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Review

Alpha-lipoic acid (ALA) supplementation effect on glycemic and inflammatory biomarkers: A Systematic Review and meta- analysis

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SUMMARY

Background & aims: Several randomized clinical trials (RCTs) have investigated the effect of Alpha - Lipoic Acid (ALA) supplementation on metabolic parameters, with conflicting results. Therefore, the present study assessed the effect of ALA on some glycemic and inflammatory parameters.

Methods: A comprehensive literature search was conducted up from inception to July 2018 on PubMed, Scopus, Cochrane databases, Google Scholar, ProQuest, Web of Science, and Embase. From among eligible trials, 41 articles were selected for the meta-analysis. Two reviewers independently assessed the risk of bias and extracted data from the included studies. Meta-analyses using the random-effects model were performed to analyze the data.

Results: Based on the Cochrane risk of bias tool, 19 articles had a good quality, 16 trials had a poor quality and 6 trials had a fair quality. The results demonstrated the significant effect of ALA on Fasting Blood Sugar (FBS) (weighted mean difference (WMD)) = −6.57, 95% confidence interval (CI: −11.91 to −1.23, P = 0.016), Hemoglobin A1c (HbA1c) (WMD = −0.35, 95% CI: −0.55 to −0.15, P = 0.004), Tumor Necrosis Factor Alpha (TNF-α) (WMD = −1.57, 95% CI: −2.29 to −0.85, P < 0.05), Interleukin 6 levels (IL-6) (WMD = −1.15, 95% CI: −1.58 to −0.72, P < 0.001), and C-reactive protein (CRP) (WMD = −0.31, 95% CI: −0.47 to −0.16, P > 0.001). No effect was detected for ALA on insulin and the homeostatic model assessment of insulin resistance (HOMA-IR).

Conclusions: These findings suggest that ALA is a viable supplement to improve some of the glycemic and inflammatory biomarkers.

1. Introduction

The cardio-metabolic disease is now recognized as a multifactorial disease related to the dysfunction of biological antioxidant systems which can lead to cardiovascular disease (CVD). Several factors such as diet, lifestyle, genetics, impaired fasting glucose, insulin resistance, and inflammation may be involved in the pathogenesis of cardio-metabolic disorders [1]. Dietary modification or supplementation can act as a useful and cost-effective strategy for preventing and managing cardio-metabolic disorders [2,3].

Alpha-lipoic acid (ALA), also known as thioctic acid (TA) and 1,2-dithiolane −3-pentanoic acid, is naturally synthesized in the liver and other tissues, isolated for the first time from the bovine liver by Reed et al. in the 1950s [4] and obtained from various animal and plant sources in the diet. ALA is a potent antioxidant, acting as a cofactor for mitochondrial enzymes, pyruvate dehydrogenase, α-keto-glutarate dehydrogenase activity, and branched chain alpha-keto acids. In addition, ALA affects numerous inflammatory pathways by modulating the NF-κB-dependent gene expression [5–8].

Several randomized clinical trials (RCTs) have demonstrated that ALA can act as a therapeutic agent in chronic diseases such as diabetes mellitus [9], cardiovascular diseases [10], and cancers [11] by decreasing chronic inflammation and improving

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glucose-insulin homeostasis and endothelial function [2]. It has also been shown that ALA exerts beneficial effects on the redox state of the plasma and endothelium-dependent vasodilation [12]. Previous studies have demonstrated that ALA can decrease lipopolysaccharide (LPS)-induced inflammatory responses and act as an anti-inflammatory agent through affecting the cyclooxygenase-2 (COX-2) [13,14] and inducible nitric oxide synthase (iNOS) [15].

ALA has been used for the treatment of diabetes based on its anti-inflammatory effects related to the inhibition of nuclear factor kappa beta (NF-κβ) activity and activation of the MAPK/ERK pathway. In addition, ALA treatment may be useful in dyslipidemia treatment, probably due to controlling the activity of enzymes involved in lipid metabolism such as HMG-CoA reductase [12].

As new studies investigate the association of ALA with various cardio-metabolic parameters, a meta-analysis of these findings will provide a better understanding of the effect of ALA on inflammation and metabolic parameters. Therefore, the present meta-analysis was conducted on the effect of ALA on some cardio-metabolic risk factors, including inflammatory markers (TNF-α, IL-6, and C-reactive protein) and metabolic parameters (fasting blood glucose, insulin, HbA1C, and HOMA-IR).

2. Materials and methods

This study was designed according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [16].

The review was performed using the PICO design.

Population: patients with cardio-metabolic disorders.

Intervention: supplementation with ALA.

Comparison: with placebo or control groups.

Outcome: changes in C-reactive protein (CRP), TNF-α, fasting blood sugar (FBS), HbA1c, insulin resistance, and interleukin 6 levels.

The protocol of this study has been registered in PROSPERO under the number CRD42017058985.

2.1. Search strategy

A systematic search was conducted on PubMed, Scopus, Cochrane databases, Google Scholar, ProQuest, Web of Science, and Embase for randomized, placebo-controlled human trials examining the effect of ALA supplementation on cardio-metabolic parameters from inception to July 2018 using the following subject headings (MeSH) and non-MeSH keywords (Table 1S): "alpha-lipoic acid" OR "alpha lipoic acid" OR "α-lipoic acid" OR "α lipoic acid" OR "thiocitic acid" combined with "cardio-metabolic disease" OR cardio-metabolic OR "Cardiovascular disease" OR CVD OR Obesity OR "Overweight" OR "Blood Pressure" OR "Diabetes" OR "T2DM" OR "fasting blood sugar" OR FBS OR "blood sugar" OR "Hemoglobin A1c", OR "HbA1C", OR "Hb A1C", OR "Glycated hemoglobin", OR "insulin" OR "insulin resistance" OR "Homeostatic Model Assessment" OR "HOMA" OR "HOMA-IR" OR "inflammation" OR "inflammatory factors" OR TNF-α OR IL-6 OR "Interleukin 6" OR "C-reactive protein" OR CRP for the outcome as the search strategy. The reference list of relevant articles was manually searched for additional studies. To find unpublished data, http://www.clinicaltrials.gov and http://www.controlledtrials.com were searched. Researchers did not apply any language restriction in the search process.

2.2. Inclusion and exclusion criteria

Human studies in which participants were supplemented with ALA were included. The criteria for selecting studies were:

- Method (including intervention (ALA) and placebo groups)
- Measurement of one or more of the primary outcomes

Other types of studies such as animal studies, reviews, letters, and observational studies were excluded. Studies were also excluded researchers had evaluated ALA effects in combination with other supplements or drugs. Moreover, the authors of some article were contacted via email if extra data were required.

2.3. Selection of studies and data extraction

Two authors (MR and AM) independently evaluated the studies for inclusion. Randomized controlled studies evaluating the effect of ALA supplementation on glycemic and inflammatory markers were included. In the first screening, the title and abstract of all studies were evaluated in endnote software (EndNote X6, Thomson Corporation, Stamford, USA) and duplications were removed. Any disagreements were resolved by discussion among reviewers. The following characteristics were extracted: surname of the first author, study design, year of publication, sample size, sex and mean age, supplement dose, study duration, inclusion and exclusion criteria, and mean and standard deviation (SD) of glycemic and inflammatory markers before and after intervention. Any disagreements regarding inclusion were resolved by discussion between the authors.

