Cardiovascular pharmacology

Does alpha-lipoic acid affect lipid profile? A meta-analysis and systematic review on randomized controlled trials

Fahimeh Haghighatdoost[a,b], Mitra Hariri[c,*]

[a] Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[c] Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran

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ABSTRACT

Randomized controlled trials (RCTs) have demonstrated that alpha lipoic acid (ALA) may change lipid profile, but their results are contradictory. The aim of this study is to conduct a meta-analysis to assess the effects of ALA on lipid profile. Electronic databases including ISI web of science, Ovid, PubMed/Medline, SCOPUS, and Google Scholar were searched up to February 2018. RCTs which assessed ALA effects on lipid profile were selected. Weighted mean difference (WMD) and 95% confidence intervals (CIs) in serum lipids concentrations were defined as intervention effects. Random effects model was used to estimate the pooled effect. Heterogeneity was measured by using I^2 test. The protocol was registered with PROSPERO (No. CRD42017072365). Database search retrieved 12 articles. Serum total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-) levels were significantly lower in subjects supplemented with alpha-lipoic acid compared with controls (WMD = −10.18 mg/dL; 95% CI: −16.16, −4.20 mg/dL; P = 0.001 and WMD = −9.22 mg/dL; 95% CI: −18.28, −0.16 mg/dL; P = 0.001, respectively), but no significant changes were found for high density lipoprotein-cholesterol (HDL-c) (WMD: 3.02 mg/dL; 95% CI: −0.39, 6.43; P = 0.082). The overall effect of ALA on serum triglyceride did not reveal any significant change, but in subgroup analysis based on health status (diabetic vs. non-diabetic), ALA decreased serum triglyceride levels in both diabetic and non-diabetic groups compared with controls. This meta-analysis revealed that ALA might favorably affect lipid profile especially LDL and TC. However, for confirming these results, more studies particularly among hyperlipidemic patients are needed.

1. Introduction

Chronic diseases such as cardiovascular diseases (CVD) have been major contributors to global mortality in recent years. The total number of death caused by CVD indicated globally increase to 17.5 million in the year 2005 from 14.4 million in 1990 (Institute of Medicine and Board on Global Health, 2010). The enhancement of serum triglyceride, low density lipoprotein (LDL) and the reduction of high density lipoprotein (HDL) are risk factors for CVD (Indolfi et al., 2016). New evidence has shown that some food supplements instead of medicine can be protective against CVD risk factors (Askari et al., 2014; Azimi et al., 2014; Feizollahzadeh et al., 2017; Haghighatdoost and Hariri, 2018).

Alpha-lipoic acid (5-(1,2-dithiolan-3-yl)-pentanoic acid; ALA) can be found in low concentrations as natural antioxidant in plant sources such as spinach, broccoli and tomatoes (Lodge et al., 1997). Furthermore, ALA can be synthesized in the mitochondria in mammalian

tissues such as testis, heart and liver which have high activity and great numbers of mitochondria (Carreau, 1979; Dupre et al., 1980; Morikawa et al., 2001).

ALA does not only act as a cofactor for alpha keto dehydrogenases (Reed, 1974) but might also have different biochemical functions such as antioxidant activities (Shay et al., 2009). Besides its direct effect as antioxidant and indirect anti-inflammatory effects through transcription factors properties (Lee and Hughes, 2002; Zhang and Frei, 2001), new articles propose that ALA might improve glycemic control, prevent diabetic complications such as neuropathy, prevent oxidation of LDL and might also have anti-obesity properties (Shay et al., 2009; Wongmekiat et al., 2013; Miao et al., 2013).

Research has led us to believe that ALA can regulate lipid metabolism in the kidney, liver, and blood by participating in various enzymatic complexes (Packer et al., 2001). In addition, it might protect liver against fat accumulation by reducing body weight, increasing

metabolism and suppressing appetite (Kim et al., 2004, 2008; Feng et al., 2013). Recent evidence proposes that decreasing effect of ALA on fat mass, body weight and body mass index (BMI) among overweight/obese participants is accompanied by a reduction in lipid profile (Kim et al., 2004; Carbonelli et al., 2010), haemoglobin-A1c (Koh et al., 2011) and inflammatory markers such as interleukin 6 (IL-6), C-reactive protein (CRP), or tumor necrosis factor-a (TNF-α) (Carbonelli et al., 2010).

Articles on animals and humans have reported possible ALA effects on lipid profile but their results are different. Carrier *et al.* indicated that ALA can protect Zucker rats against hypercholesterolemia and diet-induced obesity (Carrier et al., 2014). Another study by Maio *et al.* indicated that ALA reduced adverse effects of a 12-wk high fat diet on lipid profile among Wistar rats (Miao et al., 2013).

So far, there are a lot of clinical trials, with varied results, assessing the effects of ALA on lipid profile. Some articles indicated lowering effect, while most of them did not report any effect on lipid profile. However, there is no meta-analysis regarding ALA effects on lipid profile. Therefore, by conducting a meta-analysis we can achieve an answer for the question whether ALA consumption affects the serum concentrations of lipid profiles.

2. Materials and methods

2.1. Search strategy

In order to identify related articles which assessed the effect of ALA on lipid profile, we used advanced search methods for searching electronic databases such as ISI web of science, Ovid, PubMed/Medline, SCOPUS, and Google Scholar up to February 2018 without time restriction.

These databases were searched by related key words including MeSH and non-MeSH terms for lipid profile and ALA: "alpha-Lipoic Acid", "Acid, alpha-Lipoic", "alpha Lipoic Acid", "Lipoic Acid", "alpha Lipoic Acid", "α-lipoic acid", "Low Density Lipoprotein Cholesterol", "Lipoproteins, LDL", "Cholesterol LDL", "Triglycerides", "LDL triacylglycerol", "Triacylglycerol", "Triacylglycerols", "HDL Lipoproteins", "Lipoproteins, HDL", "High-Density Lipoproteins", "Lipoproteins, High-Density", "High Density Lipoproteins", "Cholesterol", "Lipoproteins, VLDL", "VLDL Cholesterol", "Very Low Density Lipoprotein Cholesterol", "Cholesterol, VLDL", "Very-Low-Density Lipoproteins", "VLDL Lipoproteins", "Lipoproteins, Very-Low-Density", "Lipoproteins VLDL", "Very Low Density Lipoproteins", "Lipoproteins, VLDL", "VLDL Lipoproteins", "VLDL", "TC", "LDL", "total cholesterol", "HDL" and "TG". The results of database searches were exported to the reference manager software; Endnote, version X6 (Thomson Reuters, New York, USA). Moreover, the reference lists of all retrieved RCTs were checked to find further RCTs. For advanced search, we used parentheses to search a group of key words, quotation mark to search the exact term and asterisks for finding all words derived from one key word. Both authors screened titles and abstracts of all retrieved articles to find relevant randomized clinical trials (RCTs). Any discrepancies were solved by group discussion. The protocol was registered with PROSPERO (No. CRD42018091243).

