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The effect of magnesium supplementation on serum concentration of lipid profile: an updated systematic review and dose-response meta-analysis on randomized controlled trials

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Abstract

Background Some evidence suggests magnesium might reduce serum levels of lipid profile. Due to the significance of this matter on hand, we centralized our aim to conduct a systematic review and meta-analysis to interrogate the effect of magnesium supplementation on serum levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) in the general population aged ≥ 18 years.

Methods In line with conducting this study first, relevant articles were found through searching databases, including five databases: Cochrane Library, ClinicalTrials.gov, ISI Web of Science, Scopus, and PubMed until January 2024. Following fulfilling the first aim, their mean differences and standard deviations were calculated to conduct the meta-analysis. Ultimately, an assessment of the statistical heterogeneity of intervention effects was performed using I-squared statistics and Cochran's Q test.

Results Regarding serum levels of TC, TG, LDL-C, and HDL-C, twenty-one, twenty-three, twenty, and twenty-five studies were included in the meta-analysis. The pooled estimates showed no significant differences in serum levels of TC, TG, and LDL-C between the magnesium group and comparison group (weighted mean difference (WMD) = 0.34 mg/dl, 95% confidence interval (CI): -1.75 to 2.43, $P = 0.749$, $I^2 = 99.1\%$; WMD=-2.06 mg/dl, 95% CI: -6.35 to 2.23, $P = 0.346$, $I^2 = 99.1$; WMD = 1.71 mg/dl, 95% CI: -0.81 to 4.24, $P = 0.183$, $I^2 = 99.4$, respectively). However, magnesium significantly increased HDL-C (WMD = 1.21 mg/dl, 95% CI: 0.58 to 1.85, $P < 0.001$, $I^2 = 99.5$).

Conclusion In conclusion, our study showed that magnesium significantly increased HDL-C levels. However, due to high heterogeneity, we must note that more research is needed to make robust recommendations regarding magnesium supplementation in clinical practice.

Registry number This study was registered in PROSPERO under the protocol number CRD42024505142.

Keywords Magnesium, Lipid profile, Systematic review, Meta-analysis

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Introduction

Worldwide, cardiovascular diseases (CVDs) are a primary cause of morbidity and mortality [1]. The major risk factors for CVDs include smoking, diabetes, hypertension, and dyslipidemia [2, 3]. Dyslipidemia involves an abnormality in lipid balance [4]. Therefore, controlling dyslipidemia could reduce the risk of CVD development. A study examining the US population found that a 10% increase in the rate of hyperlipidemia treatment would prevent 8000 deaths per year [5].

Expanding the domain of affecting factors, researchers delineated that low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C), have a significant effect on CVD progression [6, 7]. HDL-C may have a protective function, whereas the other components of the lipid profile may have adverse effects on CVD [8]. The term "lipid profile" refers to lipids, including LDL-C, HDL-C, TG, and TC.

Looking at the deeper layers, scientists recommend that some nutrients might modulate lipid profile [9–12]. Magnesium is considered one of the important intracellular cations that participates in numerous enzymatic processes as a vital catalyst [13] and is found in leafy green vegetables, whole grains, nuts, and legumes [14, 15]. Some evidence suggests that a higher dietary intake of magnesium may enact beneficial effects and roles on a range of metabolic conditions namely hypertension [16], insulin resistance [17], dyslipidemia [18], metabolic syndrome [19], CVDs [20], and type 2 diabetes mellitus [21]. Observational studies have also highlighted an inverse association between dietary magnesium intake and key biomarkers for these conditions such as TG [22, 23], low HDL-C [22, 23], fasting insulin [24], as well as markers of endothelial dysfunction and inflammation [25].

Within lipid metabolism, magnesium enacts a fundamental role by enhancing the activity of certain enzymes such as lecithin-cholesterol acyltransferase, lipoprotein lipase, and desaturase [26], reducing the activity of β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase, and insulin signaling [27]. Putting all this evidence together, the effect of these enzymes on lipid metabolism has remained unclear.

Supporting this issue on hand through the lenses of clinical research, some randomized controlled trials (RCTs) have assessed the effect of magnesium supplementation on serum levels of lipid profile, though their results are contradictory. Some RCTs showed that magnesium supplementation could improve lipid profile [28–34], while others did not [35–39]. Finding more robust evidence, one systematic review and meta-analysis in 2017 revealed no significant effect of magnesium supplementation on lipid profile [40], whereas another systematic review and meta-analysis in 2020 showed that magnesium significantly led to diminishing serum levels of LDL-C among diabetic patients [41]. However, the effect of magnesium supplementation on the general population aged ≥ 18 years after the publication of new RCTs remained unclear.

Nonetheless, the results of these new RCTs might not be sufficient for concluding about the efficacy of magnesium supplementation in this context. By employing meta-analysis techniques, the sample size increases, the likelihood of random results reduces, and the significance of statistical findings improves. Therefore, we conducted a systematic review and meta-analysis on RCTs results to assess the impact of oral magnesium supplementation on lipid profile among the overall population.

Methods

The present systematic review and meta-analysis followed the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and was registered in PROSPERO under the protocol number CRD42024505142.

This systematic search was conducted using various databases, including the Cochrane Library, ClinicalTrials.gov, ISI Web of Science, Scopus, and PubMed until January 2024. Medical subjects heading (MeSH) and non-MeSH terms related to Magnesium, LDL-C, HDL-C, TG, TC, and clinical trials were used to search. Designing systematic search was performed by utilizing asterisks, quotation marks, parentheses, and Boolean operators (AND and OR) to maximize search outcomes. The search strategies for these databases are presented in supplementary Table 1. In line with collecting data, several steps have been taken. At first, the relevant and found articles were exported, and following that their titles and abstracts were separately reviewed by two individuals (MH and AGh) using the EndNote X21 reference manager. Completing the existing stages, efforts were made to find any missed articles by checking the references of relevant and reviewed articles. If there were any uncertainties, clarification was sought by emailing the corresponding authors.

Study eligibility criteria

In this study, PICOS (Patient/Population, Intervention, Comparison, Outcome, Study types) framework was employed as the inclusion criteria. We included RCTs involving magnesium supplements with a comparison arm, employing either a cross-over or parallel design. The study participants were adults aged 18 or above and we considered studies that reported changes in LDL-C, HDL-C, TG, and TC, along with their corresponding standard deviations (SDs), or that provided data allowing for the calculation of these values.

Two independent reviewers (MH and AGh) carried out all aspects of the systematic review, including screening studies, selecting them, assessing methodological quality, assessing based on inclusion and exclusion criteria, and extracting data. Any disagreements were resolved through group discussions until a consensus was reached. The exclusion criteria were established as follows: (1) RCTs where participants consumed other nutrients besides magnesium; (2) RCTs lacking placebo or comparison groups; (3) RCTs lacking data on serum levels of lipid profile before or after intervention in both study groups or any information for calculation; (4) RCTs using figures to show the results instead of clearly reporting the mean and SD of serum levels of lipid profile; (5) RCTs without magnesium dosage; (6) RCTs involving pregnant women; (7) RCTs using intravenous form of magnesium; (8) Non-English trials.

Data extraction

Information was extracted using a data collection form, with two independent investigators extracting the following details: first author's name, publication year, study title, trial design, geographical region, intervention duration, participants' age, sex, health status, body mass index (BMI), study sample size, magnesium dose, changes in the mean of lipid profile, and their corresponding SDs. For RCTs with more than one intervention or comparison group, each was considered as a separate study in the systematic review and meta-analysis. Any ambiguous data were addressed by reaching out to the corresponding author for clarification. Discrepancies were resolved through group discussions to reach a consensus during this stage.

Quality assessment

A modified version of the Cochrane risk-of-bias (Rob2) tool and the respective Excel application were used to assess the quality of each RCT [42]. Evaluation of RCTs was performed on the basis of several factors, including the randomization process, bias arising from period and carryover effect (just for cross-over trials), deviations from intended interventions, missing outcome data, measurement of outcome, and selection of reported results. According to the criteria of this tool, RCTs were categorized as having a low risk of bias (good quality), some concerns regarding bias (fair quality), or a high risk of bias (weak quality) [42]. Two reviewers (MH and AGh) independently assessed each RCT, and any disagreements were resolved through discussion and consensus with a third person (MS).

Data synthesis and statistical analysis

By determining the mean differences (MDs) and their SDs for lipid profile, the meta-analysis has been carried out. If these values were not provided, we calculated them using the information in the articles. According to the Cochrane Handbook, we calculated the effect size by taking the changes in the mean of lipid profile from baseline and their SD for both the intervention and the comparison groups [43]. Additionally, when the median or range of lipid profile was provided instead of the mean, we calculated the mean using the Hozo method [44]. If the standard errors (SEs) were reported, we derived the SDs by multiplying the SEs in the square root of the sample size [44]. If there was significant heterogeneity, a summary of the overall effects and heterogeneity using the DerSimonian and Laird random effects model was presented [45]. We assessed the statistical heterogeneity of intervention effects using the I-squared statistic and Cochran's Q test. We considered significant heterogeneity to be a p-value of ≤ 0.10 by Cochran's Q test or a value of $\geq 50\%$ in the I-squared statistic [46].

Besides considering the level of significance in heterogeneity, identification of its causes was of great importance and thus, it was carried out by conducting subgroup analyses based on factors such as magnesium dose, trial design, geographical region, intervention duration, baseline lipid profile, participants' health status, age, sex, BMI, study sample size, RCTs' quality, and publication year. We assessed publication bias using Begg's rank correlation test, Egger's weighted regression test, and visual examination of Begg's funnel plot [47, 48]. All effect sizes were accompanied by 95% confidence intervals (CIs) and STATA version 14 (Stata Corp, College Station, TX) was utilized for all analyses.

