



## The effects of alpha-lipoic acid supplementation on glucose control and lipid profiles among patients with metabolic diseases: A systematic review and meta-analysis of randomized controlled trials



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### ABSTRACT

**Objective:** This systematic review and meta-analysis of randomized controlled trials (RCTs) was performed to summarize the effect of alpha-lipoic acid (ALA) supplementation on glycemic control and lipid profiles among patients with metabolic diseases.

**Methods:** We searched the following databases till October 2017: MEDLINE, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials. The relevant data were extracted and assessed for quality of the studies according to the Cochrane risk of bias tool. Data were pooled using the inverse variance method and expressed as standardized mean difference (SMD) with 95% confidence intervals (95% CI). Heterogeneity between studies was assessed by the Cochran Q statistic and I-squared tests ( $I^2$ ). Twenty-four studies were included in the meta-analyses.

**Results:** The findings of this meta-analysis showed that ALA supplementation among patients with metabolic diseases significantly decreased fasting glucose (SMD -0.54; 95% CI, -0.89, -0.19;  $P = 0.003$ ), insulin (SMD -1.01; 95% CI, -1.70, -0.31;  $P = 0.006$ ), homeostasis model assessment of insulin resistance (SMD -0.76; 95% CI, -1.15, -0.36;  $P < 0.001$ ) and hemoglobin A1c (SMD -1.22; 95% CI, -2.01, -0.44;  $P = 0.002$ ), triglycerides (SMD -0.58; 95% CI, -1.00, -0.16;  $P = 0.006$ ), total- (SMD -0.64; 95% CI, -1.01, -0.27;  $P = 0.001$ ), low density lipoprotein-cholesterol (SMD -0.44; 95% CI, -0.76, -0.11;  $P = 0.008$ ). We found no detrimental effect of ALA supplementation on high density lipoprotein-cholesterol (HDL-cholesterol) levels (SMD 0.57; 95% CI, -0.14, 1.29;  $P = 0.11$ ).

**Conclusions:** Overall, the current meta-analysis demonstrated that ALA administration may lead to an improvement in glucose homeostasis parameters and lipid profiles except HDL-cholesterol levels.

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## 1. Introduction

There are multiple primary and secondary causes of metabolic disturbances related to metabolic syndrome (MetS) including impaired glucose tolerance and hypertriglyceridemia, such as genetics, lifestyle and diet especially obesity and reduced physical activity [1,2]. Previous studies have reported that *MetS* is linked to a 2-fold increased risk of cardiovascular disease (CVD) and a 5-fold increased risk of type 2 diabetes mellitus (T2DM) over the next 5 to 10 years [3]. In addition, dyslipidemia [(hypertriglyceridemia, increased levels of total- and low density lipoprotein-cholesterol (LDL-cholesterol) and decreased levels of high density lipoprotein-cholesterol (HDL-cholesterol) is often correlated with insulin resistance, chronic diseases [4,5], and increased risk of atherosclerotic events [6].

Common treatments for managing markers of insulin metabolism and lipid profiles in patients with metabolic diseases include lifestyle changes such as weight loss through an energy-restricted diet together with increased energy expenditure through physical activity, various dietary patterns, and the appropriate use of pharmacological agents to reduction the specific risk factors [7,8]. To increase compliance and adherence of patients with metabolic diseases to lifestyle changes, complementary therapies including antioxidants supplementation can be useful [9]. Existing evidence has documented the beneficial effects of several antioxidants supplements including phenolic compounds [10], some vitamins and minerals [9,11,12] on complications related to metabolic disorders. Investigations on antidiabetic and antilipidemic characteristic of antioxidants have demonstrated that they can inhibit the expression of cyclooxygenase-2 and P-selectin [13] and stimulate the peroxisome proliferator-activated receptor gamma transduction pathway [14]. Despite reported antidiabetic and antilipidemic characteristics of alpha-lipoic acid (ALA) in some clinical trials [15–17], several studies did show no positive effects of ALA on glycemic control and lipid profiles [18,19]. In addition, two previous meta-analyses studies have reported the beneficial effects of ALA supplementation on weight loss and body mass index, and inflammatory markers [20,21]. Therefore, ALA supplementation to promote glycemic status and lipid fractions remains controversial. Discrepancies in findings might be the result of differences in study design, characteristics of study populations, dosage of ALA used and duration of the studies.

Despite several randomized controlled trials (RCTs), we are aware of no systematic review and meta-analysis of RCTs about the effect of ALA supplementation on glycemic control and lipid profiles among patients with metabolic diseases. This meta-analysis was performed to summarize the available evidence of RCTs to establish the effect of ALA supplementation on glycemic control and lipid profiles among patients with metabolic diseases.

## 2. Methods

### 2.1. Search Strategy and Selection Studies

The design, implementation, analysis, and reporting of this study were conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. We performed a search of Cochrane Library, EMBASE, MEDLINE, and Web of Science databases for relevant RCTs studies published till October 2017. Databases (International Standard Randomized Controlled Trial Number Register and Meta-register for RCTs) were searched for

ongoing trials. RCTs retrieved that examined the association between ALA supplementation on glycemic control and lipid profiles using the following MeSH and text keywords: patients ["metabolic disease" OR "MetS" OR "diabetes" OR "T2DM" OR "overweight" OR "obese" OR "gestational diabetes mellitus (GDM)" OR "polycystic ovary syndrome (PCOS)"], intervention ("ALA" OR "α-lipoic acid" AND "supplementation" OR "intake"), and outcomes ["triglycerides (TG)" OR "total-cholesterol (TC)" OR "LDL-cholesterol" OR "LDL-C" OR "HDL-cholesterol" OR "HDL-C" OR "fasting plasma glucose (FPG)" OR "insulin" OR "homeostasis model assessment of insulin resistance (HOMA-IR)" OR "hemoglobin A1c" OR "HbA1c"]. The references list of all known related studies were reviewed to identify additional potential publications that was not captured based on the electronic searches. We applied studies published in the English language without time restrictions for publication. Two independent authors (RT, MA) have selected studies in two-stage process. In the first stage, authors observed the titles and/or abstracted to find trials had potential eligibility. In the second stage, the full texts of related trials were retrieved for detailed evaluation. In the event of a discrepancy, it is resolved by consensus or discussion with a third author (ZA). Studies were selected according to the following criteria: 1) original studies, 2) human RCTs in design, 3) the target population were patients with metabolic diseases, 4) intervention group received of ALA supplements or ALA plus other nutrients, whereas the control group received placebo, and 5) the trials reported mean changes of glycemic control and/or lipid profiles with standard deviation (SD) for the intervention and control groups.

### 2.2. Data Extraction and Quality Assessment

Two authors (VO and MA) independently extracted, as well as two authors assessed (RT and MA) the quality of all relevant studies when there was disagreement, it was resolved by discussion with third author (ZA) or until consensus was reached. The Cochrane Collaboration risk of bias tool used to assess the quality of the included RCTs based on information on the following domains: randomization generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting, and other sources of bias.

### 2.3. Data Analysis

All statistical analyses were performed using STATA version 12.0 (Stata Corp, College Station, TX) and RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK). Heterogeneity between included primary studies was estimated using Cochran's Q test and I-square statistic. I-square higher than 50% with  $p < 0.05$  represented significant heterogeneity. This study estimated the standardized mean difference (SMD) with 95% confidence interval (CI) by inverse variance method and Cohen statistics. Since the indications could effect on pooled SMD were different between included studies, we used random-effects models for meta-analysis. Subgroup analyses were performed to assess the source of heterogeneity between studies heterogeneity. To explore the contribution of a particular study to the overall mean difference was performed sensitivity analysis. Egger's test and funnel plot were applied to identify the presence of publication bias for the primary outcome measure. The *P*-value of (2-tailed)  $< 0.05$  were considered as statistically significant.

### 3. Results

#### 3.1. Search Results

Our initial search found 1012 potential citations. After screening articles, 24 papers were found to be eligible for our meta-analysis. The details of step by step study identification and selection were illustrated in Fig. 1. Fourteen studies were double-blind design, eight studies were randomized, placebo-controlled trial, and two were RCT. Twelve trials examined the effects of ALA on glycemic control and lipid profiles among patients with T2DM [15,17,19,22–30] and the remaining studies were among other metabolic diseases. Overall, nineteen trials have reported changes in lipid profiles include triglycerides, total-, LDL- and HDL-cholesterol, and twenty studies have reported changes in and glucose metabolism including FPG, insulin, HOMA-IR, and HbA1c. The duration of intervention among studies varied from 2 to 51 weeks. The dosage of ALA supplements used was from 200 to 1800 (mg/day). Six studies were conducted in China [18,22,23,29–31], five in Italy

[27,32–35], two in Republic of Korea [28,36], Iran [15,37], and Spain [16,38], and one in Brazil [19], Bosnia and Herzegovina [17], India [24], Austria [26], USA [39], Thailand [25], and New Zealand [40]. Table 1 shows the details of the included study characteristics into meta-analysis. The quality of included studies, which was explored using the Cochrane Collaboration risk of bias tool by the judgments of author are presented in Fig. 2. The findings of risk of bias assessment indicated that three studies were rated at low risk of bias, 19 studies were at unclear risk of bias, and 2 studies were at high risk bias based on the judgments of author.