2.4. Quality assessment

The Cochrane risk-of-bias tool [17] utilized for quality assessment included: sequence generation, allocation and concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. According to the Cochrane guideline, the words "yes", "no", and "unclear" demonstrated a low, high, and unknown risk of bias, respectively. Finally, if a study had all the necessary criteria, that study earns a good quality (G). If One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results, studies earns a fair quality (F). If, two or more criteria listed as high or unclear risk of bias, that article earns a poor quality (P). The overall quality of the present meta-analysis was also assessed by the use of NutriGrade scoring system which takes the following seven domains to score the meta-analyses of randomized clinical trials (RCTs) into account: risk of bias, study quality, and study limitations; precision; heterogeneity; directness; publication bias; funding bias and study design [18].

2.5. Data synthesis and meta-analyses

The influence of ALA supplementation was evaluated on a change in the following outcomes: FBS (mg/dl), HbA1C (%), CRP (mg/dl), TNF-α (ng/ml), and IL-6 (ng/ml). The mean and SD of change in FBS, HbA1C, CRP, TNF-α, and IL-6 were used to calculate the effect size. The following formula was employed to calculate the SD, by calculating the correlation coefficient according to the Cochrane guideline:

$$\sqrt{(\text{SD pre} - \text{treatment})^2 + (\text{SD post} - \text{treatment})^2 - (2R \times \text{SD pre} - \text{treatment} \times \text{SD post} - \text{treatment})}$$

If SE was reported instead SD, researchers converted this to SD using SD= SEM × sqrt (n), where "n" is the number of participants in each group. Effect size for the meta-analysis was defined as the weighted mean difference (WMD; value at the end of the trial minus the value at the baseline) and 95% CI. The heterogeneity among studies was measured by Cochrane's test (Q test) and I^2 index. Heterogeneity was considered statistically significant if $P < 0.01$ or $I^2 > 50\%$ [19]. Moreover, to find the possible source of heterogeneity, subgroup analysis and meta-regression were performed according to the following indicators: ALA dosage, study duration, and study quality (low or high).

The leave-one-out method was employed for the sensitivity analysis to explore the influence of each trial on the overall effect size [20]. All statistical analyses were conducted using the Stata SE software version 12.

3. Results

3.1. Study characteristics

As depicted in Fig. 1, after removing duplicate records, a total of 1639 articles were reviewed; 1508 studies were excluded due to reporting unrelated data, and 131 full texts were examined. From these, 90 studies were excluded for the following reasons: not being an RCT and not describing the primary outcome. Finally, 41 articles were included in the present meta-analysis [21–61]. The characteristics of the trials are listed in Table 1. From the all included articles, two studies was cross-over trial [26,47] and the others were parallel trials. The included studies had a total of 2564 participants aged 15–74 y with a BMI range of 19–35, and the majority of studies were conducted on both sexes.

Eligible studies were published between 1999 and 2018 in Spain [21,54], New Zealand [22], China [23,28,32,55], Italy [24,25,29,40,45,47,48], Korea [51,52,61], USA [26,42,43,60], Iran [27,30,35,53,56–58], Bosnia [31], India [33], Thailand [34], Germany [36,46,50], UK [37], Brazil [38], Bulgaria [39], Egypt [41, 59], Poland [49], and Austria [44]. The duration of ALA supplementation varied between 2 [28] and 192 weeks [36]. The duration of ALA supplementation was between 2 [28] to 192 weeks [36].

3.2. Quality assessment

Based on the Cochrane risk of bias tool, 19 articles had a good quality [22,24,26–30,34,35,40,42,44,46,48,51,53,54,57,60], 16 trials had a poor quality [21,23,31,32,37–39,41,47,49,50,52,56,59,61] and 6 trials had a fair quality due to the lack of randomization or double-blinding [33,36,43,45,55,58] (Table 2) and Fig. 2.

3.3. ALA supplementation and glycemic control

Twenty-three studies with a total of 1665 participants reported FBS as an outcome. Results pooled from the random-effects model

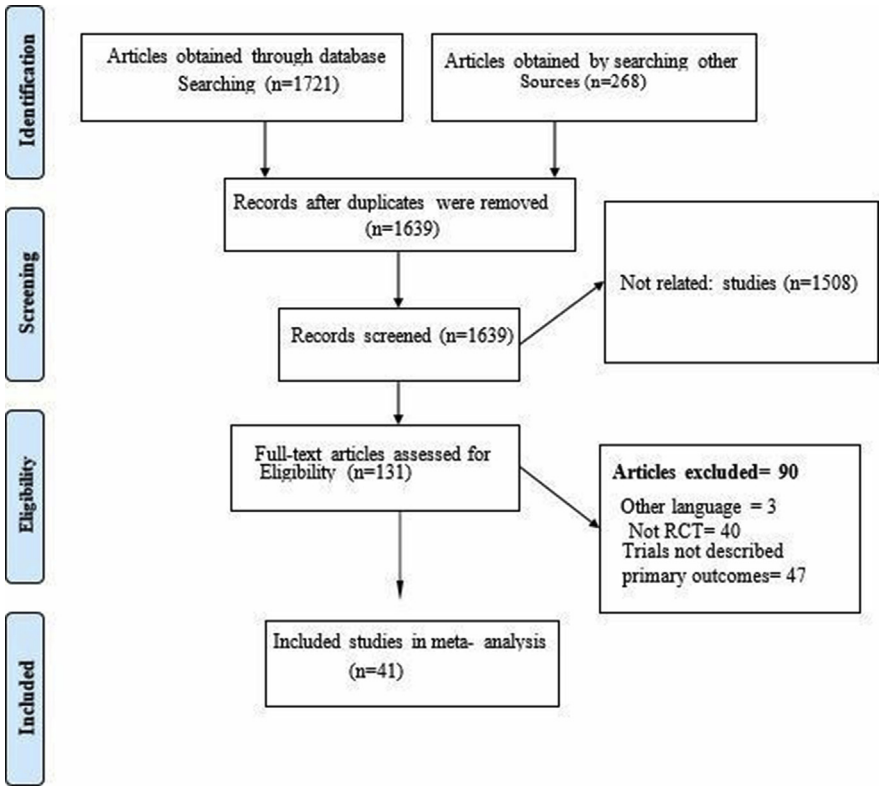

Fig. 1. Flow diagram of literature search according to the PRISMA statement.

Table 1
Summaries of clinical trials included in the meta-analysis.

