Effects of coenzyme Q10 supplementation on glycemic control: A GRADE-assessed systematic review and dose-response meta-analysis of randomized controlled trials

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Summary

Background Previous reviews reported that the effects of CoQ10 on glycemic control were inconsistent. There is no review exploring the optimal intake of CoQ10 for glycemic control. We aimed to investigate the efficacy of CoQ10 on glycemic control and evaluate the dose−response relationship via integrating the existing evidence from randomized control trials (RCTs).

Methods Databases (PubMed, Embase, and Cochrane Library) were searched to identify RCTs for investigating the efficacy of CoQ10 on fasting glucose, fasting insulin, HbA1c, and HOMA-IR up to March 12, 2022. We performed a meta-analysis on 40 RCTs of CoQ10. Weighted mean difference (WMD) and 95% confidence intervals (CIs) were calculated for net changes. Evidence certainty was assessed using GRADE. Dose-response relationships were evaluated using 1-stage restricted cubic spline regression model. The protocol was registered in PROSPERO (CRD42021252933).

Findings Forty studies (n = 2,424 participants) were included in this meta-analysis. CoQ10 significantly reduced fasting glucose (WMD: -5.22 [95% CI: -8.33, -2.11] mg/dl; P <0.001; I^2=95.10%), fasting insulin (-1.32 [-2.06, -0.58] μIU/ml; P < 0.001; I^2=78.86%), HbA_{1c} (-0.12% [-0.23, -0.01]; P =0.04; I^2=49.10%), and HOMA-IR (-0.69 [-1.00, -0.38]; P <0.001; I^2=88.80%). The effect of CoQ10 on outcomes was greater in diabetes with lower heterogeneity. A "U" shape dose-response relationship curve revealed that 100-200 mg/day of CoQ10 largely decreased fasting glucose (χ^2 = 12.08, $P_{nonlinearity}$ =0.002), fasting insulin (χ^2 = 9.73, $P_{nonlinearity}$ =0.008), HbA_{1c} (χ^2 = 6.00, $P_{nonlinearity}$ =0.049), HOMA-IR (χ^2 = 25.89, $P_{nonlinearity}$ <0.001).

Interpretation CoQ10 supplementation has beneficial effects on glycemic control, especially in diabetes, and 100-200 mg/day of CoQ10 could achieve the greatest benefit, which could provide a basis for the dietary guidelines of CoQ10 in patients with glycemic disorders.

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Keywords: Coenzyme Q10; Dose-response; GRADE; Glycemic control; Meta-analysis

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Research in context

Evidence before this study

We searched PubMed for manuscripts published in English from inception and until November 30, 2021 with "coenzyme Q10" in combination with "glycemic control", "dose-response effects" and "meta-analysis". We found zero meta-analysis assessing the dose-response effects of CoQ10 supplementation for glycemic control in adults. Previous meta-analysis of the effects of CoQ10 in diabetes have reported inconsistent results. Only one meta-analysis reported that low dose of CoQ10 could reduce fasting glucose and HbA_{1c}, without mentioning the optimal supplementary dose.

Added value of this study

In this updated meta-analysis of 40 randomized controlled trials, CoQ10 supplementation has beneficial effects on glycemic control, especially in diabetes patients. Taking 100-200 mg/day of CoQ10 could achieve the greatest benefit for glycemic control.

Implications of all the available evidence

These findings add new information about the beneficial effects of CoQ10 supplementation on glycemic control, and are conducive to setting up nutrition guidelines for recommended daily intake of CoQ10 in patients with glycemic disorders.

Introduction

Over the past few decades, cardiovascular disease (CVD) remains the leading cause of global deaths and disability, and the number of CVD deaths steadily increased year by year.[1] In 2019, about 523 million adults were suffering from CVD, about twice as many as in 1990.[1] The development of CVD is mainly driven by cardiometabolic risk factors, such as glucose metabolism disorder. Patients with disorder of glucose metabolism are at high risk of developing hyperglycemia-related CVD and metabolic diseases, including diabetes, obesity, dyslipidemia.[2–4] There is mounting evidence that glycemic control can effectively reduce the risk of CVD and metabolic disease.[5,6] In this point, early intervention in the management of glycemic level is an important target to reduce the risk of CVD and other metabolic diseases.[7]

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a lipid-soluble benzoquinone similar to vitamins. CoQ10 has a wide distribution in plant and animal tissues, especially in meat, fish, nuts, and some oils. Under normal physiological conditions, endogenous synthesis was thought to be the main source. However, with the growth of age, the synthetic ability of CoQ10 decreased, which could not meet the needs of healthy adults.[8] In addition, average dietary intake of CoQ10 was only 3-6 mg per day, which was far less than the demand for CoQ10. Supplementation of CoQ10 could increase the level of CoQ10 in vivo to some extent. CoQ10, as a nutritional supplement, has a wide range of biological effects, including antioxidation, maintenance of normal blood pressure and cholesterol concentrations, maintenance of normal cognitive function, and improving insulin resistance.[9,10] Clinical trials of the effects of supplementary CoQ10 on glycemic control have reported inconsistent results. Previous meta-analysis of randomized control trials (RCTs) have focused on the effect of CoQ10 on glycemic control for specific populations, such as type 2 diabetes[11,12] and diabetic kidney disease.[13] However, these populations did not focus on other hyperglycemia-related diseases. While the prior meta-analysis included many relevant studies, the newly published studies in recent years still need to be updated. In addition, the current reviews are lack of an analysis of the optimal intake dose of CoQ10 supplement, and there is not enough evidence to set up nutrition guidelines for recommended daily intake of CoQ10. Therefore, further evaluation of the evidence quality is also needed to ascertain the efficacy of CoQ10 in glycemic control.

The aim of this meta-analysis is to 1) investigate the efficacy of CoQ10 supplementation in improving glycemic control in adult with hyperglycemia-related diseases, 2) update the latest published studies, 3) assess evidence certainty according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methods, and 4) conducted dose–response meta-analysis using a 1-stage restricted cubic spline regression model, so as to provide a basis for nutrition guidelines of recommended CoQ10 intake in patients with hyperglycemia-related diseases.

Methods

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14] and have been prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the identifier CRD42021252933.

Search strategy

Two investigators (YL and DZ) independently searched the PubMed, Embase, and Cochrane Library for RCTs concerning the effects of CoQ10 supplementation on outcomes of glycemic control, including fasting glucose, HbA_{1c}, fasting insulin, and HOMA-IR up to March 12, 2022. In addition, we also searched relevant review and meta-analysis articles for eligible studies. Specific search strategies are presented in Supplemental Table S1.

Study inclusion and exclusion

Only studies that satisfied the following inclusion criteria were included: 1) the participants were over 18 years old; 2) the studies used CoQ10 as the intervention approach with duration more than 2 weeks; 3) the trials

used placebo or other suitable controls; 4) baseline and follow-up mean for fasting glucose, fasting insulin, HbA_{1c}, or HOMA-IR were reported (or could be calculated); 5) the studies were randomized controlled trials of either parallel or crossover design, with no limits on the language of publication. Studies were excluded if it: 1) was an acute feeding trial; 2) recruited pregnant or lactating women; 3) had a multifactorial study design so that the effects of CoQ10 cannot be isolated; 4) did not provide adequate data to estimate the effect sizes of CoQ10.

The selection of the studies was performed independently by the investigators (YL and DZ), screening on the titles and abstracts. For studies that could not be determined, full texts were evaluated. Any discrepancies during selection of studies were resolved by a third reviewer (ZT).

Data extraction

Two investigators (YL and QJ) independently extracted the following items from each eligible study: first author's name, year of publication, country where the study was performed, source of funding, study design and duration, sample size, intervention approach, dose of CoQ10, control approach, subject characteristics, and changes in the glycemic control outcomes aforementioned.

Mean changes and standard deviations (SDs) from baseline to the end of follow-up in both intervention and control groups were used to estimate the effect size of CoQ10. If the mean changes were not provided directly, the effect values before and after the intervention were extracted and converted into the mean changes and SDs as follows:

$$\Delta mean = mean_{end} - mean_{baseline}$$

$$\Delta SD = \sqrt{SD_{end}^2 + SD_{baseline}^2 - 2 \times R \times SD_{end} \times SD_{baseline}}$$

assuming a correlation coefficient (R) = 0.5. When standard errors of the mean (SEMs) rather than SDs were reported, the SDs were estimated using the following formula:

$$SD = SEM \times \sqrt{n}$$

where n was the number of subjects. When the outcome measures were reported as means and 95% confidence intervals (CIs), the SDs were estimated using the following formula:

$$SD = (\text{upper limit} - \text{lower limit}) \div 3.92$$

where n was the number of subjects. When studies were reported with median and range, we estimated SD as

$$SD = \frac{P_{75} - P_{25}}{1.35}$$

provided by Cochrane Handbook recommendation.[15] For multi-armed parallel trials, we treated each intervention group and corresponding control as an independent comparison. Crossover trials were regarded similarly to parallel trials, with separate CoQ10 and control arms.

For data extraction, two investigators (YL and QJ) processed articles independently. Inconsistency in particular information between researchers was resolved by discussion or negotiation with a third researcher (ZT).

Quality assessment

The Cochrane risk-of-bias tool (Review manager version 5.4)[16] was used to evaluate the quality assessment of included studies, including domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Other biases, including study design rationality and compliance with treatment, were also assessed. We rated studies that satisfies four or more of seven low-risk domains of bias as low risk with the rest as high risk. Two investigators (YL and ML) evaluated the risk of biases independently, with any discrepancies adjudicated by a third researcher (DZ).

Statistical analysis

Stata software (version 16.0) was used to calculate pooled effect size estimates, which were expressed as weighed mean difference (WMD) with 95% CIs. Inter-study heterogeneity was assessed using Cochran Q test and I^2 statistics. Given that we did not work with just one population, pooled estimates and 95% CIs of effect sizes were calculated using random-effects modeling with DerSimonian-Laird methods.[17] Forest plots were generated to visually evaluate the pooled effect size estimates. P-values < 0.05 were considered statistically significant for all statistical test used.

