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PII: S1043-6618(15)30223-1
DOI: http://dx.doi.org/doi:10.1016/j.phrs.2016.01.030
Reference: YPHRS 3056

To appear in: *Pharmacological Research*

Received date: 5-12-2015
Revised date: 25-1-2016
Accepted date: 27-1-2016

Please cite this article as: Sahebkar Amirhossein, Simental-Mendía Luis E, Stefanutti Claudia, Pirro Matteo.Supplementation with coenzyme Q10 reduces plasma lipoprotein(a) concentrations but not other lipid indices: a systematic review and meta-analysis.*Pharmacological Research* http://dx.doi.org/10.1016/j.phrs.2016.01.030

Supplementation with coenzyme Q_{10} reduces plasma lipoprotein(a) concentrations but not other lipid indices: a systematic review and meta-analysis

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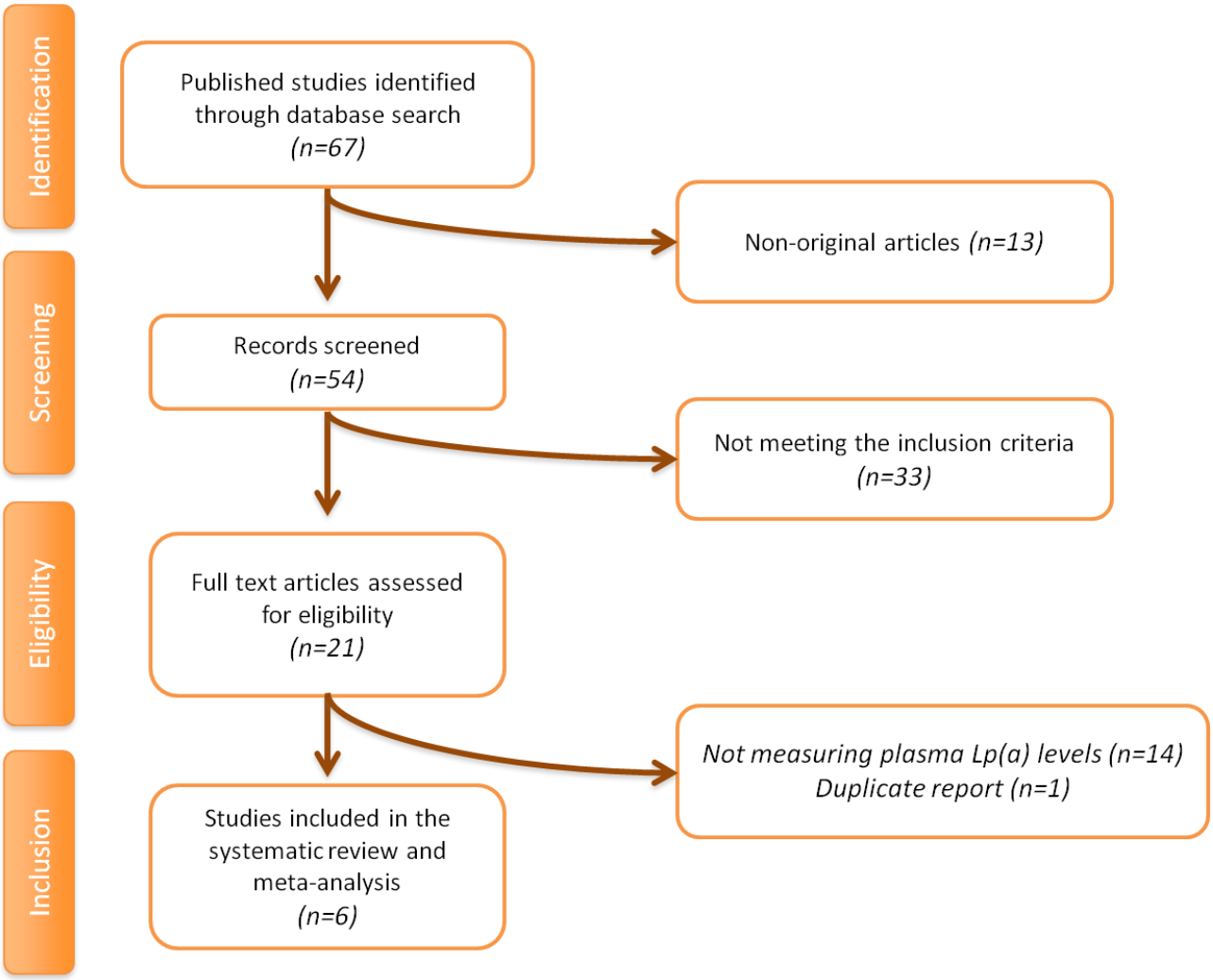
Graphical Abstract

Flow chart of the number of studies identified and included into the meta-analysis.



Abstract

Plasma lipoprotein(a) [Lp(a)] elevations are associated with increased cardiovascular risk. Coenzyme Q_{10} (CoQ_{10}) is a member of the mitochondrial respiratory chain with a prominent role as a potent gene regulator. The Lp(a)-lowering efficacy of CoQ_{10} has been investigated in different clinical settings with contrasting results.

A systematic literature search in Medline, SCOPUS, Web of Science and Google Scholar databases was conducted to identify controlled trials investigating the efficacy of CoQ_{10} supplementation on plasma Lp(a) levels. Inverse variance-weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated for net changes in Lp(a) levels using a random-effects model. Random-effects meta-regression was performed to assess the effect of putative confounders on plasma Lp(a) levels.

Seven randomized controlled trials with a total of 409 subjects (206 in the CoQ_{10} arm and 203 in the control arm) met the eligibility criteria. Overall, CoQ_{10} supplementation was paralleled by a slight but significant reduction of plasma Lp(a) levels (WMD: -3.54 mgl/dL, 95% CI: -5.50, -1.58; $p<0.001$), this effect being more robust in those trials with higher baseline Lp(a) levels (slope: -0.44; 95% CI: -0.80, -0.08; $p=0.018$). Reduction of plasma Lp(a) levels was consistent across different CoQ_{10} doses, with an inverse association between administered CoQ_{10} dose and Lp(a) lowering (slope: 0.04; 95% CI: 0.01, 0.07; $p=0.004$). Neither total cholesterol and cholesterol subfractions, nor triglyceride levels were affected by CoQ_{10} supplementation.

In conclusion, CoQ_{10} supplementation, in the tested range of doses, reduces plasma Lp(a) concentrations, particularly in patients with Lp(a)≥30 mg/dL. Other lipid indices were not altered by CoQ_{10} supplementation.

Abbreviations

Lp(a): lipoprotein(a)
CVD: cardiovascular disease
CETP: cholesteryl ester transport protein
PCSK9: proprotein convertase subtilisin/kexin type 9
CoQ_{10}: coenzyme Q_{10}
BMI: body mass index
LDL-C: low-density lipoprotein cholesterol
HDL-C: high-density lipoprotein cholesterol

CMA: comprehensive Meta-Analysis
SDs: standard deviations
SEM: standard error of the mean

Keywords: Lipoprotein(a); Coenzyme Q10; Lipids; Nutraceuticals.

1. Introduction

Lipoprotein(a) [Lp(a)] is considered a strong genetically determined risk factor for cardiovascular disease (CVD) [1]; accordingly, prospective studies on circulating Lp(a) and Mendelian randomization studies indicate a relevant association between Lp(a) and CVD risk [2,3]. A report by the Emerging Risk Factors Collaboration [4] focusing on low to intermediate risk populations showed that Lp(a) improves CVD prediction in addition to total and LDL cholesterol [4]. Also, although earlier prospective studies suggest that the relation between Lp(a) concentration and CVD risk may involve a threshold [5], more recent evidence supports the possibility of a continuous association without a definite threshold [6].