2.2. Inclusion criteria

Studies selected for this meta-analysis have the following criteria: 1) Randomized controlled trial; 2) Human articles with age 18 or more; 3) Using intravenous or oral intake of ALA as intervention; 4) Clear information related to intervention dose and duration; 5) Not taking any other food supplements beside ALA; 6) Assessing lipid profile as outcome variables.

2.3. Exclusion criteria

Articles with the following criteria were excluded: 1) Unclear Table; 2) Intervention less than 1 week; 3) Taking other food supplements besides ALA in intervention; 4) Taking food supplements or any other type of intervention in control group which not performed in intervention group; 5) Not having control group; 6) Measuring cholesterol and triacylglycerol in subcutaneous adipocyte.

2.4. Quality assessment

Delphi checklist was used to assess the quality of selected articles. The checklist contains the following items: I) Using standard randomization; II) Concealing intervention allocation; III) Blinding the patients; IV) Blinding the care provider; V) Blinding outcome assessor; VI) Similarity between intervention and control group at baseline; VII) Defining eligibility criteria; VIII) Presenting variability of the outcome; and IX) Performing intention to treat analysis. Delphi score allocates RCTs scores between zero (very poor) and nine (rigorous) (Verhagen et al., 1998).

2.5. Data extraction

After screening the titles and abstracts, we chose related RCTs by reading the full text and considering inclusion and exclusion criteria and selected eligible articles. The following information was extracted from eligible articles: name of the first author, study location, publication year, ALA dose, placebo, sample size in each group, male and female number in each group, mean ± S.D. for lipid profile before and after intervention, participants' characteristics (such as basic disease, BMI, age) (Table 1).

2.6. Statistical analysis

All statistical analyses were performed using STATA, version 11 (Stata Corp, College Station, TX, USA). The mean change in the concentrations of serum lipids from baseline was calculated and the difference between the mean changes in the intervention and control group was calculated as the weighted mean difference. Weighted mean difference (WMD) and 95% confidence intervals (CIs) in serum lipids concentrations were defined as intervention effects. In original articles where data were presented as median and quartiles, they were converted to mean and standard deviation (Wan et al., 2014), then random effects model was used to estimate the pooled effect. Heterogeneity was measured by using the I^2 test and values > 50% were considered as the significant heterogeneity (Higgins et al., 2003). Potential sources of heterogeneity were explored by using sub-group analysis based on gender of participants, geographical region (Asia vs. non-Asia), duration of supplementation (< vs. ≥ 10 wk) and health status (diabetic vs. non-diabetic). Moreover, meta-regression analyses were performed to examine the dose- and duration-effect relation between alpha-lipoic acid and serum lipids changes. Publication bias was examined using Begg's and Egger's tests. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or group. P < 0.1 presents a significant publication bias. In the existence of a bias, trim and fill analysis was conducted to detect the contribution of the bias to the overall effect.

3. Results

3.1. Study characteristics

Through our search strategy, we retrieved 741 articles from which there were 469 duplicate articles. By further screening the titles and abstracts, we excluded 242 articles and eventually selected 30 articles for full text reading. Following our inclusion and exclusion criteria, a

Table 1
Randomized controlled trial studies included in the systematic review and meta-analysis.

Code Author (year) (country)	Subjects and gender	Age range (y) or mean ± SD	BMI range or mean ± SD	RCT	Intervention	Control	Duration (wk)	subjects	Score	Result
1 Chang, J. W. Korea (2007)	N = 50 M[d]: 27 F[a]: 23	63 ± 6	16.4–27.9	Randomized clinical trial	ALA 600 mg/day	Not mention	12 weeks	Diabetic End-Stage Renal Disease Patients	7	Between group comparison revealed TC[c] didn't change significantly.
2.1 de Oliveira, A. M. Brazil (2011)	N = 52 F: 21 M:31	38–75[b]	N/M[d]	Randomized, double-blind, placebo-controlled trial	ALA 600 mg/day	Not mention	16 weeks	Patients with type 2 diabetes mellitus	6	There were not any changes in lipid profiles in between group comparison.
2.2 de Oliveira, A. M. Brazil (2011)	N = 50 M: 35 F: 15	38–75[b]	N/M	Randomized, double-blind, placebo-controlled trial	800 mg a-tocopherol + 600 mg ALA	800 mg a-tocopherol	16 weeks	Patients with type 2 diabetes mellitus	6	There were not any changes in lipid profiles in between group and within group comparison.
3 Gianturco, V Italy (2009)	N = 14 F = 6 M = 8	58 ± 16	N/M	Randomized clinical trial	ALA 600 mg/day	Not mention	4 weeks	Patients with type 2 diabetes	5	Between group comparison revealed HDL[c] increased in intervention group, but LDL[c], TC, and TG[c] didn't change
4.1 Huerta, A. E. Spain (2015)	N = 40 F = 40	39 ± 8	N/M	Randomized double blind placebo-controlled trial	ALA 300 mg/day	sunflower oil	10 weeks	Overweight and Obese Women	7	There were not any changes in lipid profiles in between group comparison.
4.2 Huerta, A. E. Spain (2015)	N = 36 F = 36	39 ± 8	N/M	Randomized double blind placebo-controlled trial	ALA 300 mg/day + 1300 mg/day EPA	sunflower oil + 1500 mg EPA	10 weeks	Overweight and Obese Women	7	LDL-c decreased in control group and TG decreased in intervention group, but between group comparison revealed any changes in lipid profiles.
5 Heinisch, B. B. Austria (2010)	N:30 F: N/M M: N/M	55 ± 8	29.7 ± 2.5	A placebo controlled randomized trial	intravenous doses 600 mg/day ALA	Normal salin	3 weeks	Patients with type 2 diabetes	6	TC and TG decreased in intervention and control group, LDL-c decreased in intervention group, and HDL-c cholesterol didn't show changes in any groups. There wasn't any report related to between group comparison.
6 Khabbazi, T. Iran (2012)	N = 52 M = 34 F = 18	53.83 ± 13.29	25.46 ± 4.18	Randomized double blind placebo-controlled trial	ALA 600 mg/day	Starch	8 weeks	Patients with End-Stage Renal Disease on Hemodialysis	7	No change in lipid profiles in between group comparison. HDL-c increased significantly in intervention group; however, this improvement was not statistically significant as compared with the placebo group.
7 Li, N. China (2017)	N = 170 F:73 M: 113	39–47[b]	26.7–30.4	Crossover randomize, double-blind, placebo-controlled trial	ALA 1200 mg/day	Not mention	8 weeks	overweight or obese subjects	6	Between group comparison revealed HDL-c and TC increased significantly in intervention group, but TG didn't change.
8 Mirtaheri, E Iran (2014)	N = 65 F= 65	38.28 ± 8.63	29.02 ± 4.71	Randomized double-blinded placebo-controlled clinical trial	ALA 1200 mg/day	maltodextrin	8 weeks	Women with Rheumatoid Arthritis	7	There were not any changes in lipid profiles in between group and within group comparison.