First author, year (ref)	Country	Design	Participants (Intervention/control)	duration/week	Intervention Dose	Disease name	Parameters
Mohammadi et al. (2018)	Iran	Parallel	67 (33/34)	12	600 mg	Stroke	FBS, Insulin
Hong et al. (2017)	China	Parallel	62 (30/32)	2	450 mg	Diabetic Nephropathy	IL-6, CRP, TNF-α
Lee SJ et al. (2017)	Korea	Parallel	75 (41/34)	24	1200 mg	T2DM	HbA1C
Sardu et al. (2017)	Italy	Parallel	73 (33/40)	48	600 mg	Atrial Fibrillation	IL-6, CRP, TNF-α
Derosa et al. (2016)	Italy	Parallel	105 (54/51)	12	600 mg	T2DM	FBS, Insulin, HOMA-IR, HbA1C
Huerta et al. (2016)	Spain	Parallel	40 (19/21)	10	300 mg	Overweight women	IL-6, CRP
Marfella et al. (2016)	Italy	Parallel	43 (22/21)	48	600 mg	Cardiomayopathy	FBS, CRP, TNF-α
Dwrocka et al. (2015)	Poland	Parallel	60 (30/30)	12	600 mg	T2DM	FBS, HbA1C
Huerta et al. (2015)	Spain	Parallel	40 (19/21)	10	300 mg	Overweight women	FBS, Insulin, HOMA-IR
Mohammadi et al. (2015)	Iran	Parallel	58 (28/30)	12	600 mg	Chronic spinal cord	FBS, IL-6, hs-CRP
Okanović et al. (2015)	Bosnia	Parallel	60 (30/30)	20	600 mg	T2DM	FBS
Rago et al. (2015)	Italy	Crossover	22 (22/22)	12	800 mg	PCOS	FBS, Insulin
Khalili et al. (2014)	Iran	Parallel	52 (26/26)	12	1200 mg	MS	IL-6, TNF-α
Nasole et al. (2014)	Italy	Parallel	16 (10/6)	2	600 mg	chronic wound	IL-6, TNF-α
Safa et al. (2014)	Iran	Parallel	61 (30/31)	8	600 mg	ESRD	TNF-α
Zhao.L et al. (2014)	China	Parallel	90 (46/44)	3	600 mg	T2DM	FBS, HOMA-IR
Ahmadi et al. (2013)	Iran	Parallel	44 (20/24)	8	600 mg	HD	Hs-CRP, IL-6
El-Nakib et al.(2013)	Egypt	Parallel	44 (22/22)	12	600 mg	HD	IL-6
Gianturco et al. (2013)	Italy	Parallel	98 (52/46)	48	400 mg	T2DM	FBS, Insulin, HOMA-IR, CRP
Hegazy et al. (2013)	Egypt	Parallel	45 (30/15)	16	600 mg	T1DM	FBS, HbA1C, TNF-α
Manning et al. (2013)	New Zealand	Parallel	74 (34/40)	48	600 mg	MetS	FBS, Insulin, HOMA-IR, IL-6, CRP, TNF-α
Khabazi et al. (2012)	Iran	Parallel	52 (24/28)	8	600 mg	HD	Hs-CRP
Porasuphatana et al. (2012)	Thailand	Parallel	16 (8/8)	24	300 mg	T2DM	FBS, HbA1C
Udupa et al. (2012)	India	Parallel	50 (25/25)	12	300 mg	T2DM	FBS, HbA1C
Ansar et al. (2011)	Iran	Parallel	57 (29/28)	8	300 mg	T2DM	FBS, Insulin, HOMA-IR
McNeilly et al. (2011)	UK	Parallel	24 (12/12)	12	1000 mg	IGT	FBS, HbA1C, hs-CRP
Oliveira et al. (2011)	Brazil	Parallel	52 (26/26)	16	600 mg	T2DM	Insulin, HOMA-IR,HbA1C
Xiang et al. (2011)	China	Parallel	92 (60/32)	3	600 mg	endothelial dysfunction	FBS, CRP
Zhang et al. (2011)	China	Parallel	22 (13/9)	2	600 mg	T2DM	FBS, HOMA-IR, HbA1C, IL-6, TNF-α
Ziegler et al. (2011)	Germany	Parallel	460 (233/227)	192	600 mg	T2DM	FBS,HbA1C
Heinisch et al. (2010)	Austria	Parallel	30 (15/15)	3	600 mg	T2DM	HbA1C
Lukaszuk et al. (2009)	USA	Parallel	23 (13/10)	12	600 mg	T2DM	HbA1C
Mc Mackin et al. (2009)	USA	Crossover	36 (15/21)	8	200 mg	Coronary Artery Disease	FBS, CRP
Chang et al. (2007)	Korea	Parallel	50 (25/25)	12	600 mg	HD	HbA1C, hs-CRP
Huang et al. (2007)	USA	Parallel	40 (30/10)	12	300 mg	T1DM	HbA1C
Lee SR et al.(2006)	Korea	Parallel	40 (20/20)	12	600 mg	T2DM	FBS
Alleva et al. (2005)	Italy	Parallel	20 (10/10)	4	600 mg	patients undergoing hyperbaric oxygen therapy	IL-6
Sola et al. (2005)	USA	Parallel	29 (15/14)	4	300 mg	MetS	IL-6
Kamenova et al. (2002)	Bulgaria	Parallel	24 (12/12)	4	1200 mg	T2DM	FBS, Insulin, HOMA-IR
Morcos et al. (2001)	Germany	Parallel	84 (35/49)	72	600 mg	DM	HbA1C
Jacob et al. (1999)	Germany	Parallel	38 (19/19)	4	600 mg	T2DM	FBS

T2DM: Type 2 diabetes, CRP: C-reactive protein, IL-6: Interleukin 6, FBS: Fasting Blood Sugar, TNF-α: Tumor necrosis factor alpha, HOMA-IR: The homeostatic model assessment.

showed that the reduction in FBS was significant following ALA consumption (WMD = −7.76, 95% CI: −11.34 to −4.18, P < 0.001) with significant heterogeneity (I^2 = 97.5%, P < 0.001) (Fig. 3). According to the subgroup analysis, supplementation dose, duration of follow-up, and study quality did not indicate the source of heterogeneity (Table 3). Results of subgroup analysis showed that the effect of dietary ALA supplementation in FBS was significant only in participants with type 2 diabetes (WMD = −9.89, 95% CI: −16.96 to −2.82, P = 0.006). The leave-one-out sensitivity analysis revealed that leaving each trial in a range of −8.31 [95% CI: −12.08, −4.55] by Gianturco et al. [24] to −7.16 [95% CI: −10.78, −3.53] by Mohammadi et al. [27] had no significant effect on the pooled effect size (Table 2S). Begg's test (P = 0.01), Egger's test (P = 0.03), and visual inspection of the funnel plot indicated a publication bias among studies.

In total 15 RCTs [28,33,34,36–38,40–44,49–52] including 1136 participants with the individual study size ranging from 16 to 460 evaluated the effect of ALA on HbA1C level. The duration of intervention varied from 2 to 192 weeks. The meta-analysis on 16 studies indicated that the consumption of ALA significantly reduced HbA1C level (WMD = −0.27, 95% CI: −0.42 to −0.11, P = 0.001) (Fig. 4), and there was a high heterogeneity among studies (I2 = 56.4, P = 0.004). The subgroup analysis demonstrated that study quality was identified as a source of heterogeneity. The leave-one-out sensitivity analysis showed that leaving each of the trials in a range of −0.30 [95% CI: −0.46, −0.14] by Huang et al. [43] to −0.2 [95% CI: −0.34, −ssssss0.08] by Udupa et al. [33] had no significant effect on the pooled effect size (Table 3S). There was no publication bias among studies according to Begg's (P = 0.73) and Egger's test (P = 0.79) and visual inspection of the funnel plot.