Unlike other lipoproteins, Lp(a) metabolism is still obscure and the influence of dietary and environmental factors on Lp(a) levels is negligible [7]. Moreover, a substantial body of research has been carried out to develop targeted therapies, yet the results have been disappointing [8]. It is known that niacin, estrogens, cholesteryl ester transfer protein (CETP) inhibitors and mipomersen might lower Lp(a) [8]. Also, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition is a novel and promising strategy to lower Lp(a) levels [9]. However, the above mentioned agents reduce Lp(a) levels in conjunction with changes in other lipoproteins [8,9]. Hence, evidence-based association between specific Lp(a) lowering and CVD risk reduction is still lacking. Treatment of symptomatic Lp(a) elevations with apheresis is an additional therapeutic option [10,11] Only recent trials in coronary heart disease patients with high Lp(a) levels showed that specific Lp(a) apheresis attenuated progression of carotid intima-media thickness and coronary atherosclerosis [12,13]. Despite the paucity of data on the clinical benefit of Lp(a) lowering, screening for Lp(a) by isoform-insensitive methods has been proposed at least once in individuals at greater CVD risk [14,15].

Coenzyme Q10 (CoQ_{10}), or ubiquinone, is a fat-soluble molecule that acts as an electron carrier in mitochondria and as a coenzyme for mitochondrial enzymes [16]. The effect of CoQ_{10} supplementation on plasma Lp(a) levels has been investigated in previous studies of patients with different clinical entry criteria and using small participant group sizes [17-22]. CoQ_{10} supplementation reduced Lp(a) levels in patients with coronary artery disease [17],

hypertriglyceridemia [18], end-stage renal disease [19] and type 2 diabetes [20], but not in patients with either obesity [21] or ischaemic left ventricular systolic dysfunction [22]. In these studies [17-22], different CoQ_{10} dosing regimens were used; also, there were variations in terms of supplementation duration and baseline plasma Lp(a) concentrations.

On the basis of the available evidence, there is substantial uncertainty about the net effect of CoQ_{10} supplementation on plasma Lp(a) levels. The present study aimed to resolve this uncertainty by systematically reviewing the literature, and meta-analysis and meta-regression of all trials investigating the effects of CoQ_{10} supplementation on plasma Lp(a) levels.

2. Methods

2.1 Search Strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [23]. PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched using the following search terms in titles and abstracts: ("Lp(a)" OR "LP (a)" OR "lipoprotein(a)" OR "lipoprotein (a)" OR "lipoprotein a" OR "lipoproteina") AND ("coenzyme Q_{10}" OR "coenzyme Q_{10}" OR "Coenzyme Q" OR CoQ_{10} OR "co Q_{10}" OR Q_{10} OR ubiquinone OR ubiquinol OR ubidecarenone) AND (placebo). The wild-card term ‘‘*’’ was used to increase the sensitivity of the search strategy. The search was limited to articles published in English language. The literature was searched from inception to May 12, 2015.

2.2 Study Selection

Original studies were included if they met the following inclusion criteria: (i) being a clinical clinical trial with either parallel or cross-over design, (ii) investigating the impact of CoQ_{10}, either as monotherapy or combination therapy, on serum/plasma concentrations of Lp(a), (iii) presentation of sufficient information on Lp(a) concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were (i) non-interventional studies, (ii)

uncontrolled studies, (iii) observational studies with case-control, cross-sectional or cohort design, and (iv) lack of sufficient information on baseline or follow-up Lp(a) concentrations.

2.3 Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) country were the study was performed; 4) study design; 5) number of participants in the CoQ_{10} and control groups; 6) intervention assigned to the control group; 7) administered dose of CoQ_{10}; 8) treatment duration; 9) age, gender and body mass index (BMI) of study participants; 10) baseline and end-trial values for total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides concentrations; 11) systolic and diastolic blood pressures; and 12) data regarding baseline and follow-up concentrations of Lp(a).

2.4 Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [24]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of “yes” indicated low risk of bias, while “no” indicated high risk of bias. Labeling an item as “unclear” indicated an unclear or unknown risk of bias.

2.5 Quantitative Data Synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [25]. Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up − measure at baseline. For single-arm cross-over trials, net change in plasma concentrations of Lp(a) were calculated by subtracting the value after control intervention from that reported after treatment. All values were collated as percent change from baseline in each group.

Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root [$(SD_{pre\text{-}treatment})^2$ + $(SD_{post\text{-}treatment})^2$ – (2R × $SD_{pre\text{-}treatment}$ × $SD_{post\text{-}treatment}$)], assuming a correlation coefficient (R) = 0.5. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects.

Net changes in measurements (change scores) were calculated for parallel and cross-over trials, as follows: (measure at the end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at the end of follow-up in the control group − measure at baseline in the control group). All values were collated in mg/dL. A random-effects model (using DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of CoQ_{10} dose, study design, treatment duration, and the characteristics of populations being studied [26]. Inter-study heterogeneity was assessed using Cochran Q test and I2 index. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method, i.e. iteratively removing one study each time and repeating the analysis [27-29].

2.6 Meta-regression

A weighted random-effects meta-regression using unrestricted maximum likelihood model was performed to assess the association between the overall estimate of effect size with potential moderator variables including CoQ_{10} dose and duration of supplementation, and baseline Lp(a) concentrations.

2.7 Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, and Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie "trim and fill" and "fail-safe N" methods were used to adjust the analysis for the effects of publication bias method was used to adjust the analysis for the effects of publication bias [30].

3. Results

3.1 Flow and characteristics of included studies

Briefly, after multiple database searches 67 published studies were identified and the abstracts reviewed. Of these, 13 were non-original articles and were excluded. Next, other 33 studies were eliminated because they did not meet the inclusion criteria. Then, 21 full text articles were careful assessed and reviewed; of which 15 studies were excluded for not measuring plasma Lp(a) levels (n=14) and duplicate report (n=1). Finally, 6 studies were eligible and included in the systematic review and meta-analysis. The study selection process is shown in Figure 1.

Data were pooled from 6 eligible studies comprising 12 treatment arms which included 409 subjects, with 206 subjects in the CoQ_{10} arm and 203 in the control arm. Included studies were published between 1999 and 2014. The clinical trials used different doses of CoQ_{10}. One study investigated CoQ_{10} 100 mg/day [19], one study investigated CoQ_{10} 120 mg/day [17], two studies investigated CoQ_{10} 150 mg/day [18,20], one study investigated CoQ_{10} 200 mg/day [21], and one study investigated CoQ_{10} 300 mg/day [22]. The range of intervention periods was from 4 weeks [17] up to 12 weeks [19,21]. Study design of almost all included studies were parallel-group [17,19-22], only one was sequential [18]. Selected studies enrolled patients with massive hypertriglyceridemia [18], ischaemic left ventricular systolic dysfunction [22], obesity [21], type 2 diabetes [20], maintenance hemodialysis [19], and coronary artery disease [17]. Anthropometric and biochemical characteristics of the evaluated studies are presented in Table 1.

3.2 Lp(a) assay methods

Different assays methods were used to measure plasma Lp(a) concentrations. On this regard, some studies [17-19,21] measured Lp(a) concentration by enzyme-linked immunosorbent assay. Mohammed-Jawad et al. [20] determined plasma Lp(a) levels by latex-enhanced turbidimetric method (Human, Germany). Only one study did not specify the method used to determine plasma Lp(a) concentrations [22].

3.3 Risk of bias assessment

Some of the included studies were characterized by insufficient information about the sequence generation [20,21], allocation concealment [19-21], and blinding of participants, personnel and outcome assessors [19,21]. Even one trial had high risk of bias related with the study design, such as open sequential [18]. Also, two studies showed high risk of bias related to blinding [18,20]. However, all evaluated studies had a low risk of bias according to incomplete outcome data and selective outcome reporting. Details of the quality of bias assessment are shown in Table 2.

