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REVIEW

Coenzyme Q10 supplementation and oxidative stress parameters: a systematic review and meta-analysis of clinical trials

Abolfazl Akbari[1] · Gholam Reza Mobini[2] · Shahram Agah[1] · Mojgan Morvaridzadeh[3] · Amirhossein Omidi[3] · Eric Potter[4] · Siavash Fazelian[5] · Seyed Hossein Ardehali[6] · Elnaz Daneshzad[7] · Sadegh Dehghani[8]

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Abstract

Purpose Oxidative stress (OS) is associated with several chronic complications and diseases. The use of coenzyme Q10 (CoQ10) as an adjuvant treatment with routine clinical therapy against metabolic diseases has shown to be beneficial. However, the impact of CoQ10 as a preventive agent against OS has not been systematically investigated.

Methods A systematic literature search was performed using the PubMed, SCOPUS, EMBASE, and Cochrane Library databases to identify randomized clinical trials evaluating the efficacy of CoQ10 supplementation on OS parameters. Standard mean differences and 95% confidence intervals were calculated for net changes in OS parameters using a random-effects model.

Results Seventeen randomized clinical trials met the eligibility criteria to be included in the meta-analysis. Overall, CoQ10 supplementation was associated with a statistically significant decrease in malondialdehyde (MDA) (SMD − 0.94; 95% CI − 1.46, − 0.41; I^2 = 87.7%) and a significant increase in total antioxidant capacity (TAC) (SMD 0.67; 95% CI 0.28, 1.07; I^2 = 74.9%) and superoxide dismutase (SOD) activity (SMD 0.40; 95% CI 1.12, 0.67; I^2 = 9.6%). The meta-analysis found no statistically significant impact of CoQ10 supplementation on nitric oxide (NO) (SMD − 1.40; 95% CI − 0.12, 1.93; I^2 = 92.6%), glutathione (GSH) levels (SMD 0.41; 95% CI − 0.09, 0.91; I^2 = 70.0%), catalase (CAT) activity (SMD 0.36; 95% CI − 0.46, 1.18; I^2 = 90.0%), or glutathione peroxidase (GPx) activities (SMD − 1.40; 95% CI: − 0.12, 1.93; I^2 = 92.6%).

Conclusion CoQ10 supplementation, in the tested range of doses, was shown to reduce MDA concentrations, and increase TAC and antioxidant defense system enzymes. However, there were no significant effects of CoQ10 on NO, GSH concentrations, or CAT activity.

Keywords Coenzyme Q10 · Oxidative stress · Malondialdehyde · Glutathione peroxidase

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✉ Sadegh Dehghani
dehghan907@yahoo.com

Abolfazl Akbari
akbariia2006@gmail.com

Gholam Reza Mobini
gmobini52@gmail.com

Mojgan Morvaridzadeh
morvaridzadeh.nut70@gmail.com

Eric Potter
Eric.potter@bswhealth.org

Seyed Hossein Ardehali
hardehali3@gmail.com

[1] Colorectal Research Center, Iran University of Medical Sciences, Tehran, Iran

[2] Cellular & Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences (SkUMS), Shahrekord, Iran

[3] Department of Nutritional Science, School of Nutritional Science and Food Technology, Kermanshah University of Medical Sciences, Kermanshah, Iran

[4] Baylor Scott & White Research Institute, Dallas, Texas, USA

[5] Clinical Research Development Unit, Ayatollah Kashani Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran

[6] Department of Anesthesiology and Critical Care, Shohadaye Tajrish Hospital, Tehran, Iran

[7] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

[8] Radiation Sciences Department, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran

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Introduction

Although oxygen is critical for aerobic metabolism in the human body, it can lead to the generation of toxic byproducts [1]. This pathway is generally limited to the mitochondrial electron transport chain which is responsible for the production of ATP—the main energy source of the cells [2]. The oxygen byproducts are comprised of unpaired electrons that are highly unstable and react easily with biological molecules [3]. Oxidative stress (OS) changes the normal intracellular equilibrium between reactive oxygen species (ROS) and the antioxidant defense systems [4] which are responsible for conducting free radical inactivation [5]. At low levels, ROS have a physiologic role; however, at high levels, ROS can damage intracellular organelles such as the mitochondria or nuclear DNA [6]. ROS can also damage the cellular membrane leading to cell lysis [7, 8]. Cells have developed antioxidant systems to reduce the negative impact caused by ROS [9] and to maintain the balance between oxidative damage and antioxidant defense systems [10]. This equilibrium system is influenced by many internal and external factors. Diet composition can impact both the magnitude of oxidative damage and antioxidant mechanisms [11, 12], and contributes to the association between diet and some non-communicable diseases, including: diabetes, atherosclerosis, and cancer [13].

Coenzyme Q10 (CoQ10) which is also known as ubiquinone (2,3-dimethoxy-5-methyl-6-multiprenyl-1,4-benzoquinone), is an antioxidant found in almost all aerobic microorganisms [14]. CoQ10 seems to have several crucial roles in cellular biogenesis and oxidative balance. The primary role of CoQ10 is to transfer electrons in the electron transport chain from complexes I and II to complex III in the mitochondrion, producing a trans membrane electrochemical gradient [15]. CoQ10 functions as a strong antioxidant in the inner mitochondrial layer. It inhibits lipid peroxidation by either scavenging ROSs directly or regenerating α-tocopherol from α-tocopheroxyl radicals [16, 17]. Several randomized clinical trials (RCTs) have investigated the impact of CoQ10 supplementation on oxidative stress parameters [18], but no systematic reviews have been performed to summarize the impact of CoQ10 supplementation on OS parameters and antioxidant enzymes. In this systematic review and meta-analysis, we have summarized the findings from RCTs to evaluate the effectiveness of CoQ10 as a primary preventive agent against OS.

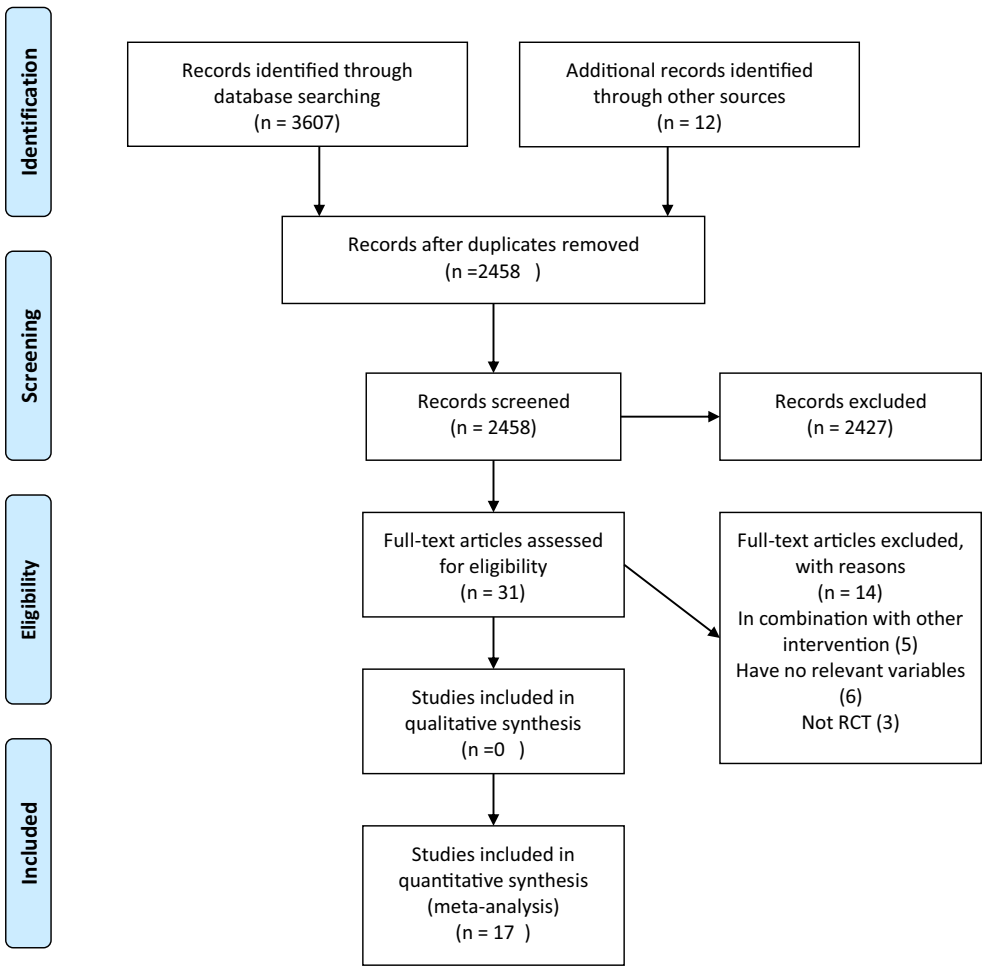
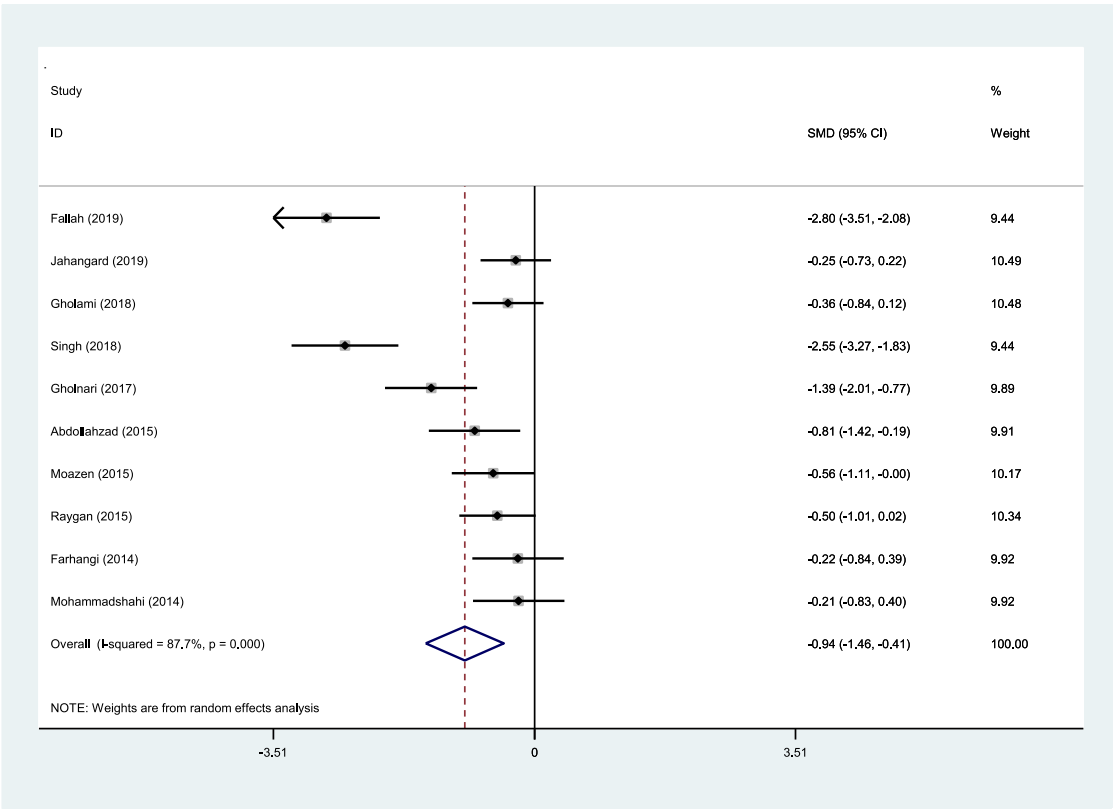