To explore potential sources of confounding and heterogeneity, we conducted subgroup analysis on outcome measures. We prespecified subgroup stratified by study design (parallel vs. crossover), study duration (shorter term <12 weeks vs. longer term ≥12 weeks), the dosage of CoQ10 (lower dose < 200 mg/day, ≥200 mg/day and < 300 mg/day, higher dose ≥ 300 mg/day), corporate sponsorship, overall study risk of bias (high risk vs. low risk), and diseases. We evaluated the robustness of pooled estimates via leave-one-out sensitivity analysis.

We performed a random-effects dose–response meta-analysis assessing the relationship between CoQ10 and fasting glucose, fasting insulin, HbA_{1c}, and HOMA-IR respectively using the 1-stage restricted cubic spline regression model with Rstudio (version 1.4) based on the dosresmeta package.[18–20]

The GRADE method was used to assess the level of evidence for major outcome indicators on the basis of risk of bias, inconsistency, indirectness, imprecision, and publication bias with GRADEpro GDT software (version 3.6).[21] Quality was appraised as "very low,"

"low," "moderate," or "high" based on risk of bias, inconsistency, indirectness, imprecision, and publication bias. Finally, we assessed the publication bias using funnel plots as well as the Egger's tests. The trim and fill methods were used to adjust theoretically missing studies and correct for funnel plot asymmetry, if any.

Role of the funding source

The funder of the study had no role in accessing the raw data, study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

Overall, a total of 3697 studies were retrieved from a search of databases, and after title and abstract screening, 2701 were excluded. Evaluation of 81 full-text reports resulted in identification of 40 randomized controlled trials articles[22–61] that could be included in the analysis. Reasons for exclusion included duration <2 weeks (n = 16), inappropriate placebo in control group (n = 10), intervention included CoQ10 and other factors (n = 12), and article cannot be obtained (n = 3). The PRISMA literature search flow diagram is presented in Figure 1.

The 40 studies, which were published between 1994 and 2020, included 2,424 participants (Table 1). The age of participants ranged 19 from 70 years. Included trials conducted in Europe (n = 8), Oceania (n = 5), North America (n = 2), Asia (n = 27). All but one study was crossover trial(33). Among the parallel studies, thirty-five trials were single-armed while the other five were multi-armed parallel trials. The number of participants were fanged from 23 to 101. The studies included subjects with CVD (n = 3), diabetes (n = 25), dyslipidemia (n = 6), obesity (n = 2), non-alcoholic fatty liver disease (n = 2), polycystic ovary syndrome (n = 2), and others (n = 4). Across trials, the dose intake of CoQ10 ranged from 100 to 900 mg, and the treatment and follow-up duration ranged from 4 weeks to 6 months.

Forty studies were evaluated for risk of bias in accordance with the Cochrane risk-of-bias tool (Supplemental Figure S1). Twenty-seven studies were rated as low risk in at least four of seven Cochrane risk-of-bias domains. Only 5 studies were rated as high risk in incomplete outcome data (n = 3)[31,50,58] and blinding of participants and personnel (n = 2).[26,42]

The overall quality of evidence among the four primary outcomes ranged from very low to moderate for the RCTs in accordance with the GRADE evidence profiles (Table 2). HbA_{1c} was found to have a moderate certainty of decreasing statistically with CoQ10 supplementation due to the degradation of indirectness. Fasting insulin was evaluated as a low evidence certainty for the downgrade of inconsistency and indirectness. Fasting glucose and HOMA-IR were found to have a very low certainty of decreasing statistically with CoQ10 supplementation because the inconsistency, indirectness and publication bias were downgraded.

Meta-analysis of data from 44 treatment arms suggested a significant reduction in fasting glucose level following CoQ10 supplementation (WMD: -5.22 mg/dl; 95% CI: -8.33, -2.11 mg/dl; P < 0.001; n = 2157 in 38 studies; I^2=95.10%) (Figure 2). Subgroup analysis of potentially modifying factors revealed that the most prominent effects on efficacy and heterogeneity were due to CoQ10 dosage, duration, the type of control, risk of bias, and industry funding (Table 3). The impact of CoQ10 on fasting glucose was greater at supplemental doses < 200 mg/day (WMD: -13.21 mg/dl, 95% CI: -18.43, -7.98 mg/dl, P < 0.001) compared with remaining two groups. With respect to treatment duration, the effect of CoQ10 on reducing fasting glucose level was better in the subsets of duration ≥ 12 weeks (WMD: -7.59 mg/dl, 95% CI: -11.66, -3.52 mg/dl, P < 0.001) compared with duration < 12 weeks. As for the type of control, the reduction on fasting glucose was greater at placebo group (WMD: -6.02 mg/dl, 95% CI: -9.56, -2.47 mg/dl, P < 0.001) rather than using other controls. CoQ10 had better efficacy in reducing fasting glucose level in the low risk of bias (WMD: -6.70 mg/dl, 95% CI: -11.28, -2.13 mg/dl, P < 0.001) and not receiving industry funding (WMD: -6.84 mg/dl, 95% CI: -10.70, -2.98 mg/dl, P < 0.001).

CoQ10 supplementation decreased HbA_{1c} to a statistically significant degree (WMD: -0.12%; 95% CI: -0.23, -0.01%; P = 0.04; n = 1505 in 31 studies; I^2=49.10%) (Figure 3). Subgroup analysis found that the effect of CoQ10 supplement on reducing HbA_{1c} has a border statistical significance at duration ≥ 12 weeks (WMD: -0.14%; 95% CI: -0.27, 0.00%; P = 0.05) and placebo as control group (WMD: -0.12%; 95% CI: -0.23, 0.00%; P = 0.05). Besides, consuming less than 200 mg of CoQ10 per day (WMD: -0.47%; 95% CI: -0.83, -0.12%; P < 0.001) and not receiving industry funding (WMD: -0.28%; 95% CI: -0.48, -0.08%; P < 0.001) had a better efficacy in reducing HbA_{1c} level (Table 4).

CoQ10 supplementation reduced fasting insulin to a statistically significant degree (WMD: -1.32 μIU/ml; 95% CI: -2.06, -0.58 μIU/ml; P <0.001; n=1234 in 24 studies; I^2=78.86%) compared with control group (Figure 4). Subgroup analysis suggested that lower CoQ10 dosage, longer duration, low risk of bias, and placebo as control group were potential factors. The impact of CoQ10 on fasting insulin was greater at supplemental doses < 200 mg/day (WMD: -1.71 μIU/ml, 95% CI: -2.57, -0.85 μIU/ml, P < 0.001) compared with remaining groups. As for the treatment duration, the effect of CoQ10 on reducing fasting insulin was better at duration ≥ 12 weeks (WMD: -1.51 μIU/ml, 95% CI:

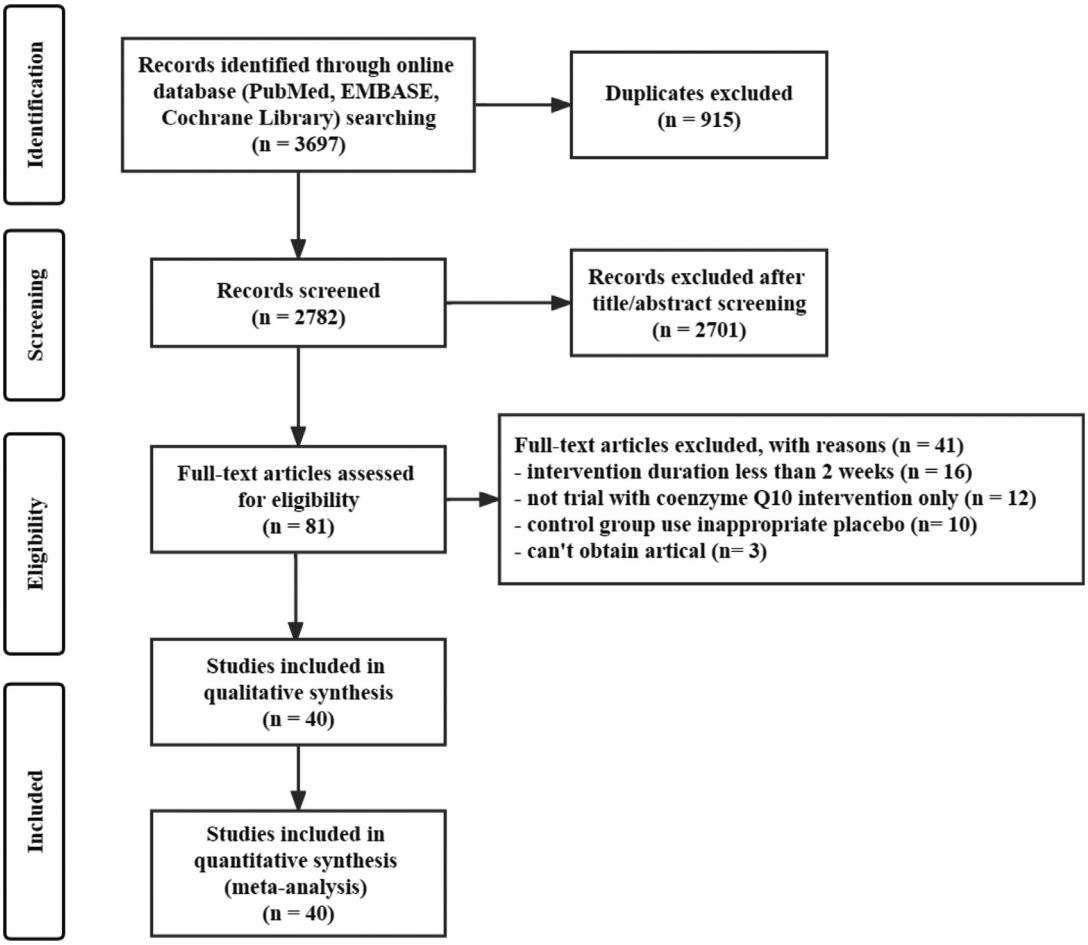

Figure 1. Flow diagram of studies search for trials, published through March 12, 2022.