3

Table 1 (*continued*)

Code Author (year) (country)	Subjects and gender	Age range (y) or mean ± SD	BMI range or mean ± SD	RCT	Intervention	Control	Duration (wk)	subjects	Score	Result
9 Mohammadi, V Iran (2017)	N = 67 F[a]N/M M=N/M	62.33 ± 6.19	27.68 ± 3.92	Randomized double blind placebo-controlled trial	ALA 600 mg/day	Wheat flour	12 weeks	Patients with Stroke	5	TG, TC, and LDL decreased significantly and HDL increased significantly in intervention group.
10 Okanovic, A Bosnia and Herzegovina (2015)	N = 60 F = 27 M= 33	61.0 ± 1.7	30.57 ± 0.46	Randomized Clinical trial	ALA 600 mg/day	Not mention	20 weeks	Obese patients with diabetes mellitus	6	In compare with placebo group TG decreased significantly in intervention group but TC didn't indicate any changes.
11 Sun, Y. D. China (2012)	N = 62 F: 41 M:21	65.78 ± 7.93	24.5 ± 7.9	Randomized clinical trial	ALA 600 mg/day	Not mention	12 weeks	Patients with Age-Related Macular Degeneration	5	There were not any changes in lipid profiles in between group and within group comparison.
12 Zhang, Y China (2011)	N = 22 F: 12 M:10	53.6 ± 9.4	30.4 ± 1.3	Randomized double blind placebo-controlled trial	ALA 600 mg/day	Normal Salin	2 weeks	Obese patients with impaired glucose tolerance	6	In compare with placebo group LDL-c, TG, and TC decreased significantly, and HDL-c increased significantly.

[a] F, female; M, male.

[b] Range.

[c] TC: Total Cholesterol, TG: Triacylglycerol, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein.

[d] n/m: not mention.

total of 12 papers were included in our meta-analysis (Chang et al., 2007; de Oliveira et al., 2011; Gianturco et al., 2009; Huerta et al., 2015; Heinisch et al., 2010; Khabbazi et al., 2012; Li et al., 2017; Okanovic et al., 2015; Sun et al., 2011; Mohammadi et al., 2017; Zhang et al., 2011; Mirtaheri et al., 2014) and 18 articles were excluded because of unclear tables (n = 3), measuring triacylglycerol in adipose tissue (n = 1), not having control group (n = 8), using other food supplement in intervention group beside ALA (n = 4) and intervention less than one weeks (n = 2) (Fig. 1). This meta-analysis included 770 participants aged between 30 and 75 years. Oral ALA supplement dose was 600 mg/day in seven articles (Chang et al., 2007; de Oliveira et al., 2011; Gianturco et al., 2009; Khabbazi et al., 2012; Okanovic et al., 2015; Sun et al., 2011; Mohammadi et al., 2017), 1200 mg/day in two articles (Li et al., 2017; Mirtaheri et al., 2014), and 300 mg/day in one article (Huerta et al., 2015). Participants in two articles took 600 mg/day intravenous form of ALA (Heinisch et al., 2010; Zhang et al., 2011). Intervention duration ranged from 2 to 20 weeks and participants included in all studies were male and female except for two articles conducted among women (Huerta et al., 2015; Mirtaheri et al., 2014).

In two studies by de Oliveira (2011) and Huerta et al. (2015), there were three intervention groups (ALA, ALA + Eicosapentaenoic acid (EPA), and EPA) and one placebo group. We considered the results of ALA + EPA and EPA groups as one effect and the results of ALA and placebo groups as another effect for both articles.

In total, ten articles measured HDL (de Oliveira et al., 2011; Gianturco et al., 2009; Huerta et al., 2015; Heinisch et al., 2010; Khabbazi et al., 2012; Li et al., 2017; Sun et al., 2011; Mohammadi et al., 2017; Zhang et al., 2011; Mirtaheri et al., 2014), nine articles measured LDL (de Oliveira et al., 2011; Gianturco et al., 2009; Huerta et al., 2015; Heinisch et al., 2010; Khabbazi et al., 2012; Sun et al., 2011; Mohammadi et al., 2017; Zhang et al., 2011; Mirtaheri et al., 2014), eleven articles measured total cholesterol (TC) (Chang et al., 2007; de Oliveira et al., 2011; Gianturco et al., 2009; Huerta et al., 2015; Heinisch et al., 2010; Khabbazi et al., 2012; Li et al., 2017; Sun et al., 2011; Mohammadi et al., 2017; Zhang et al., 2011; Mirtaheri et al., 2014), and eleven articles measured triacylglycerol (TG) (de Oliveira et al., 2011; Gianturco et al., 2009; Huerta et al., 2015; Heinisch et al., 2010; Khabbazi et al., 2012; Li et al., 2017; Okanovic et al., 2015; Sun et al., 2011; Mohammadi et al., 2017; Zhang et al., 2011; Mirtaheri et al., 2014).

