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The beneficial effects of curcumin supplementation on blood lipid levels among patients with metabolic related diseases in Asia area: a systematic review and meta-analysis of randomized controlled trials

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Objective: Published studies suggest that the effects of curcumin on blood lipids in adults are controversial, and it is unclear whether there is a dose response to lipid changes following curcumin supplementation. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effects of curcumin on triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL) in the Asian populations with metabolic diseases.

Methods: We systematically searched four electronic databases, including Web of Science, PubMed, Google Scholar, and Cochrane Library, for randomized controlled trials (RCTs) of the effects of curcumin on TG, TC, LDL, and HDL in the Asian populations with metabolic diseases. Mean difference (MD) indicates effect size with combined 95% confidence interval (95% CI). Heterogeneity among studies was assessed by I^2 . Subgroup analyses were performed to explore potential sources of heterogeneity.

Results: Evidence from 23 RCTs for TG, 21 RCTs for TC and LDL, and 22 RCTs for HDL showed that curcumin supplementation significantly reduced TG (MD: -18.07 mg/dL, 95% CI: $-30.30, -5.85$, $P < 0.01$), TC (MD: -13.29 mg/dL, 95% CI: $-20.43, -6.16$, $P < 0.01$), and LDL (MD: -10.44 mg/dL, 95% CI: $-16.87, -4.00$, $P < 0.01$), but no effect on HDL (MD: 1.66 mg/dL, 95% CI: $-0.13, 3.44$, $P = 0.07$). In the non-linear dose-response analysis, we observed a significant effect of curcumin supplementation dose on TG levels (P -non-linearity = 0.022).

Conclusion: In conclusion, curcumin may be beneficial in reducing TG, TC, and LDL levels in the Asian populations with metabolic diseases. The dose of curcumin intervention may be an underlying factor influencing TG levels.

KEYWORDS

blood lipid, curcumin, dose-response analysis, metabolic related diseases, meta-analysis

Introduction

Dyslipidaemia manifests clinically as abnormally high blood lipid concentrations, particularly elevated triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL). In recent years, metabolic diseases have become the largest burden of non-communicable diseases worldwide due to their rapidly increasing prevalence (GBD 2017 Causes of Death Collaborators, 2017). Metabolic diseases include those associated with type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), hyperlipidaemia, obesity, overweight, and non-alcoholic fatty liver disease (NAFLD) (Rothschild et al., 2014).

Research suggests that patients with metabolic diseases are at increased risk of developing dyslipidaemia; for example, the prevalence of dyslipidaemia is higher in patients with T2DM than in the healthy population, and children and adolescents who are overweight or obese are more likely to develop dyslipidaemia and MetS (Rašlová, 2016; Reuter et al., 2016). In addition, dyslipidaemia is a major risk factor for cardiovascular disease (Haghighatdoost and Hariri, 2018; Cao et al., 2022b). Due to the side effects of chemical drugs, many patients prefer to use foods with medicinal value for prevention and treatment (Houston et al., 2009). Since ancient times, traditional medicinal foods have played an important role in the prevention and treatment of metabolic diseases. Turmeric, a natural spice that can be made into condiments such as curry paste and mustard, is widely used in cooking and is particularly popular among Asian people (Kochhar, 2008). Curcumin (diferuloylmethane), an antioxidant polyphenol with anti-inflammatory properties, is extracted from the rhizome of turmeric (*Curcuma longa*). Numerous studies have shown that curcumin has a variety of pharmacological activities, including antibacterial, antitumour, anti-inflammatory, antioxidant, anticoagulant, and is particularly prominent in improving metabolic diseases (Asai and Miyazawa, 2001; Ejaz et al., 2009).

Curcumin has been reported to promote weight loss, improve hyperlipidaemia, and reduce hepatic steatosis (Menon and Sudheer, 2007; Ak and Gülçin, 2008). In addition, curcumin has been shown to have therapeutic effects on various diabetic complications such as nephropathy and cardiovascular disease in patients with type 2 diabetes (Jeenger et al., 2015). A meta-analysis showed that curcumin supplementation also significantly reduced levels of inflammatory markers and biomarkers of oxidative stress in patients with MetS (Sun et al., 2022). Second, the potential mechanisms by which curcumin improves obesity and lowers blood lipids have received increasing attention. For example, curcumin blocks preadipocyte differentiation *in vitro* (Sakuma et al., 2017) and inhibits the expression of inflammatory cytokines in TNF α -stimulated adipocytes (Gonzales and Orlando, 2008).

Curcumin also inhibits 3T3-L1 adipocyte differentiation and promotes preadipocyte apoptosis (Wu et al., 2019).

Although many studies have reported the positive effects of curcumin on lipid levels, the results have been inconsistent. Curcumin has been reported to significantly affect TG, TC, LDL, and HDL levels (Anand et al., 2007; Chong et al., 2014; Lopresti et al., 2015). However, some studies have reported an insignificant hypolipidaemic effect of curcumin (Shehzad et al., 2011; Rivera-Mancía et al., 2015). Two existing meta-analyses have reached different conclusions regarding the effects of curcumin on blood lipids (Sahebkar, 2014; Qin et al., 2017). A systematic review of seven randomized trials of turmeric and curcumin in patients with cardiovascular disease found a beneficial effect on TG and LDL levels, but no effect on TC and HDL (Qin et al., 2017). Sahebkar et al. pooled five trials and found no significant improvement in TC, LDL, TG, and HDL levels with curcumin supplementation (Sahebkar, 2014). Furthermore, the relationship between the dose of curcumin supplementation and blood lipids is unclear.

Given that turmeric is a popular spice in Asia and that its major constituent, curcumin, has the potential to modulate dyslipidemia, we synthesized and updated studies from the past 10 years to assess the effects of curcumin on dyslipidemia in Asian populations with metabolic disorders and added a dose-response relationship to provide a more comprehensive view of the effects of curcumin on lipid modulation in Asian populations.

