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Review article

Effect of alpha-lipoic acid supplementation on lipid profile: A systematic review and meta-analysis of controlled clinical trials

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A B S T R A C T

Several studies have shown the effect of alpha-lipoic acid (ALA) on lipid profile. However, findings remain controversial. This systematic review and meta-analysis was conducted to systematically summarize the available clinical trials that examined the effects ALA supplementation on the lipid profile of adults. A systematic search through PubMed and Scopus was done for studies published in English up to April 2017. Effect sizes were combined with fixed- or random-effects analysis, where appropriate. Between-study heterogeneity was evaluated by Cochran's Q test and I^2. Eleven clinical trials with 452 adults (51.5% women, 48.5% men) were included in this meta-analysis. Combining effect sizes of 10 studies on serum triacylglycerol (TG) concentrations revealed a significant effect of ALA supplementation on serum TG compared with the placebo group (weighted mean difference [WMD], −29.185 mg/dL; 95% confidence interval [CI], −51.454 to −6.916; $P = 0.010$). We also found significant changes in serum total cholesterol and low-density lipoprotein (WMD, −10.683 mg/dL; 95% CI, −19.816 to −1.550; $P = 0.022$, WMD, −12.906 mg/dL; 95% CI, −22.133 to −3.679; $P = 0.006$, respectively). Significant changes were not observed in serum high-density lipoprotein (WMD, −0.092 mg/dL; 95% CI, −3.014 to 2.831; $P = 0.025$). Supplementation dosage and body mass index were potential sources of heterogeneity, in which those with body mass index >30 kg/m^2 who received >600 mg/d ALA showed better improvements in lipid profile. Our findings showed that supplementation with ALA significantly decreased the serum concentrations of TG, total cholesterol, and low-density lipoprotein but did not affect serum levels of high-density lipoprotein in adults.

Introduction

Coronary artery disease (CAD) is a major health problem with a high rate of mortality throughout the world [1]. As has been shown in previous studies, dyslipidemia, particularly disturbances in the level of low-density lipoprotein cholesterol (LDL-C), is associated with a higher risk for CAD [2,3]. The American Heart Association has estimated that one-third of the American population has a moderately high-level total cholesterol (TC; >200 mg/dL) and >34 million American adults have a high-level of TC (>240 mg/dL) [4]. The most common lipid disorders (80%) are associated with diet and lifestyle. Hence, dietary recommendation is an effective way to treat dyslipidemia. Nevertheless, these methods have made only modest improvements [5,6].

In recent years, the lipid-lowering effects of a large number of nutraceuticals have been examined in available trials [7]. Alpha-lipoic acid (ALA) or thioctic acid, an eight-carbon compound containing sulfhydryl groups, is an essential cofactor for mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase [8]. Moreover, ALA is considered a strong antioxidant that elicits its effects by clearing free radicals and chelating metal ions. Furthermore, it acts on other antioxidants such as ascorbic acid and vitamin E and increases intracellular glutathione levels [9]. Accordingly, ALA is expected to improve inflammatory conditions in the human body. Given that ALA is an antioxidant agent, previous studies have shown that it has lipid-modulating features that are related to the antiappetite characteristic of this supplement

SMM and KD conducted the study. SMM, MK, and SS-B searched the literature, extracted data, and performed the independent review process. SMM, AM, and HKV conducted the statistical analyses and wrote the manuscript. SS-B and KD finalized the manuscript. All authors read and accepted the manuscript. The authors have no conflicts of interest to declare.

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[10,11]. Some studies found an inverse relation between ALA supplementation and serum concentrations of the lipid profile [12,13], whereas other studies did not identify any significant linkage [14,15]. Thus, studies evaluating the association between ALA supplementation and lipid profile have reported controversial findings [16].

Although many studies have assessed the effects of ALA supplementation on lipid profile, no systematic approach has been used to summarize the previous findings. In the present study, we aimed to systematically review all published controlled trials that examined the effects of ALA supplementation on lipid profile components in adults.

Methods

Search strategy

We searched online databases for relevant articles up to April 27, 2017, through PubMed and SCOPUS, with no time restriction. Only English-language articles were included in this study. For this purpose, we used the following combination of MeSh and text words: “Thioctic Acid” OR “α-Lipoic” OR “alpha-lipoic” OR “lipoic acid” OR “thioctic” OR “α-LA” OR “alpha-lipoic acid” AND “Triacylglycerols” OR “Lipoproteins, HDL” OR “Cholesterol, HDL” OR “Cholesterol, LDL” OR “Lipoproteins, LDL” OR “Hyperlipidemias” OR “Dyslipidemias” OR “Hypercholesterolemia” OR “lipoprotein triacylglycerol” OR “LDL” OR “HDL” OR "Total cholesterol" OR “TG” OR “Triacylglycerol” OR “Triacylglycerol” OR “TAG” OR “lipid profile” OR “low density lipoprotein” OR “high density lipoprotein” OR “blood lipids” OR “lipids*” OR “triglycerid*” OR “trigly*” OR “triacylglycerol” OR “cholesterol” OR “LDL-C” OR “HDL-C” OR “Hyperlipidemia” OR “Hyperlipidemic” OR “Dyslipidemia” OR “Dyslipidemic” OR “Hypercholesterolaemia” OR “Hypercholesterolemic” OR “hypercholesterolaemic”. To avoid missing any relevant articles, we reviewed the reference lists of all review publications. Unpublished studies were not included in this study.

Inclusion criteria

Studies were included if they

- were controlled clinical trials in design;
- supplemented an oral ALA (we also included studies that solely supplemented ALA);
- reported admissible outcomes including triacylglycerols (TG), TC, or LDL-C or high-density lipoprotein cholesterol (HDL-C);
- were conducted on adults (>18 y of age); and
- reported lipid profile parameters after the intervention.

If multiple articles with the same data set were identified, only the most comprehensive were considered [17]. Preferred Reporting Items of Systematic Reviews and Meta-Analysis guidelines were used to perform and report the current meta-analysis [18].

Exclusion criteria

Letters, comments, short communications, conference papers, ecologic studies, reviews, meta-analyses, and ecologic studies were not included in the present study. Studies were excluded if they

- were done on animals, pregnant women, or children;
- were observational studies such as cohort and case−control studies;
- simultaneously examined the effects of other interventions along with ALA supplementation;
- did not have a control group; and
- reported incomplete data.