Fig. 1 PRISMA flow diagram of study selection

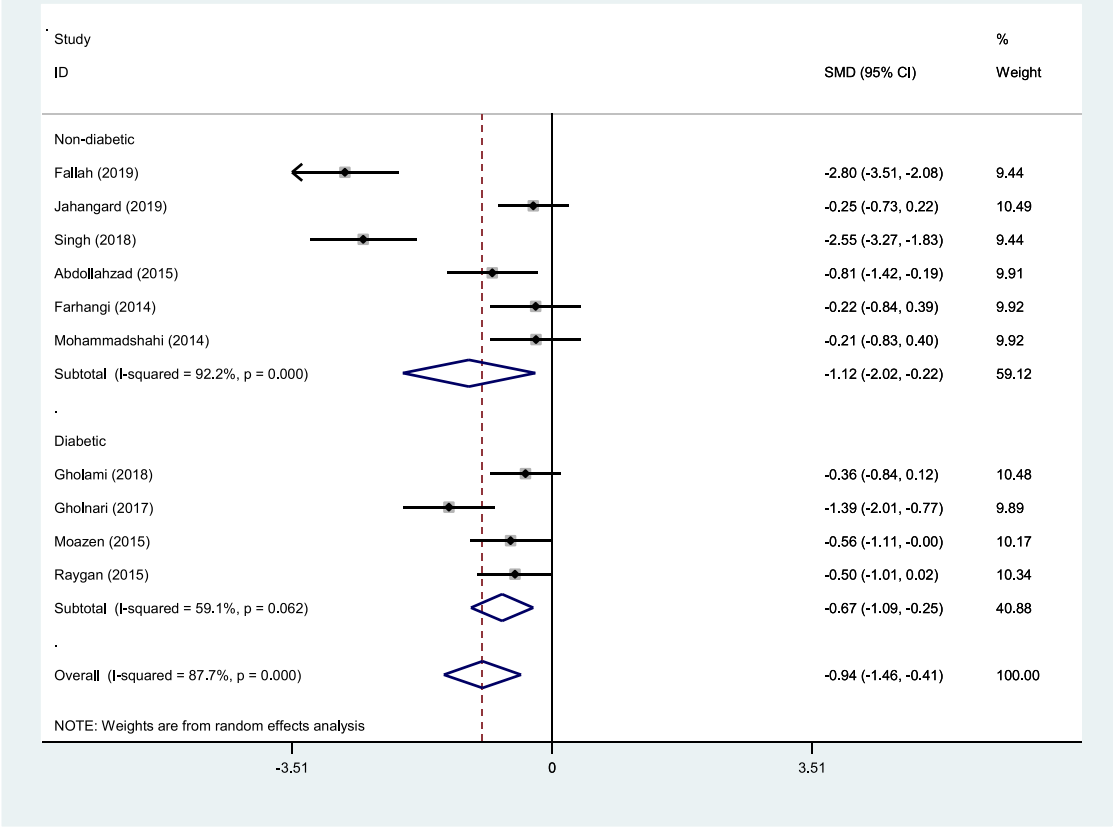
Table 1 Main characteristics of included studies

First author, year	Country	Population	Race, *n* (%)	Study design	Dose of CoQ10 (mg/d)	Sample size (including in analyses)	Duration (weeks)	Gender (percentage of women)	Age (mean ± SD)	BMI (mean ± SD) kg/m^2	Main results
Jahangard et al 2019 [22]	Iran	Patients with bipolar disorders	Iranian, 69 (100)	Double-blind, RCT, parallel	200	69	8	77.8	Int 37.47 ± 10.69 Ctrl 39.52 ± 10.82	-	↔MDA, ↔CAT, ↑TAC, ↓NO
Fallah et al 2018 [23]	Iran	Hemodialysis patients	Iranian, 60 (100)	Double-blind, RCT, parallel	120	60	12	-	Int 64.8 ± 11.5 Ctrl 59.4 ± 12.2	-	↑TAC, ↑NO, ↔MDA, ↔GSH
Gholami et al 2018 [24]	Iran	T2DM patients	Iranian, 68 (100)	Double-blind, RCT, parallel	100	68	12	100	Int 53.1 ± 6.23 Ctrl 53.35 ± 6.56	Int 29.44 ± 0.60 Ctrl 28.53 ± 0.53	↓MDA, ↓8-isoprostane
Zarei et al 2018 [38]	Iran	T2DM patients	Iranian, 68 (100)	Double-blind, RCT, parallel	100	68	12	100	Int 53.1 ± 6.23 Ctrl 53.35 ± 6.56	Int 29.44 ± 0.60 Ctrl 28.53 ± 0.53	↑CAT, ↑TAC
Singh et al 2018 [25]	India	Patients with acute coronary syndrome	Indian, 55 (100)	Double-blind, RCT, parallel	120	55	24	18.2	Int 48.5 ± 7.2 Ctrl 47.0 ± 6.4	Int 24.0 ± 1.4 Ctrl 23.2 ± 1.3	↓MDA, ↓TBARS
Nattagh-Eshtivani et al 2018 [26]	Iran	Patients diagnosed with migraine	Iranian, 46 (100)	Double-blind, RCT, parallel	400	46	12	100	Int 33.57 ± 7.91 Ctrl 31.82 ± 7.97	Int 26.12 ± 3.75 Ctrl 24.19 ± 3.75	↓MMP-9, ↓NO
Liu et al 2015 [28]	Taiwan	Hepatocellular carcinoma patients	Taiwanese 39 (100)	Single-blind, RCT, parallel	300	39	12	30.7	Int 61.5 ± 11.0 Ctrl 59.7 ± 8.3	Int 24.7 ± 3.2 Ctrl 23.1 ± 2.6	↑SOD, ↑CAT, ↑GPx
Abdollahzad et al 2015 [27]	Iran	RA patients	Iranian, 44 (100)	Double-blind, RCT, parallel	100	44	8	88.6	Int 48.77 ± 11.58 Ctrl 50.41 ± 11.28	-	↓MDA, ↔TAC
Rodríguez-Carrizalez et al 2015 [29]	Mexico	T2DM patients	Mexican, 60 (100)	Double-blind, RCT, parallel	400	60	24	52	Int 58.5 ± 1.9 Ctrl 57.8 ± 1.9	Int 28.2 ± 3.7 Ctrl 29.3 ± 0.8	↑CAT, ↑GPx, ↔TAC
Raygan et al 2015 [30]	Iran	T2DM patients	Iranian, 46 (100)	Double-blind, RCT, parallel	100	60	8	-	Int 65.9 ± 12.5 Ctrl 59.9 ± 13.1	Int 28.2 ± 5.2 Ctrl 30.7 ± 5.9	↔TAC, ↓MDA, ↑GSH
Moazen et al 2015 [31]	Iran	T2DM patients	Iranian, 52 (100)	Single-blind, RCT, parallel	100	52	8	46	Int 50.67 ± 7.01 Ctrl 52.79 ± 7.66	Int 25.31 ± 2.14 Ctrl 25.34 ± 2.39	↓MDA
Akbari-Fakhrabadi et al 2014 [32]	Iran	T2DM patients	Iranian, 62 (100)	Double-blind, RCT, parallel	200	62	12	75	Int 56.7 ± 6.4 Ctrl 54.8 ± 6.7	Int 28.7 ± 4.1 Ctrl 29.6 ± 3.1	↑TAC
Mohammadshahi et al 2014 [33]	Iran	NAFLD Patients	Iranian, 41 (100)	Double-blind, RCT, parallel	100	41	12	-	-	Int 28.23 ± 3.60 Ctrl 29.69 ± 5.76	↔MDA
Carrasco et al 2014 [34]	Spain	Renal injury patients	Spanish, 100 (100)	Doube-blind, RCT, parallel	200	100	1	-	Int 49.85 ± 11.45 Ctrl 50.60 ± 10.77	-	↔SOD, ↔GPx, ↔GSH
Farhangi et al 2014 [35]	Iran	NAFLD Patients	Iranian, 41 (100)	Double-blind, RCT, parallel	100	41	4	24	Int 42.73 ± 10.77 Ctrl 42.18 ± 10.80	Int 30.59 ± 3.98 Ctrl 28.75 ± 4.02	↑TAC
Lee et al 2013 [36]	Taiwan	CAD patients	Taiwanese 42 (100)	Single-blind, RCT, parallel	300	42	12	26	Int 71.7 ± 11.5 Ctrl 66.5 ± 11.1	Int 25.9 ± 3.5 Ctrl 26.7 ± 3.2	↑SOD, ↑CAT, ↑GPx
Dai et al 2011 [37]	Hong Kong	Patients with ischemic left ventricular systolic dysfunction	Chinese 56 (100)	Double-blind, RCT, parallel	300	56	8	7	Int 67.7 ± 9.4 Ctrl 70.1 ± 9.8	Int 25.3 ± 3.2 Ctrl 24.7 ± 3.2	↔SOD, ↔8-isoprostane