3.2. Findings from the meta-analysis

3.2.1. Effect of alpha-lipoic acid on lipid concentrations

The changes in serum total cholesterol, LDL-C, HDL-C and triglyceride were the primary outcomes measured. In this study, thirteen comparisons from eleven studies that included 352 subjects supplemented with alpha-lipoic acid versus. 352 subjects as control, reported mean changes in total cholesterol concentrations. The mean difference in total cholesterol levels was significantly lower in subjects supplemented with alpha-lipoic acid compared with controls (WMD = -10.18 mg/dL; 95% CI: -16.16, -4.20 mg/dL; P = 0.001) and there was significant heterogeneity between studies (I^2 = 91.1%, P < 0.0001) (Fig. 2). Furthermore, eleven comparisons from nine studies that included 240 subjects supplemented with alpha-lipoic acid and 244 subjects as controls also reported mean changes in LDL-C concentrations. LDL-C was significantly reduced in alpha-lipoic acid group compared with control group (WMD = -9.22 mg/dL; 95% CI: -18.28, -0.16 mg/dL; P = 0.001) and there was also a significant evidence of heterogeneity (I^2 = 96.4%, P < 0.0001) (Fig. 3). Similarly, the mean changes of serum HDL-C were reported in 12 comparisons from 10 studies which included 327 subjects in intervention group and 327 subjects in placebo group. The serum HDL-C tended to be higher in intervention group compared with placebo group, but it was not significant (WMD: 3.02 mg/dL; 95% CI: -0.39, 6.43; P = 0.082). There was a considerable inter-study heterogeneity (I^2 = 96.6%, P < 0.0001)

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│  Articles identified through database search: │
│              n= 741                  │
└─────────────────────────────────────┘
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┌─────────────────────────────────────┐
│  Remaining article after duplicated removed │
│              n= 272                  │
└─────────────────────────────────────┘
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                  ├────────▶│ 242 articles excluded after reading │
                  │         │        title/abstract     │
                  ▼         └──────────────────────────┘
┌─────────────────────────────────────┐
│     Full text studies assessed       │
│        for eligibility               │
│              n=30                    │
└─────────────────────────────────────┘
                  │         ┌──────────────────────────┐
                  │         │   Unclear tables (n=3)    │
                  ├────────▶│ Measuring triacylglycerol in │
                  │         │    adipose tissue (n=1)   │
                  │         │ Not having control group (n=8) │
                  │         │ Using other food supplement in │
                  │         │ intervention group beside ALA │
                  │         │          (n=4)            │
                  │         │ Intervention less than one │
                  │         │        weeks (n=2)        │
                  ▼         └──────────────────────────┘
┌─────────────────────────────────────┐
│     Studies included in the          │
│  systematic review and meta-         │
│           analysis                   │
│              n=12                    │
└─────────────────────────────────────┘
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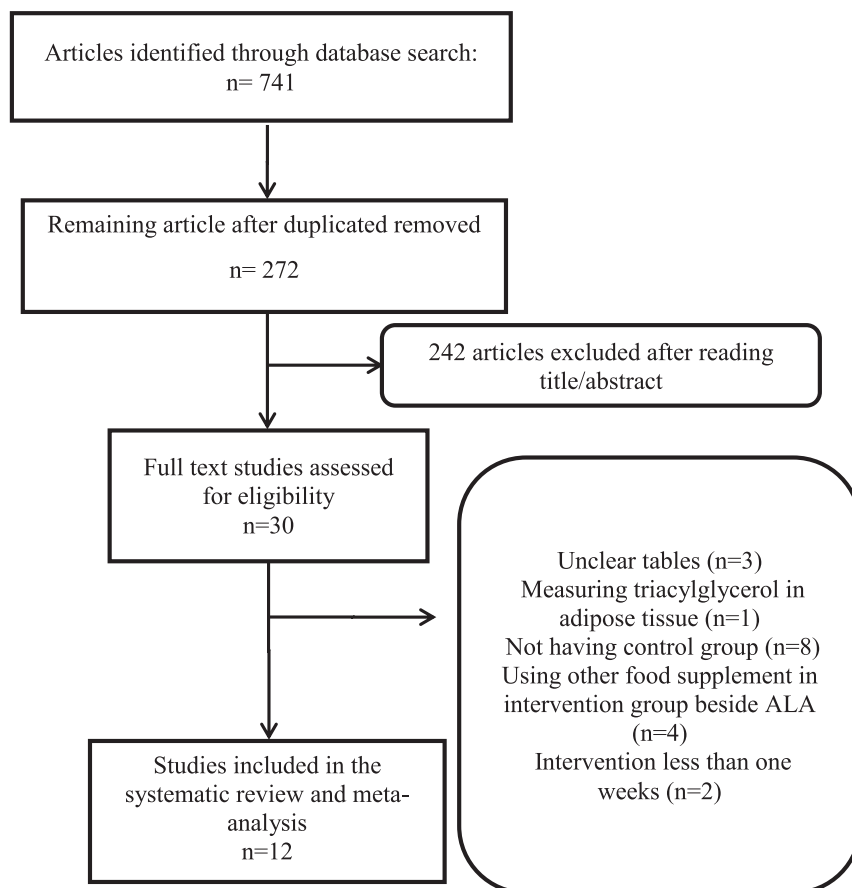
Fig. 1. Flow chart of the study selection.

(Fig. 4). Finally, the results for serum triglyceride were reported in 13 comparisons from 11 studies that had 357 subjects in intervention group and 357 subjects in control group. Meta-analyses indicated that alpha-lipoic acid supplementation had no significant effect on serum triglyceride levels in the intervention group compared with the placebo group (WMD: -19.15 mg/dL; 95% CI: -44.12, 5.83; P = 0.133). However, there was evidence of significant heterogeneity between the studies ($I^2 = 98.5\%$, P < 0.0001) (Fig. 5).

3.2.2. Subgroup analysis

To explore the source of heterogeneity, subgroup analysis was conducted according to the gender, geographical region (Asia vs. non-Asia), duration of supplementation (< vs. ≥ 10 wk) and health status (diabetic vs. non-diabetic) of the participants (Table 2).