3.4 Effect of CoQ_{10} supplementation on plasma Lp(a) concentrations

Meta-analysis of data from 12 treatment arms suggested a significant reduction in plasma Lp(a) concentrations following CoQ_{10} supplementation (WMD: -3.54 mg/dL, 95% CI: -5.50, -1.58, $p < 0.001$) (Figure 2, panel A). The pooled effect size was robust and remained significant in the leave-one-out sensitivity analysis (Figure 2, panel B). Subgroup analysis suggested that the impact of CoQ_{10} on plasma Lp(a) was greater at supplemental doses < 150 mg/day (WMD: -9.24 mg/dL, 95% CI: -15.19, -3.29, $p = 0.002$) compared with doses ≥ 150 mg/day (WMD: -2.75 mg/dL, 95% CI: -4.28, -1.23, $p < 0.001$) (Figure 3). With respect to treatment duration, the magnitude of reduction in plasma Lp(a) levels was numerically the same in the subsets of trials lasting < 8 weeks (WMD: -4.00 mg/dL, 95% CI: -5.45, -2.54, $p < 0.001$) and ≥ 8 weeks (WMD: -3.99 mg/dL, 95% CI: -11.15, 3.18, $p = 0.275$), though statistical significance was reached only in the former subset (Figure 4, Panel A). There was also a numerically greater reduction in plasma Lp(a) concentrations in the subset of trials with baseline Lp(a) values ≥ 30 mg/dL (WMD: -11.72 mg/dL, 95% CI: -21.01, -2.42, $p=0.013$) compared with the subset with baseline values < 30 mg/dL (WMD: -3.14 mg/dL, 95% CI: -4.92, -1.35, $p=0.001$) (Figure 5).

3.5 Effect of CoQ_{10} supplementation on other lipid indices

The impact of CoQ_{10} supplementation on plasma concentrations of total cholesterol, LDL-C, HDL-C and triglycerides was reported in 12, 5, 12 and 10 treatment arms, respectively. Meta-analysis did not suggest any significant change in plasma levels of total cholesterol (WMD: -0.91 mg/dL, 95%

CI: -4.27, 2.44, p=0.593), LDL-C (WMD: -8.15 mg/dL, 95% CI: -17.89, 1.58, p=0.101), HDL-C (WMD: 0.64 mg/dL, 95% CI: -0.34, 1.63, p=0.200) and triglycerides (WMD: -35.31 mg/dL, 95% CI: -79.95, 9.33, p=0.121) following CoQ_{10} supplementation (Figure 6).

3.6 Meta-regression

Random-effects meta-regression was performed to evaluate the impact of putative moderators on the estimated effect size. A significant inverse association was observed between the Lp(a)-lowering effect of CoQ_{10} and administered CoQ_{10} dose (slope: 0.04; 95% CI: 0.01, 0.07; p=0.004) (Figure 7, Panel A). With respect to treatment duration, although an inverse association was observed, this did not reach statistical significance (slope: 0.85; 95% CI: -0.001, 1.70; p=0.050) (Figure 7, Panel B). A direct association was also found between the Lp(a)-lowering effect of CoQ_{10} and baseline Lp(a) values (slope: -0.44; 95% CI: -0.80, -0.08; p=0.018) (Figure 7, Panel C).

3.7 Publication bias

Visual inspection of funnel plot did not suggest a significant potential publication bias in the meta-analysis of CoQ_{10} effect on plasma Lp(a) concentrations (Figure 8). This observation was confirmed by the results of Egger's linear regression (intercept = -0.62, standard error = 0.94; 95% CI = -2.73, 1.48, t = 0.66, df=10, two-tailed p=0.523) and Begg's rank correlation (Kendall's Tau with continuity correction =0, z=0, two-tailed p-value=1.000) tests. The "fail-safe N" test showed that 68 studies would be needed to bring the WMD down to a non-significant (p>0.05) value.

4. Discussion

The results of this meta-analysis suggested a significant lowering effect of CoQ_{10} supplementation on plasma Lp(a) levels. Overall, among the trials included in the present meta-analysis, the degree of plasma Lp(a) reduction after CoQ_{10} supplementation was significant, yet modest (- 3.54 mg/dL); however, a greater Lp(a) reduction (-11.72 mg/dL, p=0.01) was observed in patients with increased baseline Lp(a) levels (≥30 mg/dL) than in patients with lower Lp(a) levels (-3.14 mg/dL, p=0.001).

Plasma Lp(a) elevations are associated with increased cardiovascular risk [2-6,31]. There have been conflicting reports on whether Lp(a) reduction emerges after CoQ_{10} supplementation, with some trials reporting little or no reduction [18,21,22], whereas other trials reporting Lp(a) reductions of about 30% [17,19,20]. Specifically, three randomized trials, two placebo-controlled [17,19] and one active-controlled [20], reporting the greatest Lp(a) lowering efficacy of CoQ_{10} supplementation were performed in high-risk patients with the highest baseline plasma Lp(a) levels. The study by Cicero et al [18] in patients with severe hypertriglyceridemia and normal baseline Lp(a) levels reported a significant yet modest Lp(a) lowering by CoQ_{10} supplementation when it was administered alone or in combination with either polyunsaturated fatty acids or fenofibrate. Finally, two randomized placebo-controlled studies using the greatest daily doses of CoQ_{10} [21,22] did not find any beneficial effect of CoQ_{10} supplementation on plasma Lp(a) levels. Particularly, Lee et al [21] enrolled obese patients with low baseline Lp(a) levels (mean 11.7 mg/dL) and without relevant cardiovascular comorbidities. Dai et al [22] failed to find any Lp(a)-lowering effect of CoQ_{10} supplementation in patients with ischaemic left ventricular dysfunction and mean baseline Lp(a) levels below 30 mg /dL.

In all these studies [17-22], different entry Lp(a) levels and CoQ_{10} dosing regimens were used; in addition, the duration of the active CoQ_{10} supplementation varied from 4 weeks to 3 months. These differences, along with small participant group sizes might have precluded the possibility to reach a definitive answer on whether CoQ_{10} supplementation is really effective in reducing Lp(a) concentrations.

The present meta-analysis, other than supporting a net Lp(a) lowering by CoQ_{10} supplementation that is more evident in patients with higher baseline Lp(a) concentrations, suggests that CoQ_{10} supplementation reduces Lp(a) levels across the different tested doses; in addition, lower CoQ_{10} doses (<150 mg/daily) were more effective in reducing Lp(a) levels than higher doses (≥150 mg/daily). The reliability of this finding should be considered with caution. That's because the relative bioavailability of CoQ_{10} is markedly influenced by its delivery systems [32]; moreover, pharmacokinetics data of the different CoQ_{10} formulations used in the studies that we have included in the present meta-analysis are lacking; hence, we cannot exclude that the inverse

association between CoQ_{10} dose and its Lp(a)-lowering efficacy might be the result of the confounding effect of an unpredictable CoQ_{10} formulation pharmacokinetics. The latter finding, although surprising, may find support in a previous pharmacokinetic study showing that, during chronic supplementation at low-moderate CoQ_{10} doses (30-300 mg/daily), the efficiency of CoQ_{10} absorption decreases as the administered dose increases [33]. This explanation of our finding is plausible, but it remains a speculative hypothesis; indeed, we do not have data on the bioavailability of the different CoQ_{10} formulations used in the trials that we included in the present meta-analysis. Instead, an alternative explanation, derived from the results of this meta-analysis, might support the inverse association between CoQ_{10} dose and the degree of Lp(a) lowering. We found that baseline Lp(a) levels were the lowest in those studies using the highest CoQ_{10} doses [21,22]. Hence, whether low baseline Lp(a) might lessen the Lp(a)-lowering efficacy of higher CoQ_{10} doses should be considered.

The present results suggested a significant Lp(a)-lowering effect in those trials with shorter duration of CoQ_{10} supplementation but not in those with longer duration. However, the absolute Lp(a) reduction was comparable between trials with either shorter or longer duration of CoQ_{10} supplementation (-4.0 mg/dL and -3.9 mg/dL, respectively); in addition, meta-regression analysis failed to find a significant association between duration of CoQ_{10} supplementation and Lp(a) reduction. Hence, the hypotesis of a potential time-dependent loss of Lp(a)-lowering efficacy of CoQ_{10} supplementation should be weighed up against the possible confounding effect of moderators and the lack of sufficient statistical power of this analysis.