#### 3.2. The Effects of ALA Supplementation on Glucose Metabolism

ALA supplementation significantly decreased FPG (SMD  $-0.54$ ; 95% CI,  $-0.89$ ,  $-0.19$ ;  $P = 0.003$ ), insulin concentrations (SMD  $-1.01$ ; 95% CI,  $-1.70$ ,  $-0.31$ ;  $P = 0.006$ ), HOMA-IR (SMD  $-0.76$ ; 95% CI,  $-1.15$ ,  $-0.36$ ;  $P < 0.001$ ) and HbA1c (SMD  $-1.22$ ; 95% CI,  $-2.01$ ,  $-0.44$ ;  $P = 0.002$ ) (Table 2& Fig. 3).

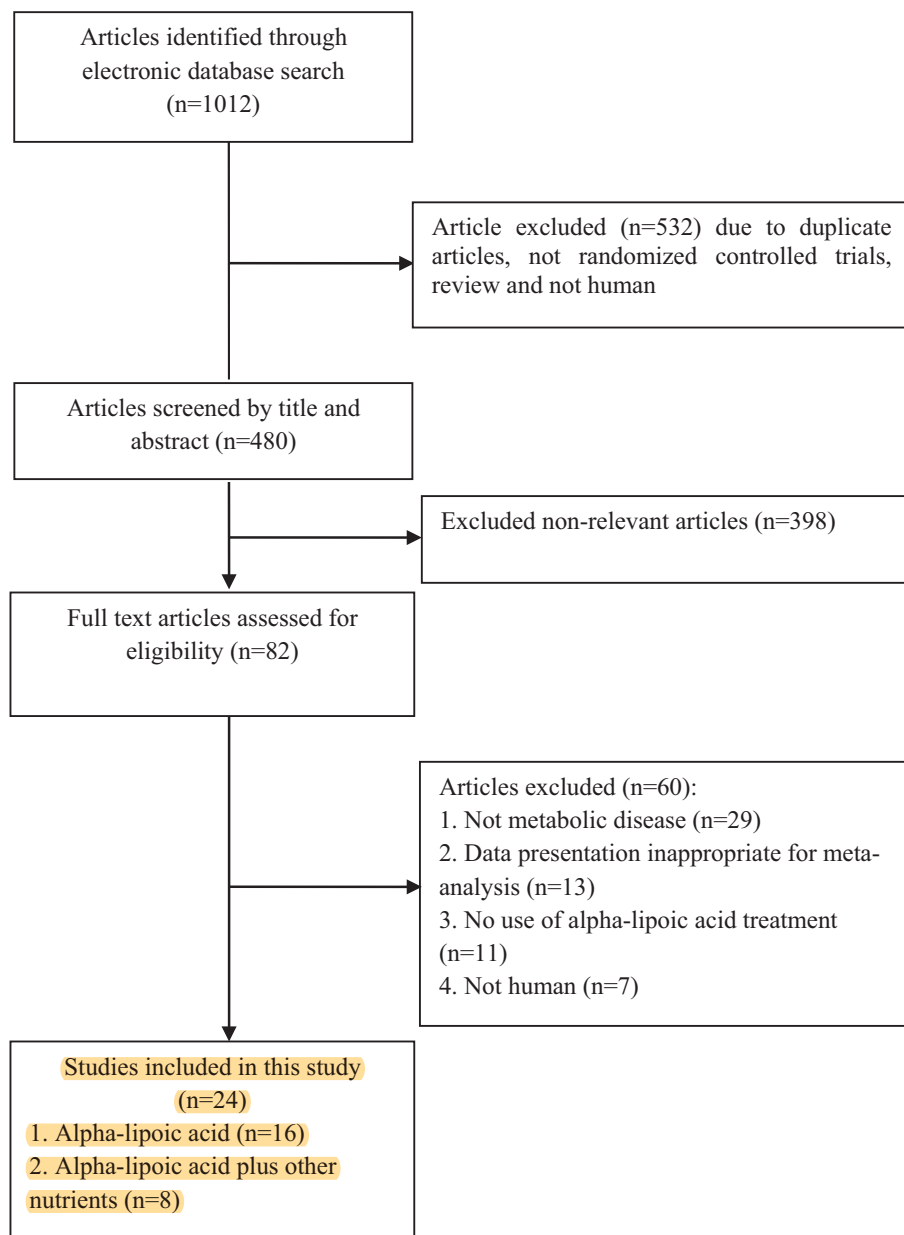


Fig. 1. Literature search and review flowchart for selection of studies.

**Table 1**  
Characteristics of included studies.

Authors (Ref)	Publication year	Sample size (control/intervention)	Country/population	Intervention (name and daily dose)	Duration	Presented data	Age (control, intervention)	Results (intervention group)
Oliveira et al. [19]	2011	26/26	Brazil/T2DM	600 mg ALA plus other nutrients	4 months	TC, TG, LDL-C, HDL-C, FPG, insulin, HOMA-IR	62.51, 59.98, range: 38–75	Decreased TC, LDL-C, TG, FPG, insulin, HOMA-IR, and increased HDL-C
Khabbazi et al. [37]	2012	28/24	Iran/HD	600 mg ALA	8 weeks	TC, TG, LDL-C, HDL-C	54.04 ± 13.96, 53.83 ± 13.29	Increased TC, TG, LDL-C, HDL-C
Capasso et al. [35]	2013	78/77	Italy/Postmenopausal women with MetS	200 mg ALA + 4 g inositol	6 months	TC, TG, HDL-C, FPG, insulin, HOMA-IR	58.2 ± 5.6, 57.71 ± 7.9	Decreased TC, TG, FPG, insulin, HOMA-IR, and increased HDL-C
Gianturco et al. [34]	2012	46/52	Italy/NAFLD	400 mg ALA	12 months	TC, TG, LDL-C, HDL-C, FPG, insulin, HOMA-IR	61.0 ± 3.8, 60.0 ± 3.9	Decreased TC, TG, LDL-C, HDL-C, insulin, HOMA-IR, and increased FPG
Cianci et al. [33]	2015	20/26	Italy/PCOS	600 mg ALA + 1 g DCI	180 days	TC, TG, HDL-C, insulin, HOMA-IR	23.8 ± 2.5, Range: 16–32	Decreased TC, TG, insulin, HOMA-IR and increased HDL-C
McMackin et al. [39]	2007	21/15	USA/CAD	400 mg ALA + 1 g acetyl-L-carnitine	8 weeks	TG, TC, LDL-C, HDL-C, insulin, FPG	64.0 ± 7.0, 62.0 ± 5.0	Decreased TC, TG, HDL-C, FPG and increased LDL-C, insulin
Li et al. [18]	2017	83/87	China/Obese or overweight patients	1200 mg ALA	8 weeks	TG, TC, HDL-C	<sup>a</sup> 43[38–47], 44[39–47]	Decreased TG and TC, increased HDL-C
Gianturco et al. [27]	2009	7/7	Italy/T2DM	400 mg ALA	4 weeks	TG, TC, LDL-C, HDL-C	58.0 ± 16.0, 61.0 ± 7.0	Decreased TC, TG, LDL-C, and increased HDL-C
Okanović et al. [17]	2015	30/30	Bosnia and Herzegovina/Obese patients with T2DM	600 mg ALA + metformin	20 weeks	TG, FPG	61.13 ± 1.34, 62.97 ± 1.46	Decreased TG and FPG
Zhao et al. [22]	2014	44/46	China/T2DM	600 mg ALA (IV)	3 weeks	TC, TG, LDL-C, FPG, HOMA-IR, Hb1Ac	71.6, range: 60–92	Decreased TC, TG, LDL-C, FPG, HOMA-IR, Hb1Ac
Zhang et al. [30]	2011	9/13	China/Obese patients with impaired glucose tolerance	600 mg ALA (IV)	2 weeks	TC, TG, LDL-C, HDL-C, FPG, insulin	52.6 ± 6.2, 52.5 ± 8.2	Decreased TC LDL-C, FPG, insulin and increased HDL-C
Udupa et al. [24]	2012	21/23	India/T2DM	300 mg ALA (IV)	90 days	TC, FPG, insulin	53.8 ± 2.1, 53.5 ± 1.4	Decreased TC, FPG, insulin
Huang et al. [23]	2013	40/40	China/T2DM	600 mg ALA (IV) for 2 weeks + CSII	3 months	TC, LDL-C, HDL-C, FPG, insulin, HbA1c	50.8 ± 9.7, 49.6 ± 10.5	Decreased TC, LDL-C, FPG, insulin, HbA1c, and increased HDL-C
Rago et al. [32]	2015	22/22	Italy/PCOS	800 mg ALA + 2 g MI	3 months	TC, TG, LDL-C, HDL-C, FPG, insulin	36.3 ± 2.8, 37.1 ± 2.7	Decreased TC, TG, LDL-C, FPG, insulin and increased HDL-C
Sun et al. [31]	2012	28/28	China/ARMD	600 mg ALA	3 months	TC, TG, LDL-C, HDL-C	64.47 ± 8.13, 65.78 ± 7.93	Decreased TC, LDL-C, and increased TG, HDL-C
Chang et al. [28]	2007	25/25	Korea/Diabetic HD	600 mg ALA	3 months	TC	66.0 ± 7.0, 63.0 ± 6.0	Decreased TC
Heinisch et al. [26]	2010	15/15	Austria/T2DM	600 mg ALA	3 weeks	TC, TG, LDL-C, HDL-C, HbA1c	56.0 ± 6.0, 55.0 ± 8.0	Decreased TC, TG, LDL-C, HDL-C, HbA1c
Xiang et al. [29]	2011	30/30	China/Patients with impaired fasting glucose	600 mg ALA	3 weeks	TC, TG, LDL-C, HDL-C, FPG	58.0 ± 9.0, 58.0 ± 10.0	Decreased TG, LDL-C, FPG and increased TC, HDL-C
Koh et al. [36]	2011	73/82	Republic of Korea/obese patients	1800 mg ALA	20 weeks	TG, HDL-C, HbA1c, FPG	40.7 ± 12.04, 41.4 ± 10.95	Decreased TG, HDL-C, HbA1c, and increased FPG
Ansar et al. [15]	2011	28/29	Iran/T2DM	300 mg ALA	8 weeks	FPG, HOMA-IR	51.82 ± 8.25, 49 ± 9.07	Decreased FPG, HOMA-IR
Huerta(I) et al. [16]	2015	22/17	Spain/Overweight and Obese Women	300 mg ALA + 1.3 g EPA	10 weeks	Insulin, HOMA-IR	39.0 ± 8.0, 39.0 ± 7.0	Decreased insulin, and HOMA-IR
Huerta(II) et al. [38]	2015	21/17	Spain/Overweight and Obese Women	300 mg ALA + 1.3 g EPA	10 weeks	FPG	38.5 ± 7.1, range: 20–45	Decreased FPG
Porasuphatana et al. [25]	2011	8/7	Thailand/T2DM	1200 mg ALA	6 months	HbA1c	42.9 ± 7.12, 47.7 ± 5.76	Decreased HbA1c
Manning et al. [40]	2012	40/34	New Zealand/MetS	600 mg ALA	12 months	FPG	57.0 ± 9.0, 55.0 ± 10.0	No effect on FPG