Results of the subgroup analysis demonstrated that reductions in total cholesterol following alpha-lipoic acid supplementation were not affected by sex, geographical region and duration of study (Table 2). However, alpha-lipoic acid supplementation significantly decreased serum total cholesterol in non-diabetic subgroup (WMD: -7.57 mg/dL; 95% CI: -12.99, -2.16; P = 0.006), and its favorable effect in diabetic patients was marginally significant (WMD: -13.46 mg/dL; 95% CI: -27.09, 0.17; P = 0.053). In contrast, the favorable effect of alpha-lipoic acid on LDL-C was influenced by sex, geographical region, duration of study and health status. Alpha-lipoic acid significantly decreased LDL-C in studies which included both sexes (WMD: -12.47 mg/dL; 95% CI: -23.49, -1.44; P = 0.027) or were conducted in non-Asian countries (WMD: -8.03 mg/dL; 95% CI: -14.60, -1.47; P = 0.016) or lasted for more than 10 weeks (WMD: -6.39 mg/dL; 95% CI: -11.70, -1.09; P = 0.018) or enrolled diabetic patients (WMD: -6.39 mg/dL; 95% CI: -11.70, -1.09; P = 0.018); however, changes were not statistically significant in the subgroups of female, Asian countries, shorter duration

and non-diabetic subjects (Table 2).

In addition, the subgroup analysis also showed that alpha-lipoic acid significantly increased HDL-C in studies with shorter duration (< 10 wk), but this was not the case in longer-term studies (WMD: 0.33 mg/dL; 95% CI: -5.30, 5.97; P = 0.908). In the subgroup analysis based on sex, HDL-C levels was significantly increased in studies which were conducted among both men and women (WMD: 4.59 mg/dL; 95% CI: 0.57, 8.60; P = 0.025), but significantly decreased in studies which were conducted only among women (WMD: -1.69 mg/dL; 95% CI: -2.94, -0.43; P = 0.008). The changes in HDL-C by alpha-lipoic acid was not influenced by the health status of subjects (Table 2). Although the effect of alpha-lipoic acid on serum triglyceride was independent from geographical region and duration of study, however, subgroup analysis on the basis of sex revealed a significant reduction in female (WMD: -6.78 mg/dL; 95% CI: -12.73, -0.83; P = 0.026), but not in studies which enrolled both sexes (WMD: -23.06 mg/dL; 95% CI: -52.99, 6.88; P = 0.131). In the subgroup analysis based on health status, serum triglyceride level was significantly lower in intervention group than controls either in diabetic or non-diabetic subgroup. There was no significant evidence of inter-study heterogeneity in non-diabetic subgroup ($I^2 = 44.8\%$, P = 0.92) (Fig. 5).

3.2.3. Sensitivity analysis and publication bias

Sensitivity analysis was performed to determine whether the effect size of any individual trial would alter the pooled effect size. No significant change was observed in the overall effects of alpha-lipoic acid on serum total cholesterol and triglyceride after removal of each effect size during sensitivity analyses. However, the significance of the pooled effect size of LDL-C disappeared after the removal of some studies, however, the removal of the study by de Oliveria et al. (2011) led to a significant increase in HDL-C levels. Begg's test and Egger's test did not
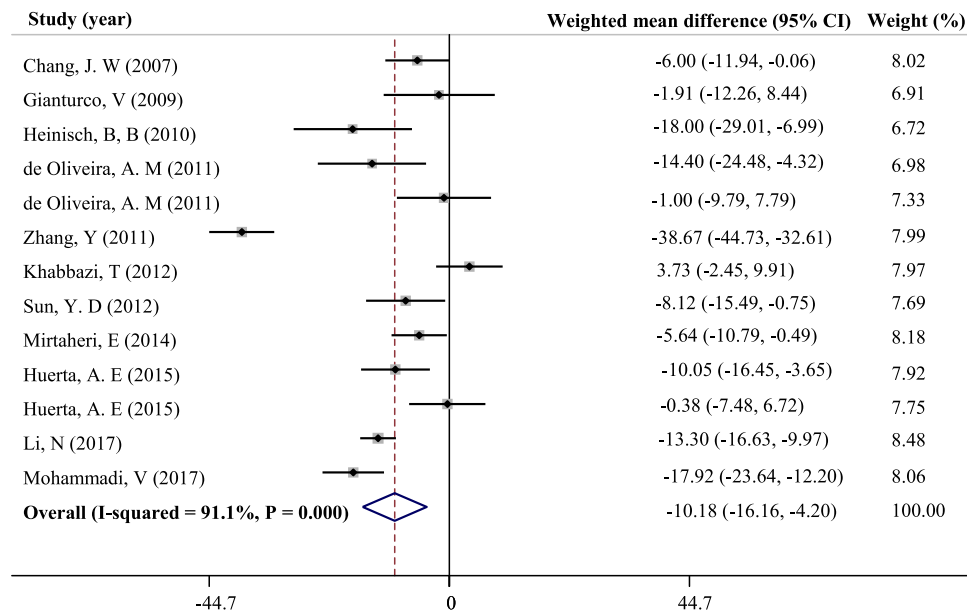
Fig. 2. Forest plot of the effect of alpha-lipoic acid supplementation on serum total cholesterol levels.

find evidence of publication bias in total cholesterol (Begg's: P = 0.855; Egger's: P = 0.617); LDL-C (Begg's: P = 0.350; Egger's: P = 0.177) and HDL-C (Begg's: P = 0.945; Egger's: P = 0.725). Nevertheless, there was evidence for significant publication bias according to the Egger's test (P < 0.1) in both diabetic and non-diabetic subgroups. Based on the trim and fill analysis, 2 additional studies in non-diabetic subgroup and 3 additional studies in diabetic group were required to balance the asymmetry. Adjusted values based on trim and fill analysis were −9.68 mg/dL with 95% CI (-15.10, -4.26) for non-diabetic individuals and −84.1 mg/dL with 95% CI (-118.55, -49.66) for diabetic patients. The trim and fill algorithm still indicated significant reduction in both groups.

Meta-regression analyses did not show dose-effect or duration effect of alpha-lipoic acid on any serum lipids concentrations. However, a marginally significant inverse effect was observed between HDL-C and the duration of study (β = -0.85, SE = 0.39, P = 0.052).

4. Discussion

In this study, the meta-analysis contained 12 articles assessing the ALA effect on lipid profile. The results indicated that ALA decreased TC and LDL significantly, but its effect on HDL was not statistically significant. Furthermore, the results of subgroup analysis based on health status revealed that ALA can decrease TG among diabetic and non-diabetic subjects. However, results showed that ALA might increase HDL in studies either with duration less than 10 weeks or on both sexes.