Lp(a) metabolism is still far to be clearly understood [7]; hence, mechanisms related to therapeutic modulation of Lp(a) levels are even less clear. It has been established that apo(a) and apoB100 production are important determinants of plasma Lp(a) levels [7]; in addition, although the major site and mode of Lp(a) clearance remain unidentified, the hepatic scavenger receptor class B type I may participate in the uptake of Lp(a) from plasma [34]. Unfortunately, there is no evidence in the literature showing an influence of CoQ_{10} on these crucial stages of Lp(a) metabolism. On the contrary, inflammation is associated with an increase in circulating levels of Lp(a) [35,36], whereas inhibition of IL-6 signalling decreases serum Lp(a) levels [37] and inhibits apolipoprotein(a)

expression and Lp(a) synthesis [38]. Because CoQ_{10} can have anti-inflammatory effects [39,40], we might speculate that Lp(a) reduction following CoQ_{10} supplemetation might be a consequence of its anti-inflammatory activity. This explanation remains however elusive and need specific demonstration.

In this study, we failed to find a significant effect of CoQ_{10} supplementation on total cholesterol, LDL- and HDL-cholesterol, and triglyceride levels. The primary objective of our meta-analysis was not to demonstrate an effect of CoQ_{10} supplementation on these lipid fractions; thus, only studies exploring the effects of CoQ_{10} on Lp(a) levels were included in this meta-analysis, whereas additional studies examining the potential effects of CoQ_{10} on additional lipid fractions were not included. However, our results are in line with previous meta-analyses showing no beneficial effects of CoQ_{10} supplementation on lipid profile [41,42]

Our study has some limitations worth attention. First, we did not have sufficient information on the CoQ_{10} formulations used in the included trials; also, data on food sources of CoQ_{10} and information on the interaction between the CoQ_{10} supplements and food consumption were not provided. Second, the number of trials exploring the effects of CoQ_{10} supplementation on Lp(a) levels was limited and with small sample sizes; thus, our results from subgroup analyses should be viewed with caution and should be integrated with the potential confounding of additional moderators. Finally, factors influencing CoQ_{10} bioavailability, and possibly CoQ_{10}-mediated effects, have been described [43-45]. Hence, lack of information on some of these possible confounders in the included trials might have had an influence on the results of the present meta-analysis; this is especially true for pharmacokinetic data of the various formulations of CoQ_{10} used in the included trials.

In conclusion, the present results suggested that a significant reduction of plasma Lp(a) levels can be achieved by CoQ_{10} supplementation, particularly in patients with higher baseline Lp(a) concentrations. Whether dosing regimen has a significant impact on the Lp(a)-lowering efficacy of CoQ_{10} requires further support by additional studies, possibly providing data on CoQ_{10} bioavailability as well.

Because the independent residual risk of Lp(a) in promoting cardiovascular diseases is substantial, the Lp(a) lowering efficacy of CoQ_{10} might represent an additional opportunity to reduce the overall cardiovascular risk. In this context, the value of combining CoQ_{10} with conventional and emerging lipid-lowering therapies [46-48] merits further investigation.

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Figure Captions

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

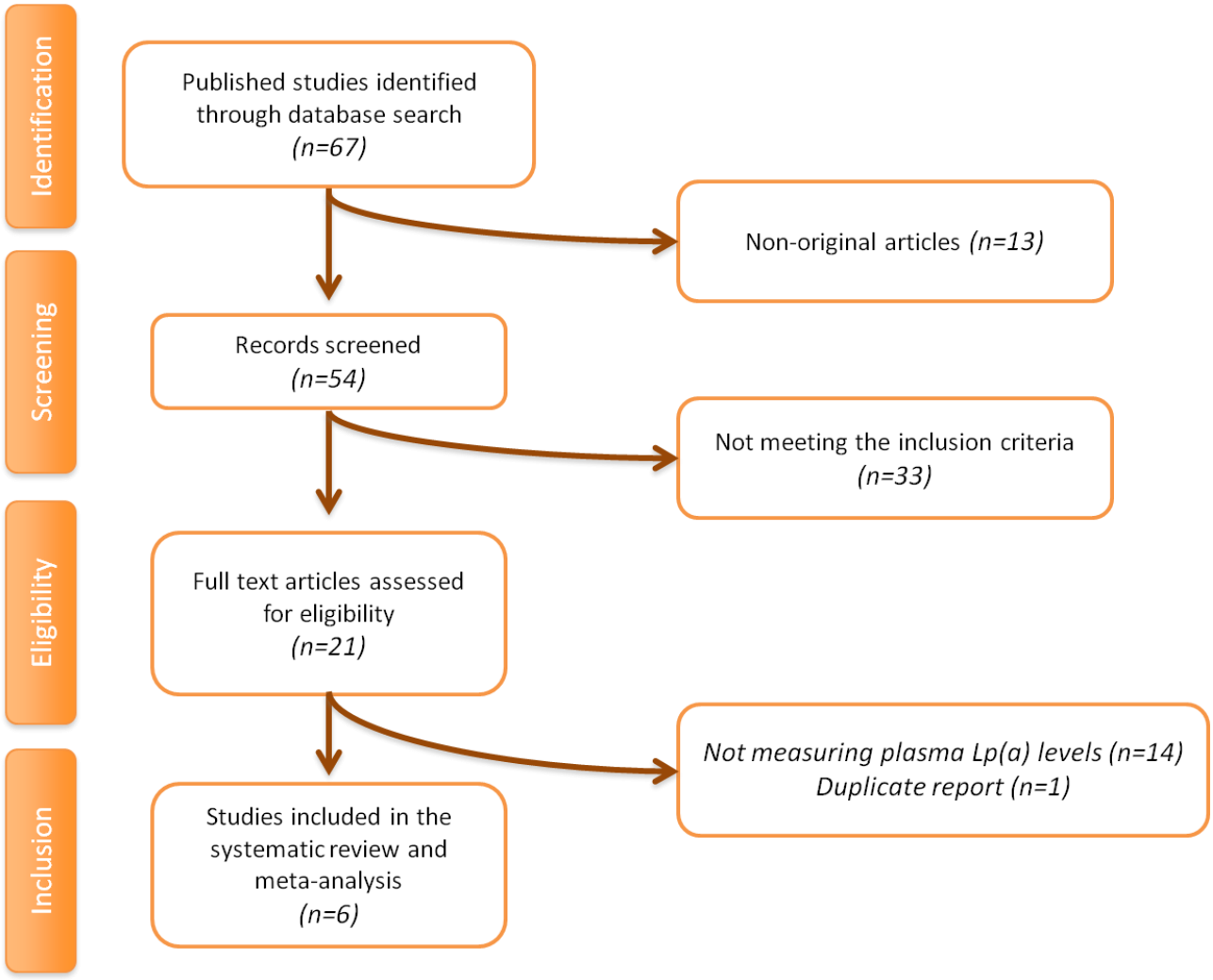
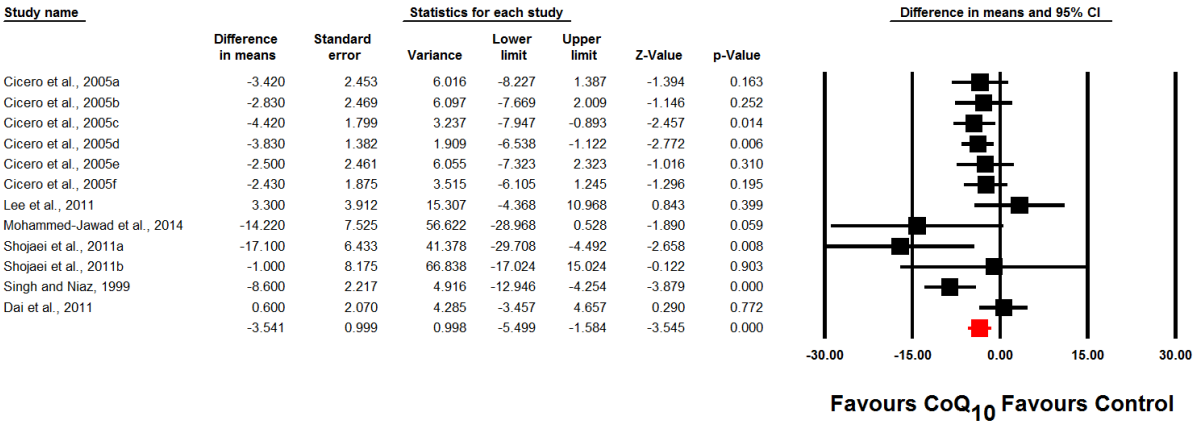
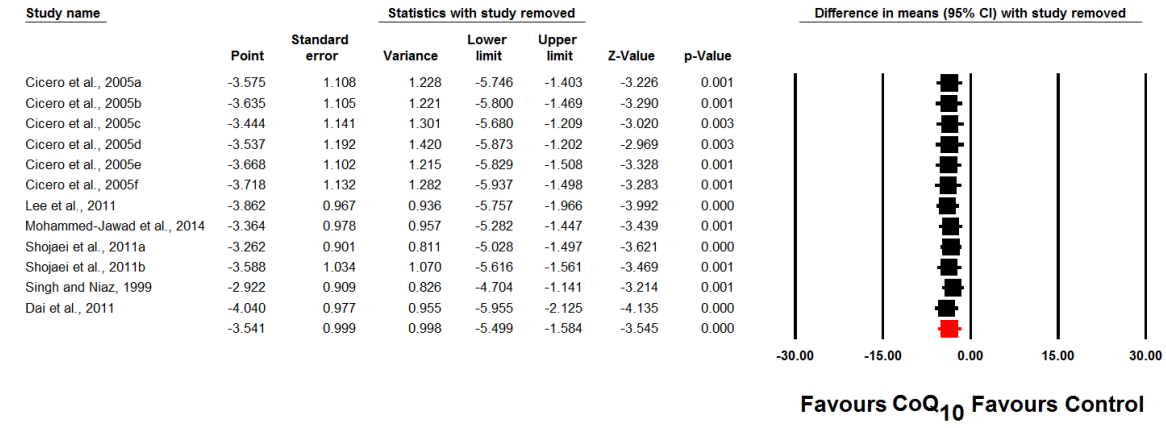


Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of CoQ_{10} supplementation on plasma lipoprotein(a) concentrations. Lower plot shows leave-one-out sensitivity analysis.



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cicero et al., 2005a	-3.420	2.453	6.016	-8.227	1.387	-1.394	0.163
Cicero et al., 2005b	-2.830	2.469	6.097	-7.669	2.009	-1.146	0.252
Cicero et al., 2005c	-4.420	1.799	3.237	-7.947	-0.893	-2.457	0.014
Cicero et al., 2005d	-3.830	1.382	1.909	-6.538	-1.122	-2.772	0.006
Cicero et al., 2005e	-2.500	2.461	6.055	-7.323	2.323	-1.016	0.310
Cicero et al., 2005f	-2.430	1.875	3.515	-6.105	1.245	-1.296	0.195
Lee et al., 2011	3.300	3.912	15.307	-4.368	10.968	0.843	0.399
Mohammed-Jawad et al., 2014	-14.220	7.525	56.622	-28.968	0.528	-1.890	0.059
Shojaei et al., 2011a	-17.100	6.433	41.378	-29.708	-4.492	-2.658	0.008
Shojaei et al., 2011b	-1.000	8.175	66.838	-17.024	15.024	-0.122	0.903
Singh and Niaz, 1999	-8.600	2.217	4.916	-12.946	-4.254	-3.879	0.000
Dai et al., 2011	0.600	2.070	4.285	-3.457	4.657	0.290	0.772
	-3.541	0.999	0.998	-5.499	-1.584	-3.545	0.000



Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cicero et al., 2005a	-3.575	1.108	1.228	-5.746	-1.403	-3.226	0.001
Cicero et al., 2005b	-3.635	1.105	1.221	-5.800	-1.469	-3.290	0.001
Cicero et al., 2005c	-3.444	1.141	1.301	-5.680	-1.209	-3.020	0.003
Cicero et al., 2005d	-3.537	1.192	1.420	-5.873	-1.202	-2.969	0.003
Cicero et al., 2005e	-3.668	1.102	1.215	-5.829	-1.508	-3.328	0.001
Cicero et al., 2005f	-3.718	1.132	1.282	-5.937	-1.498	-3.283	0.001
Lee et al., 2011	-3.862	0.967	0.936	-5.757	-1.966	-3.992	0.000
Mohammed-Jawad et al., 2014	-3.364	0.978	0.957	-5.282	-1.447	-3.439	0.001
Shojaei et al., 2011a	-3.262	0.901	0.811	-5.028	-1.497	-3.621	0.000
Shojaei et al., 2011b	-3.588	1.034	1.070	-5.616	-1.561	-3.469	0.001
Singh and Niaz, 1999	-2.922	0.909	0.826	-4.704	-1.141	-3.214	0.001
Dai et al., 2011	-4.040	0.977	0.955	-5.955	-2.125	-4.135	0.000
	-3.541	0.999	0.998	-5.499	-1.584	-3.545	0.000

Figure 3. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of CoQ_{10} supplementation on plasma lipoprotein(a) concentrations in trials with supplemental doses < 150 mg/day (upper plot) and ≥ 150 mg/day (lower plot).

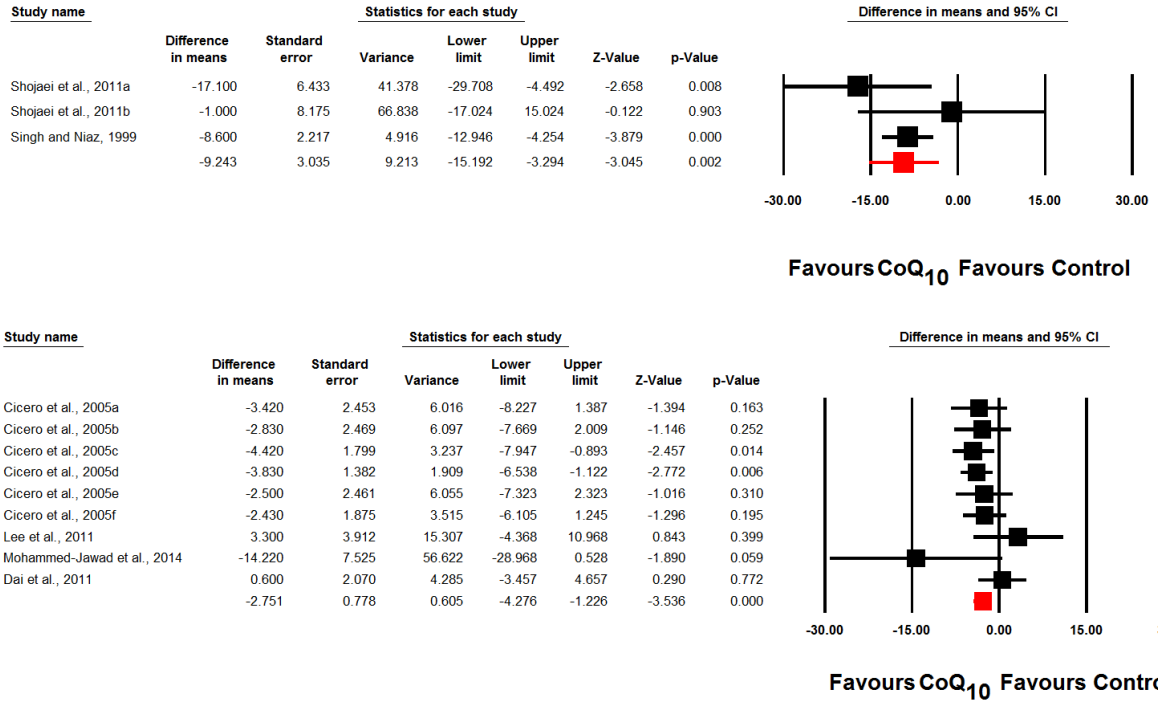


Figure 4. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of CoQ_{10} supplementation on plasma lipoprotein(a) concentrations in trials with treatment durations of < 8 weeks (upper plot) and ≥ 8 weeks (lower plot).

