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Meta-analysis

The effects of coenzyme Q10 supplementation on biomarkers of exercise-induced muscle damage, physical performance, and oxidative stress: A GRADE-assessed systematic review and dose-response meta-analysis of randomized controlled trials

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SUMMARY

Purpose: This study aims to elucidate the dose-dependent effect of coenzyme Q10 supplementation (CoQ10) on exercise-induced muscle damage (EIMD), physical performance, and oxidative stress in adults.

Methods: A systematic search was conducted through PubMed, Scopus, and ISI Web of Science databases up to August 2023, focusing on randomized control trials (RCTs) that investigated the effects of CoQ10 supplementation on EIMD recovery, physical performance and oxidative stress mitigation in adults. The weighted mean difference (WMD) and 95 % confidence interval (95 %CI) were estimated using the random-effects model.

Results: The meta-analysis incorporated 28 RCTs, encompassing 830 subjects. CoQ10 supplementation significantly decreased creatine kinase (CK) (WMD: −50.64 IU/L; 95 %CI: −74.75, −26.53, P < 0.001), lactate dehydrogenase (LDH) (WMD: −52.10 IU/L; 95 %CI: −74.01, −30.19, P < 0.001), myoglobin (Mb) (WMD: −21.77 ng/ml; 95 %CI: −32.59, −10.94, P < 0.001), and Malondialdehyde (MDA) (WMD: −0.73 μmol/l; 95 %CI: −1.26, −0.20, P = 0.007) levels. No significant alteration in total antioxidant capacity was observed post-CoQ10 treatment. Each 100 mg/day increase in CoQ10 supplementation was correlated with a significant reduction in CK (MD: −23.07 IU/L, 95 %CI: −34.27, −11.86), LDH (WMD: −27.21 IU/L, 95 %CI: −28.23, −14.32), Mb (MD: −7.09 ng/ml; 95 %CI: −11.35, −2.83) and MDA (WMD: −0.17 μmol/l, 95 %CI: −0.29, −0.05) serum levels. Using SMD analysis, "very large" effects on LDH and "moderate" effects on CK and MDA were noted, albeit nonsignificant for other outcomes.

Conclusion: CoQ10 supplementation may be effective in reducing biomarkers of EIMD and oxidative stress in adults. Nevertheless, given the preponderance of studies conducted in Asia, the generalizability of these findings warrants caution. Further RCTs, particularly in non-Asian populations with large sample sizes and extended supplementation durations, are essential to substantiate these observations.

1. Introduction

Skeletal muscle function is notably compromised by exercise-induced muscle damage (EIMD), necessitating prioritized research in identifying efficacious recovery agents [1]. This is

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particularly relevant given the deleterious effects of oxidative stress on muscle tissues, where an imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract their harmful effects through antioxidants can lead to muscle fatigue and damage. Amidst variables influencing peak athletic performance, the role of nutritional supplements has garnered substantial attention, being ubiquitously used by athletes across all levels [2]. These supplements, encompassing complementary foods, food components, or nutrients, are intended to augment the regular diet, thereby fostering optimal performance via enhancements in endurance capacity, modulation of mood, alleviation of musculoskeletal discomfort, and expedited recovery [3,4].

A prominent supplement, coenzyme Q10 (CoQ10), has garnered attention in research for its antioxidant and anti-fatigue properties. CoQ10, an endogenous, lipophilic, vitamin-like molecule, is integral to the mitochondrial respiratory chain, functioning as an electron carrier [5–7]. Post dietary absorption, CoQ10's oxidized form, ubiquinone, is reduced to ubiquinol, thereby manifesting potent antioxidant capabilities. This conversion enables ubiquinol to safeguard phospholipids, mitochondrial membrane proteins, and deoxyribonucleic acid (DNA) from peroxidative damage, effectively scavenging ROS and synergizing with vitamin E [8–11].

Diverse studies have evaluated CoQ10's supplementation effects on EIMD and physical performance [12–18]. While most studies indicate that CoQ10 supplementation mitigates EIMD and enhances physical performance [14,17,18], others report inconsistent outcomes [12,16,19]. Consequently, the definitive efficacy of CoQ10 supplementation in adults remains unclear. This systematic review and dose-response meta-analysis were thus undertaken to resolve these inconsistencies by examining all published randomized clinical trials (RCTs) that assess the effects of varying CoQ10 doses on EIMD biomarkers, physical performance, and oxidative stress in adult individuals.

2. Methods

The methodology employed in this research adhered to the protocols outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [20] and utilized the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [21]. This study was registered in the PROSPERO database with the registration code CRD42022383583.

2.1. Search strategy

A systematic search was conducted in several databases, including PubMed, Scopus, and ISI Web of Science, until the cut-off date of August 2, 2023. This search was facilitated by the use of suitable keywords, as detailed in Table S1. To ensure rigor in the selection process, two investigators (ST and MR) separately screened titles, abstracts, and subsequently full texts.

Any arising discrepancies in the screening process were resolved through consultation with a third investigator (HM). Additionally, the search included an examination of reference lists from pertinen reviews on the effects of CoQ10 on biomarkers of EIMD, physical performance, and inflammation. The detailed search strategy employed to identify RCTs for inclusion in this dose-dependent meta-analysis is displayed in Table S1. There were no restrictions based on the language or the publication date of the studies.

2.2. Selection criteria

We regarded controlled trials as eligible if they met all the outlined criteria: 1) RCTs with a cross-over or parallel design, performed in healthy subjects aged 18 years and older; 2) trials that used the specified amount of CoQ10 in the treatment group; 3) trials that explored the impact of CoQ10 supplement in comparison with placebo or other appropriate control groups on our outcomes of interest [creatine kinase (CK), myoglobin (Mb), mean power, total antioxidant capacity (TAC), lactate dehydrogenase (LDH), and malondialdehyde (MDA)]; and 4) published papers that revealed the means and standard deviations (SDs) of changes for the mentioned outcomes in either the treatment or control groups, or provided sufficient data to compute those values. If more than one published trial existed for one dataset, the one with the most complete set was chosen for inclusion (Table S2).

Trials were excluded when they: 1) had a multivariate design in such a manner that the effect of CoQ10 could not be separated; 2) assessed the effect of CoQ10 supplementation combined with other substances; 3) did not possess an appropriate control group; 4) lacked sufficient information to compute the effect sizes of CoQ10; and 5) recruited children, adolescents, and childbearing or lactating women. The main reason for excluding children, adolescents, and childbearing or lactating women was the lack of established data on the safety and efficacy of CoQ10 supplementation in these groups [22]. Also, there are age-related differences in CoQ10 serum concentrations between children and adults [23], which may require different doses of CoQ10 supplements for adults and children to observe beneficial results. The trials were carefully selected by two investigators (ST and MR) through screening of titles/abstracts, followed by full-text review (Fig. 1). Any conflicts arising during the study selection process were resolved by a third investigator (HM).

2.3. Data extraction

Two investigators (ST and MR) separately extracted the outlined information from all selected trials: the last name of the first author; length and location of trial; sex; trial design (cross-over or parallel); year of publication; mean age; training status; sport/activity; training testing; sample size (treatment and control); description of intervention and comparison groups; dosage of CoQ10 supplementation; type of Q10 molecule; and means and SDs of changes in the mentioned outcomes from the beginning for both arms (treatment and control). When different units were used for the outcomes mentioned above, we standardized them to the most commonly applied unit.

2.4. Risk of bias assessment

Two investigators (SZM and MR) assessed the risk of bias (RoB) using the Cochrane RoB tool [24]. Any discrepancies were addressed by consensus. RoB tool contains seven domains to evaluate the study quality, which include: 1) generation of random sequence; 2) allocation concealment; 3) subjects and personnel blinding; 4) outcome assessors blinding; 5) incomplete outcome data; 6) selective reporting; and 7) other sources of bias. Finally, the overall quality for each domain was rated by using terms including “Low risk of bias,” “Some concerns,” or “High risk of bias” (Table S3).