To evaluate the effect of ALA supplementation on insulin level, nine RCTs were included in the final analysis [22,24,35,38–40,47,53,54] and pooled results showed that ALA supplementation did not significantly change insulin level (WMD = 0.03, 95% CI: −0.72 to 0.77, P = 0.94) (Fig. 5). There was a high heterogeneity among studies. Several subgroup

Table 2
Quality assessment of clinical trials (according to the Cochrane guideline) included for meta-analysis.

Study	Random sequence generation	Allocation concealment	Blinding of Participants & personnel	Incomplete outcome data	Selective reporting	Other bias	Total Quality
Okanović et al. (2015)	U	U	H	U	L	L	P
Mohammadi et al. (2015)	L	H	L	L	L	L	G
ZHAO.L et al. (2014)	L	U	H	L	L	L	P
Manning et al.(2013)	L	L	L	L	L	L	G
Porasuphatana et al.(2012)	L	L	L	L	L	L	G
Zhang et al.(2011)	L	L	L	L	L	L	G
Ansar et al.(2011)	L	L	L	L	L	L	G
Jacob et al.(1999)	L	L	L	L	L	L	G
Hegazy et al.(2013)	L	U	H	L	L	L	P
Udupa et al.(2012)	L	L	L	U	L	L	F
Ziegler et al.(2011)	L	U	U	L	L	L	F
McNeilly et al.(2011)	L	U	H	L	L	L	P
Oliveira et al.(2011)	U	U	H	L	L	L	P
Kamenova et al.(2002)	H	H	H	U	L	L	P
Lee SJ et al.(2017)	L	L	L	L	L	L	G
Sarddu C et al.(2017)	L	L	L	L	L	L	G
Ahmadi et al.(2013)	L	U	H	L	L	L	P
Chang et al.(2007)	L	H	H	L	L	L	P
El-Nakib et al.(2013)	L	H	H	L	L	U	P
Gianturco et al.(2013)	L	L	L	L	L	L	G
Hong et al.(2017)	L	U	U	L	L	L	F
Huerta et al. (2015)	L	L	L	L	L	L	G
Huerta et al.(2016)	L	U	L	H	L	U	P
Khabazi et al.(2012)	L	L	L	L	L	L	G
Marfella et al.(2016)	L	L	L	L	L	L	G
Nasole et al.(2014)	L	U	L	U	L	L	F
Safa et al.(2014)	L	L	L	H	L	L	F
Sola et al.(2005)	L	L	L	L	L	L	G
Derosa et al.(2016)	L	L	L	L	L	L	G
Mohammadi et al.(2018)	L	L	L	L	L	L	G
Dwrocka et al.(2015)	H	U	H	L	L	U	P
Rago et al.(2015)	H	H	H	L	L	L	P
Mc Mackin et al.(2009)	L	L	L	L	L	L	G
Xiang et al.(2011)	H	U	H	L	L	L	P
Lukaszuk et al.(2009)	L	L	L	L	L	L	G
Huang et al.(2007)	L	L	L	H	L	L	F
Heinisch et al.(2010)	L	L	L	L	L	L	G
Morcos et al.(2001)	H	H	H	L	L	L	P
Alleva et al.(2005)	L	L	L	L	L	L	G
Sang RL et al.(2006)	H	H	H	L	L	L	P
Khalili et al.(2014)	L	L	L	L	L	L	G

L: Low risk of bias, H: Low risk of bias, U: Unclear risk of bias, G: Good quality, P: Poor quality, F: Fair quality.

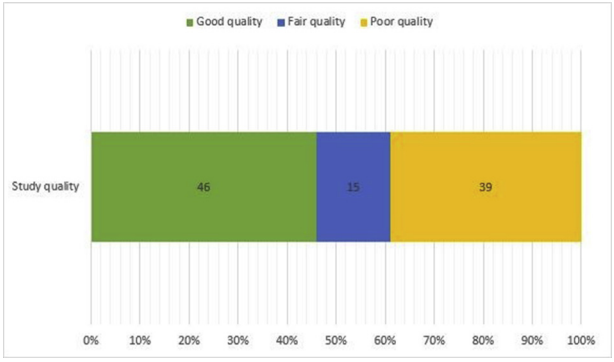

Fig. 2. Qualitative status of trials.

analyses were performed to identify the source of heterogeneity, and study quality and duration of follow-up were identified as sources of heterogeneity. Results of subgroup analysis showed that the effect of dietary ALA supplementation on insulin level did not significantly differ in participants with type 2 diabetes compared to other subjects. The sensitivity analysis did not provide further information for insulin (Table 4S), and no publication bias was found among studies.

Fig. 6 illustrates the pooled analysis for the effect of ALA on HOMA-IR which showed no significant effect (WMD = 0.04, 95% CI: −0.19 to 0.27, P = 0.72). There was a high heterogeneity among the studies for HOMA-IR (I^2 = 49.3, P = 0.045). Subgroup analysis and sensitivity analysis did not provide any further information for HOMA-IR.

3.4. ALA supplementation and inflammatory factors

Fifteen trials, including 782 subjects (389 treated and 393 controls) provided data on the effect of ALA on CRP level [21–27,37,48,51,52,55–57,61]. The quantitative meta-analysis displayed a significant reduction in CRP level (WMD = −0.31, 95% CI: −0.47 to −0.16, P > 0.001), (I^2 = 91.3%, P < 0.001) (Fig. 7). The subgroup analysis suggested that CRP concentration was reduced in trials with a good quality (WMD = −0.74, 95% CI: −1.33 to −0.16, P = 0.01), but was not significantly changed in low quality studies. Duration of follow-up (≥9 weeks or < 9 weeks) and supplement dose did not show the source of heterogeneity. Results of subgroup analysis showed that the effect of dietary ALA supplementation on CRP level was significant only in participants without type 2

