Effects of Coenzyme Q10 Supplementation on Biomarkers of Oxidative Stress in Adults: A GRADE-Assessed Systematic Review and Updated Meta-Analysis of Randomized Controlled Trials

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Abstract: Evidence shows that exogenous CoQ10 supplementation may potentially attenuate oxidative stress status. However, its effective dose and evidence certainty require further evaluation in the general population via more updated randomized controlled trials (RCTs). Databases (PubMed, Embase and Cochrane Library) were searched up to 30 March 2022. Evidence certainty was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Thirty-four RCTs containing 2012 participants were included in this review. Pooled effects of significant increase in total antioxidant capacity (TAC) (standardized mean difference: 1.83, 95%CI: [1.07, 2.59], p < 0.001) and significant reduction in malondialdehyde (MDA) concentrations (−0.77, [−1.06, −0.47], p < 0.001) were shown after CoQ10 supplementation compared to placebo. However, we could not determine that there was a significant increase in circulating superoxide dismutase (SOD) levels yet (0.47, [0.00, 0.94], p = 0.05). Subgroup analyses implied that CoQ10 supplementation was more beneficial to people with coronary artery disease or type 2 diabetes. Additionally, taking 100–150 mg/day CoQ10 supplement had better benefits for the levels of TAC, MDA and SOD (all p < 0.01). These results to a statistically significant extent lent support to the efficacy and optimal dose of CoQ10 supplementation on attenuating oxidative stress status in adults.

Keywords: coenzyme Q10; oxidative stress; total antioxidant capacity; superoxide dismutase; malondialdehyde; meta-analysis

1. Introduction

Oxidative stress, specifically referring to the imbalance between oxidation processes and antioxidant defenses, seems to play a relevant role in the pathogenesis of many age-associated chronic diseases [1–5], and aging or age-associated chronic diseases could also increase the level of oxidative stress [6,7]. The reactive oxygen and nitrogen species (RONS) are highly reactive and toxic molecules continuously produced from the oxidation process [8]. Malondialdehyde (MDA) is the typical product of lipid peroxidation, in which process free radicals attack lipids containing carbon-carbon double bond(s), such as polyunsaturated fatty acids [9]. The body antioxidant defenses contain the enzymatic scavenger of RONS by superoxide dismutase (SOD), which can convert superoxide (O2•−) into oxygen.
and hydrogen peroxide [10]. Total antioxidant capacity (TAC), also named nonenzymatic antioxidant capacity, is usually evaluated as the moles of oxidants neutralized by one liter of body fluids [11]. Under the oxidative stress status, the excessive oxidation products suppress the antioxidant defense system of cells, with MDA overproduced and the levels of SOD decreased [11–13]. Emerging evidence from long-term prospective studies has suggested that the antioxidant supplementation may be effective in attenuating the outcomes of age-associated chronic diseases [14–16].

Coenzyme Q10 (CoQ10) is a lipid-soluble antioxidant mainly biosynthesized by the body itself [17]. In vivo, CoQ10 is present in the inner membrane of mitochondria as an electron carrier where it contributes to oxidative phosphorylation by transporting electrons from complex I and II to complex III [18]. Apart from this, CoQ10 also obtains much attention from its capability of neutralizing free radicals in lipid structures [19]. Although CoQ10 can be endogenously biosynthesized, the production of CoQ10 declines with aging, especially for people with age-associated chronic diseases [20]. In the light of the fact that only minor proportion of CoQ10 is obtained from our diet, the administration of CoQ10 supplements warrants more consideration [21].

Prior systematic reviews of randomized clinical trials (RCTs) have focused on the effects of CoQ10 supplementation on oxidative stress status, but there was less study extended to the general population [22–26]. The number of studies included for the same oxidative stress biomarkers was inconsistent, although the search deadlines were very close [27,28]. Furthermore, less information on evidence quality and evidence certainty was made to ascertain potential clinical translatability and effective dose of CoQ10 supplementation targeting oxidative stress. In this context, a comprehensive systematic review and meta-analysis including more RCTs based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method are needed to evaluate the efficacy and optimal dose of CoQ10 supplementation in improving oxidative stress status.

Therefore, we employed this updated systematic review and meta-analysis with the objective to evaluate the role and effective dose of CoQ10 supplements on oxidative stress biomarkers such as TAC, SOD and MDA in the general population. Furthermore, we assessed the evidence certainty of the antioxidant effect of CoQ10 based on the GRADE approach.

2. Materials and Methods

The study followed the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol for conducting systematic reviews and meta-analyses normatively [29]. This systematic review has been registered on PROSPERO. The registration number is CRD42021252933.

2.1. Search Strategy

We searched online databases including PubMed/Medline, Embase and Cochrane library database for the time period until 30 March 2022. To comprehensively find RCTs on the effects of CoQ10 supplementation, we used the following terms in our search strategy: (Coenzyme Q10 OR CoQ10 OR Ubiquinone) AND (malondialdehyde OR superoxide dismutase OR MDA OR SOD OR total antioxidant capacity OR TAC) (see Appendix A Table A1). The search was restricted to studies published in the English language.

2.2. Inclusion Criteria

Inclusion was given to studies meeting all of the following criteria: (1) RCTs with a parallel or crossover design; (2) use of a determined amount of CoQ10 intervention; (3) the intervention duration lasting for at least 14 days; (4) available data regarding the pre- and postintervention or changed levels of TAC, MDA and SOD; (5) the control group received placebo or other suitable controls. Studies were excluded if they contained one or more
of the following characteristics: (1) acute feeding trials; (2) studies on the pregnant or breastfeeding women; (3) trials with a multifactorial design.