2.5. Data analyses

Weighted or standardized mean differences (MDs) and 95 % confidence intervals (CIs) were calculated to identify CoQ10 effects on CK, LDH, Mb, mean power, TAC, and MDA performing random effects analysis [25]. To calculate the pooled effect sizes, we applied the mean change and the SD of each outcome in the CoQ10 and control groups. When the articles did not state the data straightly, the mean changes were computed by subtracting before the intervention measures from values after the intervention. In this regard, SD changes were also calculated using the formula: SD

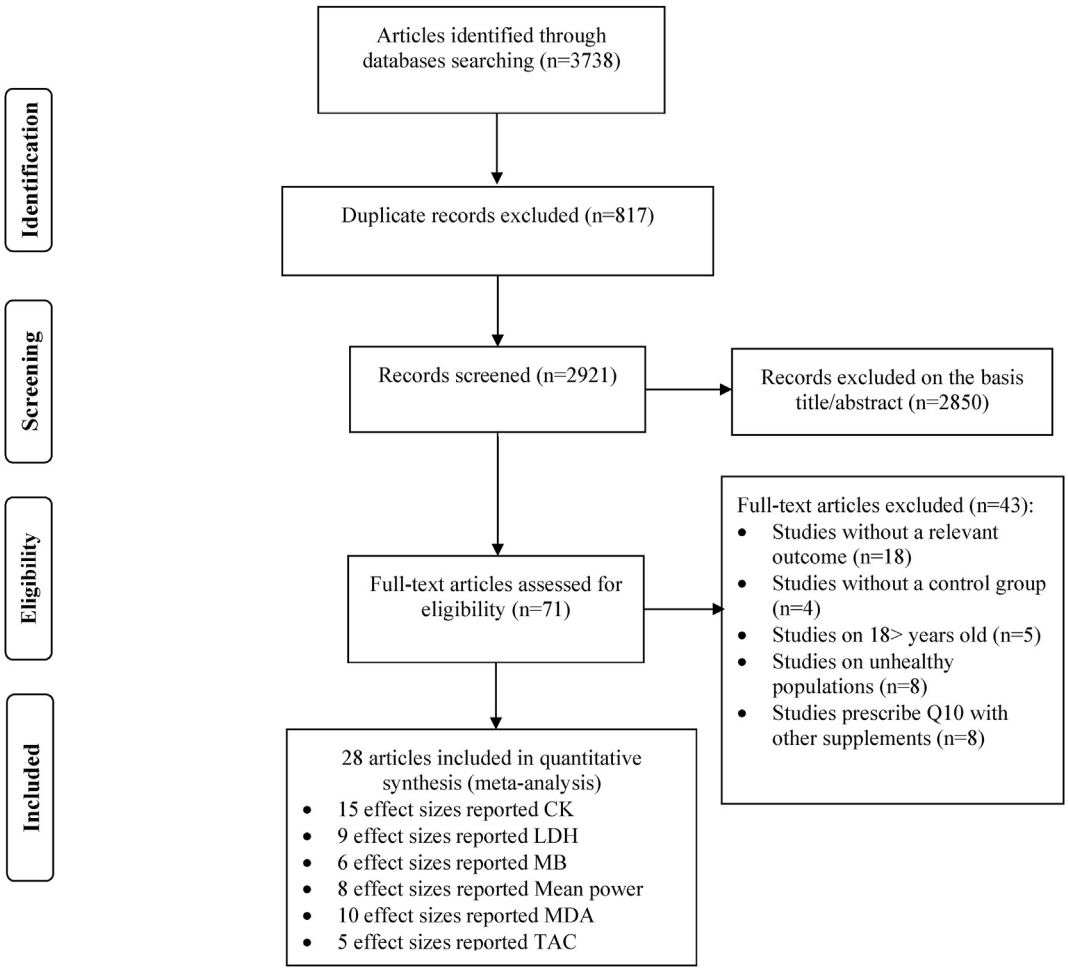

Fig. 1. Literature search and review flow diagram for selection of studies.

change = radical of $[(SD^2_{baseline} + SD_{Final}{}^2) - (2 \times R \times SD_{Baseline} \times SD_{Final})]$, assuming 0.5 as a correlation coefficient (R) [26]. In addition, 95 %CIs, interquartile ranges, and standard errors (SEs) were converted to SD using the relevant formula [27]. To interpret the magnitude of effect estimates, the estimated standardized mean differences (SMDs) were categorized as follows: trivial effect (0.0–0.2), small effect (0.2–0.6), moderate effect (0.6–1.2), large effect (1.2–2.0), very large effect (2.0–4.0), and extremely large effect (≥4.0) [28].

Additionally, we utilized the approach outlined by Crippa & Orsini [29] for computing mean differences and SEs of changes in the mentioned outcomes for every 100 mg/d increase in CoQ10 supplementation in the treatment versus the control group in each trial. Certain findings were combined using a random-effects model with the DerSimonian-Laird method [25]. This approach requires the overall number of subjects, the mean and SD of changes, and the amount of CoQ10 supplementation (mg/d) in each study arm.

To identify potential sources of heterogeneity, we conducted predefined subgroup analyses based on study duration (14 d/≥14 d), the amount of CoQ10 (≤200 mg/d/>200 mg/d), and training status (trained/untrained). We also conducted post hoc subgroup analyses according to the type of Q10 molecule (CoQ10/ubiquinol/ubiquinone) and sex (males/both). To evaluate the impact of every RCT on the final results, we used sensitivity analysis [26]. Publication bias was examined using Begg's [30] and Egger's [31] tests. Moreover, to examine the between-study heterogeneity, we applied Cochran's Q test and I-squared (I^2) statistic [32]. P-values <0.05 and I^2>50 % were regarded as indicating considerable between-study heterogeneity.

Ultimately, a dose-response analysis was done to determine the dose-dependent effect of CoQ10 supplementation on CK, LDH, Mb, mean power, TAC, and MDA. Non-linear dose-response relations were evaluated using fractional polynomial modeling [33]. We applied STATA software, version 17.0 (StataCorp, College Station, TX, USA) for conducting all tests. A P-value below 0.05 was deemed statistically significant.

2.6. Rating the evidence

We used the GRADE framework for each outcome for rating the evidence certainty [34]. Two investigators (SZM and ST) independently conducted the GRADE assessment. The overall evidence certainty is rated as high, moderate, low, or very low using the GRADE tool. Table S4 presents the complete information regarding the domains of the GRADE.

3. Results

3.1. Study selection

As presented in Fig. 1, a total of 3738 records were identified from initial database searches and reference lists. After screening the titles and abstracts, 2850 irrelevant articles were excluded. The evaluation of 71 full texts led to the identification of 28 RCTs that

were acceptable for inclusion in this review [12–19,35–54]. Reasons for exclusion included no relevant outcomes (n = 18), lack of a control group (n = 4), subjects under 18 years old (n = 5), an unhealthy population (n = 8), and interventions that prescribed CoQ10 with other supplements (n = 8) (Table S5).

3.2. Study characteristics

The 28 RCTs, published between 1992 and 2023, consisted of 830 subjects, with 420 subjects in the intervention group and 410 in the control group (Table S2). These trials were conducted in the USA [15,37,39,40], Norway [53], Spain [42,54], Finland [48], Italy [38,52], Germany [36], Japan [14,17,18,47], Taiwan [13], Turkey [16,41,45], Iran [12,19,35,43,44,46,50,51], and Sweden [49]. The mean age of the subjects ranged from 17.66 to 63.8 years. All but five studies had parallel designs [18,37,45,48,52,54]. Over half of the trials (25 out of 28; 89 %) used subjects who were trained. Six trials included both male and female subjects [13,18,36,37,40,53], while the other 21 trials were conducted among males only [12,14–17,19,35,38,39,41–52,54]. The dosage of CoQ10 ranged between 90 and 300 mg/d and 2.5–5 kg/mg/d. Two trials applied varying amounts of CoQ10 as low and high doses [18,41]. The follow-up duration of the studies ranged from 1 day to 12 weeks.