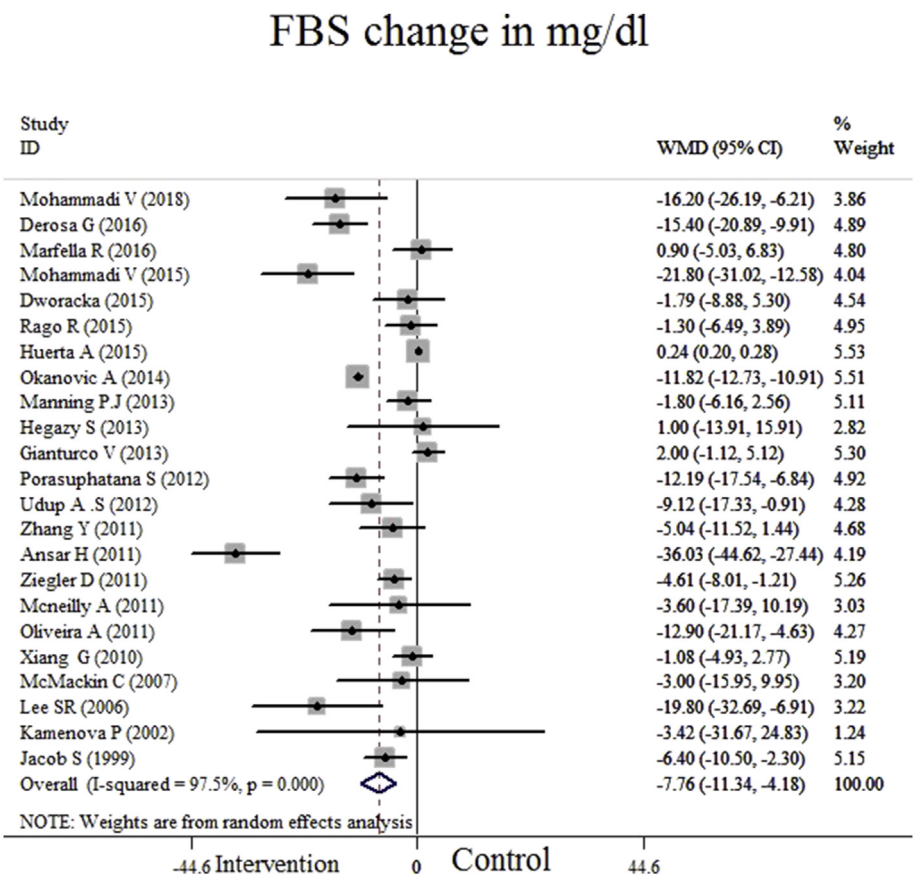

Fig. 3. Pooled estimates studies assessing the effect of ALA vs. control on FBS concentration.

diabetes (WMD = −0.4, 95% CI: −0.58 to −0.23, P < 0.001). Furthermore, the sensitivity analysis did not indicate any change in the results related to CRP level (Table 5S). For trials considering ALA effect on CRP level, neither Begg's (P = 0.1) and Egger's test (P = 0.13) nor a visual inspection of the funnel plot demonstrates any publication bias.

Overall, nine studies provided sufficient data regarding the effect of ALA supplementation on TNF-α level with 448 subjects (228 treated and 220 controls) [22,25,28,30,41,45,48,55,58]. The quantitative meta-analysis displayed the significant lowering effect of ALA supplementation on TNF-α levels (WMD = −1.52, 95% CI: −2.06 to −0.99, P < 0.05, I^2 = 73.3%, P < 0.001) (Fig. 8). The subgroup analysis of study duration (above nine weeks or less) and quality score (high or low quality) did not indicate the heterogeneity source. Sensitivity analysis suggested no difference in the results following the exclusion of any of the trials (Table 6S). In addition, the funnel plot demonstrated no publication bias for trials in investigating the effect of ALA supplementation on TNF-α level (Egger's test: P = 0.21; Begg's test: P = 0.25).

Results for mean differences in the IL-6 level between ALA intervention and control groups are reported in Fig. 9. These studies include 13 trials with a total of 561 participants (278 treated and 283 controls) [22,25,27–30,54–56,59,62]. According to these studies, ALA intake was correlated with a significant reduction in IL-6 level compared to placebo (WMD = −2.34, 95% CI: −3.33 to −1.36, P < 0.05). There was a high heterogeneity among these studies (I^2 = 93.8%, P < 0.001). The potential sources of variation were evaluated by subgroup analysis, and it was found that subgroup by supplement dose was identified as a source of heterogeneity, but study quality and study duration did not provide further information for detecting the sources of heterogeneity.

The leave-one-out sensitivity analysis indicated that leaving each of the trials in a range of −2.54 [95% CI: −3.62, −1.45] by Zhang et al. [28] to −2.03 [95% CI: −2.98, −1.07] had no significant effect on the pooled effect size (Table 7S). For trials considering the IL-6 level, Begg's test (P = 0.013), Egger's test (P = 0.011), and visual inspection of the funnel plot showed publication bias.

4. Discussion

The present meta-analysis of RCTs explored the effects of ALA supplementation on several cardio-metabolic factors. Results indicated that ALA supplementation can be beneficial and exert a significant effect on FBS, HbA1C, CRP, TNF-α, and IL-6, but is non-significant on insulin and HOMA-IR.

The present meta-analysis illustrated the significant lowering effect of ALA supplementation on FBS and HbA1C. Existing evidence suggests that ALA reduces complications related to diabetic neuropathy by modulating the deficits of neuropeptides, including neuropeptide Y and substance P, in the spinal cord [63]. According to previous studies, it was suggested that ALA can decrease FBS and HbA1C level, probably by increasing GLUT-4 transportation to muscle and fat cell membranes and increasing glucose uptake [27,64]. Also, some beneficial effects of ALA on FBS were due to an increase in skeletal muscle glucose transport activity [65]. However, skeletal muscle is not the only site of the action of ALA, as ALA is shown to suppress gluconeogenesis in the liver as well [66]. ALA enhances insulin-stimulated glucose uptake in obese Zucker rats [67]. In addition, ALA partially improves insulin metabolic pathways. It is reported that ALA enhances the activity of some proteins of the insulin signaling pathway such as insulin receptor (IR), insulin receptor substrate 1 (IRS1), phosphatidylinositide 3-kinase

Table 3
Results of subgroup-analysis.