Results

Our systematic search yielded 2889 articles. After removing duplicates, 1789 articles were screened based on their titles and abstracts. Upon review, 1729 articles were excluded for various reasons, such as being cross-sectional studies, study protocols, congress abstracts, lack of lipid profile measurement, non-human studies, and review articles. Subsequently, the full texts of 60 articles were assessed according to our inclusion and exclusion criteria leading to the exclusion of 33 articles for various reasons, including taking magnesium from a diet with a high amount of magnesium instead of a supplement ($n=1$), not being randomized ($n=1$), taking magnesium besides other nutrients ($n=17$), not having comparison group ($n=5$), not reporting baseline data ($n=1$), not reporting data after intervention ($n=1$), not reporting the elemental magnesium-dose ($n=4$), conducting the study on pregnant women ($n=2$), taking magnesium in intravenous form ($n=1$). Finally, twenty-seven articles met our criteria and were included in the systematic review and meta-analysis [28–39, 49–63] (Fig. 1). However, regarding TG, two studies were excluded from the

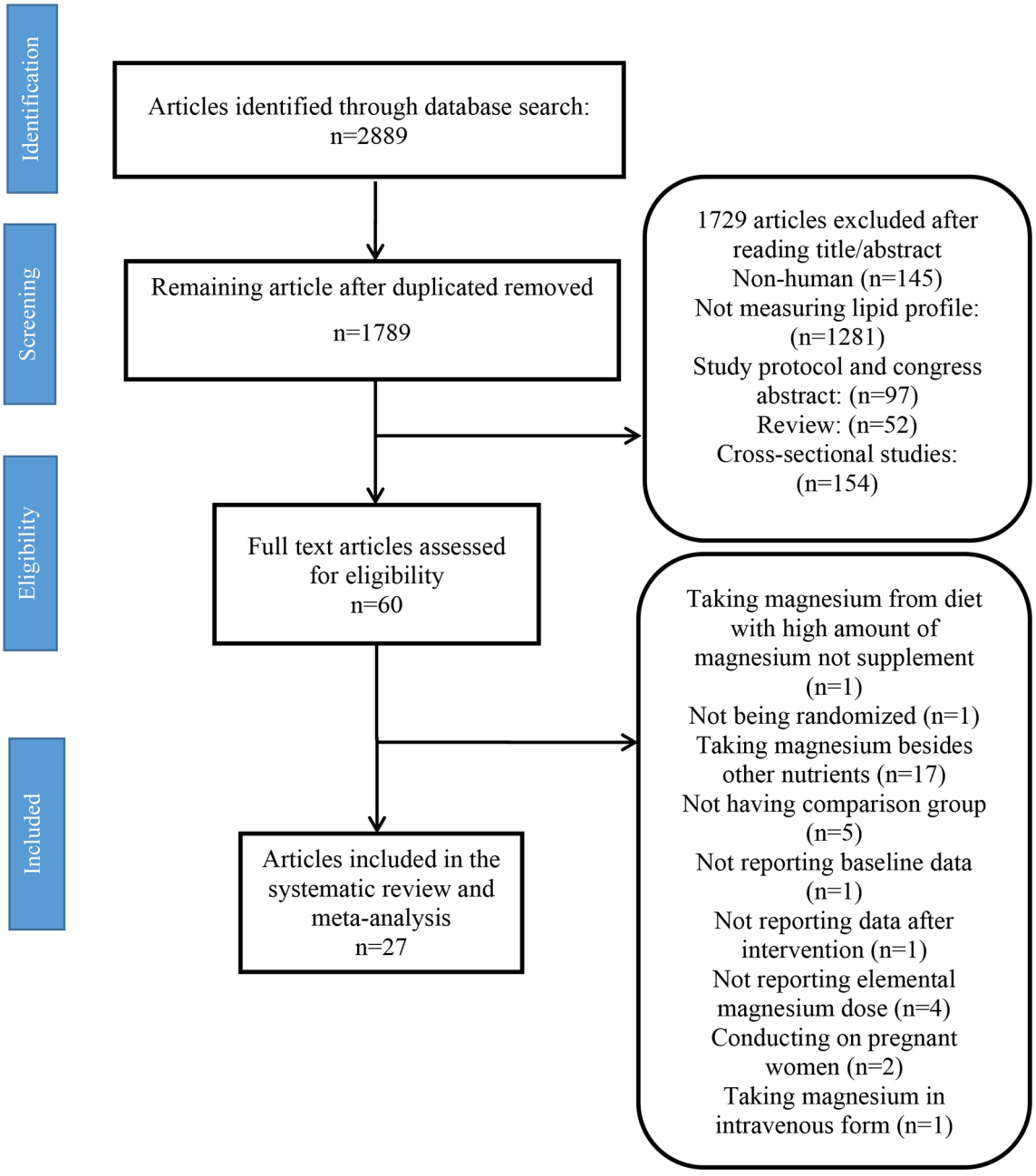

Fig. 1 Flowchart of study selection process

meta-analysis due to having a large effect size (outliers) compared to the other trials [57, 58].

Study characteristic

Based on our systematic review results, the effect of magnesium supplementation on serum levels of LDL-C, HDL-C, TG, and TC was assessed in twenty [29, 30, 32–39, 49, 52–56, 59–62], twenty-five [29, 30, 32–39, 49–63], twenty-five [28–39, 50–62], and twenty-one studies [28–30, 32–39, 52–56, 59–63], respectively. The dose of magnesium ranged from 20 mg/day to 548 mg/day in the form of magnesium citrate [28, 31], magnesium chloride [29, 50, 51, 57, 58], magnesium oxide [30, 34, 37, 38, 55, 56, 62], magnesium pidolate [32], magnesium bicarbonate [33], magnesium sulfate [39, 49, 61], magnesium hydroxyl [35], magnesium aspartate [53, 63], magnesium lactate [54], while four studies did not report the formulation of magnesium [36, 52, 59, 60]. The intervention duration ranged from 4 weeks to 24 weeks.

The design of three studies was cross-over [31, 32, 54], while twenty-four studies [28–30, 33–39, 49–53, 55–63] had a parallel design. Regarding health status, three

studies were on subjects with metabolic syndrome [28, 52, 58], nine studies on subjects with diabetes [29, 37, 50, 54–56, 59, 61, 62], three studies on obese/overweight participants [31, 39, 53], three studies on prediabetes [38, 51, 60] and healthy subjects [32, 33, 35], two studies on women with polycystic ovary syndrome [30, 34], one study on subjects with moderate coronary artery disease [49], one study on nonalcoholic fatty liver disease [36], one study on metabolically obese normal-weight individuals [57], and one study on mild to moderate hypertension [63].

In one study by Albaker, W. I et al. [29] the effect of magnesium was assessed at different doses, including 20 mg/day and 50 mg/day for twelve weeks; therefore, this study was considered as two studies in the systematic review and meta-analysis. Farshidi, H et al. [49] assessed the effect of magnesium in 12 weeks and 24 weeks; therefore, we considered this study as two separate studies, and two effect sizes were calculated. Furthermore, in two other studies, the effect of magnesium was assessed at two time points; thus, those studies were reviewed as four separate studies in both the systematic review and meta-analysis, and four effect sizes were calculated [35, 39]. Consequently, twenty studies with twenty-four effect sizes assessed the effect of magnesium on LDL-C levels, twenty-five studies with twenty-nine effect sizes assessed the effect of magnesium on HDL-C levels, twenty-five studies with twenty-six effect sizes assessed the effect of magnesium on TG levels, and twenty-one studies with twenty-four effect sizes assessed the effect of magnesium on TC levels. We presented the details of the study characteristics in Table 1.

Quality assessment

Figure 2 shows the results of the quality assessment for each article and the percentage of articles based on quality assessment results in each item. As can be seen, out of twenty-seven studies, ten studies had a high risk of bias [29, 32, 34–36, 49, 51, 52, 55, 63] due to deviations from intended interventions [52], missing outcome data [29, 34, 49, 51, 52, 55], and measurement of the outcome [32, 35, 36, 52, 55, 63]. More details are presented in Fig. 2.

Meta-analysis results

Twenty-one studies with twenty-four datasets were included in the meta-analysis of the effect of magnesium on the serum level of TC (Fig. 3A). The high heterogeneity was observed between studies (Cochrane's Q test, $P<0.001$, $I^2=99.1\%$). As depicted in Fig. 3A, differences in serum levels of TC between the magnesium group and the comparison group (weighted mean difference (WMD) = 0.34 mg/dl, 95% CI: -1.75 to 2.43, $P=0.749$) were non-significant. Subgroup analyses also revealed a non-significant change in serum levels of TC following magnesium supplementation in most subgroups with more than two trials (Table 2). The between-group heterogeneity was significant in most subgroups with more than two trials (Table 2).

Figure 3B depicts the result of the meta-analysis regarding the effect of magnesium on the serum levels of TG. Twenty-three studies with twenty-six datasets were included in the meta-analysis. Since there was significant heterogeneity (Cochrane's Q test, $P<0.001$, $I^2=99.1\%$) between studies, the random-effect model was used and its results indicated no significant effect of magnesium on serum levels of TG (WMD=-2.06 mg/dl, 95% CI: -6.35 to 2.23, $P=0.346$). The non-significant effect of magnesium supplementation on TG levels did not change in all subgroup analyses (Table 3).