2.3. Data Extraction and Quantitative Synthesis

Two investigators (D.Z. and Y.L.) undertook data extraction and quantitative synthesis independently. Confronted with differences of opinions, all the authors partook in a discussion to reach consensus. Extracted data contained the following information: title, the first author, year of publication, study location, study design (parallel or crossover), sample size (intervention and control), study duration, intervention characteristics (form, daily dose), participant characteristics (age, sex and health status), and changes of TAC, MDA and SOD levels. For both the intervention group and control group, the changes of the three biomarkers above were calculated by final mean values minus baseline mean values. Standard deviations (SDs) of the mean difference were obtained by the calculation formula: $SD = \sqrt{SD_{baseline}^2 + SD_{final}^2 - 2R \times SD_{baseline} \times SD_{final}}$, assuming the R of 0.5. For trials not reporting the SD values or even mean values, we calculated them from available figures or data including standard error of the mean (SEM), median and range by the reliable formula [30]. Of note, data extraction of crossover trials was based on the first intervention period.

2.4. Data Analysis

To pool the effect sizes of CoQ10 supplementation, the standardized mean differences (SMDs) and 95%CIs were used because the data extracted could not convert to a uniform unit. The I-square ($I^2$) statistic and Cochran’s Q test were performed to assess the heterogeneity between the included studies. $I^2 > 50\%$ and $p$-values < 0.05 were recognized as substantial heterogeneity and significance. Under this circumstance, the random-effects model approach of DerSimonian–Laird was adopted to estimate the overall effects of CoQ10 supplementation on oxidative stress biomarkers. Otherwise, the fixed-effects model with the method of inverse variance was utilized.

Considering that the study duration, intervention dose, health status of participants, control type and study quality may have an association with the net changes of circulating TAC, MDA and SOD levels, we conducted subgroup analyses based on these prespecified variables. Furthermore, the other objective of subgroup analysis was to recognize the potential sources when there was a great heterogeneity between studies. To explore the robustness of the overall effects, we conducted a sensitivity analysis, eliminated the trials one by one and reassessed the overall estimation of the effect. Additionally, the possibility of publication bias was assessed through Egger’s test and inspecting the symmetry of funnel plots. All the statistical analysis was conducted using STATA, version 16.0 (StataCorp, College Station, TX, USA), and R software, version 4.1.2 (http://www.r-project.org/, accessed on 15 March 2022). For all analyses, $p$-values < 0.05 was considered statistically significant.

2.5. Quality Assessment

Two investigators (S.D. and Z.L.) assessed the risk of bias of studies using the Cochrane risk-of-bias tool. It covers seven domains to assess the study bias, which contains random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential bias. Terms including “low”, “unclear” or “high” were given to represent the risk of each domain. A trial owning the result of at least four domains in low risks was considered a relatively good quality. Once a high risk existed, the trial was classified as bad quality. The other trials were thought as fair quality.

2.6. Certainty Assessment

The overall certainty of evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method [31]. According to the
corresponding evaluation criteria, the effect estimates of oxidative stress biomarkers were graded into four levels, including high, moderate, low, and very low quality.

3. Results
3.1. Search Flow

A total of 3979 studies were identified through the initial database search, 1308 of which were removed for duplication. After scanning through title and abstract, 2567 records were excluded. Correspondingly, we assessed the remaining 104 articles for eligibility. Based on the detailed reading of full texts, we finally included 34 RCTs in our analyses. The flow chart of systematic literature search for RCTs that met the study inclusion and exclusion criteria is shown in Figure 1.

Figure 1. Flow chart of systematic literature search for RCT, published through March 2022, that met the study inclusion and exclusion criteria.

3.2. Study Characteristics

The characteristics of each included RCT are shown in Table 1. We collected data from 34 studies (including 39 arms) between 1997 and 2020. Up to 32 (94%) studies applied a parallel design. Over half of the studies were performed using participants with cardiovascular or metabolic diseases. Sample sizes varied from 18 to 144. In total, 2012 participants were engaged with these trials, where 1017 subjects were randomly allocated to CoQ10 related intervention group and the remaining 995 were in control group. The range of mean age among these participants was from 17.2 to 79.2 years. Five studies only contained male subjects in healthy status or special occupation [32–36]. Conversely, there were two studies conducted among women only [37,38]. Overall, the 39-arm trials comprised a roughly similar number of male and female subjects, although two trials did not describe the gender distribution of subjects. Daily dose of CoQ10 intervention ranged from 30 mg to 500 mg. The duration of trials lasted from 14 days to 12 months. The summary of risk bias assessment on these included studies is shown in Appendix A Figure A1.
Table 1. Characteristics of included RCTs to investigate the effects of CoQ10 on oxidative stress biomarkers.