-2.52, -0.50 μIU/ml, $P < 0.001$) compared with duration < 12 weeks. With respect to the risk of bias and industry funding, the reduction on fasting insulin was greater at low risk of bias (WMD: -1.50 μIU/ml, 95% CI: -2.29, -0.71 μIU/ml, $P < 0.001$) and not receiving industry funding (Table 5).

The pooled estimate of the effect of CoQ10 supplementation on HOMA-IR was -0.69 (95% CI: -1.00, -0.38; P <0.001; n=988 in 18 studies; I^2=88.80%) (Figure 5). Subgroup analysis suggested that consumption of CoQ10 less than 200 mg/day can greatly reduce HOMA-IR (WMD: -0.97, 95% CI: -1.44, -0.50; P <0.001), and the same effect could be achieved in the subsets of duration ≥ 12 weeks (WMD: -1.03, 95% CI: -1.40, -0.65; P <0.001), low risk of bias (WMD: -0.68, 95% CI: -1.00, -0.37; P <0.001), placebo as control group (WMD: -0.76, 95% CI: -1.13, -0.39; P <0.001), and not receiving industry funding (WMD: -0.99, 95% CI: -1.42, -0.55; P <0.001) (Table 6).

Considering an existing difference of subjects among included studies, we further performed subgroup analysis of diseases (Supplemental Table S2). Subgroup analysis of fasting glucose suggested that CoQ10 supplementation had the best effect on patients with diabetes (WMD: -13.12 mg/dl; 95% CI: -18.91, -7.32 mg/dl; P <0.001; I^2=64.32%) (Supplemental Figure S2), compared with CVD (WMD: -10.28 mg/dl; 95% CI: -23.67, 3.11 mg/dl; P = 0.13), and dyslipidemia (WMD: -2.12 mg/dl; 95% CI: -7.18, 2.94 mg/dl; P = 0.41). Supplementation of CoQ10 could statistically reduce HbA_{1c} in diabetic patients (WMD: -0.15%; 95% CI: -0.29, -0.01 %; P = 0.04; I^2=55.00%) (Supplemental Figure S3), but there was no statistical difference in patients with CVD and dyslipidemia.

CoQ10 significantly lowered fasting insulin level in population with diabetes (WMD: -1.90 μIU/ml; 95% CI: -3.04, -0.76 μIU/ml; $P < 0.001$; I^2=74.12%) (Supplemental Figure S4), compare with other diseases. Only one trial, concerning CVD, showed that fasting insulin levels have been decreased by - 6.20 μIU/ml on average after CoQ10 treatment.

The reduction in HOMA-IR was significant in diabetic patient (WMD: -1.26; 95% CI: -1.48, -1.04; P < 0.001; I^2=0.00%) (Supplemental Figure S5), compare

Study/Country	Study design	Sample size (Intervention/ Control)	Gender Male/ female	Intervention		CoQ10 form	Mean age (years)	Duration	Population	Received industry funding
				CoQ10 intake, mg/day	Control					
Akbari Fakhrabadi *et al.* 2014[39]/Iran	Parallel	62(32/30)	QG: 10/22 PG: 6/24	200	placebo	Ubiquinone	QG: 56.7 ± 6.4 PG: 54.8 ± 6.7	12w	type 2 diabetes	no
Andersen *et al.* 1997[23]/ Danmark	Parallel	34(17/17)	QG: 10/7 PG: 9/8	100	placebo	Ubiquinone	QG: 33.5 ± 2.0 PG: 35.3 ± 2.4	12w	insulin dependent diabetes mellitus	yes
Bargossi *et al.* 1994[22]/ Italy	Parallel	30(15/15)	QG: 10/5 PG: 11/4	100	simvastatin	ubiquinone	QG: 53.7 ± 10.1 PG: 52.8 ± 10.8	3m	primary hypercholesterol	no
Chew *et al.* 2008 (I)[31]/ Australia	Parallel	36(16/20)	QG: 13/3 PG: 14/6	200	placebo	Ubiquinone	QG: 61.3 ± 4.1 PG: 62.4 ± 8.8	6m	type 2 diabetes	yes
Chew *et al.* 2008 (II)[31]/ Australia	Parallel	38(19/19)	QG: 13/6 PG: 13/6	200	fenofibrate	Ubiquinone	QG: 63.0 ± 9.4 PG: 64.8 ± 7.3	6m	type 2 diabetes	yes
Dai *et al.* 2011[35]/China	Parallel	56(28/28)	QG: 27/1 PG: 25/3	300	placebo	Ubiquinone	QG: 67.7 ± 9.4 PG: 70.1 ± 9.8	8w	ischemic left ventricular systolic dysfunction	yes
Eriksson *et al.* 1999[24]/ Finland	Parallel	23(12/11)	NA	100	placebo	Ubiquinone	QG: 65.0 ± 5.0 PG: 64.0 ± 7.0	6m	type 2 diabetes	yes
Fallah *et al.* 2018[51]/Iran	Parallel	60(30/30)	QG: 22/8 PG: 18/12	120	placebo	Ubiquinone	QG: 59.4 ± 12.2 PG: 64.8 ± 11.5	12w	diabetic hemodialysis	no
Farhangi *et al.* 2014[40]/ Iran	Parallel	41(20/21)	QG: 15/5 PG: 16/5	100	placebo	Ubiquinone	QG: 42.7 ± 10.8 PG: 42.2 ± 10.8	4w	Non-alcoholic fatty liver disease	no
Gholami *et al.* 2018[52]/ Iran	Parallel	68(34/34)	QG: 0/34 PG: 0/34	100	placebo	Ubiquinone	QG: 53.1 ± 6.2 PG: 53.3 ± 6.6	12w	type 2 diabetes	no
Gholami *et al.* 2019[58]/ Iran	Parallel	70(35/35)	QG: 0/35 PG: 0/35	100	placebo	Ubiquinone	QG: 53.0 ± 1.0 PG: 53.7 ± 1.1	12w	type 2 diabetes	no
Gholnari *et al.* 2018[53]/ Iran	Parallel	50(25/25)	QG: 8/17 PG: 8/17	100	placebo	Ubiquinone	QG: 61.1 ± 11.3 PG: 61.6 ± 10.0	12w	diabetic nephropathy	no
Hamilton *et al.* 2009[33]/ Australia	crossover	46(23/23)	NA	200	placebo	Ubiquinone	68.0 ± 6.0	12w	type 2 diabetes	yes
Henriksen *et al.* 1999[25]/ Danmark	Parallel	34(17/17)	QG: 10/7 PG: 9/8	100	placebo	Ubiquinone	QG: 35.5 ± 8.2 PG: 35.3 ± 10.0	3m	type 1 diabetes	yes
Hernandez-Ojeda *et al.* 2012[37]/Mexico	Parallel	49(24/25)	QG: 5/19 PG: 6/19	400	placebo	Ubiquinone	QG: 55.3 ± 8.4 PG: 57.0 ± 8.9	12w	diabetic polyneuropathy	yes
Ho *et al.* 2020[61]/China	Parallel	29(15/14)	QG: 8/7 PG: 12/2	300	placebo	Ubiquinone	QG: 19.9 ± 1.3 PG: 19.6 ± 1.3	12w	healthy	no
Hodgson *et al.* 2002 (I)[27]/Australia	Parallel	37(19/18)	QG: 14/5 PG: 14/4	200	Fenofibrate	Ubiquinone	QG: 51.7 ± 7.0 PG: 53.6 ± 10.2	12w	type 2 diabetes and dyslipidemia	no

Table 1 (Continued)

Study/Country	Study design	Sample size (Intervention/ Control)	Gender Male/ female	Intervention		CoQ10 form	Mean age (years)	Duration	Population	Received industry funding
				CoQ10 intake, mg/day	Control					
Hodgson *et al.* 2002 (II)[27]/Australia	Parallel	37(19/18)	QG: 17/2 PG: 13/5	200	placebo	Ubiquinone	QG: 52.3 ± 6.1 PG: 55.2 ± 9.8	12w	type 2 diabetes and dyslipidemia	no
Hosseinzadeh-Attar *et al.* 2015[44]/Iran	Parallel	64(31/33)	QG: 19/12 PG: 18/15	200	placebo	Ubiquinone	QG: 45.2 ± 7.6 PG: 47.1 ± 8.3	12w	type 2 diabetes	no
Ikematsu *et al.* 2006[29]/ Japan	Parallel	85(PG:20 QG1:21 QG2:22 QG3:22)	PG: 9/11 QG1: 11/10 QG2: 11/11 QG3: 22/0	QG1: 300 QG2: 600 QG3: 900	placebo	Ubiquinone	Male: 20.0～60.0 Female: 24.0～55.0	4w	healthy	yes
Izadi *et al.* 2019(I)[59]/Iran	Parallel	43(21/22)	QG: 0/21 PG: 0/22	200	vitamin E	Ubiquinone	QG: 27.2 ± 5.8 PG: 28.3 ± 5.5	8w	polycystic ovary syndrome	no
Izadi *et al.* 2019(II)[59]/ Iran	Parallel	43(22/21)	QG: 0/22 PG: 0/21	200	placebo	Ubiquinone	QG: 27.6 ± 5.2 PG: 26.0 ± 4.5	8w	polycystic ovary syndrome	no
Kolahdouz Mohammadi *et al.* 2013[38]/Iran	Parallel	64(31/33)	QG: 19/12 PG: 18/15	200	placebo	Ubiquinone	QG: 45.2 ± 7.6 PG: 47.2 ± 8.3	12w	type 2 diabetes	no
Kuhlman *et al.* 2019[60]/ Danmark	Parallel	35(18/17)	QG: 14/4 PG: 8/9	400	placebo	Ubiquinone	QG: 62.0 ± 1.0 PG: 64.0 ± 2.0	8w	patient in primary prevention with simvastatin ≥40 mg/d	yes
Lee *et al.* 2011[36]/Korea	Parallel	36(17/19)	QG: 11/15 PG: 10/15	200	placebo	Ubiquinone	QG: 42.7 ± 11.3 PG: 42.5 ± 11.2	12w	obesity	no
Lim *et al.* 2008[32]/Korea	Parallel	80(40/40)	QG: 17/23 PG: 22/18	200	placebo	Ubiquinone	QG: 54.0 ± 9.0 PG: 53.0 ± 9.0	12w	type 2 diabetes	yes
Majid Mohammadshahi *et al.* 2014[41]/Iran	Parallel	41(20/21)	NA	100	placebo	Ubiquinone	19.0～54.0	12w	non-alcoholic fatty liver disease	no
Mehrdadi *et al.* 2017[48]/ Iran	Parallel	56(26/30)	QG: 17/9 PG: 15/15	200	placebo	Ubiquinone	QG: 46.0 ± 7.0 PG: 48.0 ± 8.0	12w	type 2 diabetes	no
Moazen *et al.* 2015[45]/ Iran	Parallel	52(26/26)	QG: 16/10 PG: 12/14	100	placebo	Ubiquinone	QG: 50.7 ± 7.0 PG: 52.8 ± 7.7	8w	type 2 diabetes	yes
Mohammed-Jawad *et al.* 2014[42]/Iran	Parallel	38(19/19)	QG: 10/9 PG: 8/11	150	placebo	Ubiquinone	QG: 49.4 ± 6.6 PG: 51.6 ± 8.1	8w	type 2 diabetes	no
Mori *et al.* 2009(I)[34]/ Australia	Parallel	38(18/20)	QG: 17/1 PG: 12/8	200	omega-3 PUFA	Ubiquinone	QG: 56.9 ± 16.5 PG: 53.3 ± 14.3	8w	chronic kidney disease	yes
Mori *et al.* 2009(II)[34]/ Australia	Parallel	36(21/15)	QG: 17/4 PG: 8/7	200	placebo	Ubiquinone	QG: 55.4 ± 12.4 PG: 58.6 ± 10.1	8w	chronic kidney disease	yes