Methods

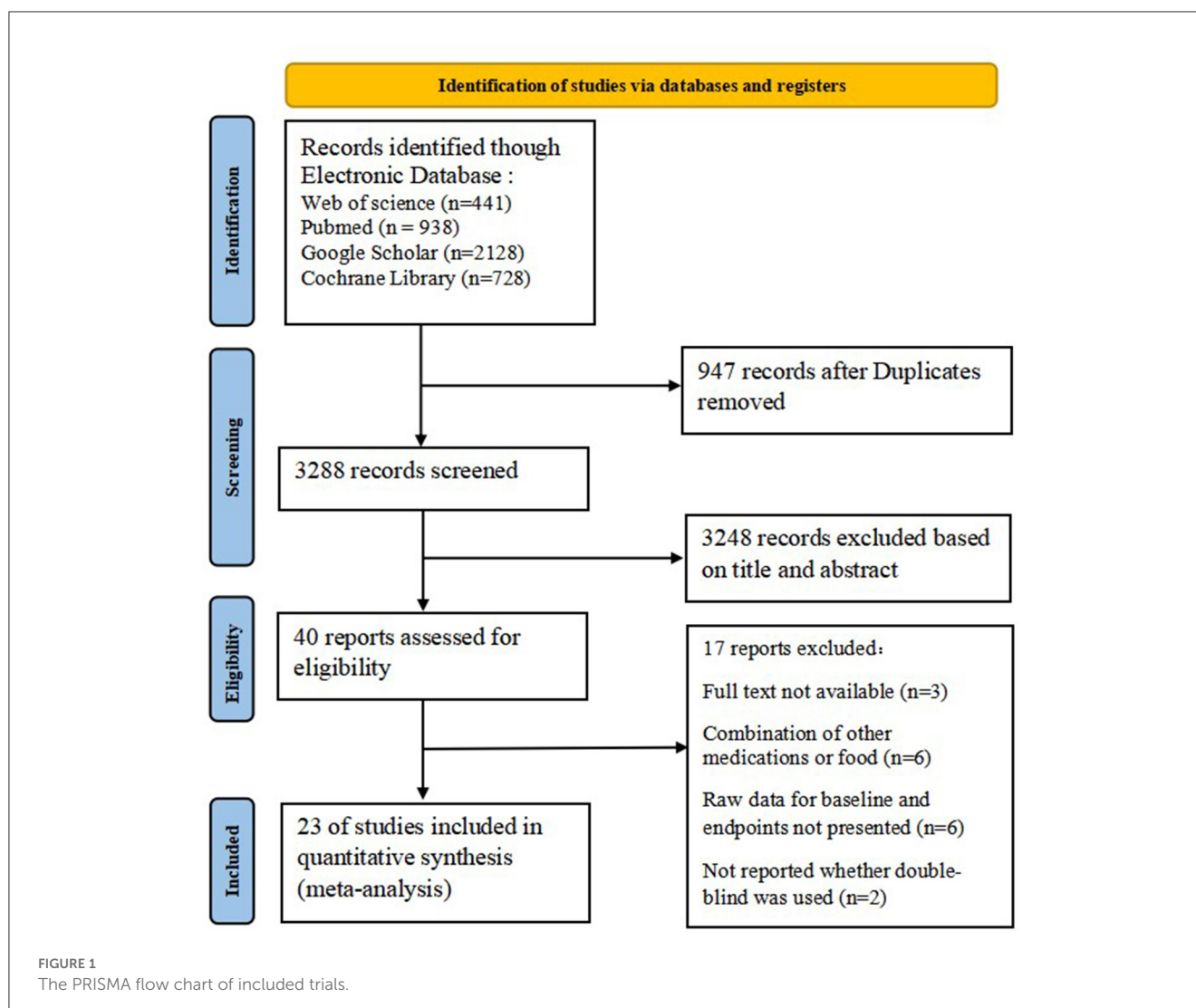
The study was designed in accordance with the guidelines for preferred reporting methods in the PRISMA (Prevention of Systematic Evaluation and Meta-analysis) statement for 2020.

Literature search strategy

We identified articles published between 30 October 2011 and 1 April 2023 by systematically searching four electronic databases: Web of Science, PubMed, Google Scholar, and the Cochrane Library. The language was restricted to English. The literature was searched using the terms in the title or abstract and MeSH. The representative search strategy was as follows: “(curcumin OR curcuminoid OR curcuminoids OR *Curcuma* OR *Curcuma longa* OR turmeric OR *C. longa* OR *Curcuma domestica*) AND (hyperlipidemia OR lipid metabolism OR dyslipidemia OR hypercholesterolemia OR hypertriglyceridemia OR triglycerides OR TG OR total cholesterol OR TC OR low-density lipoprotein cholesterol OR LDL OR high-density lipoprotein cholesterol OR HDL) AND (Clinical Trial [ptyp] AND Humans [MeSH] AND Clinical Trial [ptyp] Sort by: Best Match).”

Second, we also identified any studies that might have been missed by hand searching, and also reviewing the reference lists of each systematic review and meta-analysis. If original data were not available, the corresponding author was contacted by e-mail to obtain. The protocol for this review was pre-registered in the PROSPERO database (International Prospective Register of Systematic Reviews; registration number: CRD42022377635; www.crd.york.ac.uk/PROSPERO).

Abbreviations: Triglyceride, TG; Total cholesterol, TC; Low-density lipoprotein cholesterol, LDL; High-density lipoprotein cholesterol, HDL; Randomized controlled trials, RCTs; Mean difference, MD; Metabolic syndrome, MetS; Type 2 diabetes mellitus, T2DM; Non-alcoholic fatty liver disease, NAFLD.



Inclusion criteria

After extensive reading, studies were selected if they met the following inclusion criteria. Inclusion criteria included: (1) The study was conducted in the Asian population; (2) The study design was a randomized controlled trial; (3) Curcumin was the only intervention, no other food or supplement was used in the intervention and placebo groups, and the duration of intervention was ≥ 4 weeks; (4) All subjects were adults (≥ 18 years) with metabolic disorders (e.g., T2DM, dyslipidaemia, overweight, obesity, Mets, or NAFLD), no primary malignancy, and no primary systemic disease (e.g., lupus erythematosus); (5) All data are available from original study, including baseline and endpoint values with mean, SD or SE, number of participants (n) in the intervention and placebo groups; baseline values are not significantly different between the intervention and placebo groups. All studies reported at least one of the outcomes TG, TC, LDL, HDL.

Original studies were excluded if they met one or more of the following criteria: single-arm, open-label or other studies of uncontrolled quality; use of an intervention with a control group;

no placebo group; presence of other lifestyle changes such as physical activity; studies on animals or cells; insufficient data; or duplicate published studies.

Data collection

The original study screening and data extraction were performed independently by two authors (ZD and KY), and any disputes were resolved in consultation with a third author (XC). The following raw data were extracted and recorded, including study characteristics, sample characteristics, intervention type, and biochemical indicators. Detailed information included: (1) Study characteristics: first author, year of publication, country, and study design; (2) Sample characteristics: subject age, male/female ratio, sample size per group; (3) Intervention dose (mg/d) and intervention duration (weeks); (4) Baseline and endpoint values for TG, TC, LDL, and HDL in the intervention and placebo groups, expressed as mean \pm SD. According to the Cochrane Handbook for Systematic Reviews, if a trial included different intervention doses and durations, we split it into separate trials with the same placebo

TABLE 1 The characteristics for all included trials.

First author	Year	Study region	Participant diseases	Sample size (curcumin/placebo)	Duration	Curcumin dose (mg/d)	Ref
Pashine	2012	India	Hyperlipidemic	48/39	13 weeks	1,400	Pashine et al., 2012
Na	2013	China	T2DM	48/50	12 weeks	300	Na et al., 2013
Chuengsamarn	2014	Thailand	T2DM	107/106	24 weeks	1,500	Chuengsamarn et al., 2014
Yang	2014	China, Taiwan	MetS	30/29	12 weeks	1,890	Yang et al., 2014
Amin	2015	Pakistan	MetS	56/52	8 weeks	2,400	Amin et al., 2015
Mirhafez	2019	Iran	NAFLD	32/27	12 weeks	250	Mirhafez et al., 2019
Rahimi	2016	Iran	T2DM	35/35	12 weeks	80	Rahimi et al., 2016
Rahmani	2016	Iran	NAFLD	40/40	8 weeks	500	Rahmani et al., 2016
Adab	2019	Iran	T2DM	39/36	8 weeks	2,100	Adab et al., 2019
Adibian	2019	Iran	T2DM	21/23	10 weeks	1,500	Adibian et al., 2019
Chashmnam	2019	Iran	NAFLD	25/20	8 weeks	250	Chashmnam et al., 2019
Funamoto	2019	Japan	T2DM	15/17	24 weeks	90	Funamoto et al., 2019
Mirhafez	2019	Iran	NAFLD	32/27	12 weeks	250	Mirhafez et al., 2019
Jazayeri	2019	Iran	NAFLD	42/42	12 weeks	80	Jazayeri-Tehrani et al., 2019
Saadati	2019	Iran	NAFLD	27/23	12 weeks	1500	Saadati et al., 2019
Sohaei	2019	Iran	PCOS	27/24	6 weeks	1,000	Sohaei et al., 2019
Vanaie	2019	Iran	T2DM	27/19	16 weeks	1,500	Vanaie et al., 2019
Husain	2020	Iran	NAFLD	32/32	8 weeks	2,000	Husain et al., 2020
Jamilian	2020	Iran	PCOS	24/26	12 weeks	500	Jamilian et al., 2020
Shafabakhsh	2020	Iran	T2DM	26/27	12 weeks	80	Shafabakhsh et al., 2020
Osali	2020	Iran	MetS	11/11	6 weeks	80	Osali, 2020
Alidadi	2021	Iran	MetS	32/27	12 weeks	500	Alidadi et al., 2021
Mokhtari	2021	Iran	T2DM	25/25	12 weeks	80	Mokhtari et al., 2021

group ([Higgins and Green, 2023](#)). If the trial included different intervention groups, we extracted information only for curcumin intervention group. If a single trial reported multiple intervention assessments at different intervention times, only the results for the longest intervention duration were included in this meta-analysis.