*↓ This symbol is a sign of decreasing variables in the intervention group, ↑ This symbol is a sign of increasing variables in the intervention group, ↔ This sign indicates that there is no difference between the two groups. *NR* not reported, *¥MDA* malondialdehyde, *NAFLD* non-alcoholic fatty liver disease, *T2DM* type 2 diabetes mellitus, *NO* nitric oxide, *TAC* total antioxidant capacity, *GSH* glutathione, *CAT* catalase, *SOD* superoxide dismutase, *GPX* glutathione peroxides, *Ctrl* control, *MMP-9* matrix metalloproteinase 9, *MMP-3* matrix metalloproteinase 3, *8OH2dG* 8-hydroxy-2-deoxyguanosine, *TBARS* thiobarbituric acid-reactive substances, *TRAP* total reactive antioxidant potential, *MS* multiple sclerosis, *RA* rheumatoid arthritis, *CAD* coronary artery disease, *RCT* randomized controlled trial


Study
ID
SMD (95% CI)
%
Weight
Fallah (2019)
-2.80 (-3.51, -2.08)
9.44
Jahangard (2019)
-0.25 (-0.73, 0.22)
10.49
Gholami (2018)
-0.36 (-0.84, 0.12)
10.48
Singh (2018)
-2.55 (-3.27, -1.83)
9.44
Gholnari (2017)
-1.39 (-2.01, -0.77)
9.89
Abdollahzad (2015)
-0.81 (-1.42, -0.19)
9.91
Moazen (2015)
-0.56 (-1.11, -0.00)
10.17
Raygan (2015)
-0.50 (-1.01, 0.02)
10.34
Farhangi (2014)
-0.22 (-0.84, 0.39)
9.92
Mohammadshahi (2014)
-0.21 (-0.83, 0.40)
9.92
Overall (I-squared = 87.7%, p = 0.000)
-0.94 (-1.46, -0.41)
100.00
NOTE: Weights are from random effects analysis
-3.51
0
3.51

a


Study
ID
SMD (95% CI)
%
Weight
Non-diabetic
Fallah (2019)
-2.80 (-3.51, -2.08)
9.44
Jahangard (2019)
-0.25 (-0.73, 0.22)
10.49
Singh (2018)
-2.55 (-3.27, -1.83)
9.44
Abdollahzad (2015)
-0.81 (-1.42, -0.19)
9.91
Farhangi (2014)
-0.22 (-0.84, 0.39)
9.92
Mohammadshahi (2014)
-0.21 (-0.83, 0.40)
9.92
Subtotal (I-squared = 92.2%, p = 0.000)
-1.12 (-2.02, -0.22)
59.12
Diabetic
Gholami (2018)
-0.36 (-0.84, 0.12)
10.48
Gholnari (2017)
-1.39 (-2.01, -0.77)
9.89
Moazen (2015)
-0.56 (-1.11, -0.00)
10.17
Raygan (2015)
-0.50 (-1.01, 0.02)
10.34
Subtotal (I-squared = 59.1%, p = 0.062)
-0.67 (-1.09, -0.25)
40.88
Overall (I-squared = 87.7%, p = 0.000)
-0.94 (-1.46, -0.41)
100.00
NOTE: Weights are from random effects analysis
-3.51
0
3.51

b

◀ **Fig. 2** Forest plot detailing standard mean difference and 95% confidence intervals for the impact of CoQ10 supplementation on MDA (μmol/L). **a** Overall. **b** Stratified by disease type. **c** Stratified by duration. **d** Stratified by age

Methods

This study was designed to conform to the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [19].

Search strategy

We searched MEDLINE (PubMed), The Cochrane Library, Web of Science, Scopus, and ClinicalTrials.gov using the following search terms: (Coenzyme Q10 OR "Q10" OR CoQ10 OR Ubiquinone OR Ubidecarenone OR Bio-Quinone Q10 OR Ubisemiquinone radical OR Ubisemiquinone OR Ubiquinol-10 OR Ubiquinol) AND (Glutathione Reductase OR Glutathione Peroxidase OR Superoxide Dismutase OR Oxidative Stress OR Malondialdehyde OR Total Antioxidant Capacity OR Total Antioxidant Status OR antioxidant OR Oxidant OR reactive oxygen species OR Catalase OR reactive nitrogen species OR protein carbonyl). The bibliographic databases were searched from inception to February 2019. We also investigated the reference lists of related studies to detect articles potentially eligible for inclusion. The search was limited to studies published in English. Our complete search strategy syntaxes are presented in Appendix file S1.

Study selection

Inclusion criteria

Original articles were eligible for inclusion in the systematic review if they met the following criteria: (1) randomized placebo-controlled trials with parallel or crossover design; (2) the treatment group received a specified amount of Q10, and the control group received placebo; (3) the intervention duration lasted for at least 1 week; (4) participants were adults 18 years or above; and (5) adequate data on total antioxidant capacity (TAC), malondialdehyde (MDA), glutathione (GSH), nitric oxide (NO) levels and glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) activities at baseline and at the end-point of follow-up in each treatment and placebo group or providing the net change values are presented.

Exclusion criteria

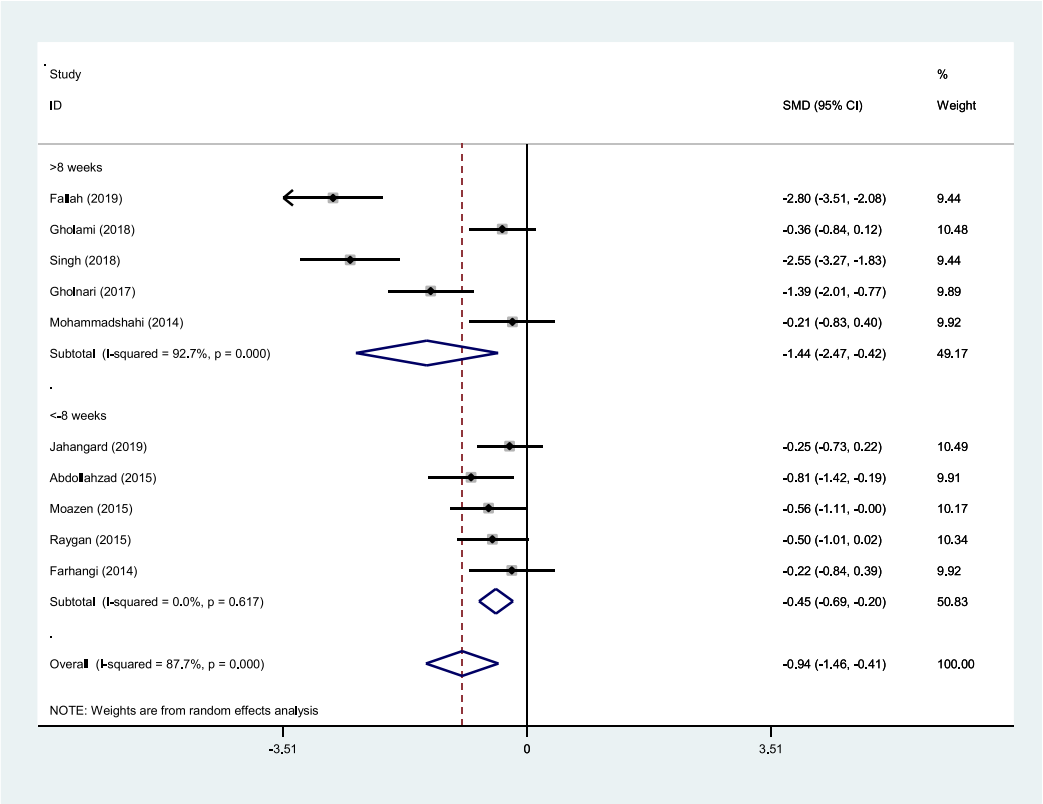
Articles were excluded if they were (1) non-interventional articles; (2) review articles; (3) uncontrolled trials; (4) case-control, cross-sectional, or cohort studies; (5) if their result measures of OS did not include both the mean change in OS parameters and the standard deviations, or if we could not obtain sufficient data from the methodology or outcomes from the paper or study authors. Eligible articles were selected by two independent reviewers (AA, MM), and the discrepancies were resolved by a third reviewer (SF).