3.3. Effect of CoQ10 supplementation on CK levels

Thirteen trials (comprising fifteen study arms) with a total of 335 subjects (intervention = 168, control = 167) evaluated the levels of CK after CoQ10 supplementation [14,16–19,35,41,43,46,47,50,52,53]. CK levels were significantly decreased in subjects treated with CoQ10 (WMD: −50.64 IU/L; 95 %CI: −74.75, −26.53, P < 0.001). However, significant heterogeneity was observed between the trials (I^2 = 96.7 %, P < 0.001) (Fig. 2). On the other hand, SMD results indicated moderate effects (SMD: −0.95; 95 % CI: −1.52, −0.37) of CoQ10 supplementation on CK levels (Fig. S1).

Subgroup analysis revealed that training status and sex were the potential sources of heterogeneity. The effect of CoQ10 on CK was more significant at supplement doses >200 mg/d (WMD: −86.44 IU/L; 95 %CI: −141.46, −31.43, P = 0.002) compared to doses ≤200 mg/d. Regarding intervention length, the effect of CoQ10 on reducing CK levels was higher in the subset with study durations of <14 days (WMD: −68.70 IU/L; 95 %CI: −121.54, −15.87, P = 0.011) compared to duration ≥14 days. CoQ10 had a more favorable effect on reducing CK levels in males (WMD: −61.84 IU/L; 95 % CI: −88.64, −35.05, P < 0.001) and trained subjects (WMD: −73.33 IU/L; 95 %CI: −103.80, −42.85, P < 0.001) (Table 2). Sensitivity analysis showed no alteration in results when individual trials were omitted step by step (Fig. S2). No publication bias was identified using Begg's test (P = 1.00) and Egger's test (P = 0.087) (Fig. S3).

A dose-dependent analysis demonstrated that every 100 mg/d CoQ10 significantly reduced CK (WMD: −23.07 IU/L; 95 % CI: −34.27, −11.86, P < 0.001; I^2 = 95 %, $P_{heterogeneity}$ <0.001; n = 15) (Fig. S4). The non-linear dose-dependent analysis demonstrated that levels of CK declined with an increase in the dosage of CoQ10 ($P_{nonlinearity}$ = 0.880, $P_{dose\text{-}response}$ = 0.002). Moreover, the greatest reduction in CK was observed in 622 mg/d CoQ10 supplementation ($MD_{622\ mg/d}$: −151.30 IU/L; 95 %CI: −263.95, −38.65; Fig. 3 & Table 3).

3.4. Effect of CoQ10 supplementation on LDH concentrations

After pooling data from seven trials (nine study arms), which included a total of 180 subjects (intervention = 90, control = 90) [12,14,18,35,41,43,50], we discovered a considerable impact of CoQ10 supplementation on reducing the LDH concentrations (WMD: −52.10 IU/L; 95 %CI: −74.01, −30.19, P < 0.001). Heterogeneity was significant (I^2 = 97.4 %, P < 0.001) (Fig. 4). On the other hand, using SMD results indicated very large effects (SMD: −2.70; 95 %CI: −4.04, −1.36) of CoQ10 supplementation on LDH concentrations (Fig. S5).

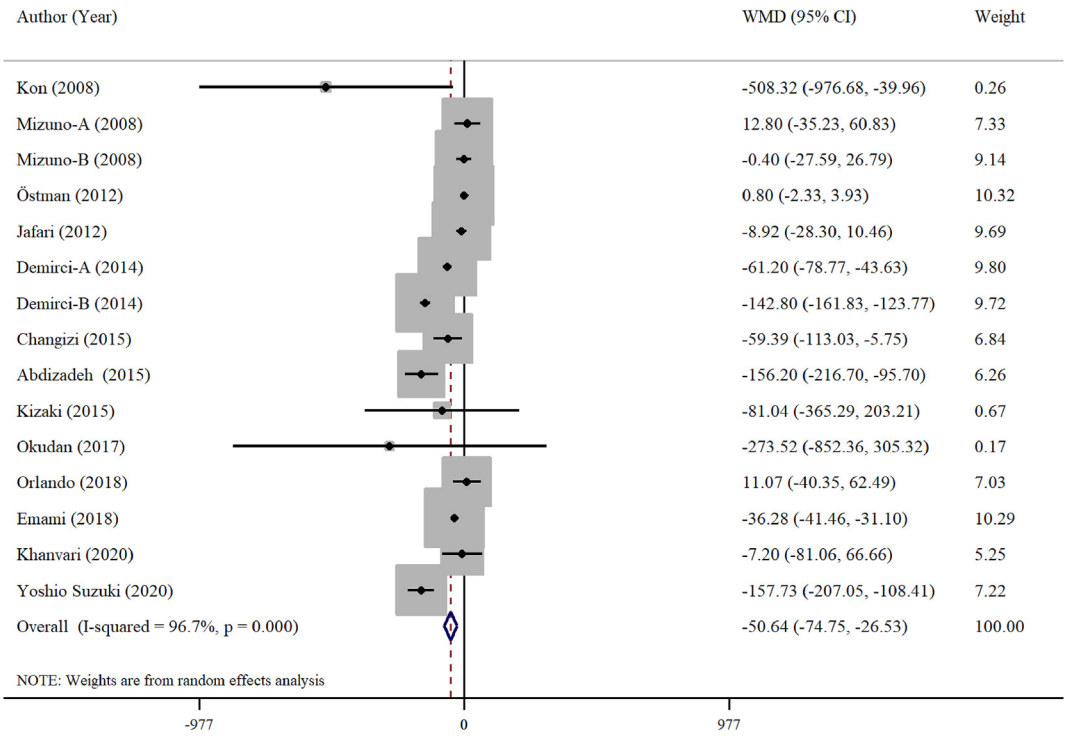

Fig. 2. Forest plot of the effect of Coenzyme Q10 supplementation on CK using random effects model. WMD: weighted mean difference, CI: confidence interval.

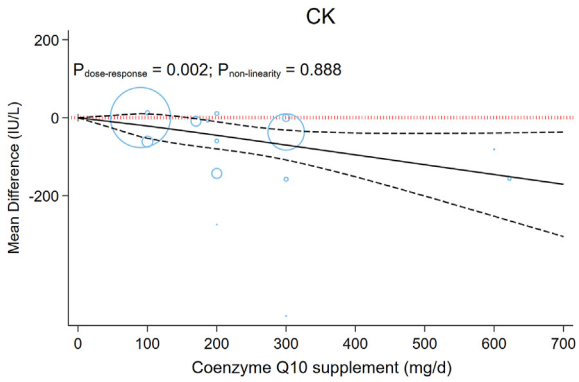

Fig. 3. The effects of different doses of Coenzyme Q10 supplementation on CK form the nonlinear dose-response meta-analysis.

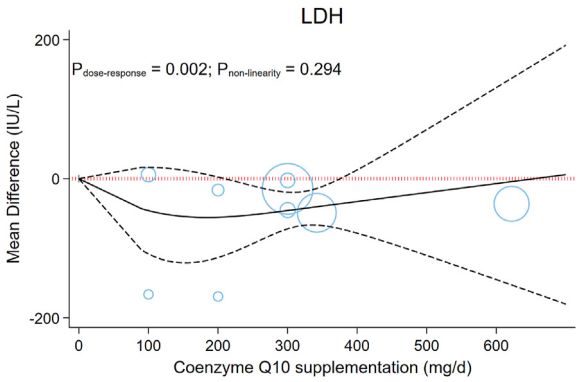

Fig. 5. The effects of different doses of Coenzyme Q10 supplementation on LDH form the nonlinear dose-response meta-analysis.