The molecular mechanisms which are responsible for the lipid-lowering effects of ALA might be due to the reduction in lipid biosynthesis, intestinal fat absorption and/or the enhancement of lipid metabolism (Ghelani et al., 2017). Recent articles proposed that ALA can change lipid profile by reducing the activity of HMGCR 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) that is involved in cholesterol biosynthesis and the enhancement of lipoprotein lipase activity that performs triglyceride turnover (Thirunavukkarasu et al., 2004). Furthermore, the results of an animal study indicated that ALA
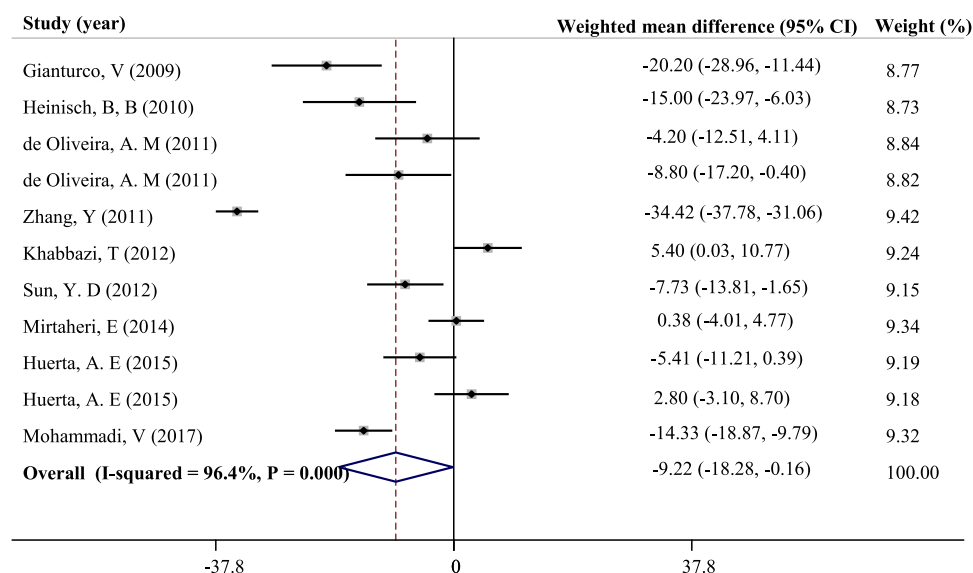

Fig. 3. Forest plot of the effect of alpha-lipoic acid supplementation on serum LDL-cholesterol levels.
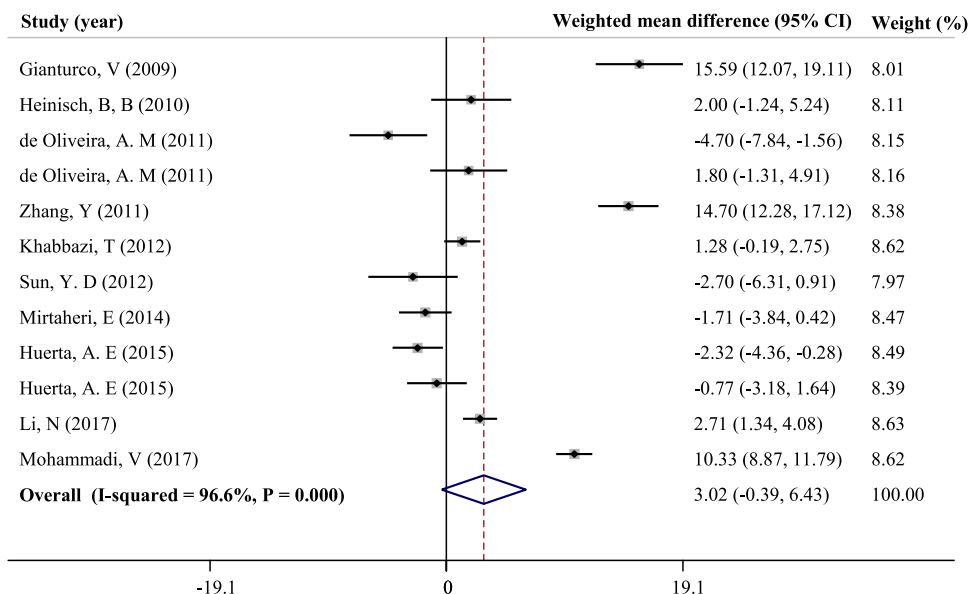
Study (year)	Weighted mean difference (95% CI)	Weight (%)
Gianturco, V (2009)	15.59 (12.07, 19.11)	8.01
Heinisch, B, B (2010)	2.00 (-1.24, 5.24)	8.11
de Oliveira, A. M (2011)	-4.70 (-7.84, -1.56)	8.15
de Oliveira, A. M (2011)	1.80 (-1.31, 4.91)	8.16
Zhang, Y (2011)	14.70 (12.28, 17.12)	8.38
Khabbazi, T (2012)	1.28 (-0.19, 2.75)	8.62
Sun, Y. D (2012)	-2.70 (-6.31, 0.91)	7.97
Mirtaheri, E (2014)	-1.71 (-3.84, 0.42)	8.47
Huerta, A. E (2015)	-2.32 (-4.36, -0.28)	8.49
Huerta, A. E (2015)	-0.77 (-3.18, 1.64)	8.39
Li, N (2017)	2.71 (1.34, 4.08)	8.63
Mohammadi, V (2017)	10.33 (8.87, 11.79)	8.62
Overall (I-squared = 96.6%, P = 0.000)	3.02 (-0.39, 6.43)	100.00

-19.1   0   19.1

Fig. 4. Forest plot of the effect of alpha-lipoic acid supplementation on serum HDL- cholesterol levels.