Risk of bias and certainty assessment

Risk of bias (RoB 2.0 tool) was used to evaluate the quality of included literature. We rated the overall certainty of evidence across RCTs according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group guidelines. Based on the evaluation criteria, the quality of evidence was classified into four categories: high, medium, low, and very low. High quality: very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: moderately confident in the effect estimate, such that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: confidence in the effect estimate is limited, and the true effect may be substantially different from

the estimate of the effect. Very low quality: very little confidence in the effect estimates, and the true effect is likely to be substantially different from the estimate of the effect.

Data analysis

The different units of the lipid indicators were uniformly converted to mg/dL (for TG, 1 mmol/L = 88.5 mg/dL; for TC, LDL, and HDL, 1 mmol/L = 38.7 mg/dL). Mean changes (mean \pm SD) in outcome indicators (TG, TC, LDL, HDL) were used to calculate overall effect sizes. We recorded sample size n, baseline and endpoint means and SDs for the intervention and placebo groups. Where studies did not directly report change in mean and SD, they were calculated using different conversion formulas. The formulas were as follows:

$$\begin{aligned} \text{mean change} &= \text{mean}_{\text{endpoint}} - \text{mean}_{\text{baseline}}; \\ \text{SD} &= \text{SE} \times \text{square root } n \text{ (n: number of participants)}; \\ \text{SD} &= \text{square root } [(\text{SD pre-treatment})^2 + (\text{SD post-treatment})^2 - (2R \times \text{SD pre-treatment} \times \text{SD post-treatment})], \end{aligned}$$

correlation coefficient $R = 0.5$; (Cao et al., 2022a; Higgins et al., 2022).

In addition, heterogeneity between studies was assessed by I^2 , with $I^2 = 50\%$ being the cut-off point for low and high heterogeneity. When $I^2 < 50\%$, a fixed-effects model was used to calculate the overall effect size, whereas when heterogeneity was $I^2 \geq 50\%$, a random-effects model was used. Subgroup analyses were performed according to intervention dose, intervention duration, and population status. Sensitivity analyses were used to assess the effect of individual studies on the overall results. Sensitivity analyses were performed by removing the original studies one at a time to calculate the effect of each original study on the overall effect size. When at least ten data points were available, we performed funnel plots and Egger's regression test to assess publication bias (Sterne et al., 2000); otherwise, funnel plots could not be used to test for publication bias. We also used fractional polynomial modeling (polynomials) to explore potential non-linear effects of curcumin dose (mg) and intervention duration (weeks) (Zhang, 2016). R software (v 4.0.3, R Core Team) and was used for all analyses in this study. A two-tailed P -value < 0.05 was considered as statistically significant.

Results

Literature search process

A total of 4,235 studies were retrieved from four electronic databases. After we removed 947 duplicate studies and 3,288 irrelevant studies based on title and abstract, the remaining 40 trials were included for further evaluation. An additional 17 records were excluded for the following reasons: full text was not available, combination with other drug treatments, raw data on baseline and endpoints were not presented, and whether double-blinding was used was not reported. Twenty-three studies that met the inclusion criteria were entered into the final meta-analysis. The selection process for the included studies is detailed in Figure 1.

The characteristics of the included studies

The characteristics of all included studies are summarized in Table 1. A total of 1,532 subjects were included in 23 studies published between 2011 and 2023, including 681 patients with T2DM, 248 with Mets, 382 with NAFLD, 87 with hyperlipidaemia,

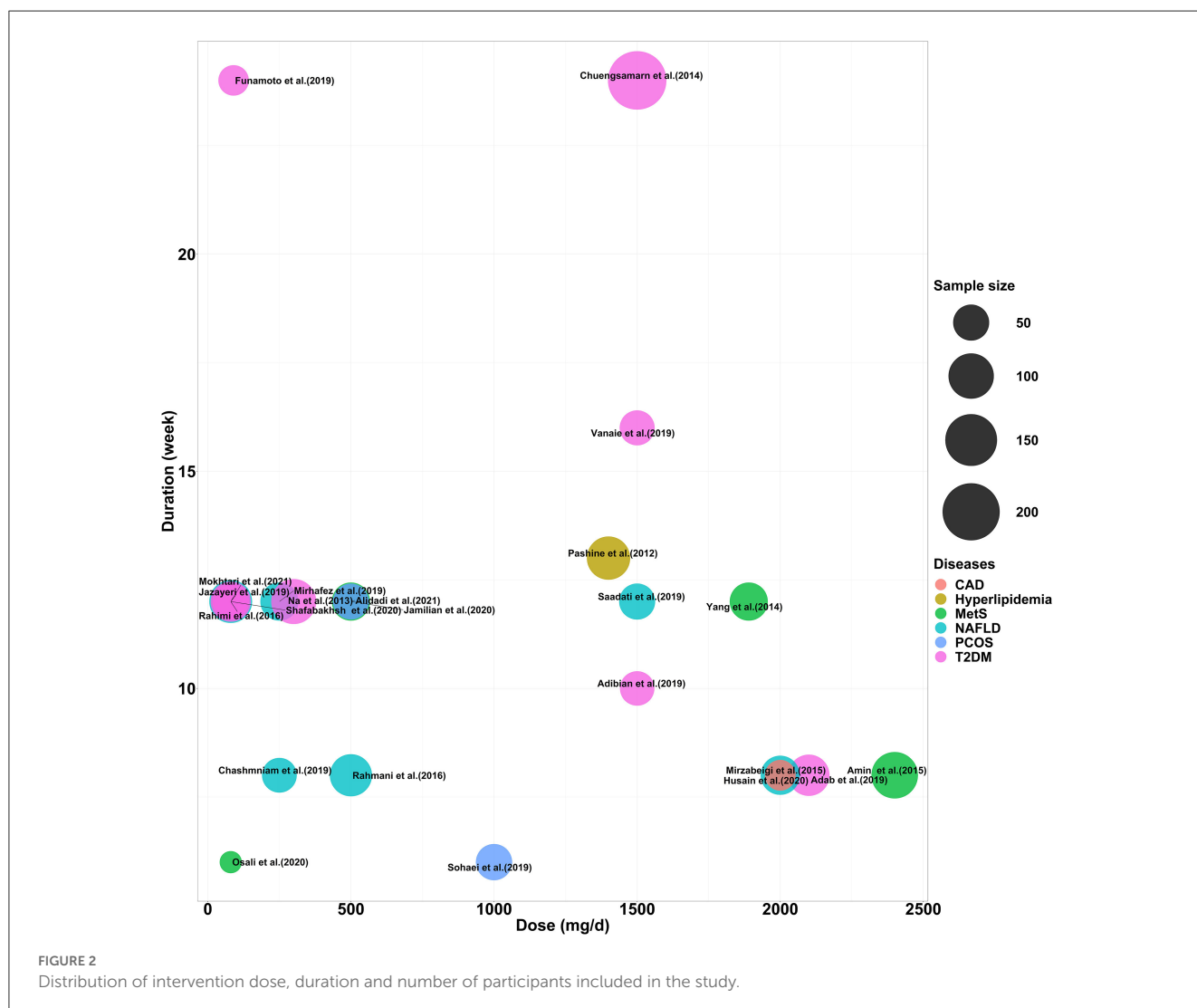
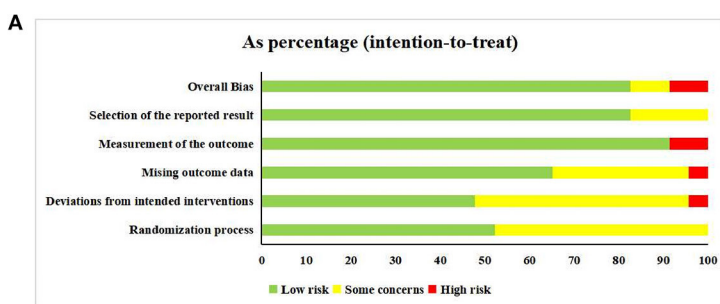


FIGURE 2 Distribution of intervention dose, duration and number of participants included in the study.



Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
1	Pashine 2012	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
2	Na 2013	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
3	Chengsuamarn 2014	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
4	Yang 2014	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
5	Amia 2015	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
6	Mirzabegi 2015	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
7	Rahimi 2016	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
8	Rahmani 2016	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
9	Adnan 2019	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
10	Adhian 2019	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
11	Chashmiani 2019	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
12	Faramaez 2019	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
13	Mirafzal 2019	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
14	Jamilian 2019	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
15	Saadati 2019	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
16	Sohaei 2019	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
17	Vansae 2019	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
18	Husain 2020	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
19	Jamilian 2020	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
20	Shafabakhsh 2020	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
21	Osali 2020	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
22	Aliadi 2021	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low
23	Mokhtari 2021	Curcumin	Placebo	NA	1	Low	Low	Low	Low	Low	Low

FIGURE 3 The Risk of bias and certainty assessment. (A, B) ROBIS assessment of included studies; (C) GRADE assessment of included study.

Question: Should Curcumin be used for reducing TG level?

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect	Quality	Importance
							Curcumin	Control			
23	Randomized trials	Low	None	None	None	None	668	629	Mean (95% CI)	MODERATE	Important

Question: Should Curcumin be used for reducing LDL-C level?

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect	Quality	Importance
							Curcumin	Control			
23	Randomized trials	Low	None	None	None	None	668	629	Mean (95% CI)	MODERATE	Important

Question: Should Curcumin be used for reducing HDL-C level?

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect	Quality	Importance
							Curcumin	Control			
23	Randomized trials	Low	None	None	None	None	668	629	Mean (95% CI)	MODERATE	Important

Question: Should Curcumin be used for reducing TG, LDL-C level?

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect	Quality	Importance
							Curcumin	Control			
23	Randomized trials	Low	None	None	None	None	668	629	Mean (95% CI)	MODERATE	Important

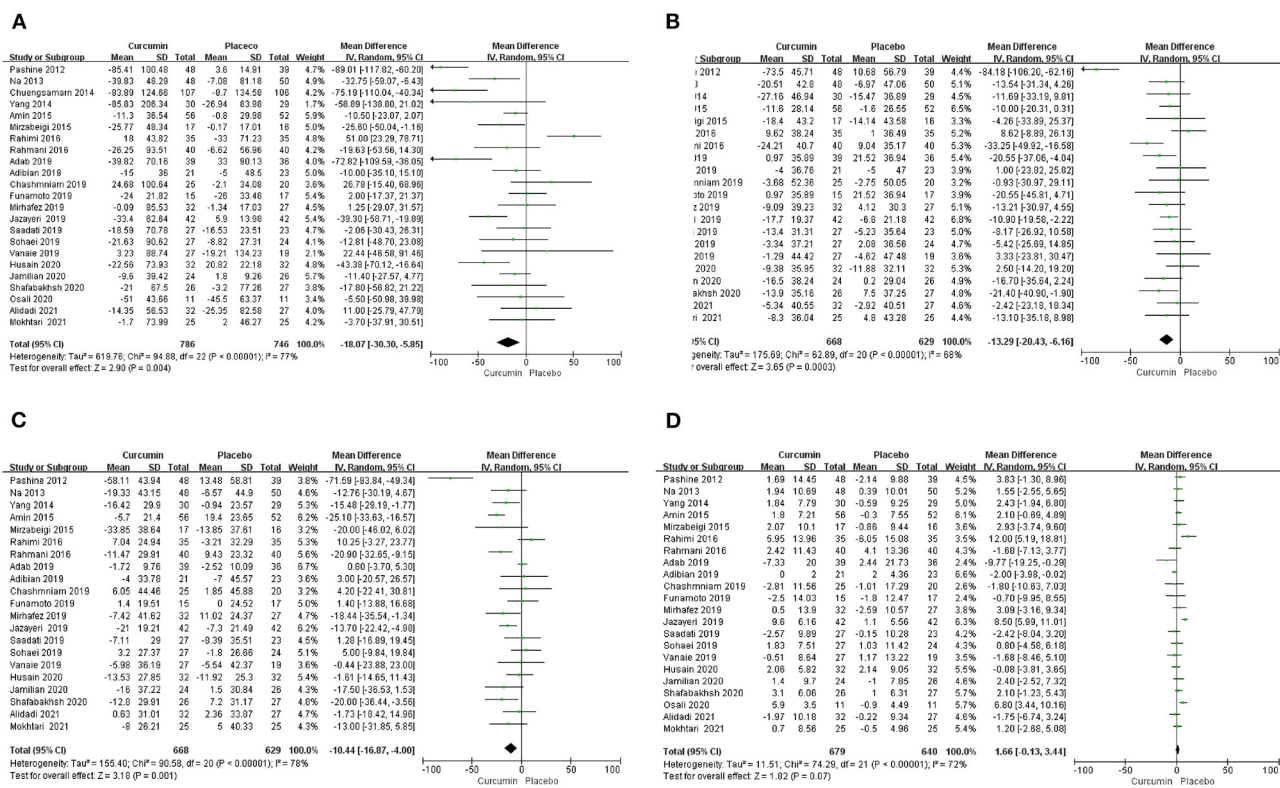


FIGURE 4 Forest plots of weighted mean difference (WMD, 95% CI) of (A) TG, (B) TC, (C) LDL, and (D) HDL change by curcumin supplementation across all included studies.

TABLE 2 Subgroup analysis about treatment period, treatment dose, and diseases for TG, TC, LDL-C, and HDL-C.