Data extraction and quality assessment

Data extraction and quality assessment of included studies were performed independently by two reviewers (GHH, SJK). Eligible articles were evaluated and the following information were extracted: (1) first author's name; (2) year of article published; (3) country of study origin; (4) type of participant disease; (5) sample size of the study; (6) dose of Q10 treatment; (7) intervention duration; (8) age and gender of study subjects; and (9) baseline and end-trial values for TAC, MDA, GPX, NO, and SOD. The Cochrane risk of bias assessment tool [20] was used to evaluate the quality of included studies. The following criteria were used for scoring the quality of each article: adequacy of randomization sequence generation (selection bias), allocation concealment (selection bias), blinding (performance and detection bias), how they addressed subjects who were lost to follow-up (incomplete outcome data and attrition bias), and other potential sources of bias. The risk of bias assessment report is presented in Appendix file S2.

Statistical analysis and data synthesis

We used Stata software (version 11.0; Stata Corporation, College Station, TX) to perform the meta-analysis. Treatment effect was appraised with mean difference in the endpoint values of outcome measures between the treatment and the placebo group. The random-effects (DerSimonian and Laird) model [21] was used for the meta-analysis to compare the mean differences in TAC, MDA, GPX, NO, and SOD due to CoQ10 treatment compared to placebo. We computed the standardized mean difference with 95% confidence intervals for net change in the OS parameters using the values of the results (TAC, MDA, GPX, NO, and SOD) from baseline to end of the intervention. Inter-study heterogeneity was evaluated using Cochran Q test and I^2 index. In order to assess the influence of each study on the overall effect size, sensitivity analysis was performed. Subgroup analyses were used to identify the effect of CoQ10 treatment on OS parameters considering relevant study characteristics (duration of follow-up, doze of CoQ10, type of disease, age of participants) as possible sources of heterogeneity. Potential publication bias was evaluated using visual inspection of funnel plot asymmetry and the Egger's regression test.



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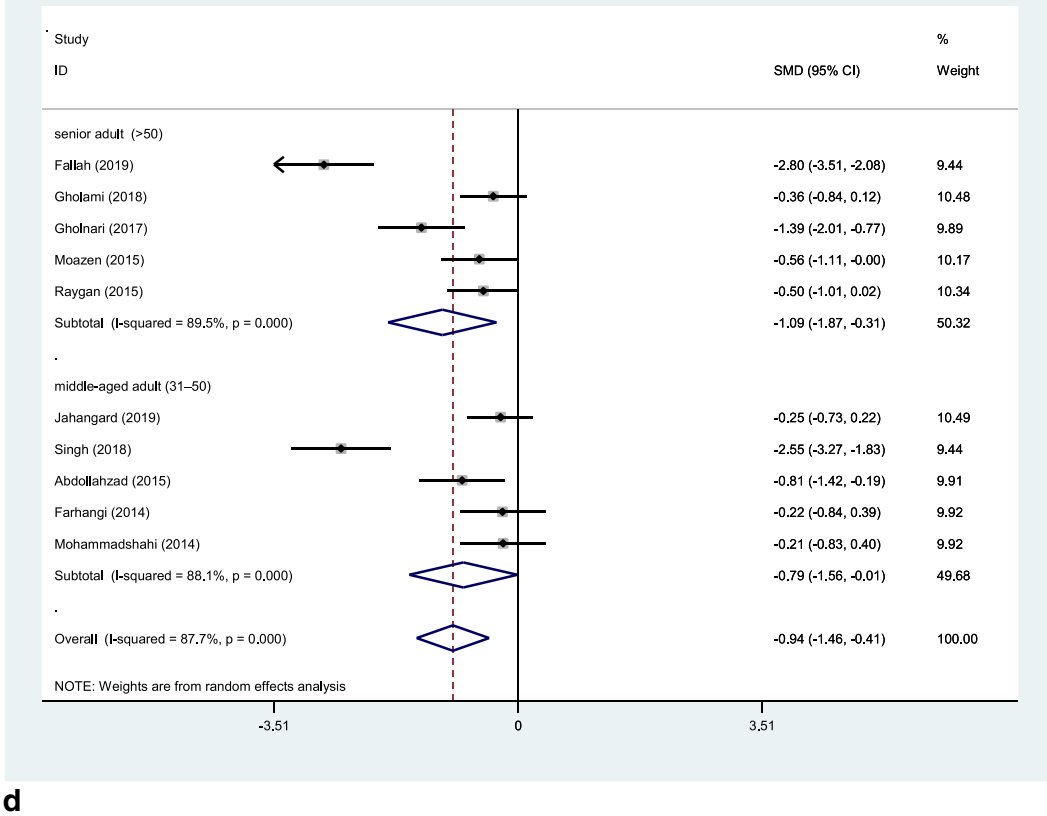


d

Fig. 2 (continued)

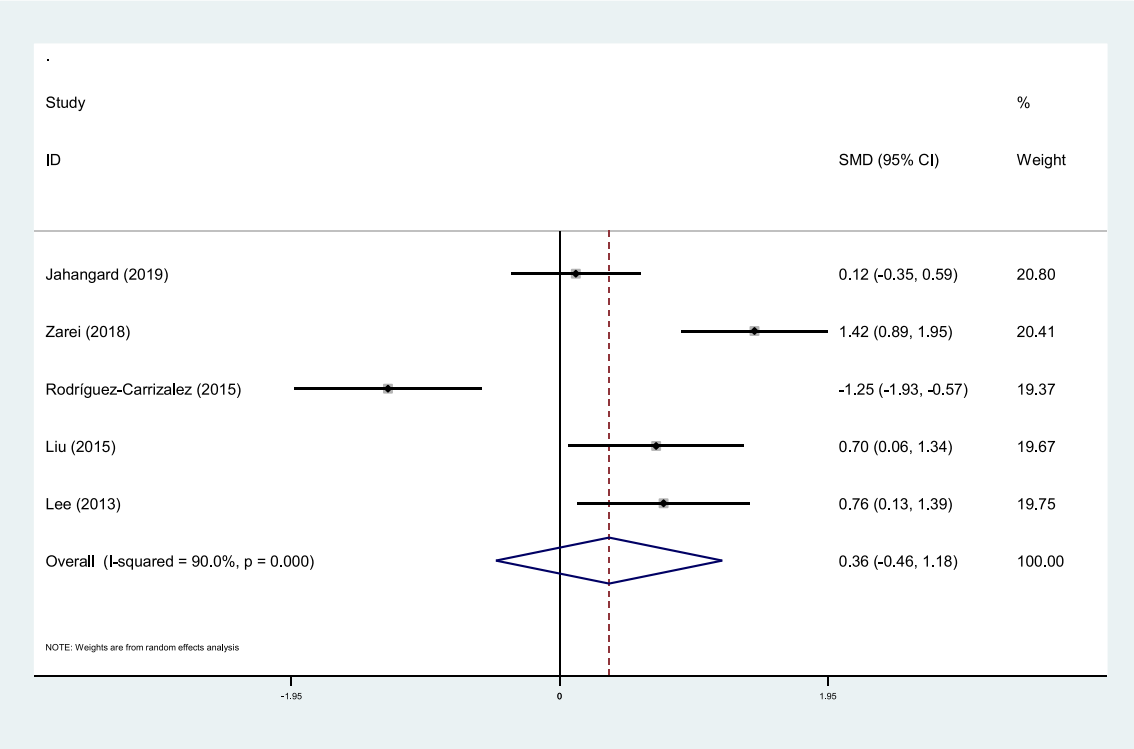


Fig. 3 Forest plot detailing standard mean difference and 95% confidence intervals for the impact of CoQ10 supplementation on CAT activity

Results

Flow and characteristics of included studies

The electronic database search yielded 3607 records: 450 from PubMed, 339 from Web of Science, 333 from Cochrane, 1734 from EMBASE, and 751 from Scopus. Potential studies were screened based on title or abstract. Among the 31 full text studies evaluated for eligibility, 17 RCTs met the inclusion criteria and were used for the final systematic review and meta-analysis [22–38]. A diagram of the study selection process is presented in Fig. 1.

In total, 963 subjects were allocated to the CoQ10 group and control group. The number of participants in these 17 RCTs ranged from 39 to 100. All the included studies were published between 2011 and 2019, and were performed in Iran (n = 11), Taiwan (n = 2), Mexico, India, and Hong Kong. The CoQ10 doses administered in these studies ranged from 100 to 400 mg/day, and the duration of supplementation ranged between 1 and 24 weeks. Six studies evaluated CoQ10 supplementation in type 2 diabetic patients, three studies evaluated subjects with cardiovascular or coronary arteries disease, two studies evaluated non-alcoholic fatty liver patients, two studies evaluated migraine and bipolar disorders, two studies evaluated subjects with hemodialysis and renal injuries, one study evaluated rheumatoid arthritis patients, and another evaluated patients with hepatocellular carcinoma. A summary of included trials are presented in Table 1.