Between-study heterogeneity was eliminated after subgroup analysis based on training status and sex. Subgroup analysis revealed that the effect of CoQ10 on reducing LDH concentrations had greater statistical significance at doses ≤200 mg/d (WMD: −85.94 IU/L; 95 %CI: −179.70, 4.80, P = 0.063) compared with supplement doses >200 mg/d. Besides, consuming CoQ10 at duration <14 days (WMD: −59.08 IU/L; 95 %CI: −104.56, −13.61, P < 0.001) and in trained subjects (WMD: −67.61 IU/L; 95 % CI: −92.69, −42.53, P < 0.001) had better efficacy in decreasing LDH levels (Table 2). The overall effect did not change when we removed individual studies step by step for sensitivity analysis (Fig. S6). No significant publication bias was identified using Begg's test (P = 0.348) and Egger's test (P = 0.238) (Fig. S7).

A dose-response analysis indicated that every 100 mg/d CoQ10 significantly reduced LDH (WMD: −21.27 IU/L; 95 % CI: −28.23, −14.32, P < 0.001; I^2 = 97.7 %, $P_{heterogeneity}$ <0.001; n = 9) (Fig. S8). The non-linear dose-dependant assessment showed that levels of LDH reduced non-significantly with an increase in CoQ10 dosage up to 200 mg/d ($P_{nonlinearity}$ = 0.290, $P_{dose-response}$ = 0.002). However, when the dosage of CoQ10 was 300 mg/d, the LDH levels were significantly reduced ($MD_{300\ mg/d}$: −45.82 IU/L; 95 %CI: −72.22, −19.42; Fig. 5 & Table 3). The levels of LDH also appeared to plateau with a trivial upward when subjects consumed over 400 mg/d CoQ10.

3.5. Effect of CoQ10 supplementation on Mb levels

According to combined results of five trials, including 231 subjects (intervention = 116, control = 115) [16,17,43,47,52,54], we identified a significant decrease in Mb levels following treatment with CoQ10 (WMD: −21.77 ng/ml; 95 %CI: −32.59, −10.94, P < 0.001; I^2 = 39.0 %, P = 0.146) (Fig. 6). On the other hand, using SMD results indicated nonsignificant effects of CoQ10 supplementation on Mb levels (Fig. S9).

The overall effect did not change when we removed individual studies step by step for sensitivity analysis (Fig. S10). No significant publication bias was discovered using Egger's test (P = 0.273) and Begg's test (P = 0.452) (Fig. S11).

A dose-response analysis showed that every 100 mg/d CoQ10 significantly reduced Mb (WMD: −7.09 ng/ml; 95 % CI: −11.35, −2.83, P = 0.001; n = 6) (Fig. S12). The non-linear dose-dependent analysis revealed that levels of Mb reduced non-significantly with an increase in the dose of CoQ10 ($P_{nonlinearity}$ = 0.940, $P_{dose-response}$<0.001). However, when the

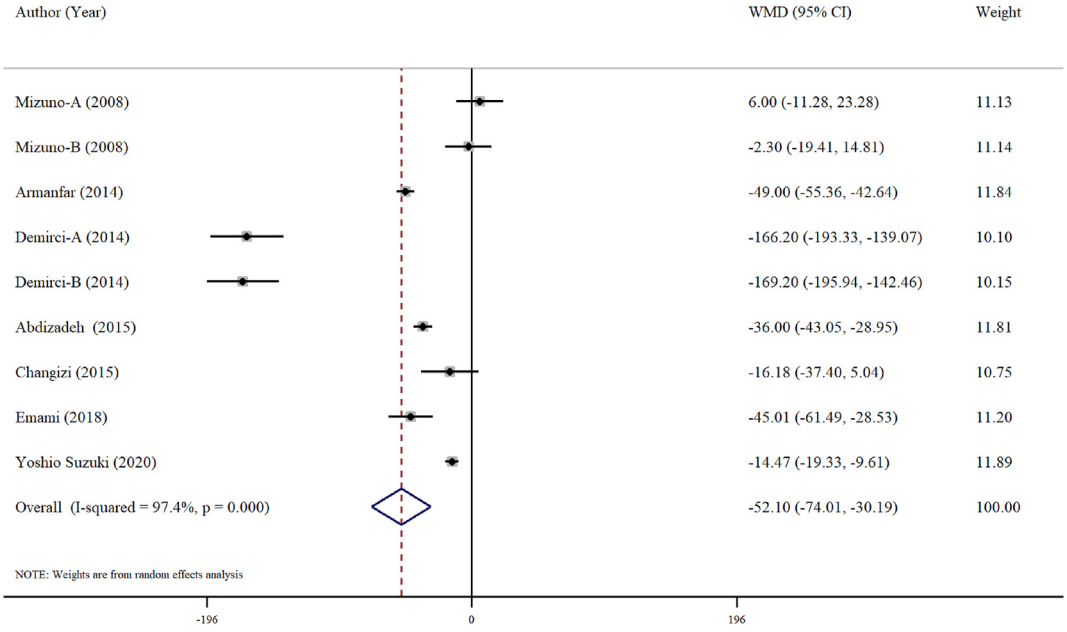

Fig. 4. Forest plot of the effect of Coenzyme Q10 supplementation on LDH using random effects model. WMD: weighted mean difference, CI: confidence interval.

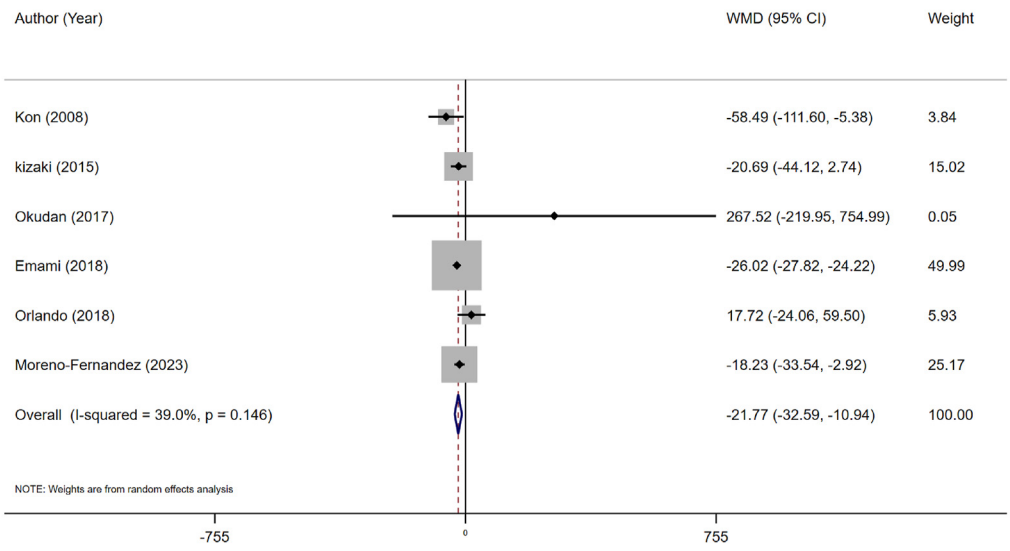

Fig. 6. Forest plot of the effect of Coenzyme Q10 supplementation on Mb using random effects model. WMD: weighted mean difference, CI: confidence interval.

doses of CoQ10 were increased, the Mb levels were significantly reduced ($MD_{600\ mg/d}$: −49.94 ng/ml; 95 %CI: −96.70, −3.17) (Fig. 7 & Table 3).