ALA, Alpha-lipoic acid; CSII, Short-term continuous subcutaneous insulin infusion; DCI, D-chiro-inositol; EPA, eicosapentaenoic acid; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; HD, heart disease; MetS, metabolic syndrome; NAFLD, Nonalcoholic fatty liver disease; CAD, coronary artery disease; PCOS, polycystic ovary syndrome; NIDDM, non-insulin-dependent diabetes mellitus; ARMD, Age-related macular degeneration; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance.

<sup>a</sup> Median [IQR].

Findings of the subgroup analyses by several suspected variables of the intervention are presented in Table 3.

Sensitivity analysis was conducted and the results remained consistent with the pooled effect (Fig. 5).

Egger's regression tests indicated no significant publication bias for meta-analyses assessing the effects of ALA on FPG ( $B = -2.25$ ,  $P = 0.42$ ), insulin ( $B = -1.33$ ,  $P = 0.75$ ), HOMA-IR ( $B = 3.06$ ,  $P = 0.75$ ), and HbA1c ( $B = -1.37$ ,  $P = 0.75$ ).

### 3.3. The Effects of ALA Supplementation on Lipid Profiles

The effects of ALA supplementation on lipid profiles were shown in Fig. 4. The results showed that ALA supplementation among patients with metabolic diseases significantly decreased triglycerides (SMD -0.58; 95% CI, -1.00, -0.16;  $P = 0.006$ ), total- (SMD -0.64; 95% CI, -1.01, -0.27;  $P = 0.001$ ) and LDL-cholesterol (SMD -0.44; 95% CI, -0.76, -0.11;  $P = 0.008$ ). We found no detrimental effect of ALA

Author (Year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other sources of bias (e.g. bias of study design, trial stopped early, extreme baseline imbalance, and fraudulent trial)
Ansari (2011)	+	+	+	+	+	+	+
Capasso (2013)	+	+	+	+	+	+	+
Chang (2007)	+	+	+	+	+	+	+
Chanel (2015)	+	+	+	+	+	+	+
Gianturco (2009)	+	+	+	+	+	+	+
Gianturco (2012)	+	+	+	+	+	+	+
Hahnisch (2010)	+	+	+	+	+	+	+
Huang (2013)	+	+	+	+	+	+	+
Huerta (1) (2015)	+	+	+	+	+	+	+
Huerta (2) (2015)	+	+	+	+	+	+	+
Khabbazi (2012)	+	+	+	+	+	+	+
Koh (2010)	+	+	+	+	+	+	+
Li (2017)	+	+	+	+	+	+	+
Manning (2012)	+	+	+	+	+	+	+
McMahon (2007)	+	+	+	+	+	+	+
Okunovic (2015)	+	+	+	+	+	+	+
Oliveira (2011)	+	+	+	+	+	+	+
Perasupathana (2011)	+	+	+	+	+	+	+
Rago (2015)	+	+	+	+	+	+	+
Sun (2012)	+	+	+	+	+	+	+
Udupa (2012)	+	+	+	+	+	+	+
Xiang (2010)	+	+	+	+	+	+	+
Zhang (2011)	+	+	+	+	+	+	+
Zhao (2014)	+	+	+	+	+	+	+

Fig. 2. The methodological quality of included studies (risk of bias).

supplementation on HDL-cholesterol levels (SMD 0.57; 95% CI, -0.14, 1.29;  $P = 0.11$ ).

Table 2 shows all meta-analyses between study population in included trials by pre and post changed in intervention and control groups. Because of existence heterogeneity, we conducted several subgroup analyses by suspected variables including type of diseases, dosage of ALA used, the duration of study, geographic area, and the type of intervention. The effects were different in some of specific groups of studies which the details of subgroup analyses were shown in Table 3.

Sensitivity analysis was performed and the results for triglycerides, total-, and LDL-cholesterol remained consistent with pooled effect size. But the pooled SMD for HDL-cholesterol found significant difference between the pre-sensitivity pooled SMD (0.57; 95% CI, -0.14, 1.29) and post-sensitivity pooled SMD (0.76; 95% CI, 0.10, 1.42) after excluding Gianturco et al. study (Fig. 5).

Egger's regression tests indicated no significant publication bias for meta-analyses assessing the effects of ALA on triglycerides ( $B = -3.64$ ,  $P = 0.12$ ), total- ( $B = -2.17$ ,  $P = 0.35$ ), HDL-cholesterol ( $B = 3.03$ ,  $P = 0.49$ ). Because there was evidence of publication bias on LDL-cholesterol ( $B = -4.38$ ,  $P = 0.01$ ), we used non parametric

method (Duval and Tweedie) to estimate the results of censored studies. The meta-analysis based on these studies showed that summary effect size on LDL-cholesterol was not significant changed between before included censored studies into meta-analysis (SMD -0.44; 95% CI, -0.76, -0.11) and after (SMD -0.44; 95% CI, -0.76, -0.11).