Subgroup	Trials, <i>n</i>	Mean difference, 95% CI (mg/dL)	Heterogeneity, I^2	<i>P</i>
TG				
Treatment period				
≤8 week	8	−21.58 [−38.28, −4.89]	62	0.01
8 week-≤12week	11	−7.95 [−23.78, 7.87]	71	0.32
>12 week	4	−38.08 [−93.45, 17.29]	91	0.18
Treatment dose				
Low dose (≤1,000-mg/d)	13	−5.05 [−18.96, 8.85]	67	0.48
High dose (>1,000 mg/d)	10	−36.64 [−57.51, −15.76]	81	<0.001
Morbid state of subjects				
T2DM	9	−15.81 [−41.32, 9.70]	84	0.22
NAFLD	6	−2.23 [−33.16, 28.71]	87	0.89
Mets	4	−9.11 [−20.50, 2.28]	0	0.12
PCOS	2	−11.64 [−26.38, 3.10]	0	0.12
CAD	1	−25.60 [−50.04, −1.16]	Not available	0.04
hyperlipidemic	1	−89.01 [−117.82, −60.20]	Not available	<0.001
TC				
Treatment period				
≤8 week	7	−14.34 [−21.29, −7.39]	0	<0.001
8 week-≤12week	11	−5.96 [−13.98, 2.06]	51	0.15
>12 week	3	−32.52 [−83.35, 18.30]	94	0.21
Treatment dose				
Low dose (≤1,000-mg/d)	12	−6.39 [−14.13, 1.36]	50	0.11
High dose (>1,000 mg/d)	9	−21.64 [−38.96, −4.33]	86	0.01
Morbid state of subjects				
T2DM	8	−4.85 [−16.55, 6.85]	63	0.42
NAFLD	6	−10.51 [−17.70, −3.32]	0	0.004
Mets	3	−13.36 [−23.14, −3.57]	0	0.007
PCOS	2	−14.04 [−35.58, 7.50]	60	0.2
CAD	1	−15.65 [−47.64, 16.34]	Not available	0.34
hyperlipidemic	1	−77.62 [−93.67, −61.57]	Not available	<0.001
LDL-C				
Treatment period				
≤8 week	7	−8.53 [−19.61, 2.55]	84	0.13
8 week-≤12week	11	−9.25 [−15.41, −3.10]	40	0.003
>12 week	3	−23.25 [−68.70, 22.20]	93	0.32
Treatment dose				
Low dose (≤1,000 mg/d)	12	−8.48 [−15.00, −1.95]	54	0.01
High dose (>1,000 mg/d)	9	−13.68 [−26.21, −1.15]	88	0.03
Morbid state of subjects				
T2DM	8	−2.69 [−9.37, 3.98]	41	0.43
NAFLD	6	−10.44 [−18.17, −2.71]	43	0.008

(Continued)

TABLE 2 (Continued)

Subgroup	Trials, <i>n</i>	Mean difference, 95% CI (mg/dL)	Heterogeneity, I^2	<i>P</i>
Mets	3	-15.64 [-28.71, -2.58]	68	0.02
PCOS	2	-5.43 [-27.42, 16.56]	70	0.63
CAD	1	-20.00 [-46.02, 6.02]	Not available	0.13
hyperlipidemic	1	-71.59 [-93.84, -49.34]	Not available	<0.001
HDL-C				
Treatment period				
≤8 week	8	1.01 [-1.76, 3.77]	60	0.48
8 week–≤12week	11	2.32 [-0.43, 5.06]	82	0.1
>12 week	3	1.41 [-2.33, 5.15]	0	0.46
Treatment dose				
Low dose (≤1,000 mg/d)	12	2.83 [0.50, 5.16]	69	0.02
High dose (>1,000 mg/d)	10	0.10 [-1.89, 2.09]	47	0.92
Morbid state of subjects				
T2DM	8	0.71 [-2.23, 3.65]	69	0.64
NAFLD	6	1.30 [-3.29, 5.90]	82	0.58
Mets	4	2.68 [-0.55, 5.91]	66	0.1
PCOS	2	1.67 [-1.96, 5.30]	0	0.37
CAD	1	2.93 [-3.74, 9.60]	Not available	0.39
hyperlipidemic	1	3.83 [-1.30, 8.96]	Not available	0.14

Bold values means significance.

101 with obese polycystic ovarian syndrome, and 33 with obesity complicated by coronary artery disease. There were 23 TG trials, 21 TC and LDL trials, and 22 HDL cholesterol trials. In the trial by Rahimi et al. (2016) the raw data for TG were presented using median values, suggesting that the distribution of baseline values may be abnormal. Secondly, five trials used nanocurcumin for intervention (Rahmani et al., 2016; Jazayeri-Tehrani et al., 2019; Osali, 2020; Shafabakhsh et al., 2020; Mokhtari et al., 2021), three trials used other highly bioavailable curcumin preparations (Mirzabeigi et al., 2015; Funamoto et al., 2019; Mirhafez et al., 2019) and 15 trials used low bioavailable curcumin preparations (e.g., homemade curcumin capsules, turmeric root powder, etc.) (Pashine et al., 2012; Na et al., 2013; Chuengsamarn et al., 2014; Yang et al., 2014; Amin et al., 2015; Rahmani et al., 2016; Adab et al., 2019; Adibian et al., 2019; Chashmnam et al., 2019; Saadati et al., 2019; Sohaei et al., 2019; Vanaie et al., 2019; Husain et al., 2020; Jamilian et al., 2020; Alidadi et al., 2021). In addition, the duration of the intervention ranged from 6 weeks to 24 weeks and the dose ranged from 80 mg/d to 2400 mg/d. The distribution of curcumin formulations, intervention doses, durations and sample sizes for all included trials is shown in Figure 2.

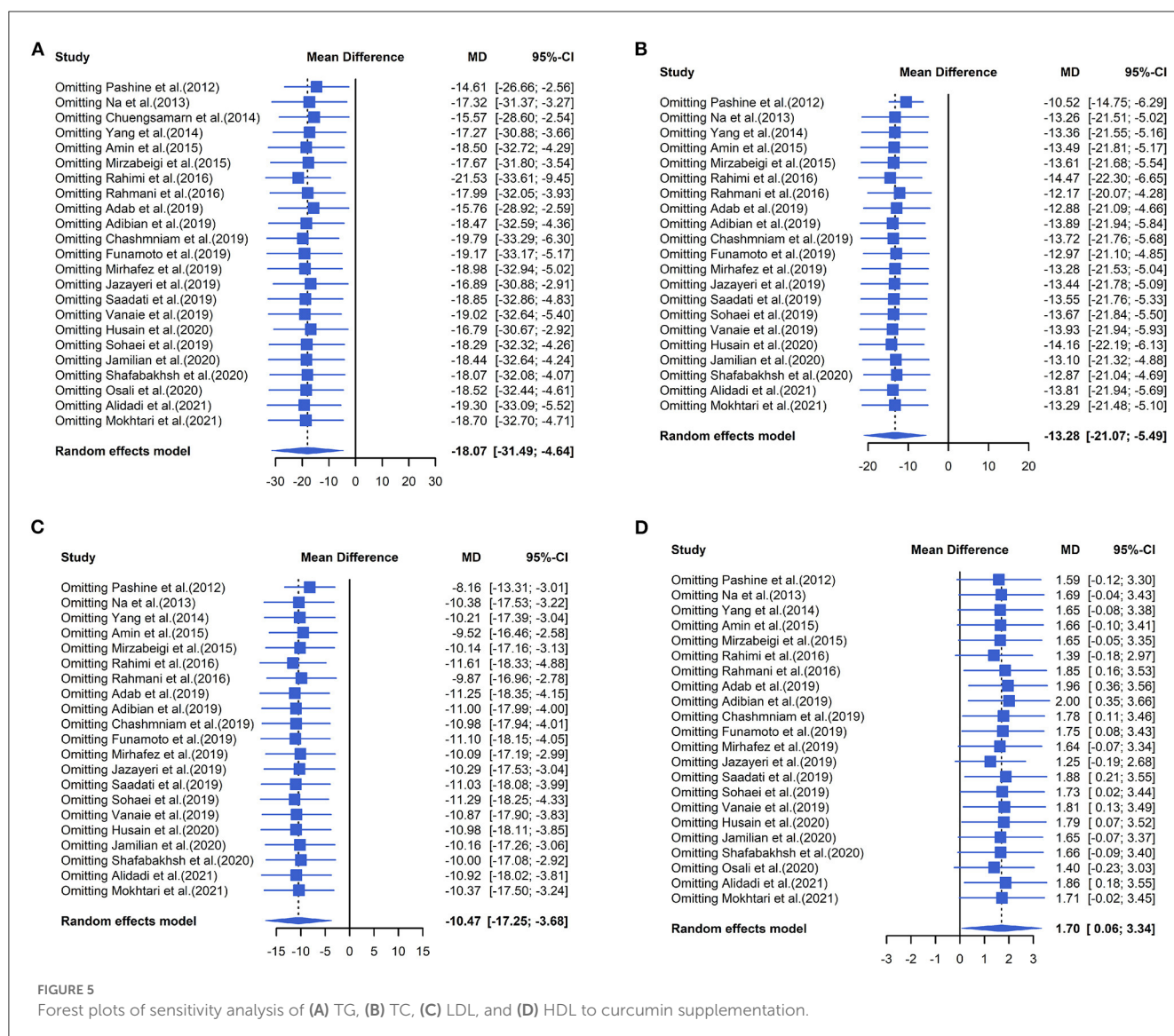
Assessment of quality

Fourteen studies were judged to be at low risk of bias while additional five studies were classified as having some concerns, and

four studies were categorized as at high risk of bias (Figures 3A, B). To assess the quality of evidence for the outcomes, the GRADE framework was implemented, determining that the evidence for TC, LDL, and HDL was downgraded to moderate, while the evidence regarding TG was determined to be low (Figure 3C).