Data extraction

Study selection and data extraction were carried out by two investigators independently. Every conflict concerning study selection was discussed and resolved by a third reviewer. Pertinent data were extracted from selected full-text studies including first author’s name, year of publication, type of study population, sample size, participants’ sex, supplementation dosage, intervention duration, baseline body mass index (BMI) of participants, mean age of participants, results (means and SDs of TG, TC, LDL, and HDL in baseline and after intervention), and list of confounders adjusted for. Any reported SEs, interquartile ranges, and 95% confidence intervals (CIs) were converted to SDs. Lipid profile components that were reported in a different unit were converted to the most common.

Quality assessment

Quality of the included studies was evaluated by the quantitative 5-point Jadad scale [19]. A value of 0 or 1 point was allocated for each of the five following criteria: randomization, appropriate description of randomization, double-blinding, appropriate description of double-blinding, and reports of withdrawals and dropouts with the eligible reason [19]. Studies that scored ≥3 and <3 were respectively considered as high and low quality [20].

Statistical analysis

Final outcomes and SDs were used to calculate the overall effect size between the ALA supplementation group and the placebo group. If there was an SE for variation of mean in a study, SD was calculated by the following formula: SE $\times \sqrt{n}$. We converted the studies that reported medians (interquartile ranges), to means (SD) as described by Hozo et al. [21]. The overall effect size was calculated using a random-effects model that takes between-study variation into account. Cochran’s Q test (significant with a $P < 0.10$) and I^2 were used to assess between-study heterogeneity [22]. Additionally, we used subgroup analysis to detect probable sources of heterogeneity. Publication bias assessment was done by visually inspecting funnel plots and Egger’s regression test [23]. Meta-regression analysis was executed to evaluate the association between overall estimate of effect size and ALA dosage and duration of supplementation. All statistical analyses were performed using Stata software version 12 (StataCorp, College Station, TX, USA). $P < 0.05$ was considered as statistically significant.

Results

Search results

The process of study selection is shown in Figure 1. After removing 149 duplicates from 1141 initially searched articles, 992 studies remained. Of the 992 studies, 955 irrelevant articles were excluded through title and abstract screening. Thus, 37 relevant articles were chosen for full-text review and detailed evaluation. Twenty-six articles were excluded because they had the following features: conducted with children or pregnant women, performed without a placebo group, reported incomplete data, supplemented ALA in combination with other bioactive components, and not did not measure lipid profile parameters. Finally, 11 eligible randomized controlled trials (RCTs) were included in this meta-analysis. Of the 11 RCTs, 10 publications reported effects of ALA on TG [12,14,17,24–30], 10 reported TC [13,14,17,24–30], 9 reported LDL [14,17,24–30], and 9 reported HDL [14,17,24–30].

Study characteristics

Eventually, 11 articles were included in this systematic review and meta-analysis [12–14,17,24–30]. All publications were RCTs and were published between 2009 and 2015. The duration of follow-up ranged from 2 to 20 wk. Overall, 452 adults (51.5% women, 48.5% men) participated in these studies. Demographic characteristics of the included studies are described in Table 1.

Among the 11 articles, 8 were conducted in developed countries [13,14,24,25,27–30] and the other 3 were conducted in developing countries [12,17,26]. Most of the participants in these studies were patients with diabetes [12,13,17,24,25,27,30], whereas others had end-stage renal disease [26], schizophrenia [28], age-related macular degeneration [14], and subclinical hypothyroidism [29]. The mean BMI range was between 24.1 and 33.8 kg/m^2. The participants taking part in these studies consisted of both sexes with the exception the studies by Salwa et al., which was confined to men [17], and Xiang et al., which was conducted with women only [29]. The age of the participants was between 21 and 79 y. The cases received daily ALA supplement with doses of 300 to 600 mg/d.