The meta-analysis of the results of twenty studies with twenty-four datasets that evaluated the effect of magnesium on serum levels of LDL-C is shown in Fig. 3C. The result of random-effect model showed non-significant differences in serum levels of LDL-C between the magnesium group and the comparison group, with high heterogeneity (WMD = 1.71 mg/dl, 95% CI: -0.81 to 4.24, $P=0.183$, Cochrane Q test, $P<0.001$, $I^2=99.4\%$).

The non-significant effect of magnesium on serum levels of LDL-C was shown in most subgroup analyses. More details regarding subgroup analysis results are presented in Table 4.

The meta-analysis of the effect of magnesium on serum levels of HDL-C is shown in Fig. 3D. As can be seen in the figure, twenty-five studies with twenty-nine datasets compared the changes in serum levels of HDL-C between the magnesium group and the comparison group. There was high heterogeneity (Cochrane's Q test, $P<0.001$, $I^2=99.5\%$) between studies, and the random-effect model found a significant increasing effect of magnesium on serum levels of HDL-C (WMD = 1.21 mg/dl, 95% CI: 0.58 to 1.85, $P<0.001$).

According to the results of subgroup analysis magnesium supplementation significantly increased serum levels of HDL-C in studies among American (WMD = 3.90 mg/dl, 95% CI: 1.83 to 5.97, $P<0.001$) not the Asian (WMD = 0.49 mg/dl, 95% CI: -0.37 to 1.35, $P=0.267$) and European participants (WMD = 0.75 mg/dl, 95% CI: -0.77 to 2.27, $P=0.335$) and participants with at risk/disease health status (WMD = 1.32 mg/dl, 95% CI: 0.52 to 2.12, $P=0.001$) not healthy (WMD = 0.34 mg/dl, 95% CI: -2.08 to 2.75, $P=0.785$), and both sex (WMD = 1.65 mg/dl, 95% CI: 0.86 to 2.44, $P<0.001$) not female (WMD=-0.08 mg/dl, 95% CI: -0.25 to 0.09, $P=0.376$), and studies with magnesium dose ≥ 300 mg/day (WMD = 2.02 mg/dl, 95% CI: 1.23 to 2.81, $P<0.001$) not ˂300 mg/day (WMD=-0.22 mg/dl, 95% CI: -1.39 to 0.95, $P=0.716$), intervention duration ≥ 84 days (WMD = 1.49 mg/dl, 95% CI: 0.79 to 2.19, $P=0.966$)

Table 1 Randomized controlled trial studies included in the systematic review and meta-analysis abbreviations: LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; TC: total cholesterol

Code Author (year) (country)	Subjects	Age (mean ± SD)	RCT	Intervention	Placebo	Duration (week)	Variables	Results
1 Afitska, K. [28] (Germany)	Subjects with metabolic syndrome *N* = 24	61.8 ± 10.7	Randomized, double-blinded, placebo-controlled trial	400 mg/day magnesium as magnesium citrate	Not mentioned	12	TG and TC	TG and TC did not change significantly
2.1 Albaker, W. I. [29] (Saudi Arabia)	Subjects with type 2 diabetes mellitus *N* = 70	57.5 ± 7.04	Randomized, double-blinded, placebo-controlled trial	20 mg/day magnesium as magnesium chloride	Water without added magnesium	12	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
2.2 Albaker, W. I. [29] (Saudi Arabia)	Subjects with type 2 diabetes mellitus *N* = 69	55.9 ± 8.9	Randomized, double-blinded, placebo-controlled trial	50 mg/day Mg as magnesium chloride	Water without added magnesium	12	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
3 Alizadeh, M. [30] (Iran)	Women with polycystic ovary syndrome *N* = 41	25.57 ± 4.88	Randomized, double-blinded, placebo-controlled trial	250 mg/day magnesium oxide	Not mentioned	8	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
4 Chacko, S. A. [31] (United States)	Overweight subjects *N* = 26	44.4 ± 13.0	Randomized, double-blind, controlled, crossover trial	500 mg/day magnesium as magnesium citrate	Not mentioned	4	TG	TG did not change significantly
5 Cosaro, E. [32] (Italy)	Healthy young men with a family history of metabolic syndrome *N* = 14	26.3 ± 3.10	Randomized, double-blind, controlled, crossover trial	16.2 mmol/day magnesium pidolate equivalent to 368 mg/day elementary magnesium	Lactose	8	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
6 Day, R. O. [33] (Australia)	Postmenopausal women *N* = 67	57 ± 4.4	Randomized, double-blinded, placebo-controlled trial	1500–1800 mL/day magnesium bicarbonate supplemented spring water equivalent to 180–216 mg/day magnesium	Non supplemented spring water	12	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
7.1 Farshidi, H. [49] (Iran)	Subjects with moderate coronary artery disease *N* = 64	61.1 ± 1.5	Randomized, double-blinded, placebo-controlled trial	300 mg/day magnesium as magnesium sulfate	wheat flour	12	LDL-C and HDL-C	LDL-C and HDL-C did not change significantly
7.1 Farshidi, H. [49] (Iran)	Subjects with moderate coronary artery disease *N* = 64	61.1 ± 1.5	Randomized, double-blinded, placebo-controlled trial	300 mg/day magnesium as magnesium sulfate	wheat flour	24	LDL-C and HDL-C	LDL-C decreased significantly, but HDL-C did not change significantly

Table 1 (continued)

Code Author (year) (country)	Subjects	Age (mean ± SD)	RCT	Intervention	Placebo	Duration (week)	Variables	Results
8 Farsinejad-Marj, M. [34] (Iran)	Women with Polycystic Ovary Syndrome *N* = 60	26.32 ± 3.92	Randomized, double-blinded, placebo-controlled trial	250 mg/day magnesium oxide	Lactose	8	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
9 Guerrero-Romero, F. [50] (Mexico)	Diabetic hypertensive adults with low serum magnesium levels *N* = 79	59.5 ± 8.9	Randomized, double-blinded, placebo-controlled trial	2.5 g/day of magnesium chloride, equivalent to 450 mg elemental magnesium	Not mentioned	16	HDL-C and TG	HDL-C increased significantly, but TG did not change significantly
10 Guerrero-Romero, F. [51] (Mexico)	Subjects with prediabetes and hypomagnesaemia *N* = 116	42.5 ± 9.5	Randomized, double-blinded, placebo-controlled trial	30 mL/day magnesium chloride equivalent to 382 mg/day of magnesium	Not mentioned	16	HDL-C and TG	HDL-C increased significantly and TG decreased significantly
11.1 Itoh, K. [35] (Japan)	Healthy subjects *N* = 33	64 ± 9	Randomized, double-blinded, placebo-controlled trial	548 mg/day magnesium as magnesium hydroxyl for men and 411 mg/d magnesium as magnesium hydroxyl for women	Not mentioned	2	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
11.2 Itoh, K. [35] (Japan)	Healthy subjects *N* = 33	64 ± 9	Randomized, double-blinded, placebo-controlled trial	548 mg/day magnesium as magnesium hydroxyl for men and 411 mg/d magnesium as magnesium hydroxyl for women	Not mentioned	4	LDL-C, HDL-C, TG, and TC	HDL-C increased significantly and LDL-C decreased significantly, but TG and TC did not change significantly
12 Karandish, M. [36] (Iran)	Subjects with nonalcoholic fatty liver disease *N* = 64	36 ± 7	Randomized, double-blinded, placebo-controlled trial	350 mg/day elemental magnesium	Lactose	12	LDL-C, HDL-C, TG, and TC	TC and LDL-C decreased significantly, but HDL-C and TG did not change significantly
13 Lima de Souza, E. [52] (Brasil)	women with metabolic syndrome *N* = 72	44.6 ± 9.7	Randomized, double-blinded, placebo-controlled trial	400 mg/day elemental magnesium	Not mention	12	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
14 Mooren, F. C. [53] (Germany)	Normomagnesemic, overweight, insulin resistant, and non-diabetic subjects *N* = 47	30–70	Randomized, double-blinded, placebo-controlled trial	15 mmol/day magnesium aspartate-hydrochloride equivalent to 365 mg/day elemental magnesium	Not mention	24	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly

Table 1 (continued)