3.6. Effect of CoQ10 supplementation on mean power

According to the combined results of eight trials, including 246 subjects (intervention = 126, control = 120) [36,38,40,44,45,49,51,53], we identified no significant rise in mean power following treatment with CoQ10 (WMD: 5.16 W; 95 %CI: −13.10, 23.42, P = 0.580; I^2 = 55.3 %, P = 0.028) (Fig. 8). On the other hand, using SMD results indicated non-significant effects of CoQ10 supplementation on mean power (Fig. S13).

The individual exclusion of studies did not alter the outcome of our findings (Fig. S14). We did not discover any publication bias with the Begg's test (P = 0.266) and Egger's test (P = 0.599) (Fig. S15).

A dose-response analysis showed that every 100 mg/d CoQ10 could not significantly reduce mean power (Fig. S16).

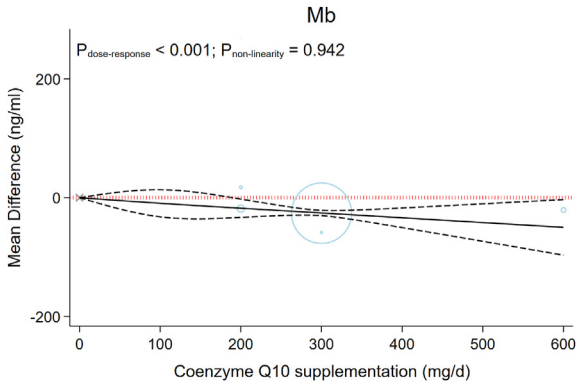

Fig. 7. The effects of different doses of Coenzyme Q10 supplementation on Mb form the nonlinear dose-response meta-analysis.

The non-linear dose-dependent assessment revealed no significant effect on mean power with an increase in the dose of CoQ10 ($P_{nonlinearity}$ = 0.790, $P_{dose-response}$ = 0.690; Fig. 9 & Table 3).

3.7. Effect of CoQ10 supplementation on TAC

According to the combined results of five trials, including 104 subjects (intervention = 54, control = 50) [12,13,35,42,43], we identified no significant reduction in TAC following treatment with CoQ10 (WMD: −0.14 mmol/l; 95 %CI: −0.36, 0.08, P = 0.230; I^2 = 93.7 %, P < 0.001) (Fig. 10). On the other hand, using SMD results indicated non-significant effects of CoQ10 supplementation on TAC (Fig. S17).

Sensitivity analysis revealed that the leave-out individual trials did not change our findings (Fig. S18). We did not discover any publication bias with the Begg's (P = 0.806) and Egger's (P = 0.234) tests (Fig. S19).

A dose-response analysis showed that every 100 mg/d CoQ10 could not significantly reduce TAC (Fig. S20). The non-linear dose-dependant assessment indicated no significant effect on TAC with an increase in the dose of CoQ10 ($P_{nonlinearity}$ = 0.750, $P_{dose-response}$ = 0.730; Fig. 11 & Table 3).

3.8. Effect of CoQ10 supplementation on MDA levels

Nine trials (ten study arms) with a total of 205 subjects (intervention = 105, control = 100) evaluated the MDA levels after supplementation with CoQ10 [12,13,15,16,35,37,39,42,48]. MDA levels were significantly decreased in subjects treated with CoQ10 (MD: −0.73 μmol/l; 95 %CI: −1.26, −0.20, P = 0.007; I^2 = 81 %, P < 0.001) (Fig. 12). On the other hand, the use of SMD results indicated moderate effects (SMD: −0.70; 95 % CI: −1.33, −0.07) of CoQ10 supplementation on MDA levels (Fig. S21).

Subgroup analysis identified dose, duration, and type of Q10 molecule as potential factors to heterogeneity. Subgroup analysis

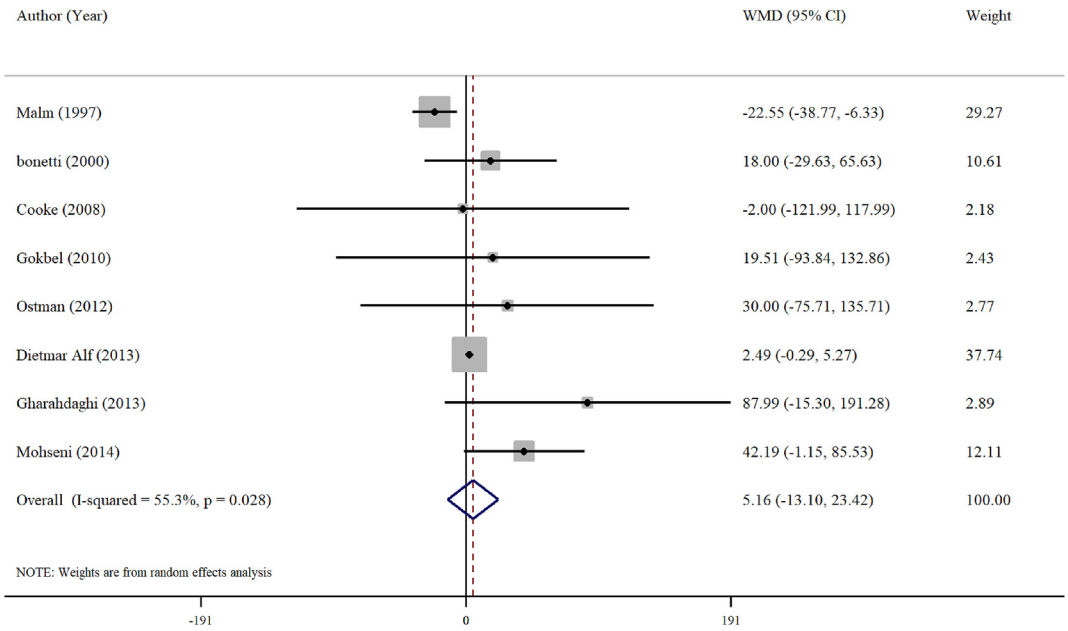

Fig. 8. Forest plot of the effect of Coenzyme Q10 supplementation on mean power using random effects model. WMD: weighted mean difference, CI: confidence interval.

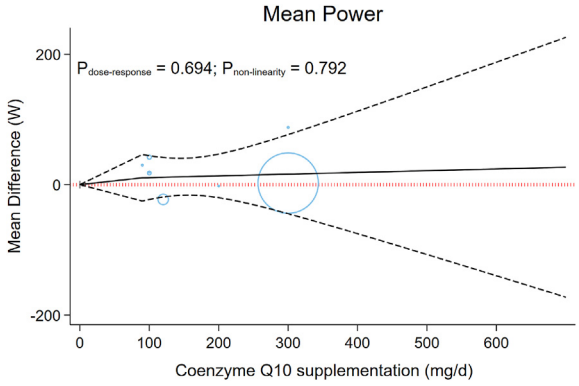

Fig. 9. The effects of different doses of Coenzyme Q10 supplementation on Mean power form the nonlinear dose-response meta-analysis.

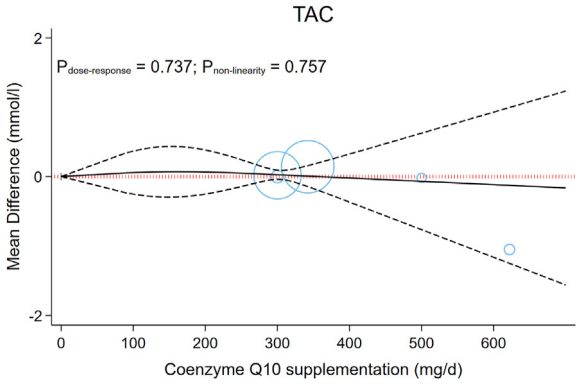

Fig. 11. The effects of different doses of Coenzyme Q10 supplementation on TAC form the nonlinear dose-response meta-analysis.