| First Author, Year | Country | Study Design | Population Features | Sample Size (T/C) | Mean (Age) Years | Sex (Male) % | T | C | Dose mg/day | Duration wk | Biomarkers |
|---------------------|---------|--------------|---------------------|------------------|-----------------|--------------|----|----|-------------|-------------|------------|
| Hormoz M. 2019 [32]| Iran    | crossover glazers | 80(40/40)           | 31.83            | 100.0%          | CoQ10       | placebo | 120 | 8 |            |             | TAC, MDA, SOD |
| Sanoobar M. 2013 [39]| Iran    | parallel multiple sclerosis | 45(22/23)      | T: 33.1 C: 30.9 | 8.9%           | CoQ10       | placebo | 500 | 12 |            |             | TAC, MDA, SOD |
| Abdollahzad H. 2015 [40]| Iran    | parallel rheumatoid arthritis | 44(22/22)   | T: 48.77 C: 50.41 | 11.4%          | CoQ10       | placebo | 100 | 8 |            |             | TAC, MDA |
| Fallah M. 2019 [41]| Iran    | parallel diabetic hemodialysis | 60(30/30)  | T: 59.4 C: 64.8 | 66.7%          | CoQ10       | placebo | 120 | 12 |            |             | TAC, MDA |
| Farhangi M.A. 2014 [42]| Iran    | parallel nonalcoholic fatty liver disease | 41(20/21) | T: 42.73 C: 42.18 | 75.6%          | CoQ10       | placebo | 100 | 4 |            |             | TAC, MDA |
| Ho C.C. 2020 [43]| China   | parallel healthy | 29(15/14)    | T: 19.9 C: 19.6 | 69.0%          | ubiquinone   | placebo | 300 | 12 |            |             | TAC, MDA |
| Jahangard L. 2019 [44]| Iran    | parallel bipolar disorder | 69(36/33)  | T: 37.47 C: 39.52 | 15.9%          | CoQ10       | placebo | 100 | 8 |            |             | TAC, MDA |
| Rahmani A. 2015 [45]| Iran    | parallel dyspeptic | 100(50/50) | T: 57.9 C: 61.0 | 40.0%          | CoQ10       | placebo | 140 | 6 |            |             | TAC, MDA |
| Raygan F. 2016 [46]| Iran    | parallel obese + T2D + coronary heart disease | 60(30/30)  | T: 65.9 C: 59.9 | unclear        | CoQ10       | placebo | 100 | 8 |            |             | TAC, MDA |
| Gokbel H. 2016 [47]| Turkey  | crossover maintenance hemodialysis | 46(23/23) | 46.6 | 15.2%          | CoQ10       | placebo | 200 | 12 |            |             | MDA, SOD |
| Lee B.J. 2012 I [48]| China   | parallel coronary artery disease | 26(14/12)  | T: 75.1 C: 77.2 | 92.3%          | CoQ10       | placebo | 60  | 12 |            |             | MDA, SOD |
| Lee B.J. 2012 III [49]| China   | parallel coronary artery disease | 28(16/12)  | T: 73.0 C: 75.6 | 92.9%          | CoQ10       | placebo | 60  | 12 |            |             | MDA, SOD |
| Lee B.J. 2012 II [48]| China   | parallel coronary artery disease | 26(14/12)  | T: 79.2 C: 77.2 | 96.2%          | CoQ10       | placebo | 150 | 12 |            |             | MDA, SOD |
| Lee B.J. 2012 IV [49]| China   | parallel coronary artery disease | 27(15/12)  | T: 77.1 C: 75.6 | 96.3%          | CoQ10       | placebo | 150 | 12 |            |             | MDA, SOD |
| Liu H.T. 2016 [50]| China   | parallel hepatocellular carcinoma | 39(20/19)  | T: 59.7 C: 61.5 | 69.2%          | CoQ10       | placebo | 300 | 12 |            |             | MDA, SOD |
| Ramezani M. 2020 [51]| Iran    | parallel acute ischemic stroke | 44(21/23)  | T: 64.10 C: 62.04 | 50.0%          | CoQ10       | placebo | 300 | 4 |            |             | MDA, SOD |
| Shao L. 2016 [52]| China   | parallel acute viral myocarditis | 82(43/39)  | T: 23 C: 25 | 51.2%          | ubiquinol + trimetazidine | other | 30  | 2 |            |             | MDA, SOD |
| Yen C.H. 2018 [53]| China   | parallel T2D | 47(24/23)  | T: 61.5 C: 59.6 | 66.0%          | liquid ubiquinol | placebo | 100 | 12 |            |             | MDA, SOD |
Table 1. Cont.

| First Author, Year | Country | Study Design | Population Features | Sample Size (T/C) | Mean (Age) Years | Sex (Male) % | T | C | Dose mg/day | Duration wk | Biomarkers |
|---------------------|---------|--------------|---------------------|------------------|-----------------|-------------|---|---|-------------|-------------|------------|
| Akbari Fakhrabadi M. 2014 [54] | Iran | parallel | T2D | 62(32/30) | T: 56.7 C: 54.8 | 25.8% | CoQ10 | placebo | 200 | 12 | TAC |
| Emami A. 2018 I [34] | Iran | parallel | healthy | 18(9/9) | T: 17.40 C: 17.20 | 100.0% | CoQ10 + precooling | precooling | 300 | 2 | TAC |
| Emami A. 2018 II [34] | Iran | parallel | healthy | 18(9/9) | T: 17.60 C: 17.71 | 100.0% | CoQ10 | placebo | 300 | 2 | TAC |
| Rodriguez-Carrizalez A.D. 2016 [35] | Mexico | parallel | T2D | 40(20/20) | T: 28.2 C: 29.3 | 50.0% | CoQ10 | placebo | 400 | 24 | TAC |
| Zarei P. 2018 [37] | Iran | parallel | T2D | 68(34/34) | T: 53.1 C: 53.35 | 0.0% | CoQ10 | placebo | 100 | 12 | TAC |
| Zhang P. 2018 [56] | China | parallel | dyslipidemia | 101(51/50) | T: 51.78 C: 50.02 | 31.7% | CoQ10 | placebo | 120 | 24 | TAC |
| Gholami M. 2018 [38] | Iran | parallel | T2D | 68(34/34) | T: 53.1 C: 53.35 | 0.0% | CoQ10 | placebo | 100 | 12 | MDA |
| Ghonhari T. 2018 [57] | Iran | parallel | diabetic nephropathy | 50(25/25) | T: 61.1 C: 61.6 | 32.0% | CoQ10 | placebo | 100 | 12 | MDA |
| Kaikkonen J. 1997 I and II [36] | Finland | parallel | smoking | 60(20/20/20) | 46 | 100.0% | CoQ10 | placebo | 90 | 8 | MDA |
| Majid Mohammadshahi F.F. 2014 [58] | Iran | parallel | nonalcoholic fatty liver disease | 41(20/21) | 19–54 (range) | unclear | CoQ10 | placebo | 100 | 12 | MDA |
| Moazen M. 2015 [59] | Iran | parallel | T2D | 52(26/26) | T: 50.67 C: 52.79 | 53.8% | CoQ10 | placebo | 100 | 8 | MDA |
| Singh R.B. 1998 [60] | India | parallel | acute myocardial infarction | 144(73/71) | T: 48.0 C: 47.6 | 79.9% | CoQ10 | B vitamin | 120 | 4 | MDA |
| Singh R.B. 2005 [35] | India | parallel | healthy | 24(12/12) | 18–55 (range) | 100.0% | CoQ10 | placebo | 200 | 20 days | MDA |
| Singh R.B. and M.A. Niaz 1999 [61] | India | parallel | acute myocardial infarction, unstable angina, angina pectoris | 47(25/22) | T: 48.4 C: 47.6 | 78.7% | CoQ10 | placebo | 120 | 4 | MDA |
| Zhao Q. 2015 [62] | China | parallel | heart failure of nonischemic origin | 102(48/54) | T: 63 C: 62 | 70.6% | CoQ10 | placebo | 30 | 48 | MDA |
| Dai Y.L. 2011 [63] | China | parallel | ischemic left ventricular systolic dysfunction | 56(28/28) | T: 67.7 C: 70.1 | 92.9% | CoQ10 | placebo | 300 | 8 | SOD |
| First Author, Year | Country | Study Design | Population Features | Sample Size (T/C) | Mean (Age) T/C (Years) | Sex (Male) % | T | C | Dose mg/day | Duration wk | Biomarkers |
|--------------------|---------|--------------|---------------------|------------------|------------------------|--------------|---|---|-----------|------------|------------|
| Emami A. 2018 III [33] | Iran | parallel | healthy | 18(9/9) | T: 17.40 C: 17.20 | 100.0% | CoQ10 + precooling | precooling | 300 | 2 | SOD |
| Emami A. 2018 IV [33] | Iran | parallel | healthy | 18(9/9) | T: 17.60 C: 17.71 | 100.0% | CoQ10 | placebo | 300 | 2 | SOD |
| Lee B.J. 2013 [64] | China | parallel | coronary artery disease | 42(23/19) | T: 71.7 C: 66.5 | 73.8% | CoQ10 | placebo | 300 | 12 | SOD |
| Toth S. 2017 [65] | Slovakia | parallel | dyslipidemia | 70(35/35) | T: 58.4 C: 61.96 | 50.0% | CoQ10 + omega-3 PUFA | omega-3 PUFA | 200 | 12 | SOD |