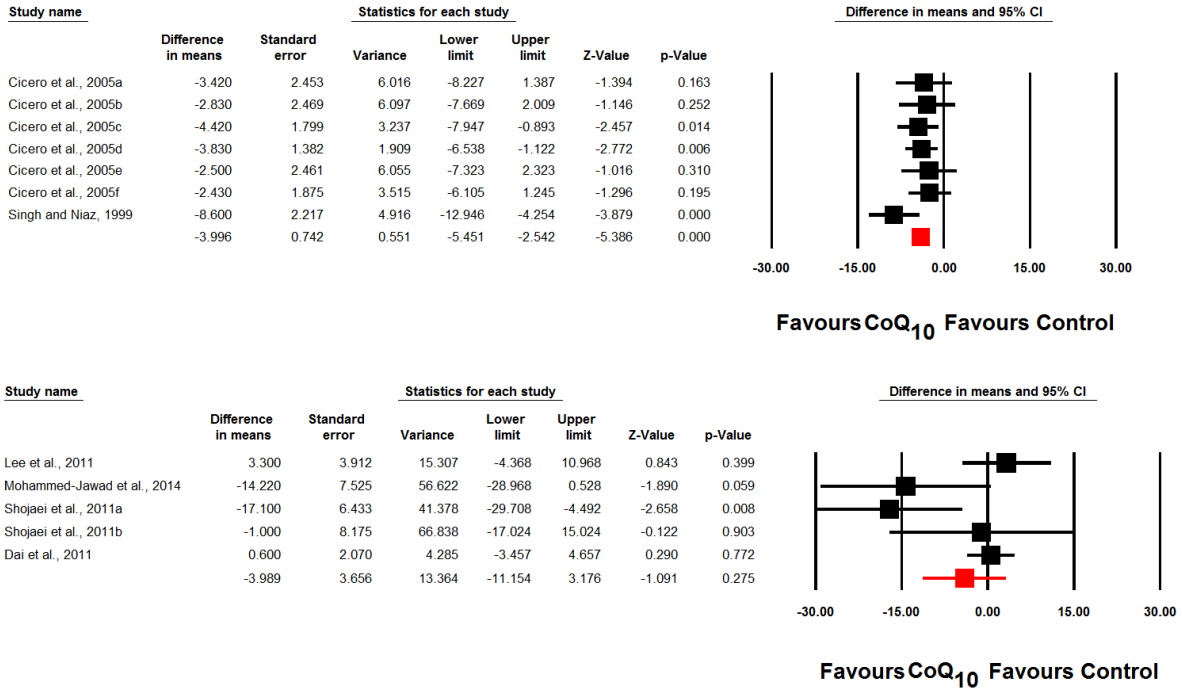


Figure 5. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of CoQ_{10} supplementation on plasma lipoprotein(a) concentrations in trials with baseline Lp(a) values < 30 mg/dL (upper plot) and ≥ 30 mg/dL (lower plot).

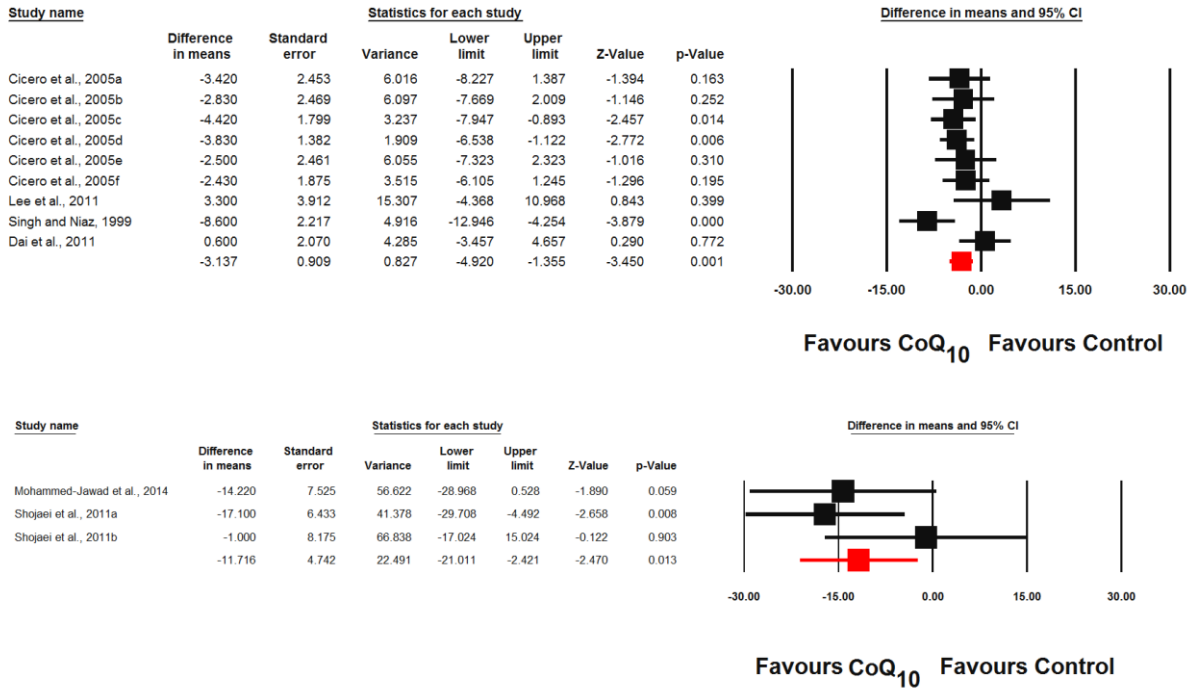
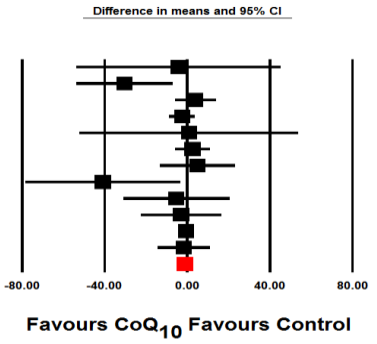


Figure 6. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of CoQ_{10} supplementation on plasma lipid profile parameters.

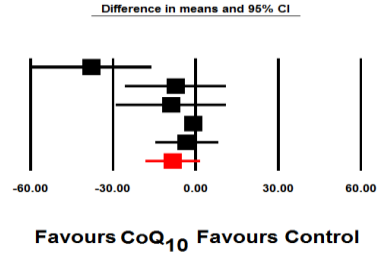
TC

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cicero et al., 2005a	-4.160	25.214	635.747	-53.579	45.259	-0.165	0.869
Cicero et al., 2005b	-30.160	11.872	140.950	-53.429	-6.891	-2.540	0.011
Cicero et al., 2005c	4.100	5.021	25.212	-5.741	13.941	0.817	0.414
Cicero et al., 2005d	-2.340	3.088	9.538	-8.393	3.713	-0.758	0.449
Cicero et al., 2005e	0.960	26.923	724.860	-51.809	53.729	0.036	0.972
Cicero et al., 2005f	2.770	4.291	18.411	-5.640	11.180	0.646	0.519
Lee et al., 2011	5.100	9.213	84.870	-12.956	23.156	0.554	0.580
Mohammed-Jawad et al., 2014	-40.650	19.034	362.310	-77.957	-3.343	-2.136	0.033
Shojaei et al., 2011a	-5.100	13.093	171.415	-30.761	20.561	-0.390	0.697
Shojaei et al., 2011b	-2.800	9.884	97.699	-22.173	16.573	-0.283	0.777
Singh and Niaz, 1999	-0.370	1.494	2.233	-3.299	2.559	-0.248	0.804
Dai et al., 2011	-1.540	6.452	41.625	-14.185	11.105	-0.239	0.811
	-0.914	1.710	2.925	-4.266	2.438	-0.534	0.593