Code Author (year) (country)	Subjects	Age (mean ± SD)	RCT	Intervention	Placebo	Duration (week)	Variables	Results
15 Mortazavi, M. [37] (Iran)	Diabetic hemodialysis patients *N* = 54	58.8 ± 10.1	Randomized, double-blinded, placebo-controlled trial	250 mg/d magnesium as magnesium oxide	Not mention	24	LDL-C, HDL-C, TG, and TC	TC and LDL-C decreased significantly, but HDL-C and TG did not change significantly.
16 Navarrete-Cortes, A. [54] (Mexico)	Subjects with type 2 diabetic *N* = 56	52.84 ± 8.42	Randomized, double-blind, controlled, crossover trial	360 mg magnesium as magnesium lactate	Not mention	12	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
17 Rashvand, S. [55] (Iran)	Subjects with type 2 diabetes mellitus *N* = 37	49.89 ± 7.83	Randomized, double-blinded, placebo-controlled trial	500 mg/d magnesium as magnesium oxide	Starch	8	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
18 Razzaghi, R. [56] (Iran)	Subjects with diabetic foot ulcer *N* = 70	60.1 ± 11.1	Randomized, double-blinded, placebo-controlled trial	250 mg/d magnesium as magnesium oxide	Not mention	12	LDL-C, HDL-C, TG, and TC	LDL-C, HDL-C, TG, and TC did not change significantly
19 Rodríguez-Moran, M. [57] (Mexico)	Metabolically obese, normal-weight individuals *N* = 47	31.9	Randomized, double-blinded, placebo-controlled trial	30 mL/day magnesium chloride equivalent to 382 mg/day of magnesium	Not mention	8	HDL-C and TG	TG decreased significantly, but HDL-C did not change significantly
20 Rodríguez-Morán, M. [58] (Mexico)	Subjects with metabolic syndrome *N* = 198	39.4 ± 9.8	Randomized, double-blinded, placebo-controlled trial	30 mL/day magnesium chloride equivalent to 382 mg/day of magnesium	Not mention	16	HDL-C and TG	TG decreased significantly, but HDL-C did not change significantly
21 Sadeghian, M. [59] (Iran)	Subjects with diabetic nephropathy *N* = 80	41.2 ± 8.8	Randomized, double-blinded, placebo-controlled trial	250 mg/day elemental magnesium	Lactose	12	LDL-C, HDL-C, TG, and TC	TC decreased significantly, but LDL-C, TG, and TC did not change significantly
22 Salehidoost, R. [60] (Iran)	Subjects with prediabetes *N* = 71	56.7 ± 5.9	Randomized, double-blinded, placebo-controlled trial	250 mg/day elemental magnesium	Starch	12	LDL-C, HDL-C, TG, and TC	HDL-C increased significantly, but LDL-C, TG, and TC did not change significantly
23 Shahmoradi, S. [38] (Iran)	Subjects with prediabetes *N* = 40	29.00 ± 4.24	Randomized, triple-blinded, placebo-controlled trial	250 mg/day magnesium as magnesium oxide	Not mention	12	LDL-C, HDL-C, TG, and TC	LDL-C and TC decreased significantly, HDL-C increased significantly, but TG did not change significantly

Table 1 (continued)

Code Author (year) (country)	Subjects	Age (mean ± SD)	RCT	Intervention	Placebo	Duration (week)	Variables	Results
24.1 Solati, M. [39] (Iran)	Overweight subjects *N* = 70	40.73 ± 11.9	Randomized, double-blinded, placebo-controlled trial	300 mg/day magnesium as magnesium sulfate	wheat bran	12	LDL-C, HDL-C, TG, and TC	LDL-C, TG, and TC did not change significantly, but HDL-C increased significantly
24.2 Solati, M. [39] (Iran)	Overweight subjects *N* = 70	40.73 ± 11.9	Randomized, double-blinded, placebo-controlled trial	300 mg/day magnesium as magnesium sulfate	wheat bran	24	LDL-C, HDL-C, TG, and TC	TG and LDL-C decreased significantly, HDL-C increased significantly, but TC did not change significantly
25 Solati, M. [39] (Iran)	Subjects with type 2 diabetes mellitus *N* = 47	46.76 ± 9	Randomized, double-blinded, placebo-controlled trial	300 mg/day magnesium as magnesium sulfate	Not mention	12	LDL-C, HDL-C, TG, and TC	LDL-C decreased significantly, but HDL-C, TG, and TC did not change significantly
26 Talari, H. R. [62] (Iran)	Diabetic hemodialysis patients *N* = 54	58.8 ± 10.1	Randomized, double-blinded, placebo-controlled trial	250 mg/d magnesium as magnesium oxide	Not mention	24	LDL-C, HDL-C, TG, and TC	TC and LDL-C decreased significantly, but HDL-C and TG did not change significantly
27 Witteman, J. C. [63] (Belgium)	women with mild to moderate hypertension *N* = 91	57.4 ± 11.9	Randomized, double-blinded, placebo-controlled trial	485 mg/day magnesium as magnesium aspartate-HCl	Not mention	24	HDL-C and TC	HDL-C and TC did not change significantly

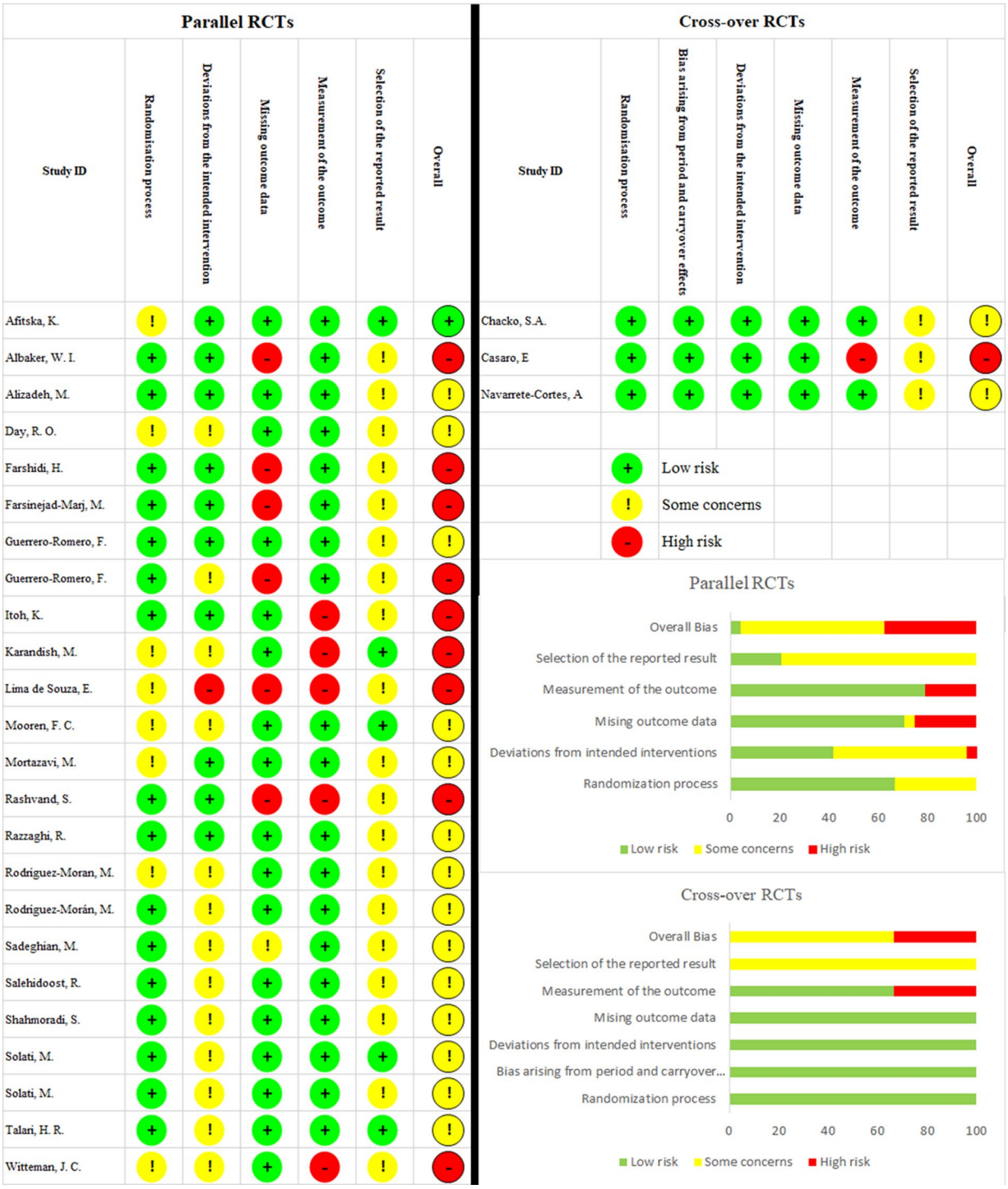

Fig. 2 Quality assessment

not ˂84 days (WMD = 0.44 mg/dl, 95% CI: -1.70 to 1.77, $P < 0.001$), baseline HDL-C < 43 mg/dl (WMD = 1.76 mg/dl, 95% CI: 0.78 to 2.73, $P < 0.001$) not ≥ 43 mg/dl (WMD = 0.74 mg/dl, 95% CI: -0.35 to 1.84, $P = 0.184$), sample size ≥ 64 persons (WMD = 1.54 mg/dl, 95% CI: 0.74 to 2.35, $P < 0.001$) not ˂64 persons (WMD = 0.70 mg/dl, 95% CI: -0.42 to 1.82, $P = 0.222$), and publication date < 2016 (WMD = 1.4 mg/dl, 95% CI: 0.95 to 1.85, $P < 0.001$) not ≥ 2016 (WMD = 0.76 mg/dl, 95% CI: -0.15 to 1.67, $P = 0.104$) (Table 5). The heterogeneity was significant in most subgroups with a number of trials more than 2 (Table 5).