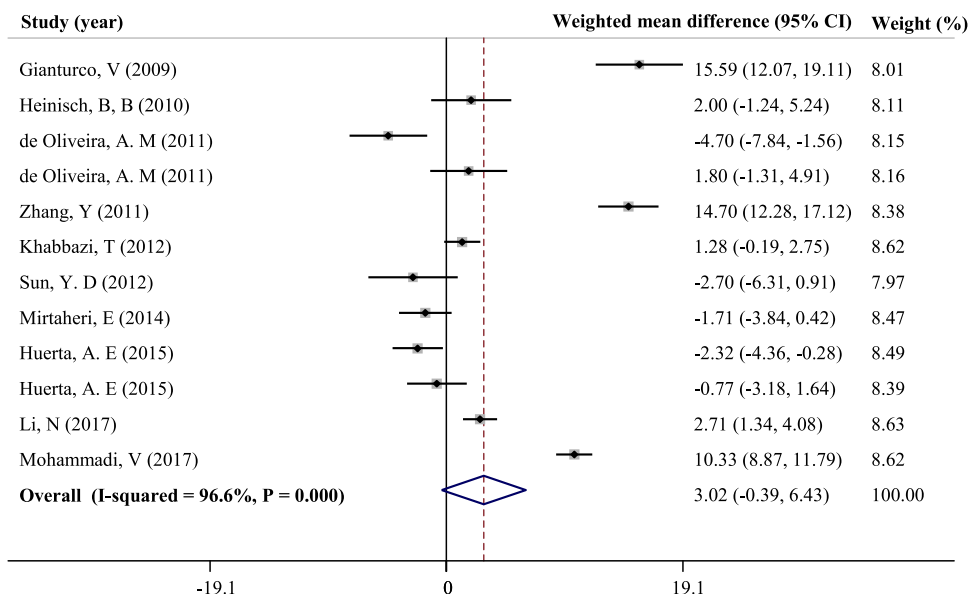| Study (year)	Weighted mean difference (95% CI)	Weight (%)
Gianturco, V (2009)	15.59 (12.07, 19.11)	8.01
Heinisch, B, B (2010)	2.00 (-1.24, 5.24)	8.11
de Oliveira, A. M (2011)	-4.70 (-7.84, -1.56)	8.15
de Oliveira, A. M (2011)	1.80 (-1.31, 4.91)	8.16
Zhang, Y (2011)	14.70 (12.28, 17.12)	8.38
Khabbazi, T (2012)	1.28 (-0.19, 2.75)	8.62
Sun, Y. D (2012)	-2.70 (-6.31, 0.91)	7.97
Mirtaheri, E (2014)	-1.71 (-3.84, 0.42)	8.47
Huerta, A. E (2015)	-2.32 (-4.36, -0.28)	8.49
Huerta, A. E (2015)	-0.77 (-3.18, 1.64)	8.39
Li, N (2017)	2.71 (1.34, 4.08)	8.63
Mohammadi, V (2017)	10.33 (8.87, 11.79)	8.62
Overall (I-squared = 96.6%, P = 0.000)	3.02 (-0.39, 6.43)	100.00

-19.1   0   19.1

Fig. 5. Forest plot of the effect of alpha-lipoic acid supplementation on serum triglyceride levels.

increased the expression of apolipoprotein-A and LDL receptor in the liver (Marangon et al., 1999). Additionally, the results of in vivo and in vitro studies have shown that ALA regulates adipose triacylglycerol lipase (ATGL), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) by the enhancement of both Sirtuin 1 (SIRT1) and 5' AMP-activated protein kinase (AMPK) activity (Chen et al., 2012). Moreover, studies have also revealed that ALA can decrease the hepatic expression of lipogenic genes such as sterol-responsive element-binding protein-1c (SREBP-1c) and carbohydrate-responsive element-binding protein (ChREBP) (Castro et al., 2013). In a study by Yang et al., it has been demonstrated that the lipid-lowering effect of ALA might be associated with an enhancement in the expression of lipolytic genes such as acyl-CoA oxidase (ACOX) and carnitine palmitoyltransferase-1 (CPT-1) (Yang et al., 2008).

This paper demonstrates that ALA might reduce TC and LDL. According to the results of subgroup analysis based on health status, ALA effect on TC and LDL is more effective among non-diabetic patients and diabetic patients, respectively. In the subgroup analysis of this

study, it was discovered that ALA effect on LDL is time dependent. To the best of knowledge, there is no narrative or systematic review summarizing ALA effect on lipid profile; therefore, it is not possible to compared the results of this analysis with others.

Scientists believe that insulin resistance in patients with type 2 diabetes is associated with dyslipidemia, thus, ALA through its antioxidant properties might be able to prevent LDL oxidation and regulate lipid metabolism abnormalities (Sabharwal and May, 2008). Studies also show that the enhancement of oxidized LDL (Ox-LDL) can increase inflammation and cardiovascular risk in patients with diabetic and metabolic syndrome (Holvoet et al., 2008). In a study by Zhang et al. (2011) ALA supplementation among diabetic patients decreased LDL, particularly in those with smaller particle sizes which impose insulin resistance more strictly than do other lipid parameters. Recent meta-analysis confirms the result of clinical trials regarding ALA effect on LDL among diabetic patients. Although from clinical point of view, changes in LDL concentration is slight, but taking ALA for more than 10 weeks among diabetic patients can be a protective supplement against

Table 2
Subgroup analysis for the effect of alpha-lipoic acid on serum lipid levels.

	No. of effect sizes	Mean difference	95% confidence interval	I²	P within group	P between groups
Total cholesterol						
Sex						< 0.0001
Female	3	− 5.55	− 10.54, − 0.56	49.1	0.140	
Both	10	− 11.66	− 19.22, − 4.09	92.5	< 0.0001	
Location						0.005
Asia	7	− 12.29	− 21.20, − 3.38	94.8	< 0.0001	
Non-Asia	6	− 7.20	− 12.88, − 1.52	61.0	0.025	
Duration						0.027
< 10 wk	6	− 12.35	− 23.83, − 0.87	95.5	< 0.0001	
≥ 10 wk	7	− 8.35	− 13.31, − 3.39	70.6	0.002	
Health status						< 0.0001
Diabetic	6	− 13.46	− 27.09, 0.17	94.0	< 0.0001	
Non-diabetic	7	− 7.57	− 12.99, − 2.16	84.8	< 0.0001	
LDL-C						
Sex						
Female	3	− 0.66	− 5.07, 3.74	51.4	0.128	
Both	8	− 12.47	− 23.49, − 1.44	96.4	< 0.0001	
Location						< 0.0001
Asia	5	− 10.20	− 25.93, 5.53	98.3	< 0.0001	
Non-Asia	6	− 8.03	− 14.60, − 1.47	78.4	< 0.0001	
Duration						< 0.0001
< 10 wk	5	− 12.74	− 30.95, 5.46	93.8	< 0.0001	
≥ 10 wk	6	− 6.39	− 11.7, − 1.09	76.8	0.001	
Health status						< 0.0001
Diabetic	5	− 16.76	− 30.25, − 3.27	94.6	< 0.0001	
Non-diabetic	6	− 3.18	− 9.42, 3.05	88.1	< 0.0001	
HDL-C						
Sex						< 0.0001
Female	3	− 1.69	− 2.94, − 0.43	0.0	0.629	
Both	9	4.59	0.57, 8.60	96.7	< 0.0001	
Location						< 0.0001
Asia	6	4.16	− 0.58, 8.90	97.5	< 0.0001	
Non-Asia	6	1.85	− 3.04, 6.75	94.5	< 0.0001	
Duration						0.466
< 10 wk	6	5.66	0.86, 10.46	96.9	< 0.0001	
≥ 10 wk	6	0.33	− 5.30, 5.97	97.0	< 0.0001	
Health status						< 0.0001
Diabetic	6	4.47	− 2.68, 11.61	96.8	< 0.0001	
Non-diabetic	6	1.63	− 2.30, 5.56	96.8	< 0.0001	
Triglyceride						
Sex						< 0.0001
Female	3	− 6.78	− 12.73, − 0.83	0.0	0.653	
Both	10	− 23.06	− 52.99, 6.88	98.5	< 0.0001	
Location						< 0.0001
Asia	6	− 19.29	− 47.59, 9.01	97.7	< 0.0001	
Non-Asia	7	− 19.24	− 59.86, 21.37	98.5	< 0.0001	
Duration						< 0.0001
< 10 wk	6	− 13.40	− 49.45, 22.64	97.7	< 0.0001	
≥ 10 wk	7	− 24.36	− 60.22, 11.5	98.8	< 0.0001	