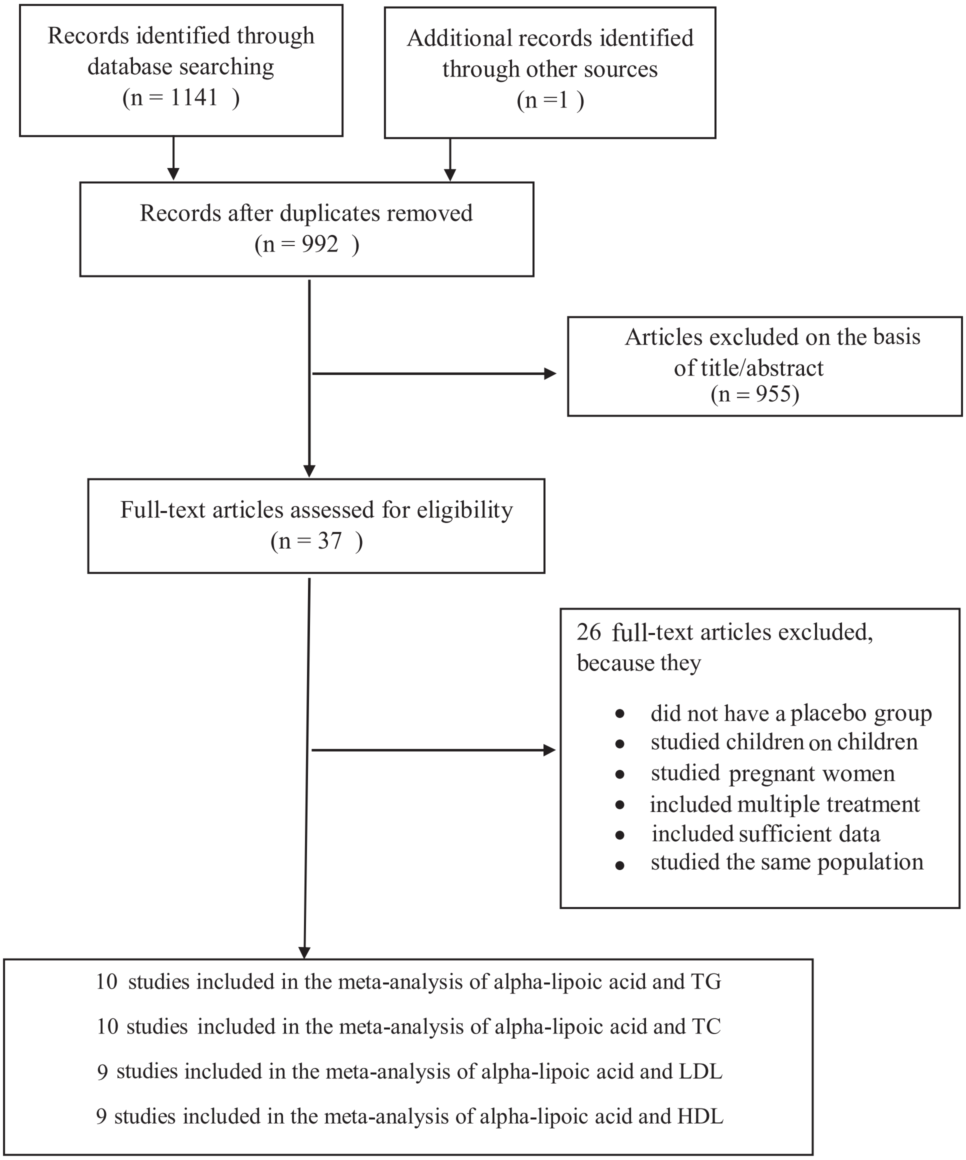

Fig. 1. Flowchart of study selection. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triacylglycerol.

Participants in seven studies were given 600 mg/d ALA supplement [12,14,17,24,26,27,29,30], and individuals in the control group received placebo. According to the Jadad scale, half of the included studies had low-quality score [12,14,17,28,29]; the other half had a high-quality score [13,25–27,30].

Findings from this meta-analysis

Pooled results from the random-effects model, which were performed on 10 studies with 194 cases and 208 controls, showed that ALA supplementation can result in a significant reduction in serum TG (mean difference (MD), −29.2; 95% CI, −51.4 to −6.9; $P = 0.01$) with significant heterogeneity between the eligible studies ($I^2 = 81.2\%$, $P < 0.0001$; Fig. 2). The subgroup analysis found that ALA dosage was a potential source of heterogeneity (<600 mg: $I^2 = 37.2\%$, $P = 0.782$) with the greater reduction in those who received 600 mg/d dose (MD, −60.5; 95% CI, −68.3 to −52.7; $P < 0.001$). BMI was another potential source of heterogeneity. Participants with BMI >30 kg/m^2 had a significant reduction in serum TG compared with those with BMI <30 kg/m^2 (MD, −65.1; 95% CI, −73.2 to −57.0 versus MD, −2.2; 95% CI, −22.2 to 17.6). Results of the subgroup analyses are summarized in Table 2.

By combining findings from 10 studies, including 189 cases and 203 controls, using a random-effects model, we found a significant reduction in serum TC with ALA supplementation (MD, −10.6; 95% CI, −19.8 to −1.5; $P = 0.022$). A significant between-study heterogeneity was noted ($I^2 = 55\%$, $P = 0.018$; Fig. 3). The subgroup analyses showed that ALA dosage (<600 mg: $I^2 = 0\%$, $P = 0.497$), baseline BMI (<30 kg/m^2: $I^2 = 0.0\%$, $P = 0.539$), study quality (<3: $I^2 = 0\%$, $P = 0.764$), and intervention duration (≥10 wk: $I^2 = 30.9\%$, $P = 0.216$) were potential sources of heterogeneity. Additionally, the most significant association was observed in the 600-mg-dose subgroup (MD, −12.2; 95% CI, −19.3 to −5.02; $P = 0.001$), obese subgroup (MD, −16.06; 95% CI, −23.05 to −9.07; $P < 0.001$), high-quality subgroup (MD, −15.6; 95% CI, −23.7 to −7.4; $P < 0.001$), and with duration of intervention ≥12 wk (MD, −11.7; 95% CI, −20.8 to −2.6; $P = 0.011$).

A pooled analysis of nine trials with 342 participants reported a significant association between ALA treatment and reduction in

Table 1
Characteristics of included studies

First author (year of publication)	country	Study design (duration)	Sex	Mean age (y)	Mean BMI (kg/m^2)	Type of study population	Sample size	ALA dosage (mg)	Study quality (Jadad score)
Gianturco et al. (2009) [25]	Italy	Randomized, placebo-controlled (4 wk)	Both	58	NR	Type 2 diabetes	14	400	3
Lukaszuk et al. (2009) [27]	US	Randomized, double-blind, controlled (13 wk)	Both	56	33.8	Type 2 diabetes	20	600	3
Xiang et al. (2010) [29]	China	Randomized, clinical trial (3 wk)	Female	57	24.1	Subclinical hypothyroidism	40	300	2
Salwa et al. (2011) [17]	Egypt	Placebo-controlled, clinical trial (8 wk)	Male	46.6	30.02	Type 2 diabetes	30	600	1
de Oliveira et al. (2011) [24]	Brazil	Randomized, double-blind, controlled (16 wk)	Both	56.2	<30	Type 2 diabetes	52	600	3
Zhang et al. (2011) [30]	China	Randomized, double-blind, controlled (2 wk)	Both	52.5	30.2	Obese with IGT	22	600	3
Khabbazi et al. (2012) [26]	Iran	Randomized, double-blind, controlled (8 wk)	Both	53.83	25.46	End-stage renal disease	52	600	4
Sun et al. (2012) [14]	China	Randomized, clinical trial (12 wk)	Both	65.78	24.5	Age-related macular degeneration	56	600	2
Udupa et al. (2012) [13]	India	Randomized, single-blind, controlled (12 wk)	Both	53.5	32.26	Type 2 diabetes	50	300	4
Vidovic et al. (2014) [28]	Serbia	Placebo-controlled, clinical trial (12 wk)	Both	39.7	26.7	Schizophrenia	56	500	1
Okanovic et al. (2015) [12]	Bosnia	Placebo-controlled, clinical trial (20 wk)	Both	62.97	30.57	Obese with diabetes mellitus	60	600	1

ALA, alpha-lipoic acid; BMI, body mass index; IGT: Impaired glucose tolerance; NR, not reported.