Effect of curcumin supplementation on TG

The effect of curcumin on TG was reported in all 23 studies (Figure 4A). According to a random effects model ($I^2 = 77.00\%$, $P < 0.01$), the mean change in TG concentration between the intervention and placebo groups differed by -18.07 mg/dL (MD: -18.07 mg/dL, 95% CI: $-30.30, -5.85$, $P < 0.01$), suggesting that curcumin significantly reduced TG concentration. As the heterogeneity exceeded 50%, subgroup analysis was performed to determine the source of heterogeneity (Table 2). The results showed that TG levels were lower in the curcumin group than in the placebo group for different intervention durations and pooled data for different intervention doses. In addition, curcumin reduced TG levels in subjects with different status, including T2DM, NAFLD, Mets and PCOS. Furthermore, both observed TG levels were significantly changed in studies with $>1,000$ mg/d curcumin (MD: -36.64 mg/dL, 95% CI: $-57.51-15.76$, $P < 0.01$) and in studies with an intervention duration of <8 weeks (MD: -21.58 mg/dL, 95% CI: $-38.28-4.89$, $P = 0.01$). However, the heterogeneity of RCTs in each subgroup remained high. After removing each



original study individually using sensitivity analyses, we found no change in the combined effect size (Figure 5A). Egger regression test showed no publication bias ($P = 0.9989$) (Figure 6A). According to the fractional polynomial model, curcumin above 80 mg/kg had a significant reduction in TG (P -non-linearity = 0.02, Figure 7A), but no effect of intervention duration on TG was observed (P -non-linearity = 0.69, Figure 8A).

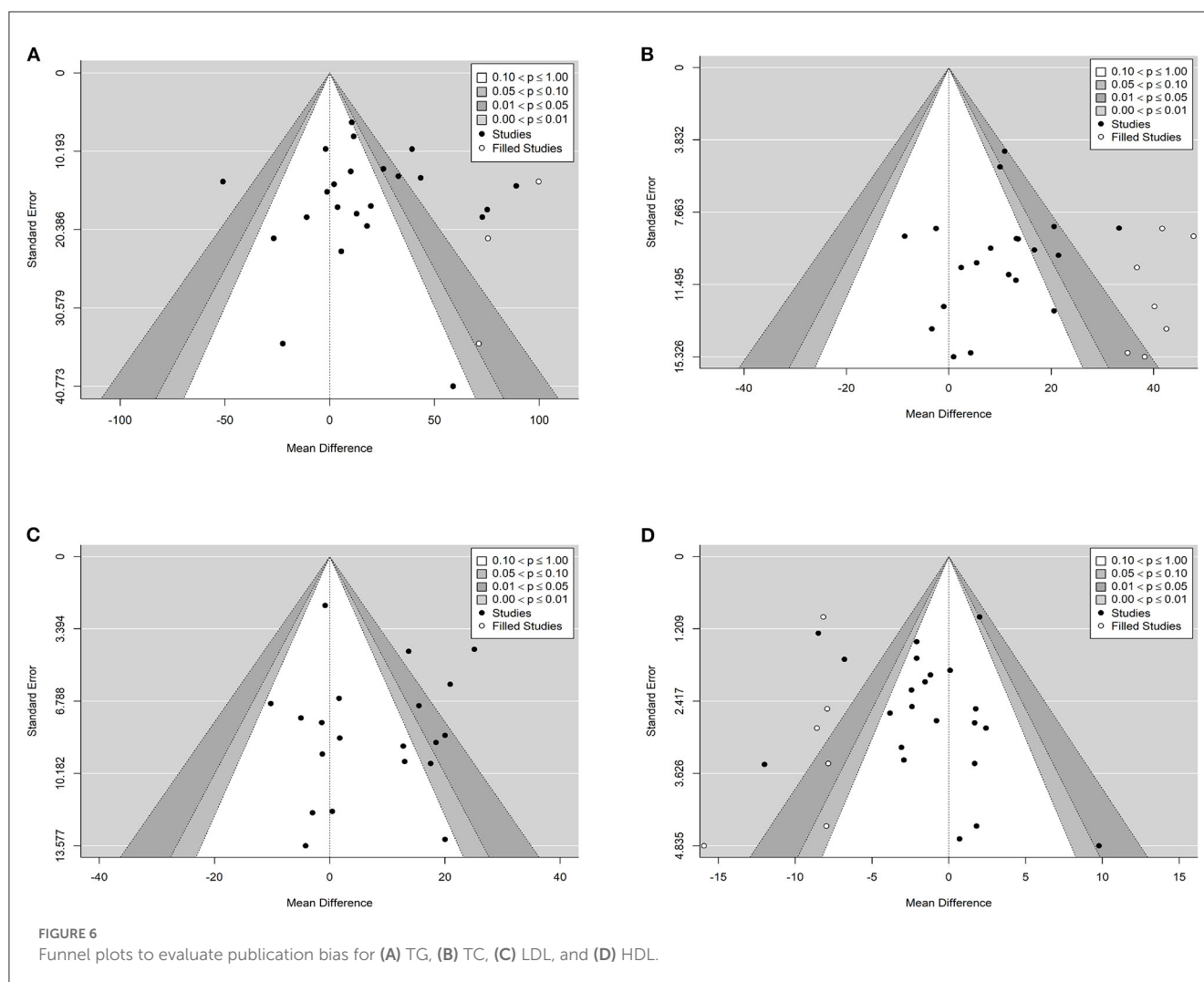
Effect of curcumin on TC

The combined results of 21 studies showed that curcumin intervention reduced TC concentrations in subjects with metabolic disorders (MD: -13.29 mg/dL, 95% CI: $-20.43, -6.16$, $P < 0.01$). There was significant heterogeneity among the included studies ($I^2 = 68.00\%$, $P < 0.01$) (Figure 4B). The results of subgroup analysis showed that the heterogeneity between studies remained high with respect to treatment dose, intervention duration, and subject population grouping. However, the use of high doses ($>1,000$ mg/d) (MD: -21.64 mg/dL, 95% CI: -38.96 to -4.33 , $P = 0.01$) of

curcumin with an intervention duration of <8 weeks (MD: -14.34 mg/dL, 95% CI: -21.29 to -7.39 , $P < 0.01$) all significantly reduced TC level. Significant downregulation of TC was observed in subjects with NAFLD (MD: -10.51 mg/dL, 95% CI: $-17.70, -3.32$, $P < 0.01$) and Mets (MD: -13.36 mg/dL, 95% CI: $-23.14, -3.57$, $P < 0.01$) (Table 2). Second, the results of sensitivity analysis showed that the overall effect size was stable (Figure 5B). The publication bias test showed that there was probably no publication bias ($P = 0.8843$) (Figure 6B). Furthermore, there was no significant non-linear relationship between dose (P -non-linearity = 0.99, Figure 7B) and intervention duration (P -non-linearity = 0.51, Figure 8B) and TC.