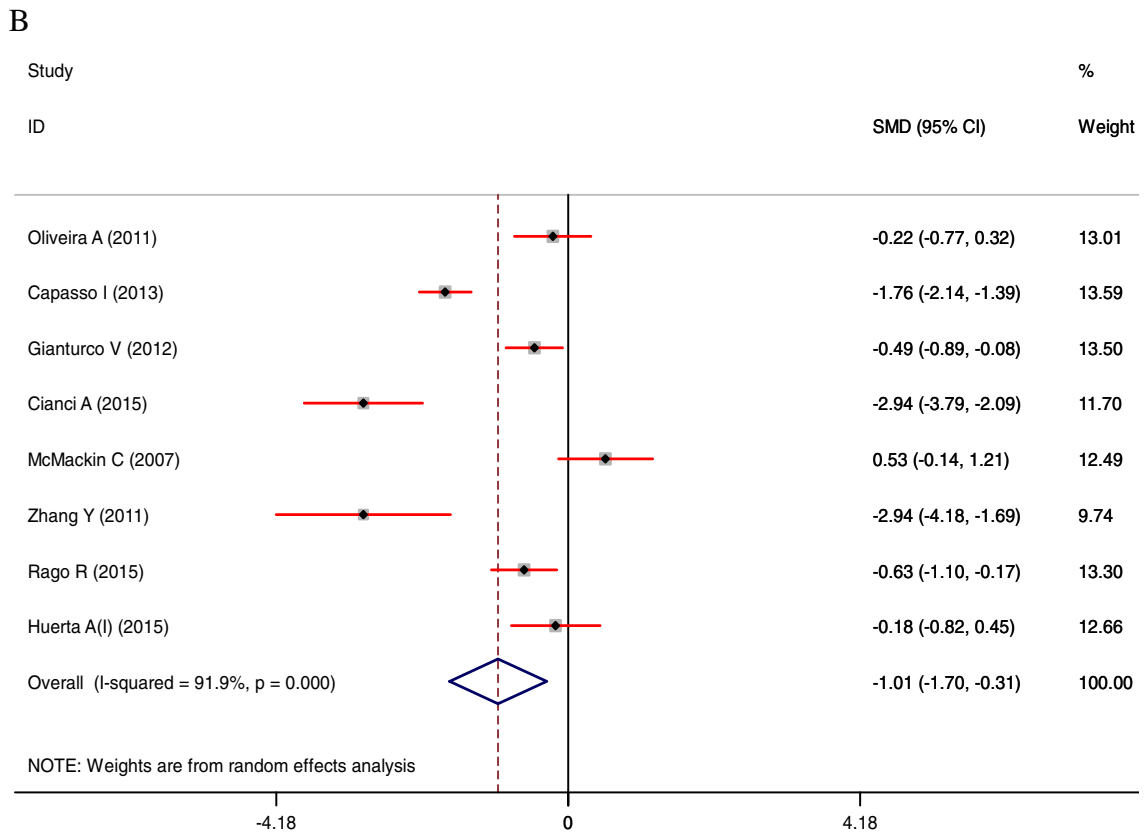
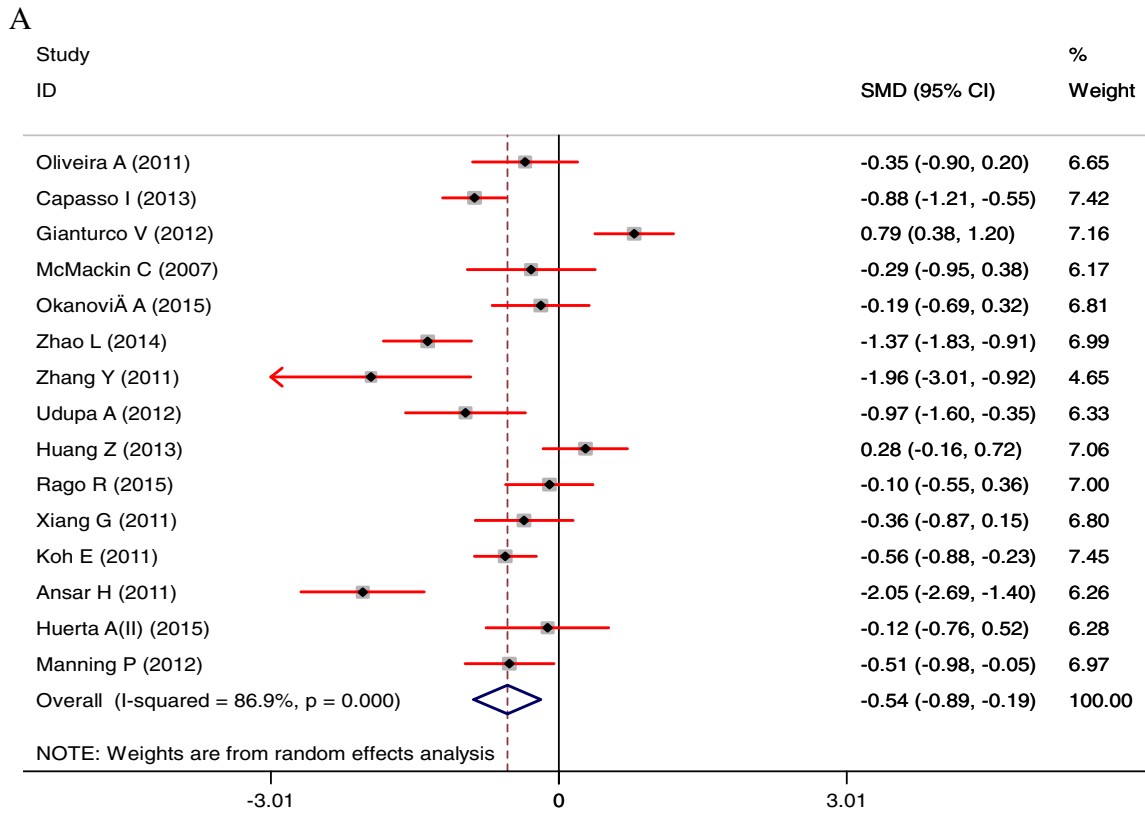
#### 4. Discussion

This systematic review and meta-analysis assessed the effect of ALA supplementation on glycemic control and lipid profiles in patients with metabolic diseases. This meta-analysis showed that ALA administration may lead to an improvement in glucose homeostasis parameters and lipid profiles except HDL-cholesterol levels. It must be kept in mind that few metabolic diseases especially diabetes mellitus may lead to neurological complications which its management focuses on glycemic control, multifactorial cardiovascular risk intervention, and pathogenesis-oriented therapy [21]. Existing evidence suggests that ALA increases glutathione levels, prevents lipid peroxidation, enhances the activity of antioxidant enzymes and increases blood flow and glucose uptake diabetic neuropathy [41,42]. Moreover, ALA may reduce

Table 2

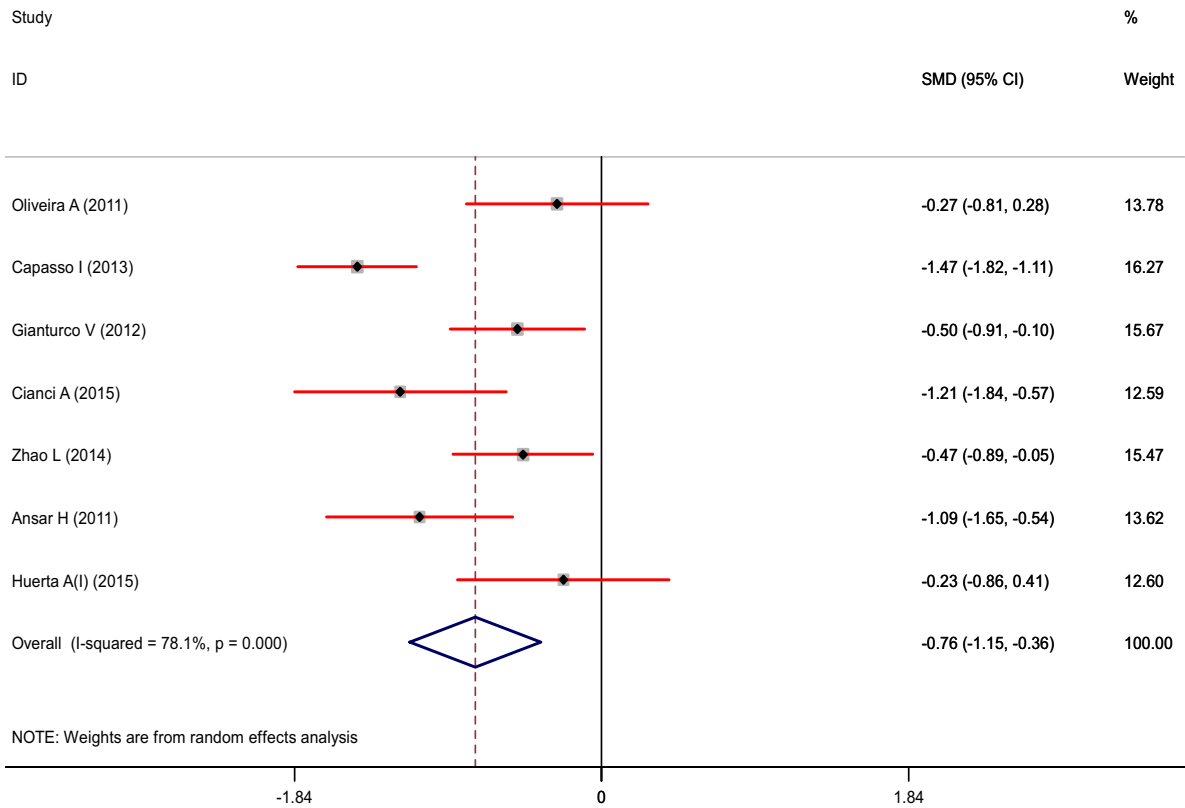
Estimation of the standardized difference means of related indicators with CI 95% between the intervention and placebo groups.

Parameter	Number of study	Standardized mean difference	CI 95%	Heterogeneity			
				I-squared (%)	Q	P-value	
Fasting glucose	Intervention group (after vs. before)	15	-0.84	-1.39, -0.28	94.3	246.92	<0.001
	Placebo group (after vs. before)	15	-0.53	-1.05, -0.01	93.5	216.15	<0.001
	Change intervention group vs. placebo group	15	-0.54	-0.89, -0.19	86.9	106.69	<0.001
Insulin	Intervention group (after vs. before)	7	-0.50	-0.88, -0.12	74.2	23.23	0.001
	Placebo group (after vs. before)	7	-0.11	-0.29, 0.08	0.0	1.47	0.96
	Change intervention group vs. placebo group	8	-1.01	-1.70, -0.31	91.9	86.74	<0.001
HOMA-IR	Intervention group (after vs. before)	6	-0.60	-0.81, -0.39	24.4	6.61	0.25
	Placebo group (after vs. before)	6	-0.06	-0.26, 0.14	15.5	5.92	0.31
	Change intervention group vs. placebo group	7	-0.76	-1.15, -0.36	78.1	27.40	<0.001
HbA1c	Intervention group (after vs. before)	5	-1.17	-2.14, -0.20	94.5	72.31	<0.001
	Placebo group (after vs. before)	5	-0.62	-1.36, 0.12	91.2	45.49	<0.001
	Change intervention group vs. placebo group	6	-1.22	-2.01, -0.44	91.1	56.48	<0.001
Triglycerides	Intervention group (after vs. before)	14	-0.59	-1.03, -0.15	89.0	118.65	<0.001
	Placebo group (after vs. before)	14	-0.29	-0.55, -0.03	69.5	42.63	<0.001
	Change intervention group vs. placebo group	16	-0.58	-1.00, -0.16	90.9	164.97	<0.001
Total cholesterol	Intervention group (after vs. before)	16	-0.56	-0.97, -0.15	88.9	135.08	<0.001
	Placebo group (after vs. before)	16	-0.29	-0.62, 0.03	82.8	87.02	<0.001
	Change intervention group vs. placebo group	17	-0.64	-1.01, -0.27	88.1	133.96	<0.001
LDL-cholesterol	Intervention group (after vs. before)	12	-0.39	-0.70, -0.08	72.3	39.75	<0.001
	Placebo group (after vs. before)	12	-0.19	-0.40, 0.02	43.2	19.36	0.05
	Change intervention group vs. placebo group	12	-0.44	-0.76, -0.11	74.4	43.01	<0.001
HDL-cholesterol	Intervention group (after vs. before)	13	0.07	-0.21, 0.35	71.1	41.57	<0.001
	Placebo group (after vs. before)	13	0.03	-0.11, 0.17	0.0	7.44	0.82
	Change intervention group vs. placebo group	15	0.57	-0.14, 1.29	96.4	390.22	<0.001