Abbreviations: RCTs, randomized controlled trials; T, treatment group; C, control group; T2D, Type 2 Diabetes.
3.3. Effect of CoQ10 Supplementation on Circulating TAC

Fourteen studies with a total of 835 participants measured the circulating TAC after following the CoQ10 supplementation. Emami, A. et al. [33,34] conducted the trial in four parallel groups; thus we included CoQ10 + precooling versus precooling and CoQ10 versus placebo as the results of two independent studies. Hence, a forest plot exhibiting the pooled effect of fifteen arms is presented in Figure 2. TAC levels were significantly increased in participants treated with CoQ10 compared with placebo or others (SMD: 1.83, 95%CI: 1.07 to 2.59, p < 0.001). However, there was considerable heterogeneity between the studies ($I^2 = 95.44\%$, p < 0.001). Sensitivity analysis showed that removal of individual studies one by one also did not change the results (see Appendix A Figure A2).

As mentioned above, we conducted subgroup analysis on prespecified variables to explore the source of heterogeneity and to evaluate the association of them with the overall effect. The corresponding results are shown in Table 2. Among all the participants with different health status, the significant increase in TAC levels still existed in the subsets of studies administering 100 mg/d CoQ10 (SMD: 2.36, 95%CI: 0.72 to 4.00, p = 0.01), studies with ≥300 mg/d supplementation dose (SMD: 3.96, 95%CI: −4.34 to 12.25, p = 0.35).
Table 2. Subgroup analyses of CoQ10 supplementation on TAC.

| Subgroup                        | No. | SMD (95%CI)   | p-Value | I²  | p for Heterogeneity | p between Subgroups |
|---------------------------------|-----|---------------|---------|-----|---------------------|---------------------|
| Overall                         | 15  | 1.83 (1.07, 2.59) | <0.001  | 95.44% | <0.001              |                     |
| Duration                        |     |               |         |      |                     |                     |
| <4 weeks                        | 2   | 4.86 (2.88, 6.85) | <0.001  | 55.77% | 0.13                | 0.001               |
| ≥4 weeks and <8 weeks           | 2   | 0.61 (−2.80, 4.02) | 0.73    | 98.54% | <0.001              |                     |
| ≥8 weeks and <12 weeks          | 4   | 0.57 (0.18, 0.96)  | <0.01   | 57.93% | 0.07                |                     |
| ≥12 weeks and <16 weeks         | 5   | 1.87 (0.19, 3.56)  | 0.03    | 96.85% | <0.001              |                     |
| ≥16 weeks                       | 2   | 4.30 (−3.33, 11.92) | 0.27    | 98.37% | <0.001              |                     |
| Intervention dose               |     |               |         |      |                     |                     |
| 100 mg/d                        | 5   | 0.26 (−0.41, 11.92) | 0.44    | 87.01% | <0.001              | 0.02                |
| 100 mg/d and ≤150 mg/d          | 4   | 2.36 (0.72, 4.00)  | <0.01   | 97.37% | <0.001              |                     |
| >150 mg/d and ≤300 mg/d         | 4   | 3.01 (0.82, 5.21)  | <0.01   | 94.41% | <0.001              |                     |
| >300 mg/d                       | 2   | 3.96 (−4.34, 12.25) | 0.35    | 98.56% | <0.001              |                     |
| Health status                   |     |               |         |      |                     |                     |
| DN                              | 1   |               | <0.001  |      |                     |                     |
| Dyslipidemia                    | 1   |               | <0.001  |      |                     |                     |
| Healthy                         | 3   | 3.23 (−0.51, 6.98) | 0.09    | 95.26% | <0.001              |                     |
| NAFLD                           | 1   |               |         |      |                     |                     |
| T2D                             | 3   | 3.63 (0.82, 6.45)  | 0.01    | 97.35% | <0.001              |                     |
| Other                           | 6   | 0.73 (0.02, 1.45)  | 0.045   | 91.37% | <0.001              |                     |
| Type of control                 |     |               |         |      |                     |                     |
| Placebo                         | 14  | 1.61 (0.86, 2.37)  | <0.001  | 95.44% | <0.001              | <0.001              |
| Other                           | 1   |               |         |      |                     |                     |
| Study quality                   |     |               |         |      |                     |                     |
| Fair                            | 3   | 3.91 (1.86, 5.95)  | <0.001  | 85.20% | 0.001               | 0.02                |
| Good                            | 12  | 1.37 (0.60, 2.14)  | 0.001   | 95.20% | <0.001              |                     |

The heterogeneity had a significant reduction in subgroups of studies administering CoQ10 supplementation for <4 weeks ($I^2 = 55.77\%, p = 0.13$) or 8–12 weeks ($I^2 = 57.93\%, p = 0.07$) but still presented significance across other subgroups.