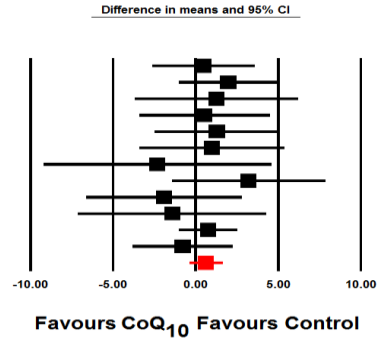
LDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Mohammed-Jawad et al., 2014	-37.730	11.073	122.621	-59.434	-16.026	-3.407	0.001
Shojaei et al., 2011a	-7.100	9.302	86.532	-25.332	11.132	-0.763	0.445
Shojaei et al., 2011b	-8.800	10.136	102.731	-28.666	11.066	-0.868	0.385
Singh and Niaz, 1999	-0.780	1.242	1.544	-3.215	1.655	-0.628	0.530
Dai et al., 2011	-3.090	5.776	33.361	-14.411	8.231	-0.535	0.593
	-8.152	4.968	24.678	-17.889	1.584	-1.641	0.101



HDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cicero et al., 2005a	0.500	1.563	2.444	-2.564	3.564	0.320	0.749
Cicero et al., 2005b	2.000	1.509	2.277	-0.958	4.958	1.325	0.185
Cicero et al., 2005c	1.300	2.513	6.317	-3.626	6.226	0.517	0.605
Cicero et al., 2005d	0.560	2.007	4.026	-3.373	4.493	0.279	0.780
Cicero et al., 2005e	1.310	1.924	3.700	-2.460	5.080	0.681	0.496
Cicero et al., 2005f	1.010	2.227	4.960	-3.355	5.375	0.454	0.650
Lee et al., 2011	-2.300	3.506	12.295	-9.173	4.573	-0.656	0.512
Mohammed-Jawad et al., 2014	3.230	2.351	5.527	-1.378	7.838	1.374	0.169
Shojaei et al., 2011a	-1.900	2.399	5.755	-6.602	2.802	-0.792	0.428
Shojaei et al., 2011b	-1.400	2.902	8.423	-7.088	4.288	-0.482	0.630
Singh and Niaz, 1999	0.780	0.887	0.786	-0.958	2.518	0.880	0.379
Dai et al., 2011	-0.770	1.541	2.375	-3.791	2.251	-0.500	0.617
	0.643	0.502	0.252	-0.340	1.626	1.281	0.200



TG

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cicero et al., 2005a	-12.340	84.797	7190.574	-178.540	153.860	-0.146	0.884
Cicero et al., 2005b	-571.420	70.104	4914.562	-708.821	-434.019	-8.151	0.000
Cicero et al., 2005c	-2.890	24.415	596.069	-50.742	44.962	-0.118	0.906
Cicero et al., 2005d	-8.720	28.832	831.289	-65.230	47.790	-0.302	0.762
Cicero et al., 2005e	-14.560	90.177	8131.880	-191.304	162.184	-0.161	0.872
Cicero et al., 2005f	-8.530	30.171	910.290	-67.664	50.604	-0.283	0.777
Lee et al., 2011	10.200	25.620	656.364	-40.013	60.413	0.398	0.691
Shojaei et al., 2011a	11.100	24.652	607.719	-37.217	59.417	0.450	0.653
Shojaei et al., 2011b	2.100	27.707	767.705	-52.206	56.406	0.076	0.940
Dai et al., 2011	-0.390	5.392	29.072	-10.958	10.178	-0.072	0.942
	-35.310	22.775	518.706	-79.948	9.328	-1.550	0.121

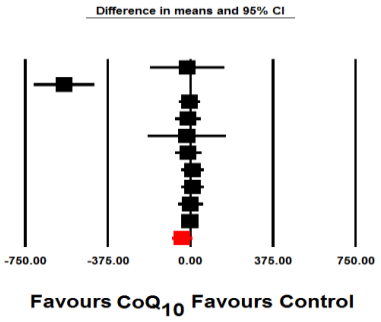


Figure 7. Meta-regression plots of the association between mean changes in plasma lipoprotein(a) concentrations with dose and duration of supplementation, and baseline lipoprotein(a) concentrations.

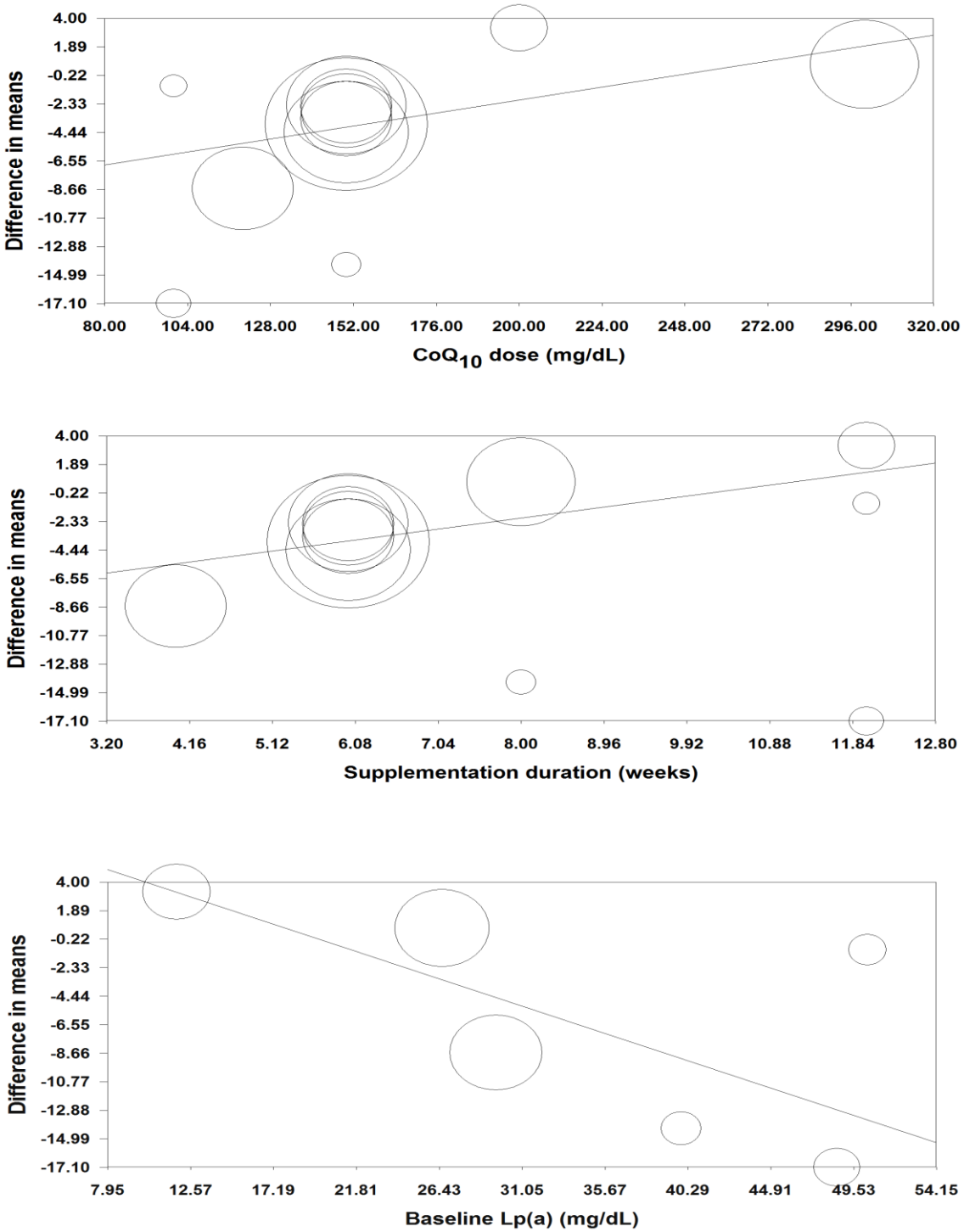
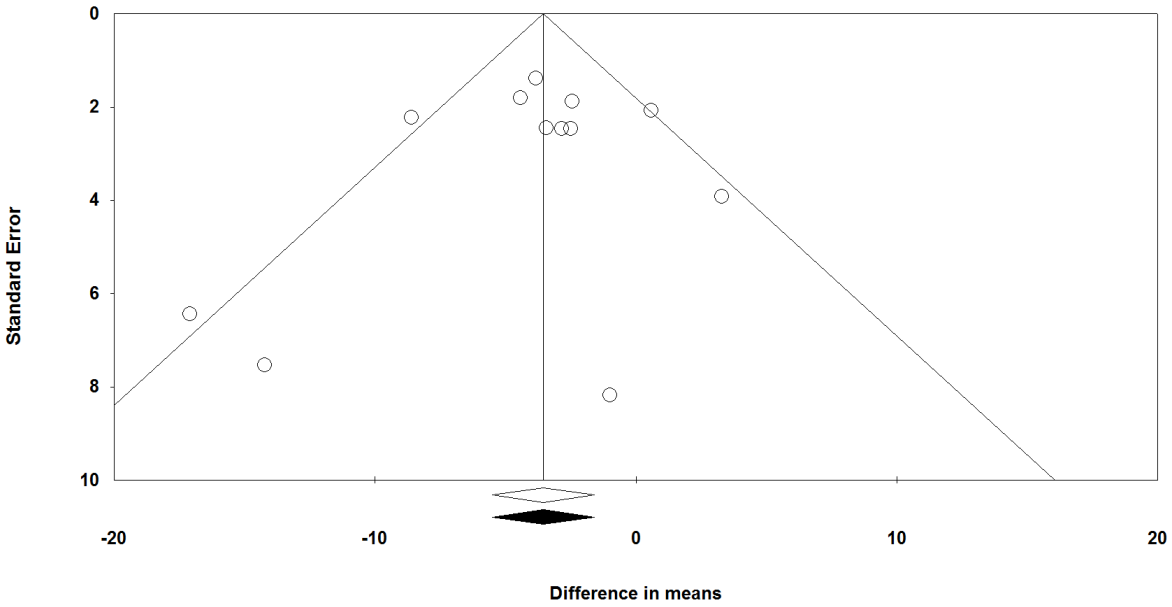