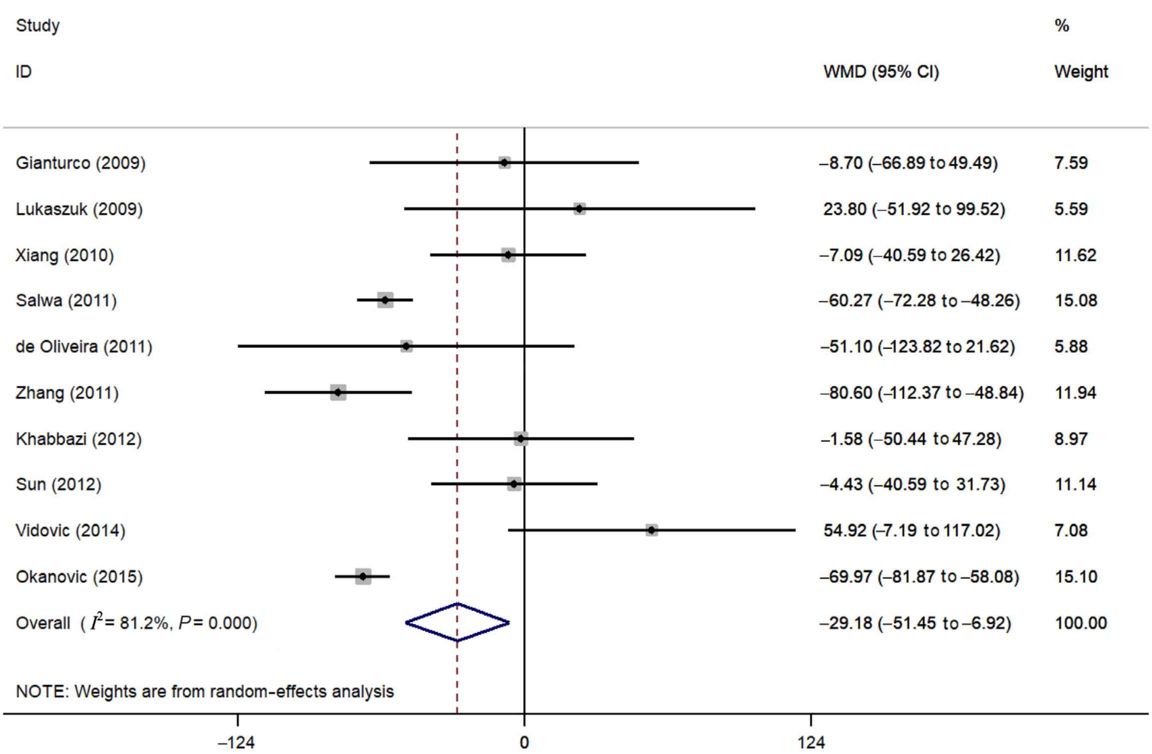

Fig. 2. Forest plot of weighted mean difference (WMD) on serum TG between supplementation with alpha-lipoic acid and placebo group. TG, triacylglycerol.

serum LDL (MD, −12.9; 95% CI, −22.1 to −3.6; $P = 0.006$), with significant between-study heterogeneity ($I^2 = 71.9\%$, $P < 0.001$; Fig. 4). The subgroup analysis showed that ALA dosage (<600 mg: $I^2 = 12.3\%$, $P = 0.320$), baseline BMI (<30 kg/m^2: $I^2 = 9.5\%$, $P = 0.352$), study quality (<3: $I^2 = 0\%$, $P = 0.829$), and intervention duration (≥12 wk: $I^2 = 0\%$, $P = 0.512$) were the potential sources of heterogeneity. Moreover, the most significant reduction in serum LDL was noticed with dose >600 mg/d (MD, −11.8; 95% CI, −14.9 to −8.7; $P < 0.001$), obese participants (MD, −12.4; 95% CI, −15.6 to −9.1; $P < 0.001$), high-quality studies (MD, −20.9; 95% CI, −28.7 to −13.1; $P < 0.001$), and <12 wk duration of intervention (MD, −11.8; 95% CI, −14.9 to −8.8; $P < 0.001$).

After merging the results from nine studies with 164 cases and 178 controls, no significant effect was observed in serum HDL between the intervention and placebo groups (MD, -0.09; 95% CI, -3.01 to 2.8; $P = 0.95$). Moreover, significant between-study

Table 2
Results of subgroup analysis of included controlled trials in meta-analysis of alpha-lipoic acid supplementation and lipid profile

Variable	Dose supplementation		Baseline BMI		Study quality		Trial duration	
TG	<600 mg	600 mg	Obese (BMI >30 kg/m^2)	Nonobese (BMI <30 kg/m^2)	Low (<3)	High (≥3)	<12 wk	≥12 wk
No. of comparisons	3	7	4	5	5	5	5	5
WMD (95% CI)	−11.751 (−21.763 to −1.740)	−60.573 (−68.351 to −52.796)	−65.154 (−73.276 to −57.032)	−2.293 (−22.202 to 17.616)	−57.039 (−64.967 to −49.111)	−42.840 (−64.826 20.854)	−53.232 (−63.478 to −42.985)	−57.854 (−68.731 to −46.977)
P-value	0.782	0.000	0.000	0.821	0.000	0.000	0.000	0.000
I^2 (%)	37.2	74.6	59.9	21.3	88.2	68	77.8	86.5
P-heterogeneity	0.203	0.001	0.058	0.279	0.000	0.014	0.001	0.000
TC								
No. of comparison	4	6	4	5	4	6	5	5
WMD (95% CI)	−10.977 (−19.784 to −2.171)	−12.175 (−19.323 to −5.026)	−16.064 (−23.054 to −9.074)	−3.961 (−13.529 to 5.606)	−8.258 (−15.869 to −0.647)	−15.607 (−23.719 to −7.496)	−11.642 (−18.645 to −4.639)	−11.795 (−20.897 to −2.694)
P-value	0.015	0.001	0.000	0.417	0.033	0.000	0.001	0.011
I^2 (%)	0.0	71.6	76.6	0.0	0.0	70.9	71.9	30.9
P-heterogeneity	0.497	0.004	0.005	0.539	0.764	0.004	0.007	0.216
LDL								
No. of comparison	3	6	3	5	4	5	5	4
WMD (95% CI)	−11.751 (−21.763 to −1.740)	−11.810 (−14.918 to −8.702)	−12.419 (−15.640 to −9.197)	−6.674 (−14.656 to 1.307)	−10.275 (−13.482 to −7.068)	−20.954 (−28.795 to −13.113)	−11.869 (−14.928 to−8.810)	−10.774 (−23.041 to 1.493)
P-value	0.021	0.000	0.000	0.101	0.000	0.000	0.000	0.085
I^2 (%)	12.3	80.9	90.5	9.5	0.0	81.4	84.7	0.0
P-heterogeneity	0.320	0.000	0.000	0.352	0.829	0.000	0.000	0.512
HDL								
No. of comparison	3	6	3	5	4	5	5	4
WMD (95% CI)	−2.212 (−6.980 to 2.555)	1.309 (0.596 to 2.021)	1.411 (0.685 to 2.136)	−2.875 (−5.946 to 0.195)	1.242 (0.518 to 1.966)	1.055 (−2.008 to 4.119)	1.346 (0.632 to 2.061)	−2.906 (−7.198 to 1.385)
P-value	0.363	0.000	0.000	0.066	0.001	0.499	0.000	0.184
I^2 (%)	84.1	0.0	0.0	27.8	73.0	37.8	40.8	57.8
P-heterogeneity	0.002	0.714	0.906	0.236	0.011	0.169	0.149	0.068

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triacylglycerol; WMD, weighted mean difference.