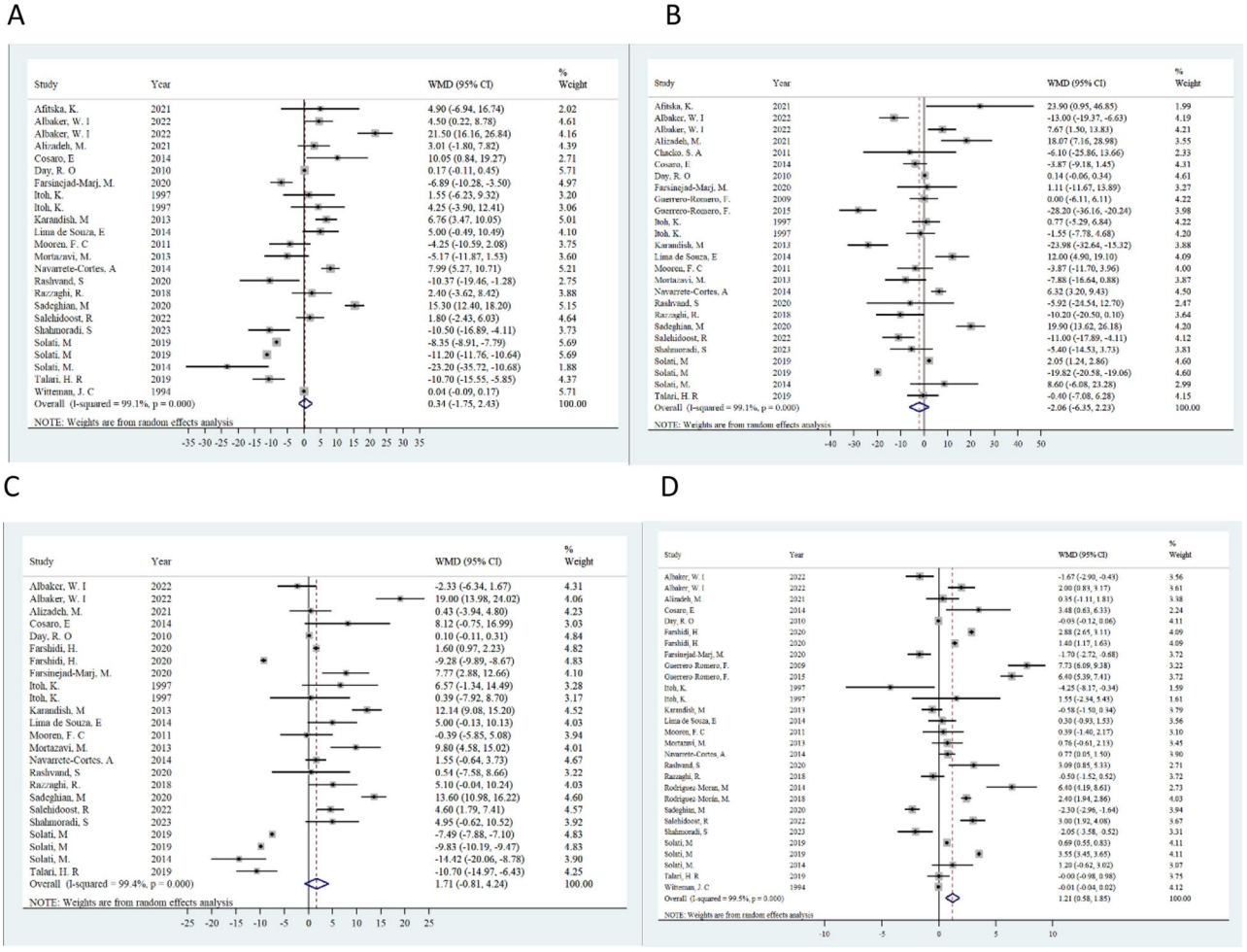

Fig. 3 Forest plot of the effect of magnesium supplementation on serum concentrations of lipid profile. **A**: TC; **B**: TG; **C**: LDL-C; **D**: HDL-C

Meta-regression analysis, publication bias, and sensitivity analysis

Despite the relatively nonsymmetrical visual inspection of the funnel plots for TC, TG, LDL-C, and HDL-C, the results of the Egger and Begg tests revealed no evidence of publication bias (Egger test $P = 0.627$ and Begg test $P = 0.102$ for TC; Egger test $P = 0.551$ and Begg test $P = 0.366$ for TG; Egger test $P = 0.562$ and Begg test $P = 0.321$ for LDL-C; Egger test $P = 0.150$ and Begg test $P = 0.822$ for HDL-C) (Fig. 4A, B, C and D). The results of the dose-response meta-regression analysis revealed a non-significant linear association between magnesium supplementation dose and the studied effect size for TC ($P = 0.629$, Fig. 5A), TG ($P = 0.862$, Fig. 5B), LDL-C ($P = 0.501$, Fig. 5C), and HDL-C ($P = 0.512$, Fig. 5D). According to the result of sensitivity analysis, excluding no trial caused significant changes in the overall effect size of magnesium on TC, TG, LDL-C, and HDL-C (Fig. 6A, B and C, and 6D).

Discussion

The present study has been the first systematic review and meta-analysis after the year 2017 which assessed the effects of magnesium supplementation on serum levels of lipid profile in the general population without considering health status. The current meta-analysis combined data from 24, 29, 26, and 24 datasets from twenty, twenty-five, twenty-three, and twenty-one studies to assess the impact of magnesium on serum levels of LDL-C, HDL-C, TG, and TC, respectively. Our results revealed magnesium supplementation cannot significantly change the serum levels of LDL-C, TG, and TC; however, the serum level of HDL-C increased significantly.

The systematic review and meta-analysis in 2017 [40] revealed no significant effect of magnesium supplementation on serum levels of lipid profile. The effect of newly published studies that were not included in that study might cause the discrepancy between our meta-analysis results and those of the earlier study. Another systematic review and meta-analysis investigating the impact of magnesium on lipid profile among diabetic patients

Table 2 Results of subgroup analyses for studies evaluating the effect of magnesium on serum TC

	Subgroup	No. of trial	Change in TC (95% CI)	*P*-value	I^2 (%)	$P_{heterogeneity}$
Total	-	24	0.34 (-1.75, 2.43)	0.749	99.1	< 0.001
magnesium dose (mg/d)	< 300 mg/d	10	1.60 (-5.18, 8.39)	0.643	95.5	< 0.001
	≥ 300 mg/d	14	-0.83 (-3.55, 1.88)	0.546	99.4	< 0.001
Trial design	Parallel	22	-0.38 (-2.55, 1.80)	0.735	99.2	< 0.001
	Cross-over	2	8.16 (5.55, 1.77)	< 0.001	0.00	0.674
Intervention duration	< 84 days	7	-1.56 (-6.99, 3.87)	0.574	80.6	< 0.001
	≥ 84 days	17	1.03 (-1.38, 3.45)	0.401	99.4	< 0.001
Baseline TC (mg/dl)	< 183 mg/dl	13	0.00 (-4.09, 4.10)	0.998	99.5	< 0.001
	≥ 183 mg/dl	11	0.89 (-2.33, 4.11)	0.588	88.1	< 0.001
Health status	Healthy	4	2.40 (-1.52, 6.32)	0.230	45.4	0.139
	At risk/disease	20	-0.39 (-3.67, 2.90)	0.818	99.2	< 0.001
Sample size	< 61 persons	12	-3.87 (-7.97, 0.22)	0.064	78.0	< 0.001
	≥ 61 persons	12	3.23 (0.53, 5.93)	0.019	99.6	< 0.001
Sex	Female	6	-0.20 (-0.96, 0.56)	0.605	84.3	< 0.001
	Male	1	10.05 (0.84, 19.27)	0.032	-	-
	Both	17	0.40 (-3.23, 4.03)	0.828	98.0	< 0.001
Age	< 52 years	12	-2.13 (-5.76, 1.50)	0.003	97.8	< 0.001
	≥ 52 years	12	1.84 (0.64, 3.04)	0.250	91.1	< 0.001
BMI	< 29.5	11	-4.19 (-7.10, -1.28)	0.005	99.6	< 0.001
	≥ 29.5	11	4.32 (-0.51, 9.14)	0.79	91.9	< 0.001
	Unknown	2	2.83 (-2.79, 8.46)	0.323	0.00	0.638
Geographical region	Asia	17	-0.89 (-4.23, 2.45)	0.600	97.6	< 0.001
	Australia	1	0.17 (-0.11, 0.45)	0.233	-	-
	Europe	4	1.16 (-3.45, 5.78)	0.621	56.8	0.074
	Americas	2	7.40 (4.96, 9.84)	< 0.001	0.00	0.338
Quality assessment	Good	1	4.90 (-6.94, 16.74)	0.417	-	-
	Fair	13	-2.54 (-6.56, 1.48)	0.216	99.4	< 0.001
	Weak	10	3.69 (-0.54, 7.93)	0.087	92.0	< 0.001
Publication year of article	< 2019	12	1.42 (0.41, 2.43)	0.723	85.5	0.001
	≥ 2019	12	-0.67 (-4.39, 3.05)	0.006	98.0	< 0.001

TC: total cholesterol, BMI: body mass index, mg/dl: milligram per deciliter, mg/d: milligram per day, CI: confidence interval

indicated that taking magnesium supplements significantly reduced serum levels of LDL-C did not have any effect on serum levels of TG, TC, and HDL-C [41]. The discrepancy in findings might be attributed to different study populations. It should be pinpointed that they limited their study to diabetic patients, while our study has centralized its focus on the general population. Furthermore, in the previous meta-analysis, the inclusion of studies lacking a proper comparison group [64] and those not reporting the exact dosage of elemental magnesium [65–67] might also have contributed to the differing results.

Extending and making a bridge between our results and the previous studies, findings from animal studies offer potential mechanisms responsible for the negative effect of magnesium deficiency on lipid profile. In this regard, a decrease in the removal of TG from the bloodstream and the lowered activity of lipoprotein lipase seem to be the primary factors contributing to high levels of lipid profile in magnesium deficiency [68, 69]. Additionally, a significant reduction in the activity of lecithin-cholesterol acyltransferase (LCAT) and decreased insulin sensitivity due to magnesium deficiency are also involved in the onset of dyslipidemia [70].