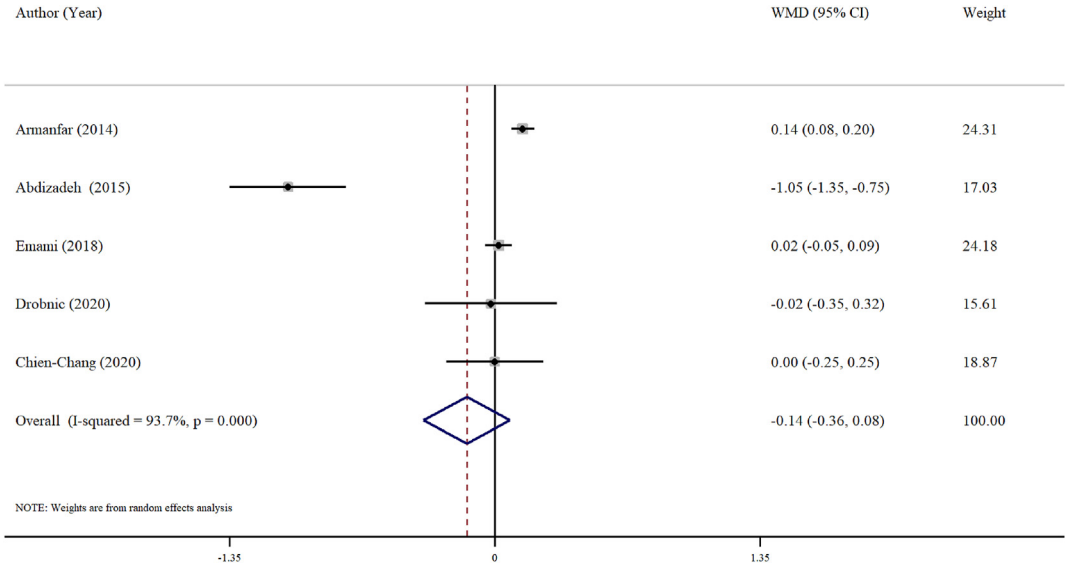

Fig. 10. Forest plot of the effect of Coenzyme Q10 supplementation on TAC using random effects model. WMD: weighted mean difference, CI: confidence interval.

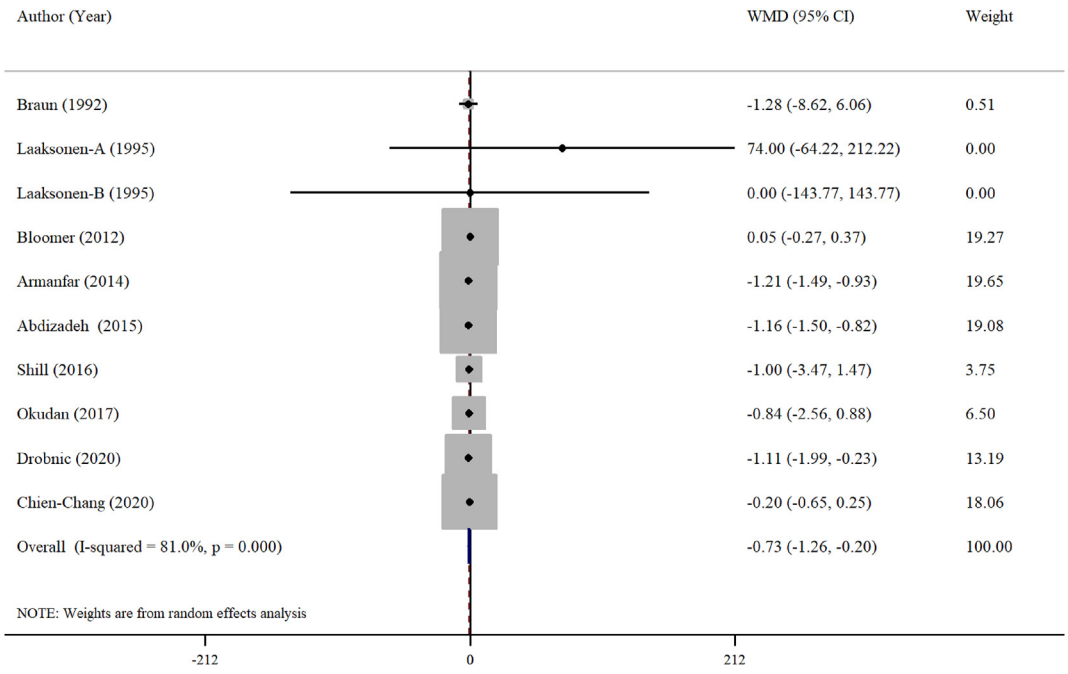

Fig. 12. Forest plot of the effect of Coenzyme Q10 supplementation on MDA using random effects model. WMD: weighted mean difference, CI: confidence interval.

proposed that intake of CoQ10 can more favorably decrease MDA in the subset of duration <14 days (WMD: −0.79 μmol/l; 95 % CI: −1.55, −0.03, P = 0.041), and male subjects (WMD: −1.11 μmol/l; 95 %CI: −1.98, −0.23, P = 0.013) (Table 2). Besides, results from sensitivity analysis revealed no alteration in the overall effect size after omitting individual trials one by one (Fig. S22). We identified no significant publication bias using Egger's test (P = 0.823) and Begg's test (P = 0.371) (Fig. S23).

A dose-dependant analysis revealed that every 100 mg/d CoQ10 significantly reduced MDA (WMD: −0.17 μmol/l; 95 % CI: −0.29, −0.05, P = 0.005; I^2 = 74.5 %, $P_{heterogeneity}$ <0.001; n = 10) (Fig. S24). The non-linear dose-dependant assessment showed that levels of MDA reduced proportionally with an increase in the dose of CoQ10 ($P_{nonlinearity}$ = 0.980, $P_{dose\text{-}response}$<0.001). Moreover, the greatest reduction in MDA was observed in 622 mg/d CoQ10 supplementation ($MD_{622\ mg/d}$: −1.19 μmol/l; 95 %CI: −1.57, −0.81; Fig. 13 & Table 3).

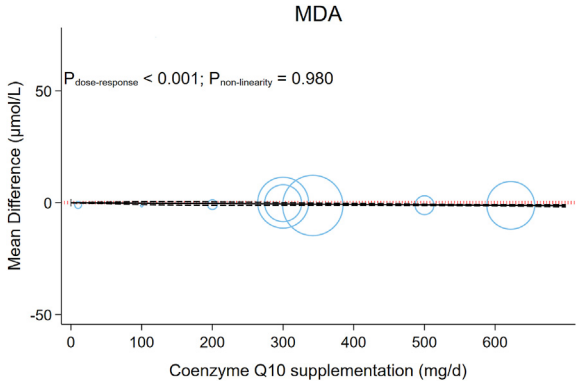

Fig. 13. The effects of different doses of Coenzyme Q10 supplementation on MDA form the nonlinear dose-response meta-analysis.

3.9. Rating the evidence

The quality of the evidence for six biomarkers associated with oxidative stress, EIMD, and physical performance varies from moderate to low, as assessed by the GRADE tool (Table 1). Mb was shown to have a moderate certainty of evidence for the downgrade of risk of bias and imprecision. CK, LDH, mean power, TAC, and MDA

Table 1
The effect of Coenzyme Q10 supplementation on biomarkers of exercise-induced muscle damage, physical performance, and oxidative stress.