**Fig. 3. A–D.** Meta-analysis glycemetic control standardized mean differences estimates for (A) fasting plasma glucose, (B) for insulin, (C) for HOMA-IR, and (D) for HbA1c in alpha-lipoic acid supplements and placebo groups (CI = 95%).

C



D

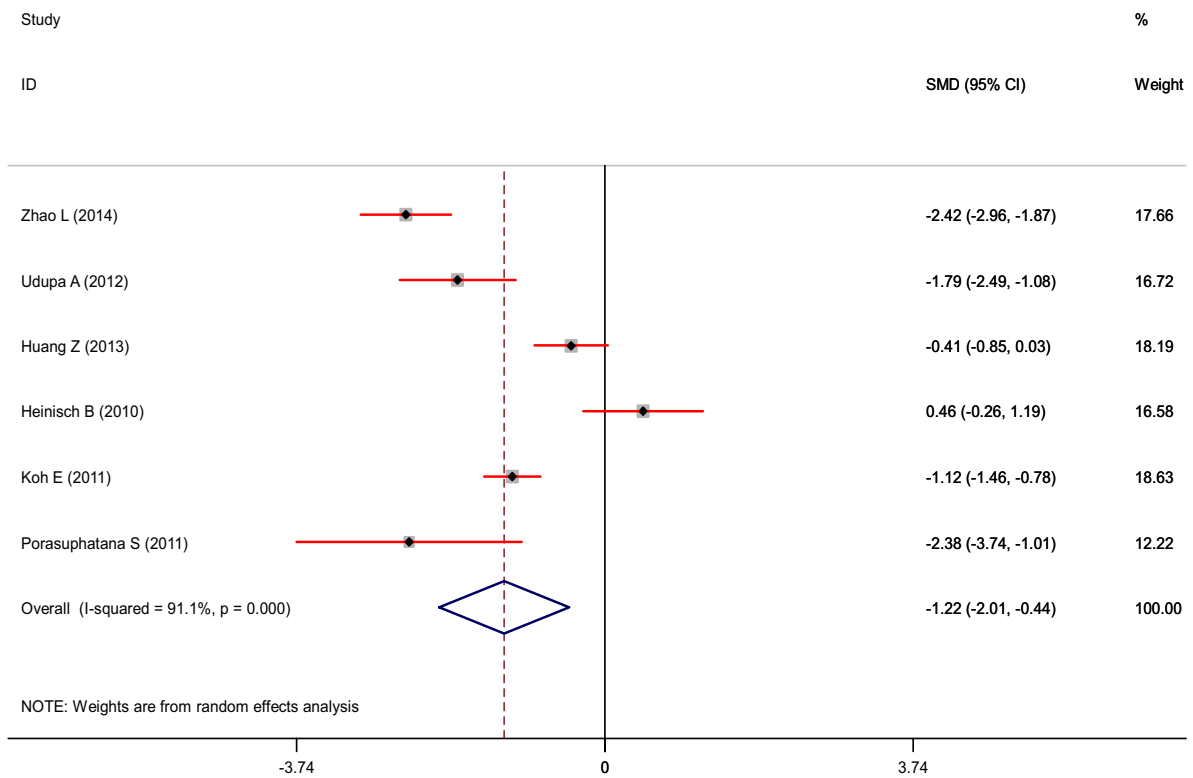


Fig. 3 (continued).

**Table 3**

The effects of alpha-lipoic acid supplementation on glycemic control and lipid profiles based on subgroup analysis.

Parameter		Number of SMD included	Subgroups	Pooled OR (random effect)	95% CI	I-squared (%)	Overall I-squared (%)
Triglycerides	Type of diseases	7	T2DM	-1.46	-2.63, -0.28	95.0	90.9
		9	Non-T2DM	-0.22	-0.53, 0.10	78.9	
	Dosage of ALA (mg/day)	4	<600	-0.25	-0.97, 0.47	86.5	
		9	=600	-1.12	-1.93, -0.31	93.6	
	Duration of study (week)	3	>600	-0.03	-0.24, 0.18	11.3	
		5	<8	-0.54	-1.27, 0.18	82.1	
		5	8–12	0.02	-0.18, 0.22	0.00	
	Geographic area	6	>12	-1.36	-2.30, -0.43	95.8	
		8	American or European	-0.99	-1.80, -0.17	94.2	
		8	Other countries	-0.30	-0.68, 0.08	80.1	
	Type of intervention	11	ALA	-0.21	-0.51, 0.08	73.2	
5		ALA + other nutrients	-1.79	-3.09, -0.49	96.2		
Total cholesterol	Type of diseases	9	T2DM	-1.03	-1.80, -0.27	92.3	88.1
		8	Non-T2DM	-0.30	-0.56, -0.03	63.5	
	Dosage of ALA (mg/day)	5	<600	-0.73	-1.17, -0.29	68.4	
		10	=600	-0.72	-1.37, -0.06	92.0	
	Duration of study (week)	2	>600	-0.28	-0.58, 0.02	23.9	
		6	<8	-1.09	-2.28, 0.10	94.8	
		7	8–12	-0.37	-0.75, 0.00	73.5	
	Geographic area	4	>12	-0.55	-0.90, -0.20	57.5	
		7	American or European	-0.39	-0.68, -0.10	54.4	
		10	Other countries	-0.87	-1.50, -0.24	92.5	
	Type of intervention	12	ALA	-0.84	-1.37, -0.31	90.7	
5		ALA + other nutrients	-0.26	-0.62, 0.10	65.0		
LDL-cholesterol	Type of diseases	7	T2DM	-0.80	-1.32, -0.27	79.2	74.4
		5	Non-T2DM	-0.09	-0.40, 0.23	47.6	
	Dosage of ALA (mg/day)	3	<600	-0.61	-1.53, 0.31	79.4	
		8	=600	-0.47	-0.90, -0.04	78.6	
	Duration of study (week)	1	>600	-0.22	-0.68, 0.23	0.00	
		6	<8	-0.93	-1.56, -0.31	82.1	
		4	8–12	-0.11	-0.54, 0.33	60.0	
	Geographic area	2	>12	-0.11	-0.43, 0.21	0.00	
		5	American or European	-0.33	-0.73, 0.08	59.0	
		7	Other countries	-0.51	-1.01, -0.01	81.6	
	Type of intervention	9	ALA	-0.59	-1.04, -0.14	80.6	
3		ALA + other nutrients	-0.15	-0.43, 0.14	0.00		
HDL-cholesterol	Type of diseases	6	T2DM	0.42	-0.35, 1.19	87.0	96.4
		9	Non-T2DM	0.58	-0.45, 1.60	97.6	
	Dosage of ALA (mg/day)	4	<600	0.57	-1.38, 2.51	97.7	
		8	=600	0.18	-0.29, 0.66	81.3	
	Duration of study (week)	3	>600	1.68	-0.82, 4.17	99.0	
		5	<8	0.70	-0.23, 1.63	88.1	
		5	8–12	1.04	-0.65, 2.74	97.9	
	Geographic area	5	>12	-0.12	-1.23, 0.99	96.9	
		7	American or European	0.38	-0.65, 1.41	95.9	
		8	Other countries	0.73	-0.34, 1.81	97.1	
	Type of intervention	10	ALA	0.71	-0.40, 1.81	97.4	
5		ALA + other nutrients	0.39	-0.32, 1.10	90.8		
Fasting glucose	Type of diseases	8	T2DM	-0.82	-1.39, -0.26	87.8	86.9
		7	Non-T2DM	-0.25	-0.69, 0.20	86.0	
	Dosage of ALA (mg/day)	6	<600	-0.58	-1.36, 0.21	92.7	
		7	=600	-0.59	-1.17, -0.00	85.8	
	Duration of study (week)	2	>600	-0.36	-0.80, 0.09	61.5	
		4	<8	-0.79	-1.71, 0.13	91.0	
		5	8–12	-0.70	-1.41, 0.02	85.9	
	Geographic area	6	>12	-0.29	-0.78, 0.20	88.0	
		7	American or European	-0.16	-0.63, 0.30	84.6	
		8	Other countries	-0.88	-1.37, -0.38	86.9	
	Type of intervention	9	ALA	-0.77	-1.31, -0.23	90.4	
6		ALA + other nutrients	-0.23	-0.62, 0.16	74.7		
Insulin	Type of diseases	2	T2DM	-1.52	-4.18, 1.14	93.5	91.9
		6	Non-T2DM	-0.89	-1.69, -0.10	92.9	
	Dosage of ALA (mg/day)	4	<600	-0.50	-1.47, 0.47	93.6	
		3	=600	-1.99	-4.05, 0.06	94.4	
	Duration of study (week)	1	>600	-0.63	-1.10, -0.17	0.00	
		1	<8	-2.94	-4.18, -1.69	0.00	
		3	8–12	-0.13	-0.80, 0.54	74.4	
	Geographic area	4	>12	-1.31	-2.31, -0.31	93.9	
		7	American or European	-0.80	-1.50, -0.09	92.1	
		1	Other countries	-2.94	-4.18, -1.69	0.00	
	Type of intervention	3	ALA	-1.01	-2.03, 0.01	87.2	
5		ALA + other nutrients	-0.98	-1.99, 0.02	93.8		
HOMA-IR	Type of diseases	3	T2DM	-0.60	-1.05, -0.15	58.1	78.1