Table 1 *(Continued)*

Study/Country	Study design	Sample size (Intervention/ Control)	Gender Male/ female	Intervention		CoQ10 form	Mean age (years)	Duration	Population	Received industry funding
				CoQ10 intake, mg/day	Control					
Nuku *et al.* 2007[30]/ Japan	Parallel	46(23/23)	QG: 12/11 PG: 11/12	900	placebo	Ubiquinone	QG: 40.0 ± 13.0 PG: 38.0 ± 11.0	4w	healthy	no
Playford *et al.* 2003(I)[28]/ Australia	Parallel	40(20/20)	QG: 14/6 PG: 14/6	200	Fenofibrate	Ubiquinone	QG: 52.7 ± 8.0 PG: 53.5 ± 9.8	12w	type 2 diabetes and dyslipidemia	no
Playford *et al.* 2003 (II)[28]/Australia	Parallel	40(20/20)	QG: 18/2 PG: 15/5	200	placebo	Ubiquinone	QG: 52.7 ± 6.3 PG: 54.7 ± 9.4	12w	type 2 diabetes and dyslipidemia	no
Raygan *et al.* 2016[46]/ Iran	Parallel	60(30/30)	NA	100	placebo	Ubiquinone	QG: 65.9 ± 12.5 PG: 59.9 ± 13.1	8w	obesity, type 2 diabetes and coronary heart disease	no
Rodriguez-Carrizalez *et al.* 2016[47]/Mexico	Parallel	40(20/20)	QG: 11/9 PG: 9/11	400	Placebo	Ubiquinone	QG: 28.2 ± 3.7 PG: 29.3 ± 0.8	6 m	diabetic retinopathy	no
Samimi *et al.* 2017[49]/ Iran	Parallel	60(30/30)	QG: 0/30 PG: 0/30	100	placebo	Ubiquinone	QG: 24·5 ± 4·3 PG: 25·3 ± 5·7	12w	polycystic ovary syndrome	no
Singh and Niaz 1999[26]/ India	Parallel	47(25/22)	QG: 19/6 PG: 18/4	120	placebo	Ubiquinone	QG: 48.4 ± 0.5 PG: 47.6 ± 0.3	4w	acute myocardial infarction, unstable angina, angina pectoris	yes
Tóth *et al.* 2017[50]/ Slovakia	Parallel	70(35/35)	QG: 17/18 PG: 18/17	200	omega-3 PUFA	Ubiquinone	QG: 58.4 ± 13.8 PG: 62.0 ± 12.2	3m	dyslipidemia	no
Yen *et al.* 2018[54]/China	Parallel	47(24/23)	QG: 17/7 PG: 14/9	100	placebo	Ubiquinol	QG: 61.5 ± 10.2 PG: 59.6 ± 11.7	12w	type 2 diabetes	yes
Yoo and Yum 2018[55]/ Korea	Parallel	78(39/39)	QG: 29/10 PG: 28/11	200	placebo	Ubiquinone	QG: 49.8 ± 8.4 PG: 52.4 ± 6.9	8w	impaired glucose tolerance	yes
Zahedi *et al.* 2014[43]/Iran	Parallel	40(20/20)	QG: 11/9 PG: 8/12	150	placebo	Ubiquinone	QG: 53.5 ± 9.7 PG: 58.8 ± 9.6	12w	type 2 diabetes	no
Zarei *et al.* 2018[56]/Iran	Parallel	68(34/34)	QG: 0/34 PG: 0/34	100	placebo	Ubiquinone	QG: 53.1 ± 6.2 PG: 53.3 ± 6.6	12w	type 2 diabetes	no
Zhang *et al.* 2018[57]/ China	Parallel	101(51/50)	QG: 14/37 PG: 18/32	120	placebo	Ubiquinone	QG: 51.8 ± 8.9 PG: 50.0 ± 10.9	24w	dyslipidemia	no

***Table 1*: Study characteristics of the 40 trials included in the analysis.**
Abbreviations: CoQ10, coenzyme Q10; QG, CoQ10 group; PG, control group; m, month; w, week; PUFA, polyunsaturated fatty acid; NA, not applicable.

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CoQ10	Placebo	Absolute (95% CI)		
Fasting glucose (follow-up 4 to 24 weeks; Better indicated by lower values)											
38	randomised trials	no serious risk of bias	serious[a]	serious[b]	no serious imprecision	reporting bias[c]	1081	1076	MD 5.22 lower (8.33 lower to 2.11 lower)	ÅOOO VERY LOW	CRITICAL
Fasting insulin (follow-up 4 to 24 weeks; Better indicated by lower values)											
21	randomised trials	no serious risk of bias	serious[a]	serious[b]	no serious imprecision	none	619	615	MD 1.32 lower (2.06 lower to 0.58 lower)	ÅÅOO LOW	CRITICAL
HbA_{1c} (follow-up 4 to 24 weeks; Better indicated by lower values)											
28	randomised trials	no serious risk of bias	no serious inconsistency	serious[b]	no serious imprecision	none	752	753	MD 0.12 lower (0.23 lower to 0.01 lower)	ÅÅÅO MODERATE	CRITICAL
Homeostasis model assessment of insulin resistance (follow-up 4 to 24 weeks; Better indicated by lower values)											
16	randomised trials	no serious risk of bias	serious[a]	serious[b]	no serious imprecision	reporting bias[c]	496	492	MD 0.69 lower (1 lower to 0.38 lower)	ÅOOO VERY LOW	CRITICAL

***Table 2*: GRADE Evidence Profile for effect of CoQ10 supplementation on glycemic control.**

[a] Significant heterogeneity in meta-analysis (I^2 >50%).

[b] Surrogate outcome measure, not patient-important endpoint.

[c] *P*-value of Egger's tests <0.05.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Abbreviations: CoQ10, coenzyme Q10; CI, confidence interval.