	No. of effect sizes	RR (95% CI)	P[a]	I^2 (%)	P[b]
Subgroup analyses for FBS and ALA supplementation					
Supplement Dose					0.0
Less than 600 mg/day	6	−9.11 (−16.33, −1.90)	0.0	94.8	
600 mg/day and more	17	−7.12 (−10.37, −1.87)	0.0	85.5	
Duration of follow up					0.0
Less than 9 weeks	6	−9.64 (−18.9, −0.38)	0.04	90.7	
9 weeks and more	17	−7.19 (−11.29, −3.09)	0.001	98.0	
Quality score[c]					0.00
Good quality	11	−6.26 (−10.47, −2.05)	0.004	84.9	
Poor and Fair quality	12	−8.84 (−13.43, −4.26)	0.00	93.4	
Subgroup analyses for HbA1C and ALA supplementation					
Duration of follow up					0.001
Less than 9 weeks	9	−0.26 (−0.47, −0.05)	0.01	69.2	
9 weeks and more	6	−0.25 (−0.47, −0.02)	0.03	14.2	
Study Quality					0.001
Good quality	5	−0.25 (−0.45, −0.05)	0.0	97.8	
Poor and Fair quality	10	−0.29 (−0.55, −0.04)	0.02	56.7	
Subgroup analyses for insulin level and ALA supplementation					
Supplement Dose					
Less than 600 mg/day	3	−0.23 (−1.40, 0.95)	0.7	66.8	0.04
600 mg/day and more	6	0.21 (−0.82, 1.23)	0.69	54.8	0.05
Quality score[c]					
Good quality	6	−0.01 (−1, 1.3)	0.98	72.7	0.003
Poor and Fair quality	3	−0.04 (−0.94, 0.87)	0.93	0.0	0.78
Duration of follow up					
Less than 9 weeks	2	1.2 (−0.22, 2.25)	0.1	0.0	0.86
9 weeks and more	7	−0.19 (−1.04, 0.66)	0.66	62.6	0.01
Subgroup analyses HOMA-IR and ALA supplementation					
Supplement Dose					
Less than 600 mg/day	3	0.31 (−0.27, 0.89)	0.29	78.6	0.009
600 mg/day and more	6	0.04 (−0.19,0.27)	0.62	21.6	0.27
Duration of follow up					
Less than 9 weeks	4	0.29 (−0.18, 0.75)	0.23	48.9	0.11
9 weeks and more	5	−0.07 (−0.22, 0.08)	0.35	7.7	0.36
Quality score[c]					
Good quality	4	0.15 (−0.1, 0.39)	0.24	0.0	0.66
Poor and Fair quality	5	0.03 (−0.39, 0.45)	0.89	67.1	0.01
Subgroup analysis CRP and ALA supplementation					
Supplement Dose					
Less than 600 mg/day	4	−0.03 (−0.05, −0.00)	0.02	0.0	0.95
600 mg/day and more	12	−0.51 (−0.87, −0.14)	0.006	92.1	0.00
Duration of follow up					
Less than 9 weeks	9	−0.14 (−0.31, 0.03)	0.11	68.8	0.001
9 weeks and more	7	−0.62 (−1.42, 018)	0.12	91.3	0.00
Quality score[c]					
Good quality	8	−0.74 (−1.33, −0.16)	0.01	91.3	0.00
Poor and Fair quality	8	−0.13 (−0.31, 0.05)	0.15	64.5	0.006
Subgroup analysis TNF-α and ALA supplementation					
Duration of follow up					
Less than 9 weeks	4	−1.31 (−2.53, −0.09)	0.03	62.9	0.04
9 weeks and more	5	−1.67 (−2.25, −1.09)	0.00	77.3	0.001
Quality score[c]					
Good quality	5	−1.72 (−2.87, −0.56)	0.004	72.2	0.01
Poor and Fair quality	4	−1.40 (−2.13, −0.68)	0.00	78.8	0.001
Subgroup analysis TNF-α and ALA supplementation					
Supplement Dose					
Less than 600 mg/day	4	−1.47 (−2.13, −0.81)	0.00	45	0.14
600 mg/day and more	9	−2.79 (−4.30, −1.29)	0.00	95.7	0.00
Duration of follow up					
Less than 9 weeks	7	−3.17 (−4.94, −1.40)	0.00	91.1	0.00
9 weeks and more	6	−1.66 (−2.69, −0.63)	0.002	91.6	0.00
Quality score[c]					
Good quality		−2.93 (−4.43, −1.44)	0.00	85.2	0.00
Poor and Fair quality		−1.94 (−3.28, −0.6)	0.004	95.3	0.00

[a] P for 'weighted mean difference (WMD)'.
[b] P for heterogeneity.
[c] Quality Scores were according to Cochrane risk of bias tool.

(PI3K), and protein kinase B (AKT) [68]. On this basis, ALA is referred to as an insulin-mimetic agent [69]. Improvement of insulin sensitivity by ALA has been reported in previous studies [70,71], but the results are controversial. In an experimental study, Woo et al. have shown that ALA activates AMPK in skeletal muscle, and it is generally considered that AMPK-activated glucose uptake is independent of insulin signaling [66]. The results of our analysis were contrary to some of the previous findings that have shown

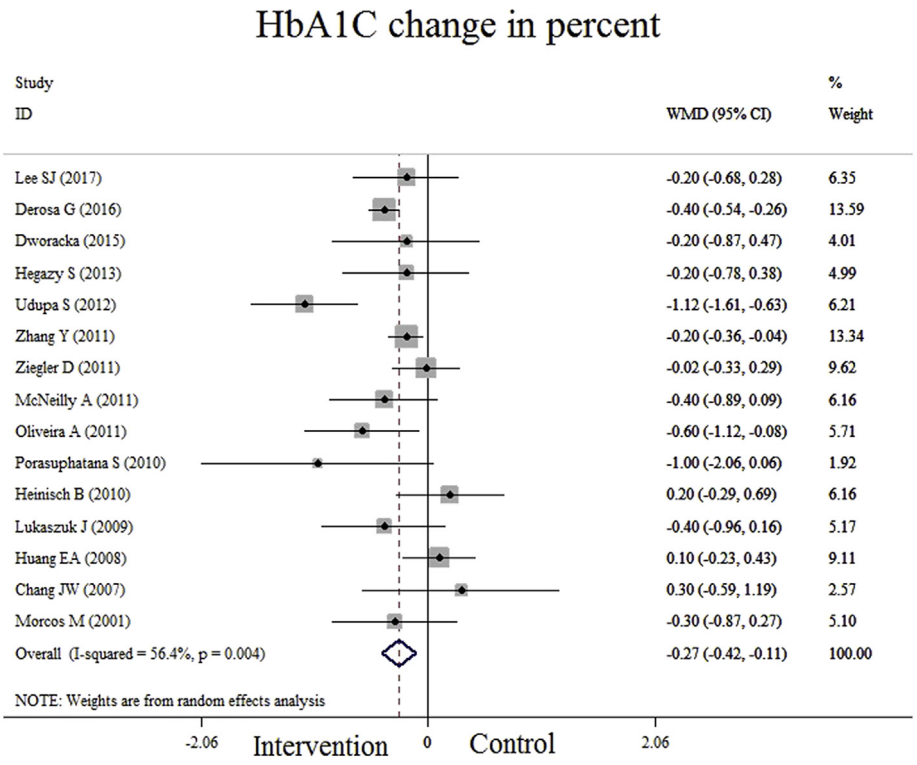

Fig. 4. Pooled estimates studies assessing the effect of ALA vs. control on HbA1C.

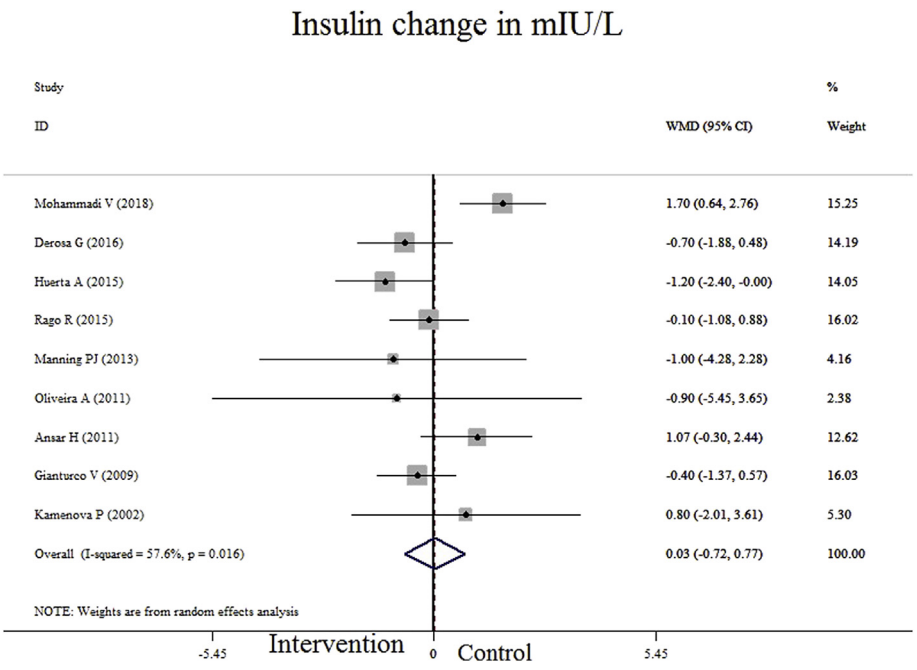

Fig. 5. Pooled estimates studies assessing the effect of ALA vs. control on insulin concentration.