(continued on next page)



Table 3 (continued)

Parameter	Number of SMD included	Subgroups	Pooled OR (random effect)	95% CI	I-squared (%)	Overall I-squared (%)		
HbA1c	Dosage of ALA (mg/day)	4	Non-T2DM	-0.87	-1.47, -0.27	83.7		
		4	<600	-0.85	-1.42, -0.27	83.4		
		3	=600	-0.62	-1.11, -0.12	62.2		
		-	>600	-	-	-		
	Duration of study (week)	1	<8	-0.47	-0.89, -0.05	0.00		
		2	8–12	-0.68	-1.52, 0.17	75.1		
		4	>12	-0.87	-1.46, -0.27	84.6		
	Geographic area	5	American or European	-0.75	-1.29, -0.21	83.1		
		2	Other countries	-0.75	-1.36, -0.15	67.1		
	Type of intervention	4	ALA	-0.58	-0.87, -0.26	38.2		
		3	ALA + other nutrients	-1.00	-1.73, -0.27	82.0		
	Type of diseases	5	T2DM	-1.27	-2.83, -0.15	92.9	91.1	
			1	Non-T2DM	-1.12	-1.46, -0.78		0.00
		Dosage of ALA (mg/day)	1	<600	-1.79	-2.49, -1.08		0.00
			3	=600	-0.80	-2.38, 0.78		95.8
			2	>600	-1.57	-2.74, -0.39		67.2
		Duration of study (week)	3	<8	-0.80	-2.38, 0.78		95.8
			1	8–12	-1.79	-2.49, -1.08		0.00
2			>12	-1.57	-2.74, -0.39	67.2		
Geographic area		-	American or European	-	-	-		
		6	Other countries	-1.22	-2.01, -0.44	91.1		
Type of intervention		5	ALA	-1.41	-2.34, -0.48	90.9		
		1	ALA + other nutrients	-0.41	-0.85, 0.03	0.00		

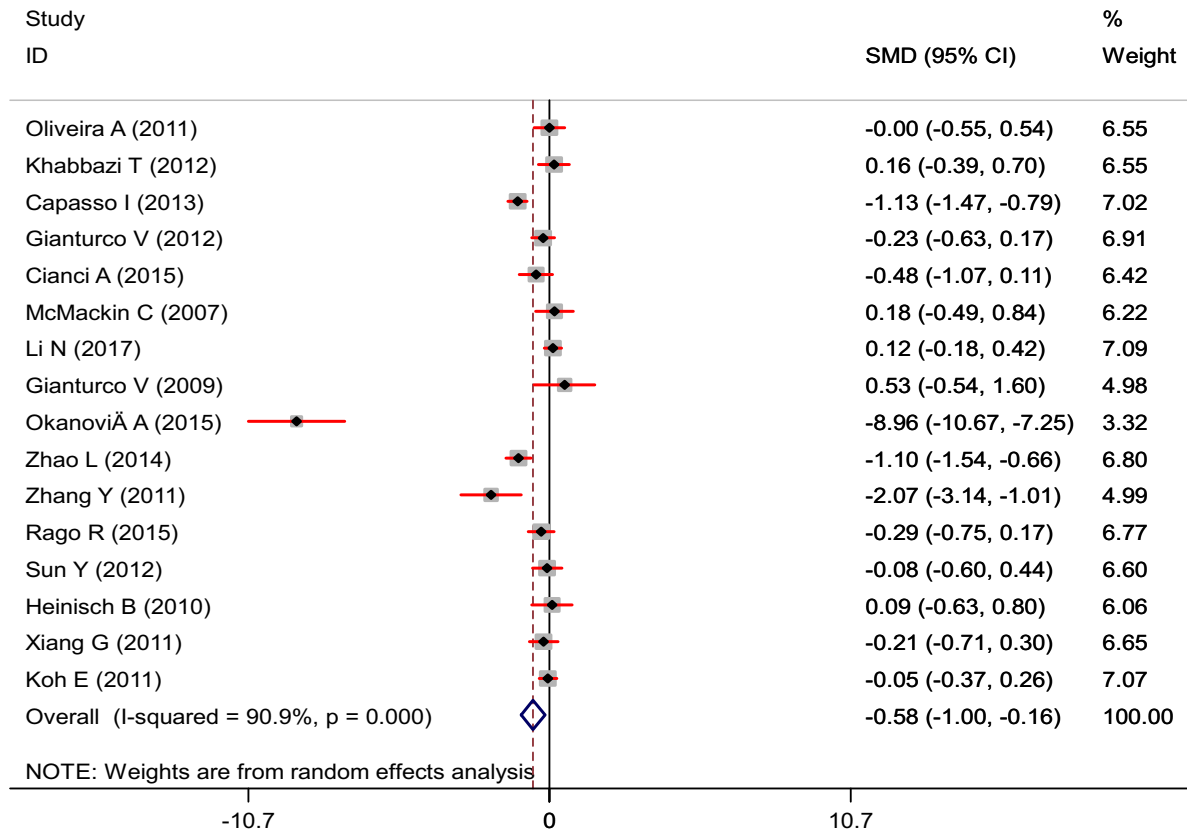
complications related to diabetic neuropathy through modulating deficits of neuropeptides including Neuropeptide Y and substance P in the spinal cord [43] and suppressing the activation of nuclear factor- $\kappa$ B in peripheral nerves [44].

Subjects with metabolic diseases are susceptible to increased risk of CVD, T2DM, and all-cause mortality [3]. The current meta-analysis of RCTs documented that ALA supplementation to populations with metabolic diseases resulted in a significant decrease in fasting glucose, insulin, HOMA-IR and HbA1c. Few studies have evaluated the beneficial effects of antioxidants supplementation on glycemic control in patients with metabolic diseases. In a meta-analysis study, we have previously showed that selenium supplementation to populations with metabolic diseases was useful in improving insulin concentrations and insulin sensitivity, but did not affect fasting glucose and HOMA-IR [9]. In addition, in a systematic study conducted by Cruz et al. [11], zinc supplementation improved insulin resistance in obese subjects of both sexes. In another meta-analysis study, magnesium supplementation significantly improved glucose parameters in populations with diabetes and also improved insulin-sensitivity parameters in those at high risk of diabetes [45]. Lifestyle can play an important function in treatment of metabolic disorders. However, some clinical trials did not point to the maintenance of usual dietary intake and physical activity levels through the treatment, and most studies did not adjust results for these parameters. Therefore, the effects of lifestyle and other confounding variables are not clear. Several mechanisms have been proposed to mediate the insulin-sensitizing actions of ALA, such as the improvement of glycemic control through the preservation of beta-cell function [46]. In addition, it has been suggested that ALA inhibits the progress of diabetes in diabetes-prone obese rats by decreasing triglycerides accumulation in non-adipose tissues such as muscle, pancreatic beta-cells, and liver [47]. On the other hand, few of these beneficial effects on insulin resistance have been proposed to be mediated by the modulation of adenosine monophosphate-activated protein kinase (AMPK) [47]. Thus, it has been documented that ALA decreases insulin resistance by activating AMPK in skeletal muscle [48] and beta-cells [49].