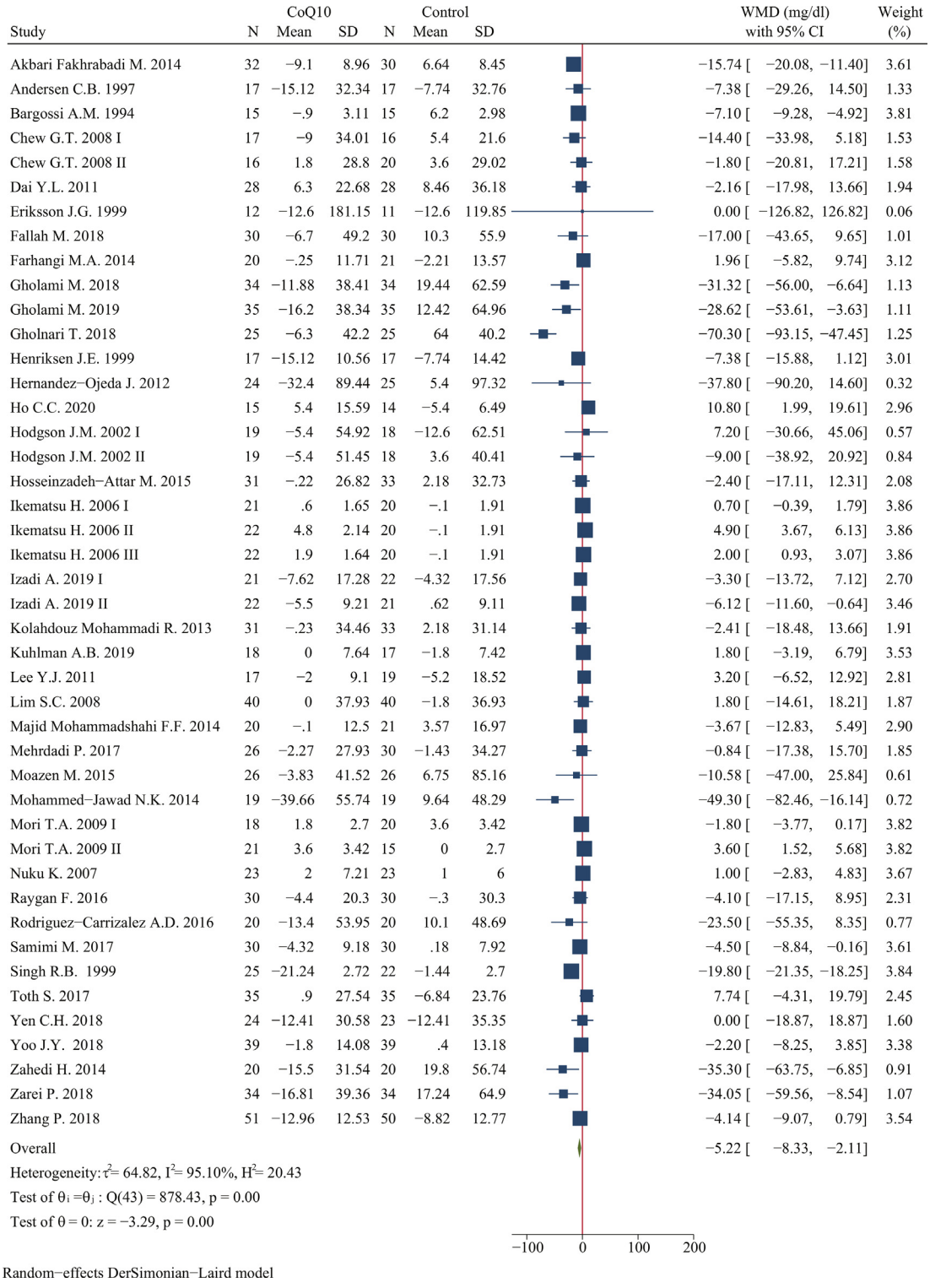

Figure 2. Forest plots of effect of coenzyme Q10 supplementation on fasting glucose. The green diamond at the bottom of each chart is the amount of overall effect size estimates in the random effects meta-analysis. The size of each blue box reflects the relative weight apportioned to the study in the meta-analysis; The horizontal line across each blue box reflects the 95% confidence intervals of the study. Abbreviations: CoQ10, coenzyme Q10; WMD, weighted mean difference; CI, confidence interval; SD, standard error.

Group	No. of trials (participates)	WMD (95% CI) , mg/dl	$P_{difference}$ [a]	I^2, %	$P_{heterogeneity}$ [b]	P [c] for between subgroup heterogeneity
Overall	44 (2157)	−5.22 (−8.33, −2.11)	<0.001	95.10	<0.001	
Study design						
Parallel	44 (2157)	−5.22 (−8.33, −2.11)	<0.001	95.10	<0.001	
Duration (weeks)						
<12	16 (738)	−2.41 (−6.87, 2.06)	0.29	97.93	<0.001	0.09
≥12	28 (1419)	−7.59 (−11.66, −3.52)	<0.001	71.78	<0.001	
CoQ10 dosage						
<200 mg/day	20 (1026)	−13.21 (−18.43, −7.98)	<0.001	89.99	<0.001	<0.001
≥200 mg/day and <300 mg/day	15 (751)	−0.71 (−3.42, 1.99)	0.61	44.31	0.03	
≥300 mg/day	9 (380)	2.37 (0.38, 4.36)	0.02	77.02	<0.001	
Control group						
Placebo	39 (1940)	−6.02 (−9.56, −2.47)	<0.001	75.39	<0.001	0.30
Other	5 (217)	−2.97 (−7.32, 1.38)	0.18	95.52	<0.001	
Risk of bias						
High	14 (544)	−1.18 (−4.44, 2.08)	0.47	88.55	<0.001	0.05
Low	29 (1613)	−6.70 (−11.28, −2.13)	<0.001	94.30	<0.001	
Received industry funding?						
Yes	18 (803)	−2.70 (−7.46, 2.06)	0.27	97.63	<0.001	0.19
No	26 (1354)	−6.84 (−10.70, −2.98)	<0.001	78.62	<0.001	

***Table 3*: Subgroup analysis of included randomized controlled trials for the effect of CoQ10 supplementation on fasting glucose.**

[a] Dersimonian-Laird random effect model was used to calculate the effect size and *P*-value.

[b] Cochrane Q test was used to detect the heterogeneity between studies.

[c] Cochrane Q test was used to detect the subgroup heterogeneity.

Abbreviations: WMD, weighted mean difference; CI, confidence interval; CoQ10, coenzyme Q10.

with dyslipidemia (WMD: -0.42; 95% CI: -0.94, 0.10; $P = 0.11$).

In the dose−response assessment of the effect of CoQ10 intake on glycemic control, we used a 1-stage restricted cubic spline regression model (Figure 6). Figure 6 shows a "U" shape dose-response curve of CoQ10 dosage and outcome indicators of glycemic control respectively in included studies. Considering the dosage subgroup analysis and dose-response curve, CoQ10 dose of 100-200 mg/day has better efficacy in improving fasting glucose (χ^2 = 12.08, $P_{nonlinearity}$ =0.002), fasting insulin (χ^2 = 9.73, $P_{nonlinearity}$ =0.008), HbA_{1c} (χ^2 = 6.00, $P_{nonlinearity}$ =0.049), and HOMA-IR (χ^2 = 25.89, $P_{nonlinearity}$ <0.001).

The pooled effect size was robust and remained significant in the leave-one-out sensitivity analysis. For fasting insulin and HbA_{1c}, visual inspection of funnel plot did not suggest a significant potential publication bias. This observation was confirmed by the results of Egger's linear regression. For fasting glucose and HOMA-IR, funnel plot and Egger's linear regression suggested a significant potential publication bias (Supplemental Figure S6). After adjustment of effect size for potential publication bias using the 'trim and fill' correction, it yielded similar results to the overall pooled effect size estimates.

Discussion

This study was a meta-analysis that regarded the effects of CoQ10 in the improvement of glycemic control. We synthesized the results from 40 RCTs involving 2427 participants to draw an overall conclusion. The major findings of meta-analysis showed that CoQ10 supplementation statistically reduced fasting glucose, fasting insulin, HbA_{1c}, and HOMA-IR. This means that CoQ10 supplementation might have beneficial effects in glycemic control. In addition, our results also show a "U" shape dose-response curve of CoQ10 dosage and outcome indicators of glycemic control, thus indicating that 100-200mg / day of CoQ10 has better efficacy on attenuating the level of fasting blood glucose, fasting insulin, HbA_{1c} and HOMA-IR.

This meta-analysis showed that CoQ10 supplementation could significantly reduce the level of fasting glucose, HbA_{1c}, fasting insulin, HOMA-IR by an average of 5.22 mg/dl (95%CI: -8.33, -2.11 mg/dl), -0.12% (95%CI: -0.23, -0.01%), -1.32 μIU/ml (95%CI: -2.06, -0.58 μIU/ml), -0.69 (95%CI: -1.00, -0.38), respectively. The results of prior meta-analysis on glycemic control were controversial. Part of the meta-analysis conducted in patients with diabetes revealed that CoQ10 could significantly decrease fasting glucose level (-11.21 mg/dl) and HbA_{1c} (-0.29%),[10] while some reported the opposite