Effect of CoQ10 supplementation on OS parameters

Ten RCTs evaluated the impact of CoQ10 supplementation on MDA levels. Compared with the placebo group, CoQ10 therapy significantly decreased MDA levels (SMD − 0.94; 95% CI − 1.46, − 0.41; I^2 = 87.7%) (Fig. 2a). Subgroup analysis based on disease type (diabetic vs. non-diabetic), duration of CoQ10 supplementation (< 8 weeks vs. ≥ 8 weeks), and age (Fig. 2b–d), respectively did not show any differences in the effect of CoQ10 supplementation on MDA. Figure 3 shows the impact of CoQ10 supplementation on CAT activity based on the results of five studies. CAT activity did not change significantly after CoQ10 supplementation compared with placebo (SMD 0.36; 95% CI − 0.46, 1.18; I^2 = 90.0%). Subgroup analysis, according to dose and duration of CoQ10 supplementation, did not change the results. Meta-analysis of four studies which evaluated the GPx activity found no statistically significant effect of CoQ10 supplementation on GPx activity (SMD − 1.40; 95% CI − 0.12, 1.93; I^2 = 92.6%) (Fig. 4). Changes in plasma NO concentrations following CoQ10 therapy were reported in four RCTs. No significant changes in plasma NO concentrations were observed following CoQ10 therapy (SMD − 1.40; 95% CI − 0.12, 1.93; I^2 = 92.6%) (Fig. 5). Four RCTs assessed the effect of CoQ10 supplementation on SOD activity. Compared with the placebo group, CoQ10 supplementation significantly increased SOD activity (SMD 0.40; 95% CI 1.12, 0.67; I^2 = 9.6%) (Fig. 6). Figure 7 a shows the effect of CoQ10 supplementation on TAC levels (eight trials). TAC significantly increased after the CoQ10 supplementation compared

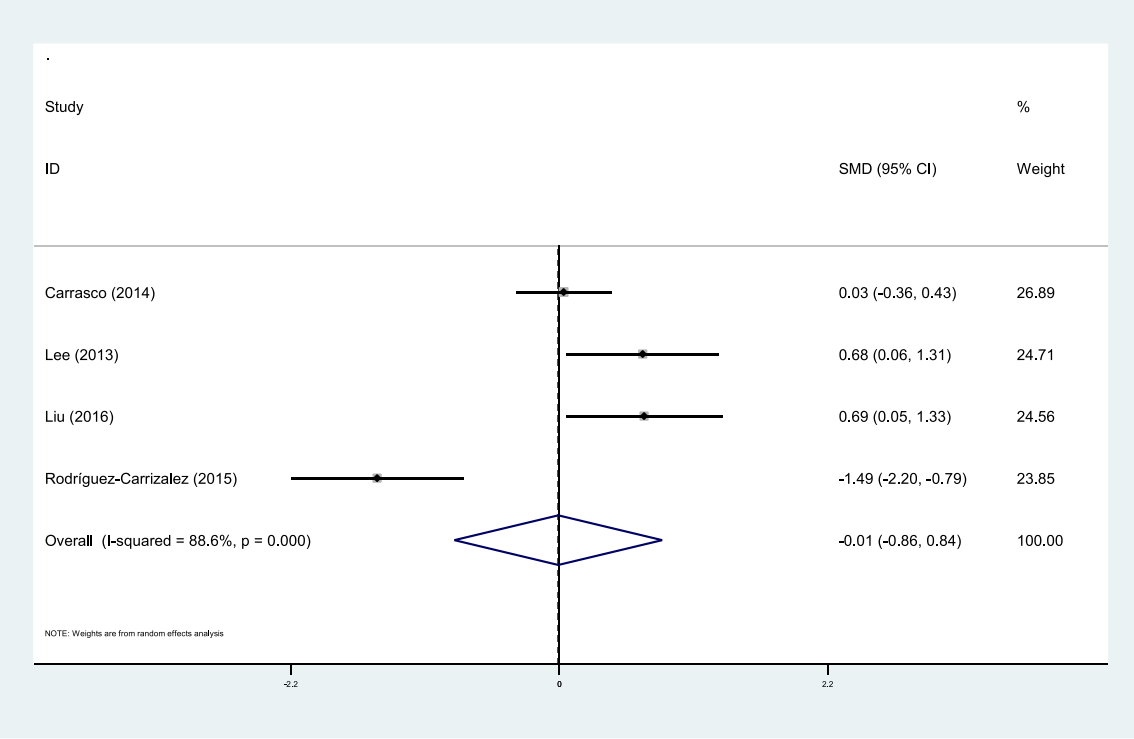


Fig. 4 Forest plot detailing standard mean difference and 95% confidence intervals for the impact of CoQ10 supplementation on GPx activity (U/mg)

to those who received placebo (SMD 0.67; 95% CI 0.28, 1.07; I^2 = 74.9%). However, subgroup analysis demonstrates that TAC elevation is significant in diabetic subjects compared to non-diabetics (SMD 0.84; 95% CI 0.32, 1.36; I^2 = 71.7%) (Fig. 7b). In addition, subgroup analysis indicated that CoQ10 supplementation greater than 8 weeks (SMD 0.94; 95% CI 0.39, 1.48; I^2 = 73.7%) (Fig. 7c), in ≥ 200 mg/day doses (SMD 1.10; 95% CI 0.38, 1.82; I^2 = 78.6%) (Fig. 7d) and in senior adults (SMD 0.88;

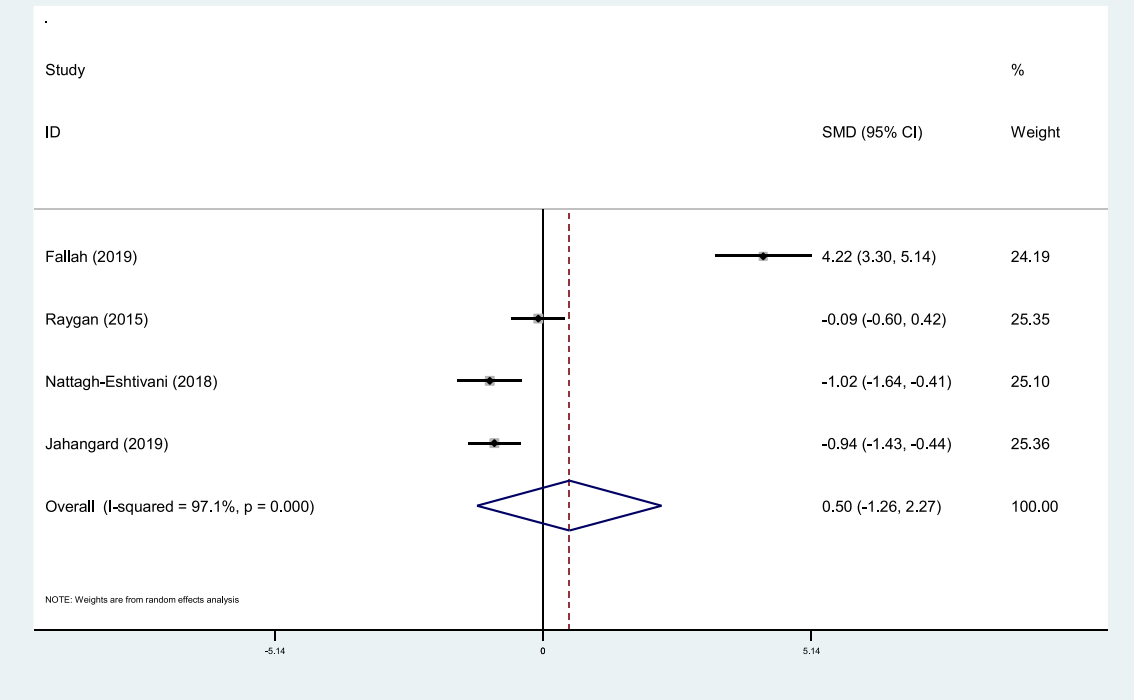


Fig. 5 Forest plot detailing standard mean difference and 95% confidence intervals for the impact of CoQ10 supplementation on NO levels (μmol/L)

95% CI 0.46, 1.30; I^2 = 65.5%) (Fig. 7e) caused a significant increase in TAC. Figure 8 shows the forest plot of the effect of CoQ10 supplementation on GSH levels. CoQ10 supplementation did not significantly change GSH levels compared to control (SMD 0.41; 95% CI − 0.09, 0.91; I^2 = 70.0%).

Quality appraisal and publication bias

Appendix Table 2 indicates the risk of bias assessment of the included trials. The funnel plot is presented in Appendix 3. There was no risk of publication bias found in the included studies.

Discussion

The results of current systematic review and meta-analysis propose that CoQ10 supplementation significantly increases TAC levels and SOD activities, as well as significantly decreases MDA levels. However, the results of this systematic review show that CoQ10 supplementation did not change NO levels, GSH levels, or CAT and GPx activity. Our findings agreed with a systematic review and meta-analysis by Jorat et al. that investigated the effect of CoQ10 supplementation on inflammatory and OS markers as they pertained only to coronary artery disease (CAD) [39]. However, to the best of our knowledge, ours is the first systematic review and meta-analysis to evaluate the effect CoQ10 on systemic OS parameters.