Our meta-analysis demonstrated that ALA supplementation to subjects with metabolic diseases was effective in reducing triglycerides, total- and LDL-cholesterol levels, but did not affect HDL-cholesterol levels. Existing evidence from animal models suggests a lipid-lowering response to ALA administration. For example, rats fed a high fat diet with 0.5% ALA shown a decrease in total lipids (21.3%), triglycerides (31.9%), total- (20.1%), LDL-cholesterol (41.1%), and free fatty acids

(33%) compared with the control group [50]. In another study, which evaluated the effects of different dosages of ALA (0, 1, 2.5, and 5 g/kg) in Sprague-Dawley rats on lipid profiles demonstrated reductions in triglycerides (68.5%), total cholesterol (25.8%), and non-esterified fatty acids (45%) [51]. In addition, limited evidence from human studies suggests that ALA may have lipid-lowering effects [52]. A short-term (2 weeks) ALA supplementation at a dosage of 600 mg/day to obese populations with impaired glucose tolerance were effective in reducing free fatty acids, triglycerides, total-, LDL-, oxidized LDL-, and VLDL-cholesterol concentrations [30]. Masharani et al. [53] demonstrated a significant reduction in triglycerides (28%) and larger, more buoyant LDL-particles in six lean women with PCOS following the supplementation of 600 mg ALA twice daily for 6 weeks. Furthermore, a significant reduction in total cholesterol of 8% and a tendency toward lower LDL- and higher HDL-cholesterol following 12 weeks of ALA supplementation at a dosage of 1200 mg/day to overweight/obese schizophrenic patients was observed [54]. Conversely, few human studies have reported no detrimental effect of ALA supplementation on lipid profiles. For example, diabetic end-stage renal disease (ESRD) populations on hemodialysis taking 600 mg/day ALA for 12 weeks exhibited no significant changes in total-cholesterol or oxidized-LDL compared with the control group [28]. In another similar study, Khabbazi et al. [37] did not observe any change in lipid fractions following the supplementation of 600 mg ALA/day for 8 weeks in patients with ESRD on hemodialysis compared with the placebo. Koh et al. [55] demonstrated even after weight loss, no significant change total-, HDL-cholesterol, and triglycerides was reported in obese populations randomized to placebo, 1200 or 1800 mg/day of ALA supplements. Increased AMPK activity following the intake of ALA in peripheral tissues including skeletal muscle has been shown to directly inhibit fatty acid synthesis, while concomitantly elevating in  $\beta$ -oxidation of fatty acids [51,56]. In addition, some studies document that the expression of the two rate-limiting enzymes in fatty acid synthesis, acetyl-CoA carboxylase and fatty acid synthase, are decreased in response to ALA administration [56,57]. On the other hand, reductions in lipid profiles following the supplementation of ALA may be secondary to decreases in insulin concentrations and insulin resistance. In addition, previous studies have demonstrated that nutraceuticals play a peculiar role in ameliorating human dyslipidaemia [58,59], which in turn effectively able to decrease the burden of the atherosclerosis process and the progress of CVD [60]. Nutraceuticals may improve lipid profiles through upregulating hepatic LDL receptors, reducing intestinal absorption of cholesterol [61], blocking carbohydrate

A



B

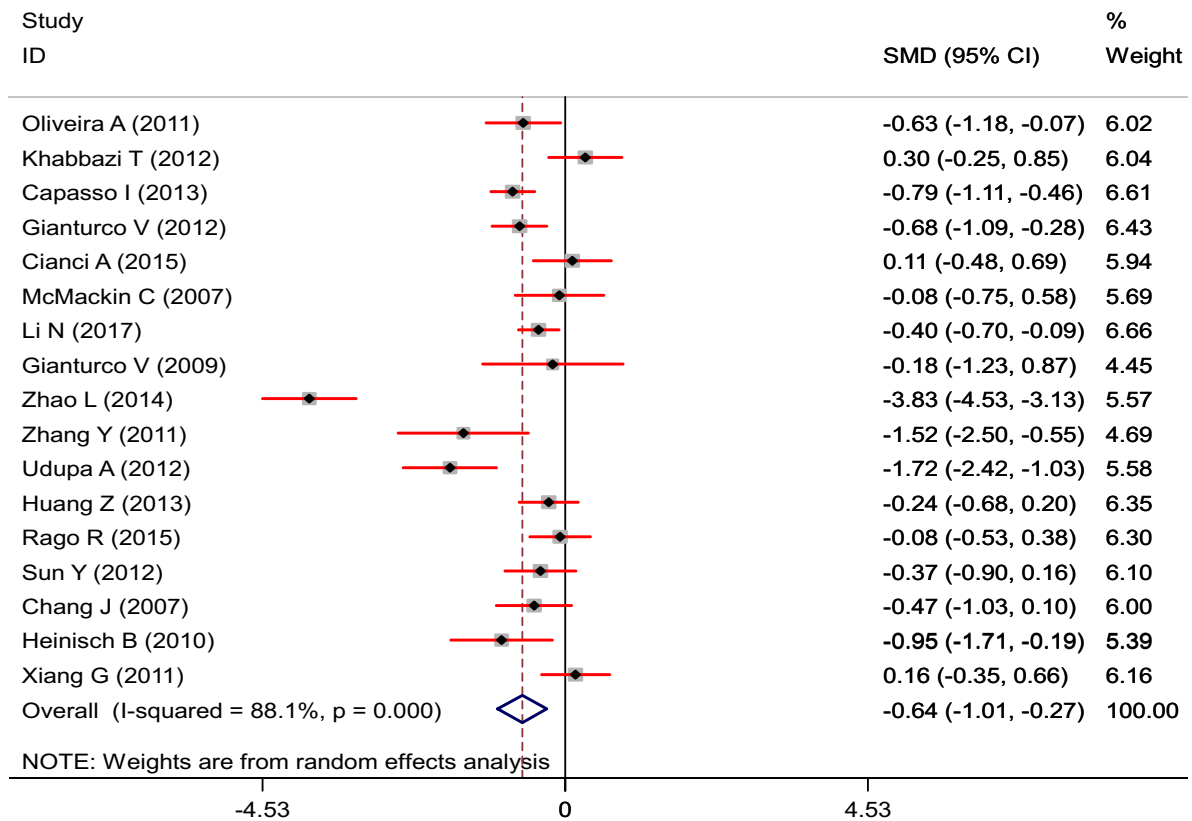
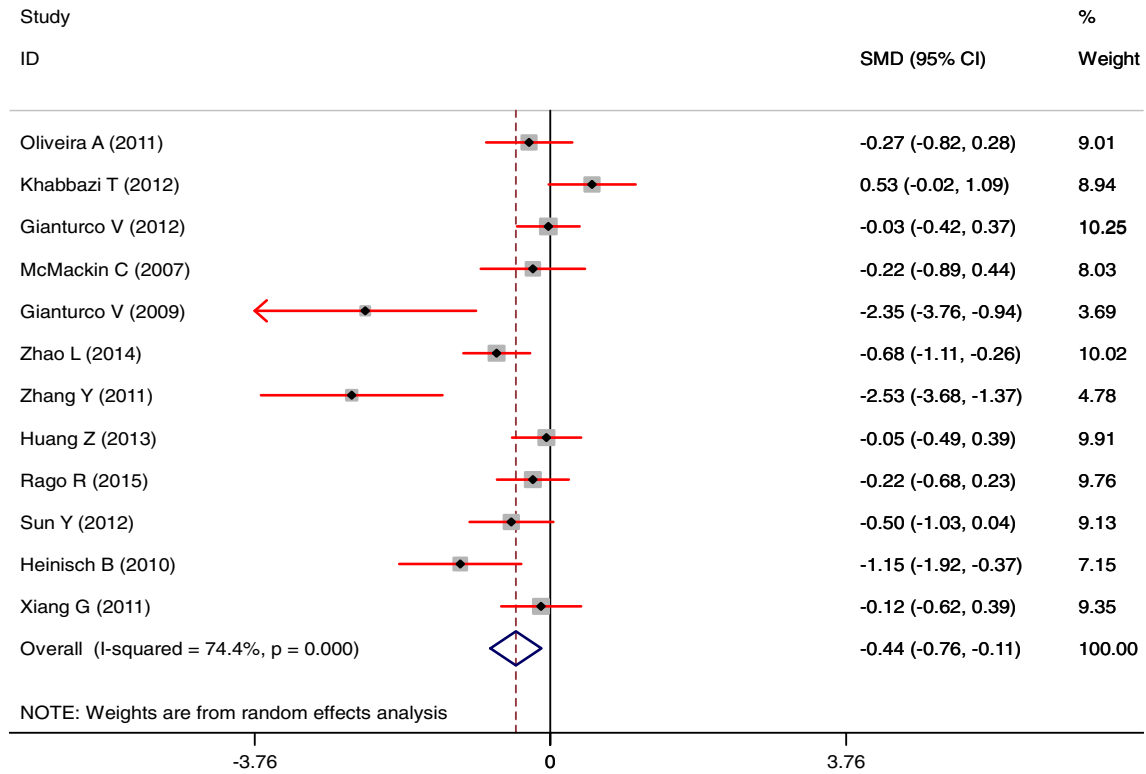


Fig. 4. A–D. Meta-analysis lipid profiles standardized mean differences estimates for (A) triglycerides, (B) for total-, (C) for LDL-, and (D) for HDL-cholesterol in alpha-lipoic acid supplements and placebo groups (CI = 95%).