ALA can improve oxidative stress-induced insulin resistance in vitro [72,73]. We did not find significant changes in insulin level and HOMA-IR index after ALA supplementation. Subgroup analyses were performed to identify the heterogeneity source, showing that supplementation dose, duration of follow-up, and study quality were not identified as sources of heterogeneity for insulin and HOMA-IR. In the present meta-analysis, supplementation with ALA resulted in a significant reduction in CRP, TNF-α, and IL-6 levels compared to placebo.

The main cause of mortality in non-diabetic and diabetic patients is CVD. Oxidative stress and a pro-inflammatory state are considered to be the most important mechanisms involved in CVD pathogenesis [74]. Increased inflammatory markers, especially TNF-α, may promote insulin resistance and increase the risk of

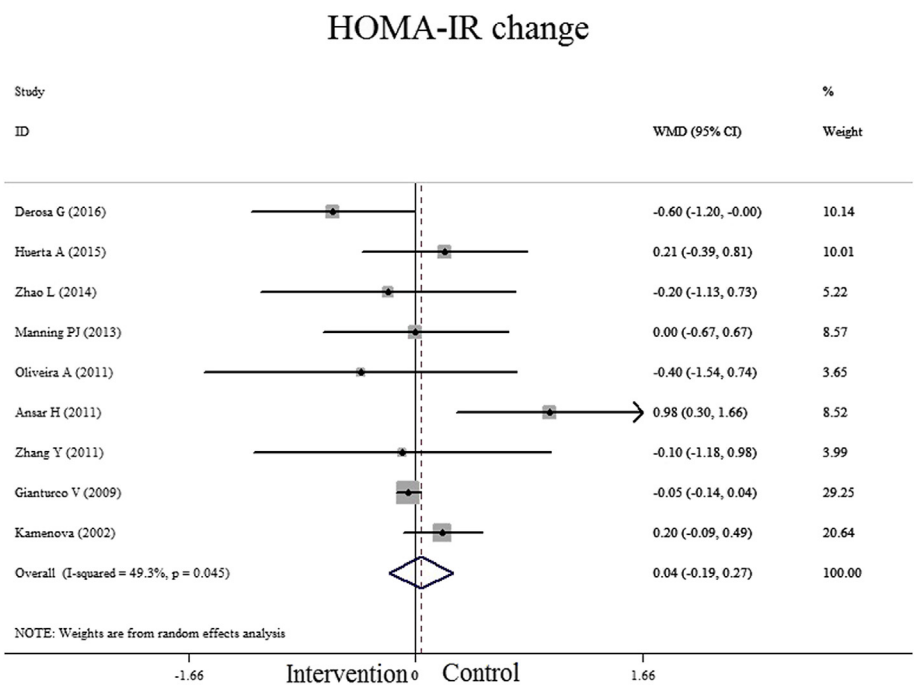

Fig. 6. Pooled estimates studies assessing the effect of ALA vs. control on HOMA-IR.

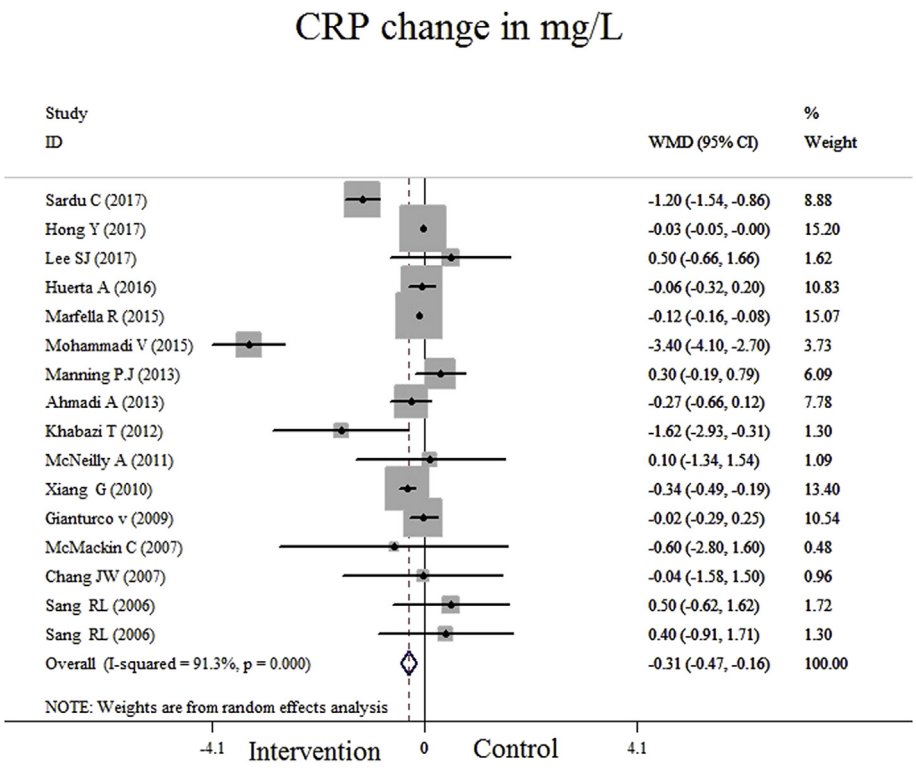

Fig. 7. Pooled estimates studies assessing the effect of ALA vs. control on CRP concentration.

cardiovascular disease [75]. In previous studies, ALA acted as a potent antioxidant as well as an anti-inflammatory agent by inhibiting the production of some pro-inflammatory cytokines [37,76–78]. The strongly suggested mechanism for the anti-inflammatory effect of ALA is through the inhibition of NF-kB. This protein is involved as a main regulator of DNA transcription, cytokine production, and cell survival [79].