3.4. Effect of CoQ10 Supplementation on MDA Concentrations

After combining the results of 28 arms from 25 trials, including a total sample size of 1501 participants, we found a significant effect of CoQ10 intervention on circulating MDA levels using the random-effects model (SMD: $−0.77$, 95%CI: $−1.06$ to $−0.47$, $p < 0.001$; Figure 3). Heterogeneity is significant ($I^2 = 86.76\%, p < 0.001$). The overall effect was robust when we omitted individual study effects one by one for sensitivity analysis (see Appendix A Figure A3).

The results of subgroup analyses in Table 3 showed that the effect of CoQ10 on circulating MDA concentrations could be associated with study duration, intervention dose and participant health status. In subgroups divided by different study duration, the decrease of MDA concentrations remained significant in each subset. In terms of intervention dose, combined results from nine studies administering 100 mg/d CoQ10 supplementation did reveal a significant reduction (SMD: $−0.46$, 95%CI: $−0.71$ to $−0.22$, $p < 0.001$) in MDA concentrations with lower heterogeneity ($I^2 = 42.51\%, p = 0.08$). In the subset of studies with 100–150 mg/d CoQ10 supplementation, the significant reduction still existed (SMD: $−1.72$, 95%CI: $−2.38$ to $−1.05$, $p < 0.001$). However, there was no significant reduction in MDA concentrations in the subset of studies administering <100mg or 150–300 mg CoQ10 supplementation. As for health status, we divided it as detailed as possible. It demonstrated that CoQ10 supplementation significantly reduced MDA concentrations in patients with coronary artery disease (CAD) with no statistical heterogeneity (SMD: $−0.55$, 95%CI: $−0.92$ to $−0.17$, $p = 0.01$; $I^2 = 0.00\%$, $p = 0.99$), as it did in patients with T2D (SMD: $−0.33$, 95%CI: $−0.64$ to $−0.03$, $p = 0.03$; $I^2 = 0.00\%$, $p = 0.49$). The significant reduction also existed in patients with acute myocardial infarction (AMI), diabetes nephropathy...
(DN) or other diseases but was not observed in healthy population or nonalcoholic fatty liver disease (NAFLD) patients, as presented in Table 3.

### Table 3. Subgroup analyses of CoQ10 supplementation on MDA.

| Subgroup | No. | SMD (95%CI) | p-Value | $I^2$ | $p$ for Heterogeneity | $p$ between Subgroups |
|----------|-----|-------------|---------|------|-----------------------|-----------------------|
| Overall  | 28  | $-0.77 (-1.06, -0.47)$ | <0.001 | 86.76% | <0.001 |  |
| Duration |     |             |         |      |                       |                       |
| <4 weeks |  2  | $-1.24 (-1.65, -0.83)$ | <0.001 | 0.00% | 0.40 | <0.001 |
| ≥4 weeks and <8 weeks | 5  | $-1.59 (-2.58, -0.60)$ | <0.01 | 93.80% | <0.001 |  |
| ≥8 weeks and <12 weeks | 7  | $-0.39 (-0.70, -0.08)$ | 0.02 | 57.43% | 0.03 |  |
| ≥12 weeks and <16 weeks | 13 | $-0.66 (-1.04, -0.29)$ | 0.001 | 77.79% | <0.001 |  |
| ≥16 weeks | 1 | - | - | - | - | - |
| Intervention dose |     |             |         |      |                       |                       |
| <100 mg | 6  | $-0.28 (-0.76, 0.20)$ | 0.25 | 76.65% | 0.001 | 0.001 |
| 100 mg/d | 9 | $-0.46 (-0.71, -0.22)$ | <0.001 | 42.51% | 0.08 |  |
| >100 mg/d and ≤150 mg/d | 7 | $-1.72 (-2.36, -1.05)$ | <0.001 | 89.04% | <0.001 |  |
| >150 mg/d and ≤300 mg/d | 5 | $-0.46 (-0.96, 0.03)$ | 0.07 | 63.93% | 0.03 |  |
| >300 mg/d | 1 | - | - | - | - | - |

Figure 3. Forest plot of the meta-analysis on the effect of CoQ10 supplementation on net changes of MDA.
Subgroup No. SMD (95%CI) p-Value I² p for Heterogeneity p between Subgroups

**Health status**
AMI 2 −2.85 (−4.87, −0.84) 0.01 93.21% <0.001 <0.01
CAD 4 −0.35 (−0.92, −0.17) 0.01 0.00% 0.99
DN 2 −1.92 (−3.01, −0.83) 0.001 82.93% 0.02
HF 1 - - - -
Healthy 4 −0.32 (−1.03, 0.39) 0.38 75.99% 0.01
NAFLD 2 −0.21 (−0.64, 0.21) 0.33 0.00% 0.99
T2D 3 −0.33 (−0.64, −0.03) 0.03 0.00% 0.49
Other 10 −0.75 (−1.13, −0.37) <0.001 80.24% <0.001

**Type of control**
Placebo 26 −0.70 (−0.10, −0.40) <0.001 84.68% <0.001 0.04
Other 2 −1.52 (−2.24, −0.81) <0.001 81.97% 0.02

**Study quality**
Bad 2 −0.58 (−1.00, −0.17) <0.01 0.00% 0.85 0.58
Fair 11 −0.63 (−1.06, −0.20) <0.01 81.42% <0.001
Good 15 −0.90 (−1.36, −0.43) <0.001 90.61% <0.001

No matter the type of control, the significant decrease in MDA concentrations was still kept in two subgroups. Additionally, a higher study quality may be associated with a more significant effect of CoQ10 supplementation on MDA levels. Furthermore, subgroup analyses revealed that duration of CoQ10 supplementation, intervention dose, health status of participants and study quality are the possible sources of heterogeneity.