Magnesium increases the activity of LCAT, which raises HDL-C level [71, 72]; moreover, the activation of desaturase enzymes is increased by magnesium as well [72]. Desaturase catalyzes the first step in the conversion of omega-3 linoleic acid into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which increases HDL-C [73, 74]. Interestingly, this study provides new evidence to support the hypothesis that magnesium supplementation can protect against CVDs, though the enhancement of HDL-C might be clinically non-significant.

Our results revealed that there was significant heterogeneity among studies, which did not reduce in most subgroups. The reasons for the heterogeneity might be attributed to various formulations/salts of magnesium (magnesium citrate, magnesium chloride, magnesium oxide, magnesium pidolate, magnesium bicarbonate, magnesium sulfate, magnesium hydroxyl, magnesium

Table 3 Results of subgroup analyses for studies evaluating the effect of magnesium on serum TG

	Subgroup	No. of trial	Change in TG (95% CI)	*P*-value	I^2 (%)	$P_{heterogeneity}$
Total	-	26	-2.06 (-6.35, 2.23)	0.346	99.1	< 0.001
magnesium dose (mg/d)	< 325 mg/d	13	-1.01 (-9.52, 7.49)	0.816	99.3	< 0.001
	≥ 325 mg/d	13	-2.94 (-7.31, 1.44)	0.188	89.4	< 0.001
Trial design	Parallel	23	-2.28 (-6.89, 2.33)	0.332	99.2	< 0.001
	Cross-over	3	0.40 (-8.49, 9.30)	0.930	82.5	0.003
Intervention duration	< 84 days	8	-0.15 (-4.82, 4.53)	0.278	52.4	0.040
	≥ 84 days	18	-2.84 (-7.96, 2.29)	0.951	99.4	< 0.001
Baseline TG (mg/dl)	< 130 mg/dl	13	0.09 (-2.70, 2.88)	0.949	77.4	< 0.001
	≥ 130 mg/dl	13	-3.43 (-12.32, 5.46)	0.450	99.3	< 0.001
Health status	Healthy	4	0.13 (-0.07, 0.34)	0.202	0.00	0.475
	At risk/disease	22	-2.05 (-8.55, 4.46)	0.538	98.8	< 0.001
Sample size	< 61 persons	13	-0.29 (-3.95, 3.36)	0.876	49.6	0.022
	≥ 61 persons	13	-4.20 (-10.11, 1.70)	0.163	99.6	< 0.001
Sex	Female	5	4.85 (-2.52, 12.22)	0.197	82.2	< 0.001
	Male	1	-3.87 (-9.18, 1.45)	0.154	-	-
	Both	20	-3.57 (-10.28, 3.14)	0.298	98.9	< 0.001
Age	< 50 years	13	-2.52 (-11.35, 6.32)	0.577	99.3	< 0.001
	≥ 50 years	13	-1.55 (-4.61, 1.52)	0.323	79.9	< 0.001
BMI	< 29.7	12	-2.30 (-8.82, 4.23)	0.490	99.6	< 0.001
	≥ 29.7	12	-1.98 (-9.80, 5.83)	0.619	93.9	< 0.001
	Unknown	2	-0.36 (-4.70, 3.99)	0.783	0.00	0.601
Geographical region	Asia	17	-2.52 (-9.87, 4.82)	0.501	99.0	< 0.001
	Australia	1	0.14 (-0.06, 0.34)	0.180	-	-
	Europe	3	-0.56 (-9.44, 8.32)	0.901	63.1	0.066
	Americas	5	-2.79 (-15.32, 9.74)	0.663	94.4	< 0.001
Quality assessment	Good	1	23.90 (0.95, 46.85)	0.041	-	-
	Fair	15	-0.75 (-6.35, 4.86)	0.795	99.5	< 0.001
	Weak	10	-5.42 (-13.21, 2.37)	0.173	91.0	< 0.001
Publication year of article	< 2017	13	-3.33 (-7.50, 0.85)	0.118	89.4	< 0.001
	≥ 2017	13	-0.09 (-8.78, 8.59)	0.983	99.3	< 0.001

TG: triglyceride, BMI: body mass index, mg/dl: milligram per deciliter, mg/d: milligram per day, CI: confidence interval

aspartate, and magnesium lactate) that were used, which could be responsible for the heterogeneity. The formulation of magnesium might affect its bioavailability [75]; therefore, the impact of the administered magnesium salt on bioavailability cannot be ignored and might be a source of heterogeneity that cannot be dismissed with certainty in this study. The penultimate source for heterogeneity might be the wide range of magnesium supplement doses. Since different health statuses might have different effects on lipid profile, the wide range of health statuses among the studied participants might be another source of heterogeneity. Aggregating all these justifications together, our results should be interpreted with caution.

Our results revealed that magnesium supplements cannot reduce serum levels of TC, TG, and LDL-C compared to the control group. One reason for the ineffectiveness of magnesium on these variables might be the homeostasis of magnesium, which is strictly controlled by renal function [76]. In the presence of normal levels of magnesium, the consumption of magnesium supplements leads to increased urinary excretion of magnesium. Hence, the beneficial effect of magnesium supplements may be diminished in normomagnesemic subjects. It is worth mentioning that in our study, in most included studies the participants had normal levels of magnesium. Furthermore, the effects of magnesium might be changed in subjects with impaired renal function. Since, in the present meta-analysis, three studies were conducted on hemodialysis patients [37, 59, 62], impaired renal function might be an important cause of the non-significant effect of magnesium.

Another reason might be the effect of different formulations/salts on magnesium bioavailability [75]. Some evidence suggests that serum levels of magnesium increase during supplementation [77]; therefore, the beneficial effects might be found over a longer period of intervention. Our results confirm this hypothesis. We found in studies with an intervention duration of ≥ 84 days, HDL-C increased significantly, but this effect did not show in studies with an intervention duration of ˂84 days. Our subgroup analysis also revealed magnesium

Table 4 Results of subgroup analyses for studies evaluating the effect of magnesium on serum LDL-C

	Subgroup	No. of trial	Change in LDL-c (95% CI)	*P*-value	I^2 (%)	$P_{heterogeneity}$
Total	-	24	1.71 (-0.81, 4.24)	0.183	99.4	< 0.001
magnesium dose (mg/d)	< 300 mg/d	10	5.20 (0.03, 10.36)	0.049	93.7	< 0.001
	≥ 300 mg/d	14	-0.83 (-4.05, 2.40)	0.615	99.6	< 0.001
Trial design	Parallel	22	1.51 (-1.12, 4.14)	0.260	99.4	< 0.001
	Cross-over	2	3.37 (-2.40, 9.14)	0.252	49.7	0.158
Intervention duration	< 84 days	7	4.02 (1.32, 6.73)	0.004	21.2	0.267
	≥ 84 days	17	0.92 (-1.99, 3.83)	0.535	99.6	< 0.001
Baseline LDL-c (mg/dl)	< 107 mg/dl	13	3.09 (-1.47, 7.65)	0.184	98.7	< 0.001
	≥ 107 mg/dl	11	0.19 (-3.63, 4.00)	0.924	99.6	< 0.001
Health status	Healthy	4	1.43 (-1.18, 4.03)	0.234	98.9	< 0.001
	At risk/disease	20	2.45 (-1.58, 6.48)	0.283	47.4	0.127
Sample size	< 63 persons	12	1.36 (-3.24, 5.97)	0.562	87.0	< 0.001
	≥ 63 persons	12	2.05 (-1.34, 5.45)	0.235	99.7	< 0.001
Sex	Female	5	3.15 (-0.12, 6.42)	0.059	74.7	0.003
	Male	1	8.12 (-0.75, 16.99)	0.073	-	-
	Both	18	0.94 (-1.80, 3.68)	0.500	99.0	< 0.001
Age	< 51 years	12	1.45 (-1.50, 4.41)	0.335	98.3	< 0.001
	≥ 51 years	12	1.80 (-1.32, 4.92)	0.259	98.9	< 0.001
BMI	< 28.8	10	-0.55 (-4.01, 2.90)	0.754	99.0	< 0.001
	≥ 28.8	12	3.22 (0.08, 6.36)	0.044	98.7	< 0.001
	Unknown	2	3.61 (-2.44, 9.67)	0.242	10.4	0.291
Geographical region	Asia	19	1.49 (-1.19, 4.18)	0.276	99.0	< 0.001
	Australia	1	0.10 (-0.11, 0.31)	0.358	-	-
	Europe	2	3.12 (-5.09, 11.33)	0.465	60.9	0.110
	Americas	2	2.46 (-0.53, 5.45)	0.106	32.1	0.225
Quality assessment	Good	-	-	-	-	-
	Fair	13	-0.26 (-3.69, 3.18)	0.884	99.6	< 0.001
	Weak	11	4.40 (-0.76, 9.55)	0.095	98.8	< 0.001
Publication year of article	< 2019	11	3.04 (-0.33, 6.42)	0.077	91.1	< 0.001
	≥ 2019	13	0.62 (-2.39, 3.62)	0.688	99.2	< 0.001

LDL-C: low density lipoprotein cholesterol, BMI: body mass index, mg/dl: milligram per deciliter, mg/d: milligram per day, CI: confidence interval

supplements are more effective in the American population compared to the Asian population. In the American population, serum levels of HDL-C significantly increased following the magnesium intake, though this effect has not been found in the Asian population. Dietary magnesium intake, efficiency of absorption in subjects, dietary components, lifestyle factors, genetic background, and medications might be responsible for this difference in results. Our results also revealed that studies with a magnesium dose of ≥ 300 mg/day significantly increased serum levels of HDL-C, but we did not observe this result in studies with a magnesium dose of ˂300 mg/day. This finding might be due to the use of organic magnesium supplementation in some studies with a dose of ≥ 300 mg/day. The organic form of magnesium supplements might be more available than the inorganic form [75]. We also found that unhealthy participants and those with serum levels of HDL-C ˂43 mg/dl derived more benefits from magnesium supplementations, which might be due to lower levels of serum magnesium in this population.