	Pairwise meta-analysis					Dose-response meta-analysis					
	Studies, *n*	MD (95 % CI)	*P value*	I^2,%	*P* heterogeneity	Dose, mg/d	Studies, *n*	MD (95 % CI)	*P* value	I^2,%	*P* heterogeneity	GRADE
CK (IU/L)	15	−50.64 (−74.75, −26.53)	<0.001	96.7	<0.001	100	15	−23.07 (−34.27, −11.86)	<0.001	95.0	<0.001	Low
LDH (IU/L)	9	−52.10 (−74.01, −30.19)	<0.001	97.4	<0.001	100	9	−21.27 (−28.23, −14.32)	<0.001	97.7	<0.001	Low
Mb (ng/ml)	6	−21.77 (−32.59, −10.94)	<0.001	39.0	0.146	100	6	−7.09 (−11.35, −2.83)	0.001	60.4	0.027	Moderate
Mean Power (W)	8	5.16 (−13.10, 23.42)	0.580	55.3	0.028	100	8	3.76 (−10.28, 17.80)	0.600	53.2	0.037	Low
TAC (mmol/l)	5	−0.14 (−0.36, 0.08)	0.230	93.7	<0.001	100	5	−0.02 (−0.09, 0.04)	0.449	94.1	<0.001	Low
MDA (μmol/l)	10	−0.73 (−1.26, −0.20)	0.007	81.0	<0.001	100	10	−0.17 (−0.29, −0.05)	0.005	74.5	<0.001	Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD; mean difference, CI; confidence interval, CK; creatine kinase, LDH; lactate dehydrogenase, Mb; myoglobin, TAC; total antioxidant capacity, MDA; Malondialdehyde.

were revealed to have a low certainty through degradation of the risk of bias, inconsistency, and imprecision (Table S6).

4. Discussion

The current investigation revealed that CoQ10 supplementation significantly diminishes levels of CK, Mb, MDA, and LDH. A pronounced reduction (large effect) in LDH levels was observed, alongside moderate decreases in CK and MDA concentrations. However, caution is advised in interpreting the Mb results, as sensitivity analysis yielded a non-significant outcome. Furthermore, no substantial changes were noted in TAC and mean power. Subgroup analysis demonstrated a significant decline in serum CK and LDH concentrations among male and trained individuals, with trained subjects exhibiting markedly lower MDA levels after CoQ10 supplementation compared to their untrained counterparts. CoQ10 supplementation for less than two weeks significantly decreased CK, LDH, and MDA levels, as per subgroup analysis. When considering intervention dosage, ≤200 mg of CoQ10 significantly decreased MDA and LDH levels, whereas dosages exceeding 200 mg appeared more effective in CK level reduction.

Dietary antioxidants are recognized for their role in mitigating oxidative damage from physical activity [55]. Previous investigations have noted the impact of other antioxidant and anti-inflammatory supplements on EIMD [56,57]. For instance, Rojano-Ortega et al. (2022) demonstrated significant reductions in

Table 2
Result of subgroup analysis of included studies in meta-analysis.

Sub-grouped by	No. of trials	Mean difference[a]	95 % CI, P-value	I^2 (%)	P for heterogeneity	P for between subgroup heterogeneity[a]
CK (All trials)	**15**	**−50.64**	**(-74.75, -26.53), <0.001**	**96.7**	**<0.001**	
Duration						**0.170**
<14 d	7	−68.70	(-121.54, −15.87), 0.011	94.2	<0.001	
≥14 d	8	−27.71	(-53.44, −1.99), 0.035	95.9	<0.001	
Dose						**0.140**
≤200 mg/d	9	−34.96	(-78.04, 8.13), 0.112	96.9	<0.001	
>200 mg/d	6	−86.44	(-141.46, −31.43), 0.002	89.8	<0.001	
Training status						**<0.001**
Trained	10	−73.33	(-103.80, −42.85), <0.001	97.9	<0.001	
Untrained	5	−4.50	(-19.19, 10.19), 0.548	0.0	0.805	
Type of Q10 molecule						**<0.001**
Coenzyme Q10	8	−54.57	(-105.84, −3.30), 0.037	97.3	<0.001	
Ubiquinol	6	−33.78	(-73.40, 5.85), 0.095	86.6	<0.001	
Ubiquinone	1	−156.20	(-216.70, −95.70), <0.001	–	–	
Sex						**<0.001**
Male	13	−61.84	(-88.64, −35.05), <0.001	97.2	<0.001	
Both	2	2.80	(-20.86, 26.47), 0.816	0.0	0.639	
LDH (All trials)	**9**	−52.10	(-74.01, −30.19), <0.001	97.4	<0.001	
Duration						**0.500**
<14 d	6	−59.08	(-104.56, −13.61), 0.011	98.0	<0.001	
≥14 d	3	−43.11	(-52.82, −33.39), <0.001	72.4	0.027	
Dose						**0.230**
≤200 mg/d	4	−85.94	(-179.70, 4.80), 0.063	98.5	<0.001	
>200 mg/d	5	−29.72	(-46.75, −12.68), 0.001	95.5	<0.001	
Training status						**<0.001**
Trained	7	−67.61	(-92.69, −42.53), <0.001	97.8	<0.001	
Untrained	2	1.80	(-10.35, 13.96), 0.771	0.0	0.504	
Type of Q10 molecule						**0.010**
Coenzyme Q10	4	−99.29	(-164.76, −33.82), 0.003	98.0	<0.001	
Ubiquinol	4	−14.12	(-31.26, 3.02), 0.106	85.4	<0.001	
Ubiquinone	1	−36.00	(-43.05, −28.94), <0.001	–	–	
Sex						**<0.001**
Male	7	−67.61	(-92.69, −42.53), <0.001	97.8	<0.001	
Both	2	1.80	(-10.35, 13.96), 0.771	0.0	0.504	
MDA (All trials)	**10**	−0.73	(-1.26, −0.20), 0.007	81.0	<0.001	
Duration						**0.490**
<14 d	4	−0.79	(-1.55, −0.03), 0.041	92.4	<0.001	
≥14 d	6	−0.41	(-0.80, −0.02), 0.037	0.0	0.456	
Dose						**0.810**
≤200 mg/d	5	−0.89	(-2.28, 0.48), 0.204	0.0	0.886	
>200 mg/d	5	−0.70	(-1.29, −0.11), 0.018	91.3	<0.001	
Training status						**0.900**
Trained	9	−0.72	(-1.27, −0.16), 0.011	83.1	<0.001	
Untrained	1	−0.84	(-2.56, 0.88), 0.339	–	–	
Type of Q10 molecule						**<0.001**
Coenzyme Q10	4	−1.19	(-1.46, −0.92), <0.001	0.0	0.978	
Ubiquinol	1	0.05	(-0.27, 0.37), 0.761	–	–	
Ubiquinone	5	−0.79	(-1.47, −0.12), 0.021	68.3	0.013	
Sex						**0.380**
Male	1	−1.11	(-1.98, −0.23), 0.013	–	–	
Both	9	−0.67	(-1.25, −0.08), 0.024	82.9	<0.001	

Abbreviations: CI; Confidence Interval, CK; Creatine Kinase, LDH; Lactate Dehydrogenase, MDA; Malondialdehyde.
[a] Calculated by Random-effects model.

Table 3
The effects of different doses of Coenzyme Q10 supplementation on biomarkers of exercise-induced muscle damage, physical performance, and oxidative stress from the nonlinear dose-response meta-analysis (mean difference and 95 % confidence interval).