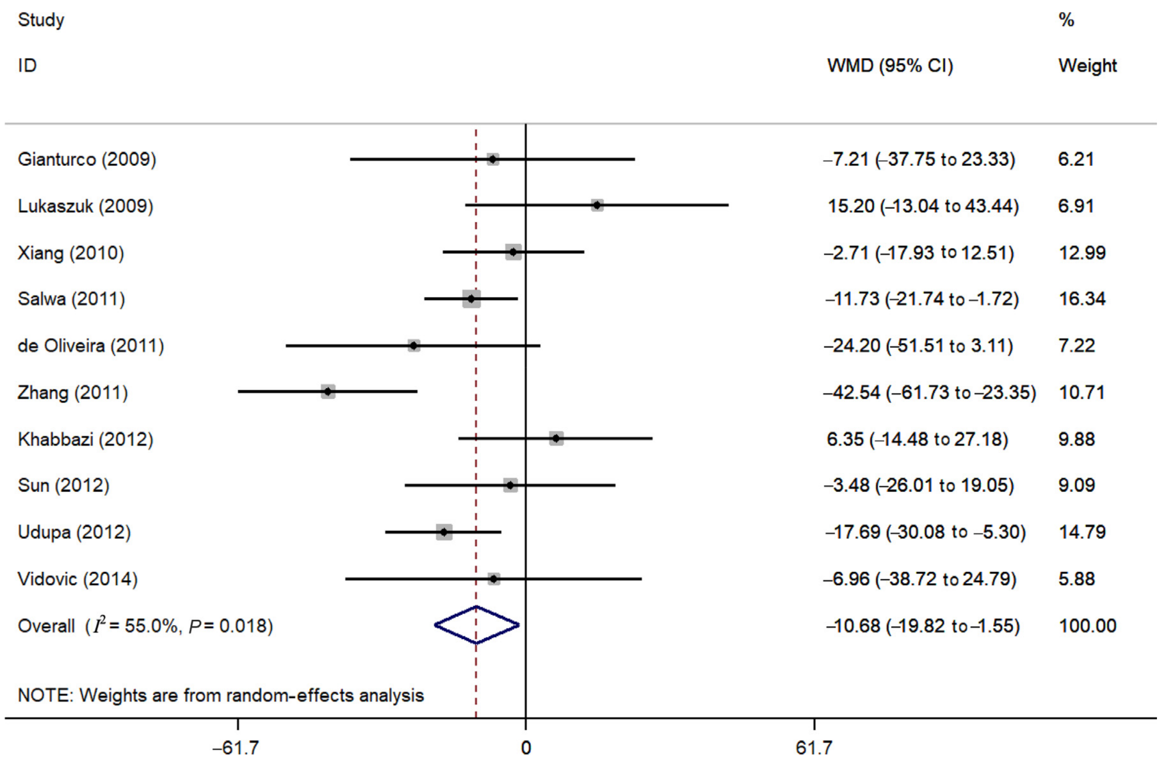

Fig. 3. Forest plot of weighted mean difference (WMD) on serum TC between supplementation with alpha-lipoic acid and placebo group. TC, total cholesterol.

heterogeneity was found ($I^2 = 54.4\%$, P 0.025; Fig. 5). The subgroup analysis demonstrated that ALA dosage (600 mg: $I^2 = 0\%$, $P = 0.714$), study quality (≥3: $I^2 = 37.8\%$, $P = 0.169$), intervention duration (<12 wk: $I^2 = 40.8\%$, $P = 0.149$), and BMI subgroups (obese: $I^2 = 0.0\%$, $P = 0.906$; nonobese: $I^2 = 27.8\%$, $P = 0.236$) were sources of heterogeneity. Furthermore, a significant increase in serum HDL was observed at a daily ALA dose of 600 mg (MD, 1.3; 95% CI, 0.59–2.02; $P < 0.001$), obese individuals (MD, 1.4; 95% CI, 0.68–2.13; $P < 0.001$), low-quality studies (MD, 1.24; 95% CI, 0.51–1.96; $P = 0.001$), and <12-wk intervention (MD, 1.34; 95% CI, 0.63–2.06; $P < 0.001$).