C



D

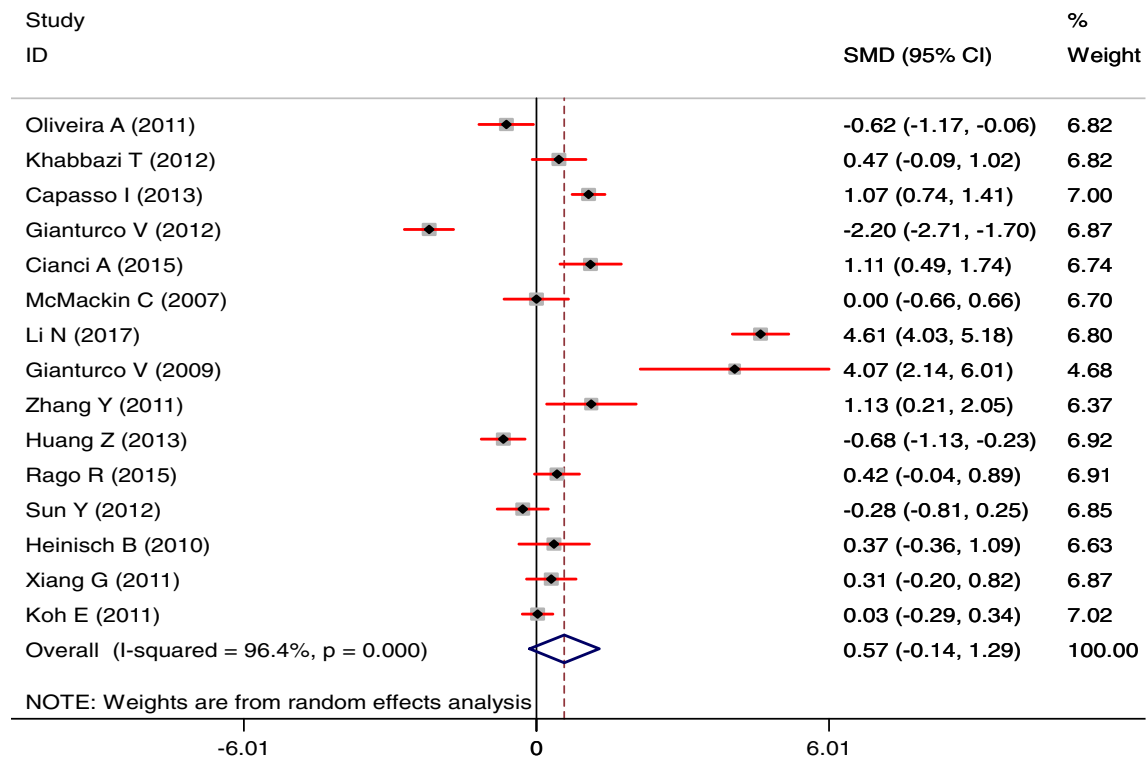


Fig. 4 (continued).

digestion and glucose absorption in the gut, decreasing glucose release from liver and activating insulin receptors [62].

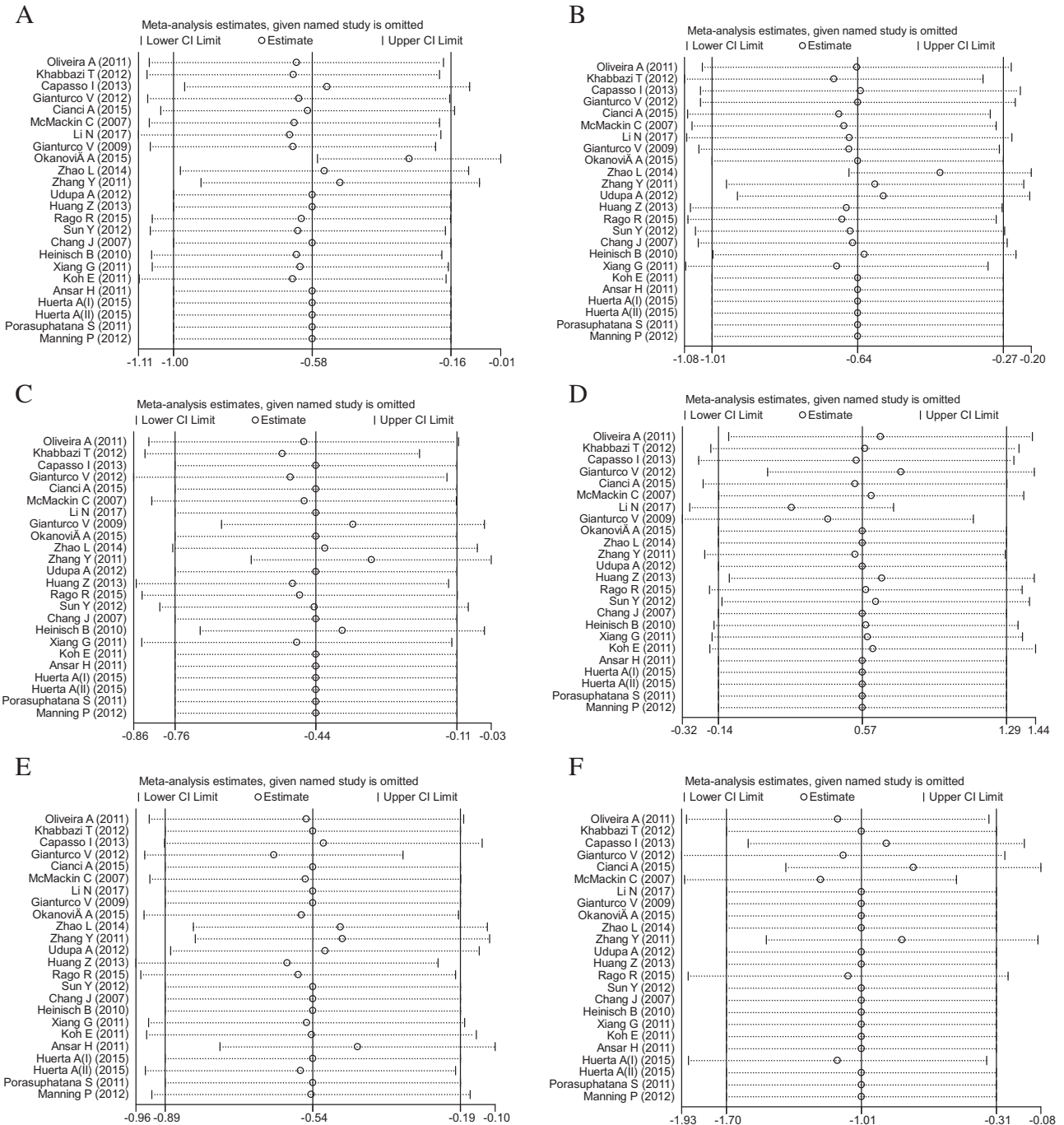
Overall, the current meta-analysis demonstrated that ALA administration may lead to an improvement in glucose homeostasis parameters and lipid profiles except HDL-cholesterol levels. The findings of this meta-analysis may have a high impact in the field of nutraceuticals and therapy for metabolic diseases. Additional prospective studies investigating the effect of ALA supplementation on glucose homeostasis parameters and lipid profiles in *MetS* are necessary.

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**Conflict of Interest**

None.



**Fig. 5. A–H.** Sensitivity analysis alpha-lipoic acid lipid profiles and glycemic control; (A) triglycerides, (B) for total-, (C) for LDL-, (D) for HDL-cholesterol (E) for fasting glucose, (F) for Insulin, (G) for HOMA-IR, (H) and for HbA1c to assess the effects of each study on pooled standardized mean differences estimates.

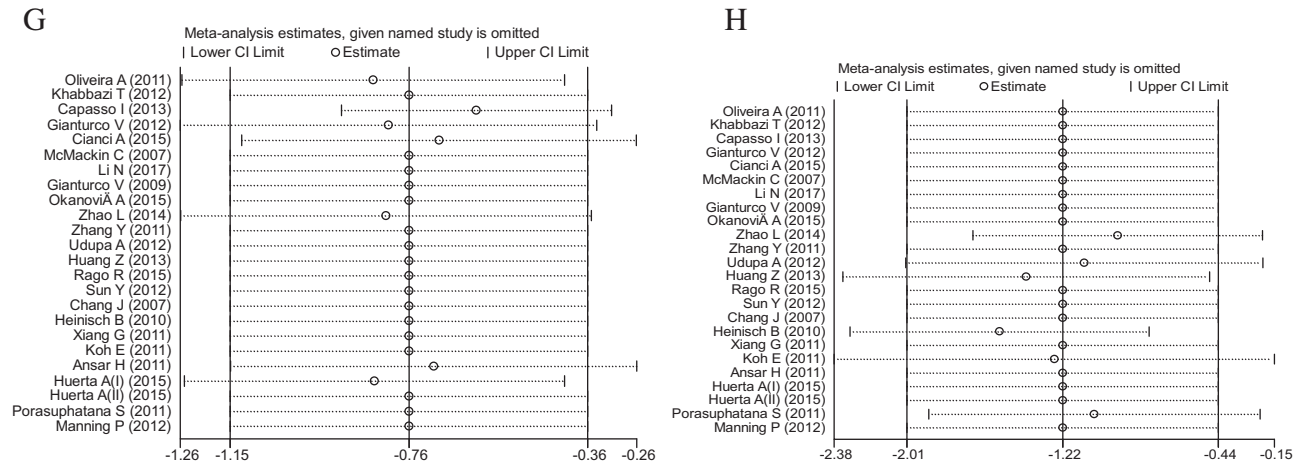


Fig. 5 (continued).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.metabol.2018.07.002>.

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