Coenzyme Q10 supplements (mg/d)	0	90	100	200	300	400	500	600	622
CK (IU/L)	0 (Ref)	−19.08 (−48.77, 10.60)	−21.34 (−52.59, 9.92)	−45.08 (−79.93, −10.23)	−70.09 (−108.39, −31.80)	−95.31 (−151.64, −38.98)	−120.53 (−201.05, −40.02)	−145.75 (−252.49,- 39.01)	−151.30 (−263.95, −38.65)
LDH (IU/L)	0	−43.13 (−102.59, 16.34)	−45.90 (−108.22, 16.42)	−55.53 (−113.45, 2.38)	−45.82 (−72.22, −19.42)	−32.89 (−78.39, 12.62)	−19.96 (−110.43, 70.52)	−7.02 (−145.02, 130.97)	−4.18 (−152.73, 144.38)
Mb (ng/ml)	0	−8.56 (−30.40, 13.28)	−9.46 (−32.28, 13.37)	−17.78 (−33.19, −2.36)	−25.82 (−30.29, −21.35)	−33.86 (−50.36, −17.36)	−41.90 (−73.44, 10.36)	−49.94 (−96.70, −3.17)	–
Mean Power (W)	0	10.56 (−25.04, 46.16)	10.83 (−22.78, 44.44)	13.48 (−19.97, 46.92)	16.12 (−44.57, 76.92)	–	–	–	–
TAC (mmol/l)	0	0.05 (−0.24, 0.34)	0.06 (−0.25, 0.37)	0.07 (−0.25, 0.38)	0.03 (−0.04, 0.09)	−0.02 (−0.37, 0.32)	−0.07 (−0.76, 0.63)	−0.12 (−1.16, 0.93)	−0.13 (−1.25, 1.00)
MDA (μmol/L)	0	−0.18 (−0.81, 0.45)	−0.20 (−0.87, 0.47)	−0.39 (−1.17, 0.38)	−0.58 (−1.19, 0.03)	−0.77 (−1.20, −0.34)	−0.96 (−1.27, −0.64)	−1.14 (−1.50, −0.79)	−1.19 (−1.57, −0.81)

Abbreviations: MD; Mean Difference, CI; Confidence Interval, CK; Creatine Kinase, LDH; Lactate Dehydrogenase, MB; myoglobin, TAC; Total Antioxidant Capacity, MDA; Malondialdehyde, MP; mean power.

muscle soreness and damage, as well as enhanced recovery after intense physical activity, with quercetin supplementation [58]. Moreover, Fang et al., in another systematic reviews and meta-analyses, revealed the effectiveness of curcumin supplementation in reducing CK concentrations and muscle soreness in adults [59]. Conversely, Yarixadeh et al. (2020) observed that L-carnitine supplementation reduced serum CK, LDH, and Mb levels at a single follow-up duration, but this effect dissipated over extended follow-up periods [60]. The notable impact of CoQ10 on EIMD biomarkers may be attributed to its antioxidant properties and its inhibitory action on lipid peroxidation, thereby preventing the leakage of CK, Mb, and LDH from cell membranes post-exercise [61].

This study also found a more favorable response to CoQ10 supplementation in male cohorts and trained individuals compared to mixed-sex cohorts and untrained subjects, potentially due to differences in mitochondrial capacity influencing muscle metabolism rates [62]. It has been observed that men generally have higher mitochondrial function than women [62,63], and trained individuals exhibit greater mitochondrial capacity compared to untrained subjects, potentially explaining the varied efficacy of CoQ10 supplementation [64].

We observed no significant effects of CoQ10 supplementation on mean power, possibly owing to inadequate muscle concentration of CoQ10 [65] or limitations in the supplementation protocol, thus precluding observable ergogenic effects on mean power and muscle strength [65]. This aligns with previous studies examining various nutritional ergogenic aids and their impact on physical performance metrics like power and fatigue perception [66–68]. For instance, Hiong Wong et al. documented no significant improvements in mean and peak power output following beetroot supplementation in high-intensity training [69]. In contrast, a recent meta-analysis has shown the effectiveness of caffeine supplementation on both power and strength [68]. However, the study mentioned should be interpreted with caution due to its inclusion of doctoral and master's theses, the small number of studies in the subgroup analysis, and the limited age range of the subjects. These discrepancies between our findings and the results of previous studies might be attributed to the type of exposure, the duration of the included studies, methodological differences, various kinds of physical activities, and diverse assessment tools.

Our investigation discerned a significant reduction in MDA levels with CoQ10 supplementation, aligning with findings from Sangsefidi et al.'s systematic review and meta-analysis [70]. Similar results were reported by Jorat et al. in another meta-analysis of 13 RCTs among coronary artery disease, indicated a significant decrease in MDA levels after supplementation with CoQ10 [71]. Conversely, Dai et al. found no impact of CoQ10 supplementation on MDA levels in healthy subjects [72]. The current study also did not observe significant enhancements in TAC levels, corroborating a meta-analysis of 34 RCTs, although significant publication bias was identified therein. On the other hand, two other systematic reviews and meta-analyses reported a remarkable increase in TAC levels after CoQ10 supplementation [70]. It's important to note that these meta-analyses included both healthy and unhealthy subjects, potentially affecting the reliability of their findings. Altogether, inconsistency between the results of the previous studies and our findings might be attributed to differences in dosage and formulation of CoQ10 supplements, duration of the study, and, importantly, the healthy status of included subjects.

Our non-linear dose-response meta-analysis identified 300 and 400 mg as the most effective CoQ10 doses for reducing biomarkers of EIMD and oxidative stress. Factors such as dose, bioavailability, supplementation duration, and diet significantly influence CoQ10

absorption effectiveness [73–76]. Huo et al.'s meta-analysis supported our findings, suggesting a more substantial reduction in inflammatory biomarkers with 300–400 mg/day of CoQ10 [77]. The potential mechanisms underlying CoQ10's effects lowering EIMD and oxidative stress include its antioxidant properties. CoQ10 is known to maintain normal electron transport in the mitochondrial electron transport chain, thus potentially reducing superoxide production [78]. Moreover, CoQ10 has a pivotal role in absorbing free radicals and ameliorating lipid peroxidation [61,79], enhancing the efficacy of antioxidant enzymes and TAC levels [80,81]. CoQ10 may also enhance gene expression of ROS-detoxifying enzymes via activation of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf-2), modulating cellular oxidative stress responses [82,83].

This systematic review and dose-response meta-analysis present the following strengths: The quality of evidence was evaluated using the GRADE approach, and a meta-analysis on healthy subjects was conducted, likely offering more reliable results than those analyses including both healthy and unhealthy individuals [70,72]. However, some limitations exist. According to the GRADE assessment tool, most evaluated outcomes were rated as having low certainty of evidence. Also, the study lacks a clear comparison between oxidized (ubiquinone) and reduced (ubiquinol) forms of CoQ10 due to the included studies not specifying the form of CoQ10 supplements used. Significant heterogeneity among study outcomes, except for Mb, might be due to varying dosages, study durations, subject ages, sexes, and antioxidant serum concentrations. The reliance on estimated data using different workaround formulas instead of actual means and standard deviations introduces potential errors. Moreover, diverse measurement methods for biomarkers and mean power in the included studies could influence the observed results.

5. Conclusion

This systematic review and dose-response meta-analysis demonstrates CoQ10 supplementation's efficacy in reducing biomarkers of EIMD, including CK, Mb, and LDH. MDA levels, indicative of oxidative stress, may also decrease following CoQ10 supplementation. An optimal dosage of 300–400 mg per day is recommended. Future RCTs with larger sample sizes and extended supplementation periods are needed to validate these findings.

Ethical approval

Not applicable.

Author contribution

The authors' contributions to the manuscript were as follows: ST, HM, and MP were responsible for the conception, design, and literature search. Data collection and analysis were performed by ST, MR, and AT. Moreover, SZM, FA, and AH contributed to the drafting of the article. AW contributed to critically revising. HM supervised the study. Final approval of the article prior to submission was performed by all authors.

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Availability of data and materials

Corresponding authors will be able to access raw data upon request.

Declaration of competing interest

The authors declare that they do not have any competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.01.015.

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