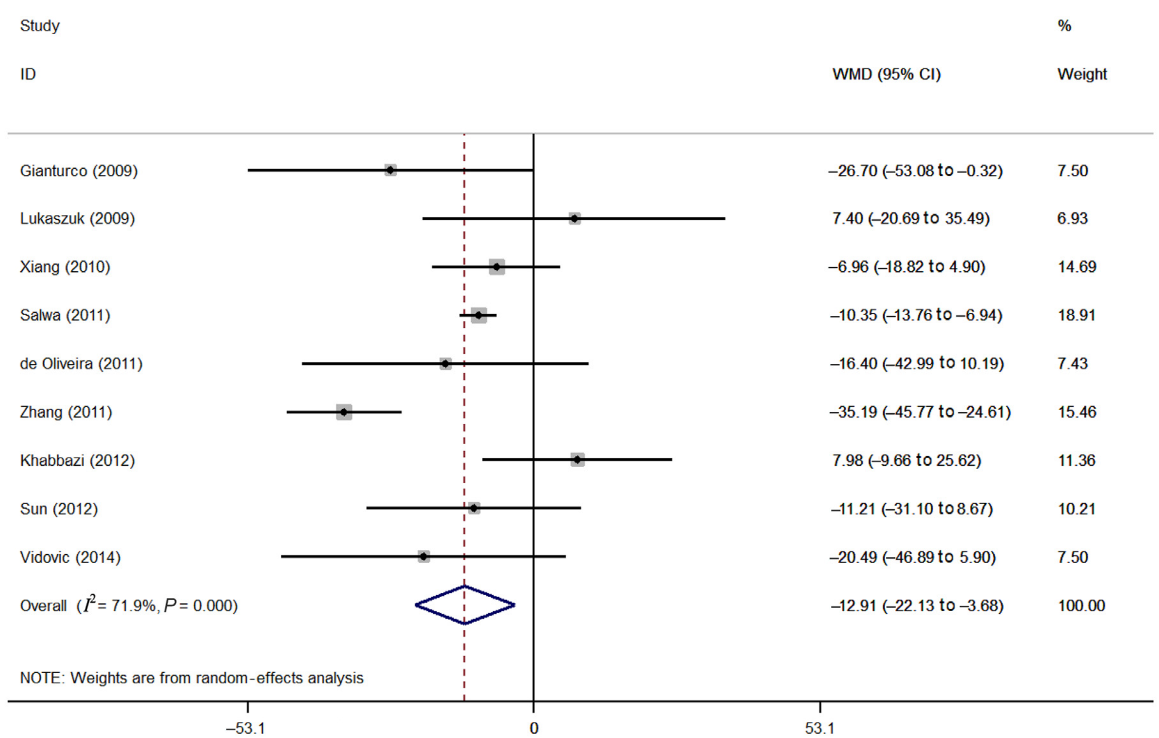

Fig. 4. Forest plot of weighted mean difference (WMD) on serum LDL between supplementation with alpha-lipoic acid and placebo group. LDL, low-density lipoprotein.

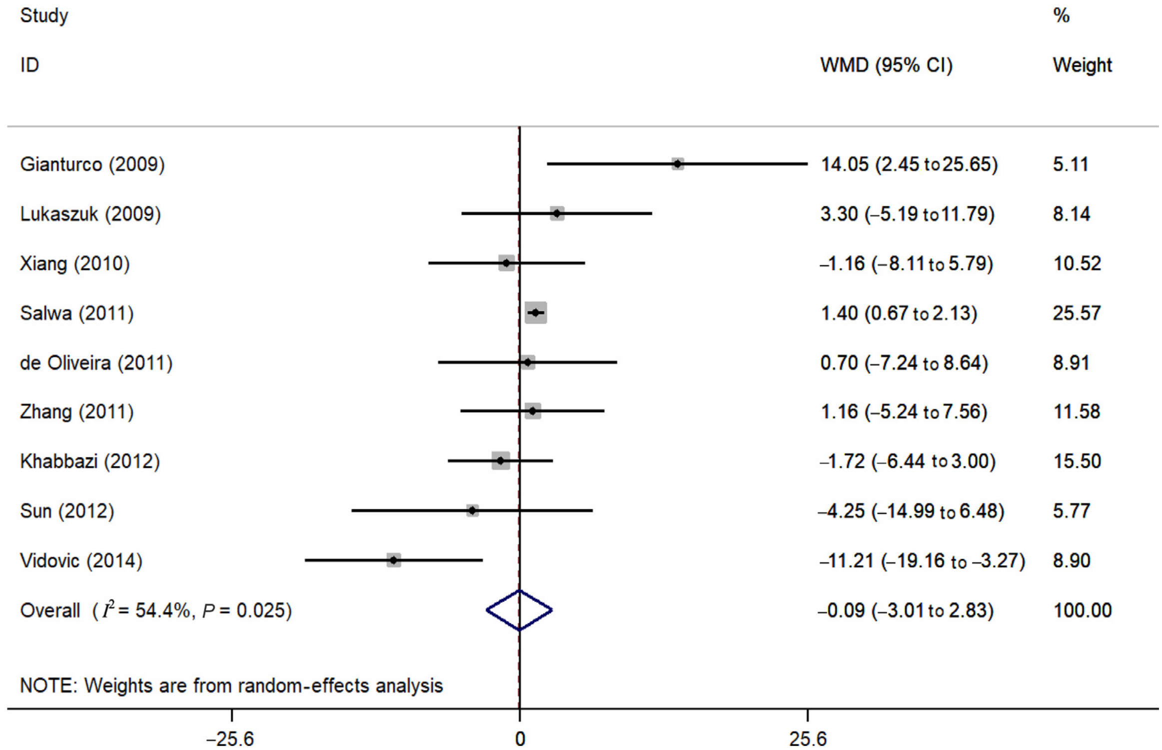

Fig. 5. Forest plot of weighted mean difference (WMD) on serum HDL between supplementation with alpha-lipoic acid and placebo group. HDL, high-density lipoprotein.