COX-2, an inducible isozyme of COX, is an important enzyme in the induction of inflammatory pathways and production of prostaglandins [80,81]. The use of inhibitors of this enzyme can relieve inflammatory response. Ha et al. have reported that ALA suppresses COX-2 and PGE2 production [14]. Moreover, it decreases the expression of iNOS gene and leads to the down-regulation of pro-inflammatory cytokine [82]. ALA intake may

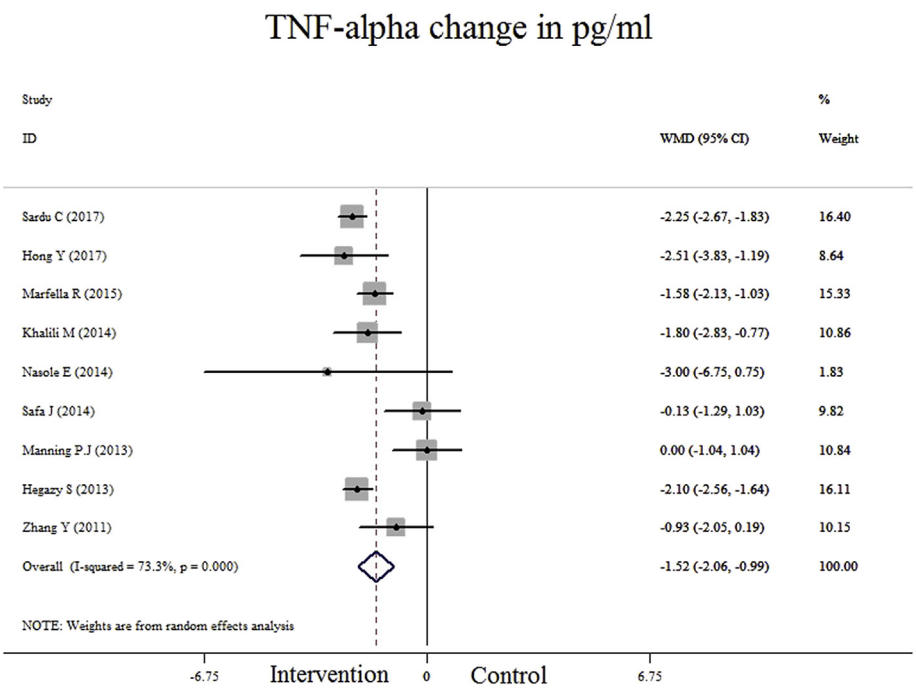

Fig. 8. Pooled estimates studies assessing the effect of ALA vs. control on TNF-α concentration.

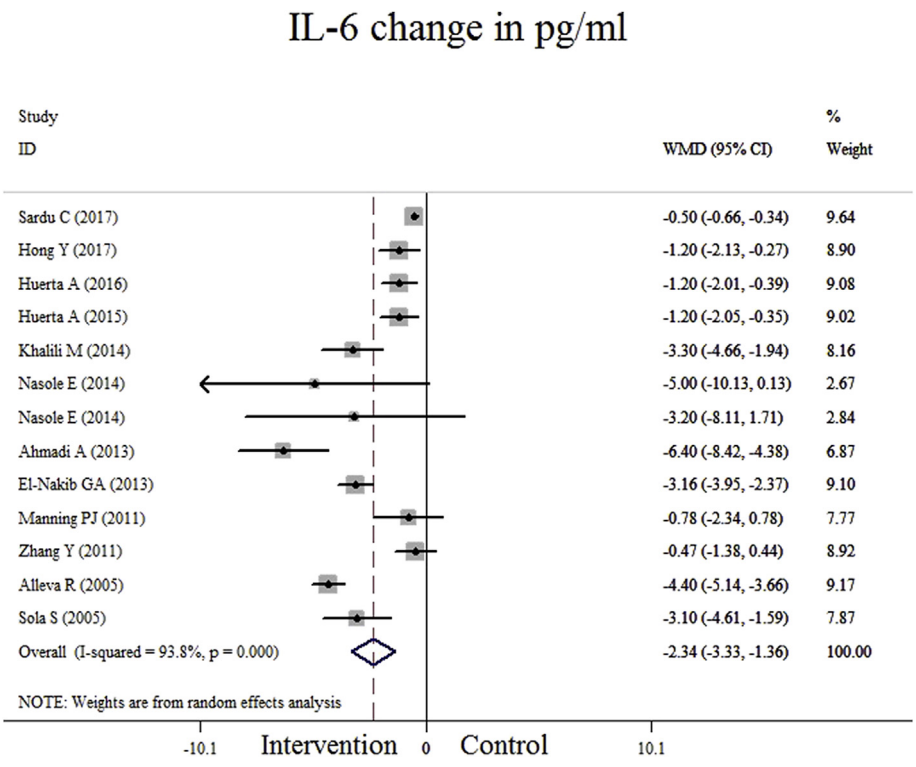

Fig. 9. Pooled estimates studies assessing the effect of ALA vs. control on IL-6 concentration.

decrease inflammatory markers through scavenging free radicals and down-regulating pro-inflammatory redox-sensitive signal transduction processes, including nuclear factor kappa B translocation, leading to a lower release of other free radicals and cytotoxic cytokines [83,84].

Furthermore, Salinthone et al. have recently demonstrated that ALA can display non-redox anti-inflammatory properties by interfering in different signaling cascades [85]. This supplement increases the activation of the immunomodulator cAMP in human inflammatory cells through various ways such as

decreasing the production of prostaglandins, EP2, and EP4 receptors [86].

Moreover, it has been demonstrated that ALA can increase intracellular levels of glutathione, which is the potent cellular antioxidant, and reduce inflammatory biomarkers levels as one of the main modulators of the thiol redox state pathway [87,88].

The most commonly reported ALA non-serious adverse effects were nausea or stomach upset, along with overstimulation, fatigue, and insomnia. In higher doses, it can cause hypoglycemia. Some patients also reported gastrointestinal symptoms, especially abdominal pain, in higher doses [89,90].

This is the first comprehensive review and meta-analysis assessing the effects of ALA supplementation on some cardio-metabolic parameters in the adult population. The strengths of this study include the identification of randomized trials with a detailed search strategy and subgroup analysis of the dose, duration of supplementation, and study quality. Nevertheless, the present study has several limitations, and findings should be interpreted with caution. First, the included studies were on different diseases, which may have affected the accuracy of the results. Second, the eligible studies were heterogeneous, and we could not identify the source of heterogeneity for some factors. Finally, some eligible studies had a small sample size which may affect the pooled effect size.

5. Conclusion

The present meta-analysis pooled results from 41 RCTs regarding the effects of ALA supplementation on some cardio-metabolic risk factors. Results indicated that ALA supplementation has beneficial effects on reducing cardio-metabolic risk factors without significant side effects. Still, more RCTs with large sample sizes are required to better understand the effects of ALA on patients with cardio-metabolic risk factors.

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Conflict of interest statement

None of the authors declare a conflict of interest.

Author contributions

Study concept and design: Mehran Rahimlou; data extraction: Mehran Rahimlou and Maryam Asadi; analysis and interpretation of data: Anahita Mansoori; drafting of the manuscript: Farideh Shishehbor and Mehran Rahimlou.

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The authors' responsibilities were as follows: M.R., N.B., and M.A. contributed to design and data extraction; A.M. and M.R. performed the data analysis; A.M., M.A., and F.S prepared the manuscript; and F.S. and M.R. conducted the critical review. The manuscript has been read and approved by all authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.03.015.

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