Our study had some limitations that should be kept in mind while interpreting our results. Firstly, renal function can be an important confounder in assessing the magnesium supplementation effect; however, the biomarkers of renal function in most included RCTs in this meta-analysis are missing. Secondly, although most enrolled studies focused on patients, no information was included about their medicine in the articles. Thirdly, different formulations/salts of magnesium were used in trials, but we could not determine the effect of every formulation/salt on magnesium effect due to the low number of clinical trials for each formulation or the lack of reporting on magnesium formulation/salt in several trails [36, 52, 59, 60]. Fourthly, serum levels of magnesium were not reported before and after intervention in most trials; therefore, we did not have any information regarding magnesium hemostasis. Fifthly, although magnesium supplements are more effective in subjects with hypomagnesemia [78], the majority of articles focused on subjects with normal magnesium levels or did not include any information regarding magnesium levels. Sixthly,

Table 5 Results of subgroup analyses for studies evaluating the effect of magnesium on serum HDL-C

	Subgroup	No. of trial	Change in HDL-c (95% CI)	*P*-value	I^2 (%)	$P_{heterogeneity}$
Total	-	29	1.21 (0.58, 1.85)	< 0.001	99.5	< 0.001
magnesium dose (mg/d)	< 300 mg/d	10	-0.22 (-1.39, 0.95)	0.716	91.4	< 0.001
	≥ 300 mg/d	19	2.02 (1.23, 2.81)	< 0.001	99.7	< 0.001
Trial design	Parallel	27	1.18 (0.53, 1.83)	< 0.001	99.5	< 0.001
	Cross-over	2	1.76 (-0.79, 4.31)	0.177	69.2	0.072
Intervention duration	< 84 days	7	0.04 (-1.70, 1.77)	0.966	81.4	< 0.001
	≥ 84 days	22	1.49 (0.79, 2.19)	< 0.001	99.6	< 0.001
Baseline HDL-c (mg/dl)	< 43 mg/dl	13	1.76 (0.78, 2.73)	< 0.001	98.9	< 0.001
	≥ 43 mg/dl	16	0.74 (-0.35, 1.84)	0.184	99.5	< 0.001
Health status	Healthy	4	0.34 (-2.08, 2.75)	0.785	72.5	0.012
	At risk/disease	25	1.32 (0.52, 2.12)	0.001	99.6	< 0.001
Sample size	< 64 persons	13	0.70 (-0.42, 1.82)	0.222	83.0	< 0.001
	≥ 64 persons	16	1.54 (0.74, 2.35)	< 0.001	99.7	< 0.001
Sex	Female	6	-0.08 (-0.25, 0.09)	0.376	72.1	0.003
	Male	1	3.48 (0.63, 6.33)	0.017	-	-
	Both	22	1.65 (0.86, 2.44)	< 0.001	98.7	< 0.001
Age	< 50 years	14	1.42 (0.24, 2.59)	0.018	99.1	< 0.001
	≥ 50 years	15	1.08 (0.55, 1.60)	< 0.001	98.4	< 0.001
BMI	< 28.8	12	0.82 (0.26, 1.38)	0.004	98.6	< 0.001
	≥ 28.8	15	1.55 (0.46, 2.65)	0.006	99.1	< 0.001
	Unknown	2	-1.35 (-7.03, 4.34)	0.642	76.4	0.039
Geographical region	Asia	19	0.49 (-0.37, 1.35)	0.267	98.9	< 0.001
	Australia	1	-0.03 (-0.12, 0.06)	0.518	-	-
	Europe	3	0.75 (-0.77, 2.27)	0.335	66.3	0.052
	Americas	6	3.90 (1.83, 5.97)	< 0.001	96.5	< 0.001
Quality assessment	Good	-	-	-	-	-
	Fair	16	1.33 (0.28, 2.37)	0.013	99.5	< 0.001
	Weak	13	1.11 (0.09, 2.12)	0.032	98.7	< 0.001
Publication year of article	< 2016	14	1.40 (0.95, 1.85)	< 0.001	95.6	< 0.001
	≥ 2016	15	0.76 (-0.15, 1.67)	0.104	99.1	< 0.001

HDL-c: high density lipoprotein cholesterol, BMI: body mass index, mg/dl: milligram per deciliter, mg/d: milligram per day, CI: confidence interval

most trials were conducted in Asia and America and only a few articles were from Europe and Australia; therefore, we could not assess the effect of geographical region on magnesium effect. Seventhly, there were not enough separate studies on males and females; therefore, the effect of sex on magnesium effect remained unclear. Eighthly, the heterogeneity between studies was statistically significant and was not eliminated by statistical methods; therefore, our findings should be interpreted with caution.

Under the shade of these limitations, this systematic review and meta-analysis enjoys.

some strengths. At the first glance, this study is at the top of the hierarchy of clinical evidence. It is noticeable to highlight that as no time limitation was imposed on our systematic search, we tried to find the source of heterogeneity through conducting subgroup analyses. In addition, following PRISMA guidelines, we attempted to perform and report the results and minimized potential bias in the systematic review process through a comprehensive search strategy as well. Finally, we excluded RCTs that assessed the effect of magnesium on lipid profile besides other interventions; consequently, the confounding effect of those interventions was removed.

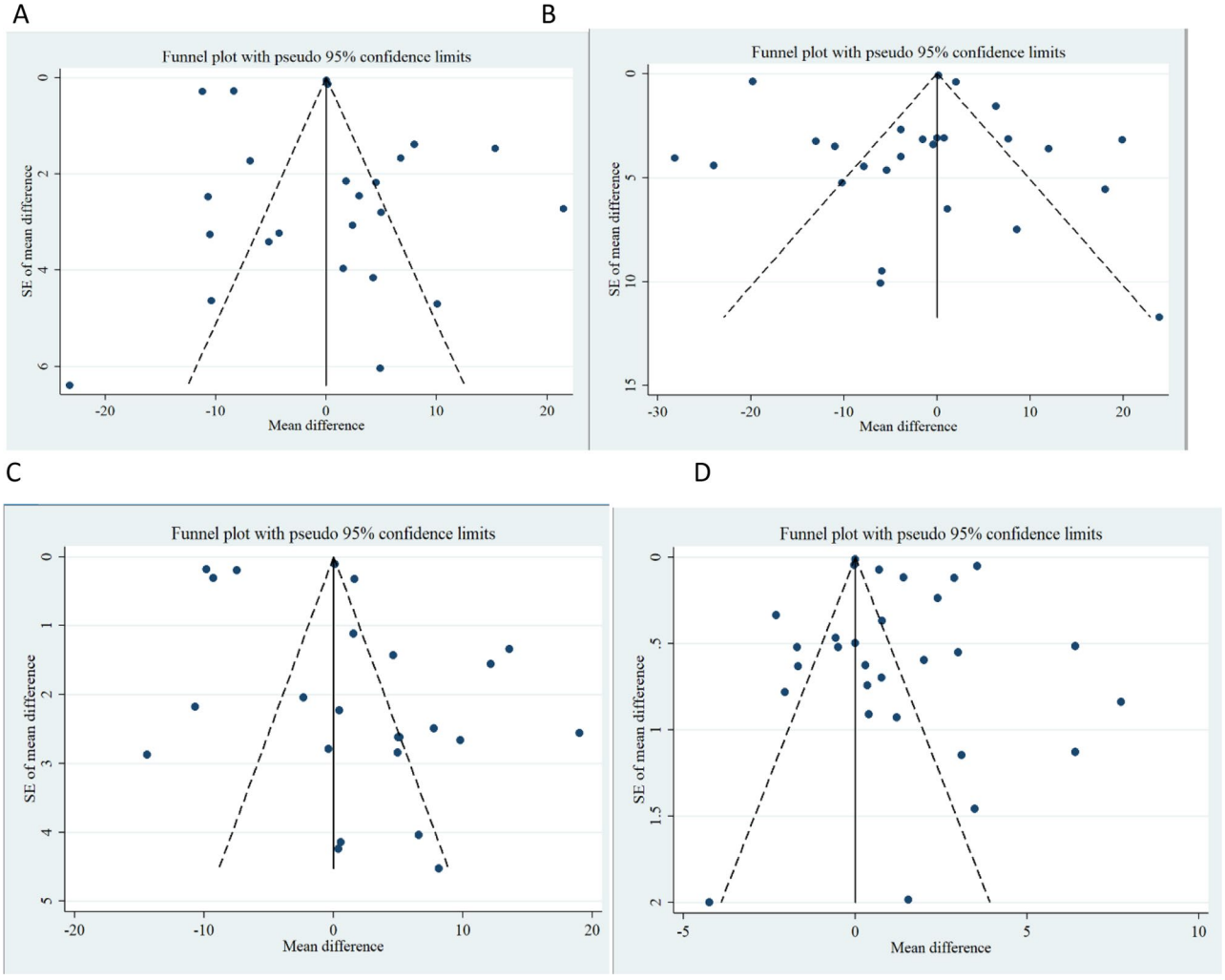

Fig. 4 Funnel plots for the studies of the effects of magnesium supplementation on serum concentrations of lipid profile. **A**: TC; **B**: TG; **C**: LDL-C; **D**: HDL-C