The results of our systematic review demonstrate that CoQ10 supplementation significantly increases TAC levels. There are no previous systematic reviews that have evaluated the effect of CoQ10 supplementation on TAC levels, though several RCTs have indicated that CoQ10 supplementation can increase TAC levels [22, 40]. Several mechanisms could be suggested for the effect of CoQ10 supplementation on TAC. For starters, TAC is a biomarker of antioxidant defense, including the antioxidant activity of enzymes such as SOD, CAT, or GPx [12, 41]. The results of our systematic review demonstrate that CoQ10 supplementation significantly increases SOD and CAT activity as well. Secondly, CoQ10 also functions as a robust scavenger of free radicals. And lastly, because of the vulnerability of ubiquinol to oxidation, it behaves as the first-line and the major active antioxidant in the primary levels of oxidation activities [42]. In fact, increased concentrations of CoQ10 in plasma and cell membranes protect cells from apoptosis and damage mediated by OS [43]. Our results subgroup analysis shows that CoQ10 supplementation significantly increases TAC in diabetic participants compared to non-diabetic participants. This may be due to a disruption of the balance between antioxidants and oxidants in diabetic patients [44], and supplementation of CoQ10 as a potent antioxidant increases TAC in diabetic more than non-diabetic individuals [45]. Subgroup analysis also shows that CoQ10 supplementation greater than 8 weeks increases TAC significantly compared to ≤ 8 weeks. In vivo studies also confirm that long-term supplementation of CoQ10 is more effective in stabilizing inflammatory and oxidative balance [46]. In addition, stratified results by doses demonstrated that more than 200 mg/day CoQ10 increased TAC significantly

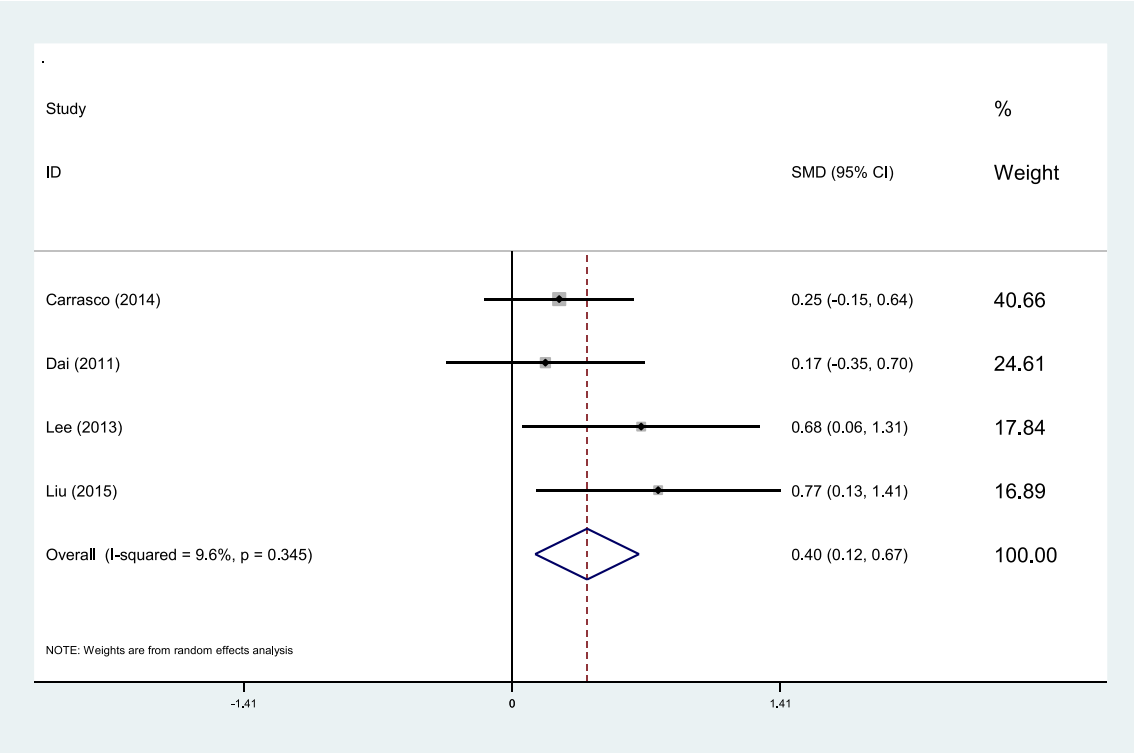
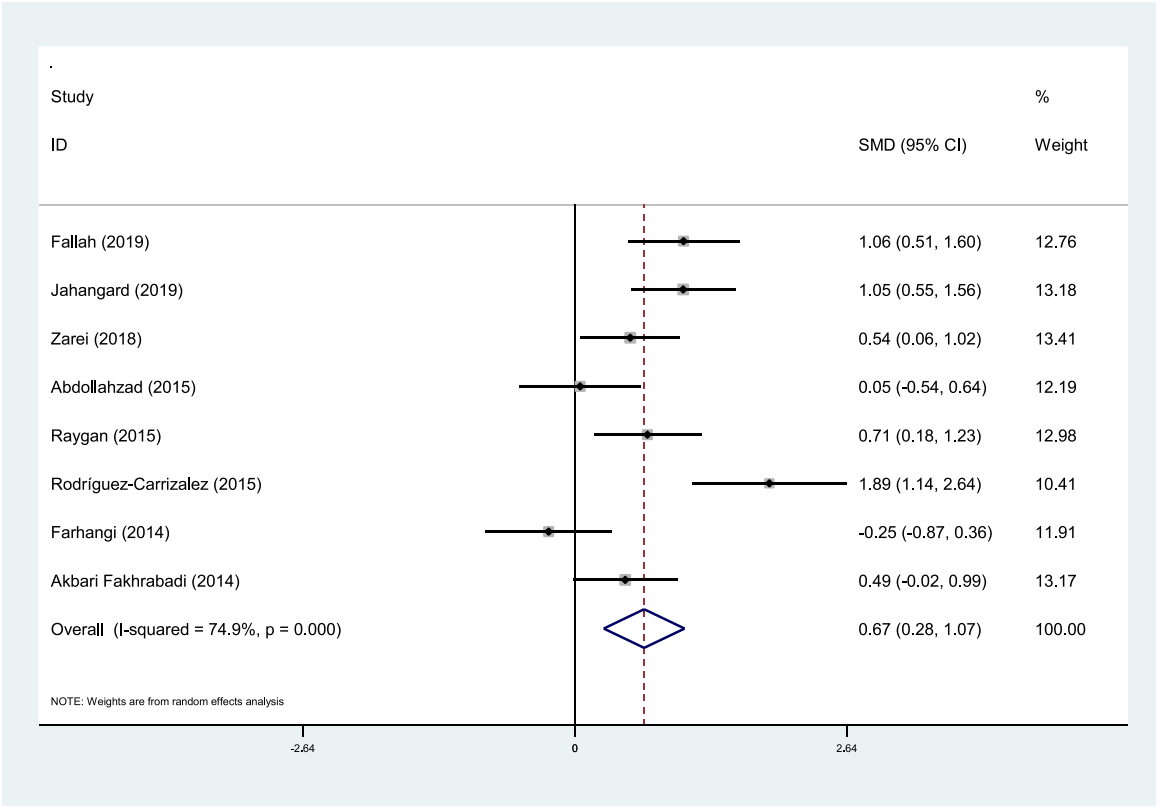
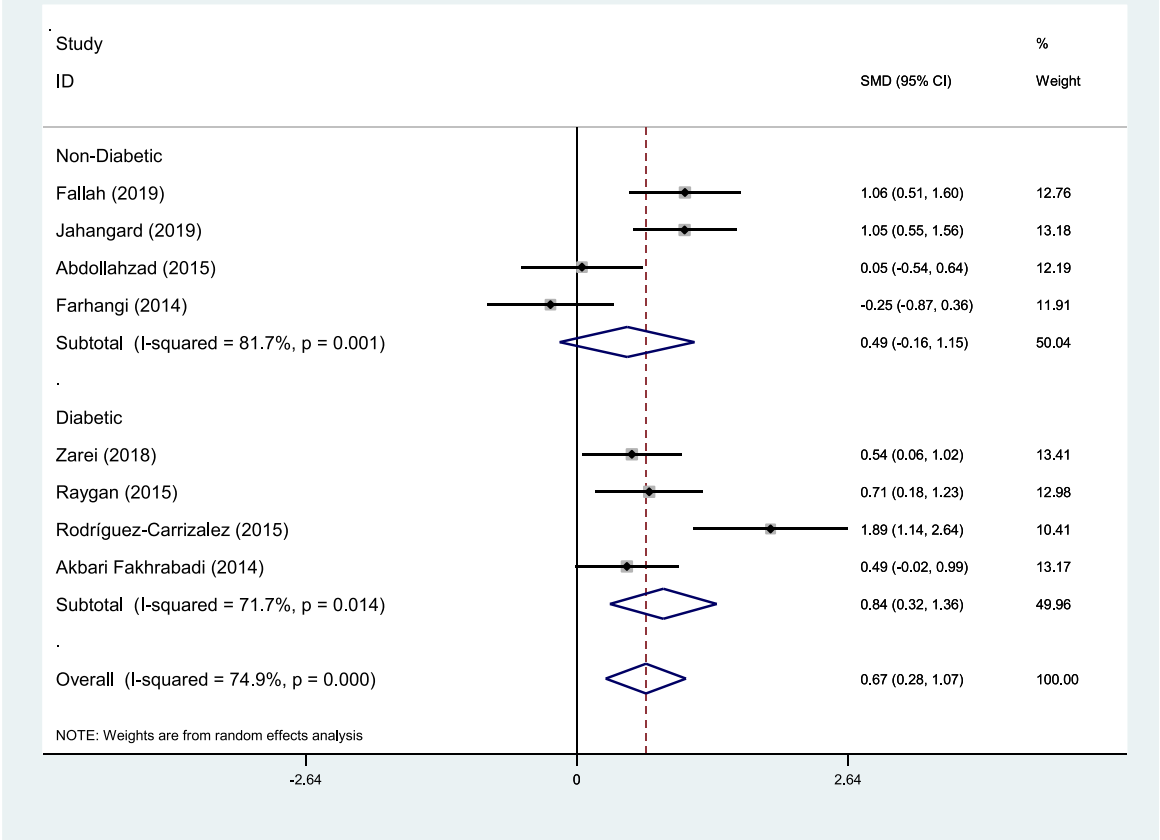


Fig. 6 Forest plot detailing standard mean difference and 95% confidence intervals for the impact of CoQ10 supplementation on SOD activity (U/mg)