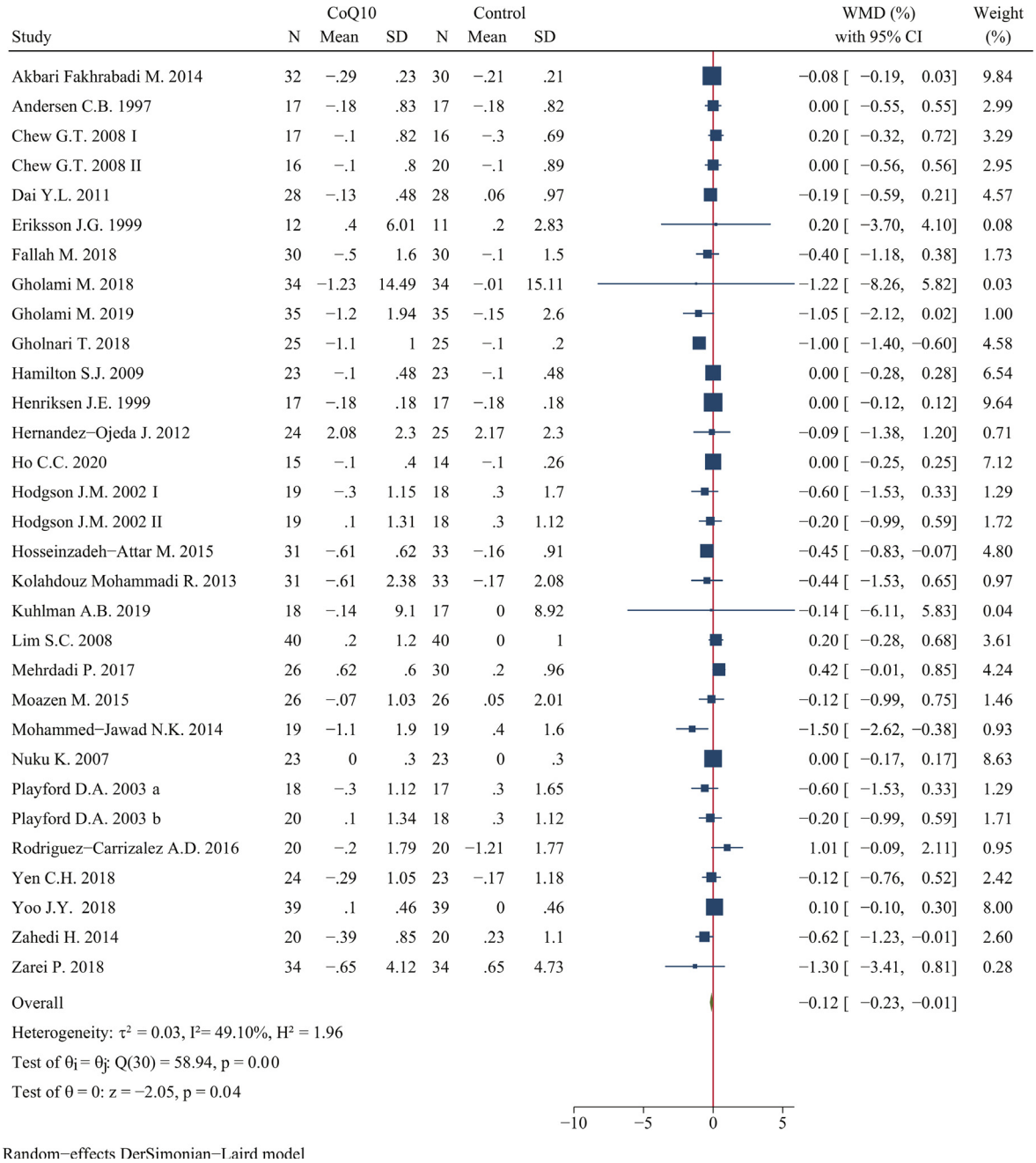

Figure 3. Forest plots of effect of coenzyme Q10 supplementation on HbA_{1c}. The green diamond at the bottom of each chart is the amount of overall effect size estimates in the random effects meta-analysis. The size of each blue box reflects the relative weight apportioned to the study in the meta-analysis; The horizontal line across each blue box reflects the 95% confidence intervals of the study. Abbreviations: CoQ10, coenzyme Q10; WMD, weighted mean difference; CI, confidence interval; SD, standard error.

results (standard mean difference of fasting glucose: 0.17, HbA_{1c}: 0.3, fasting insulin: 0.09 μIU/ml).[10,62,63] The difference between our meta-analyses and the latter one is the fact that the publication for included studies[62] only limited from 2015 to 2018. In our meta-analysis, we synthesized all the available studies concerning on the glycemic control in hyperglycemia-related diseases ranging from 1997 to 2021. Notably, our review contained 28 additional studies for these outcomes that were published since that prior reviews.[10,62]

Group	No. of trials (participates)	WMD (95% CI) , %	$P_{difference}$ [a]	I^2, %	$P_{heterogeneity}$ [b]	P^c for between subgroup heterogeneity
Overall	31 (1505)	−0.12(−0.23, −0.01)	0.04	49.10	<0.001	
Study design						
Parallel	30 (1459)	−0.13(−0.25, −0.01)	0.04	50.64	<0.001	0.40
Crossover	1 (46)	0.00(−0.28, 0.28)	1.00	-	-	
Duration (week)						
<12	6 (305)	−0.06(−0.28, 0.16)	0.59	43.10	0.12	0.56
≥12	25 (1200)	−0.14(−0.27, 0.00)	0.05	51.10	<0.001	
CoQ10 dosage						
<200 mg/day	12 (584)	−0.47(−0.83, −0.12)	<0.001	69.17	0.00	0.05
≥200 mg/day and <300 mg/day	13 (666)	−0.03(−0.15, 0.10)	0.70	27.85	0.16	
≥300 mg/day	6 (255)	−0.01(−0.14, 0.12)	0.92	0.00	0.54	
Control group						
Placebo	29 (1434)	−0.12 (−0.23, 0.00)	0.05	51.39	<0.001	0.82
Other	2 (71)	−0.18 (−0.72, 0.36)	0.52	14.87	0.29	
Quality of study						
High	11 (397)	−0.18 (−0.41, 0.04)	0.12	23.84	0.22	0.53
Low	20 (1108)	−0.10 (−0.23, 0.03)	0.15	57.92	<0.001	
Received industry funding?						
Yes	13 (603)	0.02(−0.07, 0.11)	0.69	0.00	0.99	<0.001
No	18 (902)	−0.28(−0.48, −0.08)	<0.001	66.30	<0.001	

***Table 4*: Subgroup analysis of included randomized controlled trials for the effect of CoQ10 supplementation on HbA1c.**
Abbreviations: WMD, weighted mean difference; CI, confidence interval; CoQ10, coenzyme Q10.
[a] Dersimonian−Laird random effect model was used to calculate the effect size and *P*-value.
[b] Cochrane Q test was used to detect the heterogeneity between studies.
[c] Cochrane Q test was used to detect the subgroup heterogeneity.

Given the moderate level of evidence certainty for HbA_{1c} findings, one of the strongest beneficial effects of CoQ10 supplementation might be a reduction in HbA_{1c}.

Because of the significant heterogeneity, subgroup analysis was performed, indicating that longer intervention duration (>12 weeks), placebo as control group, low risk of bias, and not receiving industry funding were potential modifying factors in terms of treatment efficacy in glycemic control. Contrary to previous meta-analysis,[63] we found that longer intervention duration can be beneficial in the reduction of the blood glucose level, because our review contained additional studies with longer duration that were published since that prior reviews. What's more, some animal experiments[64,65] found that chronic ingestion of CoQ10 has been shown to increase the concentration of CoQ10 in plasma in rodent models. In addition, a study[66] found that the average blood CoQ10 concentration increased by times after 90mg CoQ10 supplementation for 3 and 9 months in healthy subjects. Therefore, long-term intervention can significantly increase the concentration of plasma CoQ10, so as to improve glycemic control.

In contrast to the prior meta-analysis,[10,62] our meta-analysis concerned on the glycemic control in difference diseases, which might be a potential modifying factor of heterogeneity. Thus, we created a subgroup analyses, revealing greater effects of CoQ10 for diabetes patients, but not for other diseases such as CVD, obesity and dyslipidemia. We also found a larger effect size in diabetes patients than did that prior review[10] (-13.12 mg/dl vs. -11.21 mg/dl), because our review further contained 14 additional studies. The main reason might be that the mean fasting baseline blood glucose level in diabetes was higher than 6.1mmol/l (109.8 mg/dl), which is considered as the upper threshold for "normal" blood glucose level, thus suggesting CoQ10 as a potent compound for blood glucose reduction. Glucose metabolism disorder also plays an important role in CVD. In our meta-analysis, only three literatures[26,35,46] had reported partial glucose outcomes in patients with CVD, which could not be analyzed. Among these literatures, CoQ10 supplementation decreased fasting glucose,[26,46] fasting insulin,[46] HbA_{1c},[35] and HOMA-IR.[46] Thus, further studies investigations in CVD are still required to evaluate effects of CoQ10 on glycemic control.

We synthesized data from included studies, finding that the dosage of CoQ10 reported in these studies was used in both higher and lower doses, ranging from 100 mg to 900 mg. Thus, we further analyzed the relationship between dosage of CoQ10 and glycemic control outcomes in order to explore the optimal intake of

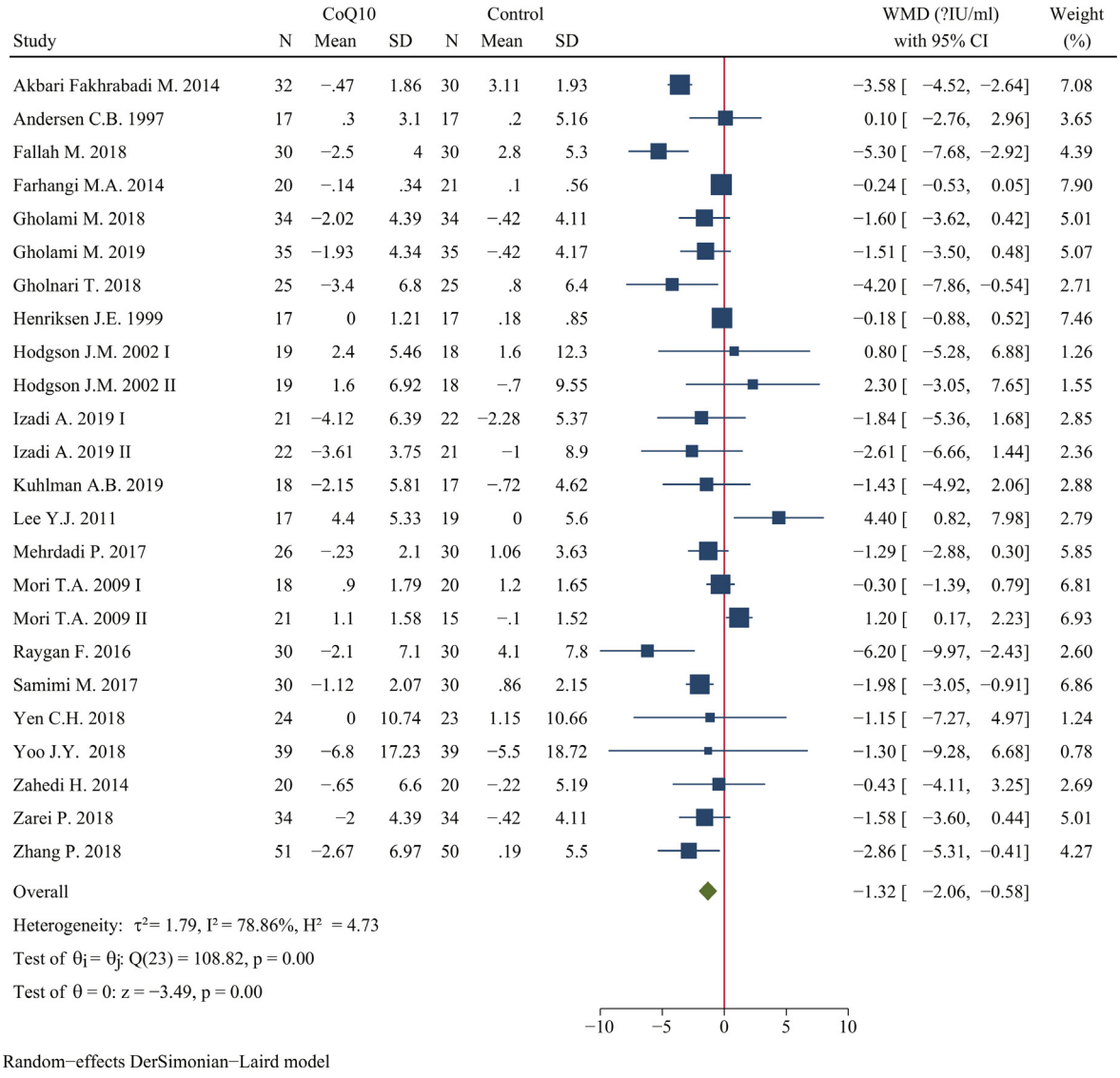

Figure 4. Forest plots of effect of coenzyme Q10 supplementation on fasting insulin. The green diamond at the bottom of each chart is the amount of overall effect size estimates in the random effects meta-analysis. The size of each blue box reflects the relative weight apportioned to the study in the meta-analysis; The horizontal line across each blue box reflects the 95% confidence intervals of the study. Abbreviations: CoQ10, coenzyme Q10; WMD, weighted mean difference; CI, confidence interval; SD, standard error.