3.5. Effect of CoQ10 Supplementation on SOD Levels

Based on the pooled results of all 16-arm studies including 694 participants, we could not yet determine that there was a significant increase in SOD levels after following the CoQ10 supplementation (SMD: 0.47, 95%CI: 0.00 to 0.94, p = 0.05; Figure 4). Sensitivity analysis demonstrated that after individually eliminating studies by Dai Y.L., Emami A., Gokbel H., Shao L. or Yen C.H. [33,47,52,53,63], the pooled effects of CoQ10 on SOD levels showed a significant elevation, as shown in Appendix A Figure A4.

In addition, results of subgroup analyses are presented in Table 4. Ten of the included studies evaluated the change of SOD levels after following 12-week CoQ10 supplementation. The combined result of the ten studies showed a significant increase in SOD levels with significantly low heterogeneity (SMD: 0.63, 95%CI: 0.37 to 0.89, p < 0.001; I² = 38.80%, p = 0.10). Pooling the results of studies in other duration categories, we could not find the significant increase in SOD levels. Following the 100–150 mg/d intervention dose, SOD levels significantly elevated with no statistical heterogeneity between studies (SMD: 1.12, 95%CI: 0.76 to 1.48, p < 0.001; I² = 0.00%, p = 0.90), while in studies with a higher dose (150–300 mg/d), such significance was eliminated (SMD: −0.18, 95%CI: −0.84 to 0.47, p = 0.58). Classifying the studies by different health statuses, we found that CoQ10 supplementation could significantly improve SOD levels in patients with CAD (SMD: 0.92, 95%CI: 0.59 to 1.25, p < 0.001). Only Emami A. et al. measured the effect of CoQ10 supplementation on SOD levels of healthy people. After combining the results of this two-arm study, we failed to find a significant change of SOD levels (SMD: −3.50, 95%CI: −6.92 to −0.08, p = 0.05). It was also revealed that circulating SOD levels were significantly increased in the subgroup of placebo control (SMD: 0.52, 95%CI: 0.19 to 0.85, p < 0.01). Compared to fair-quality studies, the combined effect of good-quality studies was significant with lower heterogeneity (SMD: 0.43, 95%CI: 0.07 to 0.80, p = 0.02).
Figure 4. Forest plot of the meta-analysis on the effect of CoQ10 supplementation on net changes of SOD.

Table 4. Subgroup analyses of CoQ10 supplementation on SOD.
The heterogeneity reduced obviously in three subgroups (12–16 weeks intervention duration, 100–150 mg/d intervention dose and CAD patients). Apart from them, the heterogeneity still remained significant.

3.6. Publication Bias

According to Egger’s test, we found no evidence of publication bias in studies examining the effects of CoQ10 supplementation on MDA \( (p = 0.64) \) and SOD \( (p = 0.12) \) levels. However, there was significant publication bias for TAC levels \( (p = 0.01) \). The results were also visually confirmed by funnel plots (Figure 5).

![Funnel plots](image)

**Figure 5.** Funnel plots representing publication bias in the included studies relevant to the effect of CoQ10 supplementation on (A) TAC, (B) MDA and (C) SOD.

3.7. Grading of the Evidence

The summary of the GRADE assessment of CoQ10 supplementation on the three oxidative biomarkers is shown in Appendix A Table A2. The evidence assessment for TAC, MDA and SOD was all downgraded to very low quality as a result of very serious inconsistency (high heterogeneity) and imprecision (relatively small sample size). Specifically, the evidence estimate of TAC was downgraded to very low quality for potential publication bias.

4. Discussion

The current systematic review and meta-analysis quantified the effects of CoQ10 supplementation on oxidative stress biomarkers in 34 RCT comparisons including 2012 participants. The major findings of this review were that CoQ10 supplementation was associated with a significant increase in circulating TAC and a significant reduction in circulating MDA concentrations but only with a border significance in the improvement of SOD levels in general population.

Our results for the effects of CoQ10 supplementation on TAC and MDA levels were in line with those of previous meta-analyses including fewer RCTs, which reported a statistically significant increase in TAC and a significant decrease in MDA levels [27,28,66]. However, the effect of CoQ10 on SOD levels was different from the results of prior meta-
analyses that suggested a significant elevation of SOD levels after CoQ10 supplementation. Notably, our review contained 10 additional RCTs for this biomarker that were not included in prior meta-analyses.

Summarizing the included RCTs, we found that the intervention duration in most studies was 12 weeks, followed by 8 weeks. Subgroup analyses on duration suggested that the 12-week CoQ10 supplementation could significantly change the TAC, MDA and SOD levels. Taking CoQ10 for 8 weeks also significantly changed the levels of them except SOD. However, it is worthy to note there were only two RCTs that included evaluating the effect of 8-week CoQ10 supplementation on SOD levels [32,63]. Only three RCTs conducted CoQ10 intervention for more than 12 weeks [55,56,62]; hence we could not conclude that longer intervention time would bring about better antioxidant effects of CoQ10 yet. Subgroup analyses on intervention dose suggested that 100–150 mg/day CoQ10 supplementation was effective to significantly change TAC, MDA and SOD levels at the same time, especially the SOD levels. Consistently, one previous meta-analysis also reported the significant effects of ≤150 mg/day CoQ10 intervention on MDA and SOD levels, although it was specific to people with CAD [23]. Our study more accurately suggested that 100–150 mg/day of CoQ10 had better antioxidant benefits in general population.

In particular, the supplementation with CoQ10 is well-tolerated and safe. All included clinical trials in our present study, with the highest dose 500 mg/d and the longest duration 12 months, showed no side effects causally or plausibly related to CoQ10. Moreover, one 16-month clinical trial using the dose of 1200 mg daily observed no adverse effects [67]. Taking these into account, the recommended 100–150 mg/d of CoQ10 for attenuating the oxidative stress status is considered low risk of side effects.