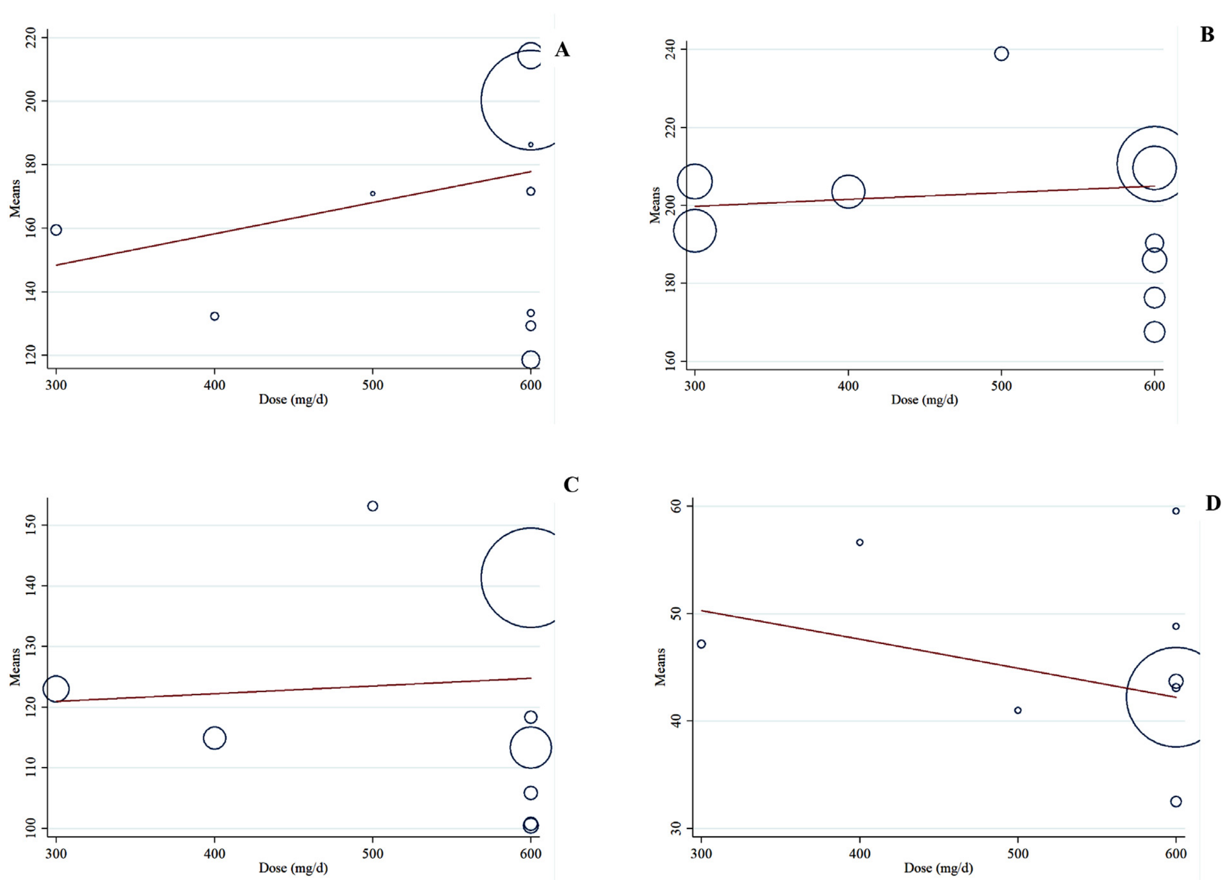

Fig. 6. Random-effects meta-regression plots of the association between ALA dosage (mg/d) and means of (A) TG, (**B**) TC, (**C**) LDL, and (**D**) HDL. ALA, alpha-lipoic acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triacylglycerol.

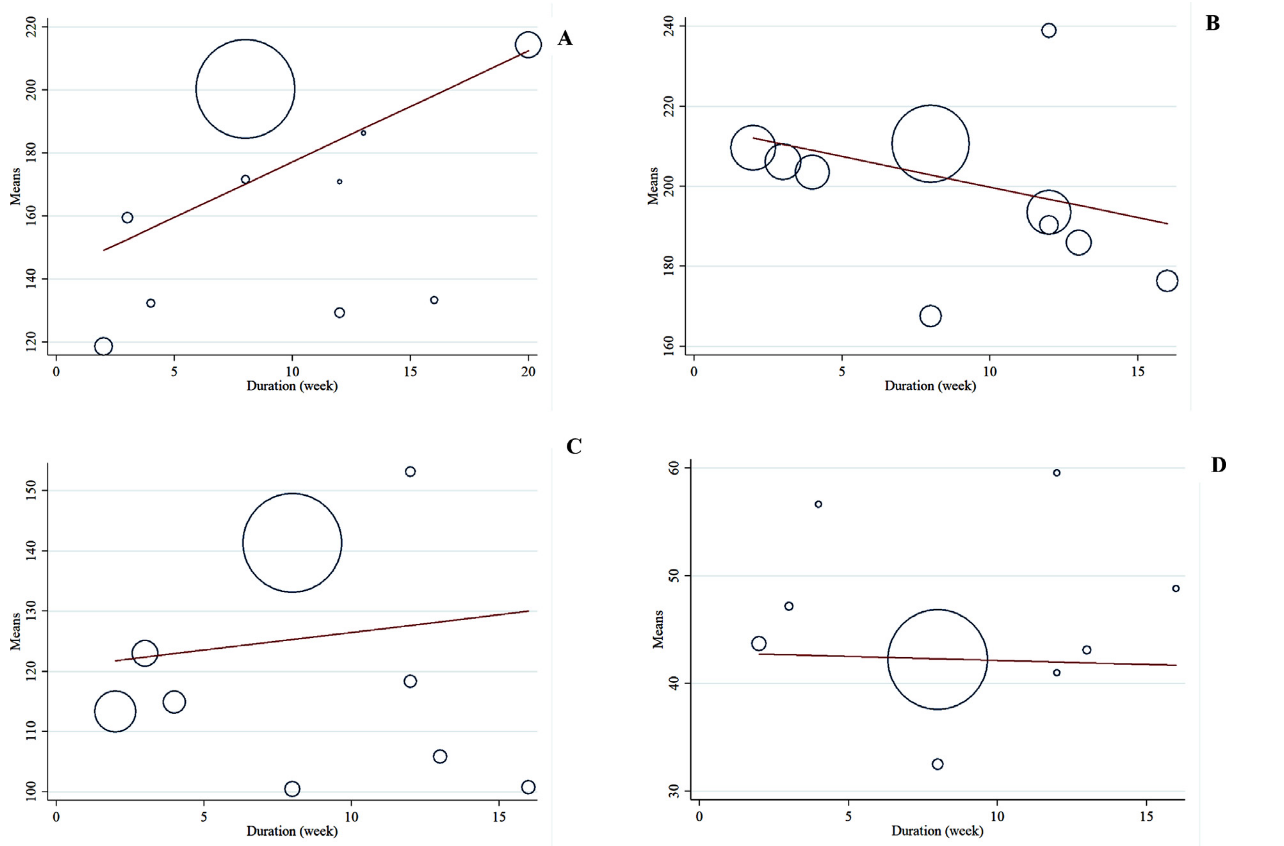

Fig. 7. Random-effects meta-regression plots of the association between duration of ALA supplementation (week) and means of (**A**) TG, (**B**) TC, (**C**) LDL, and (**D**) HDL. ALA, alpha-lipoic acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triacylglycerol.

Meta-regression analysis

Meta-regression analysis was performed to explore the association between lipid profile indices and potential moderator variables. The effect of ALA supplementation on TG (slope, 0.098; 95% CI, −0.355 to 0.552; $P = 0.63$), TC (slope, 0. 017; 95% CI, −0.115 to 0.149; $P = 0.77$), LDL (slope, 0. 012; 95% CI, −0.165 to 0.191; $P = 0.86$), and HDL (slope, −0.026; 95% CI, −0.103 to 0.049; $P = 0.43$) is independent of ALA dosage. Considering the duration of intervention, significant association was not found with TG (slope, 3.51; 95% CI, −2.32 to 9.35; $P = 0.20$), TC (slope, −1.52; 95% CI, −5.99 to 2.93; $P = 0.45$), LDL (slope, 0. 58; 95% CI, −4.28 to 5.46; $P = 0.78$), and HDL (slope, −0.07; 95% CI, −1.87 to 1.72; $P = 0.92$) (Fig. 6).