The effect of curcumin on LDL

A total of 21 trials reported the effect of curcumin on LDL. According to the random effects model ($I^2 = 78.00\%$, $P < 0.01$), curcumin significantly reduced LDL level (MD: -10.44 mg/dL, 95% CI: $-16.87, -4.00$; $P < 0.01$) (Figure 4C). Subgroup analysis



showed that TC levels were significantly lower in the pool of participants taking both high ($>1,000$ mg/d) (MD: -13.68 mg/dL, 95% CI: $-26.21, -1.15$, $P = 0.03$) and low doses ($\leq 1,000$ mg/d) of curcumin (MD: -8.48 mg/dL, 95% CI: $-15.00, -1.95$, $P = 0.01$).

The LDL-lowering effect of curcumin was more pronounced in subjects with NAFLD (MD: -10.44 mg/dL, 95% CI: $-18.17, -2.71$, $P < 0.01$) and Mets (MD: -15.64 mg/dL, 95% CI: $-28.71, -2.58$, $P = 0.02$). Sensitivity analyses showed that combined OR and 95% CI did not change significantly when any of the studies were removed, suggesting the stability of the results of current analysis (Figure 5C). Egger regression testing showed no difference between the observed and estimated values ($p = 0.6216$) (Figure 6C). Regarding the non-linear dose-response analysis, there was no significant effect of supplementation dose (P-non-linearity = 0.60, Figure 7C) and intervention duration (P-non-linearity = 0.99, Figure 8C) on LDL levels.

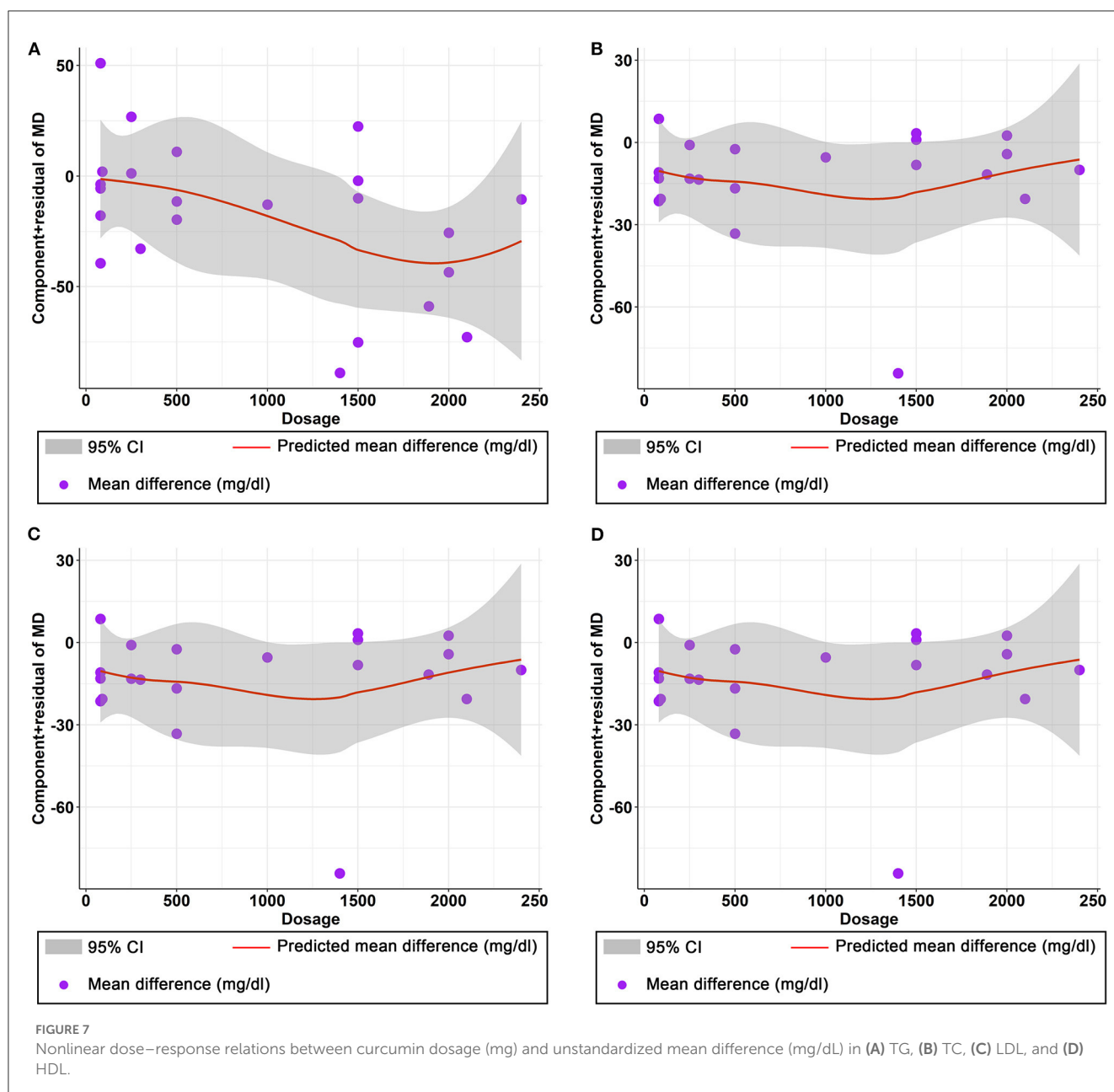
Effect of curcumin on HDL

The combined effect of 22 trials showed no effect of curcumin intake on HDL level (MD: 1.66 mg/dL, 95% CI: $-0.13, 3.44$; $P =$

0.07). Subgroup analysis showed that low doses ($\leq 1,000$ mg/d) of curcumin may increase HDL levels (MD: 2.83 mg/dL, 95% CI: $0.50, 5.16$, $P = 0.02$) (Figure 4D). The effect sizes did not change after the removal of individual studies in the sensitivity analysis (Figure 5D). Publication bias analysis showed no differences between observed and estimated values ($P = 0.1801$) (Figure 6D). Furthermore, the effects of curcumin dose (P-non-linearity = 0.58, Figure 7D) and intervention duration (P-non-linearity = 0.93, Figure 8D) on HDL levels were not significant.