cardio vascular disease.

Although results of this study indicated ALA cannot change HDL significantly, excluding studies on female or removal of the study by de Oliveria (de Oliveira et al., 2011) changed the results of this analysis from non-significant to significant. Moreover, subgroup analysis based on health status revealed that ALA might be able to reduce TG among non-diabetic and diabetic patients and inter-study heterogeneity in non-diabetic subgroup disappeared.

ALA may increase HDL concentration by stimulating HDL maturation (Thirunavukkarasu et al., 2004) through its effect on lecithin cholesterol acyl transferase (LCAT). Animal studies have demonstrated that ALA significantly reduces the atherogenic index (AI) in streptozotocin (STZ)-induced type 2 diabetes and high fat diet-fed rats (Amom et al., 2008; Seo et al., 2012). AI, an important indicator of CVD, predicts the deposition of foam cells or fatty plaque in blood vessels and gives information related to HDL and LDL lipoprotein particle size (Kwiterovich, 2000). The reduction of AI in animal study can correspond to the decrease of LDL and the increase of HDL. Different results for HDL between studies on women and studies on both women and men might be because of sex hormones effects. Cross-sectional articles

have indicated that testosterone and sex hormone binding globulin (SHBG) concentrations correlate with HDL cholesterol concentration which lead to higher levels of HDL among women (Pugeat et al., 1995). However, the results of this meta-analysis were derived from only two studies (de Oliveira et al., 2011; Mirtaheri et al., 2014) with three effect size.

Butler et al. (2009) illustrated that ALA can decrease TG concentration by the inhabitation of hepatic lipogenic gene expression, decreasing TG secretion from liver, and the enhancement of TG-rich lipoproteins clearance. Animal studies have indicated that although ALA can decrease gene expressions of enzymes which are responsible for lipogenesis in white adipose tissue and liver, it however, increases markers of fatty acid catabolism in skeletal muscle and liver (Carrier et al., 2014; Castro et al., 2013; Butler et al., 2009; Chen et al., 2000).

A narrative review by Pashaj et al. (2015) illustrated that ALA was more efficient in diseases with high levels of TG such as diabetes and metabolic syndrome. In contrast, ALA cannot reduce TG in situation with normal blood TG levels.

High heterogeneity across studies for LDL, HDL and TC might be explained by different reasons such as the study sample diversity and

varied study aims. Of those 12 articles, there was not any article designed for hyperlipidemia management, which exclusively recruited hyperlipidemic patients. Furthermore, the primary aim of included studies in this meta-analysis varied by their study population. On the other hand, the study populations of included studies in this meta-analysis consisted of subjects with diverse health problems, such as obesity (Huerta et al., 2015; Li et al., 2017; Zhang et al., 2011) stroke (Mohammadi et al., 2017), diabetes (Chang et al., 2007; de Oliveira et al., 2011; Gianturco et al., 2009; Heinisch et al., 2010; Khabbazi et al., 2012; Li et al., 2017), macular degeneration (Sun et al., 2012) and rheumatoid arthritis (Mirtaheri et al., 2014); and thus, these studies aimed primarily to evaluate the effects of ALA on conditions like glycemic control and inflammation rather than lipid profile changes.

This article has several limitations. First of all, there was evidence for significant publication bias with regard to diabetic and non-diabetic subgroup and we needed two additional studies in non-diabetic subgroup and three additional studies in diabetic group to balance the asymmetry. Secondly, the different effects of ALA on lipid profile among male and female remained unknown due to limited number of studies among females. Since females and males have different sex hormones and these hormones have different effects on lipid profiles especially on HDL, ALA effect on lipid profile separately on men and women should be investigated. Thirdly, we could not compare intravenous and oral intake of ALA effect on lipid profile, because there were just two articles that showed intravenous intake of ALA on lipid profile. Fourthly, even though weight changes can affect lipid profile concentration, most articles did not report changes in anthropometric variables and we could not perform subgroup analysis based on weight changes. Fifthly and lastly, there was no article exclusively on hypercholesteremic patients, and articles did not consider taking lipid lowering agents as exclusion criteria.

This meta-analysis has some strength; our database search results revealed our meta-analysis is the first meta-analysis related to ALA effect on lipid profile. We included studies which used pure ALA; therefore, confounding effect of other nutrients was excluded. We limited the effect of sex, location, duration, and health status on our result by subgroup analysis. We had articles from different part of the world; therefore, differences in lifestyle and habits were considered in this study. We performed our data search without any limitation on time and language.

In conclusion, this meta-analysis revealed that ALA might favorably affect lipid profile especially LDL and TC. However, for confirming these results, more studies particularly among hyperlipidemic patients and considering lipid lowering medicines are needed. Since sex hormones might change the result of ALA on HDL, more articles on perimenopause and post menopause women and men are needed. However, regarding the clinical practice, ALA may be an effective complementary therapy in hyperlipidemia management. ALA with its antioxidant and anti-inflammatory properties can protect cardiovascular system against CVD.

Conflict of interest

There is no conflict of interest.

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