Study
ID
SMD (95% CI)
%
Weight
Fallah (2019)
1.06 (0.51, 1.60)
12.76
Jahangard (2019)
1.05 (0.55, 1.56)
13.18
Zarei (2018)
0.54 (0.06, 1.02)
13.41
Abdollahzad (2015)
0.05 (-0.54, 0.64)
12.19
Raygan (2015)
0.71 (0.18, 1.23)
12.98
Rodríguez-Carrizalez (2015)
1.89 (1.14, 2.64)
10.41
Farhangi (2014)
-0.25 (-0.87, 0.36)
11.91
Akbari Fakhrabadi (2014)
0.49 (-0.02, 0.99)
13.17
Overall (I-squared = 74.9%, p = 0.000)
0.67 (0.28, 1.07)
100.00
NOTE: Weights are from random effects analysis
-2.64
0
2.64

a


Study
ID
SMD (95% CI)
%
Weight
Non-Diabetic
Fallah (2019)
1.06 (0.51, 1.60)
12.76
Jahangard (2019)
1.05 (0.55, 1.56)
13.18
Abdollahzad (2015)
0.05 (-0.54, 0.64)
12.19
Farhangi (2014)
-0.25 (-0.87, 0.36)
11.91
Subtotal (I-squared = 81.7%, p = 0.001)
0.49 (-0.16, 1.15)
50.04
Diabetic
Zarei (2018)
0.54 (0.06, 1.02)
13.41
Raygan (2015)
0.71 (0.18, 1.23)
12.98
Rodríguez-Carrizalez (2015)
1.89 (1.14, 2.64)
10.41
Akbari Fakhrabadi (2014)
0.49 (-0.02, 0.99)
13.17
Subtotal (I-squared = 71.7%, p = 0.014)
0.84 (0.32, 1.36)
49.96
Overall (I-squared = 74.9%, p = 0.000)
0.67 (0.28, 1.07)
100.00
NOTE: Weights are from random effects analysis
-2.64
0
2.64

b

◀ **Fig. 7** Forest plot detailing standard mean difference and 95% confidence intervals for the impact of CoQ10 supplementation on TAC (mmol/L). **a** Overall. **b** Stratified by disease type. **c** Stratified by duration. **d** Stratified by dose. **e** Stratified by age

compared to less than 200 mg/day. Primary studies also indicated that a higher dose of CoQ10 might conduct rapid and stable antioxidative effects compared to lower doses [47]. And finally, subgroup analysis by age demonstrated that CoQ10 significantly increased TAC in senior adults compared to middle-aged adults. It seems that greater oxidative factors in older age may be more impacted by an antioxidant supplement such as CoQ10 [48].

In our systematic review and meta-analysis, CoQ10 supplementation significantly decreased the MDA levels. The effect of CoQ10 supplementation on MDA seems to be robust, as the results of subgroup analysis showed that classification by disease type, supplementation duration, and age of participants did not change these results. MDA is the best evaluated product of lipid peroxidation [49, 50], and it has been shown in in vitro and in vivo studies that CoQ10 supplementation protected against lipid peroxidation [51, 52]. There are no systematic reviews that evaluate the effect of CoQ10 supplementation on MDA, but several primary studies have shown that CoQ10 reduces MDA. Lee et al. demonstrated that 150 mg/day CoQ10 can significantly reduce MDA in coronary artery disease patients [47]. In another RCT, Hormozi et al. indicated that 160 mg/day CoQ10 reduced MDA levels significantly in glazers with occupational cadmium exposure [53]. Gholami et al. also demonstrated that 100 mg/dzy CoQ10 supplementation significantly reduced MDA levels in type 2 diabetic patients [24]. In another study in diabetic patients, Golnari et al. indicated that 100 mg/day CoQ10 supplementation for 12 weeks significantly decreased MDA levels [54]. Various mechanisms are suggested for the effect of CoQ10 supplementation on MDA. First of all, CoQ10 is a part of the respiratory chain in the mitochondria and restricts endogenous ROS production in mitochondria [55], and it has been shown that lower ROS is correlated with decreased levels of MDA [56]. In addition, it has been shown that CoQ10 regulates lipid metabolism and prevents lipid oxidation in several cellular and gene expression ways.

In vivo studies have indicated that dietary supplementation with CoQ10 significantly decreased white adipose tissue and ameliorated the activity of brown adipose tissue by modulating expression of lipid metabolism-related factors [57]. CoQ10 has been shown to regulate the function of transcription factor C-FOS and suppress gene expression of PDE4, a cAMP-degrading enzyme, which led to intracellular cAMP elevation. High amounts of cAMP cause AMPK activation, inhibit de novo generation of fatty acids, and decrease fatty acid peroxidation [58, 59].

The results of our meta-analysis show that CoQ10 supplementation non-significantly increased GSH levels. Our meta-analysis results also showed that CoQ10 supplementation was ineffective on GPx activity, though, contradictory results in the primary studies made it difficult to draw conclusions in this regard. While the Rodríguez-Carrizalez et al. study [29] demonstrated that CoQ10 significantly reduced GPx, while the Lee et al. [47] and Liu et al. [28] studies demonstrated a significant increase of GPx, the results of sensitivity analysis showed that dropping the results of any of these studies did not change the overall results significantly.

The results of our systematic review and meta-analysis demonstrate that CoQ10 supplementation significantly increases SOD activity. There are no similar systematic reviews about the effect of CoQ10 on SOD activity, but several RCTs indicated that CoQ10 supplementation can increase the SOD activity [28, 53, 60]. It has been accepted that SOD is one of the major detoxifying enzymes in the mitochondria [61]. One of the possible mechanisms by which CoQ10 can act as a mitochondrial antioxidant is by decreasing ROS in the mitochondria, thereby leading to an increase in SOD activity [62]. In addition, FOXO3a (one of the main Forkhead transcription factors) has been shown to regulate SOD gene expression. Increased FOXO3a activation increases SOD activity [63], and recent studies have indicated that CoQ10 can increase FOXO3a [64].

The results of our meta-analysis indicated that CoQ10 supplementation increased CAT activity in a non-significant manner. The result of our meta-analysis also shows that CoQ10 supplementation has no significant effect on NO concentrations. Great heterogenicity and a low number of primary studies maybe the reasons that we could not find a significant effect of CoQ10 supplementation on NO concentrations and CAT activity. However, the results of other studies investigating the effect of CoQ10 supplementation on NO concentrations are also controversial [65, 66], and there are no concrete conclusions in these regards.

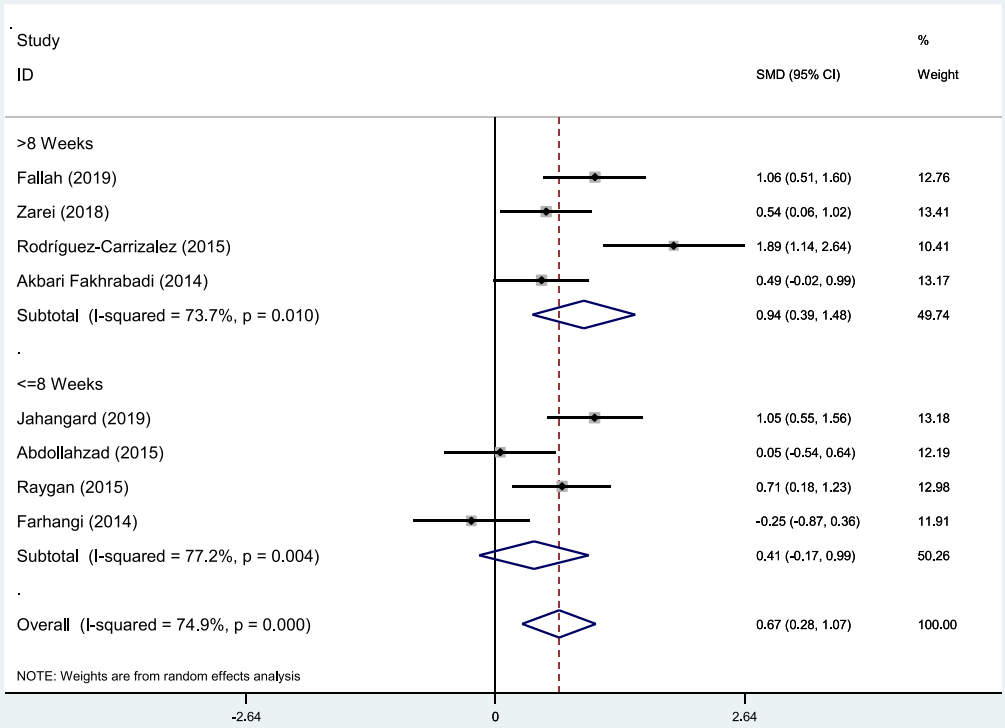
It is important to acknowledge some limitations of our study. Of the available studies that we were able to include in our meta-analysis model, there was a considerable diversity among individuals with respect to underlying disease and comorbidities, making it difficult to compare. Additionally, there were a small number of included studies that evaluated most of the variables that we were interested in, making it difficult to perform subgroup analysis. Finally, we have no protocol registration for our systematic review and meta-analysis.

We conclude that CoQ10 can improve OS as indicated by a statistically significant change in TAC and MDA concentrations, as well as SOD activity, compared with placebo. Future studies looking at long-term results, and specific evaluation of OS parameters, are required to confirm its efficacy for combating OS. Future studies with more homogeneous etiologies are also needed to draw a more robust conclusion for why some patients benefit and others do not from CoQ10 supplementation in regards to OS parameters such as NO.