Publication bias

Funnel plots and Egger's regression tests indicated no evidence of substantial publication bias for TC ($P = 0.600$), LDL ($P = 0.784$), or HDL ($P = 0.443$(. However, there was a significant study effect for TG ($P = 0.009$) (Fig. 7).

Discussion

Results from the present study demonstrated that ALA consumption significantly decreased serum levels of TG, TC, and LDL, but a significant effect was not found on serum HDL with a high level of between-study heterogeneity. Supplementation dose and BMI were the potential sources of heterogeneity in all components. To the best of our knowledge, this is the first study to summarize the effects of ALA supplementation on the serum concentrations of lipid profile indices including TG, TC, LDL, and HDL.

ALA is produced naturally in animals and humans. It plays an important role in lipid metabolism in the liver, kidneys, and blood. It is also a cofactor of enzymes in carbohydrate metabolism [31,32]. Recently, it has been shown that ALA supplementation might affect the lipid profile by influencing lipid metabolism. However, these findings remain controversial [14,16,24]. Based on the findings in the present systematic review and meta-analysis, ALA supplementation reduced the serum levels of TG. In line with our findings, Carrier et al., in an animal experimental study, reported ALA decreased the serum levels of TG in high-fat diet-fed obese rats [33]. In another animal study, Miao et al. examined the effect of ALA in Wistar rats fed a high-fat diet for 12 wk and observed similar results [34]. In contrast, Hamano et al. did not find significant changes in serum TG levels [16]. The mechanisms through which ALA regulates serum levels of TG are still unknown. The probable lipid-lowering mechanism might be explained by beneficial effects of ALA on mitochondrial fatty acid β-oxidation through activation of AMP-activated protein kinase. Protein kinase inhibits the activation of acetyl-conezyme A carboxylase [35]. The next possible mechanism might be relevant to the blood glucose-lowering effect of ALA [36] that contributes to increasing the level of cAMP [37], which in turn decreases TG levels [35].

We found that ALA supplementation reduced the serum level of TC and LDL. Findings of some previous studies were in line with our results. An animal study that examined the effect of ALA on obese rats reported a significant change in serum cholesterol and LDL [38]. Zulkhairi et al., in another experimental study, showed the lipid-lowering effect of ALA [39]. However, some studies were not consistent with these results [16,24,26]. Some previous studies investigated that ALA might reduce TC or LDL by the following mechanisms:

- increased the activity of lipoprotein lipase
- synthesis LDL receptors in the liver lead to transmission of cholesterol to the hepatic system and increased synthesis of Apolipoprotein A [40]
- increased plasma adiponectin levels, which improved free fatty acid β-oxidation [41,42]

Overall, our findings indicated that ALA supplementation did not show any significant effect on serum HDL. In line with our result, Amom et al. examined the lipid-lowering effect of ALA in hypercholesterolemic animals. They observed that the level of HDL did not change significantly among the ALA and control groups [43]. Also, several human studies have shown the same result [14,24]. However, a number of studies have shown that ALA may affect serum HDL [25,26,44]. The pathway by which ALA affects the serum HDL is still unknown.

The present meta-analysis showed that a supplementation dose of ALA had an effect on the lipid profile. Subgroup analysis showed a significant reduction in serum TG, TC, and LDL as well as a significant increase in serum HDL concentration after a daily dose of 600 mg ALA. These findings may be described by the subsequent increase in circulating ALA after supplementation. Additionally, higher dosages are safe [45] and possibly could be more effective on the lipid profile than these dosages. Koh et al. performed a clinical trial on obese individuals with two doses of ALA (1200 and 1800 mg). They found the higher dose of ALA was more effective in reducing weight [46]. Therefore, a higher dose of ALA may lead to more reductions in the lipid profile; however, this needs to be proven in further studies.

We observed the higher effect of ALA intervention among obese (BMI $\geq$30 kg/m^2) participants. Subgroup analysis showed the levels of TG, TC, and LDL in obese individuals decreased more than in nonobese participants. Additionally, a significant increase in serum HDL was observed in the obese population than in those who were not obese. All studies with obese individuals reported weight loss during the intervention, which could be a reason for improvments in the lipid profile by ALA intervention. Kucukgoncu et al., in the recent meta-analysis, found that ALA supplementation significantly reduced weight loss compared with placebo [47]. As has been shown in previous publications, weight loss can improve lipid profile parameters in obese individuals [48,49]. In other words, individuals with higher BMI were more likely to be affected by this supplement.

Trial duration was another factor that influenced the lipid modulation of ALA supplementation. Subgroup analysis showed a significant reduction in serum TG and TC with trial durations of $\geq$12 wk. Also, supplementation duration <12 wk resulted in a significant reduction in serum LDL and an increase in serum HDL. We achieved conflicting results in regard to trial duration. Lipid profile changes soon after changing diets; however, long-term supplementation may need to confer promising results. Therefore, long-term, high-quality, double-blind, RCTs are needed to verify the long-term effects of ALA on lipid metabolism.

Limitations

The present study has some limitations. First, because of different study populations, different doses of supplementation, and differences in duration of interventions in the RCTs studied, high levels of heterogeneity were observed in the most analyses. Second, the present findings showed that TG and HDL had more improvements in low-quality studies but not in higher-quality studies. Third, about half of the eligible studies had a sample size <50 participants [17,25,27,29,30]. Additionally, the present search strategy was limited to English-language publications.

Interpretation of our meta-analysis findings on lipid levels should be done with caution. It should be noted that studies using different methodologies, evaluation of different populations, using ALA in various dosages, and in different durations. Further studies are selective for patients with dyslipidemia or considering the use of lipid-lowering agents as an exclusion criteria are necessary.

Conclusion

The present meta-analysis combined findings from 11 RCTs evaluating the effect of ALA consumption on the lipid profile. We found ALA supplementation might be effective in reducing serum levels of TG, TC, and LDL but not serum HDL in adults. Additionally, supplementation at 600 mg in obese individuals (BMI $\geq$30 kg/m^2) resulted in significantly improved parameters of the lipid profile. However, more studies with larger sample sizes, adequate durations, higher dosage, and various populations are needed to examine the beneficial effects of ALA supplementation on lipid profile components.

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