CoQ10. Through the dosage subgroup analysis of glycemic control, we found that the low-dose group (100 to 200 mg/day) can significantly improve glycemic control, while the medium (200 to 300 mg/day) and high-dose groups (>300 mg/day) have no significant statistical difference. This result was consistent with the results reported in previous meta-analysis.[63] However, prior meta-analysis reached this conclusion only through subgroup analysis, and could not find the optimal dose of CoQ10 intervention. Thus, in order to explore the optimal intake dose of CoQ10, we further analyzed the dose-response relationship according to the data in the included studies. We newly used a 1-stage restricted cubic spline regression model to matching the data. We found that 100-200 mg/day was sufficient to beneficially improve glycemic control including fasting glucose, fasting insulin, HbA_{1c} and HOMA-IR, which could be conducive to set up nutrition guidelines of daily recommendation in patients with hyperglycemia-related diseases. Reasons for the disappearance of glycemic control effect of high dose CoQ10 might be related to the decrease of intestinal absorption and utilization.[67] CoQ10 was a lipid-soluble substance with a complex active transport process absorption in the

Group	No. of trials (participates)	WMD (95% CI) , μIU/ml	$P_{difference}$ [a]	I^2, %	$P_{heterogeneity}$ [b]	P [c] for between subgroup heterogeneity
Overall	24 (1234)	−1.32(−2.06, −0.58)	<0.001	78.86	<0.001	
Study design						
Parallel	24 (1234)	−1.32(−2.06, −0.58)	<0.001	78.86	<0.001	
Duration (week)						
<12	8 (374)	−0.59(−1.59, 0.42)	0.26	64.37	<0.001	0.20
≥12	16 (860)	−1.51(−2.52, −0.50)	<0.001	75.24	<0.001	
CoQ10 dosage						
<200 mg/day	13 (733)	−1.71(−2.57, −0.85)	<0.001	74.31	<0.001	0.41
≥200 mg/day and <300 mg/day	10 (466)	−0.43(−2.12, 1.27)	0.62	84.82	<0.001	
≥300 mg/day	1 (35)	−1.43(−4.92, 2.06)	0.42	-	-	
Control group						
Placebo	22 (1153)	−1.39 (−2.20, −0.57)	<0.001	0.00	0.41	0.16
Other	2 (81)	−0.44 (−1.48, 0.61)	0.41	80.57	<0.001	
Quality of study						
High	4 (148)	0.32 (−1.65, 2.29)	0.76	0.00	0.87	0.09
Low	20 (1086)	−1.50 (−2.29, −0.71)	<0.001	82.28	<0.001	
Received industry funding?						
Yes	7 (302)	0.10(−0.46, 0.66)	0.72	7.87	0.37	<0.001
No	17 (932)	−1.84(−2.89, −0.80)	<0.001	82.84	<0.001	

***Table 5*: Subgroup analysis of included randomized controlled trials for the effect of CoQ10 supplementation on fasting insulin.**
Abbreviations: WMD, weighted mean difference; CI, confidence interval; CoQ10, coenzyme Q10.
[a] Dersimonian−Laird random effect model was used to calculate the effect size and *P*-value.
[b] Cochrane Q test was used to detect the heterogeneity between studies.
[c] Cochrane Q test was used to detect the subgroup heterogeneity.

gastrointestinal tract. Some studies found a non-linear or zero-order absorption process, suggesting that CoQ10 plasma concentration decreases as dosage is increased.[68]

Potential antihyperglycemic mechanisms of CoQ10 action might plausibly include antioxidant and anti-inflammatory effects of CoQ10 that promote improved insulin sensitivity. Tarry-Adkins et.al demonstrated that CoQ10 could prevented the programmed reduction in insulin receptor substrate-1 and p110-β and the programmed increased in IL-6.[69] In addition, supplementation of CoQ10 could increase the activity of tyrosine kinase, phosphatidylinositol kinase, and adiponectin receptors in diabetes mice, and decrease the activity of insulin receptor isoforms and glucose transporters.[70] In vitro studies showed that CoQ10 could improve the apoptosis of mouse pancreatic beta cells line MIN6 induced by staurosporine, improving the mitochondrial stress of pancreatic beta cells.[71]

CoQ10 widely exists in various natural foods, but the content of different kinds of foods varies greatly. The main food intake comes from meat, and a small amount comes from grains, fruits and vegetables. While our study only investigated effects of supplemental CoQ10 on outcomes, it is possible that regular high dietary intakes of CoQ10 could yield similar outcomes. However, there is a serious lack of survey data on CoQ10 dietary intake assessment. In a study published in the 1990s,[72] based on the food consumption data of the Danish dietary survey and the detection data of CoQ10 content in specific foods, it was estimated that the average dietary intake of CoQ10 was 3-5 mg/day, which was far less than the results of this review. However, since it had been published for a long time, it is necessary to further update the content of CoQ10 in daily diet, which is our next work to calculate the intake of CoQ10 in daily diet according to the data of some databases.

Our findings, which are based largely on short-term studies with low evidence quality, suggested that CoQ10 supplementation may be potentially effective for improving glycemic control. Compared with previous meta-analyses,[10,62] the strength of the present study was that we comprehensively analyzed the glycemic control effect of CoQ10 in different hyperglycemia-related diseases. As a result, we concluded that CoQ10 could significantly improve the glycemic control level of diabetic patients with minor heterogeneity. Furthermore, we newly used a 1-stage restricted cubic spline regression model to analyze the dose-response relationship between CoQ10 dose and glycemic control, so as to achieve the greatest benefit for glycemic control.

However, a limitation of this review was the absence of exploratory subgroup and meta regression analysis of outcomes based on plasma CoQ10 status as most

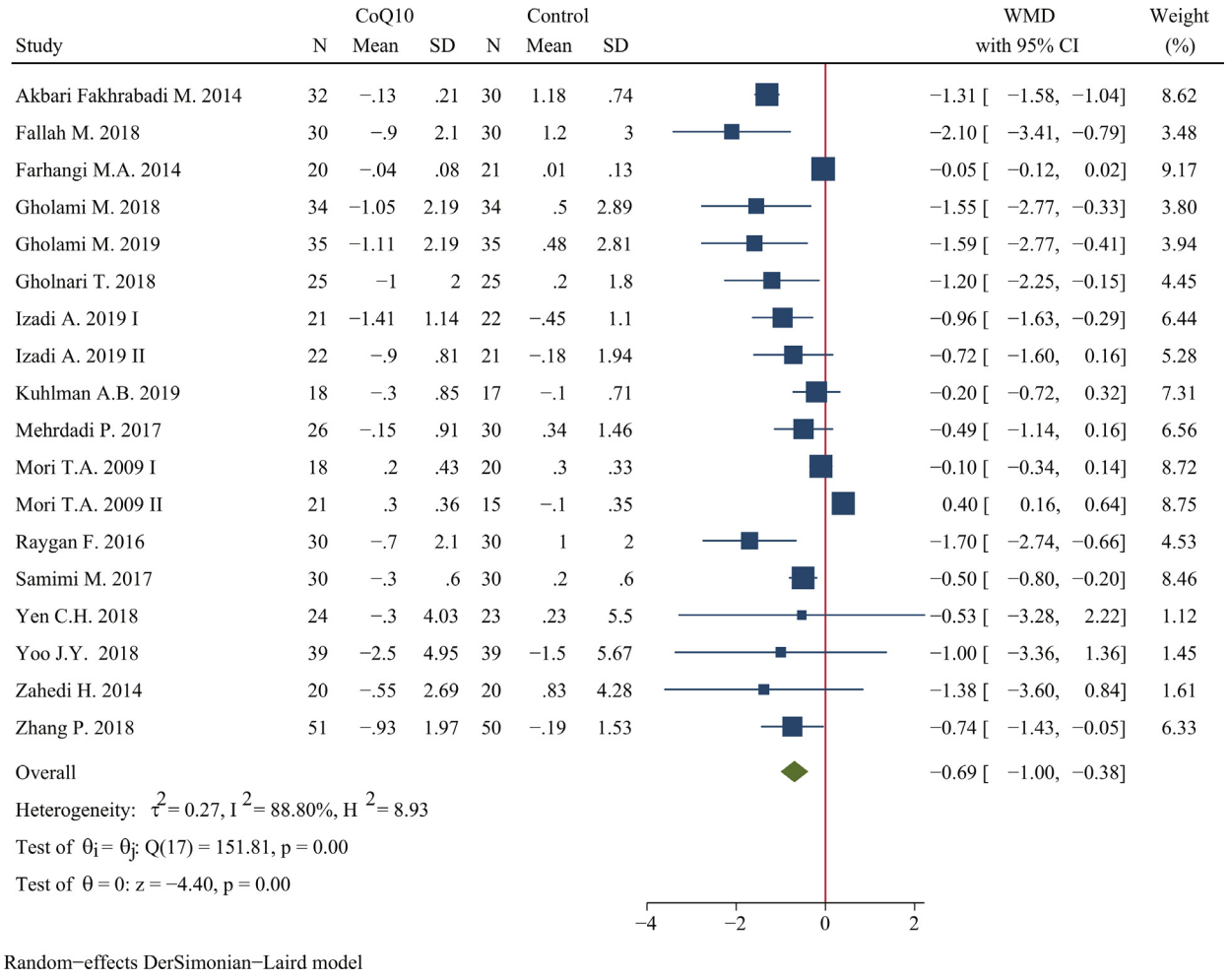

Figure 5. Forest plots of effect of coenzyme Q10 supplementation on HOMA-IR. The green diamond at the bottom of each chart is the amount of overall effect size estimates in the random effects meta-analysis. The size of each blue box reflects the relative weight apportioned to the study in the meta-analysis; The horizontal line across each blue box reflects the 95% confidence intervals of the study. Abbreviations: CoQ10, coenzyme Q10; WMD, weighted mean difference; CI, confidence interval; SD, standard error.