Discussion

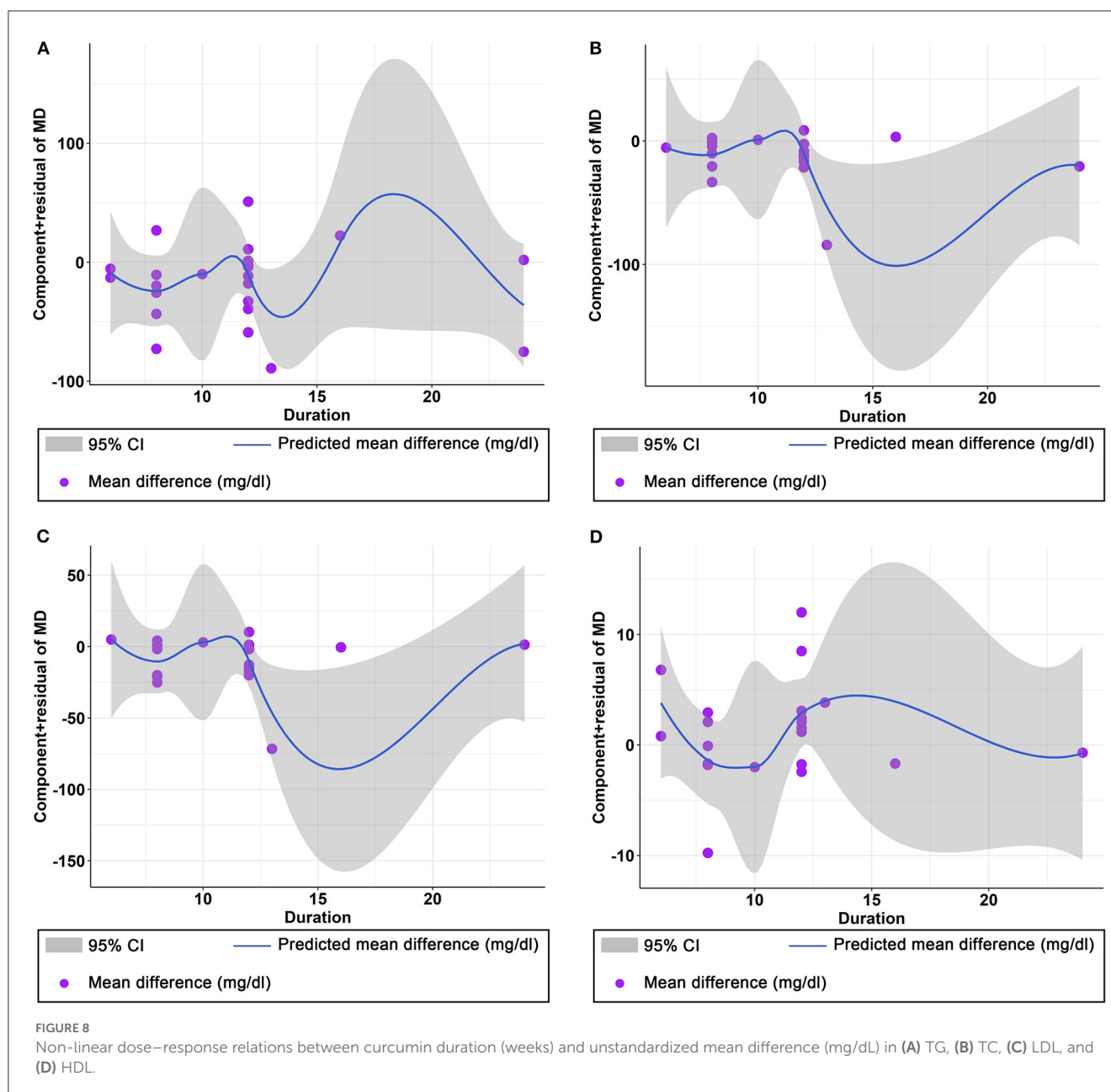
Studies have shown that lifestyle modification and calorie control are effective treatments for metabolic disorders, but many patients are unable to complete them due to poor adherence and persistence (Narayan et al., 2002; Maruthur et al., 2013). In addition, the use of nutritional products to correct the lipid profile of patients with metabolic disorders has received increasing attention due to the high cost and side effects of chemical drugs (Houston, 2012). Evidence from our analysis of 23 RCTs showed that curcumin supplementation significantly reduced TG, TC, and



LDL levels, but not HDL, in patients with metabolic disorders in the Asian population. When analyzing more homogeneous trials based on the underlying disease of subjects, beneficial effects of curcumin on TG, TC, and LDL levels were observed in subjects with NAFLD and Mets; however, such beneficial effects on HDL levels were not observed in subjects with T2DM, NAFLD, Mets, PCOS, and CAD. In addition, there was a more beneficial effect on TG and TC when the curcumin intervention was administered at high doses (>1,000 mg/d) for <8 weeks. In a non-linear dose-response analysis, we observed a significant effect of curcumin supplementation dose on TG levels. In addition, larger studies in patients with metabolic disorders may be needed to investigate the effect of curcumin on lowering lipid concentrations.

There were some similar and discrepant results in our meta-analysis compared to the three available meta-analyses: Qin

et al. (2017) reported that curcumin significantly reduced LDL and TG levels, but did not significantly improve HDL levels. This is similar to our findings. However, Yuan et al. (2019) reported that curcumin reduced TG, TC, LDL and increased HDL. Sahebkar et al. (2017) and Saedi et al. (2022) found no effect of curcumin on TG, TC, LDL, and HDL levels. The results of our analysis showed that curcumin significantly reduced TG, TC, LDL, and had no significant effect on HDL. We can suggest several explanations as to why their results are contrary to those analyzed in the present study. First, the trials included different ethnic groups, and our review only included trials in the Asian populations. Second, the studies we included were all randomized, double-blind, placebo-controlled trials; studies from parallel and cross-over randomized trials were not included because these studies may have affected the final results. Thirdly, the



study by Yuan and Sahebkar included trials in which subjects took curcumin in combination with other therapeutic measures in addition to curcumin (Khajehdehi et al., 2011; Yang et al., 2014; Panahi et al., 2017), whereas the subjects included in this meta-analysis took curcumin only. Finally, the disease status of the included population may also partially explain this difference. The present meta-analysis only included patients with various chronic metabolic diseases, whereas the studies by Sahebkar et al. (2017) and Saeedi et al. (2022) also included healthy subjects, and these differences may have contributed to the different results. In addition, the evidence from our study is likely to be stronger because of the larger number of trials and more stringent inclusion criteria.

A number of recent findings have revealed mechanisms by which curcumin may improve hyperlipidaemia. First, curcumin

may affect cellular transduction pathways associated with obesity and metabolic disease. Curcumin can alter transduction signaling (Akt, AMPK), balance gene expression of specific transcription factors (Foxo1/3a, Nrf2, Srebp1/2, CREB, CREBH, PPAR γ , and LXR α) and factors related to lipogenesis (aP2/FABP4, CD36, HMG-CoA reductase and carnitine palmitoyltransferase-1) (Zingg et al., 2013); Curcumin also activates Wnt/ β -catenin signaling, inhibits preadipocyte differentiation, macrophage expansion and infiltration into white adipose tissue, thereby reducing adipocyte numbers and inhibiting inflammatory adipokine secretion (Ahn et al., 2010). In addition, curcumin may modulate lipid metabolic pathways affected by statins and exert an anti-obesity effect (Urasaki and Le, 2022). Overall, a variety of mechanisms may be responsible for the hypolipidaemic effects of curcumin.

In this meta-analysis, we also performed a dose-response analysis and found a non-linear relationship between curcumin dose and TG levels, suggesting that the effect of curcumin on TG is dependent on the intervention dose. The results showed that just over 80 mg/d of curcumin reduced TG. In the subgroup analysis, we also found that >1,000 mg/d curcumin showed a significant change in TG levels, which is consistent with the upward trend we observed in the dose-response plots. The results of this analysis suggest that dose may be a key factor in curcumin supplementation.

It must be acknowledged that the current meta-analysis still has some limitations. Firstly, the manufacturing process of curcumin, the dose of the intervention and the duration of treatment varied between the included trials; secondly, most of the results had a high degree of heterogeneity that could not be resolved by appropriate subgroup analysis. Data from some of the trials were based on formulas from the Cochrane Handbook of Systematic Reviews, which may have been a source of heterogeneity; thirdly, the large proportion of randomized controlled trials from the Middle East affected the applicability of the results. Due to the apparent heterogeneity and the limited number of RCTs, this meta-analysis may not lead to precise conclusions. Therefore, more homogeneous and high-quality randomized controlled trials should be conducted to demonstrate the effects of curcumin on blood lipids.

In conclusion, this meta-analysis suggests that curcumin supplementation may significantly affect TG, TC, and LDL levels, but not HDL levels. Furthermore, the dose of curcumin intervention is an important factor that should be considered with caution. The results of this meta-analysis may be useful in making recommendations for the use of curcumin as a dietary supplement. Given the limitations of this meta-analysis, more and higher quality RCTs are needed to confirm these results.

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Author contributions

WG designed the idea for the systematic review and meta-analysis. HX revised the original manuscript. ZD, KY, XC, and HM were involved in obtaining and analyzing the data. ZD drafted the manuscript. All authors read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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