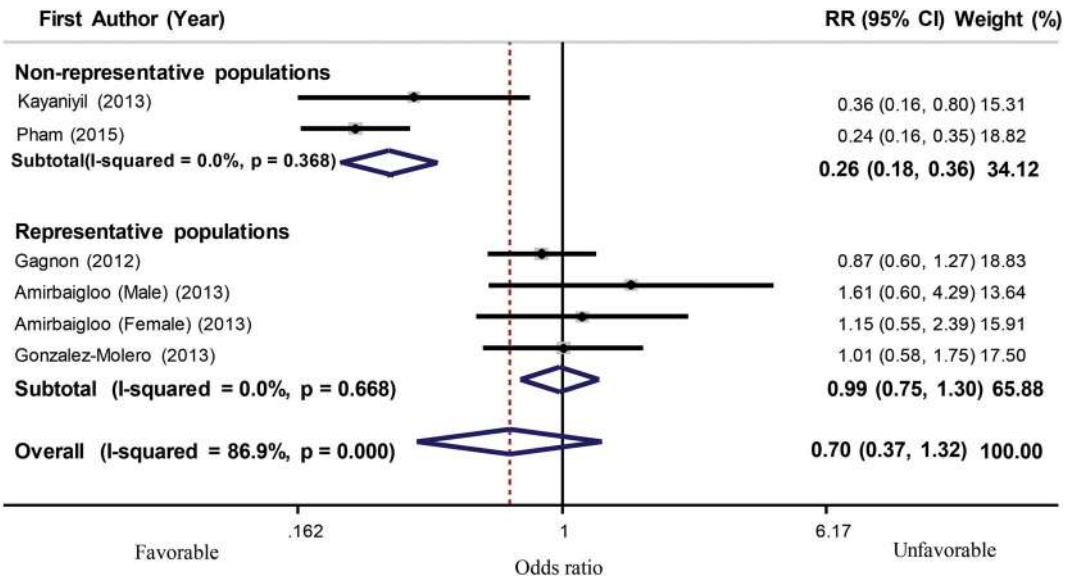

FIGURE 5 Forest plots of the association of the highest versus the lowest level of serum vitamin D and metabolic syndrome in prospective studies, stratified by representativeness of populations

D concentrations and body mass index (BMI),[88] gestational diabetes mellitus (GDM),[89] hypertension,[90] CVDs, T2DM,[91] breast cancer,[92] and all-cause mortality.[93] However, further prospective studies and meta-analyses of randomized clinical trials are needed to confirm the causal relation between vitamin D status or vitamin D supplementation and incidence of NCDs or mortality.

Various underlying mechanisms have been suggested for the association of serum vitamin D with MetS and its components. Firstly, there is an inverse significant relation between blood vitamin D concentration and abdominal obesity.[94] As the vitamin D is a fat-soluble vitamin, it tends to be stored in adipose tissues; so, its bioavailability and circulating levels are lower in those with abdominal obesity. Moreover, the vitamin D synthesis in liver of obese individuals is lower than others.[95] Secondly, considering the crucial role of vitamin D in expression of insulin receptors and increasing insulin responsiveness for glucose transporters (GLUTs), serum vitamin D deficiency involves in incidence of insulin resistance and type 2 diabetes.[96] Thirdly, vitamin D has a key role in expression of lipoprotein lipase (LPL) in muscle and adipose tissues. Through the clearance of lipoproteins and modifying lipid profiles, LPL attempts to decrease serum TG and increase serum HDL; therefore, serum vitamin D deficiency increases risk of dyslipidemia.[97,98] Fourthly, vitamin D has known as antihypertensive agent because of its direct effect on vascular cells, suppression of the renin–angiotensin–aldosterone system, calcium metabolism, and prevention of secondary hyperparathyroidism.[99] Parathyroid hormone (PTH) also involves in process of lipogenesis; therefore, vitamin D deficiency indirectly involves in lipogenesis.

As we know, this is the first meta-analysis that examined the relation of serum vitamin D levels with MetS in a representative population of adults; so, the findings could be generalizable to whole population. Moreover, a large population was included in the analysis, and subgroup analyses were applied based on several confounders. Furthermore, through dose–response analysis, we revealed an inverse linear relation between serum vitamin D levels and MetS. Nevertheless, some limitations to our study should be addressed. The design of most included studies was cross-sectional, and further prospective studies are needed to confirm the causality of this relationship. In some included studies, the relation of circulating 25(OH)D with MetS was not separately reported in men and women. In addition, included studies have used different methods to assess serum vitamin D status and MetS. In addition, the prevalence of MetS in developed countries might be higher than developing communities, due to technology development and sedentary lifestyle. These restrictions might increase between-study heterogeneity that did not been completely eliminated, even after subgroup analysis and meta-regression.

In conclusion, this meta-analysis indicated an inverse association between serum vitamin D concentrations and risk of MetS in general adult populations in cross-sectional studies in a dose–response manner. However, no significant association was found in a small number of cohorts. More prospective studies are needed to confirm the causality of this relationship.

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CONFLICT OF INTEREST

The authors declared no personal or financial conflicts of interest.

AUTHOR CONTRIBUTIONS

ZH, FS, EM, FM, and PS contributed in conception, design, statistical analyses, data interpretation, and manuscript drafting. All authors approved the final manuscript for submission.

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SUPPORTING INFORMATION

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