The potential mechanisms underlying the effects of CoQ10 supplementation on these oxidative stress biomarkers in the general population mainly contain direct and indirect aspects. From the direct aspect, CoQ10 maintains the normal electron transportation in the mitochondrial electron transport chain (METC); thus less superoxide (O$_2^{-}$) would be produced in the process [17]. Besides, both in vivo and in vitro studies have suggested that CoQ10 supplementation could ameliorate lipid peroxidation [68,69]. From the indirect aspect, CoQ10 can regenerate α-tocopherol, the reduced active substance of vitamin E, by converting the product from the reaction of vitamin E and lipid peroxidative free radicals [70]. Additionally, CoQ10 could eliminate oxidative stress from the gene aspect by activating nuclear factor erythroid 2-related factor 2 (Nrf-2), a transcription factor regulating cellular responses to oxidative stress through the regulation of a number of ROS-detoxifying enzymes [71–73].

Subgroup analyses implied that CoQ10 supplementation was conducive to ameliorating oxidative stress status in patients with T2D or CAD while having no significant effects on oxidative stress biomarkers among healthy counterparts. Concordant with our findings, Jorat et al. reported via the meta-analysis that CoQ10 supplementation significantly increased SOD and decreased MDA levels among patients with CAD [23]. A prior systematic review also found a significant reduction of serum MDA levels after CoQ10 supplementation in a subgroup analysis of diabetic patients [66]. This could be attributed to the decrease of endogenous CoQ10 synthesis in patients with CAD or T2D [74,75], as well as the elevation of circulating CoQ10 concentration after supplementation. For instance, previous studies suggested that CoQ10 levels were significantly lower in T2D patients than those in healthy people and the levels could be restored through exogenous CoQ10 supplementation [76,77].

Factors that have been reported regarding the deficiency of CoQ10 include aging and the use of statin-type drugs. In humans, the endogenous production of CoQ10 begins to decline after the age of 20, and the myocardial concentration of CoQ10 is decreased to about half at the age of 80 [20]. Besides, the endogenous synthesis of CoQ10 is suppressed by the extensive use of statin-type drugs in the treatment of several abnormalities linked to CVDs, such as hypercholesterolemia [78,79]. Because the mechanism of statin-type drugs lies in the inhibition of hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase, a
rate-limiting enzyme acting both in cholesterol synthesis and in the process of CoQ10 biosynthesis [21]. Therefore, low levels of CoQ10 are observed in patients with CVDs or T2D for one or more of the possible factors above.

This meta-analysis comes with some strengths. The primary strength is that the present study elucidated the association between CoQ10 supplementation and oxidative stress biomarkers in adults through a systematic review and meta-analysis of updated RCTs. Another advantage of this meta-analysis is that we firstly assessed evidence certainty based on the GRADE approach. Nevertheless, our study has some potential limitations. Firstly, due to different measurement methods and different units of these biomarkers, we could not investigate the association between baseline TAC, MDA or SOD levels and the effects of CoQ10 supplementation on them. Also, although our current data indicated that CoQ10 supplementation could attenuate TAC and MDA levels compared to the control group, it is difficult to conclude that CoQ10 could normalize them to the physiological level, which is undefined until now due to the discrepancy of laboratory methods [6]. Secondly, most studies included in this review did not measure participants’ circulating CoQ10 concentrations. Hence, it remains unclear whether circulating CoQ10 status might affect the outcomes explored in this review. Besides, because part of the included studies merely provided the range of age [35,58], we could not make the preplanned subgroup analysis based on the age variable to explore the effects of CoQ10 supplementation varying with the participants’ age. Finally, publication bias may exist in the present study, as in any meta-analysis.

The presence of significant heterogeneity among studies needs to be discussed. An important source of heterogeneity could be due to the discrepancy in laboratory methods used to evaluate the oxidative stress biomarkers. Different techniques on different samples were performed in the included studies. In addition, the formulation of CoQ10 used was various among most included studies, and there was no quantification of CoQ10 intake with diet. Although it was not possible to conclusively ascertain sources of heterogeneity, some implications were given by the subgroup analyses.

5. Conclusions

In conclusion, the present systematic review and meta-analysis of 34 RCTs indicates that CoQ10 supplementation may be effective to attenuate oxidative stress status in the general population, especially in people with CAD or T2D. The supplementation of 100–150 mg/day CoQ10 is recommended for ameliorating the oxidative stress status. Further investigations using larger sample size, broad age range of elderly people and longer supplementation period are required to research on the effects of different doses of CoQ10 supplements as well as the circulating CoQ10 levels on people with age-associated chronic diseases.

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Conflicts of Interest: The authors declare no conflict of interest.
Appendix A

Figure A1. Risk of bias assessment for the included studies. Trials with a low or high risk of bias in key domains were categorized as having a “low risk of bias” or “high risk of bias”, respectively. Otherwise, trials were categorized as having an “unclear risk of bias”.

Figure A2. Sensitivity analysis for the effects of CoQ10 on TAC through removal of individual trials one by one.
Table A1. Search strategy. For all databases, searches were performed for the time period until 30 March 2022.

| Malondialdehyde Study | Standardised Mean Difference | SMD | 95%CI |
|------------------------|-------------------------------|-----|-------|
| Omitting Abdollahzad H. 2015 | -0.76 | -1.07; -0.46 |
| Omitting Fallah M. 2019 | -0.70 | -0.99; -0.41 |
| Omitting Farhangi M.A. 2014 | -0.79 | -1.09; -0.48 |
| Omitting Gholami M. 2018 | -0.78 | -1.09; -0.47 |
| Omitting Gholnari T. 2018 | -0.74 | -1.05; -0.44 |
| Omitting Gokbel H. 2016 | -0.80 | -1.10; -0.50 |
| Omitting Ho C.C. 2020 | -0.78 | -1.09; -0.47 |
| Omitting Hormozi M. 2019 | -0.76 | -1.07; -0.45 |
| Omitting Jahangard L. 2019 | -0.79 | -1.09; -0.48 |
| Omitting Kaikkonen J. 1997 | -0.80 | -1.10; -0.50 |
| Omitting Kalkkonen J. 1997 II | -0.80 | -1.10; -0.50 |
| Omitting Lee B.J. 2012 ... | -0.77 | -1.08; -0.47 |
| Omitting Lee B.J. 2012 I | -0.78 | -1.08; -0.47 |
| Omitting Lee B.J. 2012 ... | -0.77 | -1.08; -0.46 |
| Omitting Lee B.J. 2012 II | -0.77 | -1.09; -0.46 |
| Omitting Liu H.T. 2016 | -0.77 | -1.08; -0.46 |
| Omitting Majid Mohammadshahi F.F. 2014 | -0.79 | -1.09; -0.48 |
| Omitting Moazen M. 2015 | -0.77 | -1.08; -0.46 |
| Omitting Rahmani A. 2015 | -0.72 | -1.01; -0.43 |
| Omitting Ramezani M. 2020 | -0.78 | -1.09; -0.48 |
| Omitting Raygan F. 2016 | -0.76 | -1.09; -0.47 |
| Omitting Sanoobar M. 2013 | -0.75 | -1.05; -0.44 |
| Omitting Shao L. 2016 | -0.75 | -1.06; -0.44 |
| Omitting Singh R.B. 1998 | -0.72 | -1.00; -0.43 |
| Omitting Singh R.B. 2005 | -0.74 | -1.04; -0.44 |
| Omitting Singh R.B. and M.A. Niaz 1999 | -0.67 | -0.94; -0.40 |
| Omitting Yen C.H. 2018 | -0.79 | -1.10; -0.49 |
| Omitting Zhao Q. 2015 | -0.80 | -1.10; -0.50 |