Group	No. of trials (participates)	WMD (95% CI)	$P_{difference}$ [a]	I^2, %	$P_{heterogeneity}$ [b]	P [c] for between subgroup heterogeneity
Overall	18 (988)	−0.69(−1.00, −0.38)	<0.001	88.80	<0.001	
Study design						
Parallel	18 (988)	−0.69(−1.00, −0.38)	<0.001	88.80	<0.001	
Duration (week)						
<12	8 (374)	−0.24(−0.52, 0.05)	0.11	79.45	0.00	<0.001
≥12	10 (614)	−1.03(−1.40, −0.65)	<0.001	61.13	0.01	
CoQ10 dosage						
<200 mg/day	10 (597)	−0.97(−1.44, −0.50)	<0.001	80.99	<0.001	0.10
≥200 mg/day and <300 mg/day	7 (356)	−0.54(−1.17, 0.10)	0.10	93.79	<0.001	
≥300 mg/day	1 (35)	−0.20(−0.72, 0.32)	0.45	-	-	
Control group						
Placebo	16 (907)	−0.76 (−1.13, −0.39)	<0.001	89.72	<0.001	0.53
Other	2 (81)	−0.47 (−1.31, 0.36)	0.27	82.16	0.02	
Quality of study						
High	1 (40)	−1.38 (−3.60, 0.84)	0.22	-	-	0.54
Low	17 (948)	−0.68 (−1.00, −0.37)	<0.001	89.38	<0.001	
Received industry funding?						
Yes	5 (234)	0.03(−0.33, 0.40)	0.86	63.99	0.03	<0.001
No	13 (754)	−0.99(−1.42, −0.55)	<0.001	90.72	<0.001	

***Table 6*: Subgroup analysis of included randomized controlled trials for the effect of CoQ10 supplementation on HOMA-IR.**
Abbreviations: WMD, weighted mean difference; CI, confidence interval; CoQ10, coenzyme Q10.
[a] Dersimonian−Laird random effect model was used to calculate the effect size and *P*-value.
[b] Cochrane Q test was used to detect the heterogeneity between studies.
[c] Cochrane Q test was used to detect the subgroup heterogeneity.

studies in the review did not measure participants' CoQ10 concentrations. Therefore, it remains unclear whether baseline CoQ10 status might affect the outcomes explored in our review. Because of heterogeneity between studies, indirectness of outcomes, and publication bias, evidence certainty is mostly low across these measures. A limitation of studies included was that they were predominantly short term (<6 months) with a relatively small participant number ($n < 50$). Further investigations using larger sample sizes and longer supplementation durations are required to confirm these potential glycemic control benefits.

Studies have shown that different molecular might have an impact on the bioavailability of CoQ10. At present, it is still controversial whether there is a difference in bioavailability between ubiquinone and ubiquinol. Some found that there is no significant difference in bioavailability between ubiquinone and ubiquinol in healthy elderly people. These two molecules mainly existed in the form of ubiquinol in blood.[73] Others suggested that ubiquinol was superior to ubiquinone to enhance CoQ10 status in older men.[74] Besides, the formulation of CoQ10 supplements can also affect the bioavailability to some extent.[75] The matrix used to dissolve CoQ10 could affect the bioavailability of CoQ10, such as nanoemulsions, cyclodextrin complexes.[76,77] In our meta-analysis, we previously considered subgroup analysis of CoQ10 in different molecular forms, but we found that only one study[54] used ubiquinol for glycemic control, and the rest used ubiquinone. Therefore, it is hard to conduct subgroup analysis to compare the effect between these two forms of CoQ10 on glycemic control. Based on this, our group decided to carry out a randomized controlled trial of ubiquinol intervention in the future to further explore the biological effects of ubiquinone and ubiquinol.

Our results found that CoQ10 supplementation might have beneficial effects on glycemic control, especially in diabetic patients. Taking 100-200 mg/day of CoQ10 could achieve the greatest benefit for glycemic control. These findings add new information about the beneficial effects of CoQ10 supplementation on glycemic control, and are conducive to setting up nutrition guidelines for recommended daily intake of CoQ10 in patients with glycemic disorders.

Contributors

YY designed research; YL, DZ, QJ, and ML extracted the data independently; ZT resolved any discrepancies; SD, SH, and ZL reviewed data; YL and DZ performed statistical analysis; YL wrote the manuscript; YY, YM, ZT and DZ contributed to the discussion and reviewed the manuscript; YY had primary responsibility for final content. All authors read and approved the final manuscript.

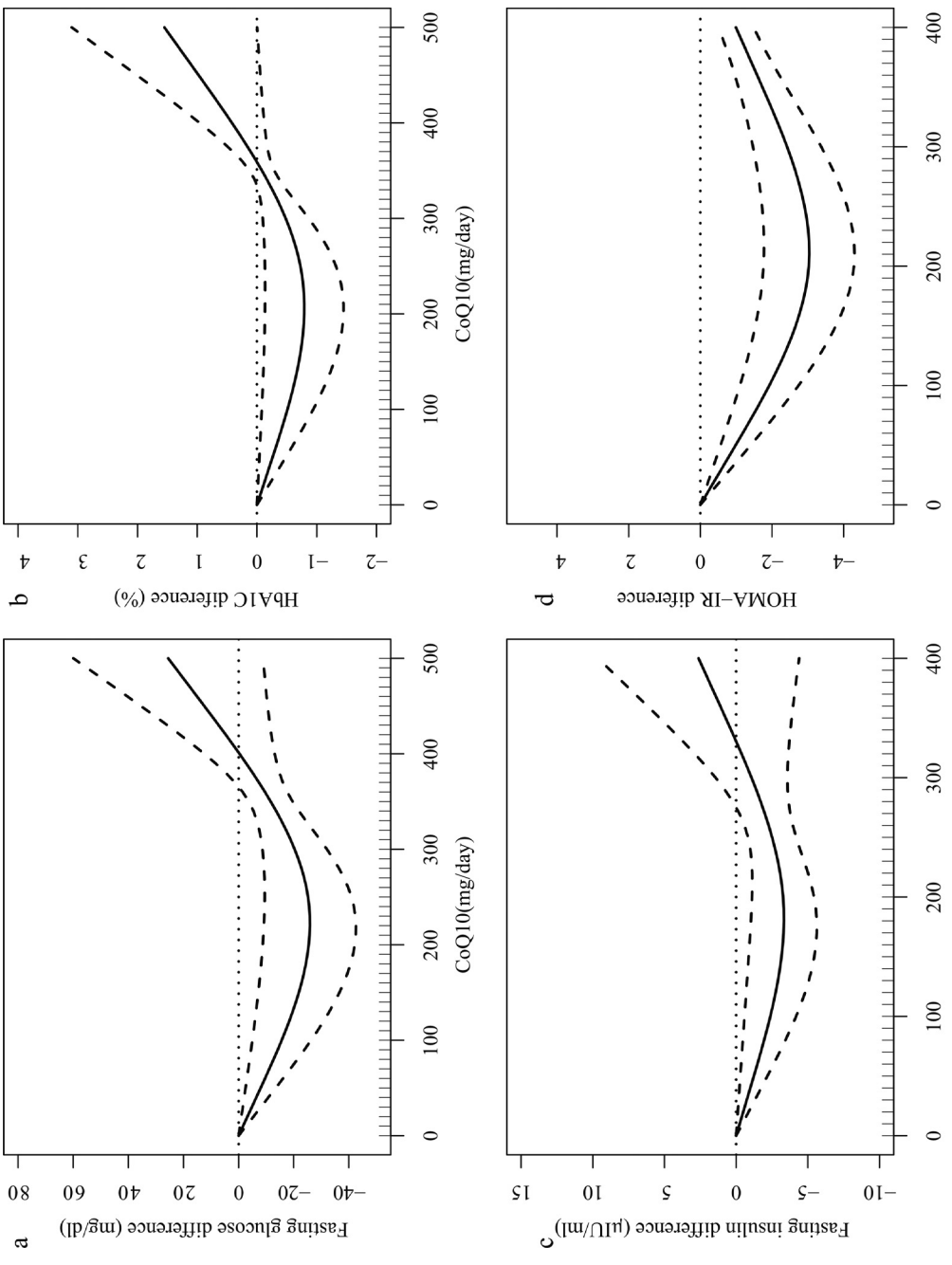

Figure 6. Dose–response meta-analysis of changes in glycemic control according to CoQ10 in the treatment and control groups at the end of the trials. (a) fasting glucose, (b) HbA_{1c}, (c) fasting insulin, (d) HOMA-IR. The average curve (solid line) with 95% confidence limits (dotted lines) was estimated with a 1-stage random-effects restricted cubic spline model, using 0 mg/day as referent. Abbreviations: CoQ10, coenzyme Q10.

Data sharing statement

Corresponding authors have accessed and verified the data, and were responsible for the decision to submit the manuscript. All data, study protocol, and statistical analysis plan will be made available upon reasonable request via email to corresponding author.

Declaration of interests

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101602.

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