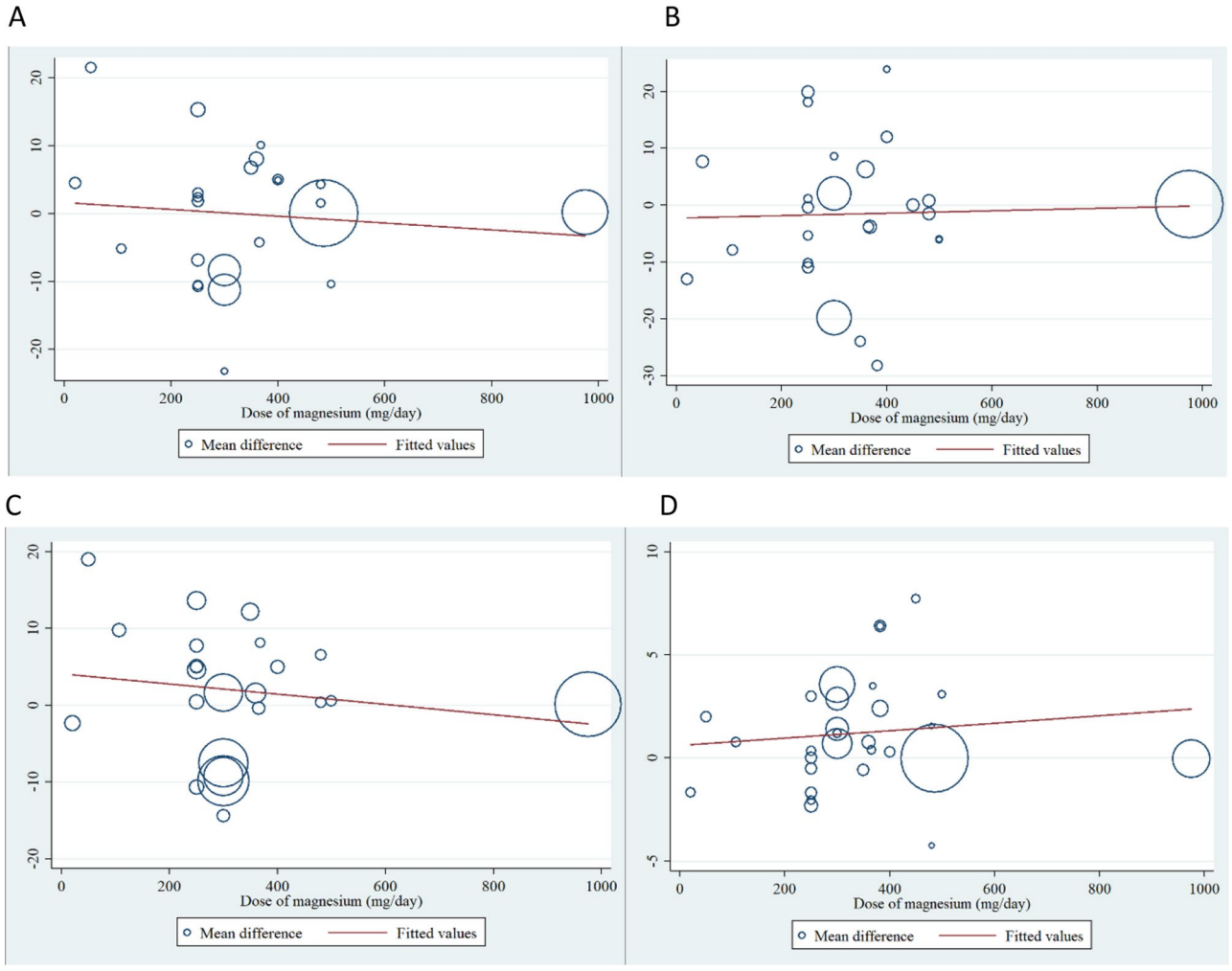

Fig. 5 Meta-regression plot of the effect of magnesium supplementation dose on serum concentrations of lipid profile. **A**: TC; **B**: TG; **C**: LDL-C; **D**: HDL-C

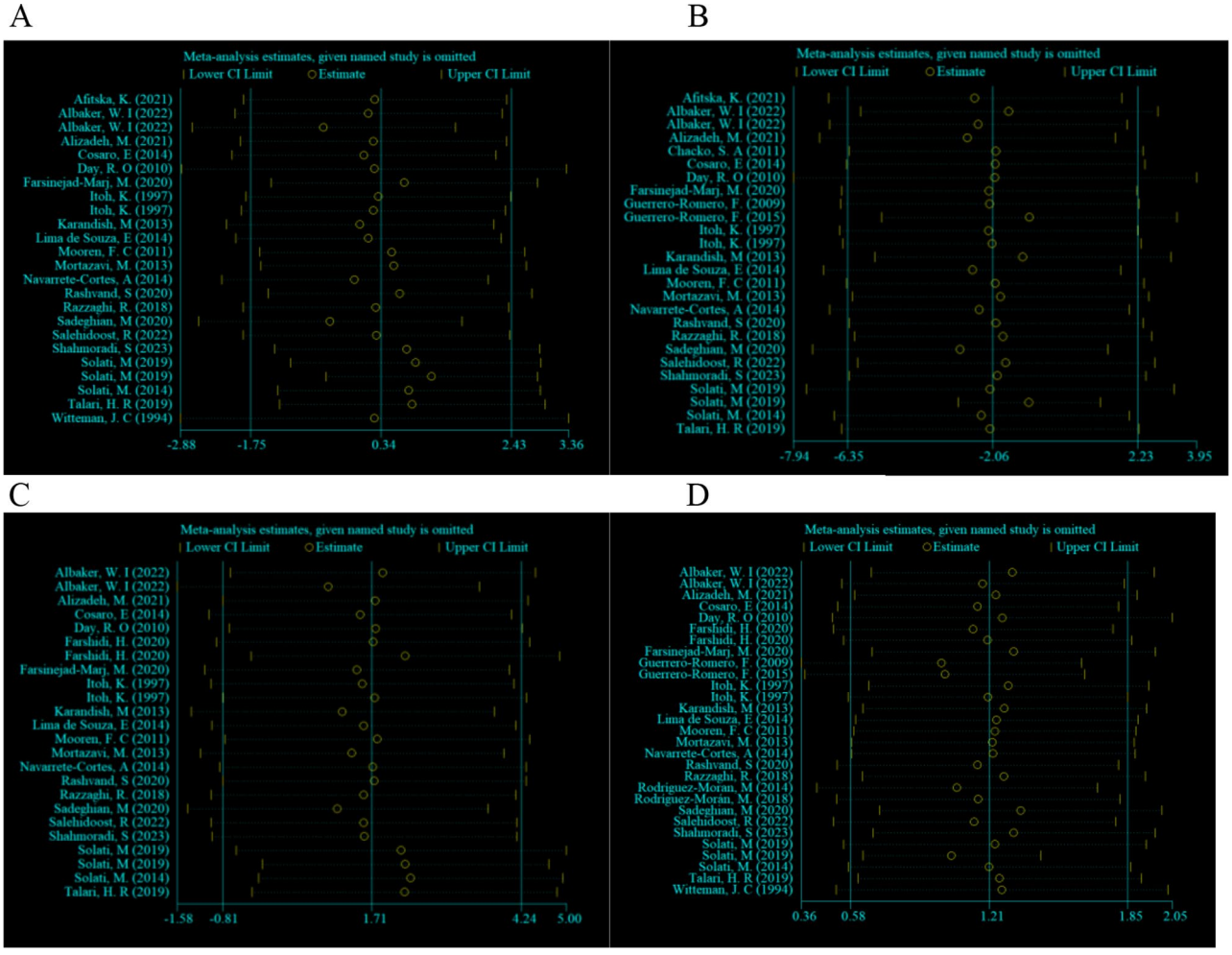

Fig. 6 Sensitivity analysis plots for the studies of the effects of magnesium supplementation on serum concentrations of lipid profile. **A**: TC; **B**: TG; **C**: LDL-C; D: HDL-C

Conclusion

In conclusion, the findings of the present study supported that magnesium supplementation significantly increased serum levels of HDL-C, but no effects were observed on LDL-C, TG, and TC. However, the results of our subgroup analyses revealed that participants with a BMI‹29.5 might benefit more from magnesium supplementation regarding TC reduction to a higher extent. Our results also indicated higher doses of magnesium (≥ 300 mg/day) and longer intervention durations (≥ 84 days) are critical for increasing HDL-C. Furthermore, magnesium is more effective in participants with disease, health risk factors, and lower HDL-C levels. Considering the high degree of heterogeneity and elucidating the role of nationality, magnesium levels, sex, and food habits on the effect of magnesium supplements, more RCTs are required to confirm these results.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	β-hydroxy β-methylglutaryl-CoA
LDL-C	Low-density lipoprotein cholesterol
MeSH	Medical subjects heading
MD	Mean differences
RCTs	Randomized controlled trials
SD	Standard deviations
SE	Standard errors
TC	Total cholesterol
TG	Triglyceride
WMD	Weighted mean difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01085-w.

Supplementary Material 1

Supplementary Material 2

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Author contributions
The design of search strategy was done by AGh. Searching data bases was done by MH and AGh, they also choose relevant RCTs based on inclusion and exclusion criteria. Reading articles full text, and data extraction was done by all authors. AGh performed statistical analysis. The manuscript was written by All authors. All discrepancies in every stage were solved through group discussions.

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Data availability
The data presented in this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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