Random effects model

Figure A3. Sensitivity analysis for the effects of CoQ10 on MDA through removal of individual trials one by one.

Table A1. Search strategy. For all databases, searches were performed for the time period until 30 March 2022.

| Superoxide dismutase Study | Standardised Mean Difference | SMD | 95%CI |
|----------------------------|-------------------------------|-----|-------|
| Omitting Dai Y.L. 2011 | 0.50 | 0.01; 1.00 |
| Omitting Emami A. 2018 III | 0.67 | 0.26; 1.08 |
| Omitting Emami A. 2018 IV | 0.63 | 0.19; 1.08 |
| Omitting Gokbel H. 2016 | 0.53 | 0.04; 1.02 |
| Omitting Hormozi M. 2019 | 0.43 | -0.07; 0.94 |
| Omitting Lee B.J. 2012 III | 0.45 | -0.04; 0.94 |
| Omitting Lee B.J. 2012 I | 0.46 | -0.03; 0.95 |
| Omitting Lee B.J. 2012 IV | 0.44 | -0.05; 0.92 |
| Omitting Lee B.J. 2012 II | 0.45 | -0.04; 0.94 |
| Omitting Lee B.J. 2013 | 0.47 | -0.03; 0.97 |
| Omitting Liu H.T. 2016 | 0.46 | -0.03; 0.96 |
| Omitting Ramezani M. 2020 | 0.49 | -0.01; 0.99 |
| Omitting Sanoobar M. 2013 | 0.46 | -0.04; 0.96 |
| Omitting Shao L. 2016 | 0.38 | 0.00; 0.76 |
| Omitting Toth S. 2017 | 0.47 | -0.04; 0.98 |
| Omitting Yen C.H. 2018 | 0.51 | 0.02; 1.01 |

Random effects model

Figure A4. Sensitivity analysis for the effects of CoQ10 on SOD through removal of individual trials one by one.
Table A1. Search strategy. For all databases, searches were performed for the time period until 30 March 2022.

| Database       | Search strategy                                                                 |
|----------------|---------------------------------------------------------------------------------|
| PubMed         | #1 ((Coenzyme Q10) OR (CoQ10) OR (Ubiquinone))                                  |
|                | #2 ((malondialdehyde) OR (superoxide dismutase) OR (MDA) OR (SOD) OR (total antioxidant capacity) OR (TAC)) |
|                | #1 AND #2                                                                        |
| Embase         | #1 ‘coenzyme q10’/exp OR ‘coenzyme q10’ OR coq10 OR ‘ubiquinone’/exp OR ubiquinone |
|                | #2 ‘malondialdehyde’/exp OR malondialdehyde OR ‘superoxide dismutase’/exp OR ‘superoxide dismutase’ OR mda OR sod OR ‘total antioxidant capacity’/exp OR ‘total antioxidant capacity’ OR tac |
|                | #1 AND #2                                                                        |
| Cochrane Library | #1 ((Coenzyme Q10) OR (CoQ10) OR (Ubiquinone))                                  |
|                | #2 ((malondialdehyde) OR (superoxide dismutase) OR (MDA) OR (SOD) OR (total antioxidant capacity) OR (TAC)) |
|                | #1 AND #2                                                                        |

Table A2. GRADE evidence profile of CoQ10 supplementation on oxidative stress biomarkers.

| Quality Assessment | No of Patients | Effect | Quality | Importance |
|--------------------|----------------|--------|---------|------------|
| No of Studies | Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | CoQ10 | Control | Absolute (95%CI) |            |           |
| Total Antioxidant Capacity (follow-up 2–24 weeks; Better Indicated by higher values) | 15 | randomized trials | no serious | very serious 1 | no serious | very serious 2 | reporting bias 3 | 420 | 415 | SMD 1.83 higher (1.07 to 2.59 higher) | ⊕ OOO | VERY LOW | CRITICAL |
| Malondialdehyde (follow-up 2–48 weeks; Better indicated by lower values) | 28 | randomized trials | no serious | very serious 4 | no serious | serious 2 | none | 758 | 743 | SMD 0.77 lower (1.06 to 0.47 lower) | ⊕ OOO | VERY LOW | CRITICAL |
| Superoxide Dismutase (follow-up 4–12 weeks; Better indicated by higher values) | 16 | randomized trials | no serious | very serious 5 | no serious | very serious 2 | none | 356 | 338 | SMD 0.47 higher (0.00 to 0.94 higher) | ⊕ OOO | VERY LOW | CRITICAL |

1 The test for heterogeneity between studies is significant (p < 0.001), and the I2 equals 95.44%. 2 The sample size is relatively small. 3 The Egger’s test for TAC to identify publication bias is significant (p = 0.01). 4 The test for heterogeneity between studies is significant (p < 0.001), and the I2 equals 86.76%. 5 The test for heterogeneity between studies is significant (p < 0.001), and the I2 equals 88.21%.
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