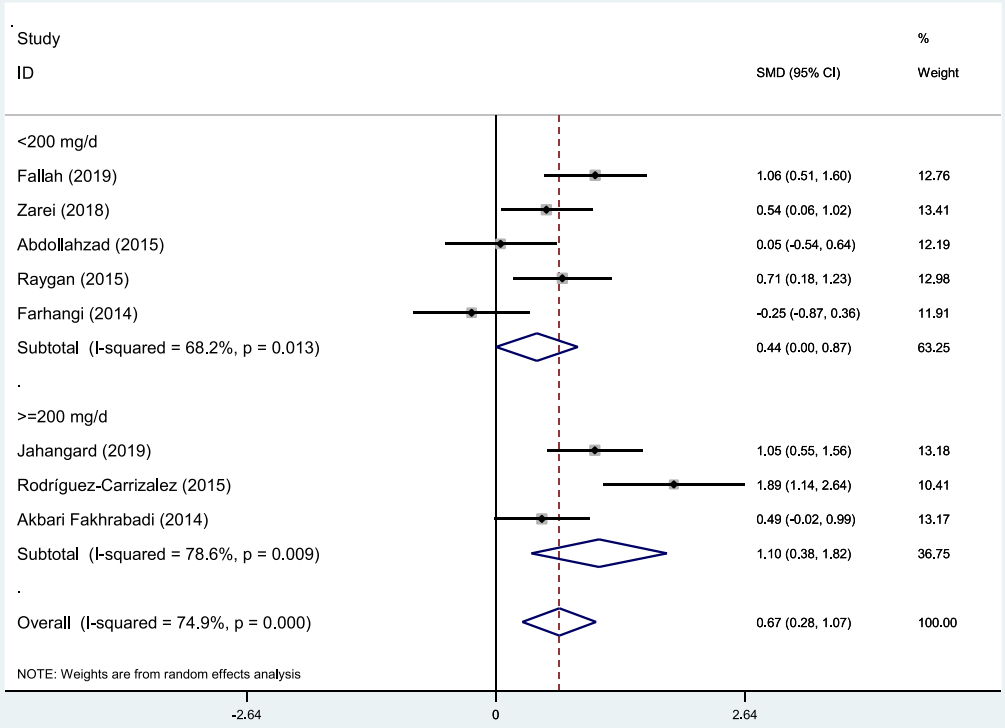
Acknowledgments N/A

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

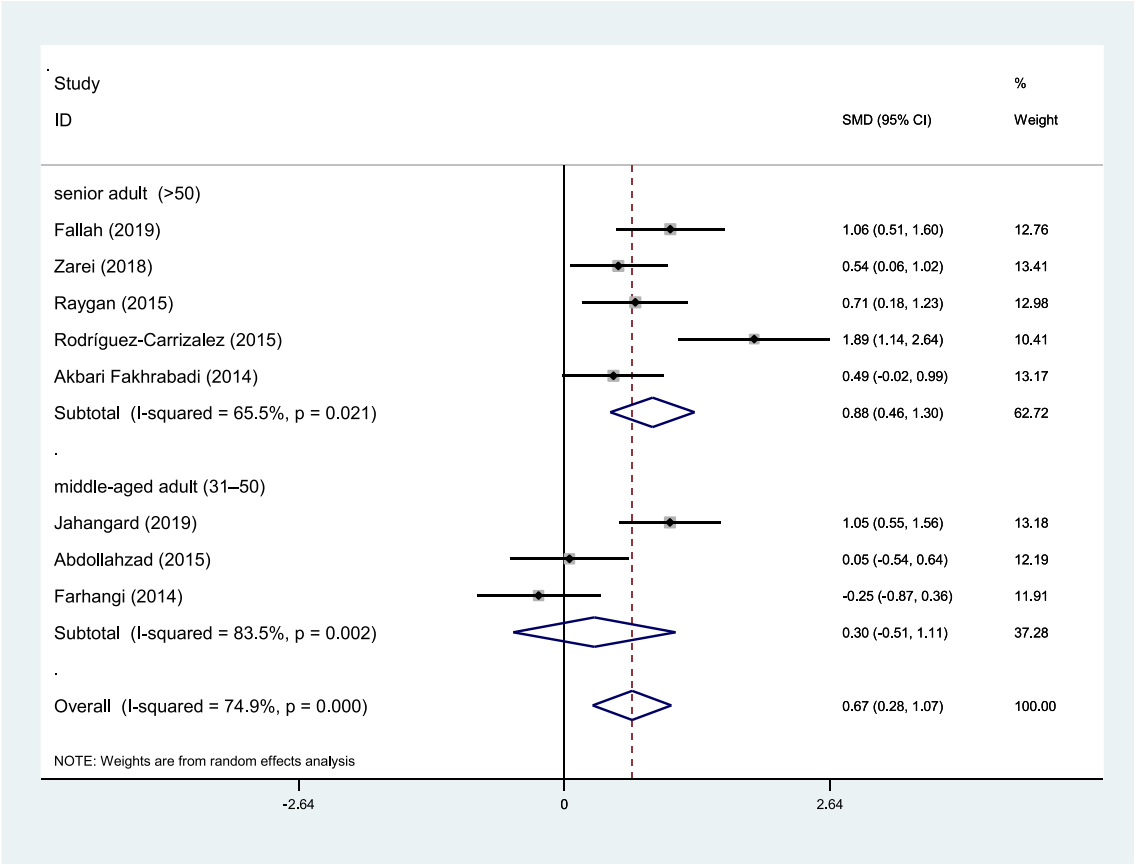


c



d

Fig. 7 (continued)



e

Fig. 7 (continued)

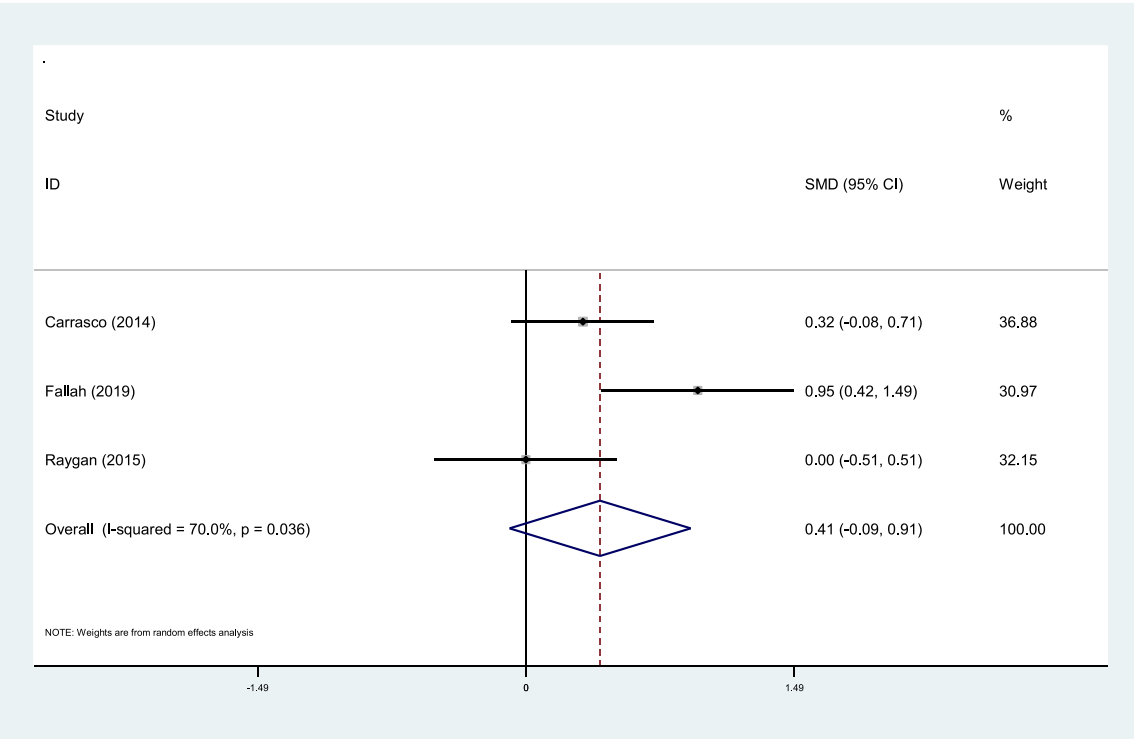


Fig. 8 Forest plot detailing standard mean difference and 95% confidence intervals for the impact of CoQ10 supplementation on GSH levels (μmol/L)

Appendix

Table 2 Assessment of the risk of bias in the included studies

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 (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdollahzad et al.(2015)[27]	–	–	–	+	?	–	–
Carrasco et al.(2014)[34]	–	–	?	+	–	–	?
Dai et al.(2011)[37]	–	–	–	?	–	–	–
Akbari-Fakhrabadi et al.(2015)[32]	–	–	–	?	–	–	–
Fallah et al.(2019)[23]	–	+	?	+	–	?	–
Farhangi et al.(2014)[35]	?	–	–	?	–	–	–
Gholami et al.(2018)[24]	?	+	?	?	–	–	–
Jahangard et al.(2019)[22]	–	–	?	?	–	–	–
Lee et al.(2013)[36]	?	+	+	+	?	–	–
Liu et al.(2016)[28]	–	–	+	+	–	–	?
Moazen et al.(2015)[31]	–	–	+	?	?	–	–
Mohamadshahi et al.(2014)[33]	?	–	?	?	?	–	–
Nattagh-eshtivani et al.(2018)[26]	–	–	–	–	?	–	–
Raygan et al.(2015)[30]	–	–	–	?	–	–	–
Rodríguez-Carrizalez et al.(2015)[29]	?	–	–	?	–	–	–
Singh et al.(2018)[25]	?	–	–	–	?	–	–
Zarei et al.(2018)[38]	–	+	?	+	–	–	–

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