Figure 8. Funnel plot detailing publication bias in the studies reporting the impact of CoQ_{10} on plasma Lp(a) concentrations.



Tables

Table 1. Demographic characteristics of the included studies.

Author	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n, %)	BMI, (kg/m^2)	Systolic blood pressure	Diastolic blood pressure	Total cholesterol (mg/dl)	LDL cholesterol (mg/dl)	HDL cholesterol (mg/dl)	Triglycerides (mg/dl)	Lipoprotein (a) (mg/dl)
Cicero et al. (2005)	Open-label, sequential	Massive hypertriglyceri-demia	6 weeks	15	CoQ_{10} 150 mg/day PUFA 3000 mg/day Fenofibrate 200 mg/day PUFA 3000 mg/day + Fenofibrate 200 mg/day PUFA 3000 mg/day + CoQ_{10} 150 mg/day Fenofibrate 200 mg/day + CoQ_{10} 150 mg/day PUFA 3000 mg/day + Fenofibrate 200 mg/day + CoQ_{10} 150 mg/day	45.1±12.5	7 (46.6)	ND	131.4±11.5	84.5±3.9	334.0±77.0	ND	36.1±5.5	1619.3±261.7	19.42±7.88
Dai et al. (2011)	Randomized, double-blind, placebo-controlled	Ischaemic left ventricular systolic dysfunction	8 weeks	28	CoQ_{10} 300 mg/day	67.7±9.4	1 (0.3)	25.3±3.2	138±18	81±9	162.8±31.3	94.7±23.2	42.2±8.9	127.5±52.3	26.6±28.0
				28	Placebo	70.1±9.8	3 (10.7)	24.7±3.2	136±16	81±9	158.5±22.8	87.4±19.3	46.8±10.8	121.3±46.1	22.8±22.7
Lee et al. (2011)	Randomized, double-blind, placebo-controlled	Obesity	12 weeks	26	CoQ_{10} 200 mg/day	42.7±11.3	11 (42.3)	27.9±2.3	124.5±12.6	74.1±9.0	183.9±28.4	ND	50.2±12.2	112.1±56.4	11.7±10.3
				25	Placebo	42.5±11.2	15 (60.0)	27.6±3.8	119.9±29.7	75.7±9.9	186.7±30.7	ND	46.4±7.3	125.5±78.8	12.2±11.7
Mohammed-Jawad et al. (2014)	Randomized clinical trial	Type 2 diabetes	8 weeks	19	L-carnitine 1000 mg/day	52.3±6.9	11 (57.8)	29.4±3.8	ND	ND	203.0±39.2	110.1±16.6	41.7±8.2	ND	41.73±18.13
				19	CoQ_{10} 150 mg/day	49.3±6.6	9 (47.3)	28.1±4.0	ND	ND	210.1±75.8	131.8±42.0	39.6±6.7	ND	39.92±22.31
				19	Control	51.6±8.1	11 (57.8)	29.5±4.2	ND	ND	187.3±49.8	100.3±28.2	41.5±7.9	ND	35.46±26.84
Shojaei et al. (2011)	Randomized, double-blind, placebo-controlled	Maintenance hemodialysis patients	12 weeks	12	L-carnitine 1000 mg 3 times/week	55.3±15.6	6 (50.0)	24.3±2.1	ND	ND	147.1±28.8	84.5±26.5	41.9±7.8	149.2±75.2	45.0±23.9
				13	CoQ_{10} 100 mg/day	53.5±11.5	6 (46.1)	23.6±2.4	ND	ND	150.9±25.6	89.5±28.7	40.9±3.2	131.0±53.2	48.6±22.8
				14	L-carnitine 1000 mg 3 times/week + CoQ_{10} 100 mg/day	52.8±10.4	8 (57.1)	23.3±2.3	ND	ND	152.5±23.5	83.2±32.2	39.4±7.0	155.9±62.6	50.3±18.4
				13	Placebo	51.6±19.2	7 (53.8)	23.6±2.6	ND	ND	156.5±31.9	84.0±13.9	42.8±5.7	150.9±76.9	31.6±7.7
Singh et al. (1999)	Randomized, double-blind, placebo-controlled	Coronary artery disease	4 weeks	25	CoQ_{10} 120 mg/day	48.4±0.5	6 (24.0)	23.6±1.2	ND	ND	206.9±5.0	121.0±4.3	46.4±3.1	ND	29.6±7.6
				22	Placebo	47.6±0.3	4 (18.1)	23.5±1.2	ND	ND	207.7±5.4	121.8±4.3	44.1±2.7	ND	30.3±8.0

Values are expressed as mean ± SD

Abbreviations: ND, no data; BMI, body mass index; CoQ_{10}, coenzyme Q_{10}; PUFA, polyunsaturated fatty acids.

Table 2. Quality of bias assessment of the included studies according to the Cochrane guidelines.

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Cicero et al. (2005)	H	H	H	L	L	H
Dai et al. (2011)	L	L	L	L	L	L
Lee et al. (2011)	U	U	U	L	L	U
Mohammed-Jawad et al. (2014)	U	U	H	L	L	U
Shojaei et al. (2011)	L	U	U	L	L	U
Singh et al. (1999)	L	L	L	L	L	L

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.